

Introduction and IFO Organization

CEO IFO Message

Dr. Marina Cerimele

Scientific Director IRE Message

Prof. Gennaro Ciliberto

Scientific Director ISG Message

Prof. Aldo Morrone

IFO Chief Medical Officer Message

Dr. Ermete Gallo

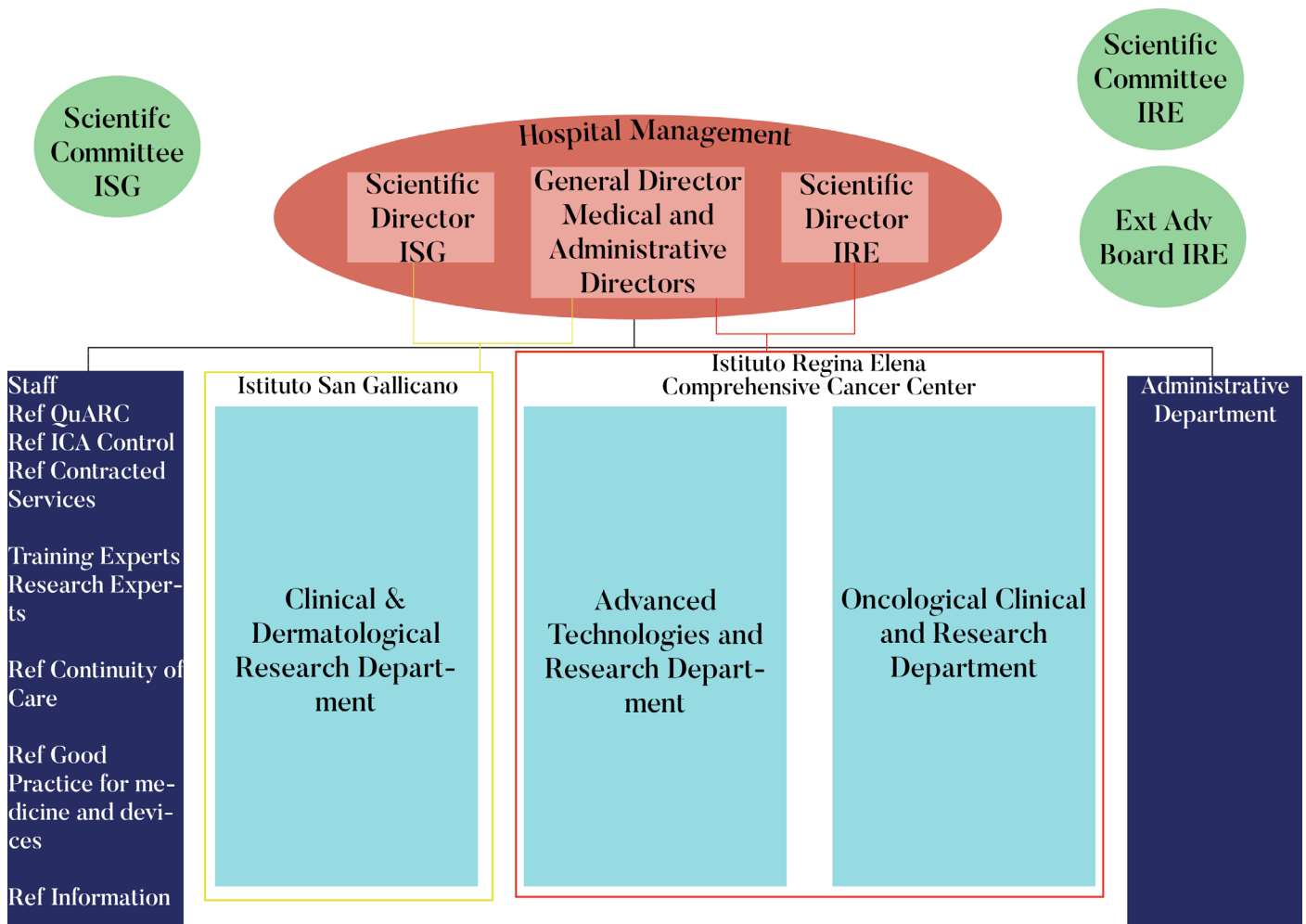
IFO Medical Directorate

Head: Dr. Domenico Bracco

IFO Administrative Direction

Head: Dr. Laura Figorilli

Organization chart of IFO



Press Office & Public Relation

Head: Dr. Lorella Salce

Education and Training Unit

Head: Dr. Tiziana Lavalle

Staff

Dr. Antonia Tramontana, Continuous Educational Organizer

Dr. Silvia Lolli, Continuous Educational Organizer

Dr. Massimo Bisozzi, Administrative support and monitor

Dr. Marcello Albanito, Administrative support

Mission

The IFOs recognize a strategic role in the development and enhancement of skills aimed at achieving the institutional objectives of responding to the health needs of citizens. The IFOs also support training as a tool for supporting organizational innovation and for improving the quality of individual and organizational performance.

Professionals in organizations are now asked to have a greater ability to “learn”, to better respond to processes of change that are not always predictable.

The Organizational Development and Human Capital unit contributes to the dissemination of the Public Health Service and IFOs values and culture, contributes to the development of technical and soft skills, supporting all professionals to do their best, placing the Citizens health at the center of the care processes.

The objectives that define the mission of the structure are:

- Scope of Organizational Development
 - Support the Strategic Management in defining corporate development policies, human and intellectual capital;
 - Support the Strategic Management and the Departments in the development of organizational models subject to reorganization or experimentation; in the evaluation and implementation of organizational innovation by focusing on the enhancement of professionalism.
 - Support the Strategic Management in the drafting and modification / integration of the Corporate Deed, taking care of its macro organization and implementation, and all subsequent obligations, integrating with the General and Legal Affairs UOC, according to the specific skills.
 - Promote and support the research activities of the Scientific Departments and that in the management field, in order to develop opportunities for the visibility of the IFO among the National IRCCS.
- Human Capital Development Area
 - Program the annual training needs of the IFO in a manner consistent with the objectives of the operational budget planning of the Departments;
 - Promote and verify the monitoring of skills in the IFO UUOOs, in order to define the value of intellectual and professional capital;
 - Design and implement a system for enhancing skills of high intellectual value and supporting unexpressed potential (cultivating talents);
 - Activate and manage the procedures relating to the ECM training program as a national provider.

Consistently with what stated above, the mission of the Training Office is:

- Enhancement, empowerment and the widest possible involvement of all staff, as a human and professional resource essential to the development of the Company;

- Elaboration of training and retraining plans and programs in relation to professional development and organizational innovations in line with the programmatic guidelines proposed by the National Health Plan and the Regional Social Health Plan, and with the corporate objectives and strategic lines;
- Acquisition of training credits for company professionals provided for by current provisions;
- Development and consolidation of synergies with universities and other training institutions for the future health professionals.

Activities of 2021

The activities carried out as Organizational Development were, during 2021:

- The preparation of reports and implementing acts of the Company Deed;
- The proposal of requirements for expressions of interest in organizational structures and objectives for the assignment of structure assignments
- The preparation of the Operating Regulations of the Departments.

The Director of the OU also, in the context of Organizational Development, performs the function of Quality Assurance (QA) for the Phase 1 testing activities of the Phase 1 Clinical Center, QA of the No-Profit Promoter Function and Clinical Trial Quality Team and, temporarily, QA also for the Phase 1 Laboratory of Pathological Anatomy. This function is foreseen “until exhaustion” as soon as the Scientific Departments have identified another senior QA for clinical trials of medicine and medical devices.

The Bastianelli Center was closed for training activities during the 2021 lockdown and from April to October 15 it was completely occupied by the IFO Vaccination Center for outsiders. On 26 October, on-site activities resumed at the Center and activities in the virtual classroom and FAD continued.

The solutions adopted, until October 15th, 2021, to still allow IFO employees access to training, were the following:

- Use of the FAD IFO platform (Faddy)
- Use of digital platform for virtual classroom courses
- Purchase of FAD training packages from external suppliers (Anti-corruption, Privacy, Code of Conduct, regulations on procurement management, standards of good clinical laboratory practice for Phase 1, clinical trial course for Phase 1)
- Purchase of training packages in webinar / virtual classroom (SImef Courses, Promis, courses for Engineers, English Course, role orientation for newly appointed persons in charge of organizational functions in the health sector)
- Purchase from external providers of face-to-face activities in places accessible and authorized despite the lockdown (BLS and ACLS courses).

At the end, the Educational Office performed 117 training courses.

	Female	Male	Total
Obligatory (safety)	1290	670	1960
Safety	932	331	1263
Professional updating	8998	4357	13355
Managerial skills	2171	781	2952
Research	846	295	1141
Total hours of training	14237	6434	20671

Quality, Accreditation, clinical
Risk management Unit
Head: Dr. Assunta De Luca

Pharmacovigilance

Head: Dr. Felice Musicco

Office of Research Administration (SAR) Head: Dr. Ottavio Latini

Staff

Dr. Giovanni Cavallotti, Archive and Protocols

Dr. Lucia D'Auria, Agreements

Dr. Maria Assunta Fonsi, Research Staff Contracts

Dr. Livia Galgano, Archive

Mrs. Giuseppina Gioffrè, Missions and Travels

Dr. Domenico Kolziu, Research Projects Management

Dr. Anna Lisa Mariani, Research Projects Management

Mrs. Catia Minutiello, Research Projects Management

Dr. Maria Laura Sarli, Research Staff Contracts

Mission

The Research Administration Office (SAR) is part of the Department of Technical-Administrative Functions of the IFO Institute and carries out research support functions.

SAR has technical-administrative autonomy. The Responsible Manager, in line with the Department's activity plans and using the human and instrumental resources assigned, carries out the activities according to the guidelines provided by the Institute and Scientific Directorates IRE and ISG and is in constant relationship with the departmental units of the clinical and research sectors of the Institute.

The SAR, in compliance with the relevant legislation and Institutional Regulations, deals in particular with:

- IT protocol and archive of research documents;
- Administrative procedure for accepting funding for national and international research projects, both public and private;
- Stipulates conventions, research agreements and related administrative documents;
- Administrative management of research projects, monitoring of deadlines and project reporting;
- Administrative procedure for the activation of contracts for personnel involved on research;
- Tax and social security obligations for the research staff;
- Administrative process for the management of reimbursements and missions on research funds;
- Support for external audits;
- Reporting to support the Scientific Director and other IFO administrative offices (Economic Resources and Budget Unit, Human Resources Unit, Goods and Services Acquisition Unit; Ethics Committee, Technology Transfer Office...);
- Drafting of internal regulations;
- Administrative procedure for the experimental protocols and agreements with the sponsors;
- Management of proceeds from experimental protocols and related distribution;

Activities

During 2021 the SAR Office dealt with managing the administrative and economical aspects of national and international, public and privately research projects funded by the Regina Elena Institute (IRE).

The SAR handled the administrative and accounting procedures of all expenses concerning grant of Italian Ministry of Health for Ricerca Corrente IRE 2021 (€ 4.239.813,42) and prepared the economic report for Ricerca Corrente IRE 2020 funding (€ 3.156.389,57).

This Office also handled the Ricerca Finalizzata fundings for total € 4.866.916,95.

The SAR Office has prepared official administrative documents to accepting funding for research projects (36) of which the IRE is the lead partner and handled relations both with the funding bodies and Internal and External Operating Units involved in the projects themselves, also has finalized economical reports for research projects.

During 2021, the SAR continued to manage projects from previous years, handled more than 130 projects and supported new projects in regards to budgets and new applications. For all the funded projects listed above, the SAR office followed through with all the administrative procedures concerning related expenditure.

The SAR office has assisted the Scientific Direction in the provision of onerous agreements (within the scope of approved projects) and free of charge licence agreements (30).

Following the stabilization of the personnel hired under TD contract Research and Support (Law 205/2017, art.1, Section from 422 to 434) the following related procedures were carried out:

- Allocation of bands in application of the adoption of the Regulations for the professional evaluation of research and support personnel and the Application Protocol for the management of the performance enhancement system;
- Appointment of the members of the Evaluation Units in application of Ministerial Decree no. 164/2019;
- Approval of the IRE plan of personnel requirements for the years 2021/2022/2023.

In application of the D.P.C.M of 21/04/2021, the company personnel selection regulations are being reviewed.

The Office will comply with all fulfillment of all regulatory obligations regarding transparency and corruption prevention, risk analysis, risk assessment process mapping, compliance with publication obligations.

The Office has also the coordination of the procedure of financing / reporting in the “Conto Capitale” projects, realized with grants of Italian Ministry of Health.

During 2021, the SAR office activated more than 128 decrees relating to the acceptance of clinical trials.

After the Finance Office issues the invoices and monitors the receipts, the SAR Office prepares the financial statements for each study, where it acquired invoices and distributed them among the departments with regulations outlined in the decree (Administration, Pharmacy, Scientific Office, Other Departments/ Offices involved in the study, PI or UOC coordinator of the study) and followed the administrative procedures relating to handling expenses on the proceeds of the clinical trials.

Goods and Services Acquisition Unit (ABS) Head: Dr. Gianluca Moretti

Staff

Mrs. Cristina Corsi
Dr. Zoe Tonda
Dr. Carol Scioscia
Mrs. Giovanna Surace
Mrs. Gabriella Ingrosso
Mrs. Anita Fiumara
Mr. Giovanni Ricci
Mr. Fabrizio Gatto

Mr. Massimiliano Romano
Mrs. Angela De Simone
Mr. Antonio De Paolis
Mrs. Domenico Fiorillo
Mr. Gianluca Murru
Mrs. Piera Brugnoli
Dr. Barbara Filipponi
Dr. Eugenio Radighieri
Mrs. Loredana De Marco

Mission

The UOC “Acquisition of Goods and Services” has the function of governing the processes relating to the acquisition of goods and services necessary for the regular performance of company activities in accordance with the legislation on public procurement from the planning stage to the conclusion of the contract.

The UOC Acquisition of Goods and Services carries out its functions by carrying out the following activities and the following offices in charge:

PROGRAMMING AND PLANNING

This is the prodromal phase to the awarding of tenders consisting of the preparation of the two-year program of purchases of goods and services (Article 21 of Legislative Decree 50/2016 and subsequent amendments) and the two-year company planning to be sent to the Lazio Region, as well as the related annual updates. In this phase, in addition to the planning of economic purchases of specific relevance, the UOC acknowledges the needs of the other Business Units (such as, for example, Pharmacy, Clinical Engineering, Heritage and Technical) for the planning of the purchases of drugs, DM, equipment and necessary services, to be coordinated with the allocated spending budgets and in compliance with the procedures provided for in the Company Regulations.

CONDUCT OF PROCEDURES IN PUBLIC EVIDENCE

This is the phase of acquisition of scheduled or urgent goods and services that goes from the planning of the acquisition referred to in art. 23, paragraph 14, of Legislative Decree 50/2016 and subsequent amendments, to the award.

EXECUTION OF CONTRACTS.

This is the phase that goes from the signing of the contract to the termination of the relationship with the contractor.

MARKET ANALYSIS

Carrying out market analysis, including through benchmarking techniques, aimed at the acquisition of goods, services and health technologies (in the latter case with the support of clinical engineers) at the best conditions in terms of quality and costs

OFFICE RACES(internal articulation of the UOC ABS)

The Office deals with the governance of the tender procedures from the design phase to the award phase by carrying out, by way of example and not limited to, the following activities:

- Collection of needs from the other Company UOs in order to prepare and transmit the two-year planning of the purchases of goods and services (both pursuant to Article 21 of Legislative Decree 50/2016, and regional);
- Verification of the compatibility of requests for urgent procedures with budget availability;
- Choice of purchase methods and verification of non-fungibility prerequisites;
- The preparation determines the contract pursuant to art. 32 of Legislative Decree 50/2016;
- Preparation of tender documents such as: tender regulations, ESPD forms, application and declaration forms, offer templates, contract templates and expressions of interest;
- Care of the publications required by the procurement code and by the legislation on transparency;
- Preparation of the acts of transposition of the regional conventions or of the Consip conventions;
- Verification of the requirements referred to in art. 80 and 83 of the legislative decree for the successful bidders by consulting the ANAC databases, the Revenue Agency, the criminal record, the bankruptcy court, the labor inspectorates, etc;
- Preparation of the award documents;
- - Verification of the quality and prices of purchases on the basis of the documentation sent by the suppliers and of the data collected by the Regional and National Price Observatory or on the initiative of the UOC itself;
- - Management of the supplier register

CONTRACTS OFFICE (internal articulation of the UOC ABS)

The Office deals with the governance of the executive phase of the contract from the preparation of the preparatory documents to the signing up to the conclusion of the contract by carrying out, by way of example and not limited to, the following activities:

- Drafting of the contract based on the type of credit line;
- Care of relations and communications with the successful bidder for the acquisition of the documents preparatory to the stipulation of the contract (security documents, insurance policies, final guarantee, etc.);
- Management of settlement activities including, in the event of a delayed settlement of fees, the settlement of default interest pursuant to Legislative Decree 231/02 accrued by suppliers;
- Determinations regarding the assignment of credits resulting from the managed contracts;
- Management of the subcontracting authorization procedure;
- Carrying out legal checks on suppliers in the execution phase;
- Rotation of company DEC on the basis of a specific company procedure;
- Updating of contractual formats for works and supplies of goods and services based on legislative and regulatory changes.

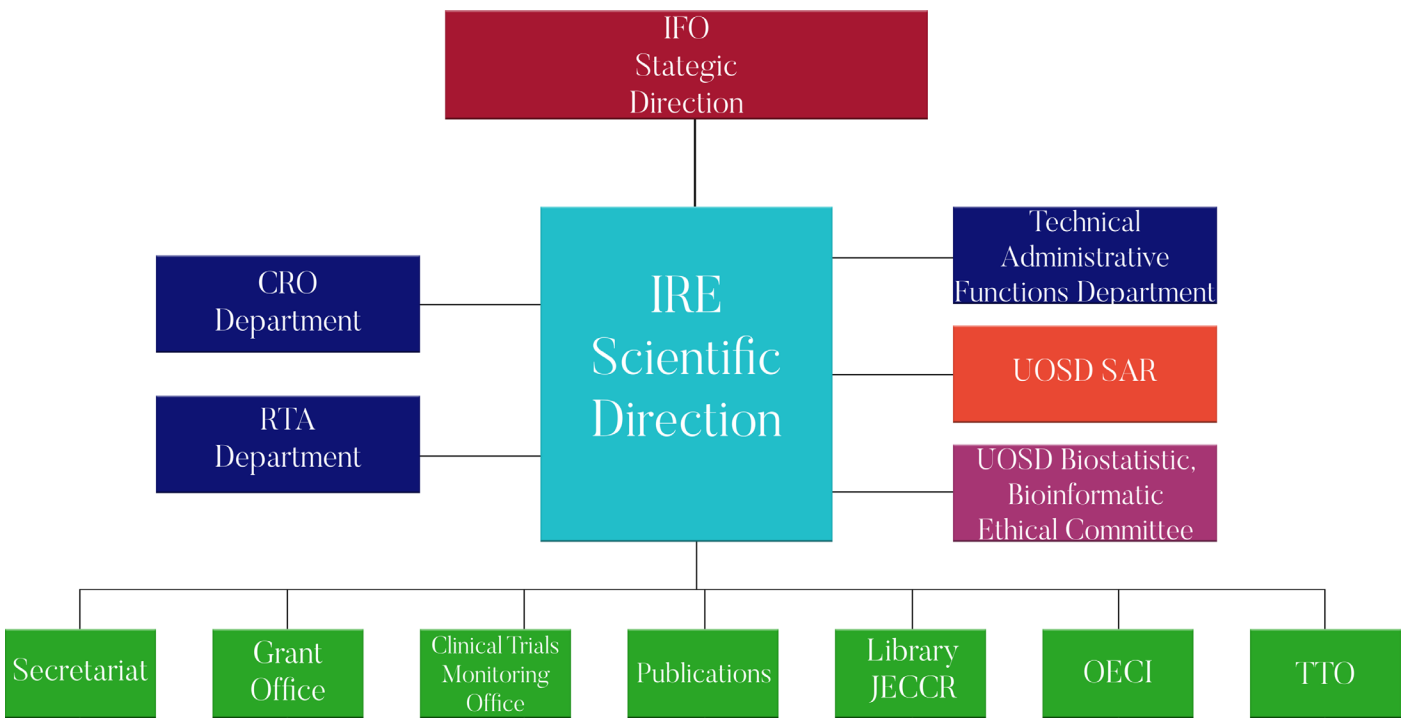
ABS OFFICE - SAR (internal articulation of the UOC ABS)

The Office deals with the governance of the procedures for the purchase of goods and services intended for Research from the phase of receipt of the purchase request by the Scientific Departments to the conclusion of the relationship with the contractors.

In particular, the office, given the peculiarities of the purchases to be made as a function of the research, carries out all the activities under the competence of the Tenders Office and the Contracts Office listed above, according to simplified procedures typical of the services in the field of Research, of non-fungible purchases. and credit lines below 40,000 Euros.

Furthermore, within the aforementioned Office, the assignments to companies specialized in the filing of national / international patent applications and the related protection of Intellectual Property are managed.

Scientific Directorate



Scientific Directorate

Staff

Prof. Gennaro Ciliberto, Scientific Director
Mrs. Carmela Matrascia, Scientific Direction Secretariat
Dr. Tania Merlino, Scientific Direction Secretariat
Mrs. Pina Gioffrè, Scientific Direction Secretariat
Dr. Federica Falcioni, Clinical Trials Office
Dr. Cecilia Fagioli, Clinical Trials Office and Publications Office
Dr. Martina Ferrazzano, Grant Office
Ing. Samantha Mengarelli, Grant Office
Mr. Marco Canfora, IT

There is an organizational structure specifically for research and development in oncology which culminates in the office of the Scientific Director.

The Scientific Director to accomplish his goals is supported by the Scientific Directorate Offices: Secretariat, Grant Office, Clinical Trials Monitoring Office, Publications Office.

Secretariat

The Secretariat office handle administrative documents for fund management: purchases, payments, missions, reimbursements, collaboration agreements between various entities, fellowships, self-employments and frequencies for various reasons. Collaborate with the organization of scientific events, seminars, national conferences and travels organization. Supports the Scientific Director organizing meeting. In the Scientific office is active a linguistic revision service and official documents translation. This office proceed to protocol official institutional documents and authorization request from research personnel with the Folium Protocol.

Grant Office

The activities of the IRE GO are: communication, promotion, support and centralization of projects submission procedures. The GO manages and coordinates all projects submission activities with the aim of promoting productivity and competitiveness of research. Every year on average the GO supports and coordinates more than 100 applications to competitive grants, Furthermore, the GO helps coordinating the generation of the yearly report of research productivity to the Ministry of Health.

Clinical Trials Monitoring Office

Provides support during the activation, management, reporting and data processing of clinical trials; manages IRE clinical database trials/SMART clinical trials platform; generates the yearly report of clinical research activity (number of active clinical trials, number of patients involved, etc.) to the Ministry of Health (Research Workflow).

Publications Office

The publications office collaborates with the Library, in the initial phase of manuscript submission, provides support to researches with a continuous monitoring, manages the manuscripts information by giving bureaucratic-administrative and economic information. The publications office invites researchers to deposit the raw-data linked to publications eligibility for the ministerial funding and guides the researchers to use a scientific integrity analysis service to avoid falsification and plagiarism.

Library

Head: Dr. Francesca Servoli

Staff

Mr. Domenico Verbicaro, Administrative staff

Dr. Virginia Scarinci, Librarian

Mr. Luca Spataro, Volunteer Universal Civil Service

Miss. Eleonora Boldrini, Volunteer Universal Civil Service

Miss. Ambra Masiello, Volunteer Universal Civil Service

Mr. Davide Sabelli, Volunteer Universal Civil Service

Miss. Federica Pepe, Volunteer Universal Civil Service

Mission

Aim of the Library is to guarantee easy access to updated scientific documentation, most on electronic support. Apart from acting as a library, it should also be considered a knowledge Centre which facilitates access to relevant documentation in order to favour the best clinical practices and the choices of patients. The Knowledge Centre aims to contribute health information literacy also promoting the exchange of information between different professional areas.

Location

The Library is located near the main entrance of the Institute and offers a multimedia room with 15 computers. The Patient Library is located, since 2005, in a dedicated room providing quality information through professional staff and civil service volunteers using booklets for patients, scientific databases and trusted health portals.

Services

The Library offers its services to the medical staff, supports research activities by offering scientific information, documentation and education and supports the institutional clinical staff offering:

- consultation of the main biomedical databases;
- document delivery through interlibrary exchange system, NILDE (in 2021 total borrowing 137, total lending 25);
- document delivery through other systems (total 230); (from July 2021, print journals, due to repository renovations, are not accessible);
- organization of training courses.

The librarian staff also offers support to the bibliographic searches, systematic reviews and meta-analyses. Other activities of the library consist of: managing monographs and periodicals following international standards; updating of national union catalogues; reference desk also through the personalized service “Book a librarian”, tailored courses on demand by the users (in 2021 20 meetings online and 33 meetings in presence). In 2021, thanks also to the Bibliosan Network, the Library subscribed electronic resources: thousands of online journals, databases as Embase, Scopus, Web of Science, Journal Citation Reports, BMJ BestPractice, Cochrane Library, Cinahl, etc. Others activities of Library are:

- Inventory and accommodation of the library’s paper heritage
- Organize training courses. In 2021 the multimedia room of the Library was booked 22 times for training courses.

The Patient Library offers information, using-booklets, databases and access to quality websites. Patients and their relatives can also use the multimedia room with Internet connection. The Patient Library is also a reception point of Aimac - Associazione Italiana Malati di Cancro, where Volunteers of Universal Civil Service conduct their activities.

There is also a Library for recreational reading. Since 2005 about 2325 patients and their relatives visited the Library. In 2021, due to the pandemic situation, Patient Library was closed to the public from January to April. From April to July,

access was restricted. The library was reopened to patients and their relatives in September 2021.

Research Activities

The Library is involved in various research and educational activity and participates in library networks.

As far as information literacy is concerned, the library organized two CME courses on scientific documentation (PubMed and Publishing in science); the total participants were 18. The Library staff is involved in the teaching and tutorship of the courses. The Library promoted knowledge of Bibliosan's resources through webinars.

The Library is involved in OECI Improvement Plan on patient involvement and empowerment, concerning humanization of the care, communication and information.

The Library is involved in IFO Institutional Working Group for Patient's Centrality. In 2018 Ethics Committee approved INFO RP - An observational study of information prescription in Italy. Patients will be directed to the consultation of information at the Patient Library, with prescription pads signed by the medical staff of the Endocrinology Unit. This study is still ongoing in 2021.

The Library staff participates in the working group for the reporting of the Institute's scientific activity, required annually by the Italian Ministry of Health, and manages the institutional archive of publications.

All Library activities have been automated using electronic shared systems. In particular, the Library participates in the following networks:

1. National Library Service (SBN) - the Library's books are catalogued following the MeSH (Medical Subject Headings) and the National Library of Medicine (NLM) Classification;
2. Network Inter-Library Document Exchange (NILDE) - document delivery service for exchanging scientific articles.
3. National Union Catalog of Periodicals (ACNP) for the cataloguing and management on the web of the periodicals;
4. Library Network of Biomedical Research Institutes (Bibliosan).

On December 1st, Dr. Francesca Servoli was appointed as a member of the Bibliosan Technical Management Committee (CTG) by the Ministry of Health representing public IRCCS

Journal of Experimental & Clinical Cancer Research

Editor in chief: Dr. Mauro Castelli, PhD

Staff

Dr. Giovanni Blandino, MD, PhD, Deputy Editor

Dr. Silvia Di Agostino, PhD, Assistant Editor

Dr. Sara Donzelli, PhD, Assistant Editor

Dr. Alice Castelli, PhD, Managing Editor

Journal of Experimental & Clinical Cancer Research (JECCR) is the official scientific journal of the “Regina Elena” National Cancer Institute since 1986 which publishes manuscripts regarding significant advances in basic cancer research and offers a translational bridge from the laboratory to the clinic.

The most important aims are to open new roads for the understanding, prevention, diagnosis and treatment of cancer and to share the scientific results with the international scientific community.

JECCR has led its editorial activity by maintaining its partnership with the publisher BioMed Central - Springer Nature in London.

Thanks to its “open access” version, JECCR improved its performance in terms of rapid publication of the articles, better widespread all scientific results and higher visibility in the scientific community confirming its position in the 1st quartile among International Oncology Journals

In 2021 JECCR has launched a new Special Issue regarding the latest highlights on drugging cancer vulnerabilities toward innovative clinical trial.

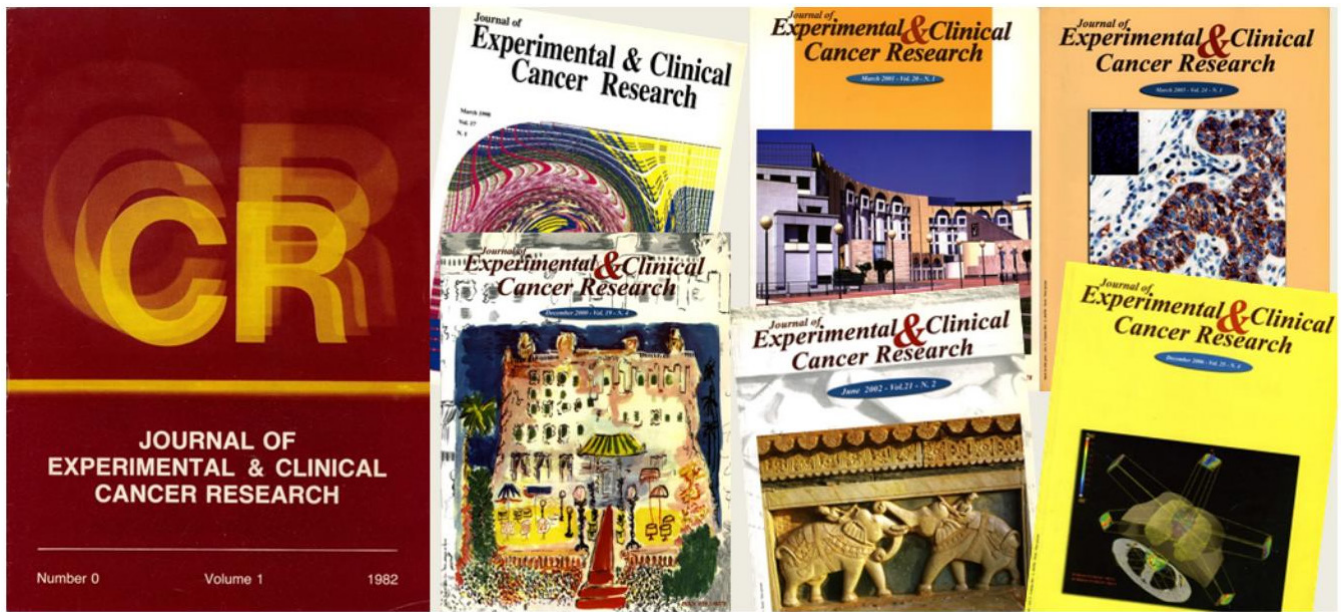
The main accomplishments achieved by JECCR in 2021 are:

- Impact Factor 11.161;
- 2,059,766 downloads;
- 2758 submissions;
- 342 published papers;

Most of submitted and published articles in the last years comes from International Oncology Institutes and Universities worldwide.

The “Journal of Experimental & Clinical Cancer Research” has reinforced its visibility in the international scientific community sharing the latest articles and collections by Social Media. JECCR online website: <https://jeccr.biomedcentral.com/>

Follow JECCR on Social Media:   



TOP 5 JECCR PUBLICATIONS MOST CITED IN 2021

1. Targeting hypoxia in the tumor microenvironment: a potential strategy to improve cancer immunotherapy

By: Bin Wang, Qin Zhao, Yuyu Zhang, Zijing Liu, Zhuangzhuang Zheng, Shiyu Liu, Lingbin Meng, Ying Xin and Xin Jiang

Volume: 40 Issue: 2 Article Number: 24 Published: JAN 9 2021 Times Cited: 27

2. Regulatory mechanisms of immune checkpoints PD-L1 and CTLA-4 in cancer

By: Hao Zhang, Ziyu Dai, Wantao Wu, Zeyu Wang, Nan Zhang, Liyang Zhang, Wen-jing Zeng, Zhixiong Liu and Quan Cheng

Volume: 40 Issue: 1 Article Number: 184 Published: JUN 4 2021 Times Cited: 22

3. LINC00460/DHX9/IGF2BP2 complex promotes colorectal cancer proliferation and metastasis by mediating HMGA1 mRNA stability depending on m6A modification

By: Lou, Guohua; Chen, Liang; Xia, Caixia; et al.

Volume: 40 Issue: 1 Article Number: 52 Published: FEB 1 2021 Times Cited: 20

4. Noncoding RNAs regulate alternative splicing in Cancer

By: Yunze Liu, Xin Liu, Changwei Lin, Xianhong Jia, Hongmei Zhu, Jun Song and Yi Zhang

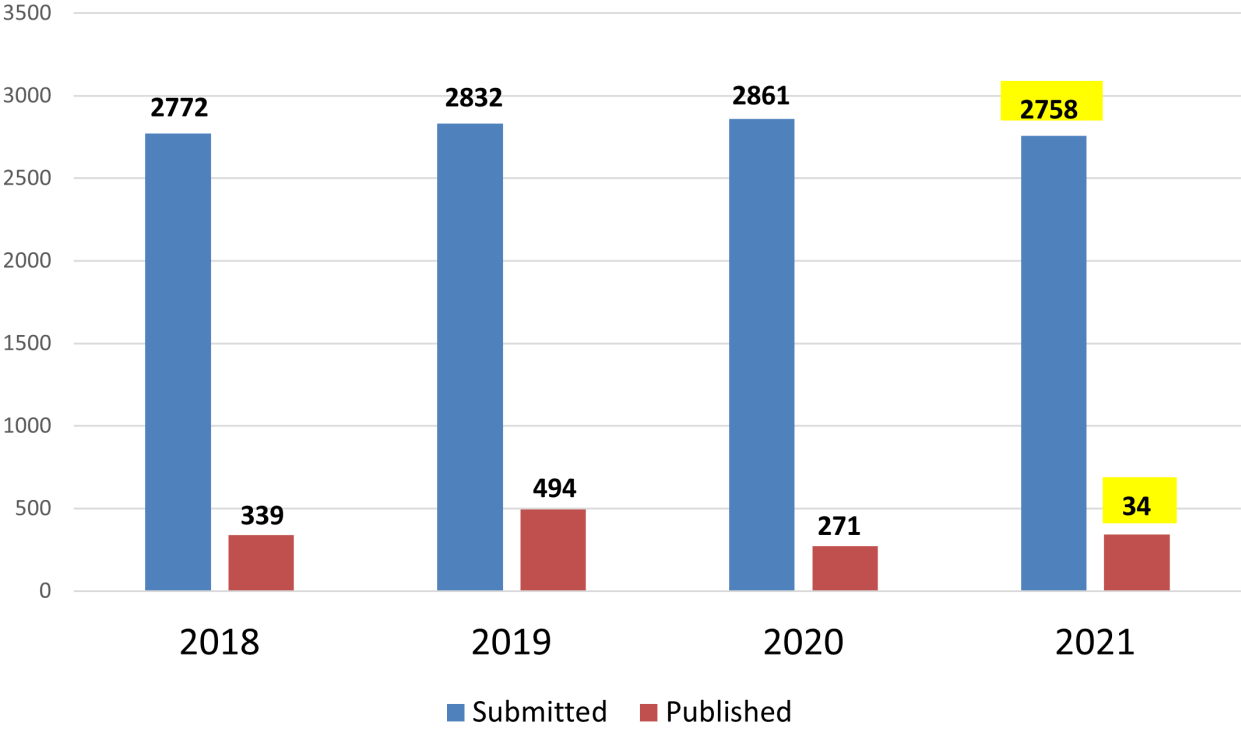
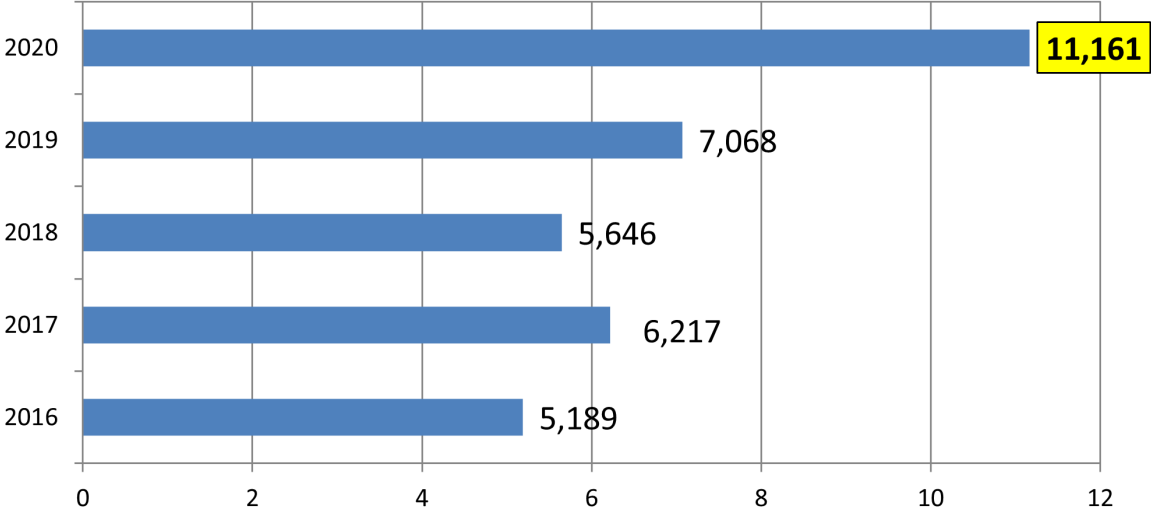
Volume: 40 Issue: 1 Article Number: 11 Published: JAN 6 2021 Times Cited: 16

5. Pyroptosis: a new paradigm of cell death for fighting against cancer

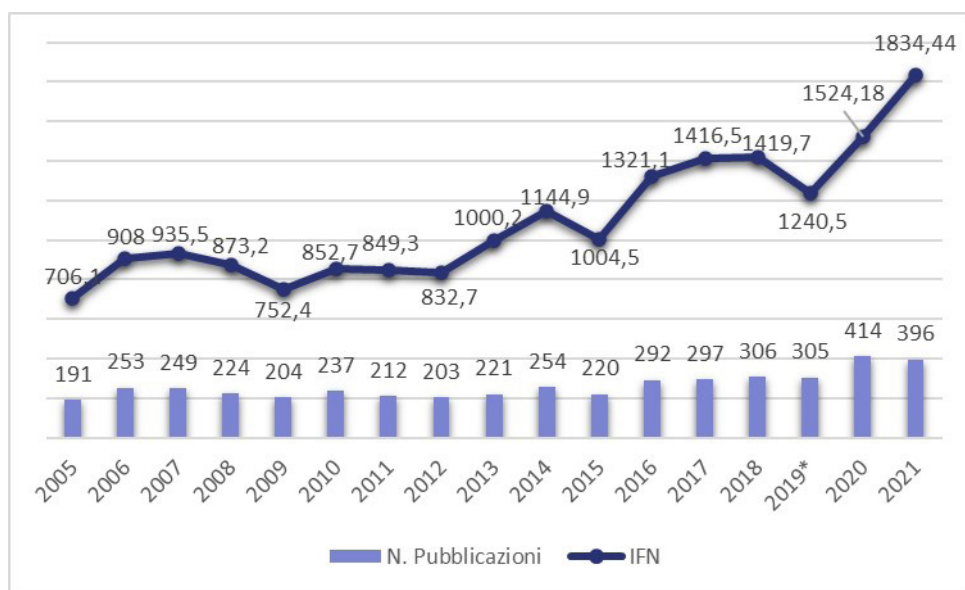
By: Yixin Tan, Quanzhu Chen, Xiaoling Li, Zhaoyang Zeng, Wei Xiong, Guiyuan Li, Xiayu Li, Jianbo Yang, Bo Xiang and Mei Yi

Volume: 40 Issue: 1 Article Number: 153 Published: MAY 3 2021 Times Cited: 1

Impact Factor



IRE Scientific Productivity Years 2005 - 2021



Graphic representation of Normalized Impact Factor (IFN) and numbers of publications from 2005 to 2021.

**From 2019 the criteria to indicate the productivity of the institute was changed, in fact the normalization refers to the values of the new quartiles that measures the prestige of a journal that, in particular for the Oncology category, have undergone an average increase of 25%. This means that journals in the Oncology category receive less IFN in the years following 2018.*

Distribution of the Main Funding Sources Supporting IRE Research

Clinical Trials

Technology Transfer Office

Staff

Dr. Gianluca Moretti

Dr. Emanuela Miceli

Dr. Giuseppe Campanella

Mission

The Technology Transfer Office (TTO) operates within the Scientific Directorates and collaborates with the IFO Patent Commission established with resolution no. 725 of 01.08.2016.

The most delicate moment of the technology transfer process is undoubtedly represented by the management and protection of Intellectual Property activities which can be summarized as follows:

1. Enhancement of research results

- Internal scouting activities aimed at the emergence of the scientific results achieved and at the mapping of the skills and technologies present;
- Support to researchers in verifying the existence of the requirements for patent protection of research results;
- Management of the procedures for the assignment of services for filing and maintaining national, European and/or international patent applications to the authorized companies accredited to UIBM, EPO, USPTO, etc...;
- Management, monitoring and evaluation of the patent portfolio;
- Matchmaking and networking activities between companies, investors and researchers;
- Support in the activities instrumental to the economic exploitation of inventions (licenses, transfers, collaborations, etc ...);
- Technical support in the stipulation of the following agreements: NDA (Non Disclosure Agreement); MTA (Material Transfer Agreement); MTDA (Material and Associated Data Transfer Agreement); DTA (Data Sharing Agreement); IIA (Inter Institutional Agreement).

2. Support for the transfer of research results

- Promotion of an Intellectual Property culture with awareness-raising initiatives that also provide informations on patent law;
- Promotion and organization of training activities aimed at spreading an entrepreneurial spirit;
- External scouting activities aimed at the actors of the innovation ecosystem and the business system to favor a successful matching between research supply and demand and identify possible synergies and spaces for collaboration;
- Study and deepening of tenders and procedures for accessing new sources of funding.

3. Support for the creation of spin-off companies

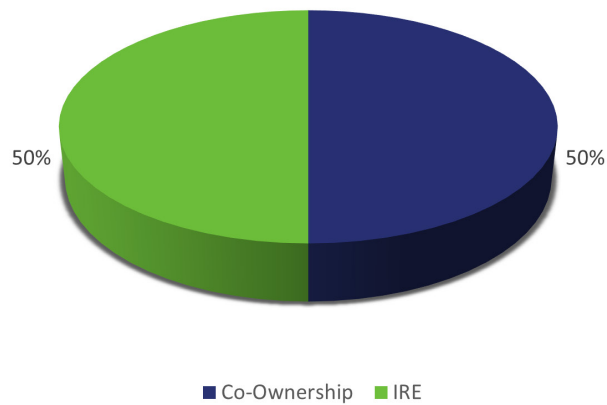
- Verification of the existence of the formal requirements indicated by the Regulation (Resolution 1133 of 28.10.2020) for the purposes of evaluating the establishment and participation of IFO in Spin-Off companies;
- Illustration of the methods of individual participation in the share capital by the proponents;
- Evaluation of any conflicts of interest between proponents and public research body.

The Patent Portfolio of the Regina Elena Institute in 2020 was composed of 14 families of international patents that were divided into two main categories: a) entirely owned by the Institute and b) co-owned with other institutes. Some of these patents have already been issued in several countries and others are still under consideration. The patent portfolio mainly protects the discovery of new prognostic and / or predictive biomarkers and detection methods within liquid and solid biopsy samples, but also nanotechnologies for targeted drug delivery.

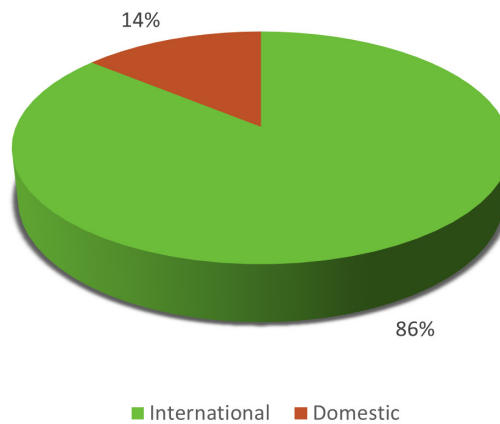
Patents

The Patent Portfolio of the Istituto Regina Elena in 2021 was composed of XX international patent families that have been divided into two main categories: a) fully owned by the Institute and b) with co-ownership with other institutes. Some of these patents have already been allowed to be issued in several countries and others are still under examination. The patent portfolio mainly protects the discovery of new prognostic and/or predictive biomarkers, but also nanotechnologies for better drug delivery.

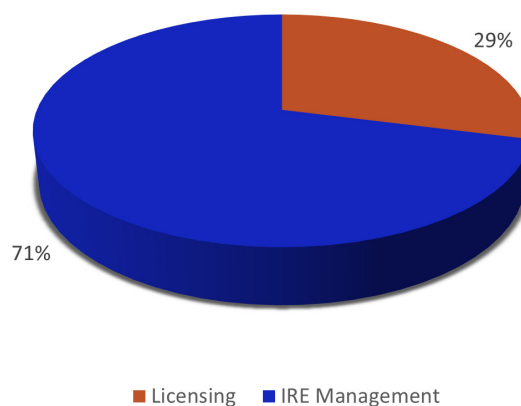
Ownership 2021



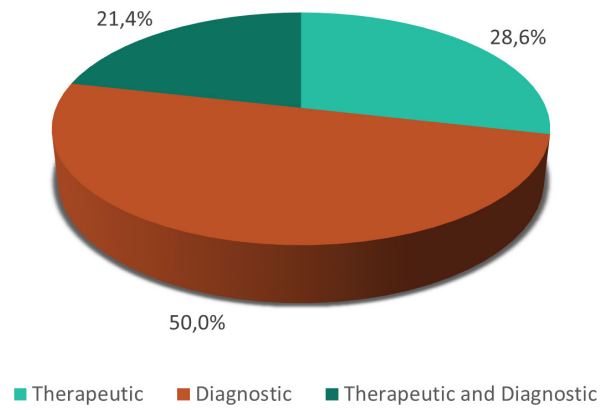
Country 2021



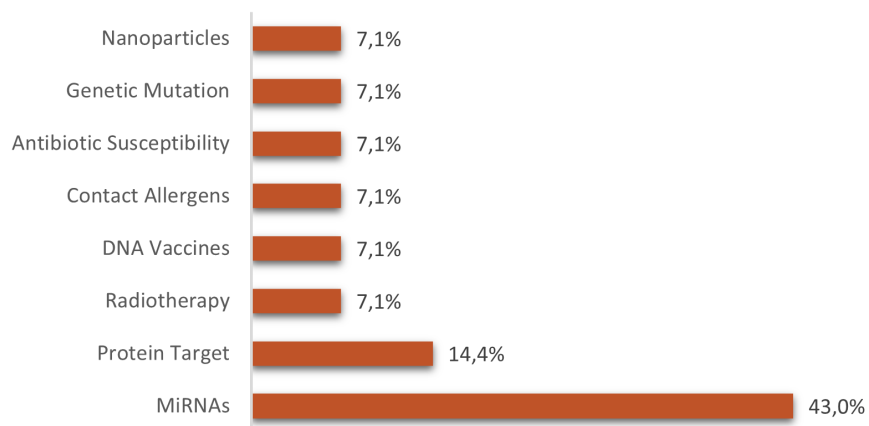
Licensing



Type of Patents



Patent Portfolio



Organisation European Cancer Institute OECI

Staff

Dr. Giuseppina Caolo,
Dr. Annunziata Di Turi

Mission

During the whole process the staff takes care of collecting documentation, writing reports and organising the site visit. It also receives and collects official documentation from the headquarters in Brussels.

Staff keep in touch with the OECI European coordinators of Bruxelles and with the other Italian IRCCS participating in the accreditation process.

In addition, the staff participated in the creation of the hospital cancer registry, requested by OECI, which it now manages, registering all new IRE patients from the three main sites (breast, lung and colon) in line with the population cancer registry of the Lazio Region.

Research Strategic Plan

The main research goal of the IRCCS Regina Elena National Cancer Institute is the translational management of cancer patients (PRESto in carico Traslazionale del paziente Oncologico - PRESTO). What does this mean? It means that the cancer patient is always placed at the center of our research objectives and with this focus, we aim to understand the distinct alterations of patients' tumors within the perspective of personalized and precision medicine; and then to transfer our research results to the patients' bedside in order to provide rapid answers to their health needs through scientific and technological innovation.

Today, providing care to cancer patients is essentially based on having several vital contributing facilities. IRE has therefore armed itself with a series of indispensable tools, from a modern and equipped biobank storing tissue and liquid samples deriving from cancer patients up to a number of the most recent technologies for "omics" analysis as well as for surgery such as robotic surgery, stereotactic radiotherapy, imaging and so on. Our Institute is the only facility in Lazio where these facilities combined with the necessary expertise (know how) are all physically concentrated in the same logistic area and dedicated to cancer patients' care. This allows us to apply all the standards of the state-of-the-art modern medicine to implement a more personalized approach towards the patient, not only considering their clinical characteristics, but also the expression of molecular determinants which are increasingly fundamental in improving diagnostic, prognostic, predictive and therapeutic performance.

It is now crucial to manage cancer patients by evaluating the expression of molecular biomarkers with cutting-edge "omics" technologies that allow to stratify patients that are able to respond or not to certain types of therapies. Even if it appears to be more challenging at first, obtaining knowledge, understanding and clinical management of these parameters provides us with an unquestionable advantage and together with the results generated can drastically improve the clinical picture (survival and quality of life) of the patient. By applying this modern approach towards cancer patient care it is also essential to increase the number of early diagnoses, which are now often possible due to the very high resolution in diagnostic imaging equipment provides, thus avoiding falling into making frequent errors in over-diagnosis and over-treatment.

The future of cancer care and patient medical records will therefore have to contain, in addition to the results of routine investigation, also a series of metadata (genomics, transcriptomics, metabolomics, proteomics, microbiomics, radiomics, etc.) that concern the molecular aspects of single neoplasms which provide the basis for an advanced prognostic / predictive / therapeutic approach. The objective is to obtain a personalized clinical report capable of highlighting the biological and clinical relevance of each identified molecular alteration. In fact, these methodologies allow identifying therapies and clinical studies that include potentially effective drugs (targeted therapy, immunotherapies and experimental therapies) that are best for each individual patient.

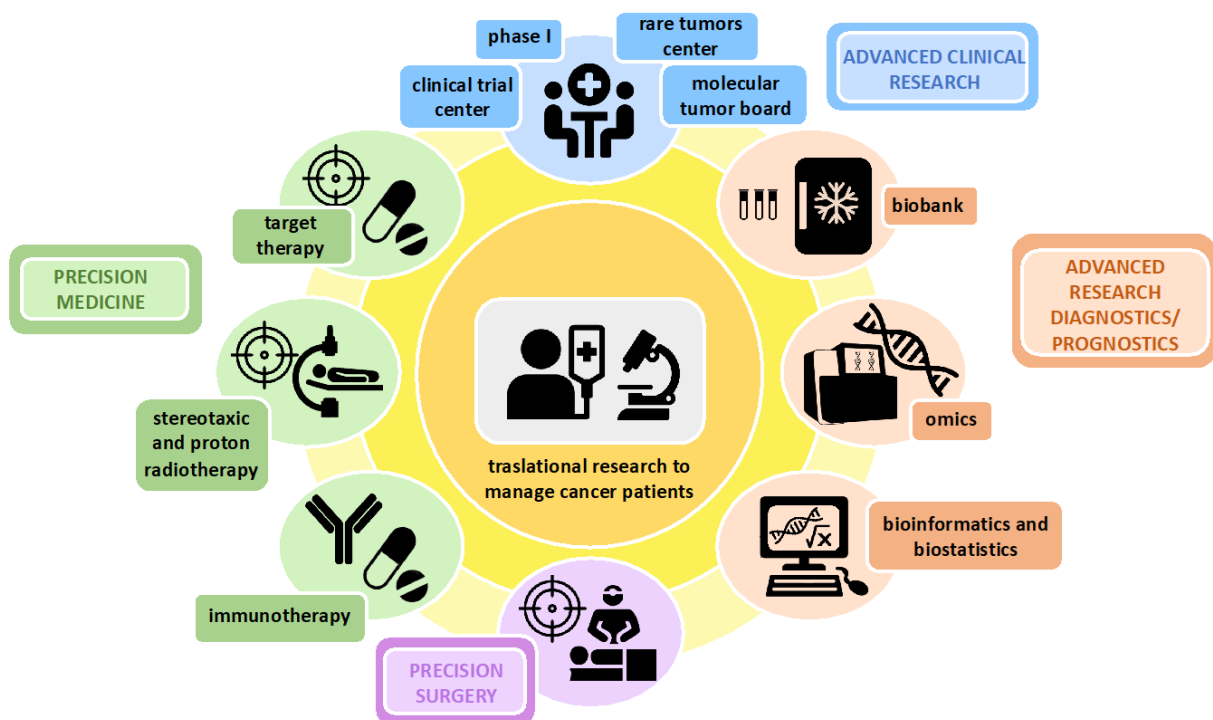
It is therefore important that the data provided by the most modern technologies are managed by a multidisciplinary team that includes not only oncologists, but also biotechnologists, molecular biologists, geneticists, pathologists, biostatistics, bioinformatics, etc.

PRESTO is summarized in the diagram above (Fig1). It is divided into four macro-areas which are highlighted by distinct colors: advanced diagnostic / prognostic research (in Orange), precision surgery (in Purple), precision medicine (in Green) and advanced clinical research (in Blue).

In the following sections the features of each macro-area will be described as well as short and long-term objectives. All together these sections constitute the elements of the research strategy, represent the research footprint of the institute and characterize its specificity in the context our national clinical cancer research.

It has to be pointed out that Regina Elena National Cancer Institute works in close collaboration within national and international networks, in first instance is one of the founders of the largest organization of clinical research cancer centers in Italy called Alliance Against Cancer (Alleanza Contro il Cancro - ACC). Furthermore, it is member of OECI, the Organization of European Cancer Institute where it has been given the highest level of accreditation as comprehensive cancer center, and finally has established strategic collaborations with prestigious research centers outside Italy such as

the Weizmann Institute in Israel. All these network collaborations help the realization of the strategic plan but we have decided not to specifically mention them in the following sections



Ministry of Health - Research Lines

In accordance with the priorities indicated by the “Programma Nazionale della Ricerca Sanitaria” every three years the Ministry of Health (MOH) approves the research activities of the IRCCS. This had to be the conclusion year for our active research lines, but, due to sanitary emergency, the MOH extended for another year the active research lines.

In the years 2018 - 2021 our Institute has five research lines, and the MOH introduced a sixth “COVID specific” line.

Line 1: Cancer Prevention and Early Detection

Coordinators of the scientific report: R. Falcioni - V. Stigliano

The mission of this Line is the identification and elucidation of the mechanisms that contribute to the risk of developing cancer, the characterization and validation of new biomarkers of susceptibility to cancer, and the development of methodologies capable of increasingly anticipating the diagnosis of cancer in subjects and/or populations at risk. Primary prevention intervenes on healthy subjects and is based on the identification of risk factors, the assessment of exposure to these factors and their modification. Secondary prevention intervenes on sick people, identifies the disease at an early stage, asymptomatic, susceptible to immediate and effective therapeutic intervention. The advent of advanced technologies, genetic characterization and molecular classification, make the prognostic stratification of tumors and early detection of cancer increasingly possible. The perspective of this Line is therefore to carry out research activities aimed at educating new diagnostic and/or behavioural procedures aimed at cancer prevention, improvement of health status and cancer control. At present, the existence of innovative molecular and instrumental diagnostic techniques makes it possible to make an early diagnosis of the tumor and to define the molecular characteristics that influence the therapeutic approach and prognosis. Fundamental elements for the success of the Line are:

1. Access to biological materials from subjects predisposed to the onset of tumors due to hereditary family causes, or environmental factors;
2. Multidisciplinary experimental approaches that take into account bio-molecular, epidemiological, nutritional, virological, radiodiagnostic, endoscopic, clinical and surgical expertise.

Line 2: Cancer Immunotherapy

Coordinators of the scientific report: A. Venuti - V. Ferraresi

The “Cancer Immunotherapy” line includes the activity of translational pre-clinical and clinical research, aimed at: improving the knowledge of anticancer immunological mechanisms; immunoevasion processes including those mediated by the microenvironment; optimizing the generation of vaccines, engineered T cells and the use of new molecules and immunomodulating strategies. Research is also based on the characterization of tumor-specific antigens and the analysis of the molecular/immune profile (immunoprofiling) of the individual patient. Finally, this Line is designed to identify new combination approaches to optimize therapy and better manage associated toxicity. It is increasingly evident that all anti-neoplastic therapies require activation of the host immune system to be effective, as historically demonstrated for CT and RT. Cancer immunotherapy represents the fourth approach to cancer treatment, together with surgery, RT and CT/biological therapy. It is a therapy that instructs and/or reactivates the cells of the immune system so that they can recognize and eliminate cancer cells. Tumors alter the immunocompetence of the host, triggering phenomena of immune resistance, in particular the functions of tumor-specific T-cells. Since many immunological checkpoints are triggered by receptor and ligand interactions, effective immunotherapies based on blocking these interactions by antibodies have developed.

The identification of predictive biomarkers of response to immunotherapy is a further fundamental information to direct the clinician towards a personalized treatment. The characterization of tumor antigens has made it possible to conceive therapeutic vaccines but the need to design more effective vaccination therapies remains. At the same time, the

molecular study of TCR allowed to engineer T cells with anti-tumor activity to be reinfused in the patient, although of problematic clinical applicability. Therapies with checkpoint inhibitors are effective but the identification of predictive response biomarkers is critical to select the patients most likely to benefit by limiting side effects. Fundamental elements for the success of the line are the biobanks and the use of samples from subjects at risk of cancer due to genetic, dietary, behavioural, environmental and occupational causes, and the multidisciplinary approach that includes biomolecular, immunological, virological, epidemiological, nutritional, radiodiagnostic, clinical and surgical expertise.

Line 3: Personalized and Precision medicine in Oncology

Coordinators of the scientific report: P. Giacomini - F. Marchesi

The knowledge of the molecular mechanisms involved in tumor pathogenesis and progression has allowed the development of innovative therapies based on the use of agents able to specifically interfere with the cell pathways responsible for the growth, survival and progression of cancer cells. This approach has been defined as personalised medicine as well as precision medicine, if a precise interaction/correlation between the administered drug and the presence of its molecular target in the tumour can be identified. The line “Personalized Medicine and Precision in Oncology” deals with research activities that aim, in the pre-clinical and clinical field, to:

1. Identify the prognostic and/or predictive relevance of genetic and epigenetic alterations of the tumour that can be exploited as potential therapeutic targets;
2. Study the role of intra-tumour heterogeneity in the response to molecular target agents;
3. Develop methods of analysis to follow the molecularevolution of tumours both in tissues and in the blood (e.g. The rationale of this line of research lies in the fact that identifying the possible mechanisms of primary and acquired resistance;
4. Systematically biobank cancer samples and longitudinal biological fluids using standardized and reproducible methods;
5. Develop clinical trials with molecular target drugs in patient populations identified by suitable biomarkers.
6. The rationale of this line of research lies in the fact that identifying the biological alterations of individual neoplasms makes it possible to use targeted and effective therapies. Therefore, studies will be conducted to:
7. Implement personalised therapy protocols in patients with progressive/metastatic disease;
8. Identify markers of intrinsic and acquired resistance to molecular target drugs;
9. Identify new diagnostic strategies for early diagnosis and prevention, and for anticipating/redirecting relapse/progression;
10. Identify new therapeutic strategies to block the processes of tumour invasion, progression and metastasis;
11. Facilitate the transversal repositioning and use (drug repositioning/repurposing) of known drugs;
12. Identify new molecular target drugs;
13. Rapidly apply and transfer the above to clinical practice in oncology, acquiring innovative know-how and technologies where necessary.

Line 4: Innovative Approaches and Technologies in Diagnostics and Therapies

Coordinators of the scientific report: G. Simone - A. Vidiri

This Line bases its assumptions on the use of innovative diagnostic approaches and technologies, functional imaging and/or molecular methodologies, and the effectiveness of minimally invasive and multimodal/integrated treatments that now represent the standard therapeutic approach for many types of cancer. Technological advances in biomolecular research, imaging, minimally invasive surgery, radiotherapy and new oncological target therapies require increasing efforts towards a more accurate diagnosis and more personalized therapy. The integration of synergistic and complementary skills (molecular biology and pathological anatomy, endoscopy, surgery, radiotherapy, radiology, nuclear medicine and medical physics) is the pivot for the improvement of diagnosis and treatment both for the most common tumors (e.g. colorectal, lung, breast and prostate) and for rarer tumors (e.g. melanoma, head-neck, thyroid, pancreas, soft tissue sarcomas, hepatocarcinomas). IRE translational research teams will allow the integration of clinical information with the parameters extracted from biomedical images and functional analysis at cellular and molecular

level, allowing a more appropriate customization of treatment. The study of new preclinical models (primary tumor cultures, 3D cell growth models, xenopatients, innovative animal models of tumor disease, development of models for drug repurposing), preclinical and clinical validation of innovative diagnostic tools (genomic tests), proteomics, metabolomics in tissues and/or biological fluids, development of new models for target identification through genetic manipulation with CRISPS/Cas9 technology), development of new combined therapeutic approaches (surgery, radiation, nanoparticles, ultrasound, heat, etc.) taking into account clinically available advanced technologies (robotic and minimally invasive surgery, focal therapies, radiotherapy, radiosurgery and SBRT, medical-nuclear therapy, radiomics) will allow to identify new prognostic/predictive biomarkers and to test innovative therapeutic approaches for personalised therapy, a goal for translational research.

Line 5: Quality of Life of the Neoplastic Patient

Coordinators of the scientific report: G. Simone - A. Vidiri

This Line bases its assumptions on the use of innovative diagnostic approaches and technologies, functional imaging and/or molecular methodologies, and the effectiveness of minimally invasive and multimodal/integrated treatments that now represent the standard therapeutic approach for many types of cancer. Technological advances in biomolecular research, imaging, minimally invasive surgery, radiotherapy and new oncological target therapies require increasing efforts towards a more accurate diagnosis and more personalized therapy. The integration of synergistic and complementary skills (molecular biology and pathological anatomy, endoscopy, surgery, radiotherapy, radiology, nuclear medicine and medical physics) is the pivot for the improvement of diagnosis and treatment both for the most common tumors (e.g. colorectal, lung, breast and prostate) and for rarer tumors (e.g. melanoma, head-neck, thyroid, pancreas, soft tissue sarcomas, hepatocarcinomas). IRE translational research teams will allow the integration of clinical information with the parameters extracted from biomedical images and functional analysis at cellular and molecular level, allowing a more appropriate customization of treatment. The study of new preclinical models (primary tumor cultures, 3D cell growth models, xenopatients, innovative animal models of tumor disease, development of models for drug repurposing), preclinical and clinical validation of innovative diagnostic tools (genomic tests), proteomics, metabolomics in tissues and/or biological fluids, development of new models for target identification through genetic manipulation with CRISPS/Cas9 technology), development of new combined therapeutic approaches (surgery, radiation, nanoparticles, ultrasound, heat, etc.) taking into account clinically available advanced technologies (robotic and minimally invasive surgery, focal therapies, radiotherapy, radiosurgery and SBRT, medical-nuclear therapy, radiomics) will allow to identify new prognostic/predictive biomarkers and to test innovative therapeutic approaches for personalised therapy, a goal for translational research.

Overseeing Committee

Control and Verification Board

Head: Prof. Paolo Marchetti

Staff

Prof. Antonio Addis

Prof. Stefano Alemà

Prof. Alfonso Celotto

Prof. Pier Giorgio Natali

Mission

Article 4 of the Regional Law N. 2/2006 legislates that leadership and guidelines functions are a responsibility of the Control and Verification Board (Consiglio di Indirizzo e Verifica - C.I.V.). The board consists of five members selected according to their expertise. The Board's chief officer is appointed by the Regional President and the Ministry of Health jointly. Three members are elected by the Regional President and one more is chosen by the Ministry of Health. They remain in office for five years.

I.F.O.'s present Control and Verification Board has been appointed by the Ministry of Health and Lazio Regional President through protocol 1546 of 19 February 2019 and Regional Decree N. T00146 of 12 June 2019. With resolution N. 604 of 2 July 2019 I.F.O. accepted and transposed the appointment of the Board.

The Control and Verification Board determines the direction and objectives of the Institute's activities on an annual and multi-annual basis and verifies all activities carried out and the results achieved by each Department.

Ethical Committee

Chairman

Prof. Francesco D'Agostino, Expert in Bioethics

Vice-Chairman

Prof. Agata Amato Mangiameli, Expert in Legal Matters

Secretary

Mrs. Anna D'Ambrosio

Technical Scientific Secretariat

Dr. Diana Giannarelli

Dr. Maria Cecilia Ciacchella

Mrs. Barbara Matrascia

Dr. Federica Struglia

Members

Clinicians: Prof. Stefano Calvieri, Prof. Vito Fenicia, Dr. Teresa Gamucci, Dr. Carlo Garufi, Prof. Carlo Capalbo

General Medicine: Dr. Mario Falconi

Pediatrician: Dr. Raffaele Cozza

Biostatistics: Prof. Annarita Vestri (until may 2021), Dr. Patrizio Pezzotti (since june 2021)

Pharmacologist: Prof. Lucia Negri

Pharmacists: Dr. Antonia Marina la Malfa, Dr. Silvia Murachelli, Dr. Nicoletta Onori

Genetist: Prof. Giovanni Neri

Volunteer Representative: Dr. Elisabetta Iannelli, Lawyer

Health Areas Representative: Dr. Laura Iacorossi (until february 2021), Dr. Fabrizio Petrone (since march 2021)

IRE Scientific Director: Prof. Gennaro Ciliberto

ISG Scientific Director: Prof. Aldo Morrone

IFO Chief Medical Officer: Dr. Branka Vujovic

Bietti Foud. Scientific Director: Dr. Monica Varano

Bietti Foud. Chief Medical Officer: Dr. Angela Mastromatteo

Clinical Engineer: Ing. Giuseppe Navaneri

Nutrition Expert: Prof. Giorgio Calabrese

58 The Central Ethical Committee IRCCS Lazio expresses its opinion on trials to be managed in Regina Elena National Cancer Institute, San Gallicano Dermatological Institute and G.B. Bietti Foundation for ophthalmology.

During years 2021 the Central Ethical Committee IRCCS Lazio examined and expressed its opinion on 206 studies including clinical trial protocols, observational studies and research projects, 266 substantial amendments.

Relatively to these items the ethics committee analysed ethical and scientific aspects, the adequacy of the investigators and the structures involved and, above all, the methods and documents to be used to inform patients and obtain their informed consent.

The Ethical Committee meetings are held monthly and, if necessary and urgent, the opinion of their members on a particular case such as the use of drugs not commercially available is obtained by mail

Technical Scientific Committee (CTS) until 01/11/21

The CTS is an advisory and a supporting body for the clinical and research activities of the Institute and is chaired by the Scientific Director of IRE. According to Regional Law 2/2006 art. 9, is composed of ten other members appointed by the Board of Directors. The CTS is informed in advance of the scientific objectives by the Scientific Director.

Staff

Prof. Gennaro Ciliberto

Scientific Director and CTS President

Dr. Roberto Biagini

Head of Orthopaedics Unit

Prof. GianLuca Grazi

Head of Hepato Biliary Pancreatic Surgery Unit

Prof. Gerry Melino

“Tor Vergata” University of Rome

Dott.ssa Paola Nisticò

Head of Immunology and Immunotherapy Unit

Dr. Sandro Pignata

“Fondazione Pascale” National Cancer Institute

Prof. Giuseppe Sanguineti

Head of Radiotherapy Unit

Dr. Branka Vujovic

Medical Director

Dr. Patrizia Vici

Head of Phase 4 Unit

Dr. Antonello Vidiri

Head of Radiology Unit

Dr. Maurizio Fanciulli

Head of SAFU Unit

Dr. Paolo Di Ridolfi

Nurse Coordinator

Biostatistic and Bioinformatic Unit

Head: Dr. Patrizio Giacomini, MD

Staff

Anna D'Ambrosio, Ethical Committee Secretary
Cecilia Ciacchella, Administrative Unit
Barbara Matrascia, Administrative Unit
Federica Struglia, Administrative Unit
Marco Canfora, Clinical Informatics
Andrea Sacconi, Bioinformatic
Matteo Pallocca, Bioinformatic
Eleonora Sperandio, Bioinformatic
Francesca Sperati, Biostatistician
Isabella Sperduti, Biostatistician
Irene Terrenato, Biostatistician
Silvia Cartolano, Research Nurse
Giulia Costantini, Research Nurse
Ilaria Farina, Research Nurse
Stefano Pacilli, Research Nurse
Valerio Basile, Biologist

Silvia Bastucci, Study Coordinator
Elisabetta Bozzoli, Study Coordinator
Arabella Bufalo, Study Coordinator
Viviana Cangiano, Study Coordinator
Barbara Conforti, Study Coordinator
Marianna Ferrara, Study Coordinator
Paola Franzoso, Study Coordinator
Marianna Introna, Study Coordinator
Vittoria Iorio, Study Coordinator
Katia Messana, Study Coordinator
Francesca Nardoza, Study Coordinator
Agnese Provenziani, Study Coordinator
Alessandra Zambardi, Study Coordinator
Ashanti Zampa, Study Coordinator
Alessandro Zennaro, Study Coordinator

Mission

The Unit includes the Clinical Trial Center (CTC) and the Biostatistic and Bioinformatic Unit.

The main objectives of CTC are:

- To promote clinical trial management according to GCP and quality standard
- To support researchers in clinical trial start-up and conduct
- To empower 'no-profit' research and the role of IRE as sponsor
- To monitor clinical trials coverage of different therapeutics area
- To attract profit clinical trials and private investment

Its core consists of

1. Ethical Committee Scientific Technical Office

- monthly meeting organization
- meeting minute
- budget and agreement negotiation
- authorization process
- income management

2. Study Coordinators

- support researchers along all study phases from Site Qualification Visit to Study Closure in the full respect of trial protocol and procedures according to GCP

3. Research Nurses

- support Medical Doctors during patients visits and treatments (blood samples, vital signs, drug administration time, PRO, questionnaires, drug contability, phone contacts...)

4. Research Biologist

- process blood samples according to quality standard procedures

The CTC has strict relationships with

5. Clinical Trial Monitoring

- through SMART cloud platform to control trial status and patients accrual

6. Institutional Review Board (CISC)

- internal studies evaluation

7. Translational Coordinators

- to improve 'from lab to bed' research and studies

8. Epidemiology and Tumor Registries

- to evaluate study feasibility in terms of patients

9. Hospital Pharmacy

- to manage drug supply and contability

10. Pharmacovigilance

- to report Adverse Events according to EUDRAVigilance standard

11. Biobank and Clinical Pathology

- to manage samples according to high quality standard

The Biostatistical and Bioinformatic Unit gives statistical advice for the protocol design related to observational and experimental studies. It is a support for the researchers in study design choice, randomization procedures identification, sample size calculation and Case Report Form definition.

Furthermore, the staff performs statistical analysis of clinical and laboratory data and develops new technique of data analysis, as required from the always increasing complexity of available information. It performs also systematic reviews and meta-analysis on clinically relevant aspects.

The Computer Science section of the Unit develops and implements databases and web apps related to clinical trial and research projects as well as particular pathologies. The Clinical Informatics department is working on a cloud eCRF/DB based on REDCap, a platform employed by thousands of clinical researchers worldwide.

The Bioinformatic section of the Unit coordinates all the activities pertaining -omics and Big Data analysis in the institute. It provides a unique platform of discussion for all the bioinformaticians in IRE, bridges the communication from data scientist to the Information Technology department for High Performance Computing analysis of Next Generation Sequencing and other -omics data such as Nanostring.

Research Activities

The Biostatistic and Bioinformatic Unit implements the most advanced statistical and methodological techniques to analyze data arrays. Along with the basic ways of analyzing data multivariate approaches are followed using available softwares as SPSS, Medcalc, Comprehensive Meta-analysis, PASS, NCSS and specific routines developed in R environment. Data coming from our single center and multicenter studies are formally checked together with investigators and strategies are constantly discussed. Our support starts with the study design and sample size determination using the most appropriate and innovative clinical trial design, and goes on focusing on protocol development and randomization scheme. During the study we support the investigators with interim analysis and database management. When writing the paper we perform the analysis and discuss the interpretation of results. Our activity includes systematic reviews and meta-analysis as well as the most recent techniques of analysis as propensity score and network meta-analysis. In

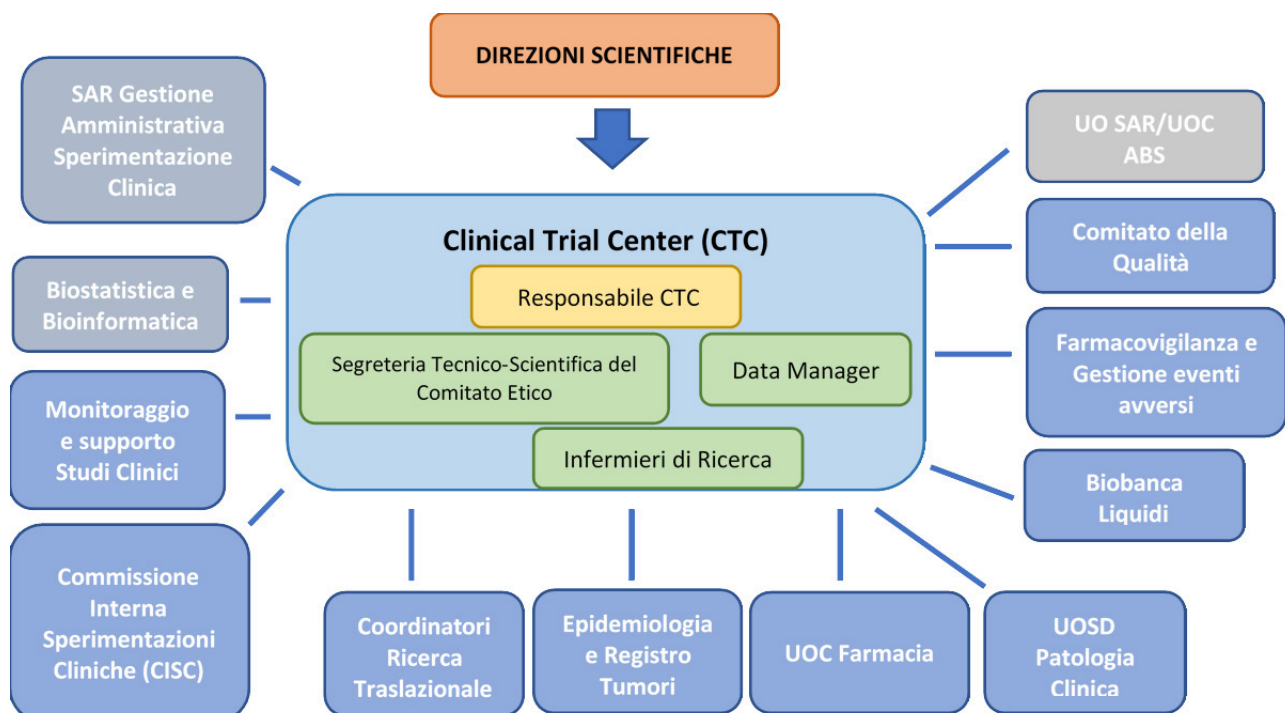
collaboration we study the possibility of reducing high-dimensional data to develop models for interpreting prognostic and predictive role of factors.

The Bioinformatic department started recently employing virtualization techniques such as Docker and Nextflow on High Performance Computing platforms in order to ensure total result reproducibility. During 2020 a “virtual machine recipe” was implemented with the basic toolbox needed for NGS data analysis. It also acts as a coordinating hub for many working groups of Alliance Against Cancer, such as ACC-Bioinformatics WP6 on Clinical Reporting and the data analysis of ACC-Immunotherapy.

IFO - Clinical Trial Center

The CTC was established by Decree No. 308 dated 24 April 2018 and subsequently amended with Decree No. 602 dated 06 August 2018. The components of both the CTC and External Units is shown in Figure 8. The CTC performs the following functions:

- Coordinates and monitors the functional activities regarding the management of clinical trials within the IFO, acting as a qualified reference point;
- Guarantees greater control of the clinical trials to the Scientific Directions of Regina Elena and San Gallicano Institutes and IFOs Medical Office;
- Particular supports in the spontaneous non-profit research;
- Interacts with the Departments involved in experimental research activities, coordinating the activities of the experiments aimed at:
 1. Providing administrative, managerial, methodological and statistical services to researchers for the conception, design, planning, start-up phase, conduction, analysis and reporting of clinical studies so that these activities are carried out in compliance with the Good Clinical Practice (GCP) and the protocols;
 2. Supporting the management of authorization procedures as well as the conduction and financial reports of clinical studies;
 3. Promoting, in profit and non-profit research, the professional development of all participating researchers in terms of compliance with GCPs and regulatory aspects;
 4. Guaranteeing quality control of studies (experimental and observational studies) with profit and non-profit study promoters;
 5. Supporting monitoring of information regarding the feasibility of studies in terms of potentially enrolled patients;
 6. Increasing the synergistic collaboration between researchers involved in the studies;
 7. Evaluating the experiments proposed by researchers at IFO, for which IFO takes on the role of Promoter, and monitors the progress of the approved studies;
 8. Identifying areas of great strategic interest for the Institute and propose initiatives necessary for promoting clinical trial projects in these areas



BioBank IRE

Head: Prof. Gennaro Ciliberto

Coordinator

Dr. Laura Conti, MD, PhD, Head of Clinical Pathology and Cancer Biobank Unit

Staff BBIRE T

Prof. Edoardo Pescarmona, MD Head of Pathology Unit

Dr. Mirella Marino, Quality Assurance

Dr. Simona di Martino, PhD Biologist

Dr. Valentina Laquintana, Biologist

Claudia Bonomo Technician

Staff BBIRE - LB

Dr. Giovanni Cigliana, Quality Assurance

Dr. Chiara Mandoj, Biologist

Dr. Giulia Orlandi, Biologist

Mustapha Haoui, Technician

Tommaso Mancuso, Technician

BBIRE is involved in a growing number of Institution projects (44 projects), and as a member of the European research network of Biobanks and Biomolecular Resources (BBMRI-ERIC) participates with European groups (EORTC- European Organisation for Research and Treatment of Cancer) to large-scale multicentre projects.

Also, BBIRE is involved in the ACC network and the primary objective of the Pathology and Biobanking Working Group is represented by the organization of a shared preanalytical workflow to obtain uniform quality of the biological samples, mainly tissue sample

Tumor Tissue BioBank IRE



Body Fluids Biobank IRE



DEPARTMENT	PATHOLOGY	PATIENTS	WITHDRAWALS	SAMPLE ALIQUOT (-500µl)				2mL*	1mL	TOTAL
				Whole Blood	Plasma EDTA	Plasma Citrate	Serum	Plasma EDTA	PBMC	
ORTHOPEDIC SURGERY	Sarcoma	880	2177	4250	8162	998	8817	5111	-	27338
THORACIC SURGERY	Thymoma	26	26	52	195	13	102	20	-	382
	Lung cancer	240	240	484	972	3	943	540	-	2942
	Lymphoma	4	4	8	26	-	16	6	-	56
MEDICAL ONCOLOGY 2	Breast cancer	105	117	232	340	456	662	137	-	1827
GYNECOLOGICAL SURGERY/ BTO (Ovarian Tissue Biobank)	Uterine cancer	575	584	1099	433	1564	2181	1709	-	6986
	Ovarian cancer	104	104	208	474	304	463	243	-	1692
RADIOTHERAPY	Prostate/	190	668	1308	2915	-	2956	1721	-	8900
	Dropharynx/ Breast cancer									
MEDICAL ONC 1/2	Lung cancer (incl. LUNGS)	100	168	403	-	-	114	1261	190	1968
NEURONCOLOGY/ NEURO SURGERY	Brain cancer	91	110	218	310	312	456	279	-	1575
		116	121	242	568	-	494	283	-	1587
ENDOCRINOLOGY	Medullary thyroid cancer	18	18	36	4	-	-	34	-	74
MED. ONCOLOGY/ PLASTIC SURGERY	Melanoma	244	597	1011	1349	6	2265	2894	-	7525
GASTROENTEROLOGY	Hereditary colon cancer	344	344	688	122	-	-	683	-	1493
HEPATOBIILIARY SURGERY	Colon/Stomach/Liver cancer	160	164	327	45	447	605	531	-	1955
MTB	Various	38	51	104	40	9	98	203	7	461
HEMATOLOGY	Lymphoma	52	70	140	46	-	125	355	136	802
TRANSFUSION M.	Healthy donor	140	438	718	105	1215	1723	907	3	4671
TOTAL		3427	6001	11528	16106	5327	22020	16917	336	72234

Body Fluids BioBank IRE



Tissue Biobank IRE



DEPARTMENT	PATHOLOGY	PATIENTS	SAMPLE PRESERVATION MODE					TOTAL
			TUMOR TISSUE CRYOPRESERVATION	NOT TUMOR TISSUE CRYOPRESERVATION	TUMOR TISSUE OCT	NOT TUMOR TISSUE OCT	FFPE	
ORTHOPEDIC SURGERY	Sarcoma	95	1022	253	55	1	87	1418
THORACIC SURGERY	Thymoma	47	357	76	11	4	46	494
	Lung tumors	290	1422	1226	83	45	2020	4796
	Mesothelioma	2	8	0	1	0	1	10
	Lymphoma	11	54	8	2	1	12	77
	Pleural effusion	51	0	0	0	0	0	0
Peripheral blood (pleural effusion)	27	0	0	0	0	0	0	0
SURGERY A/PLASTIC SURGERY	Breast cancer	143	207	591	22	12	138	961
GYNECOLOGICAL SURGERY	Uterine cancer	147	1011	299	27	3	96	1436
	Ovarian cancer	56	883	32	13	3	43	974
	Ovarian cancer + peritoneal wash	41	494	95	19	3	34	645
	Peritoneal washing	21	0	0	0	0	0	0
Uterine carcinosarcoma	6	77	17	7	0	6	107	
UROLOGY SURGERY	Renal Cancer	100	855	357	38	12	88	1350
UROLOGY SURGERY	Bladder Cancer	60	485	252	22	13	54	826
NEURO SURGERY	Brain cancer	31	125	5	2	1	29	163
HEPATOBIILIARY SURGERY	Colon cancer	115	588	454	27	18	107	1194
	Colon cancer/hepatic	7	91	75	0	0	11	177
	Hepatic metastasis	49	337	231	5	2	40	615
	Stomach cancer	19	71	52	7	5	15	150
	Liver cancer	33	260	141	14	0	30	465
	Pancreas cancer	43	205	83	10	4	35	337
	Gist	4	48	5	1	0	4	58
	Retroperitoneal sarcoma	6	118	32	2	1	5	158
	Cholangiocarcinoma	12	127	81	2	2	15	227
	Biliary tract cancer	6	8	0	1	1	3	13
	Melanoma	2	18	9	0	0	2	29
	OTOLARYNGOLOGY SURGERY	Head and neck cancer	15	80	24	4	0	4
OTHERS	Metastasis (melanoma)	26	138	10	6	0	19	173
Total		1465	9610	4408	386	136	2944	16965

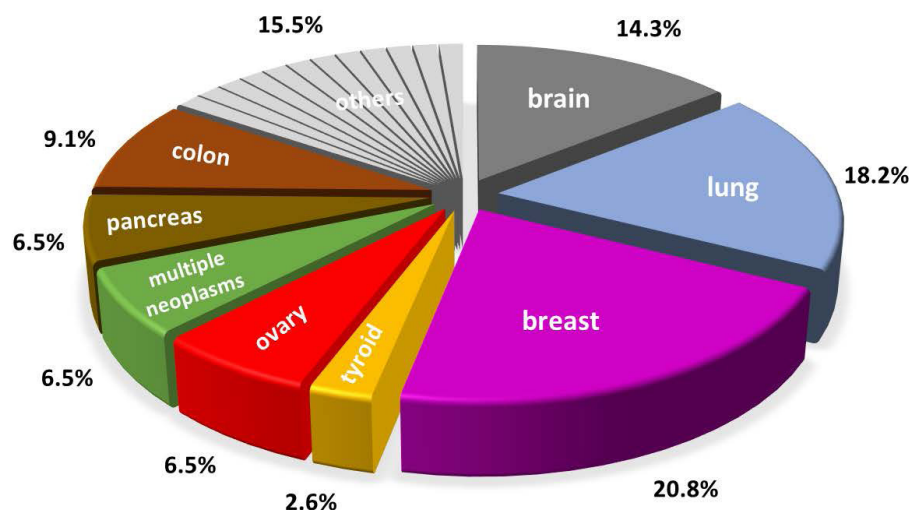
Molecular Tumor Board - MTB

The Molecular Tumor Board (MTB) at the Regina Elena National Cancer Institute (IRE) is active since September 2018. During the last year, our MTB consolidated its reputation within Regione Lazio by stably expressing recommendations for the treatment of complex, intramural but also external, clinical cases. Particularly, during 2020, 22 MTB sessions, at 15-day intervals, have been made. Overall, 23 neoplastic patients bearing common (e.g. lung, colorectal, breast carcinomas) or rare (e.g. sarcomas) cancers with no therapeutic options left have been analyzed. In all cases, after a revision of the clinical history and the available genomic data, the MTB requested additional molecular testing, most often based on massive parallel sequencing. Next Generation Sequencing (NGS) was carried out in-house by small targeted panels (e.g. 50 genes) and genome-wide (Whole Exome Sequencing, WES) approaches, or by outsourcing from prime International NGS Service Providers (e.g. Foundation Medicine). Particular care was exercised in selecting the analyte (or analyte combination) most suitable for each individual patient. Either or both tissue and circulating DNA (tDNA and ctDNA) were used to investigate the genomic profile of patients, often through the implementation of serial blood drawings and/or, when ethically acceptable, tissue re-biopsy. Digital PCR (dPCR) custom assays were designed, validated and deployed when no commercial solutions were available in order to confirm the presence of a specific tumor alteration. Immunohistochemistry (e.g. PD-L1 status) and in situ hybridization (e.g. FGFR1 amplification or ROS1 fusion) were also requested and applied in some cases. All the collected data were integrated as orthogonal confirmatory measures and/or evaluated as self-standing assays. Non-standard assays were backed up by (and integrated with) CE-IVD testing whenever possible. In 14 cases (61%), at least one peculiar molecular alteration associated with a potential, additional tumor vulnerability was identified. Following MTB case review, a non-standard targeted therapy (mostly OncoKB levels 3A and 3B) was recommended for 11 patients (48%). In 2 colorectal cancer patients identification of EGFR mutations strongly suggested the discontinuation of the ongoing standard line of therapy.

It is important to acknowledge that all the costs associated with supplemental genomic analyses were entirely covered by the Regina Elena Institute. None of the patients was requested to pay, or incurred in any disbursement for any kind of molecular testing, or for the purchase and administration of the selected drugs. In specific situations, when applicable, the MTB entertained a collaborative effort with the Italian National and local Health Authorities to obtain special permits and economical support finalized to free drug administration. Additional collaborative efforts are in progress to extend the MTB approach.



81 pts
have been
discussed



45/81 (**55.6%**) pts showed ≥ 1 actionable mutation

29/45 (**64.4%**) pts have received therapeutic recommendations

19/29 (**65.5%**) started recommended therapy

Partecipation to National and International Networks

Alleanza Contro il Cancro - ACC

The IRCCS Regina Elena National Cancer Research (IRE) is one of the founder members of Alliance Against Cancer (ACC), the largest Italian organization for cancer research, that was established in 2002 by the Italian Ministry of Health as a network of six high standard institutes for comprehensive cancer patient care and research (IRCCS).

The primary aim of ACC is to promote the network among oncologic institutes pursuing mainly clinical and translational research in order to bring state of the art diagnostics and advanced therapeutics to patient care.

In addition to the aims of translational medicine, ACC also fosters research through international collaborative networks of excellence, such as Transcan ACC is one of the funding agencies in this European network that coordinates translational research projects that are selected by means of high standard evaluation procedures.

The Association is currently made up of 26 Comprehensive Cancer Center, AIMaC, Italian Sarcoma Group, CNAO Foundation and the Istituto Superiore di Sanità.

Actually, eleven Working Groups (WGs) that deal with the main types of cancer (Colon, Breast, Lung, Glioblastoma, Melanoma and Sarcoma) and clinical research (Genomics, Pathological Anatomy and Biobanks, Oncohematology, Immunotherapy and Radiomics) are active in the ACC. These are collaborative groups formed by the best national reference experts who deal with programming clinical research and optimizing the use of new drugs for each individual tumor pathology. The IRE Institute participate to all WGs with the participation of pre-clinical and clinical representative.

WG	Pre-clinical representative	Clinical representative
Colon	A. Biroccio	M. Maugeri Saccà
Glioblastoma	M. Paggi	A. Pace
Immunotherapy	P. Nisticò	V. Ferraresi
Breast	G. Blandino	P. Vici
Melanoma	P. Giacomini	V. Ferraresi
Sarcoma	R. Falcioni	V. Ferraresi
Lung	P. Nisticò	M. Maugeri Saccà
Oncohaematology	M. Fanciulli	F. Marchesi
	Wet Lab	Bioinfo
Genomics	S. Buglioni	M. Pallocca
Anathomo Pathology	S. Di Martino	E. Pescarmona
Radiomics		A. Vidiri

Eatris

A-IATRIS, Association Italian Advanced Translational Research Infrastructure, is a network of institutions of excellence on the national scene able to make specific and complementary contributions in the area of translational medicine. A-IATRIS represents the Italian node of EATRIS (European Advanced Translational Research Infrastructure in Medicine).

EATRIS is designed to bridge the gaps and deficits in the panorama of European translational medicine. Its objectives for EATRIS are:

- To support the process of translating research results into innovative strategies aimed at the prevention, diagnosis and treatment of diseases of particular health and economic importance for European member states;
- To build a better space in which the flow of information between basic research and clinical observations is bidirectional



The future of cancer therapy

EORTC

European Organization for Research and Treatment of Cancer Is an independent, non-profit cancer research organization, its mission is to coordinate and conduct international translational and clinical research to improve the standard of cancer treatment for patients

EURACAN

The management of rare cancers poses significant diagnostic challenges, sometimes having major consequences for patients' quality of life and outcome. Inappropriate management of these patients may also result in an increase risk of relapse, and even death. In order to solve these issues, EURACAN was established in year 2016

EURACAN acts as a virtual network connecting patients and expert healthcare professionals across Europe. The aim is to tackle these complex and rare cancers that require highly specialized treatment and concentrated knowledge and resources.

More than 300 rare cancers have been identified. EURACAN covers all rare adult solid tumor cancers, grouping them into 10 domains:

1. Connective tissue (sarcomas)*
2. Female genital organs and placenta
3. Male genital organs and urinary tract*
4. Neuroendocrine system*
5. Digestive tract*
6. Endocrine organs*
7. Head and neck
8. Torax*
9. Skin and eye melanoma*
10. Brain and spinal cord*



*Domains where the Istituto Regina Elena has been an accredited Euracan Member since year 2016

OECI

The “Organization of European Cancer Institutes” is a nongovernmental, no-profit legal Entity established in 1979 to promote greater cooperation among European Cancer Centres and Institutes with the following Aims:

- Create a critical mass of knowledge and skills that can identify and share new and improved models of care
- Improve the quality of cancer care and translational research
- Improve the quality of life for cancer patients
- Provide a path of continuous improvement in order to homogenize the care of cancer patients according to shared
- Achieve high European standards and quality levels.
- Facilitate the development of European multi-centre studies and the use of EU research funds

With time OECI has grown to include more than 100 Cancer Institution mainly in Europe but also in other Continents. The OECI aims to promote efficient partnership, reduce fragmentation and increase competitiveness amongst European cancer centres and institutes. This goal is being achieved by promoting and enhancing the concept of “comprehensiveness” and “multidisciplinarity”, supporting quality in cancer care and dynamically working in crosscut expertise by involving our Working Groups, our Members and promoting synergies with other cancer Organisations.

OECI, on September 10, 2015, has certified that IRE meets the quality standards for cancer treatment and research and has therefore awarded to IRE the qualification of Comprehensive Cancer Centre, namely an Institute with the combination of characteristics such as translational research, multidisciplinary, continuous improvement of care, the production of guidelines and diagnostic-therapeutic pathways, continuous training and centrality

Year 2019 has to be remembered as the year in which for the first time the annual meeting of OECI called “Oncology Days” has been held in Italy. The meeting was held in Bari from June 19 to June 21. All Italian OECI Members, including IRE contributed to the organization of the program. A dedicated roundtable session with the title: The OECI Italian Institutions Network Alliance Against Cancer (ACC), A Country Based Model took place as a central event in the meeting

In Year 2019 IRE has applied to undergo a new OECI Accreditation and Designation Programme. Upon approval of the IRE application on June 5, 2019, a self-assessment period started that was completed in January 2020. A provisional Accreditation as Comprehensive Cancer Center has been assigned as well as in March 2020 a GO decision was communicated and a peer review visit planned for May 12 and 13. Unfortunately that date was cancelled due to the COVID-19 pandemic and at the time of writing this report it has not yet been rescheduled



UICC

The Union for International Cancer Control's (UICC) rapidly increasing membership base of over 1000 organizations in more than 160 countries, represents the world's major cancer societies, ministries of health and patient groups and includes influential policy makers, researchers and experts in cancer prevention and control. UICC also boasts more than 50 strategic partners



Weizmann Institute

In 2020 the IRE has established a collaboration with the Weizmann Institute of Science (WIS) in Rehovot, Israel. These two institutes have called an internal research grant for collaborative research between an IRE PI and a WIS PI. This grant will support the research for two years with €25.000,00 per year. This first edition was won by the team Yarden - Bagnato and Krizhanovsky - Bossi



מכון ויצמן למדע

WEIZMANN INSTITUTE OF SCIENCE

Translational Interest Work Group

Genomics

By Dr. Patrizio Giacomini

The IRE Working Group (WG) Genomics is a multidisciplinary group spanning in expertise from basic-translational approaches to clinical Next Generation Sequencing (NGS). Although NGS is our main focus, members of the group implement many ancillary nucleic-acid-based methods for research and advanced diagnostics. Biologists, Biotechnologists, Bioinformaticians, Pathologists and Clinical Pathologists provide the WG Genomics with a solid biotech core, but all the activities (from study design to patient enrollment and treatment, through data collection and analysis) build on the strong contributions of medical oncologists, radiologists, surgeons, and Biostatisticians. Integrative approaches are being carried out including radiogenomics, liquid biopsies, whole-genome and single-cell sequencing, big data interrogation, model building and clinical trial design. The goal is to harmonize diverse skills and institutional needs into a common finalized effort (see figure).

Achievements

During 2020, clinical NGS panels of increasing complexity have been employed to reflect the expansion of the druggable genome. In parallel, we have witnessed a considerable increase in the number of NGS-based diagnostic tests performed, as follows: 1120 patients (colorectal, lung, thyroid, gastric carcinomas, brain tumors, sarcoma and melanoma), 780 of whom displayed pathogenetic or likely pathogenetic alterations, and 670 had targetable or potentially targetable alterations either in the standard of care setting or in the context of ongoing clinical trials. More in general, rather than adopting the one-size-fits-all scheme so common to commercial outsourcing models, we find it most useful to tailor different NGS solutions for different clinical-pathological patient groups.

The Genomics WG entertains a close collaboration with the institutional BioBank. Whether occurring in the context of standard of care, or during a clinical trial, we do our best to biobank tissue, blood, and other body fluids for future reference, molecular 'second look', and retrospective analysis.

The WG Genomics includes members of our Genetic Testing Unit, focusing on the most frequent Hereditary Cancer syndromes (HCS) such as the Lynch syndrome (LS), the Peutz-Jeghers syndrome (PJS), the Juvenile polyposis syndrome (JPS), The Cowden syndrome (CS) the Hereditary Breast and Ovary Cancer syndrome (HBOC), APC-associated polyposis and MUTYH-associated polyposis (AAP and MAP), and the Multiple Endocrine Neoplasia syndrome type 1 and type 2 (MEN1 and MEN2). Molecular testing is performed in the framework of genetic interview/counseling through the activities of our outpatient's clinics. Moreover, a substantial fraction of cases are referred from other institutions all over the country. During 2020, testing 375 probands resulted in the discovery of 67 affected patients, e.g. we have further optimized the affected/tested percentage of our testing, which attests to an improved clinical-molecular integration in our multidisciplinary HCS unit.

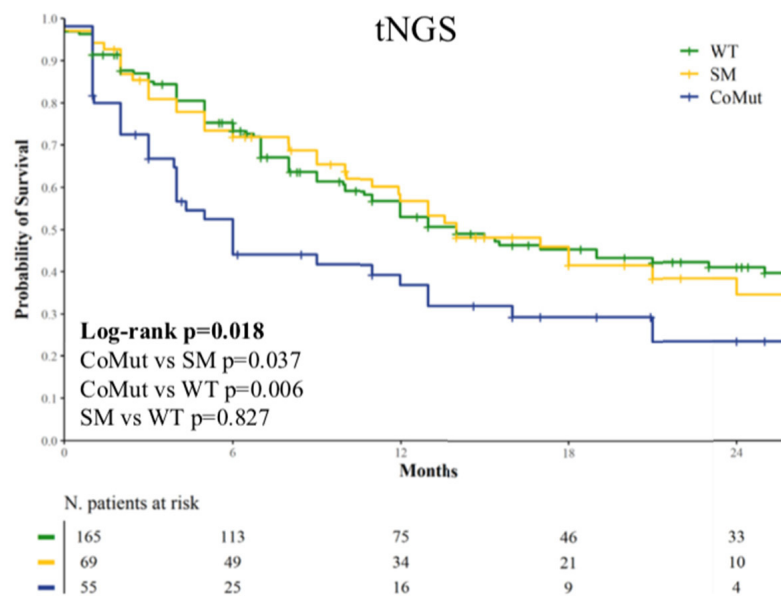
Hereditary Cancer testing allows an in-depth cancer risk assessment for each patient, leading to improvements in health outcomes of both carriers and family members.

During 2020, the throughput of our advanced genomics facilities has been considerably expanded through the purchase of new equipment and personnel training/acquisition. This has resulted in an improved support to research projects and, most importantly, to the Molecular Tumor Board. To this end, during 2020, we have carried out 6 WES analyses, and have greatly streamlined and automatized bioinformatic support. This has resulted in both more accurate data for research purposes and an extension in our ability to investigate rare cancers and uncover unsuspected vulnerabilities in fragile patients.

Research Activities

Several studies are ongoing to identify epigenetic mechanisms involved in tumor transformation, including miRNA signatures in melanoma, head and neck cancer, and hematological malignancies. Recently, members of the Genomic

Translational Group have reported that KEAP1-driven co-mutations make lung adenocarcinoma unresponsive to immunotherapy despite high Tumor Mutational Burden (Fig. ...). This study helps to explain why our ability to predict the efficacy of this important class of therapeutic agents has lagged behind.



A specific combination of mutations impairs immune checkpoint blockade in lung carcinoma. Patients whose tumors hosts co-mutations (blue line) have a short overall survival compared to patients whose tumors either lack the selected set of mutations (WT, green line) or have a single mutation (SM, yellow). From Marinelli et al. Ann. Oncol. <https://doi.org/10.1016/j.annonc.2020.08.2105>

Non Coding RNAs (NCR)

By Dr. Giovanni Blandino

Recent studies have revealed that about 90% of the eukaryotic genome is transcribed. Interestingly, only 1-2% of these transcripts encode for proteins, the majority are transcribed as non-coding RNAs (ncRNAs).

During the past few years ncRNAs, previously thought as transcriptional junk, have become a research goldmine. The functions of ncRNAs are likely diverse, and their underlying mechanisms are just beginning to be understood. For sure ncRNAs are important regulatory molecules of many cellular processes in development and diseases, among which cancer, and have been identified as the key gene expression regulators.

The NCR group is mainly focused on three classes of ncRNA: microRNAs (miRNAs) long-non-coding RNAs (lncRNAs) and circular RNAs (circRNAs).

MiRNAs are small single-stranded molecules (20-24 nt) that derive from transcripts with distinctive hairpin structures. The hairpin is processed into mature miRNA by two endonucleases, Drosha and Dicer, and forms the RNA induced silencing complex (RISC). The miRNAs will pair with complementary sequences on target mRNAs transcripts through the 3'UTR, leading to gene silencing of the target.

lncRNAs are non-protein coding transcripts >200 nt in length that have been shown to control every level of the multi-level regulated gene expression pathway. For example, they are implicated in post-transcriptional gene regulation through controlling protein synthesis, RNA maturation and transport, the amount of available functional miRNAs, and in transcriptional gene silencing through regulating the chromatin structure.

CircRNAs are a large class of endogenous RNAs formed by exon skipping or back-splicing events as covalently closed loops, which are expressed abundantly in mammalian cells. CircRNAs can regulate transcription, RNA splicing and, as for lncRNAs, they can function as miRNA sponges.

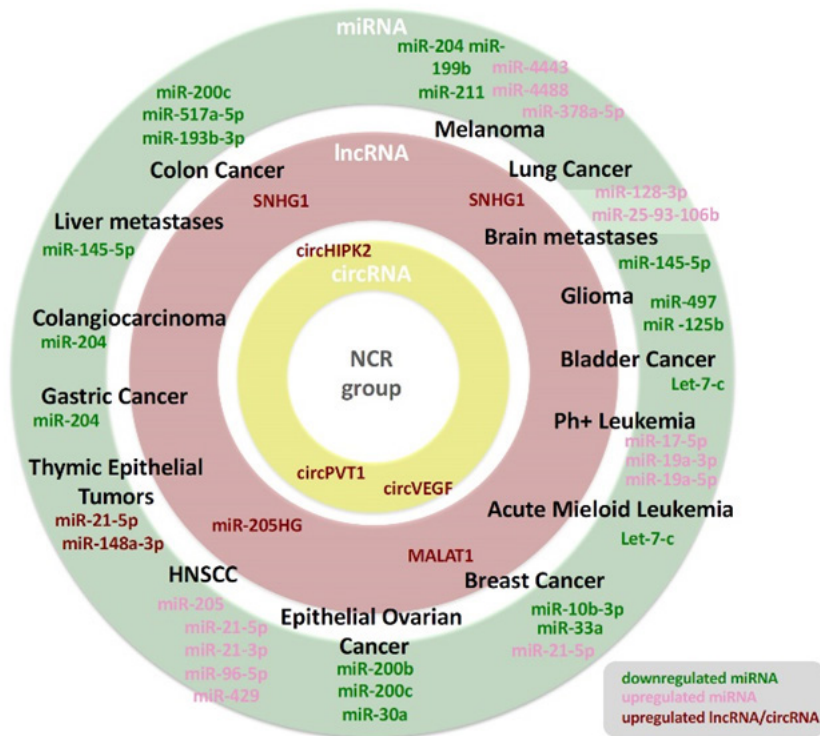
The studies conducted by the NCR group are based on two principal approaches: a) one of more basic research approach that is intent to discovery the molecular mechanisms at the basis of miRNAs, lncRNAs and circRNAs deregulation and functions in cancer cells; b) the other one is based on translational research approaches aimed to identify, by genome-wide screening, miRNA, lncRNAs and circRNAs deregulated in tissue and liquid biopsies derived from cancer patients of our Institute, in way to discovery novel molecular biomarkers with clinical-prognostic impact and to develop innovative and more effective therapeutic approaches.

The research activity of NCR group, conducted in the last years, allowed to the identification of an intricate network between the three different classes of noncoding factors in several cancer types (Figure). Moreover, several studies focused on circulating ncRNAs in cancer patients, underling their promising use as novel powerful biomarkers. The obtained results lead to a deeper understanding of the molecular pathways involved in tumorigenesis and represent the basis for the identification of novel powerful biomarkers.

In the last year the research activity of the group led to the possibility of patenting new biomarkers such as miRNA and circRNA.

In particular 3 projects led to the filing of 3 patents:

1. The identification of a 4 miRNAs signature associated with the occurrence of relapse in patients with head and neck cancers.
2. The identification of a circRNA as a biomarker involved in the recurrence of breast tumors, in particular TNBC.
3. The identification of a miRNA signature as biomarkers for the development of mucositis. A project in collaboration with the San Gallicano Institute.



Melanoma (Joint IRE - ISG)

By Dr. Emilia Migliano and Dr. Patrizio Giacomini

During year 2020, the group has built on a pre-existing collaborative network and has strengthened the interactions among the Melanoma Disease Management Team, the institutional Melanoma 4P project, and work in the context of Alliance Against Cancer (ACC).

Organization

The Melanoma DMT convenes on Tuesdays to discuss the most critical clinical cases, but is also a forum for the dissemination of the ongoing clinical and clinical-translational projects and ideas. Melanoma 4P stands for Precision, Predictive, Personalized and Participated.

During 2020, we have been able to enrol in this study 97 more patients, 68 from the cohort at early stages, and 29 from the late-stage cohort. The total numbers of enrolled patients is now 149 (since May 2019) which demonstrates our commitment to make precision oncology available to an expanding cohort of high-risk patients. The project is run under the supervision of Professors Gennaro Ciliberto and Aldo Morrone, Scientific Directors of the Regina Elena National Cancer Institute and S. Gallicano Dermatological Institutes, respectively. Collaboration of our twin Institutes is a plus enabling Melanoma 4P to span from prevention and Dermatology to Medical and Molecular Oncology in a single uninterrupted flowchart.

Achievements

Rare Tumors

By Dr. Virginia Ferraresi

Tumors are for definition considered rare when incidence is less than 6 cases in 100.000 people per year, but altogether rare tumors account for approximately 25%, of all cancers (approximately 18% solid rare cancers and 7% rare hematological diseases). Rare tumors are almost invariably associated with 5-year overall survival rates globally less than 50% as compared to 65% in common cancers. This overall worse prognosis is substantially linked to the limited medical expertise and the lack of evidence-based treatment guidelines that ultimately result from low frequency with scanty tissue banks and registries, few clinical trials, misdiagnosis (both clinical and pathological) and delayed diagnosis, all of which are serious obstacles to clinical decisions.

The estimates of incidence, prevalence and survival of rare cancers in Italy are based on the pool of the AIRTUM cancer registries (years 2000-2010) and it was estimated that about 360.000 people were diagnosed with new cancers in Italy in 2011, with an annual incidence rate of about 200 rare cancers per 100,000 corresponding to about 89,0000 new diagnoses annually.

With a yearly admittance of 1,000 new cases and 3,000 total patients being followed per year, IRCCS Regina Elena represents one recognized center for the diagnosis and treatment of rare solid tumors.

Over the past 10 years, IFO played an active role in the collaborative efforts of the national network on rare tumors (Rete Tumori Rari, RTR). Since 2016 IFO are involved in EURACAN (EUropean network for Rare Adult solid CANcer) and have become a European Referral Center for eight rare tumors (soft tissue, viscerae and bone sarcomas, rare neoplasm of the male genital organs, and of the urinary tract, neuroendocrine tumors, rare neoplasm of the digestive tract, rare neoplasm of endocrine organs, rare neoplasm of the thorax, rare neoplasm of the skin and eye melanoma, rare neoplasm of the brain and spinal cords). Main objectives of EURACAN are to improve the quality of care of all European patients affected with rare cancers enabling a major improvement in the access to centers of excellence for diagnosis and treatment and unifying the availability of optimal clinical practices in the EU by centralizing knowledge and experience, medical research, training, and resources. A European Collaborative Platform and a Clinical Patient Management System (CPMS) are actually in development in order to discuss and to share clinical cases of patients with rare tumors all over the European centers of the network. In 2019, IFO domain leaders have been involved in virtual meetings and asked to participate in panel of experts

Our Institute is actively involved in International collaboration and revision of specific guidelines of various type of rare tumors and is engaged in national and international clinical trials. Since 2018, the Rare Tumors Translational Group has been participating in the European trial ARCAGEN (EORTC-SPECTA) whose aim is to perform a molecular characterization of rare cancers on retrospective and prospective biological samples. Retrospective cases have been collected and the accrual of prospective cases is actively ongoing.

In 2020, IRE became one of the 9 EURACAN and OECI Italian national cancer institutes of project Rarity. The project is sponsored and funded by Alliance Against Cancer (ACC) and aims at initiating the Italian part of the EURACAN registry (STARTER project).

Clinical cases of rare tumors having access to our institute are discussed in meeting, scheduled on weekly or biweekly basis, by dedicated multidisciplinary disease management teams in order to assure an adequate clinical, radiological and pathological assessment leading to a correct diagnosis and an appropriate treatment inside or outside national or international experimental trials.

From January 2018 a dedicated group of data managers is actively involved in the prospective registration of all new case of rare tumors accessing to our Institute on a database including all relevant clinical information and follow up updates. To date, about 3,500 new patients have been registered and for some rare tumors (for example soft tissue and bone sarcomas) a regular process of institutional biobanking of blood and pathologic specimens is ongoing.

In 2020, integrate care pathways in rare tumors have been further elaborated in order to assure timely taking charge of the patients. In order to facilitate the access of patients with rare tumors and diseases and to offer them dedicated diagnostic and therapeutic pathways, in December 2020 a helpdesk has been activated. It is coordinated by a doctor, a nurse and an administrative employee and will guide patients through paths that can facilitate quick access to facilities dedicated to individual rare tumors.

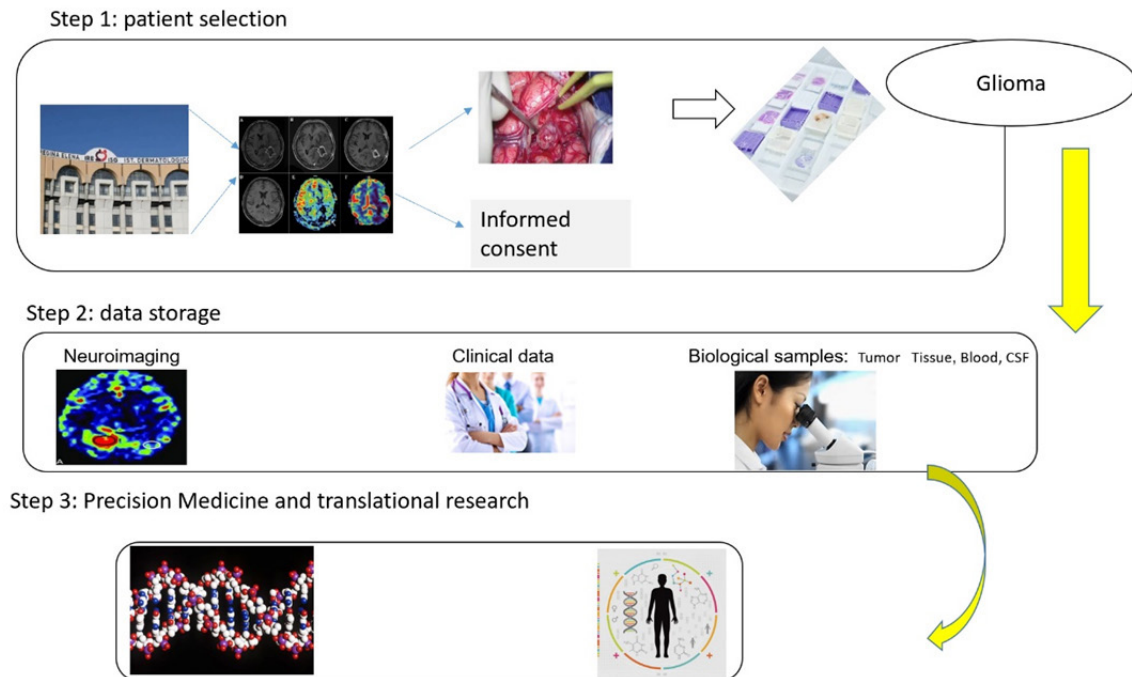
Increasing emphasis is moreover given to the collaboration with basic researchers to identify, as for more common cancers, molecular diagnostic, prognostic or predictive biomarkers and regular translational meetings, under the supervision of our Scientific Direction, are organized on bimonthly basis.

Finally, in June 2020 a departmental Unit on Sarcomas and Rare Tumors was activated. The unit is specifically addressed to the diagnosis, clinical management and translational research in patients with sarcoma and will be responsible for coordinating the activities on Rare Tumors in the Institute and in the EURACAN project.



Brain Tumors

By Dr. Veronica Villani



Despite standard multimodality treatment including surgical ablation followed by radiotherapy plus concomitant and adjuvant chemotherapy with temozolomide, the prognosis of malignant gliomas remains unsatisfactory. Median survival in Glioblastoma Multiforme (GBM) patients is of 14.6 months and the average 5-years survival rate is less than 9.8%, with very few cases of long-term survivor, thus justifying the research on novel more effective therapies. The understanding of the molecular mechanisms of Glioma tumors has significantly evolved over the last decade and translational programs based on a large clinicobiological database are required to improve our understanding of GB biology, potentially facilitating the development of personalized and specifically targeted therapies and research applications. Successful biomaterial collection is a key requirement for the application of contemporary methodologies for the validation of candidate prognostic factors, discovery of new biomarkers and clinical implementation of precision medicine (eg, target therapies and immunotherapies).

Recent progress has been made possible by using advanced molecular analysis of brain tissue specimens systematically collected and stored in tissue repositories, including bioinformatics analysis of molecular data and integration with clinical information.

In the last years, the Regina Elena Cancer Institute promoted the Glioma Translational Group through multidisciplinary collaboration between clinicians and researchers.

The primary aim of this collaborative group was to create a joint repository of tumor tissue, blood and CSF samples developing and maintaining a neuroncological biobank.

Collection and storage of biospecimens are offered to all patients undergoing surgery or submitted to neuroncological treatments including those obtained not only at disease onset but also at recurrence. In general, brain tumor patients are followed longitudinally from diagnosis throughout their disease course. An imaging repository is annexed to the clinical data and specimens that include MRI studies following a standardized protocol with pre- and postcontrast T1, T2, diffusion and non-morphological sequences.

With tissue specimens and pertinent clinical information the database has a role in both clinical and research development: at an individual level a personalized approach to precision medicine allows direct patient treatment

At present, several translational studies are ongoing:

- Radiomic imaging studies are under development to align patterns in MR images with molecular and clinical features (Glioma Project);
- In the framework of glioma's group, Next generation sequencing in glioma patients for identification of potential target therapy: NGS panels assessment such as Ion-AmpliSeq (Thermo Fisher Scientific) to identify either the presence of point variants and fusion genes or variations in the number of gene copies with a panel of 50 genes that are recognized to have a key role in tumour development, with the aim to identify potential therapeutic target. Also for In order to dissect the microenvironment heterogeneity of our samples, we started applying whole transcriptome sequencing (RNA-seq) on a subset casuistry of the Glioma Project.
- To investigate if circulating miRNAs could mirror the mutational status of IDH1 we explored, through genome-wide methodologies, the miRNA expression profile in serum samples of a discovery cohort of IDH1 mutant and IDH1wt glioma patients. We found, on the basis of prognostic value and IDH1 status, a serum signature of 10 miRNAs with a promising diagnostic and prognostic value as non-invasive tool to stratify gliomas according to IDH1 status and useful to complement the molecular analyses routinely carried out on formalin-fixed paraffin-embedded tissue biopsies.

Translational approach and the development of dedicated biobank are critical to promote translational researches in neuroncology

Immunotherapy

By Dr. Paola Nistico'

Over the past few years, novel anticancer immunotherapy strategies, such as immune checkpoint inhibitors (ICI) and adoptive T-cell therapies, have shown remarkable clinical success across several tumor types, generating a wave of optimism in the oncology field. However, the durable regression of the disease achieved by immunotherapy approaches is currently limited to a subset of patients. The variability in patient response to cancer immunotherapies is due to the dynamic and complex nature of anticancer immunity, the existence of multiple immune-regulatory receptors/ligands and the heterogeneity in immunological composition, localization and function of the tumor immune microenvironment (TIME) cells.

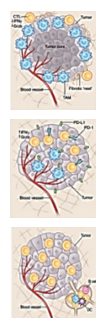
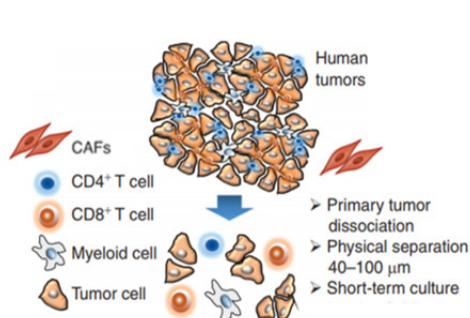
The group is developing a platform comprising of bioinformatics workflows and models that will stem from patient multi-omics integration. This asset will be exploited in future studies to guide optimal selection of best immunotherapeutic strategies for NSCLC patients, also in the framework of ongoing Alliance Against Cancer (ACC) network clinical trials.

In particular, several lines of actions have been pursued:

- In the framework of the ACC Network, we have applied multi-omics platforms (RNAseq, NanoString, HLA typing, TCR-Seq, Whole Exome Sequencing) and deconvolution algorithms to identify biomarkers of response in ICI treated NSCLC patients.
- We posit to identify mechanisms of resistance in ICI non responder patients to design strategies to stimulate a non-immunogenic microenvironment TIME, e.g. radiotherapy.

CAR T-cell therapy is based on the administration of genetically modified T-lymphocytes specifically redirected to the tumor target by the expression on the lymphocyte cell surface of Chimeric Antigen Receptors (CARs). This therapy has been particularly effective in the context of B-cell lymphoproliferative diseases, while in other hematological malignancies and in solid tumors, so far, the efficacy has been much more limited. CAR T-cells therapy remains a challenge in solid tumors due to the presence of a TIME that may act as a physical barrier hampering CAR T-cell trafficking. The group is involved in a research project promoted by the Ministry of Health and developed under the aegis of Alliance Against Cancer. In particular, we are focused on the development of different strategies aiming at modulating the immunosuppressive elements to overcome the inhibition exerted by TIME to CAR T-cell therapy. The group currently carries out the following tasks :

- By bioinformatics methods and Machine Learning techniques we identified CAF-specific RNA signatures responsible of immune exclusion as putative target of CAR T
- We delivered oncolytic viruses in a murine model of head and neck cancer to support CAR T-cell penetration.
- We have planned to identify innovative biomarkers to predict CAR T-cell therapeutic response in human sarcomas



Identification of tumor microenvironment components participating to ICI resistance, focusing on cancer associated fibroblasts (CAF), extracellular matrix (ECM) and immune cell presence and localization

Artificial Intelligence AI and Imaging

By Dr. Matteo Pallocca

Precision Medicine is now a common practice and an established diagnostic paradigm, revolutionizing therapeutic approaches thanks to novel multidisciplinary schemes. One pillar of these new techniques is Artificial Intelligence (AI), the umbrella world defining all the computational techniques able to mimic or reproduce intelligent behaviors, such as language, pattern recognition, or classification. These techniques are able to provide novel models of prediction and prognosis to our patients in order to enable a new era of High-Resolution, other than Precision, Medicine.

Mission

With the purpose to give a basic framework and round table of discussion to all the several units dealing with structured and unstructured data in the Institute, the Scientific Direction prompted the creation of the Interdepartmental group of Artificial Intelligence and Imaging. The final aim is also to accelerate the Digitalization process of several data types and the employment of complex AI models on biomedical data.

The team is interdisciplinary in nature and comprises Bioinformaticians, Radiologists, Medical Physicists, Engineers, Medical Doctors, Biologists, Physics, Statisticians, and Experts in Scientific Communication.

Regarding unstructured data, Images are the bulkiest and largest set of data generated in a research hospital setting. Radiological data, for instance, are born digital, but they do need to undergo several *in silico* processing steps in order to extract modeling-ready numeric features. Furthermore, the Pathology Department of a cancer center processes thousands of Immunohistochemistry slides via human analysis and data curation. Now, the automated digitalization of said images enables an unprecedented power to reanalyze with novel techniques and algorithms hundreds of patient slides altogether and to overcome the intrinsic inter-operator human variability.

When it comes to structured data, -omics are the bread and butter of many diagnostic Units, with Next Generation Sequencing being applied to thousands of patients (ref. Genomics group), along with several other facilities such as Lipidomics and Metabolomics. The future of AI in Precision Medicine lies in multi-omics integration, with its numerous technical challenges due to data heterogeneity and batch effect distribution.

Novel synergies among Units

During the first months, the main focus of the AI and Imaging group has been the presentation of several modeling and analysis activities among Units that have been physically and strategically separated, such as Radiology/Medical Physics with the Genomics/Bioinformatics department.

For instance, the Radiology unit and the Medical Physics Laboratory shared their experience on Radiomics analysis of oropharyngeal squamous cell carcinomas and Head and Neck cancer. These projects were strongly related to AI not only for the feature extraction methods but also for the Machine Learning models employed on imaging features that exhibited a classification accuracy of over 90% for benign/malignant parotid lesions. Another joint-venture ongoing with the Galeazzi Orthopaedic Institute is focused on the Texture Analysis of Rare Tumor lesions, with the intent to better separate benign from malignant lesions from the TC and RM data.

Furthermore, during 2020 the interaction between the Digital Pathology and the Bioinformatics group enabled the expansion of the implementation of the Aperio AT2 System for digitalization with the GENIE tool for automatized segmentation of digitalized slides. This tool enables to train the macro-regions of interests of each slide, to then apply the Aperio scoring algorithms to identify immunohistochemical staining specific to each cell in every region (such as tumor, stroma, etc).

This system enabled to accelerate two projects already in place employing Digital Pathology: a digitalization effort on PD-L1 staining on Head and Neck Cancer and another casuistry of Non-Small Cell Lung Cancer treated with Immuno-Checkpoint inhibitors stained with PD-L1 and other CD* immunological markers, with the intent to define a novel predictive immunoscore (ref. Immunology Unit).

The Lung radiogenomics Pilot

The first project stemmed from the AI & Imaging group pertains a complete multi-omic profiling of a casuistry of 150 Non-Small Cell Lung Cancer Patients who underwent surgery in our Thoracic Surgery department. These patients have pre-surgery TC scans from our Radiology Unit, complete oncogene sequencing from the Pathology, and clinical data annotation concerning treatments, progression events, and comorbidities such as smoking. This multi-omics integrative analysis will enable to shear light on how molecular mechanisms such as somatic mutations influence imaging data and whether a combined radiogenomic model improves biomarker modeling for prognostic and predictive endpoints.

Components

Matteo Pallocca (coordination, Bioinformatics)

Eleonora Sperandio (Bioinformatics)

Simona Marzi (Medical Physics)

Francesca Piludu (Radiology)

Vincenzo Anelli (Radiology)

Alessio Annovazzi (Nuclear Medicine)

Antonello Vidiri (Radiology)

Enzo Gallo (Digital Pathology)

Edoardo Pescarmona (Pathology)

Simona Di Martino (Biobank)

Laura Conti (Biobank)

Irene Terrenato (Biostatistics)

Paola Nisticò (Immunology)

Giovanni Blandino (Epigenomics)

Maurizio Fanciulli (Genomics)

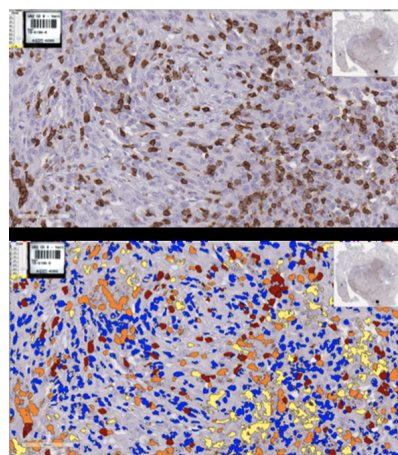
Roberto Biagini (Surgery)

Giuseppe Sanguineti (Radiotherapy)

Lorella Salce (Communication)

Eriseld Krasniqi (Oncology)

Rosa Sciuto (Nuclear Medicine)



Digitalization and computational image analysis of CD8 staining in Non-Small Cell Lung Cancer in Digital Pathology

Disease Specific Units

Breast Unit

Coordinator: Prof Roy De Vita, MD

Mission

To offer an integrated and quality program to guarantee the care of patients with a diagnosis of suspected or ascertained breast cancer in the various phases of diagnostic confirmation and therapy, in order to improve the continuity of care, consistent with the lines guide based on the available evidence and with the most current scientific research lines.

All patients will be offered the same entry possibilities into clinical trials that may be underway at the Institute for each individual case.

The program also aims to:

- Improve waiting times for the therapeutic diagnostic process, by setting company standards;
- Improve the information and communication aspects with the patient,
- Optimize and monitor the quality levels of the care provided, through the identification of process and outcome indicators and the development of a data collection and analysis system.

Moreover the program intends to consolidate the relationships with voluntary associations through systematic participation, scientific dissemination initiatives, with the General Practitioners Association and with the Medical Association of Rome.

The program also implements the systematic data collection for patient monitoring using the EUSOMA software and according with EUSOMA requirements and standards in order to be able to compete at European level.

Clinical Activities

1. The program is divided into the following phases:
2. Organization of activities: the assistance model
3. Patient access
4. Diagnostic phase: diagnostic therapeutic evaluation of the multidisciplinary team
5. Therapeutic phase
6. Follow-up
7. Advanced treatment of cancer

Clinical Activities

Developing strategies for permanent professional training and information addressed to the citizens are part of the scientific/informative activities of the Breast Unit

HPV Unit

Coordinator: Dr. Aldo Venuti, MD

Mission

To formalize an organizational model of a “unified and coordinated space” in which originate jointly initiatives related to the topic of HPV is the mission of HPV-Unit, in particular, the clinical management (diagnosis and treatment guidelines, facilitated routes and more), and the scientific matching (creation of ad hoc database, experimental researches, clinical trials, sharing of researches and more). This model is an instrument to inform, train and network both patients and health workers. Different health workers are involved in HPV-related pathologies as they span from gynecological area to skin, including ENT, urological and proctologic diseases. Finally, HPV-Unit provides for HPV vaccination of women and men.

Clinical Activities

HPV UNIT is involved in second level diagnosis of virus-associated cancers, not only HPV, but also EBV and polyomavirus in different anatomical areas. Main activity was focused on coordinating activities of different structures within the Unit. About 2000 patients were seen for HPV-related pathologies including women attending IRE Gynecology, males attending ISG STD and both women and men attending IRE ENT. Other activities of HPV-Unit were outpatients counseling and advising in preventive actions like individual screening or HPV vaccination. In particular, HPV vaccination was delivered to women as adjuvant therapy after conization; to adult men as prevention of HPV-associated pathologies and as adjuvant therapy for condylomata. HPV-UNIT is a coordinating Center for a large multicentric (V503-049) study on HPV vaccine for prevention of oral cancer. Enrollment was terminated reaching the assigned number of patients and a three-year follow-up is underway. Another clinical trial on circulating HPV DNA in oropharyngeal cancer is just started. HPV-Unit received a grant from LILT for an observational study of HPV-associated oropharyngeal cancer. In this study presence of HPV16 E5 oncogene expression will be evaluated by a specific assay developed within HPV-Unit. It is expected that E5 expression could define progressing lesions.

Research Activities

Scientific/informative activities of HPV-UNIT are for developing strategies to deliver information to citizens and for training health workers. In particular, HPV-UNIT is organizing the International HPV awareness day in partnership with IPVS to give information about HPV. Translational researches are main scientific activities of HPV Unit, as briefly summarized:

- Molecular biology.

It was developed a new micro-structured substrate for a sensitive ELISA for anti-HPV16 E7 Antibodies New immunotherapies of HPV-associated cancers.

New intrabodies targeting HPV16 E6 and E7 oncoproteins were developed and validated for therapy of HPV-associated tumors in HPV-UNIT-developed murine models. These intrabodies by intratumor delivering were able to decrease tumor growth.

- Molecular epidemiology.

It was evaluated the association between HPV infection and middle ear squamous cell carcinoma, and its prognostic role. Finally, during SARS-CoV2 pandemic HPV-UNIT was involved in studying and analyzing data on health worker immunological response to vaccines.

Department of Clinical and Experimental Oncology

Department Director
Message
Dr. Enrico Vizza

Medical Oncology 1 Unit

Head: Prof. Francesco Cognetti, MD

Staff

Dr. Paolo Carlini, MD
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Michelangelo Russillo, MD
Dr. Paola Malaguti, MD
Dr. Domenicangela Pellegrini, MD
Dr. Vanja Vaccaro, MD
Dr. Emanuela Dell'Acquila, MD
Dr. Vincenzo Pio Di Noia, MD
Dr. Alberto Fulvi, MD
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Agnese Provenziani, Data Manager
Marianna Ferrara, Data Manager
Alessandra Zambardi, Data Manager
Dr. Elisabetta Bozzoli, Data Manager
Barbara Conforti, Data Manager
Dr. Francesca Sabbatini, Secretariat
Massimo Zaratti, Nurse Coordinator
Maria Di Santo, Nurse Coordinator
Pietro Calabretta, Nurse
Roberto Ferro, Nurse
Gigliola Mammana, Nurse
Giovanni Cortese, Nurse
Emanuele Esposito, Nurse
Immacolata D'Orsi, Nurse
Maria Grazia Cioffi, Nurse
Ornella Barlone, Nurse
Massimo Colantoni, Nurse
Massimo Andaloro, Administrative Collaborator

Mission

The Division of Medical Oncology 1 has been dedicated for a long time and every day dedicates itself in diagnosing and treating solid cancers. The Division's clinical activity spends its efforts in guaranteeing the best evidence-based treatments and healthcare quality for cancer patients requiring therapy, disease monitoring and follow up. The fundamental strategy is based on a multidisciplinary approach to all clinical aspects in order to assure a personalized and integrated approach to the disease in the respect of the patient centrality and quality of life. Moreover, the activity of the Division is strictly devoted to the enrollment of cancer patients in clinical trials and to rapidly transfer them the results coming from clinical trials. The Division has been developing clinical research and new treatment strategies on solid tumors using both new immunotherapeutic agents such as checkpoint inhibitors or targeted agents for different tumors in addition to the classic antineoplastic drugs. The medical team is strongly oriented in promoting collaborative pathways with national and international working groups and scientific societies and in participating to the strategic aims of the Institute.

Activities

The Division of Medical Oncology 1 consists in 3 separate units:

1. the In-patient Unit which includes 22 beds dedicated to invasive diagnostic procedures, complex antineoplastic treatments, management of severe toxicities;
2. the Out-patient Unit dedicated to the first visit of new patients and clinical follow up and oncologic genetic counseling;
3. the Day Hospital Unit for administration of oral or intravenous antineoplastic drugs and eventually supportive care. Clinical activity is supported by weekly divisional meeting in order to share decisions on patients at first observation or in critical situations and to improve the internal standards of care.

Physicians of the Medical Oncology 1 are actively involved in all the Disease Management Teams (DMT), a multidisciplinary group of expert physicians who ensure to apply the best decision for each clinical scenario following the most recent state of the art in the management of each solid tumor, according to the national and international guidelines.

The main research topics of the Division is concentrated in introducing and using several new drugs (targeted or immunological checkpoint inhibitors) alone or in combination/sequence with chemotherapy, or in developing new strategies of integrated treatments in almost all solid tumors of the adults. The Division is committed to conducting national and international clinical trials in collaboration with industries or no-profit cooperative groups. During 2021, ... clinical studies were ongoing in different tumors, with the enrolment of ... patients. Field of interest of the Division is also the involvement in projects that investigate and promote patient's quality of life in collaboration with patient associations. The clinical research activity of the Division is sustained by ... fully trained data manager with expertise in conducting clinical trials in good clinical practice. Special emphasis is moreover given to the collaboration with basic researchers to identify molecular prognostic or predictive biomarkers. This latter activity is shared with the internal laboratories department and with the research branch of other national cancer institutes. The main field of activity is aimed at understanding the mechanisms of signal transduction to individuate and introduce novel and efficient therapeutic agents in small cohorts of patients. Several translational projects have been recently approved and financed, while others have been presented to obtain funds provided by national research organizations. In addition, most physicians of the Division are involved in scientific boards, guidelines editing groups, and in national and international network.

Medical Oncology 2 Unit

Head: Prof. Federico Cappuzzo, MD

Staff

Dr. Antonella Amodio, MD	Dr. Sara Becchetti, Nurse
Dr. Maddalena Barba, MD, PhD	Dr. Viviana Boncristiano, Nurse
Dr. Elisabetta Capomolla, MD	Dr. Chiara Brunetti, Nurse
Dr. Silvia Carpano, MD	Dr. Massimo Capezzuoli, Nurse
Dr. Francesca Conti, MD	Dr. Geolina Amora Jualita, Nurse
Dr. Eriseld Krasniqi, MD	Dr. Alice Leonardi, Nurse
Dr. Lorenza Landi MD	Dr. Marta Panuccio, Nurse
Dr. Chiara Manai, MD	Dr. Claudia Quaranta, Nurse
Dr. Gabriele Minuti MD	Dr. Martina Romano, Nurse
Dr. Giancarlo Paoletti, MD	Dr. Sabrina Pieretti, Nurse
Dr. Laura Pizzuti, MD	Dr. Stefano Bucci, Nurse
Dr. Domenico Sergi, MD	Dr. Biglione Anita, Nurse
Dr. Livia Tosetto, MD	Dr. Alessandro Busini, Nurse
Dr. Patrizia Vici, MD	Dr. Rossella Criscolo, Nurse
Dr. Marcello Maugeri-Saccà, MD, PhD	Dr. Alessandro Zennaro, Data Manager
Dr. Stefania Di Paolantonio, Chief nurse	Dr. Laura Canali, Data Manager
Dr. Valeria Colamartino, Chief nurse	Mrs. Anna Maria Edlisca, Executive Assistant
Dr. Arianna Bassotti, Nurse	

Mission

While encompassing the overall mission of National Cancer Institute Regina Elena the particular goals of the Medical Oncology 2 Unit (OM2) are to provide the highest quality of care to our patients and to advance the treatment of solid tumors, with special interest on thoracic malignancies, gastrointestinal cancers, neuroendocrine tumors, head and neck cancers, gynecology and urogenital tract cancers.

Our investigations involve many of the most promising molecularly targeted agents, immunotherapy and combinations of agents currently known. We emphasize rigorous study conduct and impeccable study design, and many of our studies have been developed through cooperative group mechanisms.

The OM2 staff directly responsible for patient care is comprised of 15 physicians, 14 nurses, 2 data managers. Among our physician team, 5 of them are dedicated to thoracic medical oncology patients, with the others who treat other diseases in those respective outpatient clinic areas.

Clinical Activities

The clinical activities of OM2 include an inpatient hospital service and outpatient clinics. All patients are evaluated by a specialized team of physicians according to their specific disease. All patients are screened for clinical trials and not eligible cases are candidate for standard medical oncology interventions including chemotherapy, hormone-therapies, target therapies, immunotherapy and/or supportive therapies. All cases are discussed with a multidisciplinary team, according to the specific site of disease.

Clinics: Oncology cases are followed and/or treated in a dedicated Day Hospital or in a specific unit. Outpatient visits are performed in dedicated rooms, according to the type of the disease (thoracic cancers, breast cancer, gastrointestinal cancer, neuroendocrine tumors, Head&Neck or gynecology cancers, genito-urinary cancer or melanoma). Two additional rooms are dedicated for visits of patients receiving active therapy in our day hospital. This service includes 13 chairs and 4 beds. The inpatient unit includes 22 beds dedicated to toxicity management, staging and therapy of complex cases,

clinical trials.

Research Activities

In 2021, our research pipeline focused mainly on genomic and clinical biomarkers of effectiveness and toxicity of anti-cancer treatments, with the aim of integrating clinical decisions for patients with solid tumors. All scientific activities are based on the active collaboration with other units (clinical, preclinical, diagnostic) and with other national and international cancer centers.

The interest is focused on thoracic malignancies and in phase I trials.

In lung cancer the Unit is now coordinating several national and international studies with immunotherapy or target therapies, in patients with non-small-cell lung cancer (NSCLC) or in small-cell lung cancer (SCLC). In all studies there is a relevant translational activity aiming at identifying molecular mechanisms involved in drug sensitivity or resistance.

Among these studies, please note the following:

- **ACC LUNG:** Validazione del pannello di geni lung acc nei pazienti con diagnosi di tumore polmonare non a piccole cellule (prospective, observational, no Profit study)
- **IMMUNOBLOOD** Studio prospettico per la valutazione dello sviluppo di anticorpi anti-inibitori dei checkpoint immunitari in pazienti trattati con immunoterapia (prospective, observational, no Profit study)
- **CAPLAND** Studio di fase II randomizzato, non comparativo, che studia la migliore sequenza di inibitori tirosin-chinasici del recettore del fattore di crescita epidermico (EGFR-TKI) nel carcinoma polmonare non a piccole cellule avanzato o metastatico (NSCLC) con mutazioni dell'EGFR (prospective, interventional, no Profit study)
- **oss NSCLC prog DURV** Studio osservazionale sulle strategie di trattamento in pratica clinica nei pazienti con NSCLC in stadio III in progressione a terapia di consolidamento con Durvalumab (prospective, interventional, no Profit study)
- **STARDUST** Studio di fase II che mira a valutare l'efficacia del Durvalumab (MEDI4736) come seconda linea di terapia nei pazienti con carcinoma al polmone non a piccole cellule che ricevono terapia (prospective, interventional, no Profit study)
- **SQUINT-FoRT 04 SQUINT** (Squamous Immunotherapy Nivolumab-Ipilimumab Trial): Studio in aperto, randomizzato, parallelo, non comparativo, di fase II su NivolumabStudio in aperto, randomizzato, parallelo, non comparativo, di fase II su Nivolumab piu' Ipilimumab versus chemioterapia a base di Platino piu' Nivolumab in pazienti affetti da carcinoma polmonare a cellule squamose metastatico o recidivante (SqLC) non pretrattati con chemioterapia (prospective, interventional, no Profit study)
- **AtezoMeso** "Studio di fase III con atezolizumab verso placebo in pazienti con mesotelioma pleurico maligno dopo pleurectomia/decorticazione" (prospective, interventional, no Profit study)
- **BRICE** Studio di fase 1/2 che studia la sicurezza, la tollerabilità e l'efficacia di BRIGatinib in combinazione con Cetuximab in pazienti con carcinoma polmonare non a piccole cellule avanzato (NSCLC) con mutazioni di EGFR o positivi per riarrangiamento di ALK o ROS1 e fase di espansione in pazienti con NSCLC EGFR mutati resistenti agli inibitori tirosin-chinasici di EGFR (EGFR-TKI) prospective, interventional, no Profit study)
- **MS201923-0050 (DDRIVER)** Studio di fase II, in aperto, a braccio singolo di Berzosertib (M6620) in combinazione con Topotecan in partecipanti con carcinoma polmonare a piccole cellule recidivante platino-resistente (profit study)
- **GO41854/SKYSCRAPER-03** Studio di fase III in aperto, randomizzato, sull'uso di Atezolizumab e Tiragolumab rispetto a Durvalumab in pazienti con carcinoma polmonare non a piccole cellule in stadio III, localmente avanzato e non resecabile, non andati incontro a progressione dopo chemioradioterapia concomitante a base di platino (SKYSCRAPER-03) (prospective, interventional, Profit study)
- **CA224-104** Studio di fase 2, randomizzato, in doppio cieco per valutare relatlimab piu' nivolumab in combinazione con la chemioterapia rispetto a nivolumab in combinazione con la chemioterapia come trattamento di prima linea per partecipanti con tumore polmonare non a piccole cellule (NSCLC) allo stadio IV o ricorrente (prospective, interventional, Profit study)

In addition, several other Phase I and phase I/II have been carried out:

- **4010-01-001 GARNET** Studio di fase 1 con aumento progressivo della dose e ampliamento delle coorti, per la valutazione di TSR-042, un anticorpo monoclonale anti-PD-1, in pazienti affetti da tumori solidi in stadio avanzato
- **TPX-0005-01** Uno studio multicentrico, in aperto, di fase 1/2, condotto per la prima volta sugli esseri umani per valutare la sicurezza, la tollerabilità, la farmacocinetica e l'attività antitumorale di TPX-0005 in pazienti con tumori solidi in stadio avanzato che ospitano riarrangiamenti dei geni ALK, ROS1 o NTRK1-3
- **BRICE** Studio di fase 1/2 che studia la sicurezza, la tollerabilità e l'efficacia di BRIGatinib in combinazione con Cetuximab in pazienti con carcinoma polmonare non a piccole cellule avanzato (NSCLC) con mutazioni di EGFR o positivi per riarrangiamento di ALK o ROS1 e fase di espansione in pazienti con NSCLC EGFR mutati resistenti agli inibitori tirosin-chinasici di EGFR (EGFR-TKI)R
- **LY-4008-101** Studio condotto per la prima volta sull'uomo dell'inibitore altamente selettivo di FGFR2, RLY-4008, in pazienti con colangiocarcinoma intraepatico (ICC) e altri tumori solidi in stadio avanzato
- **MCLA-128-CL01 (eNRGy)** Studio di Fase I/II su MCLA-128, un anticorpo bispecifico di tipo IgG1 full length diretto contro i recettori HER2 e HER3, in pazienti con tumori solidi (eNRGy)
- **BDTX-189-01** "Masterkey-01: Studio di Fase I-II, in Aperto, in Due parti, Multicentrico, per Valutare la Sicurezza, la Tollerabilità, la Farmacocinetica e l'Attività Antitumorale di BDTX-189, un Inibitore delle Mutazioni Allosteriche di ErbB, in Pazienti con Tumori Maligni Solidi in Stadio Avanzato"
- **MCLA-129-CL01** Studio di fase 1/2 di incremento della dose ed espansione volto a valutare MCLA-129, un anticorpo bispecifico umano anti-EGFR e anti-c-MET, in pazienti con carcinoma polmonare non a piccole cellule (NSCLC) avanzato e altri tumori solidi

Concerning solid tumors other than thoracic malignancies and phase I trials, we also adhered to several studies for breast cancer patients. Among these:

- **CLEE011A2404 (COMPLEMENT-1) COMPLEMENT-1:** studio di fase IIIb, multicentrico, in aperto per valutare la sicurezza e l'efficacia di ribociclib (LEE011) in combinazione con letrozolo per il trattamento di uomini e donne in pre/post-menopausa con carcinoma mammario in stadio avanzato positivo per i recettori ormonali, HER2 negativo, non sottoposti a terapia ormonale precedente per la malattia in stadio avanzato (prospective, interventional, Profit study)
- **MO39196 (IMpassion131)** Studio di fase III multicentrico, randomizzato, in doppio cieco, controllato con placebo, per la valutazione di Atezolizumab (anticorpo ANTI-PD-L1) in associazione a paclitaxel rispetto a placebo in associazione a paclitaxel in pazienti con tumore mammario localmente avanzato o metastatico, non trattato in precedenza, triplo negativo, inoperabile (prospective, interventional, Profit study)
- **IBCSG 48-14/BIG 8-13-POSITIVE** Studio volto a valutare gli esiti della gravidanza e la sicurezza dell'interruzione della terapia endocrina in giovani donne con carcinoma mammario ormono-sensibile che desiderano una gravidanza (POSITIVE) (prospective, observational, no Profit study)
- **TiLTStudy** Infiltrato linfocitario tumorale nel carcinoma della mammella triplo negativo pT1 pN0 (prospective, observational, no Profit study)

We also focused on the HIPPO pathway in locally advanced/metastatic gastric cancer, with the study "GR-2016-02362025 Validazione prospettica di una signature molecolare di danno al DNA e del pathway di Hippo in pazienti con tumore gastrico avanzato" (prospective, observational, no Profit study)

For gynecological tumors, we join several MITO projects, the in-ACTO study and participate to multicenter TRAMANT-01 trial, Terapia di mantenimento con Trabectedina dopo terapia di combinazione con Doxorubicina Liposomiale e Trabectedina verso terapia di combinazione con Doxorubicina Liposomiale e Trabectedina in pazienti affetti da carcinoma ovarico recidivato tra 6 e 12 mesi dopo chemioterapia a base di platino" (prospective, interventional, no profit study)

The head of the Unit, Prof. Cappuzzo, has received the followings grants (ongoing in 2021):

- 2018: Research grant from Fondazione Ricerca Traslazionale (FoRT) for the study "STARDUST: Phase II trial evaluating the efficacy of durvalumab as second-line therapy in Non-Small-Cell Lung Cancer patients receiving concomitant steroids"
- 2019: Research grant from Fondazione Ricerca Traslazionale (FoRT) for the study CAPLAND: "A randomized,

non-comparative, phase II study investigating the best epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) sequence in advanced or metastatic non-small-cell lung cancer (NSCLC) harboring EGFR mutations”

- 2019: Research grant from Fondazione Ricerca Traslazionale (FoRT) for the study NTRK: “NTRK 1,2,3 rearrangements in patients with solid tumors”
- 2019: Research grant from Fondazione Ricerca Traslazionale (FoRT) for the study BRICE: “A Phase 1/2 Study Exploring Safety, Tolerability and Efficacy of BRigatinib in Combination With CEtuximab in Subjects With Advanced EGFR mutated or ALK or ROS1 positive Non-Small Cell Lung Cancer and Expansion Phase in Subjects with Advanced EGFR mutated Non-Small Cell Lung Cancer who are resistant to EGFR tyrosine kinase inhibitors”
- 2019: Research grant from Fondazione Ricerca Traslazionale (FoRT) for the study “A phase II, two cohorts, randomized trial comparing standard of care versus immune-based combination in relapsed stage III non-small-cell lung cancer (NSCLC) pretreated with chemoradiotherapy and durvalumab”.

In 2021 a total of 29 paper have been published.

Anesthesia, Intensive Care and Reanimation Unit

Head: Dr. Ester Forastiere, MD

Staff

Dr. Cecilia Coccia MD,
Dr. Alessandra Costantino MD,
Dr. Maria Carla Sofra MD,
Dr. Piera Di Angelo MD,
Dr. Luana Fabrizi MD,
Dr. Federico Pierconti MD,
Dr. Francesca Romana Giordano MD,
Dr. Giulia Torregiani MD,
Dr. Marco Covotta, MD
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Dr. Emanuela Venti MD,
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Dr. Valeria Giorgerini MD,
Dr. Maria Elena Marcelli MD,
Dr. Antonio Calamaro MD,
Dr. Carmela Stigliano MD,
Dr. Gabriele Tola MD,
Dr. Marco Prologo MD,
Dr. Lorenzo Fabbrocile, MD
Dr. Giulia Maria Vitelli MD,
Dr. Paolo Moricca MD,
Dr. Ilaria Monteferrante, MD

Mission

The main activities concerning our unit are:

- Perioperative evaluation of surgical patients.
- Management of intraoperative anesthesiology.
- Perioperative assistance to patients undergoing surgery.
- Intensive care of medical and surgical oncologic patients.
- Non operating room anesthesia (NORA).
- Pain management of oncologic patients.

Management of in-hospital emergency.

Our unit deals with the perioperative management of patients for the following surgeries: thoracic surgery, urology, gynecology, plastic and reconstructive surgery, breast surgery, dermatology, neurosurgery, major orthopedic surgery, otorhinolaryngological surgery, digestive surgery, hepatobiliopancreatic surgery.

The organisation of pre-hospitalisation and the production of ad hoc perioperative clinical paths have contributed to the increase in minimally invasive surgery (laparoscopic and robot-assisted) with a total number of 500 robotic operations per year (2021), performed in Uro-Gynaecology, Thoracic Surgery, Colorectal Surgery, Hepatobiliopancreatic Surgery, and Otorhinolaryngologic surgery.

For intraoperative vital function monitoring, anaesthetists use newer tools, such as electrical impedance tomography for ventilation, Bispectral index for anaesthetic depth, TOF (train of four) for neuromuscular monitoring and cardiac output monitoring by wave contour analysis.

The doctors in our team are also actively involved in the management of acute postoperative pain both invasive (using peripheral, plexic and truncular anaesthesia) and non-invasive techniques such as patient controlled anaesthesia techniques

Anesthesiologists participate in the Disease management teams of the various surgical teams.

The intensive care unit is dedicated to surgical, oncologic and hematological patients.

In addition, our unit carries out anaesthesiological procedures in non-operating room: interventional radiology, bronchoscopy, digestive endoscopy, endoscopic retrograde cholangiopancreatography, EndoBronchial UltraSound-guided TransBronchial Needle Aspiration.

About pain therapy clinic, we deal with positioning of vascular accesses, treatment of oncologic pain with invasive and non invasive procedures.

Cinical Activities

Clinical research for the year 2021 was mainly focused on perioperative medicine and the management of cancer patients in the sars-cov-2 pandemic.

As a unit we collaborated in the following multicentre observational studies:

InPut - International Point Prevalence Study of Intensive Care Units Transfusion Practices PI: Alexander P.J. Vlaar, University of Amsterdam

Squeeze - (started in year 2020 and ended in year 2021) A prospective multi-centre international observational study of postoperative vasopressor use PI: Dr. Ib JAMMER, University of Bergen, Norway

We participated in the following national survey:

Emotional status and fear in patients scheduled for elective surgery during COVID-19 pandemic: a nationwide cross-sectional survey (COVID-SURGERY)

We initiated collaboration in the following prospective multicentre randomised clinical trial:

GUARDIAN - Tight Perioperative Blood Pressure Management to Reduce Serious Cardiovascular, Renal, and Cognitive Complications PI_ Prof Sessler, Cleveland Clinic

We have completed enrollment of the prospective study regarding esophageal pressure in patients undergoing a deep trendelenburg position.

We continued recruitment of the prospective randomised study of patients undergoing pulmonary monitoring by electrical tomography.

Hepato Biliaric Pancreatic Surgery Unit Head: Prof. GianLuca Grazi, MD, PhD

Staff

Dr. Marco D'Annibale, MD

Dr. Andrea Oddi, MD

Dr. Pasquale Perri, MD

Dr. Andrea Scarinci, MD

Dr. Giovanna Grazioli, Chief Nurse

Dr. Roberta Maccioni, Nurse Case Manager

Mission

To increase the knowledge for hepato-biliary-pancreatic diseases surgically treatable. To treat, to propose innovation in the evaluation and in the cure and to study neoplastic diseases of the liver, pancreas and biliary tree. To evaluate the application of newly proposed surgical techniques, such as laparoscopy and robotics. To improve the postoperative approach of the patients with specific protocols of enhanced recovery after surgery

To offer surgical treatment for neoplastic colorectal diseases in a multidisciplinary setting. To define specific paths, from first suspected diagnosis to the appropriate treatment. To establish a stable network for referral and management of patients with hepatobiliary, pancreatic and colorectal tumors, in the view of the Regina Elena National Cancer Institute acting as a tertiary referring center for patients carrying such neoplasms.

Cinical and Research Activities

This is a General Surgery Unit with the main task of treating diseases of the liver, pancreas and the biliary tract. The vast majority of these surgical procedures are performed for malignant diseases, but also complex operations needed for benign diseases are carried out.

Liver metastases from colorectal cancer are the condition for which the larger portion of the surgical procedures are performed.

The second most frequent disease is hepatocellular carcinoma, which can arise in cirrhotic and non-cirrhotic patients.

The remaining portion of liver resection are performed for cholangiocarcinomas, both in intrahepatic and in perihilar locations. The Unit is among the three of the Lazio Region Health System which constantly perform more than 50 surgical procedures for primary liver tumor each year.

There are a consistent number of procedures performed for pancreatic cancers, either for pancreas head or tail. Furthermore, the unit provides treatment for patients with colorectal neoplastic diseases. A multimodal approach for rectal cancers is usually offered to the patients.

A mini-invasive surgical program based on the laparoscopic and on the robotic techniques is fully active for hepatobiliary, pancreatic and colorectal procedures. 70 robotic liver resections have been already performed, including major procedures.

The average value of the DRG's produced by the Unit is 2.60.

Gynecologic Oncology and Oncofertility Center Unit

Head: Dr. Enrico Vizza, MD

Staff

Mission

Cinical Activities

Orthopaedics Unit

Head: Prof. Roberto Biagini, MD

Staff

Dr. Leonardo Favale, MD

Dr. Nicola Salducca, MD

Dr. Barbara Rossi, MD

Dr. Jacopo Baldi, MD, PhD

Dr. Carmine Zoccali, MD, PhD

Dr. Giovanni Meogrossi, Coordinator

Mrs. Grazia Amato, Nurse

Dr. Paolo Asquini, Nurse Quality Control Manager

Dr. Daniele Cacciarelli, Nurse

Dr. Fabio Conti, Nurse

Dr. Antonella Cutini, Nurse

Dr. Carolina Destito, Nurse

Dr. Monica Barrucci, Nurse

Dr. Sabrina Ganzenua, Nurse

Dr. Stefano Landi, Nurse

Dr. Alessia Milotti, Nurse

Dr. Alex Casula, Nurse

Dr. De Martino Stefania

Dr. Francesca Mastropietro, Nurse

Dr. Wioletta Faltyn, Nurse

Dr. Elisa Checcucci, Data Manager

Mission

The Oncological Orthopedics Unit offers cutting-edge solutions for all primary or secondary neoplasms of bone and soft tissues, involving the Musculoskeletal System in pediatric and adult age. We provide a comprehensive service to patients of all ages from the first consultation, through investigation, to multimodal treatment, rehabilitation and follow-up, seeing about 200 new patients with sarcoma each year. The surgeons deal with specific operative techniques for a dedicated surgery to cancer patients, which includes combined and sometimes complex procedures. The surgeons staff follow standard guidelines and widely accepted recommendations of good clinical practice (i.e. OECI certification) to manage patients affected from these rare disease and, as a part of the European Rare Cancer Network "EURACAN", it represents a center of excellence for Osteoncology.

Musculoskeletal Oncology requires the collaboration of numerous specialists both in the medical field (Oncologist, Radiotherapist, Nuclear Doctor, ...) and in surgery (General, Thoracic, Vascular, Neurosurgeon, ...). It also makes use of the experience of the Pathologist and the Radiologist. Twice a week takes place the Disease Management Team (DMT) meeting for the multidisciplinary discussion of clinical cases. As a reference center for sarcoma in Lazio region and Italy, many consultations and second opinions are requested to our unit by conventional orthopedic hospitals.

Our strong technological footprint supports the needs of surgeons and patients and uses tools such as intraoperative CT combined with navigation system and 3D printing prostheses.

The attention to research is due to the close and constant collaboration with the Biobanks of biological tissues and liquids, with the Institute's Research Laboratories and with the Skeletal Muscle Tissue Bank of the Lazio Region (BTMS) based in the IFOs. indeed, our aim is to perform translational and clinical research in this field.

Activities

The Oncological Orthopedics Unit of the Regina Elena Institute offers cutting-edge solutions for all primary or secondary neoplasms of bone and soft tissues, involving the Musculoskeletal System in pediatric and adult age.

As Sarcoma Unit we're honored to be members of National Network of Rare Cancers and European Rare Cancer Network EURACAN.

The Orthopaedic Unit is a Center of Excellence for Osteoncology and adheres to national and international guidelines from AIOM, ISG (Italian Sarcoma Group), ESMO and SIOT (National Society of Orthopaedic and Traumatology). Young pediatric patients with primary malignant neoplasms are treated at the Oncology Unit of the Bambino Gesù Children's Hospital in Rome. In selected cases, we collaborate with UOS of Hand Surgery of Ospedale Israelitico of Rome for recon-

structive surgery hand surgery and microsurgery. Patients with bone metastases are managed in collaboration with IRE Medical Oncology 2 Unit. Besides the medical and nursing staff above-described, 4 Residents from Umberto I Hospital “Sapienza” University alternate every 4 months to inward and surgical activities.

Patients who need surgery are hosted in the ward (13 regular beds). The ward has a fully furnished (and painted) pediatric room with telematic-teaching service (available for long-term patients), videogames, books and comics. All the patients' rooms are decorated with the intent of improving the hospitalization experience. Surgical activity is performed on 12h-long operating theatre/2 times a week, every month, in one of the eight operating room of the operating block. The orthopedic staff is always available on call in order to assure emergency room h24. The number of surgical interventions during 2021 accounts overall 288 procedures and the Unit counted a total of 252 inward patients.

Biopsies for bony or soft tissue lesions are performed, once a week, in a dedicated small operating room.

In 2021 a total of 176 surgical biopsies have been performed.

There are a total of three specialistic orthopedic outpatient clinics par week: on Monday for benign and low-grade malignant tumors; on Wednesday for high grade sarcomas (multidisciplinary clinic in collaboration with Oncologist and Psychologist); on Friday for metastatic disease involving musculoskeletal system. On the first Friday of every month there is a dedicated ultraspecialistic outpatient clinic for exostoses and cartilaginous tumors (benign to low-grade malignant) and other rare osteometabolic disorders. In 2021 a total number of 1317 visits were performed for high grade sarcomas (211 first visits).

The research activity carried out by the Oncological Orthopedics Unit focuses on:

- development of new surgical approaches, through the use of intraoperative CT combined with navigatio system, for the treatment of tumors of the pelvic girdle and spine;
- design and development of custom-made prosthetic implants made with the support of 3D printing whose results have been edited in a monograph published by a prestigious international publishing house;
- development of cell cultures starting from bone, tendon and muscle tissue aimed at the engineering of scaffolds made with 3D printer technology (in collaboration with the Faculty of Biology of the University of Rome “Tor Vergata”) result of PhD work published in high impact factor international journals;
- artificial intelligence for the characterization of cartilage matrix bone and soft tissue tumors still ongoing;
- prospective multicentric observational no profit study on patients surgically treated for bone metastases - SOFIA, in collaboration with Italian National Institute of Health ;
- medium-long term results of using the new R.O.M.A. prosthesis (resection oncological modular arthroplasty - Lepine®) for reconstruction after tumors resection of the proximal femur;
- spontaneous, multicentric, observational, prospective, open-label uncontrolled clinical study to verify the effectiveness of the DAC® (Denfensive Antibacterial Coating) gel kit in the prevention of septic complications in mega-prosthetic surgery in patients undergoing reconstruction after large bone resections;
- spontaneous, multicentric, observational, prospective, open-label uncontrolled clinical study to verify the effectiveness of the DAC® (Denfensive Antibacterial Coating) gel kit in the prevention of septic complications in patients undergoing reconstruction with megaprosthesis after large bone resections.
- retrospective observational comparative monocentric study on efficacy of virtual dmt during covid19 pandemic.

Brest Surgery Unit

Head: Dr. Claudio Botti, MD

Staff

Mission

Otolaryngology Head and Neck Surgery Unit

Head: Dr. Raul Pellini, MD

Staff

Dr. Valentina Manciocco, MD, PhD
Dr. Barbara Pichi, MD
Dr. Paolo Marchesi, MD
Dr. Jacopo Zocchi, MD
Dr. Francesco Mazzola, MD Specialist LP
Dr. Gerardo Petruzzi, MD, Specialist LP
Dr. Silvia Moretto, MD, Researcher
Dr. Flaminia Campo MD, Researcher
Dr. Antonio Martano, Audiometrist
Dr. Sonia Gambardella, Audiometrist

Dr. Alessandra Masiello, Speech Therapist
Dr. Maria Antonietta Picano, Nurse Coordinator
Dr. Alba Ara Pina, Nurse
Dr. Bruna Boldrini, Nurse
Dr. Serena Cucchiella, Nurse
Dr. Fernando Golino, Nurse
Dr. Marina Macis, Nurse
Dr. Iolanda Mantuano, Nurse
Dr. Francesco Mautone, Nurse
Dr. Debora Cacciato, Nurse Case Manager

Mission

We are committed to maintaining our status as leader in the discovery, innovation and implementation of the best practices, research and clinical care in otolaryngology and head & neck surgery.

We contribute to improve the health of individuals and populations through innovation and excellence in otolaryngology and head & neck surgical practice and research. Our program has a strong multidisciplinary translational approach focused on different aspects of Head and Neck Oncology.

Clinical Activities

Ear, nose and throat and maxillofacial oncological surgery. Treating of fairly common head and neck cancers to more complicated and difficult cases. Highly specialized surgical protocols and/or procedures are performed by the staff and every decision regarding clinical cases is submitted to the Head and Neck Disease Management Team, which includes specialists in surgery, radiation oncology, medical oncology, endocrinology, radiology, pathology, speech therapy, plastic and reconstructive surgery, dental and maxillofacial prosthetics, nutrition, and pain management. The group meets weekly and works together to meet their patients' diverse needs. The Unit of Otolaryngology Head and Neck Surgery provides a complete spectrum of head and neck services including Endocrine, Microvascular surgery and minimally invasive approaches or transoral robotics surgery

Research Activities

Human papillomavirus involvement in Head and Neck cancer.

Feasibility and efficacy of electrochemotherapy in Head Neck Cancer .

mRNA expression profiling in Head Neck Cancer.

Immunotherapy in Head and neck cancer.

Thoracic Surgery Unit

Head: Dr. Francesco Facciolo, MD

Staff

Plastic & Reconstructive Surgery Unit

Head: Prof. Roy De Vita, MD
Staff

Mission

Clinical Activities

Research Activities

Urology Unit

Head: Dr. Giuseppe Simone, MD, PhD

Staff

Dr. Umberto Anceschi MD, PhD

Dr. Alfredo Maria Bove, MD

Dr. Aldo Brassetti MD

Dr. Manuela Costantini MD, PhD

Dr. Maria Consiglia Ferriero MD, PhD

Dr. Salvatore Guaglianone MD

Dr. Riccardo Mastroianni, MD

Dr. Leonardo Misuraca MD

Dr. Gabriele Tuderti MD, PhD

Mrs. Ashanti Zampa, Data Manager

Dr. Giulia Rosati, Data Manager

Dr. Silvia Cartolano, Research Nurse

Dr. Giuseppe Spataro, Research Nurse

Mission

The Urology Department mission is focused on providing the highest quality of medical and surgical care to uro-oncology patients, developing and standardizing complex surgical procedures in uro-oncology, and expanding indications for minimally invasive procedures especially robot- assisted procedures. We have gained considerable experience in robotic radical cystectomy with totally intracorporeal reconstruction of orthotopic and etherotopic diversions, robot assisted radical nephrectomy with inferior vena cava tumor thrombectomy and in minimally invasive off clamp partial nephrectomy. All these complex surgical procedures are today a standard of care in our Institution.

We also developed several uro-oncologic research lines, targeting those diseases with the highest incidence and, with the strongest impact on life quality and healthcare costs. Clinical research investigates new minimally invasive surgical techniques, imaging advances in early cancer detection or imaging-guided surgery and oncologic outcomes after surgical treatments as our main research objectives. Translational research on molecular biomarkers, genetic and microenvironment tumor profiling, stem cells investigation, together with new precision medicine diagnostic. The Urology Unit has also been National site coordinator of observational studies, and it is involved in multiple clinical trials on prostate cancer treatments, renal cancer and urothelial cancer.

The paramount advantage obtained by conducting basic science and translational research along with clinical research, is represented by the solid bridge we built between the bench and the bedside.

Activities

In terms of basic science, we have published studies validating urine LOX-1 and Volatilome as a less invasive tool for early diagnosis of renal cancer. With the same aim, we validated the proteomic profiling of serum-derived extracellular vesicles in prostate cancer.

In terms of clinical research, we investigated every step along the patients' care pathway, including the diagnostics, the intra- and peri-operative procedures and the patients' follow-up.

In 2021, 10 manuscript have been published on indexed international Journals by our research group, on bladder cancer, often in collaboration with other tertiary centers across Europe or US. In particular we investigated:

1. impact of surgeon's learning curve on long-term functional outcomes after robot assisted radical cystectomy (RARC) with intracorporeal neobladder, proving that patients treated at the beginning of the learning curve show worse perioperative and functional results.
2. Late complications of RARC with totally intracorporeal urinary diversion. Results were in line with those of open

radical cystectomy, supporting the robotic approach as a safe and effective surgical option for the treatment of muscle-invasive bladder cancer in tertiary referral centers.

3. The oncologic outcomes of Variant Histology Bladder Cancer after Radical Cystectomy, showing that it is associated with greater recurrence risk than urothelial bladder cancer. Hence, we presented a personalized approach for surveillance.
4. Accuracy of Transurethral Resection of the Bladder (TURB) in Detecting Variant Histology of Bladder Cancer Compared with Radical Cystectomy, showing relatively low accuracy of TURB, and underlying the need of additional diagnostic tools in order to identify variant histology at precystectomy time improving patient survival outcomes.
5. We assessed the oncological outcomes of three different bacillus Calmette-Guérin strains in patients with high-grade T1 non-muscle-invasive bladder cancer, proving that Moreau and TICE strains might be superior to the RIVM strain in terms of recurrence free survival.
6. The role of adjuvant chemotherapy in patients with bladder cancer variant histology treated with radical cystectomy with curative intent, concluding that adjuvant chemotherapy did not provide any survival benefit in terms of overall recurrence and cancer specific mortality.
7. We assessed whether the absence of detrusor muscle in TURB specimens for Ta low-grade urothelial carcinoma impacted the recurrence free survival, proving that it had no impact, and therefore it doesn't require additional attention.
8. We conducted a multi institutional study to validate a novel nomogram to predict cancer specific survival in patients treated with radical cystectomy for bladder cancer (COBRA nomogram).
9. We investigated the impact of delaying intravesical BCG immunotherapy after TURBT for non-muscle invasive bladder cancer, proving that it is associated with an increase of tumor recurrence and progression.
10. The impact of treatment modality on survival in non-metastatic patients with clinical node-positive bladder cancer, proving a beneficial effect in terms of overall survival when treated with induction chemotherapy followed by radical cystectomy with lymphadenectomy when compared to surgery alone.

Since our Department has a leading experience in the field of minimally invasive, off clamp, nephron sparing surgery for renal malignancies, many research projects have been carried out during 2021, and results published on international indexed journals. Among all, we investigated:

1. Long term (7 years) outcomes after RAPN, showing an overall survival (OS) of 92%, cancer specific survival (CSS) of 98% and disease-free survival (DFS) of 92%. Only 20% of the patients showed chronic kidney disease (CKD). These excellent outcomes are comparable to those achieved in historical series of open and laparoscopic surgery.
2. Functional and oncologic outcomes after RAPN for clinical T3a renal masses across several tertiary centers, using a Trifecta composite outcome. The trifecta achievement rate was 64%. Greater age, increasing "RENAL" nephrometry score, and blood loss >300ml were predictive of trifecta achievement failure. OS, CSS and DFS were 91%, 93% and 82% respectively, confirming acceptable survival and functional outcomes in experienced hands.
3. Outcomes after RAPN for completely endophytic renal tumors through a Trifecta composite outcome. This multicentric study showed a trifecta achievement rate of 51%. Tumor size is the only predictor of trifecta achievement.
4. Outcomes of RAPN for "very small" (<2cm) renal masses. This multicentric series showed a trifecta achievement of 91% with minimal complication incidence. As such, we concluded that whenever an active treatment is indicated, RAPN represents a minimally invasive option that provides excellent outcomes with minimal impact on renal function and negligible risk of complications.
5. The impact of anticoagulant and antiplatelet drugs therapy on perioperative outcomes after purely off clamp RAPN, proving that in expert hands the use of anticoagulant and antiplatelet is associated only to an increased risk of perioperative transfusions (11% vs 5%), without increasing complication incidence.
- 6) Risk factors for CKD progression after RAPN in elderly patients. This multicentric analysis documented how hypertension, on-clamp approach and failure to achieve Trifecta were independent predictors of progression to severe chronic kidney disease.
7. Perioperative and functional outcomes after on-clamp RAPN versus off-clamp RAPN in solitary kidneys. This multicentric study demonstrated how on-clamp RAPN is associated with higher risk of progression to CKD stage 3, 4 or 5, and higher perioperative complication rate than off clamp RAPN. Multivariable analysis identified eGFR at discharge and warm ischemia time as independent predictors of progression to CKD.
8. Impact of learning curve on perioperative outcomes after off-clamp RAPN. This propensity score matched comparison between training vs expert series showed negligible differences between groups in terms of hospital stay,

hemoglobin and renal function at discharge. However, such results are achievable only if the training surgeon has already a consolidated experience in minimally invasive surgery.

9. Impact of histology and tumor grade on clinical outcomes beyond 5 years of follow-up after surgery for Renal cell Carcinoma (RCC). Analysis on a large series (1679 patients) strongly supported histology- and grade-tailored surveillance strategies and long-term follow-up for RCC patients, since after 5 years the overall probability of metastasis or recurrence was high, even for less aggressive histological subtypes, such as papillary RCC type 1 (35%) and grade I clear cell RCC (17%). However, collecting duct carcinomas and high-grade clear cell RCC presented the worst survival outcomes.
10. Finally we compared our novel Trifecta to the standard one, to predict oncologic and functional outcomes after robotic assisted partial nephrectomy (RAPN). Results proved how the Trifecta originally described as comprehensive measures of perioperative outcomes, needs to stand the test of time. Compared to the “old” one, our novel Trifecta is an independent predictor of clinically significant endpoints such as survival and End-stage renal disease development probabilities.

We also conducted a research line focused on Prostate Cancer (Pca). Five papers have been published during 2021, on international indexed journals reporting the results of our investigations in cooperation with the main referral centers across Euaope/USA on this topic and in particular:

1. We investigated the efficacy in terms of detection rate of Fusion ultrasound/MRI prostate biopsy using a computer aided diagnostic system “CAD”. Results confirmed an improvement in detecting clinically significant Pca located in the anterior/transitional zone.
2. We validated a prediction tool based on multiparametric magnetic resonance imaging (MRI) parameters and MRI-targeted biopsy predicting extracapsular extension and seminal vesicle invasion at radical prostatectomy for Pca patients. An improvement of patient selection was not clearly demonstrated when compared with available models based on clinical parameters, and implementation of MRI in this setting still needs to be clarified.
3. We investigated the potential impact of delayed radical prostatectomy (due to COVID-19 pandemic) on oncological outcomes. Delay of several months did not adversely impact oncologic results for intermediate- and high- risk Pca, supporting the tendency of deferring surgery, in line with urologic societies’ recommendation during COVID pandemic
4. We analyzed efficacy and safety of Enzalutamide in metastatic, castration resistant, Pca patients. The analysis of multicentric data showed an effective and safe profile of Enzalutamide in patients affected by a metastatic, castration resistant, Pca.
5. We reviewed indications for, and complications of pelvic lymph node dissection in prostate cancer, externally validating the accuracy of available nomograms to predict lymph node invasion (LNI) in Pca patients. In particular we tested the performances of the following nomograms: Memorial Sloan Kettering Cancer Centre (MSKCC), Briganti 2012, Briganti 2017, Briganti 2019, Partin 2016 and Yale model. All those nomograms had similar performances and limitations in the prediction of LNI. However, in patients with only systematic biopsy, the MSKCC and Briganti 2012 nomograms were superior in the prediction of LNI. The overall lymph node dissection related complication rate was 9%.

Ongoing participation to international clinical trials are aimed to explore novel molecular targets for RCC recurrence early diagnosis, high risk prostate cancer management, muscle invasive bladder cancer treatment strategies.

Haematology and Stem Cell Transplantation Unit

Head: Dr. Andrea Mengarelli, MD

Staff

Dr. Paolo Falcucci, MD
Dr. Svitlana Gumenyuk, MD
Dr. Francesco Marchesi, MD
Dr. Francesca Palombi, MD
Dr. Francesco Pisani, MD
Dr. Daniela Renzi, MD
Dr. Atelda Romano, MD
Dr. Antonio Spadea, MD
Dr. Elena Papa, MD, Quality Manager, Clinical Research Collaborator
Dr. Emanuele Sbraga, Data Manager
Dr. Caterina Viggiani, Nurse Coordinator
Dr. Gianluca Falzone, Nurse
Dr. Ambra Albertini, Nurse
Dr. Anna Attico, Nurse

Dr. Giuseppina Cafarella, Nurse
Dr. Roberta Capobianco, Nurse
Dr. Eleonora Cerasoli, Nurse
Dr. Antonio Ciccotto, Nurse
Dr. Silvia Di Fraia, Nurse
Dr. Katia Di Prospero, Nurse
Dr. Graziella De Luca, Nurse
Dr. Andrea Longo, Nurse
Dr. Marco Prete, Nurse
Dr. Anna Petrucci, Nurse
Dr. Fabrizio Pochettino, Nurse
Dr. Romina Riccio, Nurse
Dr. Simona Sgromo, Nurse
Dr. Raffaele Speranza, Nurse

Mission

The Hematology and Transplant Unit identifies its own reason for existence with the provision of care services and assistance of patients with hematologic malignancies, according to the policy and mission of the IRCCS Regina Elena National Cancer Institute of Rome. In this framework, through scientific research, the development of medical knowledge and collaboration with other organizations at national and international level, Unit resolved to be a center of excellence for the diagnosis and treatment of such pathologies. Hematology and Transplant Unit is specialized in the evaluation, treatment and care of patients with lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome and myeloproliferative disorder. Although chemotherapy remains an integral component of the treatment for most hematologic malignancies, the development and use of disease-specific or targeted therapeutics or biomarkers represents the research goal of our Unit investigators.

Treatments are delivered according to National and International clinical trials coordinated by Companies and cooperative groups (like GIMEMA, FIL, EORTC, IELSG) involved in the treatment of several hematological malignancies. For patients outside clinical trials, treatments are delivered according to Guide-Lines proposed by the most important Italian (SIE-SIES-GITMO) and International (ESMO-ELN-NCCN) hematologic clinical societies. Moreover, in order to better standardize the diagnostic and therapeutic algorithms for patients outside clinical trials, five PDTA (Percorsi Diagnostici Terapeutici Assistenziali Aziendali) were recently updated by the Institute for the following malignancies: acute myeloid leukemia, chronic myeloid leukemia, follicular lymphoma, multiple myeloma and diffuse large B cell lymphoma.

Stem cell transplantation often is indicated for the treatment of hematologic malignancies. Our Unit is one of the 6 Institutions located in Rome who belongs to Rome Transplant Network (RTN), a Metropolitan Hematopoietic Stem Cell Transplant Program for adult patients established as a cooperative network. RTN is an innovative entity, which follows rules and standards established by the Joint Accreditation Committee ISCT-EBMT (JACIE) accreditation program. In June 2013, Policlinico "Tor Vergata" University Hospital, Regina Elena National Cancer Institute and Campus Biomedico University Hospital have been found to meet the standards of the JACIE for Autologous & Allogeneic Transplantation in Adult Patients, as certificated on 21.01.2014; the renewal of certification took place on 18.01.2021.

In 2021 RTN registered 180 Transplants (54 allogeneic and 126 autologous), 31 of them performed in our Unit.

The objectives of the RTN are: 1) to standardize transplants procedures; 2) to improve quality of transplant care; 3) to extend the potential of transplant activity over the metropolitan area; 4) to share expertise and professional education among healthcare providers; 5) to promote excellence of single transplant Centres; 6) to rationalize cost-management of public health. The effort of Hematology and Transplant Unit was aimed at carrying out clinical trials of primary relevance in different hematological malignancies working in cooperation with other hematological institutions. In particular, our Unit is a member of the following cooperative group: Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA), European Organisation for Research and Treatment of Cancer (EORTC), Fondazione Italiana Linfomi (FIL), International Extranodal Lymphoma Study Group (IELSG), Gruppo Romano Mielodisplasie (GROM), Gruppo Laziale Sindromi Mieloproliferative Croniche Ph1 neg.

Sorveglianza Epidemiologica Infezioni Fungine in Emopatie Maligne (SEIFEM), Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON), Gruppo Italiano Trapianto Midollo Osseo (GITMO).

Research Activities

COVID-19 and anti-SARS-CoV-2 vaccine in hematological malignancies

During 2021 our research activity in the field has allowed to publish several original papers both from single Institution and multicenter studies concerning COVID-19 epidemiology, BNT162b2 immunogenicity and safety, breakthrough SARS-CoV-2 infections and antibody kinetics after primary BNT162b2 vaccine in patients with myeloproliferative and B-cell derived malignancies. Overall, the rate of breakthrough SARS-CoV-2 infections and COVID-19 after BNT162b2 vaccine may be higher in immunocompromised people than general population. Alongside clinical outcomes, serologic and/or cellular testing to assess immune response to SARS-CoV-2 vaccines are a landmark for studies on immunocompromised populations, although the exact correlation between antibody levels and protection from COVID-19 remains uncertain

Biofilm in hematologic malignancies patients with bloodstream infection (BSI)

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a prominent cause of nosocomial infections associated with high rates of morbidity and mortality, particularly in oncological patients. The hypermucoviscous (HMV) phenotype and biofilm production are key factors for CRKP colonization and persistence in the host. Our research activity in 2021 aimed at exploring the impact of CRKP virulence factors on morbidity and mortality in oncological and hematological patients. Carbapenem resistance-associated genes, antibiotic susceptibility, the HMV phenotype, and biofilm production were evaluated. The non-HMV phenotype and strong biofilm-producing strains were associated with increased CRKP infection-related mortality. Notably, the multivariate analysis showed that infection with strong biofilm-producing CRKP was an independent predictor of mortality. CRKP infection caused a high risk of death among oncological patients, particularly when pneumoniae and sepsis were present. In infected patients, the presence of strong biofilm-producing CRKP significantly increased the risk of death. Thus, the assessment of biofilm production may provide a key element in supporting the clinical management of high-risk oncological patients with CRKP infection.

Circulating and tissue microRNAs in Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL is an aggressive, heterogeneous neoplasm where prognostication and therapeutic decision are challenging. The available prognostic tools are not able to identify all patients refractory to treatment. MicroRNAs, small RNAs frequently deregulated in cancer, stably circulate in biofluids, representing interesting candidates for non-invasive biomarkers. In 2021 we validated serum miR-22, an evolutionarily conserved microRNA, as a prognostic/predictive biomarker in DLBCL. Moreover, we found that its expression and release from DLBCL cells were related to therapy response and adversely affect cell proliferation. These results suggest that miR-22 is a promising complementary or even independent non-invasive biomarker for DLBCL management.

Transcriptional and epigenetic landscape in Multiple Myeloma (MM)

During 2021, we aimed to identify the transcriptional and epigenetic mechanisms responsible for the resistance of MM patients treated with first-line chemotherapy schemes by characterizing the transcriptome in order to quantify neo-

plastic cells that have the same gene/epigenetic profile as the treatment-resistant cell population. A prospective multi-center clinical study is underway, in collaboration with the Hematology Unit of the Tor Vergata University and Campus Bio-Medico University of Rome. The ultimate goal of this project is to be able to understand the epigenetic mechanisms underlying resistance to treatments for multiple myeloma and to be able to personalize the therapy based on the genomic background of the disease.

Multomics characterization of acute myeloid leukemia (AML) and aggressive B-cell lymphomas

During 2021, a collaborative study on behalf of Onco-Hematology Working Group of Alliance Against Cancer aimed to perform a multiomics analysis of hematologic malignancies. In particular, we aim to study through Whole-Exome Sequencing (WES) bone marrow samples of secondary and therapy-related AML patients treated with CPX-351, in order to better understand the genomic basis of treatment resistance in this high-risk group of patient. As for aggressive B-cell lymphomas, we aimed to highlight new genomic factors of chemo-resistance in patients with primary mediastinal B-cell lymphoma through T-GEP (nanosting platform) and T-NGS (146 genes) analysis on FFPE samples of enrolled patients.

Target therapies

The efficacy and safety of Zandelisib, a new PI3K delta inhibitor with high target-binding affinity, administered on intermittent dosing in patients with relapsed or refractory follicular lymphoma, was primarily analysed from the global phase 2 TIDAL study at the end of 2021. Results will be reported during ASCO and EHA Congress in 2022.

Psychological Functioning and quality of life after autologous stem cell transplantation in patients with hematological disease

This project continued in 2021. The objective of this prospective longitudinal study is to assess the impact of graft on the quality of life and psychological functioning of adult patients undergoing ASCT, and to identify potential demographic, clinical, and psychological predictors of variables under study. The hypothesis is that patients with high scores of physical well-being, more education, lower levels of anxiety and depression, more resilient, more adaptive coping strategies, higher self-efficacy and increased social support before transplantation are those with better quality of life and psychological functioning immediately after transplantation and in a one year follow-up. In 2019 we completed the enrollment in the study for an overall population of 80 patients; in 2021 we continued follow-up evaluation of all patients enrolled in the study and administered a total of 286 questionnaires for measuring the quality of life, the perceived social support, the psychological distress, the resilience and self-efficacy before and after transplant procedure. Data analysis and manuscript preparation is ongoing.

Digitalization

Progettoema.it is a software whose system features are diversified and projected to allow the construction of disease-specific data-bases and is designed to meet the most important control requirements of the clinical endpoints such as survival, relapse, effectiveness of treatment protocols and more. This system provides for the transfer of clinical data of about a thousand of patients from paper to electronic format. In recent months the database has been continuously updated and modified according to the needs which arise during data entry. The work that has preceded the actual data entry aimed at recovering all the records of patients who died, were lost or left the follow-up. A computer file was then created in which 1500 patients are included. The Unit chose to start with two diseases: Follicular Lymphoma (FL) and Diffuse Large Cell Lymphoma (DLBCL). To date 200 patients were included with FL and 368 patients with DLBCL. The activity of the Secretariat and Data Manager also provides the database update of DMT and satisfaction questionnaires.

Clinical Trials

In 2021, Dr Marchesi won intramural funds from the Italian Ministry of Health as young researcher with the research project entitled "A restricted signature of circulating/serum miRNAs in diffuse large B-cell lymphoma: from the molecular function to the clinical application" (Prot. N. 14614 November 17th, 2021).

Speeches

9th European Conference on Infections in Leukemia (ECIL-9). COVID-19 in Hematology-Oncology patients: working group guidelines presentation. Virtual Conference, September 16th, 2021 (Dr Marchesi)

Vaccinazione anti SARS-CoV-2 nei pazienti ematologici. Congresso internazionale COVID-19 e fragilità. Il virus delle disuguaglianze alla prova dei vaccini e del PNNR. Roma, 1-2 luglio 2021 (Dr Marchesi)

-Il ruolo del BAL nella diagnostica degli infiltrati polmonari nei pazienti con neoplasia ematologica. Corso FAD Le complicanze infettive nel paziente immunocompromesso con malattia ematologica maligna. Formazione FAD a distanza, 30 giugno 2021 (Dr Marchesi)

Sarcomas and Rare Tumors Unit Head: Dr. Virginia Ferraresi, MD

Staff

Sabrina Vari, MD

Concetta Elisa Onesti, MD PhD

Wioletta Faltyn, Nurse Caswe Manager

Elisa Checcucci, EURACAN Project Secretary

Silvia Bastucci, Data Manager

Marianna Introna, Data Manager

Francesca Nardoza, Data Manager (RARITY Trial, ACC)

Mission

Rare Tumours (RT), that accounts for less than 6 cases/100.000 inhabitants/year, represent overall about 25% of all new malignancies and affect about 900.000 patients each year in Italy.

These tumors notoriously represent an unmet clinical need due to various problems. Among them there are: a) epidemiological issues because of their difficult systematization and classification that prevent the annotation of all cases in a well standardized national register; b) frequent diagnostic errors and delays especially outside referral centers that lead to therapeutic inadequacy; c) difficulties in producing guidelines based on recommendations with high levels of evidences due to the low number of patients; d) poor molecular knowledge which means that innovative treatments and target therapies are much less available for RT than for any other neoplasm; e) low interest of pharmaceutical companies not so attracted by therapeutic areas deemed unprofitable. This series of difficulties unfortunately translates in a worse prognosis than patients with frequent tumors and RT therefore require special management because they are “orphan” diseases from many points of view.

With a yearly admittance of about 1,000 new cases, IRCCS Regina Elena National Cancer Institute (IRE) represents one recognized center for the diagnosis and treatment of rare solid tumors. Over the past 10 years, Istituti Fisioterapici Ospitalieri (IFO) played an active role in the collaborative efforts of the national network on RT (Rete Tumori Rari, RTR) with a particular interest in soft tissue sarcomas and GIST. Since 2016 IFO are moreover involved in EURACAN (EUropean network for Rare Adult solid CANcer) and have become a European referral center for eight RT (soft tissue and bone sarcomas, rare neoplasm of male genital organs and urinary tract, neuroendocrine tumors, rare neoplasm of digestive tract, rare neoplasm of endocrine organs, rare neoplasm of the thorax, rare neoplasm of the skin and eye melanoma, brain and spinal cords tumors).

The deliberation in IRE of a departmental Unit specifically dedicated to RT arises from the forementioned cultural background of our Institutes and from the endowment of multidisciplinary expertise covering all therapeutic areas by anatomical sites. The Departmental Unit on Sarcomas and Rare Tumors (UOSD SRT) was activated in June 2020. Thanks to the decennial experience of the chief, Dr. Virginia Ferraresi, the UOSD is specifically addressed to the diagnosis, medical management and translational research of bone and soft tissue sarcomas and aggressive benign musculoskeletal diseases. Dr. Ferraresi is moreover the representative on behalf of IFO in EURACAN and the UOSD has a role of coordination of the institutional activities on RT under the European network.

Clinical cases of sarcomas of any anatomical origin having access to IFO are managed by the Sarcoma Disease Multidisciplinary Team (DMT) that meets on a biweekly basis in order to assure an adequate clinical, radiological and pathological assessment leading to a correct diagnosis and an appropriate treatment as per current national and international guidelines. Two outpatient multidisciplinary clinics are dedicated every week for new patients and patients in follow

up. One outpatient clinic is composed by an oncologist of the UOSD SRT, an orthopedic surgeon and by a dedicated psychologist and is aimed at patients with sarcomas of extremities, pelvis, spine, and trunk. The other one is managed by the oncologist and by an abdominal surgeon and is addressed to patients with visceral and dermic sarcomas and other RT. A dedicated case manager is also committed to facilitating patient management in the diagnostic-therapeutic process. The UOSD SRT is also equipped with inpatient ward to manage complex chemotherapy regimens, severe side effects or invasive diagnostic procedures and with Day Hospital spaces for chemotherapy, immunotherapy, target therapies and medical infusion support.

Clinical Organizational Activities

In order to facilitate the access of patients with Rare Tumors and Diseases to IFO and to offer them dedicated diagnostic and therapeutic pathways, in December 2020 an helpdesk was activated and its activities were then implemented during 2021. The service is coordinated by a doctor and also include a case manager and an administrative employee. Via emails, phone call, or on sight access, the help desk filters request for information and/or taking charge directing patients to the most suitable clinics under the supervision of the UOSD SRT as concern RT.

The UOSD SRT also had a coordinating role in the data collection activities relating to all new cases of patients with RT who accessed the IFO. Since 2016 all new cases of rare malignancies are recorded on an internal platform called “EURACAN platform” thanks to a pool of data managers actively involved in this task. The continuous updating of the platform leading to an accurate counting of the new patients and of the research activities that revolve around RT are then reported on a bi-annual basis at European level. In fact, the main objective of EURACAN project is to improve the quality of care of all European patients affected by rare cancers enabling a major improvement in the access to centers of excellence for diagnosis and treatment and unifying the availability of optimal clinical practices in the EU by centralizing knowledge, experience, medical research, training, and resources. A European Collaborative Platform and a Clinical Patient Management System (CPMS) are also active in order to discuss and to share clinical cases of patients with rare tumors all over the European centers of the network and IFO domain leaders are actively involved in virtual meetings and asked to participate in panel of experts.

For some RT (including soft tissue and bone sarcomas) a regular process of institutional biobanking of blood and pathologic specimens is ongoing.

Scientific Activities

Regular translational meetings involving clinicians and researchers dedicated to RT under the supervision of our Scientific Direction, continued to be held in 2021 in virtual modality due to the persistence of pandemic emergency.

In 2020-2021, IRE became one of the 9 EURACAN and OECI Italian National Cancer Institutes of project RARITY. The project is sponsored and funded by Alliance Against Cancer (ACC) and aims to initiating the Italian part of the EURACAN registry (STARTER project). Aims of the Project are to set-up the IT (Information Technology) platform of the Italian part of the EURACAN registry to prospectively collect clinical data on rare adult cancers and clinically annotated virtual biobanking data for carrying out real world data collaborative research in Italy and Europe. The platform of the Italian project will be interoperable with the EURACAN registry and will cover all EURACAN domains. Its objectives will be: a) to help describe the natural history of rare adult solid cancers; b) to evaluate factors that influence prognosis (e.g. mortality, survival, progression free survival) and treatment response; c) to assess treatment effectiveness (systemic, radiotherapy, surgery, target therapy, immunotherapy and possible combinations); d) to measure indicators of quality of care (diagnostic and staging procedures, treatment strategies, follow-up etc.).

Always in the context of the activities related to the EURACAN project, Rare Tumors Translational Group has been participating in the European trial ARCAGEN (EORTC-SPECTA) whose aim is to perform a molecular characterization of rare cancers on retrospective and prospective biological samples. Retrospective cases have been collected and the accrual of prospective cases is actively ongoing thanks to the active participation of the institutional biobank.

Remaining within the framework of scientific research organizations, Dr. Ferraresi is part of the working groups of Sarcomas and of Musculoskeletal Tumors of ACC. In ACC, since 2021 IRE is the coordinating center of PROGENSARC trial. PROGENSARC is a multicenter retrospective trial involving Italian reference center for sarcomas. It is aimed to as-

sess the aptitude for the use of of genomics profiling methods for therapeutic purposes and evaluation by institutional Molecular Tumor Board (MTB) in patients with advanced sarcomas without valid therapeutic alternatives or with histotypes known to be chemoresistant and without driver mutations already validated at the therapeutic level.

It is known that access to referral centers, often far from one's residence, is a factor that can influence the prognosis in patients with RT. In order to assess the impact of the COVID-19 pandemic in RT such as sarcomas and aggressive benign musculoskeletal tumors, a retrospective study (SarCorD, Sarcoma Coronavirus diagnostic Delay) was conducted in 2021. Primary objective of the study was to determine on a consecutive series of patients visited at the IRE Sarcoma Clinic between 9.03.2020 (date on which the national lockdown was declared) and 8.03.2021 whether the COVID-19 pandemic has resulted in a diagnostic delay compared to a historical control of the same population. Secondary objectives were also to assess the impact on the stage at diagnosis, survival outcomes (DFS, PFS, OS), the number of first visits, and the number of patients included in clinical trials. The quality of life and the emotional and psychosocial impact of the pandemic on the diagnostic-therapeutic process of the disease were also investigated. The results of the study are currently under evaluation and will be the subject of a publication. Preliminary results seem however to show that the pandemic led to a delay in diagnosis but not in the initiation of treatment when the patient was managed, as in our case, in a referral center.

In 2021, retrospective observational studies on osteosarcoma and Ewing's sarcoma with both localized and metastatic disease were activated in the Unit.

Accrual was also continued in prospective clinical trials evaluating new class of agents in advanced soft tissue sarcomas such as olaparib, a PARP-1 inhibitor, in combination with trabectedin (TOMAS2 trial). A multicenter phase 1-2, open-label study evaluated moreover the safety and activity of DCC-3014, a selective CSF1R inhibitor, in patients with advanced tumors and Tenosynovial Giant Cell Tumors (TGCT). TGCT is infact a neoplasm featuring non malignant macrophages as the predominant cell type within the tumors and is characterized by aberrant over-production of CSF1 ligand caused by a translocation at a genomic level driving recruitment of macrophages leading to local destruction of joints. Based on the experience gained on this rare benign but highly disabling pathology and the collaboration with our Department of Orthopaedic, two international phase 3 trials (MOTION study and SynOx SNX-301-020 study) are currently being activated at the UOSD SRT.

Other lines of research have explored the area of nutrition and factors related to the development of sarcomas. The study METABOLSARC is evaluating the eating habits, metabolomic, immune (CD3, CD4, CD8, NK) and microbiota profile in patients over 12 years of age with a diagnosis of primary bone sarcomas.

As for more common tumors, it was moreover tested the application of narrative medicine in the treatment of sarcoma patients (AMENAS trial) in order to evaluate the utility of the narrative digital diary integrated in the care pathway of patients with sarcomas (local or advanced disease).

Since 2014 Dr. Ferraresi is a member of the board of directors of Italian Sarcoma Group (ISG) and since 2019 of the board of directors of Intergruppo Melanoma Italiano (IMI). She is moreover a component of the scientific boards for the guidelines of melanoma and of soft tissue sarcomas and GIST for AIOM (Associazione Italiana di Oncologia Medica)

In 2021 she became a member of the FOSTER Osteosarcoma Consortium and is a component of the Working Group aimed at exploring the field of imaging and radiomics.

The UOSD SRT medical staff authored more than 20 papers during 2021 including ESMO-EURACAN guidelines on Soft Tissue and Visceral Sarcomas, GIST, Bone Sarcomas and a consensus paper on epithelioid hemangioendothelioma.

Neurosurgery Unit

Head: Dr. Stefano Telera, MD

Staff

Dr. Laura Raus, MD

Dr. Francesco Maurizio Crispo, MD

Dr. Catia Pompea Delfinis, MD

Dr. Mario Lecce, MD

Dr. Fabrizio Rasile, MD

Mission

The activity of Neurosurgical Unit is mainly devoted to research, diagnosis and treatment of central and peripheral nervous system neoplastic diseases.

Our activity is deeply embedded in the multidisciplinary group of Neuro-Oncology, with the principal aim of defining more specific diagnostic and therapeutic strategies for the most relevant brain and spine tumors. The research activity of the Unit of Neurosurgery is focused on several relevant topics, regarding translational and clinical studies on new bio-molecular characterization and therapeutic approaches in the integrated diagnosis and treatment of primitive and secondary tumors of the nervous system. As such, we take active part either to national and international cooperative groups or to relevant academic and sponsored clinical trials.

In the field of secondary CNS lesions, we cooperate with the Hematologic, Oncologic and Radiotherapy Units, offering important support into diagnostic and therapeutic processes of systemic and hematologic tumor diseases.

The combination of advanced researches and cutting edge technology available at our Center as neurophysiologic monitoring, ecography, intraoperative CT-scan allows the application of the most recent treatments for the patients.

Activities

In 2021, despite the severe limitations provoked by the coronavirus Covid-19 pandemic, the Unit of Neurosurgery performed 119 surgical procedures, for intracranial pathologies, spine lesions and tumors of the peripheral nervous system.

Our activity is devoted to increase the efficacy of therapeutic strategies for primitive brain tumors based on fluorescence guided microsurgical resection, neurophysiologic monitoring, intra-operative ecography followed by adjuvant chemotherapy, radiotherapy or Radiosurgery. The latest upgraded Neuronavigation System has been introduced in service, allowing in combination with intraoperative Ecography, to further refine the precise and tailored removal of primitive and metastatic brain tumors.

The new intraoperative CT-scan AIRO® coupled with Neuronavigation System has become fully operational in 2021. It represents a unique asset in Latium region and allowed the more effective methodology to reduce radiation risk for surgeons and operative personnel increasing at the same time the accuracy and safety of spine surgery.

The Italian Society of Neurosurgery (SINCH) have created a Task Force (ST is a member of this group), to draw consensus review of evidence and recommendation for diagnosis, staging, and treatment options of cerebral metastases. The endoscopic activity, both intraventricular and transphenoidal, has been maintained and developed. The recent acquisition of the new Exoscopic 3D system for implemented visualization in microsurgical and open surgical procedures, is able to combine the benefits of microsurgery and endoscopy, improving ergonomic work and workflow of the entire neurosurgical team in difficult accessible brain and spine area. Patients affected by metastatic spinal tumors may be treated with standard operndecompression surgery and fixation or ins elected cases, with “Separation Surgery” consisting of a combination of mini-invasive techniques as vertebro/kyphoplasty, open decompression and

percutaneous stabilization, followed by Radiosurgery. The introduction of silicon products allowed to perform complex cases with an

increased margin of safety and efficacy.

For intradural-extramedullary tumors the unilateral mini-invasive approach has become the standard of care, reducing surgical aggressiveness and time of hospitalization. Neurophysiologic monitoring of the motor and sensory function is commonly employed during surgery of all intradural tumors. A large experience on treatment of peripheral nerve sheath tumors like schwannomas, has been also developed in the last twenty years.

Research activity has been oriented either toward translational Neuro-Oncological projects as well as toward new, innovative, more effective surgical techniques. The aim of our multi-specialist translational group was to identify new molecular glioma biomarkers useful for better determine the diagnosis, prognosis and/or therapeutic response. To accomplish this goal, we take advantage of an extensive database including retrospective as well prospective case series collected at IRE.

We currently participate to the Glioma Project which has been developed by the Neuro-Oncology Unit, to combine the results of Radiomics and molecular analysis of primitive brain tumors and we will contribute to the CLINGLIO randomized, double blind, placebo-controlled adjuvant trial in newly diagnosed primary glioblastoma, to assess the efficacy and safety of 2-hydroxyleic acid (2-OHOA) in combination with Radiotherapy and Temozolamide standard of care treatment.

A relevant issue is related to research and identification of circulating biomarkers for detection and prognosis of primary brain tumors. We are evaluating eleven circulating serum microRNAs, previously associated with brain tumors, as potential non-invasive diagnostic biomarkers for glioma patients.

The role of microRNA has been also investigated in brain metastases. In particular, it has been assessed whether aberrant expression of specific microRNAs could contribute to brain metastases. Comparison of primary lung tumors and their matched metastatic brain disseminations identified shared patterns of several microRNAs, including common down-regulation of miR-145-5p, which appeared to play a pivotal role in malignancy progression and in metastasis.

The Neurosurgical Unit continues to be actively involved in the METAMECH (Master Protocol Mechanobiology Translational Research in Breast Cancer) a multicenter study funded by AIRC, with the primary aim to build a resource of clinical annotated biological samples feeding the consortium laboratories and allowing a mechano-focused “precision research” in breast cancer. The potential contributes of CSF cytometry analysis for early detection and characterization of tumor cells in the presence of leptomeningeal carcinomatosis and lymphomas, is also under investigation.

Fluorescence-guided resection with 5-ALA, can reliably increase the extent of surgery in primitive brain tumors. Our experience regarding more than 130 patients has been presented in several scientific meetings.

In 2021 several researches have been published in peer reviewed international Journals:

1. In Reply to the Letter to the Editor Regarding “Hemorrhagic Attitude in Frameless and Frame-Based Stereotactic Biopsy for Deep-Seated Primary Central Nervous System Lymphomas in Immunocompetent Patients: A Multicentric Analysis of the Last Twenty Years”.
Maria Callovini G, Sherkat S, Gazzeri R, Telera S.
World Neurosurg. 2021 Aug;152:244. doi: 10.1016/j.wneu.2021.05.129.
2. Surgical treatment of solitary intradural extramedullary spinal cord metastases from solid cancers of non-neurogenic origin. A multicenter study.
Gazzeri R, Telera S, Galarza M, Callovini GM, Sperduti I, Alfieri A.
J Neurooncol. 2021 Aug;154(1):101-112. doi: 10.1007/s11060-021-03804-9. Epub 2021 Jul 13.
3. Major Differences in Lymphocyte Subpopulations Between Cerebrospinal Fluid and Peripheral Blood in Non-Hodgkin Lymphoma Without Leptomeningeal Involvement: Flow Cytometry Evidence of a Cerebral Lymphatic System.

Cordone I, Masi S, Giannarelli D, Pasquale A, Conti L, Telera S, Pace A, Papa E, Marino M, de Fabritiis P, Mengarelli A.

Front Oncol. 2021 Jun 3;11:685786. doi: 10.3389/fonc.2021.685786. eCollection 2021.

4. Eribulin in brain metastases of breast cancer: outcomes of the EBRAIM prospective observational trial.
Fabi A, Terrenato I, Vidiri A, Villani V, Tanzilli A, Airoidi M, Pedani F, Magri V, Palleschi M, Donadio M, Catania G, Nisticò C, Carapella C, Rudà R, Pace A, Maschio M, Telera S, Cognetti F; AINO (Associazione Italiana Neuro-Oncologia).
Future Oncol. 2021 Sep;17(26):3445-3456. doi: 10.2217/fon-2021-0300. Epub 2021 May 28.
5. Surgical treatment of intramedullary spinal cord metastases: functional outcome and complications-a multicenter study.
Gazzeri R, Telera S, Galarza M, Callovini GM, Isabella S, Alfieri A.
Neurosurg Rev. 2021 Dec;44(6):3267-3275. doi: 10.1007/s10143-021-01491-8. Epub 2021 Feb 9.
6. 6) Hemorrhagic Attitude in Frameless and Frame-Based Stereotactic Biopsy for Deep-Seated Primary Central Nervous System Lymphomas in Immunocompetent Patients: A Multicentric Analysis of the Last Twenty Years.
Callovini GM, Sherkat S, Sperduti I, Crispo F, Raus L, Gazzeri R, Telera S.
World Neurosurg. 2021 May;149:e1017-e1025. doi: 10.1016/j.wneu.2021.01.035. Epub 2021 Jan 19.

Finally a Book has been published dealing with mini-invasive techniques as Vertebroplasty and Kyphoplasty and their clinical application in spine disease together with Orthopedics colleagues from prestigious Centers like the Istituto Ortopedico Rizzoli, Bologna and Maggiore Hospital, Bologna.

Published Book “Vertebral Body Augmentation, Vertebroplasty and Kyphoplasty in Spine Surgery”

Authors: Stefano Telera, Laura Raus Valerio Pipola, Federico De Iure, Alessandro Gasbarrini, Springer Nature Switzerland AG 2021

<https://doi.org/10.1007/978-3-030-76555-2>

Oncological Endocrinology

Unit

Head: Dr. Marialuisa Appetecchia, MD

Staff

Dr. Rosa Lauretta, MD

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Dr. Marta Bianchini, MD

Dr. Giulia Puliani, MD

Dr. Eros Floridi, Nursing Coordinator

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Dr. Emiliana Marinucci, Nurse

Dr. Giuliana Panico, Nurse

Dr. Sonia Girasole, Nurse

Dr. Enrica Ruffo, Nurse

Dr. Marianna La Vaccara, Nurse

Dr. Francesco Malci, Care Technician

Dr. Claudia Di Frischia, Case manager DMT Thyroid Cancers

Mission

The Oncological Endocrinology Unit of the IFO deals with the diagnostics and therapy of oncological pathologies of the endocrine glands (thyroid, pituitary, adrenal, parathyroid) and neuroendocrine tumors. It also deals with the management of osteoporosis and endocrine-metabolic sequelae in cancer patients. The Unit includes doctoral students from the School of Specialization in Endocrinology and Metabolic Diseases and a research doctorate in Endocrinology within the framework agreement with the University of Rome "Sapienza".

The Unit maintains collaborative relationships and participates in multicentre clinical trials with the main national and international universities and research institutes (Sapienza University of Rome, Biomedical Campus of Rome, Catholic University of the Sacred Heart of Rome, University of Pisa, University of Florence, University of Siena, University of Milan, EOC Swiss Cantonal Hospital) and with many Scientific Societies (eg SIE, SIOMMS, AIOM, ESMO, ITANET, ENETS, AIT). The mission is to achieve excellence in the prevention, diagnosis and treatment of endocrine and neuroendocrine tumors, in the management of endocrine-metabolic sequelae and drug-induced endocrine toxicities in cancer patients. In addition, the Unit is part of the Onco Bone Network, which brings together all the regional reference centers of Bone Health. It complies with OEI and ISO 9001 certification.

The Oncological Endocrinology Unit is the coordinator for the G4 (neuroendocrine neoplasms) and G6 (endocrine neoplasms) domains of IFOs in ERN-EURACAN network. The Unit is part of the Lazio Rare Diseases Information System (SiMaRaL) and is a reference center for rare endocrine diseases including syndromes due to genetic predisposition to cancer. Furthermore, since the IRE Gastroenterology and Digestive Endoscopy Unit is a Reference Center of the Lazio Region for Familial Polyposis (FAP), a rare disease in which a higher risk of developing thyroid cancer has been demonstrated compared to general population, the Unit has activated a facilitated path for these patients. The Unit is part of the Endocrine-Metabolic Network of the Lazio Region. It has also been identified as a "Hub" center for thyroid disease. As a Hub Center, it also deals with the dissemination of information and knowledge on the territory, is in contact with scientific societies and patient associations.

The Unit was also identified as a "Spoke" Center for neuroendocrine, pituitary, parathyroid, adrenal tumors and for the management of osteoporosis. The Unit pays particular attention to gender medicine in both care and research. The Head of the Oncological Endocrinology Unit is the coordinator of the Disease Management Team (DMT) of Thyroid Cancers and of the DMT of Neuroendocrine Tumors which bring together all the specialists involved in the management of these diseases. She is the EURACAN representative in EJP-RD (European Joint Program for Rare Disease) which aims to create a global and sustainable ecosystem that allows a virtuous circle between research, assistance and medical innovation in rare diseases. Since May 2020, she is a member of the international network EGOI (Experts Group on Inositol in Basic and Clinic research), is the IFO referent in the Gender Medicine Table at the Ministry of Health and the referent of the national IRCCS for Gender Medicine at the Gender Medicine Observatory at National Institute of Health (ISS).

Clinical and Research Activities

The research activities of the Oncological Endocrinology Unit are focused on the evaluation and development of new tools useful in the diagnosis, treatment and monitoring of endocrine and neuroendocrine tumors with particular attention to precision medicine and to translational research. In addition, the Unit has a specific interest in the management of the endocrine and metabolic toxicities and sequelae in cancer patients.

All scientific activities are based on the active collaboration with other Units (preclinical, translational and clinical) and with other national and international Centers.

Below are listed the main research lines:

1. “Identification of prognostic and predictive factors in endocrine and neuroendocrine tumors”.

Responsible: Marialuisa Appetecchia

Endocrine and neuroendocrine neoplasms (NEN) are rare tumors since the number of new cases per year is less than 5 per 100,000 people. Endocrine tumors are rare (thyroid, NEN) or very rare (adrenal / paraganglioma and parathyroid tumors) with difficult diagnostic and therapeutic strategies, for which the new frontiers of molecular target therapies and immunotherapy pose new challenges, both for the efficacy and toxicity. These tumours are clinically and biologically different, the complex management of which requires the expertise of different specialists (pathologist, medical oncologist, surgeon, nuclear medicine radiologists, endocrinologist, gastroenterologist, interventional radiologist, nutritionist, radiotherapist). The main scientific interest of the research line is the identification of new diagnostic biomarkers and the development of new innovative therapeutic approaches for endocrine and neuroendocrine tumors. Particular emphasis is placed on the identification and development of molecular and biochemical diagnostic tools, as the identification of indicators that allow a personalized approach to the diagnosis and treatment of patients, through the development of preclinical models and clinical validation. In a view of the personalization of care, the research line pays attention to gender perspective, an crucial determinant of health with implications for ‘therapeutic adherence, efficacy and toxicity of oncological drugs. Regarding Gender Medicine, in 2021 the Unit contributed to the drafting of the second edition of the national document on Gender medicine and COVID-19 on behalf of the Ministry of Health.

2. “Endocrine toxicities of oncological treatment”.

Responsible: Rosa Lauretta

The research line deals with the endocrine toxicities of antineoplastic drugs and the toxicities of treatments used for endocrine and neuroendocrine tumors. In recent years, the prognosis of many solid tumors has improved thanks to the use of new treatment strategies, as tyrosine kinase inhibitors (TKI) and immunotherapy, that can be burdened by adverse events, including endocrine toxicities. Among the toxicities induced by antineoplastic drugs there is also “cancer treatment induced bone loss” in patient affected by breast and prostate cancer in estrogen and androgen adjuvant hormonal blockade respectively. The main aims of this research line are the early identification of endocrine toxicities, the evaluation of predisposing factors, the treatment of the toxicities, and the evaluation of possible gender differences in the manifestation of endocrine toxicities.

The center in the year 2021 has participated to single-center and multi-centers trials in the field of Oncological Endocrinology and Gender Medicine. These research protocols were both translational and clinical. Translational trials aimed to characterize the molecular gene mutations and fusions of endocrine and neuroendocrine tumors, for a deeper understanding of cancer pathogenesis and for personalizing treatment in each patient basing not only on the histotype but also to the molecular profile of the tumor. These trials have strengthened the collaboration with other Units in the Institute, as Pathology, molecular biology and Basic Research. The Unit has been part of two International randomized controlled multi-centers studies on the use of cabozantinib and selpercatinib respectively in patients affected by iodine-refractory differentiated thyroid cancer and medullary thyroid cancers. In addition, the Unit coordinated and collaborated in the enrolling of patients affected by advanced thyroid cancers in multicenter clinical trials, aiming to evaluate the quality of life and the treatment side effects, with a special focus on the gender difference. Finally, the Unit is part of some other observational studies, including the Italian registry of patients affected by neuroendocrine tumors.

The Chief of the Oncological Endocrinology Unit have organized three congresses about Neuroendocrine Tumor “News

in the diagnosis and therapy of GEP-NEN: expert opinion” (28 October 2021); Gender Medicine and Covid-19 (5 October 2021) and a FAD Course: Violence and Healthcare Workers (Oct-Dic 2021). In 2021 the physicians of the Unit took part as speakers in divulgative streaming events for patients and population on thyroid tumors and bone health in cancer patients and as moderators/speakers in several international and national congresses and meetings including European conferences within the EJPRD, EURACAN network and European Neuroendocrine Tumor Society (ENETS).

Cardiology Unit

Head: Prof. Francesco Rulli, MD

Staff

Armando Carpino, MD

Maria Paola Cicini, MD

Fabio Maramao, MD

Nicola Antonio Morace, MD

Marcello Casale, Coordinator

Laura Cervellione, Nurse

Gianni Chiarabini, Nurse

Antonella Cutini, Nurse

Sabrina Ganzenua, Nurse

Mission

The Cardiology Task Force performs all non-invasive cardiac diagnostic current required by the surgical facilities, medical oncology and dermatology Institutes. The patients are studied by consulting cardiac ECG, echo, stress ECG, 24 hours ECG and 24 hours monitoring blood pressure. Patients who belong to our Unit, with a path shared by colleague practitioners, have a predetermined follow-up and facilitate in terms of access benefits with waiting times of 48 hours.

Clinical Activities

The Cardiology Unit carries out assistance activities and clinical-instrumental advice to all cancer patients Institute Regina Elena and S. Gallicano Institute.

The outpatient activity is dedicated to cancer patients who belong to the take in charge, to Day-hospital, DaySurgery at the two Institutes and to all people in need of evaluation and ongoing monitoring of chemoradiotherapy or remote treatment within the follow set up programmed by shared treatment protocols.

Research Activities

Support to surgery in terms of preoperative cardiovascular function evaluation in the intra-operative emergency and in any patient's appreciation as a result of complications.

The state of cardiac evaluation of the patient to be subjected to chemotherapy or radiotherapy, pre or postsurgery, given the already documented cardiotoxicity of some therapeutic lines and in particular of some specific groups of drugs. To this is added the periodic monitoring, clinical and instrumental, the treated patient, and in accordance with research protocols defined and shared with colleague oncologists conforming with the guidelines defined by available.

The UO Cardiology is part of the most solid and accredited reality associational cardiology and cardio-oncology, in the evaluation of cardiotoxic effects of some anticancer drugs, in research and in the development of myocardial damage markers in outcome and patient who underwent cardiac surgery for cancer.

Gastroenterology and Digestive Endoscopy Unit

Head: Dr. Vittoria Stigliano, MD

Staff

Mission

Pulmonary Physiopathology Unit

Head: Dr. Maria Papale, MD

Staff

Dr. Eliccua Mastroapasqa, MD

Dr. Giorgio Piperno, MD

Dr. Angela Fortunato, Nurse

Dr. Virnia Signore, Nurse

Mission

Physiopathology Respiratory Unit has forwarded its traditional mission addressing and programming in research activity through useful objectives aimed at the prevention, diagnosis, cure and rehabilitation of pulmonary diseases, in particular oncology and smoke related diseases. The directives have been:

- primary and secondary prevention in the field of pneumology through education clinical-functional diagnostics
- respiratory therapy and rehabilitation for both inpatients and outpatients
- participation in research program
- participation and organization of courses, conferences and congresses both for reports as well as professional updating.

Regarding the activities and objectives the Unit confirms his commitment to respiratory rehabilitation activities with the aim to improve the patients quality of life and respiratory functionality and, at the same time, to reduce the days of hospitalization.

The Unit is also dedicate to patients suffering from Interstitial lung disease and IPF (Idiopathic pulmonary fibrosis), rare diseases but frequently found in our Institute as outcomes of administered therapies.

The early diagnosis and therapy of the IPF contributes to the prevention of the lung cancer associated with IPF.

The smoking quitting clinic (referral Centre for the Observation of Smoke, Alcohol and Addiction, I.S.S.), has continued its own activity helping patients to quit smoking even with pharmacologic treatment.

The Unit continues to dedicate a protocol to the staff of the institute for the treatment, education and counseling of smokers.

Clinical and Research Activities

During 2021 about 19.000 services (visits, consultations, instrumental tests and respiratory rehabilitation activity) have been conducted on patients coming from different Units of the Institute.

Cooperation, above all, with Thoracic Surgery, for a more accurate identification of surgical risks, has been particularly intense.

We had about 12.000 services conducted for outpatients who came for pulmonary oncology and other diseases or to quit smoking or to run respiratory rehabilitation.

Respiratory rehabilitation activity is offered mainly to external patients who have to undergo major thoracic or abdominal surgery, or have already undergone pulmonary resection for cancer and suffer from COPD.

In 2021, about 9.500 services of respiratory rehabilitation have been performed on internal patients and 3600 services on external patients.

In 2021 the persistence of the COVID-19 pandemic continued to represent a potential risk of transmission of the infection to all patients attending for lung function services and for the Unit staff.

Consequently, in accordance to ERS statement, the execution of respiratory functional tests have been carried out only to patients who required it the most and always with all appropriate disinfection and prevention measures.

For this reason the services conducted for outpatients has undergone a reduction, compared to the pre-pandemic period, while the activity concerning internal patients remained the same.

The Unit continued to participate in the study BR31 “A phase III prospective double blind placebo controlled randomized study of adjuvant medi4736 in completely resected non-small cell lung cancer”, currently in the follow-up stage

The Unit, while continuing to participate in research line 1 “Prevention and early diagnosis of Cancer” “Role of the estradiol axis in the carcinogenesis and prevention of mesothelioma”, which will resume the enrollment of patients to be subjected to functional respiratory evaluation in relation to the pandemic situation

The Unit has taken part in “Registro asma grave- Studio osservazionale e/o retrospettivo non interventistico, multicentrico, nazionale” coordinated by the Italian Association of Hospital Pneumologists (AIPO) contributing to the publication: “Severe asthma management in the era of biologics: insights of the Italian Registry on Severe Asthma (IRSA)” (Eur Ann Allergy Clin Immunol Vol 53, N.3, 103-114, 2021)

The Unit has taken part in a national, multicentre observational study: “The impact on the health status and adherence in a real life setting of Italian patients with chronic obstructive pulmonary disease in treatment with a fixed triple association pmd b.i.d.: a 12-month prospective observational study triple therapy in real life: impact on adherence and health status (TRITRIAL)”

The Unit began collaboration with the radiotherapy Unit under study: “Microcitoma polmonare malattia estesa: Studio prospettico di associazione della radioterapia toraco-mediastinica al trattamento di immunoterapia di mantenimento con Atezolizumab”

Participation in the project IFO-ENS “Project Facilitating access to care and health of deaf and severely hearing impaired people” has also been started. We also contributed to the realization of the course carried out within the project “Come ti senti?- conceived by ENS and co-funded by the Ministry of Labour and Social Policies. (Directorate General of the Third Sector and Social and Corporate Responsibility. Notice no. 1/2018) and aims to raise awareness among the staff of health facilities throughout Italy on deaf people, their needs.

Neuroncology Unit

Head: Dr. Andrea Pace, MD

Staff

Dr. Edvina Galiè, MD

Dr. Marta Maschio, MD

Dr. Dario Benincasa, MD, PhD

Dr. Veronica Villani, MD, PhD

Dr. Antonio Tanzilli, Neuro-psychologist

Dr. Stefano Di Felice, Physiotherapist

Dr. Cristiano Parisi, Physiotherapist

Dr. Alessia Zizzari, Physiotherapist

Dr. Giuliana Graziano, Technician

Dr. Gianluca Petreri, Technician

Dr. Silvia Focarelli, Data Manager

Dr. Annamaria Biscu, Nurse Case Manager

Dr. Maria Andreina Rotondi, Social worker

Dr. Margaux Lamaro, Physiotherapist

Dr. Roberta Rafaelli, Nurse

Dr. Valentina Buonuomo, Nurse

Dr. Francesca Cardone, Nurse

Dr. Michiela Tomaiuolo, Nurse

Mission

Clinical and research activity of Neuroncology Unit is dedicated to the diagnosis, therapeutical approaches and supportive and palliative care of primary brain tumors. Moreover, the Unit is involved in clinical and research activity related to Central and Peripheral Nervous System neurological complications of cancer and neurotoxicity of anticancer treatments.

The clinical activities of Neuroncology Unit include:

- Neurology clinic
- Neuro-oncology clinic
- Center for Tumor-related Epilepsy
- Neuropathic Pain Clinic
- Neuropsychology and cognitive rehabilitation
- Neuro-oncologic Day Service for chemotherapy and supportive treatment of brain tumor patients
- Neurophysiology lab (Electromyography, Electroencephalography, Evoked Potentials)
- Rehabilitation service specialized in cancer rehabilitation for in- and out-patients
- Palliative and supportive home care for brain tumor patients

The research activity of Neurology Unit is focused on several topics. These include:

- Clinical neuro-oncology - The role of chemotherapy in recurrent malignant brain tumor has been evaluated in phase II trials exploring the activity and toxicity of several anticancer agents. Active trials include: weekly carboplatin AUC2 in recurrent malignant glioma; cloropromazine associated to temozolomide in newly diagnosed GBM, Regorafenib in recurrent GBM.
- Traslational research - Next generation sequencing in glioma patients for identification of potential target therapy: NGS panels assessment allowing the simultaneous analysis of both DNA and RNA with a panel of 50 genes with the aim to identify potential therapeutic target
- Cognitive impairment assessment and rehabilitation - The role of cognitive rehabilitation has been investigated in different setting of care (in patients, outpatients, home care setting). Preliminary results have been presented in national and international scientific meetings.
- Home-care for brain tumor patients - The efficacy of a program of comprehensive palliative care for brain tumour patients supported by the Lazio Regional Health System was evaluated analyzing outcome of qualitative of care with administrative data. The results of this project have been presented in national and international scientific meeting.

- Palliative neuro oncology and telemedicine
- We developed a health WEB site portal applied to Neuro-Oncology supportive and palliative care issues (www.portaleneuroncologia.it). Neuroncology Unit of IRE is involved in an international project aimed to define guidelines and treatment recommendations on supportive and palliative care in brain tumor patients.
- Peripheral neurotoxicity of anticancer drugs - We are involved in an international study: The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization (CIPerInoms) specifically designed to compare the validity and reliability of different methods proposed for the assessment of chemotherapy-induced peripheral neuropathy in a formal way. The results have been published on Neurology Journal
- Rehabilitation in Oncology - Neuroncology Unit research activity includes the clinical research and methodological assessment of rehabilitation strategies in oncology. The definition of the role of rehabilitation in different setting of care (early rehabilitation of anticancer treatment sequelae; long term survivors rehabilitation needs, palliative rehabilitation) is the main object of several research projects.
- Tumor related Epilepsy - The Center of Tumor-related Epilepsy is Coordinator of Italian League Against Epilepsy (LICE) Study Group on “Brain tumor-related Epilepsy”. This group includes 35 Italian epilepsy centers. The CET is one of the only 4 European Centers, and the only Italian member, included in the world network on Tumor Epilepsy, the International Brain Tumor-Related Epilepsy Research Consortium: <http://tumorepilepsy.com/index.html>

Clinical and Research Activities

Neuroncology Unit is involved in several national and international research networks including: ERN Domain 10 (rare CNS Tumors), ACC (Alliance against Cancer), RIN (Italian Neuroscience Network)

- Ongoing Clinic Trials are mainly focused on clinical neuroncology:
- RACTAC-Rational drug repositioning for an efficient and safe combined therapeutic approach to glioblastoma multiforme. Antipsychotic chlorpromazine in combination with temozolomide in first line treatment of unmethylated Glioblastoma patients. A multicentric phase II trial.
- A model of comprehensive care and tele-health in brain tumor related epilepsy patients
- Incidence of neurological complications of immunotherapy. A multicentric prospective trial.
- Efficacy and tolerability of low dose vs standard doses of AEDs in newly diagnosed epileptic patients (STANDLOW). Multicentric, randomized trial.
- Coagulation/complement activation and cerebral hypoperfusion in relapsing-remitting multiple sclerosis MoH
- Regorafenib in Glioblastoma recurrent. REGOMA-OS prospective multicentric trial
- Glioma Project: Traslational study. Ongoing

Guidelines production

- AIOM 2021, neurotoxicity in long survivors
- AIOM, 2021 neurotoxicity induced by immunotherapy
- SIN, AINO, SICP Palliative care in neuro-oncology
- EANO-ESMO 2021 Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up

Psychology Unit

Head: Dr. Anita Caruso, MD

Staff

Dr. Alessandro Bonucci, Psychologist
Dr. Maria Franca Condoleo, Psychologist
Dr. Giovanna D'antonio, Psychologist
Dr. Chiara Falcicchio, Psychologist
Dr. Massimo Giuliani, Psychologist

Dr. Lara Guariglia, Psychologist
Dr. Sonia Ieraci, Psychologist
Dr. Gabriella Maggi, Psychologist
Dr. Maria Perrone, Psychologist
Dr. Stefania Torelli, Psychologist

Mission

The Psychology Unit is focused on the development of collaborative research networks on prevention, measurement, treatment and rehabilitation of psychological suffering in the oncologic patient, along the different phases of the disease and different medical treatments.

The research lines of interest of the Psychology Unit are:

Early assessment of psychological distress.

The psychological distress, when undetected and untreated, is associated, in cancer patient, with poor quality of life, lengthening of rehabilitation times, minor adherence to treatments and lower survival. These reasons, stress the need of multicentre studies aimed to develop shared strategies of detection of distress in all stages of the disease. The early assessment of distress allows for adequate support that can also help improve patient compliance.

The assessment of psychosocial risk factors in the context of genetic counseling.

Many variables affects adherence to the counseling path; the psychological impact of the counseling process in the mid and long term; the impact of receiving a positive result; the adequate assessment of the factors that influence the decision-making process related to prophylactic treatments or procreation choices. The knowledge of these factors is fundamental in order to favor the process of adaptation of the consultant to the risk condition.

Psychological aspects in rehabilitation.

The line is aimed to evaluate the psychological dimensions involved during the follow-up phase for healed, chronic and long-term survivor patients, also to improve their quality of life and respond to new emerging needs. In fact, little is known about the problems of people free from disease or potentially cured and, consequently, little is done to respond to their needs and thus safeguard their quality of life.

The measurement of the quality of life in different types of diagnosis, medical treatments and phases of oncological disease.

The quality of life (QoL) represent a strong measure of the well-being of oncologic patient. The line is aimed to ensuring it as much as possible, the identification of treatments that have less impact on the personal, family, social and sexual well-being of patient and to test the use of QoL level to assess the need and outcomes of rehabilitation interventions.

The quality of the care provided.

The quality of psycho-social care in oncology is the cornerstone of the well-being of patients. Great attention must be placed to the quality of the communication and relationship between doctor and patient. In this line the attention is also placed both on the communicative and relational needs of patients and methods of communication of the careers, particularly to communicate "bad news".

The well-being of the careers.

The well-being of the health providers is essential in oncology. Thus, the investigation of the psychological, behavioral and social dimensions of the operators along the care course of cancer is crucial to intercept barriers to good clinical practices. The assessment concerns the possible states of discomfort in relation to the various conditioning factors:

internal models of approach to work, behavioral methods and relationships with the patient and his family, external environment understood as climate, power relations and quality of the organization.

The most suitable assessment tools.

Up to date, the psycho-oncology approach has developed a large body of tools to assess dimensions involved in the processes of adaptation to the disease. Many of these tools were validated in non-Italian speaking populations. The objectives of the line are both to validate selected tools using Italian samples and to import the use of them in the clinical practice of Italian psychoncologists.

Clinical and Research Activities

Projects:

The study “Facilitators and/or barriers to access to psychological support in cancer patients: a multicenter study” aims to identify the clinical, demographic, psychosocial factors and the pathway of patients sending associated with adherence to psychological support in cancer patients. The study coordinator is IRE, in collaboration with the psycho-oncology structures of the Lazio Region.

The multicenter study “Rehabilitation needs in patients with early stage breast cancer: the use of an approach based on patient reported outcome (PRO)”, coordinated by IRE and in collaboration with the other Italian oncological IRCCS, is based on validation of a PRO questionnaire for the detection in the survival phase of rehabilitation needs in women early breast cancer.

The study on “Moral Distress: the incidence and the determining factors” focuses on the detection of a specific dimension of psychological well-being, the moral distress, or the discomfort perceived by health professionals when they have to make decisions that have implications on an ethical level and therefore personal. It is therefore an investigation on different levels: individual, the context in which the operators carry out their work and the quality of the organization. The aim of the study is the detection of Moral Distress within the population of the IFO health personnel and to compare the incidence of this dimension in the management of different pathologies.

Educational events:

Organized Courses

23rd two-year course in Oncological Psychology, sponsored by the Italian Society of Psycho-Oncology. The course is aimed at psychologists, doctors, nurses, physiotherapists, social workers and all operators who work or intend to work in the oncology field. The course is divided into 200 teaching units and lasts two years. The training is aimed at expanding the skills of each professional in the psycho-oncology field and acquiring specific psychological knowledge in view of a team work according to an integrated approach.

Online course “Suicide prevention in the hospital”. In compliance with Ministerial Recommendation No. 4, March 2008, “Prevention of patient suicide in hospital”, a company training event was organized, which included two editions (November-December), with the aim of providing health professionals, doctors and nurses belonging to the IFO wards, work tools and operational indications on the procedures to be adopted to prevent and / or reduce suicides and suicide attempts of hospitalized patients.

Teaching in courses

Online training course for the Universal Civil Service “Informacancro project”. FAVO, March 12, 2021

Course “Investigators responsible for supervising compliance with the legislation on smoking in healthcare environments”. Rome, IFO June 4, 2021; September 29, 2021.

1° Training course on the donation of musculoskeletal tissue. Rome, June 14, 2021.

2° Training course on the donation of musculoskeletal tissue. Rome, June 25, 2021

Training event aimed at nurses assigned to procurement of musculoskeletal tissue. Ariccia, 13 ottobre, 2021.

Course FAD “Violence and health workers”. October-December 2021

Course “Nursing Assessment”. Rome, IFO, November 22-23, 2021.

Online course “Biennial School of Training in Psycho-Oncology Clinic”. Italian Society of Psychoncology (SIPO), December 3, 2021.

Pediatric Orthopedic Oncology Surgery Course. Rome, IFO December 14, 2021

Report / Moderation at Congresses, Conferences and Symposiums:

Online conference “Advanced breast cancer; fight cancer-related fatigue “. Psycho-oncology session. May 21, 2021.

Online conference “Past, present and future psycho-oncology”. May 25, 2021.

V National SIPO Day 2021 “Psycho-Oncology and COVID-19, from emergency to resilience”. Rome, September 26, 2021

1st International Congress “The treatment of the patient in plastic surgery during the COVID-19 pandemic: what happened and what has changed”. Rome, October 1st, 2021

XXIV National Congress and AINO residential course. “Advance directives of treatment in the patient in the advanced stage of the disease”. Ancona. October 28-29, 2021

IPUE National Congress: “The existential dimensions of the body and the psyche: experiential compared in Psychotherapy”. Rome, December 10, 2021.

Phase 1 Clinical Trial Center

Head: Dr. Lorenza Landi, MD

Staff

Dr. Anastasia Laudisi, Oncologist
Dr. Isabella Bertazzi, Chief nurse
Dr. Sonia Di Berardino, Nurse
Dr. Elisabetta Canofari, Nurse
Dr. Gabriella Lecce, Nurse
Dr. Maria Carmela Giordano, Nurse
Dr. Marianna Introna, Data management

Mission

According to the overall mission of the National Cancer Institute Regina Elena, the goal of the Phase 1 Clinical Trial Unit is to integrate preclinical drug discovery, proof-of-principle phase I trials, and tumor-specific evaluation of novel agents. Moreover, because our Institution is formed by Regina Elena and San Gallicano Dermatological Institute, our Clinical Trial Unit serves as the center for the conduction of phase I trials of both Institutes.

Ongoing and upcoming studies involve many of the most promising molecularly targeted agents, immunotherapy, and combinations of agents in early phase of development. We assure rigorous study conduction and design. The staff of the Phase 1 Unit is directly responsible for patient care and adherence to study protocol.

Clinical and Research Activities

The clinical activities include inpatient and outpatient (pre-screening activities and follow-up) hospital care. All patients are evaluated by a specialized team according to their tumor and are treated in a dedicated Day Hospital (DH) or in a specific unit. Outpatient visits are performed in a dedicated room and treatments are delivered in a DH service, including 3 chemotherapy chairs and 2 beds. The inpatient service includes 2 beds dedicated to trial procedures and/or management of adverse events.

In addition, according to Phase 1 procedures, we guarantee:

- Technologies for monitoring and surveillance of patients as a sub-intensive therapy.
- A network of support Clinical Units and Professionals for each type of study according to the AIFA Resolution n. 809/2015 AIFA conformity certifications for phase 1 studies “Temperature controlled” transport systems
- Operating procedures for activities related to the investigation paths and relations with other internal or external structures of the IFO.

In 2021, a total of five studies were active/recruiting or completed accrual

A. Phase 1 Dose Escalation and Cohort Expansion Study of TSR-042, an anti-PD-1 Monoclonal Antibody, in Patients with Advanced Solid Tumors

B. A phase Ib, open-label, multicenter study (BO40933) evaluating the safety and efficacy of ipatasertib in combination with rucaparib in patients with advanced breast, ovarian, or prostate cancer

C. BLU-667-1101: A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors

D. MK-1308-001 Study of Quavonlimab (MK-1308) in Combination with Pembrolizumab (MK-3475) in Advanced Solid Tumors

E. DCC-3014-001: A Multicenter Phase 1/2, Open-Label Study of DCC-3014 to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics in Patients with Advanced Tumors and Tenosynovial Giant Cell Tumor.

In addition, three phase I trials (two in lung tumors and one in hematologic malignancies) are planned to be activated in the first semester of 2022.

Future Perspectives

The activity of the Phase 1 Clinical Trial Unit is continuously growing with an increasing number of clinical trials including no-profit Phase 1 studies, First-in-human studies, and collaboration with other institutions. Moreover, the physician staff will grow in size with the arrival of new dedicated oncologists. Participation in multicentric studies and international meetings, will increase the Center visibility and patient recruitment. The Center will also undertake general, non-trial-specific advertising and screening procedures to recruit potential trial participants, before inviting them to participate in a specific trial. Finally, intensive educational activities involving physicians and nurses will be supported by our Center.

Department
of Research
Advance
Diagnostic and
Technological
Innovation

Department Director

Message

Dr. Antonello Vidiri

The Department of Research Advance Diagnostic and Technological Innovation (RTA) is a unique environment in which cancer diagnosis, treatment and research are actively pursued within integrated frame combining biological repositories and advanced imaging with high-throughput infrastructures.

Most of the RTA activities are performed with state of art technology such as Cyberknife in radiotherapy, the PET-CT and the 3T MRI, which allows non-morphological studies such as diffusion, perfusion and spectroscopy.

The Interventional Radiology Unit in collaboration with Nuclear Medicine Unit allows obtaining new treatment as radio-embolization of liver tumors with Y90 e Holmium 166.

The Immunotransfusion unit supports the Oncoematologic Unit in the cellular therapies. Bio-Bank stores carefully annotated cancer tissues and biological fluids related to patients accrued consecutively at Regina Elena Cancer Institute. The Research Area comprises 5 Units whose activities range from immunotherapy, tumor microenvironment, metastasis, cell cycle regulations, drug repurposing, metabolism translational epigenetics and oncogenomics.

The experimental work is performed both in preclinical settings and in vivo systems with the aid of advanced genomic facilities integrated with a branched Bioinformatic and data analysis Units.

Pathology Unit

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Staff

Mariantonia Carosi, M.D.

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Ferdinando Marandino, M.D.

Mariangela Novello

Letizia Perracchio, M.D. Pathologist

Andrea Russo, M.D. Pathologist

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Simona di Martino, Biologist (Biobank IRE)

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Sabrina Lori, Technician

Patrizia Palmarelli, Technician

Claudia Bonomo, Technician

Aldo Palange, Technician

Mission

The Pathology Unit plays a main role both in the diagnostic services and in the clinical protocols and research studies in oncology. As a matter of fact, the Pathology Unit provides the 'state of the art' in pathological anatomy and molecular pathology, a crucial point for patients' care in terms of neoplastic disease prevention, diagnosis and treatment, in a coordinated, comprehensive and cost-effective manner. Further, the Pathology Unit aims to implement the diagnostic expertise, mainly by setting up novel molecular assays to be applied to the diagnosis and treatment of tumours in the era of 'precision medicine', and facilitating the collaboration with the other clinical and research Units. In particular, the application of Next Generation Sequencing (NGS) for detailed oncogenomic profiling of the main human malignant tumors has been consistently implemented. In addition, the Pathology Unit is involved in the promotion of innovative scientific programs, spanning the spectrum from basic to translational to clinical research. As a matter of fact, the participation to multidisciplinary and/or multicentric research studies is an essential task of the overall clinical and research mission. Finally, as custodians of the tumour tissues biobank (BBIRE), an additional role of the Pathology Unit mission is the proper, authorized and certified use of tumour tissue samples for research purposes.

Clinical and Research Activities

In 2021 the clinical activities of the Pathology Unit have included as a rule macroscopy and conventional histopathology on biopsy and surgical samples (surgical pathology), cytology on cytological samples (diagnostic cytology), and clinical necroscopy (autopsies). In addition, immunohistochemistry, FISH/SISH analysis, HPV detection and/or genotyping, and gene mutational status (mainly by NGS) have also been routinely performed whenever required. Surgical and biopsy samples from about 11.500 patients and cytological samples from about 7.500 patients, encompassing the whole spectrum of the main human tumors, have been studied. All cases of malignant tumors have been histologically typed and graded according to the updated WHO classifications, and pathologically staged (pTNM) according to the updated TNM/UICC/AJCC editions. Whenever required, ancillary studies (histochemistry, immunohistochemistry and molecular) have been performed. In particular, about 23.000 tests of diagnostic immunohistochemistry, including tumor immunohistological typing and assessment of tumor prognostic and/or predictive factors, have been performed. Further, about 400 FISH/SISH tests, mainly in cases of breast carcinoma (HER2 gene), of lung adenocarcinoma (ALK and ROS1 genes), and in selected cases of high-grade B-cell lymphomas (c-Myc, Bcl2 and Bcl6 genes), sarcomas, and CNS primary tumors have been performed. In addition, the mutational status (gene mutations, gene fusions, gene copy number variations) of about 1200 cases of non small cell lung carcinoma (NSCLC), colorectal adenocarcinoma,

melanoma, sarcoma, CNS primary tumors and other malignant tumors have been investigated, mainly by NGS analysis based on different and wide panels of 'target' genes (up to about 60 genes). Finally, about 700 molecular tests for MGMT promoter gene methylation status and IDH1-IDH2 genes mutational status in primary CNS tumors, BRCA1-BRCA2 somatic mutational status (mainly) in ovarian cancer, and MSI evaluation (mainly) in colorectal cancer, have been performed.

As far as the scientific activity is concerned, in 2021 the Pathology Unit has collaborated in the publication of more than 50 peer-reviewed scientific papers, with a cumulative Impact Factor (I.F.) higher than 400. The most significant scientific publications are mainly related to breast cancer, lung cancer, HPV associated tumors, and some immunological and clinical aspects of anti-SARS-CoV-2/COVID 19 vaccination in oncohaematological patients.

In breast cancer, we have investigated the role of USP19 gene/protein in cancer cell migration and invasion, and we have demonstrated that USP19 acts as a novel prognostic marker in patients with early breast cancer ; we have shown that PIK3CA mutations is a molecular target for hormone receptor- positive HER2-negative metastatic breast cancer ; we have demonstrated that the aberrant transcriptional and post-transcriptional regulation of SPAG5, a YAP-YTAZ-TEAD downstream effector, fuels breast cancer cell proliferation ; we have investigated the prognostic relevance of HER2-positivity gain in metastatic breast cancer in the ChangeHER trial ; we have shown that liquid biopsy identifies actionable dynamic predictors of resistance to Trastuzumab Emtansine (T-DM1) in advanced HER2-positive breast cancer.

In lung cancer, we have prospectively validated the Italian Alliance against Cancer Lung Panel (about 300 target genes) in patients with advanced non-small cell lung cancer ; we have demonstrated the feasibility of the Idylla EGFR mutation test when the reuse of stained tissue slides is the only available option ; we have shown that KEAP1 and TP53 frame genomic, evolutionary and immunological subtypes of lung adenocarcinoma with different sensitivity to immunotherapy.

In HPV associated tumors, we have investigated the intrabodies targeting human papillomavirus 16 E6 and E7 oncoproteins for therapy of established HPV-associated tumors ; we have participated to the NTCC2 Working Group on p16/Ki67 and E6/E7 mRNA accuracy and prognostic value in triaging HPV DNA-positive women ; we have performed a systematic review and meta-analysis on cell-free human papillomavirus-DNA for monitoring treatment response of head&neck squamous cell carcinoma ; we have shown that HPV sensitizes oro-pharyngeal squamous cell carcinoma cells to cisplatin-induced apoptosis by inhibiting autophagy through E7-mediated degradation of AMBRA1.

As far as the immunological and clinical studies on SARS-Cov-2/COVID 19 vaccination in oncological patients are concerned, we have investigated the immunogenicity and safety of anti-SARS-Cov-2 BNT162b2 vaccine and the kinetics of anti-SARS-COV-2 antibodies in patients with different haematological malignancies (multiple myeloma and myeloproliferative neoplasias), and the impact of anti-CD20 monoclonal antibodies on serologic response to BNT162b2 vaccine in patients with B-cell non-Hodgkin's lymphomas.

As far as the BBIRE activities are concerned, BBIRE has played a fundamental role in the above mentioned immunological and clinical studies on SARS-Cov-2/COVID 19 vaccination in oncohaematological patients ; in addition, BBIRE has been involved in a large number (> 50) of institutional scientific projects, is a member of the European research network of Biobanks and Biomolecular Resources (BBMRI-ERIC), participates with the European Organization for Research and Treatment of Cancer (EORTC) to large scale international multicentric projects, and is also involved in the Italian Alleanza Contro il Cancro (ACC) network.

Radiology Unit

Head: Dr. Antonello Vidiri, MD

Staff

Anelli Vincenzo, MD	Gianluca Lattanzi, Radiology Technician
Luca Bertin, MD	Anna Longo, Radiology Technician
Federico Cappelli, MD	Rita Pasqualucci, Radiology Technician
Maria Ciolina, MD	Franco Rea, Radiology Technician
Francesca Romana Ferranti, MD	Francesco Rinaldi, Radiology Technician
Marcello Greco, MD	Elisa Tomassini, Radiology Technician
Laura Greco, MD	Simone Trotta, Radiology Technician
Ramy Kayal, MD	Giulio Strino, Radiology Technician
Annelisa Marsella, MD	Tolu Sebastiano, Nurse, Coordinator
Carlo Paglicci, MD	Fabio Rosi, Nurse
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Giuseppe Pizzi, MD	Alba Cicconardi, Nurse
Laura Scardella, MD	Serena Del Vecchio, Nurse
Giulio Vallati, MD	Roberto Fantozzi, Nurse
Francesca Fodde, Radiology Technician Coordinator	Matteo Ferraro, Nurse
Lorenzo D'Auria, Radiology Technician, System Administrator	Franco Guido, Nurse
Rodolfo De Leo, Radiology Technician	Stefano Landi, Nurse
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Michele Farella, Radiology Technician	Cristina Boi, Administrative Coll.
Gaetano Fetonti, Radiology Technician	Cristina Settembrini, Administrative Coll.
Stefania Fringuelli, Radiology Technician	Flavia Farella, Administrative Coll.
Martina Gessani, Radiology Technician	Martina Casella, Administrative Coll.

Mission

The mission of the Radiology Unit is diagnosis and staging of the tumor, target for surgical and radiotherapy treatments, guide patient stratification, predict and monitor therapeutic efficacy. In the Unit there are two MR at 1.5 T and 3T, three multidetector CT, two at 128 and one at 68 Layers, Ultrasound with color-doppler and with use of contrast-medium and Elastasonography, Digital Mammography, Contrast Enhanced Mammography (CESM), Digital Breast Tomosynthesis (DBT) and Mammotome. There is an Interventional Service image-guided for diagnosis and treatment of neoplasms.

Topics are: evaluation of head-neck and prostate cancer, lung cancer and pleural mesothelioma, integrated breast diagnostic, neuro-oncology, soft and osseous tumors. The unit is also involved in all diagnostic therapeutic ways (PDTA) and participates in all Disease Management Team (DMT) meetings.

Clinical Activities

The clinical diagnostic activity includes detection, characterization and monitoring of the tumors, utilizing Traditional X-ray, Ultrasound, CT, MR, and Mammography that are performed every day (morning and afternoon) except Saturday afternoon.

The Interventional service is open from Monday to Friday. MR unit offers service as functional imaging, diffusion and perfusion, in brain, head-neck, breast, soft tissue neoplasms and prostate tumors; in the Breast unit is possible to obtain biopsy image-guided with mammotome, Digital Mammography, and Digital Breast Tomosynthesis (DBT).

In US is possible to perform exam with contrast medium infusion in particular in the evaluation of liver lesions. In

the Interventional unit are performed biopsy and treatment with thermoablation, radiofrequencies and with the use of radionuclide (Sirtex); Interventional Radiology has more years of experience in the loco-regional treatment of liver tumors through the use of both Endovascular Procedures such as Traditional Chemoembolization (TACE), Chemoembolization with controlled release microspheres of chemotherapy drug (precision Tace) and experience, in the Urological field with urinary or prostatic neoplasms embolization, preoperative tagging and placement of ureteral stents.

In the field of Muculoskeletal Intervention, the collaboration with Oncological Orthopedics allows to perform embolic treatments for preoperative purposes of neoplasms and combined techniques of preoperative vascular derivation preparatory to delicate interventions. Pulsed radiofrequency or vertebroplastic procedures are also performed in oncological pain therapy. Is possible to obtaine prostate biopsy with fusion imaging between MR and US

Research Activities

Radiomic: involves the analysis and translation of medical images into quantitative data with the underlying hypothesis that imaging reflects not only macroscopic but also the cellular and molecular properties of tissues. The objective of radiomics is to generate image-driven biomarkers that serve as instruments that provide a deeper understanding of cancer biology to better aid clinical decisions. We are using this technique in lung cancer to correlate the radiomics features with mutational status, in head and neck tumors, in the differentiation of parotid lesions and in the evaluation of the HPV status in patients affected by oropharyngeal SCC and in patients with liver metastases from colon-rectal carcinoma, underwent surgery after chemotherapy ,to predict overall survival.

Radiogenomic : field of research aimed at developing tools for non-invasive genotyping by identifying imaging biomarkers for genomic subtypes. Radiogenomic analysis refers to the integration of radiophenotypes and genomic data in order to find radiogenomic association. A correlation study is underway between CT radiomic features and specific drivers mutational status of NSCLC.

In Head and Neck tumors underwent surgery we investigate the correlation between the parameters identified by perfusion imaging (neo-vascularization) and diffusion (cellularity) with those of the immunohistochemistry and digital pathology, RNASEQ, and with the immunoprofiling of the cells of the immune system in the periphery. The aim of this research is to define the possible role of diffusion and perfusion MRI in depicting the heterogeneity and microstructural complexity of the neoplasm and the microenvironment.

Investigate the possibility to obtaine before treatment, diagnostic elements predictive of the response to treatment.

Multiparametric-MR prostate studies before and after therapy, in particular in the evaluation of the alterations after radiotherapy compared with those PET-CT scan.

Neo-adjuvant treatments using 3T MR with functional sequences (diffusion and perfusion) in the sarcomas, osteosarcoma and Ewing sarcoma.

In the Interventional service we use targeted therapy dosimetry - guided that may significantly impact on patient's specific therapy selection and treatment.

In the brain tumors we are investigating the correlation between MR imaging, with morphological and functional imaging (diffusion and perfusion), with those pathological date and molecular profile as IHD1 and 2, MGMT methylation, ATRX (Glioma Project).

Radiotherapy Unit

Head: Prof. Giuseppe Sanguineti, MD

Staff

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Dr. Mondati Mara, Nurse
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Dr. Monica Montano, Therapist
Dr. Bedini Fabio, Therapist
Dr. Canciani Laura, Therapist
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Mission

The Department of Radiotherapy is characterized by experienced professionals and technology that allow the realization of high-precision irradiation techniques such as Intensity Modulated Radiotherapy (IMRT), Rapid Arc (RA)/Volumetric Modulated Arc Therapy (VMAT), Stereotactic Radiotherapy Surgery (SRS) and Stereotactic Body Radiotherapy (SBRT). Image guidance is achieved with cone beam CTs or DRRs. The latter ones are implemented within the Cyberknife system to track the position of the target in real time. Moreover, respiratory movement control techniques are available to reduce the confounding effect of the position of the target to be irradiated. A constant collaboration with the Radiology and Nuclear Medicine allows us to have access to advanced imaging solutions to correctly identify the location of the disease prior to treatment planning, such as multiparametric MRI and novel tracer PET-CT.

Clinical Activity: Clinical activity covers all options of photon-based external beam radiotherapy including IMRT, VMAT, SRS, SBRT, IORT. Moreover, the recent introduction of Cyberknife (CK) allows SRS/SBRT of both intracranial and extracranial lesions (both malignant and benign) with high precision and live motion tracking.

Clinical and Research Activities

1.

A prospective randomized phase II trial of DCE-MRI hypoxia-targeted boost chemoradiotherapy for head and neck cancer. This is a randomized, prospective, single-institution, phase II trial, planning to enroll 91 patients affected by HNSCC. Patients will undergo a DCE-MRI before treatment (baseline, MR1). Only patients with at least 5cc or more

hypoxic volume at the primary site will be considered eligible and randomized between stIMRT and deIMRT. A second DCE-MRI will be performed at 2 weeks into CRT (MR2), and the hypoxic volume will reassessed; in case of a larger than initial hypoxic sub-volume, the IMRT plan in the deIMRT arm will be adapted accordingly. Patients will then be followed for primary tumor response and recurrence. Actuarial Kaplan Meier) local control rates in the two arms will be compared with the log rank test at 2 yrs after treatment completion.

2.

Phase I-II study to evaluate feasibility and the effectiveness of SBRT with Linear Accelerator in 3 fractions for low/intermediate risk Prostate cancer: evaluate the feasibility and locoregional toxicity of SBRT in 3 fractions using LINAC; evaluate the effectiveness hypofractionated “extreme” (3 fractions) delivered using SBRT for low /intermediate risk localized prostate cancer.

3.

Evaluation of neurotoxicity in cancer patients with multiple (4-10) brain metastases treated with stereotactic radiation therapy : This is a prospective observational study that aims to evaluate neuro-cognitive toxicity, quality of life and incidence of radionecrosis in patients treated with stereotactic radiation therapy for multiple lesions (from 4 to 10).

4.

Radio-induced modifications of lymphoid subpopulations involved in resistance and escape mechanisms to the treatment of localized prostate cancer: This prospective study aims to evaluate the effect of radiotherapy on immunoregulatory B, plasma cells, NK, T, and T lymphocyte populations in order to evaluate any toxicity effects and selective decrease / increase of the various populations and to correlate these effects with the clinical course of the disease. We hypothesize that the radio-induced effects are extremely early, to justify an investigation already after the first treatment session. Furthermore, we hypothesize that different RT dose fractionation schemes may induce different modifications on cell populations, allowing to identify scheduling that minimizes the risk of induction of immunosuppressive cells.

5.

Toxicity and its possible association with the immune response during Radio-Cetuximab therapy in Patients with Squamous Carcinoma of the Head and Neck District, stage III or IV disease. This is a prospective cohort study aimed at assessing the impact of systemic therapy with cetuximab associated with radiation therapy on the burden of acute symptoms of the treatments proposed in locally advanced squamous carcinomas of the cervicocephalic district. It also investigates the possible correlation between activation of the ADCC and skin toxicity. For the objectives, see the statistical considerations.

6.

Pilot study evaluating the use of ⁶⁴Cu-PET / CT total body in patients with recurrence in the prostate lodge visible in mpMR. The study in question has the following objectives: a. Primary objective: To evaluate the detection rate of ⁶⁴Cu-PET / CT of relapses in patients undergoing radical prostatectomy and subsequent biochemical recurrence;

Secondary objectives: To evaluate any change in radiotherapy strategy in terms of lesion delineation and dose distribution planning. Evaluate the performance of both methods (mpMR and ⁶⁴Cu-PET / TC) in evaluating the response to radiation treatment with or without hormone therapy

7.

Single vocal cord stereotactic Radiotherapy for early stage glottis cancer (cTis-1): Prospective phase I-II study to evaluate feasibility and the effectiveness of SBRT for early stage (cTis-1N0M0) glottic cancer.

8.

Accelerated Hypofractionated radiotherapy inclusive of nodal radiation after conservative surgery for women with node-positive breast cancer. Feasibility study. To evaluate acute toxicity of radiotherapy schedule in which therapy was completed in 11 fractions over 3 weeks inclusive of a sequential boost.

9.

Longitudinal Evaluation of Intestinal, Haematological and Urinary Toxicity From Pelvic Irradiation for Prostate Cancer (IHU-WPRT-TOX): The aim of this study is to develop predictive models of IMRT-WPRT induced patient-reported

intestinal, hematologic and urinary toxicity in PCa treatment.

10.

The rationale of the prophylactic irradiation of pelvic lymph-nodes by means of Whole-Pelvis Radiotherapy (WPRT) in prostate cancer (PCa) is to eradicate subclinical lymph-nodal involvement. Even though delivered by means of modern Intensity-Modulated Radiotherapy techniques, WPRT may result in intestinal, hematologic and urinary toxicity severely affecting patients' daily health- related quality-of-life (HRQoL) within the so-called and inadequately investigated Pelvic Radiation Disease.

11.

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of JNJ-56021927 in Subjects with High-risk, Localized or Locally Advanced Prostate Cancer Receiving Treatment with Primary Radiation Therapy: To determine if JNJ-56021927 plus gonadotropin releasing hormone (GnRH) agonist in subjects with high-risk, localized or locally advanced prostate cancer receiving primary radiation therapy (RT) results in an improvement of metastasis-free survival (MFS) evaluated by blinded independent central review (BICR)

12.

DUE02 - Urinary and Erectile Dysfunction - 02. Validation of predictive toxicity models after radiotherapy treatment for prostate cancer: The prospective observational study (DUE02) proposes to enroll patients with prostate cancer treated with high-dose external radiotherapy and to follow them during follow-up, in order to be able to validate the models developed in the previous study DUE01 on an independent population.

13.

Acral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO): This study is aimed at estimating the effectiveness of definitive radiotherapy as compared to standard surgical treatment for patients with primary sacral chordoma who are candidates to a complete en-bloc resection, in term of relapse-free- survival (RFS).

14.

A Randomized, Phase 3, Double-Blind Study of Chemoradiotherapy With or Without Pembrolizumab for the Treatment of High-risk, Locally Advanced Cervical Cancer (KEYNOTE-A18 / ENGOT-cx11): the primary objective is to compare concurrent chemoradiotherapy plus pembrolizumab with concurrent chemoradiotherapy plus placebo with respect to progression-free survival per RECIST 1.1 as assessed by blinded independent central review or by histopathologic confirmation of suspected local disease progression (in the absence of radiographic disease progression per RECIST 1.1).

15.

1Sbrt±Tad for Unfavorable iNtermediate risk/high risk prostate cancer (STUNNIN): a Randomized Phase II Study: The primary objective of the study is 3-yr bNED survival. If bNED survival is not significantly different between the two experimental arms, the one without AD will be chosen in a future comparison with the standard of care.

16.

Granisetron transdermal system (GTDS) in preventing nausea and vomiting induced by cisplatin-based chemotherapy and concurrent radiotherapy for head and neck cancer: the primary objective is to evaluate the activity of Snacuso patch in controlling nausea and vomiting in patients with HNC undergoing chemo-radiotherapy treatment.

17.

Radio-Hyperthermia in soft tissue sarcomas: MRI and PET functional imaging response criteria related to anatomopathological and clinical data: Primary endpoint is to evaluate the diagnostic accuracy of the various PET and post-therapy MRI parameters (alone or in combination) in predicting histological response to radiotherapy/hyperthermia.

18.

Lung Microcytoma Extended Disease: Prospective Study Combining Thoraco -Abdominal (mediastinal) Radiation Therapy with Atezolizumab Maintenance Immunotherapy Treatment

Nuclear Medicine Unit

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Mission

The mission of the Nuclear Medicine Unit is to perform clinical and research activities in nuclear oncology aiming to the following main objectives:

- Achieve professional excellence both in nuclear diagnostics and in nuclear therapy according national and international standards
- Develop and validate innovative technologies and new radiopharmaceuticals for molecular imaging and molecular target therapy in the context of theranostic models
- Transfer research results into clinical practice and national health system program
- Monitor process influence on final outcome according to a vision of a process-oriented culture and patient's centered care

The management of our organization is inspired by the following values:

- we respect the Patient, who is at the center of our paths, our activities, our continuous improvement efforts and with whom we try to have a relationship based on honesty and sincerity
- we believe in the professionalism of the people who work in our organization, whatever their role, and we try to create transparent communication channels based on mutual respect
- we believe in teamwork and in multidisciplinary confrontation:

The activities of the Nuclear Medicine Unit include both therapy and diagnostics with radionuclide in main oncology fields. Standard of all diagnostic and therapy activities are assured by ISO 9000 and professional quality certification is assured by AIMN-Bureau Veritas.

Therapy

Therapy, as the main field of clinical activities, includes: radioiodine treatment of thyroid carcinoma, selective internal radiotherapy of liver tumors using ^{90}Y and ^{166}Ho microspheres, target therapy of bone metastases using alfa-emitters and Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors using ^{177}Lu Oxodotreotide. The therapies are performed in the specialized nuclear medicine ward, equipped with sophisticated radioprotection instrumentation. Pre and post-treatment visits are carried out in the outpatient clinic of Nuclear Medicine. Throughout this process, the

patient-user is followed by a Nuclear Medicine specialist, thus ensuring the unity of assistance.

The Centre is leader in Italy and Europe in the field of selective internal radiation therapy of liver tumors with more than 1000 treatment performed and followed. Biological optimization of radiation dose studies have been performed using new algorithms and integrated imaging to evaluate heterogeneous dose distribution in tumor lesions and to develop personalized therapy plans. To note that the Center is the one of the few in the world to use all types of radiopharmaceuticals available for this type of treatment with the possibility of selecting the most suitable one on a case-by-case basis according to the concept of precision medicine.

Training on innovative treatments with new alpha-emitters radiopharmaceuticals and with ^{177}Lu Oxodotreotide were also performed and clinical protocols validated.

Diagnostic

The Nuclear Medicine Unit play a key role in the diagnostic-therapeutic-assistance path (PDTA) of the oncological patients of the Institute thanks to PET / CT and SPET / CT diagnostics.

Main diagnostic activities are - PET / CT imaging with FDG and non FDG tracer and in particular the Centre is leader in F-Choline and PSMA (^{64}Cu and ^{18}F) PET imaging of prostate cancer and FDG PET imaging of musculoskeletal tumors ; ^{68}Ga -Dotatoc PET/CT is also available for neuroendocrine Tumors imaging: - all traditional planar and SPET oncological scan (mainly sentinel node mapping, cardiac gated-SPET and ^{131}I whole -body scan) and state of art SPET/CT imaging.

The choice of imaging, the clinical question and the results of the examinations are usually discussed collectively in the disease management team (DMT) with a view to improving their appropriateness and effectiveness.

Clinical and Research Activities

Clinical activity of the Nuclear Medicine Unit was focused on supporting all Institutional surgical and oncological paths. In 2021 over 10.000 therapeutic and diagnostic procedures were performed with approximately 300 cancer radionuclide treatments.

Research activities of the Nuclear Medicine Unit in 2021 focus on radionuclide therapy and molecular imaging SPET/CT and PET/CT in different tumors (thyroid, head and neck, sarcoma, gynecological and urological tumors, lymphoma, breast and lung cancer, liver tumors) aiming to improve early diagnosis, biological characterization and response monitoring, biological volume contouring to guide radiotherapy.

Main currently specific topic of research includes:

- new PET radiopharmaceuticals (^{64}Cu and ^{64}Cu -PSMA) performance and safety evaluation in prostate cancer
- role of FDG PET in clinical management of musculoskeletal tumors
- radiomic studies
- multicentric evaluation of FDG PET role in interstitial pneumonia suggestive of COVID-19
- biodistribution, radiobiological effects and long-term safety studies after treatment with alpha-emitter (^{223}Ra) in metastatic prostate cancer patients and adapted protocols
- role of integrated imaging with ^{131}I SPET/CT and ^{18}F -FDG PET/CT in advanced thyroid carcinoma both for diagnosis than for biological and dosimetric optimization
- identification of specific selective internal radiation therapy with ^{90}Y - and ^{166}Ho -microspheres indications and optimization on a basis of single disease status
- quantitative 3D dosimetry based on hybrid imaging and biomarkers correlation to optimize therapy in HCC patients treated with ^{90}Y and ^{166}Ho microspheres and in NET tumors treated with ^{177}Lu - Oxodotreotide

Clinical Pathology and Cancer Biobank Unit

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Mission

Clinical Pathology and Cancer Biobank performs laboratory biological tests using the most modern techniques of investigation, that contribute to the clinical management of oncologic patients submitted to conventional and experimental therapies. The Unit participates as a Reference Laboratory in the activities of the Phase1 Clinical trials Centre (CCF1) studies and supports the Clinical Trial Center (CTC) activities for the subsequent Phase studies. The Unit has already certified with a UNI EN ISO 9001:2015.

In 2014 the tumor Biobank of Regina Elena National Cancer Institute (BBIRE) was established as a joint initiative between the Clinical Pathology and Pathology Unit with the financial support of the Scientific Directorate. BBIRE is involved in a growing number of Institution projects (53 projects), and as a member of the European research network of Biobanks and Biomolecular Resources (BBMRI-ERIC) participates with European groups (EORTC- European Organization for Research and Treatment of Cancer) to large-scale multi-center projects. Also, BBIRE is involved in the ACC network and the primary objective of the Pathology and Bio-banking Working Group is represented by the organization of a shared pre-analytical workflow to obtain uniform quality of the biological samples, mainly tissue sample. BBIRE currently stores more than 72234 samples of biological fluids (whole blood, serum, plasma, PBMC) from more than 3427 patients and more than 18690 tumor tissue samples (Formalin-fixed paraffin-embedded (FFPE), Snap Frozen, Optimal Cutting Temperature (OCT) and Fresh Tissue (96 cases for Organoids) from more than 1635 patients.

Innovative activities are performed in different subject areas: - Flow Cytometry in Primary Central Nervous System Lymphoma diagnosis and Minimal Residual Disease assessment in Multiple Myeloma; - Non Small Cell Lung Carcinoma (NSCLC) patients Liquid Biopsy assay to identify specific EGFR mutations, making patients eligible for EGFR-targeted therapies and for disease progression monitoring and detection of resistance mechanisms to EGFR-targeted therapies; - Genetic testing with NGS technology on the genes associated with the most frequent HCS such as: Lynch syndrome (LS), Hereditary Breast and Ovary Cancer syndrome (HBOC), APC-associated polyposis and MUTYH-associated polyposis (AAP and MAP) and Multiple Endocrine Neoplasia syndrome type 1 and type 2 (MEN1 and MEN2); - Hereditary Hemochromatosis genetic testing for five different forms of the disease and corresponding genes (HFE, HAMP, HJV, TFR2 and SLC40A1) according to the diagnosis suspicion; - Porphyria genetic testing according to the clinical

manifestations of the disease and the associated genes (UROD, ALAS2, HMBS, PPOX, FECH); - Pheochromocytoma and paraganglioma genetics testing of the specific disease-related genes. - in Pharmacogenetics, DPYD and UGT1A1 genotyping to reduce the risk severe toxicity are performed. - Cytogenetics Laboratory, specialized in the analysis of chromosome abnormalities in blood diseases.

Clinical and Research Activities

Biobank of Regina Elena National Cancer Institute (BBIRE)

Since the beginning of the Pandemic, BBIRE has been involved in several studies concerning approaches and metrics to evaluate the impact and improve the results of patients with frailty in the COVID-19 era. Studies to evaluate the efficacy and antibody titre of the BNT162b2 vaccine by BioNTech and Pfizer in a sample of 274 health professionals from the IFO, a sample of 82 patients over 80 years of age and a sample of 400 fragile patients belonging to our Institute. The biomaterials collected in the BBIRE consist of: serum, plasma, whole blood and PBMC collected at different time-points. Collection of biological fluid samples from healthy subjects belonging to the Institute's Immunohematology and Transfusion Medicine Service to set up a control group and for quality checks on stored biological samples (4671 samples, 140 Donors).

In the spirit of its enhancement and a precise definition of its activities, a Quality Manual/Regulation together with the necessary definition of the two operational bodies the Steering Committee and the Operational Group has been drafted and deliberated (resolution n 431 of 13 June 2017 / revision of resolution 1360 of 30/12/2021).

HEMOCELL Haemostasis and Thrombosis

A solution designed specifically for Hemostasis testing, integrating the best-in-class ACL TOP 750 LAS testing systems, HemoHub Intelligent Data Manager, and a Laboratory Automation track, HemoCell optimizes testing to achieve greater efficiencies and enhanced quality. Advanced automation of all phases of testing for unmatched workflow optimisation: Pre-analytical: Real-time sample control (Sample sorting-Centrifugation-Decapping); Analytical: QA for every result (sample checks: HIL, tube-fill height, clot potential); Post-analytical: Power of HemoHub (Centralised QC control; Critical-results monitoring; Clot-signature curves; Custom reflex/rerun rules)

Diagnostic harmonization initiative on Multiple Myeloma for Gruppo Laziale Mieloma Multiplo (GLMM).

The project aims to reach a consensus among regional laboratories specialized on onco-haematology diagnosis regarding the flow cytometry antibodies panel, data analysis and clinical report for Multiple Myeloma (MM) diagnosis and monitoring.

The network is also focusing on the positive selection of the plasma cell population by immune-magnetic beads separation, for a better assessment of the cytogenetic profile in plasma cell disorders.

New forms have been designed, approved and introduced on RedCap, the clinical and laboratory database shared among all the GLMM Centers. The new collection forms focus on cytogenetic and immunophenotype data of MM patients at diagnosis and on follow up.

A National project is ongoing to create an "Italian MM MRD network" that will share the same method for MRD analysis in MM patients across hub-Haematology centers in Italy. The most common employed methods for MRD evaluation (both flow cytometry and molecular biology-based) will be harmonized among the involved "start-up" centers.

Phenotypic and cytogenetic subclones identification in multiple myeloma by flow cytometry and FISH analysis after immunomagnetic beads selection of the plasma cell population.

The study is a multicenter retrospective cohort study on patients with MM who underwent diagnostic bone marrow (BM) puncture at diagnosis or in relapse / disease progression according to routine clinical practice. A subset of monoclonal gammopathy of uncertain significance (MGUS) have been also included.

Primary aim of the study was to document the role of the FC study after immunomagnetic separation for the evaluation

of the PC enrichment procedure (yield), the type and percentage of residual leukocytes (non PCs) and a possible selection of the PC population after enrichment.

Secondary objectives were:

1. to identify, by the evaluation of Ig light chain expression on the PC surface markers, the presence and percentage of clonal and normal PC subpopulations;
2. to compare the percentage of phenotypic and cytogenetic subclones taking in account the proportion of normal PC and/or contaminating leukocytes after immunomagnetic enrichment;
3. to compare phenotypic and cytogenetic PC subclones at diagnosis and document any qualitative and / or quantitative changes at disease progression;
4. to evaluate a possible prognostic correlation between phenotypic and/or cytogenetic subclones expression

Cerebrospinal fluid (CSF) flow cytometry has a crucial role in the diagnosis of leptomeningeal disease in onco-haematology. We have evaluated the cytometry characterization of 138 CSF samples from patients affected by non-Hodgkin lymphoma, negative for disease infiltration. The aim was to focus on the CSF non-neoplastic population, to compare the cellular composition of the CSF with paired peripheral blood samples and to document the feasibility of flow cytometry in hypocellular samples.

We have documented that T lymphocytes are the most abundant subset in CSF with a predominance of CD4-positive over CD8-positive T cells (CD4/CD8 ratio = 2) together with a minority of monocytes. No B cells are present. The differences between CSF and paired peripheral blood lymphoid phenotype has demonstrated the existence of an active mechanism of lymphoid migration through the meninges.

Cordone I, Masi S, Giannarelli D, et al. Major Differences in Lymphocyte Subpopulations Between Cerebrospinal Fluid and Peripheral Blood in Non-Hodgkin Lymphoma Without Leptomeningeal Involvement: Flow Cytometry Evidence of a Cerebral Lymphatic System. *Front Oncol.* 2021;11:685786. Published 2021 Jun 3. doi:10.3389/fonc.2021.685786.

Sole of CD138 in breast cancer prognosis. Metastasis is the main cause of breast cancer (BC) mortality. We have recently documented a possible role of syndecan-1 (CD138) expression as a prognostic marker involved in leptomeningeal metastatic. In collaboration with Department of Radiological, Oncological and Pathological Sciences, Sapienza University, Rome, Italy, a study aimed to investigate and compare syndecan-1 tissue expression and localization in primary and secondary BC, focusing the attention on brain metastasis, has been started. A total of 23 patients, 10 paired cases and 13 brain metastases for which the primary tumor was not available, have been selected and evaluated for syndecan-1 expression in both primary and metastatic BC. Preliminary results support syndecan-1 overexpression as a marker of aggressive BC disease and poor prognosis.

MYC translocation in MM. Our work aims to validate the central role of MYC activation development and progression of MM. Clinical and biological data have informed about frequent MYC locus rearrangements and gains, MYC mRNA overexpression, MYC protein stabilization, and deregulation of pathways involving MYC. IMWG (International Myeloma Working Group) actually do not recommend MYC evaluation in MM patients.

We performed FISH evaluation on 360 MM patient samples of CD138+plasma cells. MYC translocations have been reported in 20% of patients with newly diagnosed MM. These translocations involve the immunoglobulin (IG) loci and some non-Ig partners. Patients bearing MYC translocations have decreased progression-free survival and overall survival.

These approaches are expected to yield new therapeutic strategies in the near future, allowing for precision medicine in MYC-driven cancers.

Medical Physics and Expert System Unit

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Mission

The Medical Physics Department (MPD) collaborates with different departments of the hospital to ensure patient safety and to lower clinical risk. Its activities are addressed to reduce the undue dose to patients, workers and environment according to national and international radiation protection guidelines and to optimize the technical aspects in all the activities that are based also on the use of other physical agents, such as magnetic resonance, ultrasounds and lasers.

MPD takes part to the installation, commissioning and acceptance testing of high technology equipment and acts to improve diagnostic accuracy and treatment precision through the implementation of quality assurance protocols, the carrying out of checks and measurements, the continuous optimization and revision of procedures.

Physicists conduct research activities in the field of diagnosis and treatment of cancer giving its perspective to the clinical team by means of its knowledge in imaging, radiological physics and radiobiological sciences.

The MPD staff daily develops personalized radiotherapy treatment plans for patients including conventional and high dose and high precision radiotherapy and intra-operative radiotherapy, while in nuclear medicine treatments the MPD staff performs patient-specific dosimetry, with the aim of improving tumour control while sparing normal tissues.

Dosimetry checks are performed on a daily basis and quality assurance programs are routinely carried out for the activities of Radiotherapy Dpt, Nuclear Medicine Dpt and Diagnostic Dpt. Support is given daily within many aspects of technical managing of clinical procedures. The MPD staff also takes part into the conceiving and drawing up of many of clinical protocols giving its contribution from the physicist perspective to novel treatment strategies and techniques.

Relevant activities in Radiotherapy (RT)

Implementation, development, optimization and quality monitoring in Modulated Intensity RT (IMRT); RT Volumetric Modulated Arc (VMAT); Robotic Stereotaxic Radio Surgery (robotic SRS); RT Guided by Images (IGRT) and RT with Respiratory Gating; Hyperthermia (HT), Combined Radio-Hyperthermia Treatments

Collaboration with the Radiotherapy Dept. for merging of images of multimodal images; drafting of research protocols / clinical trials; design and implementation of hypo-fractionated RT protocols; development of radiobiological models aimed at describing dose-effect relationships, based on clinical data; implementation of clinical studies relating to

breast, prostate, head and neck cancer, sarcomas.

Relevant activities in Radiology and Diagnostic Imaging

Analysis of diagnostic reference levels (LDR) and application of statistical methods for the solution of various problems relating to data quality;

Development of methods for setting and analyzing data from observer performance studies in diagnostic imaging;

Study of an artificial intelligence algorithm for the classification of digital breast tomosynthesis images for the automated diagnosis of breast cancer;

Radiomic analysis of CT images with the aim of identifying potential indicators of tumor aggression and survival, and building multifactorial predictive models with the guidance of machine learning algorithms;

Elaboration and analysis of functional studies (DCE-MRI, DWI with advanced techniques, fMRI); Support for the optimization of MRI sequences in the definition of clinical protocols.

Relevant activities in Nuclear Medicine

Assessment of the patient-specific dosimetric study in radiotherapeutic treatments with specific isotopes: I-131, Lu-177, Y-90, Ra-223 and Ho-166;

Absorbed dose measurements and calculation, in order to minimize the probability of toxicity of treatment and to maximize its efficacy. Levels of radiation emitted both by blood samples and by the patient's body are measured using well counter and quantitative PET-SPECT/CT images to calculate the quantity of radiopharmaceutical present in tumor and organs.

Clinical and Research Activities

The activities of our laboratory are promoted by a continuous interaction with the Radiology and Diagnostic Imaging Department, Nuclear Medicine Department and Radiotherapy Department of our institute and are made possible also thanks to external collaborations with universities, research institutions and industries interested in our lines of research.

The Role of Patient- and Treatment-Related Factors and Early Functional Imaging in Late Radiation-Induced Xerostomia in Oropharyngeal Cancer Patients

The advent of quantitative imaging in personalized radiotherapy (RT) has offered the opportunity for a better understanding of individual variations in intrinsic radiosensitivity. We aimed to assess the role of magnetic resonance imaging (MRI) biomarkers, patient-related factors, and treatment-related factors in predicting xerostomia 12 months after RT (XER12) in patients affected by oropharyngeal squamous cell carcinoma (OSCC). Patients with locally advanced OSCC underwent diffusion-weighted imaging (DWI) and dynamic-contrast enhanced MRI at baseline; DWI was repeated at the 10th fraction of RT. In our conclusion, non-invasive biomarkers from DCE-MRI, in combination with dosimetric variables and self-assessed acute XQ scores during treatment may help predict grade 2 XER12 with a fair to good accuracy.

Multiparametric MRI Evaluation of Oropharyngeal Squamous Cell Carcinoma. A Mono-Institutional Study

The aim of this study is to define the pre-treatment radiological characteristics of oropharyngeal squamous cell carcinoma (OPSCC) using morphological and non-morphological magnetic resonance imaging (MRI), based on HPV status, in a single-institution cohort. In total, 100 patients affected by OPSCC were prospectively enrolled in the present study. All patients underwent 1.5T MR with standard sequences, including diffusion-weighted imaging with and intravoxel incoherent motion (IVIM-DWI) technique and a dynamic contrast-enhanced (DCE) MRI. We detected no significant difference in DCE-MRI parameters by HPV status. Based on a multivariate logistic regression model, the combination of clinical factors, such as tumor subsite and alcohol habits, with the perfusion-free diffusion coefficient D_t of LNs, may help to accurately discriminate OPSCC by HPV status.

MRI-Based Radiomics to Differentiate between Benign and Malignant Parotid Tumors With External Validation

The differentiation between benign and malignant parotid lesions is crucial to defining the treatment plan, which highly depends on the tumor histology. We aimed to evaluate the role of MRI-based radiomics using both T2-weighted (T2-w) images and Apparent Diffusion Coefficient (ADC) maps in the differentiation of parotid lesions, in order to develop predictive models with an external validation cohort. A sample of 69 untreated parotid lesions was evaluated retrospectively, including 37 benign (of which 13 were Warthin's tumors) and 32 malignant tumors. The model with the final feature set was achieved using the support vector machine binary classification algorithm. Radiomic analysis of ADC, T2-w images, and qualitative scores evaluating margins and CE allowed us to obtain good to excellent diagnostic accuracies in differentiating parotid lesions, which were confirmed with an external validation cohort.

Thermo-radiotherapy treatment: a synergistic approach to treat superficial soft tissue sarcomas evaluated by Dynamic Contrast Enhanced Magnetic Resonance Imaging (DCE-MRI)

The aim of this work is to evaluate the combination of radiotherapy and hyperthermia (RT-HT) in superficial soft tissue sarcomas (SSTS). A clinical protocol approved by our ethics committee has just begun to evaluate pre- and post-treatment data by advanced MRI imaging. In 2021 two patients with pleomorphic liposarcoma and myxofibrosarcoma have been enrolled in the protocol so far. Patients underwent a baseline and post-treatment magnetic resonance (MR) 3T exam with DCE-MRI to evaluate perfusion maps. In addition, a whole body CT-PET with 18F pre and post treatment were performed. Patient accrual is ongoing, these preliminary results show that DCE-MRI is a potentially helpful tool to monitor modifications in tissues after RT treatment. Metabolic data from PET should improve the accuracy of volumetric maps.

A wearable radiation measurement system for collection of patient-specific time-activity data in radiopharmaceutical therapy: system design and Monte Carlo simulation results

A high level of personalization in Molecular Radiotherapy (MRT) could bring advantages in terms of treatment effectiveness and toxicity reduction. This work concerns a proof-of-concept Monte Carlo simulation study of "WIDMApp" (Wearable Individual Dose Monitoring Apparatus), a multi-channel radiation detector and data processing system for in vivo patient measurement and collection of radiopharmaceutical biokinetic data. This study demonstrates that it is possible, to reconstruct the organ cumulated activity by measuring the time dependence of counts recorded by several detectors placed at selected positions on the patient's body. The WIDMApp approach could provide an effective tool to characterize more accurately the radiopharmaceutical biokinetics in MRT patients, reducing the need of resources of nuclear medicine departments to perform individualized biokinetics studies. The results obtained justify development of an actual prototype system to characterize this technique under realistic conditions.

Dosimetric Evaluation of Automated Optimization based on GPS for Prostate and Lymph Node VMAT Treatment Planning cases in RayStation

The aim of this work is to provide a comprehensive dosimetric evaluation of genetic planning solutions (GPS) on RayStation treatment planning system for the radiotherapy of prostate and lymph nodes. 15 prostate with lymph nodes VMAT treatment plans originally created with Eclipse TPS and clinically accepted were reoptimized in Raystation a) by using GPS3.0 algorithm, b) manually adjusting the plan obtained with GPS 3.0 (MA) and c) by using GPS4.0 algorithm especially developed for this patients' population. In our Conclusion GPS4.0, being a personalized script, has shown to have an overall better performance respect to GPS3.0 and to be challenging compared to the MP in terms of plan quality and robust automation. Moreover, the speed of the whole process of optimization and the consistency in regard to the planner experience suggest to implement these techniques in the clinical practice.

Comparison of rigid and deformable coregistration between mpMRI and CT images in radiotherapy of prostate bed cancer recurrence

The purpose was to evaluate the accuracy of rigid coregistration between multiparametric magnetic resonance (mpMR) and computed tomography (CT) images for radiotherapy of prostate bed cancer recurrence. Fifty-three patients (59 nodules) accrued in a prospective study on salvage radiotherapy for prostatic bed recurrence were suitable for the analysis. In our conclusion rigid image coregistration is sufficiently accurate in this setting. The results indicate that the deformable registration tends to shrink the voxels and to dislocate the ROI, the adopted expansion for the recurrence volume adequately accounts for the observed deformation and dislocation, provided that organ filling is controlled.

Response on DCE-MRI predicts outcome of salvage radiotherapy for local recurrence after radical prostatectomy

To assess the predictive role of response on dynamic contrast enhancement on magnetic resonance imaging (DCE-MRI) of visible local lesions in the setting of salvage radiotherapy (sRT) after radical prostatectomy. All patients referred for sRT for biochemical failure after radical prostatectomy from February 2014 to September 2016 were considered eligible if they had been restaged with DCE-MRI and had been found to have a visible lesion in the prostatic bed, but no distant/nodal disease on choline positron emission tomography (PET)-computed tomography (CT). Eligible patients were contacted during follow-up and offered reimaging with serial DCE-MRI until lesion resolution. In our conclusions patients whose lesions disappear during follow-up have a better outcome than those with unchanged lesions after sRT alone.

Organ motion in linac-based SBRT for glottic cancer

The purpose of this study is to evaluate inter- and intra-fraction organ motion as well as to quantify clinical target volume (CTV) to planning target volume (PTV) margins to be adopted in the stereotactic treatment of early stage glottic cancer. Stereotactic body radiotherapy (SBRT) to 36 Gy in 3 fractions was administered to 23 patients with early glottic cancer T1N0M0. In the setting of controlled swallowing during treatment delivery, intra-fraction motion still needs to be taken into account when planning with estimated CTV to PTV margins of 3, 5 and 3 mm in the X, Y and Z directions, respectively.

Tranfusion Medicine Unit

Head: Dr. Maria Laura Foddai, MD

Staff

Mission

Epidemiology and Cancer Registry Unit Head: Dr. Valerio Ramazzotti, MD

Staff

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Dr. Giuseppina Caolo, Research Assistant

Dr. Annunziata Di Turi, Research Assistant

Mission

The 'Epidemiology and Cancer Registry' Unit operates within the framework of public health, aiming at the monitoring, control and prevention of cancer. The unit is mainly involved in descriptive epidemiology based on cancer registration; evaluative epidemiology based on data from regional and national programs for the evaluation of health care interventions; assessment of tools for the application of medical humanities and telemedicine in clinical practice within the framework of personalization of care. The unit actively takes part in the ongoing projects included in the 'improvement action plan' and contributes to the implementation of the Institute's Information and Communication Technology system, aiming at facilitating access and analysis of clinical and research data.

Mission

Descriptive Epidemiology

Population and hospital cancer registers are the core of the activities. Population cancer registration is a crucial tool in assessing the frequency and distribution of tumors in order to understand their causes and to adopt appropriate prevention and treatment measures. Hospital cancer registers, instead, support clinical research and management in the hospital's setting.

Population-based cancer registry of Lazio region

In accordance to a regional law establishing the Population-based Cancer Registry of the Lazio region (RTL) in 2015, the Unit has assumed - under the coordinating action of the Department of Epidemiology for the Lazio Regional Health Service - the role of 'functional unit' for the 'Città metropolitana di Roma' area, covering a population of over 4,330,000 inhabitants and more than 24,000 estimated incident cases of malignant neoplasms per year.

The Functional Unit has been involved in the validation, coding and registration of the cases collected by a dedicated regional platform. In addition, the Unit has started combining the data from the regional platform with the clinical data detected at IFO, in order to improve the quality of the registration. In 2021 the database of reference for the selection and registration of incident cases exceeded the threshold of 122,000 elaborated records across all available years.

Hospital-based cancer registry of the National Cancer Institute 'Regina Elena'

The hospital-based cancer registry (RTO) of the National Cancer Institute 'Regina Elena' was designed to define the occurrence, the topography and the morphology of the treated cases per year, to provide statistical reports according to the OECI standards, and - as collaborative unit of the Clinical Trial Centre IFO - to estimate the number of eligible patients for the clinical trials by specific neoplastic features. The registration activity continued with reference to the

neoplastic sites of the breast, lung and colorectal for the years 2016-2019, reaching over 7,000 registrations in 2021. Periodic data analysis was performed for internal reports and for scientific publications.

EURACAN (EUropean network for Rare Adult solid CANcer)

EURACAN is going to enable a major improvement in the access to excellence diagnosis and treatment for European patients. IFO has been recognized as an ERN (European Reference Network) member with expertise in eight groups of rare tumors. The Unit has been particularly involved in designing and implementing an institutional database collecting data on the rare solid cancer patients diagnosed and/or treated at the Institute.

In 2021, the Unit focused on the implementation of the digital platform dedicated to rare cancer cases registered in IFO since 2018; at the end of 2021 over 3.500 cases were registered. The Unit has also conducted training of the personnel involved in the process of identification and registration of cases. Other activities have included periodic data analysis and reporting and the participation as Guest Editor for JCM Special Issue Bone and Soft Tissue Sarcomas. The Unit was involved in the organization of a course for rare tumors networking held within the framework of the 2021 IFO ECM training plan.

Rarity Project

The Unit has been participating in the national ACC RARITY project (Register rAre adult solid canceRs in ITaly). The goal of the project is to create an Italian clinical register, shared between the Italian centres accredited to EURACAN, which will collaborate within the European STARTER project for the definition of the European clinical register on rare cancers. The activity in 2021 focused on head and neck rare cancers, participating in the selection of core variables to be collected and analysed, and in CRF (Case Report Form) testing and implementation.

Evaluative Epidemiology

The evaluation of the outcomes of health interventions is of particular relevance for an 'Istituto di Ricovero e Cura a Carattere Scientifico' (IRCCS) such as the Regina Elena Institute. The evaluation, based on multiple indicators - both quantitative and qualitative - allows comparisons with other IRCCSs and hospitals, both at the regional and national level. The data obtained allow to monitor specific indicators for several neoplastic sites and to evaluate the quality of the coding diagnosis and treatments in the discharge hospital report, taking into account concurrent risks in patients.

The Unit was involved in the internal audit for: 1) the Regional Outcome Evaluation Program (P.Re.Val.E.); 2) the National Outcome Evaluation Program (PNE). The main objectives are: observational assessment of the efficacy and the effectiveness of health-care interventions; identification of factors within the health-care delivery process that affect outcomes; monitoring levels of care. In this framework, technical reports for the National Cancer Institute 'Regina Elena' (Report on P.Re.Val.E. 2021; Report on PNE 2020) were submitted to the Medical Directorate.

The Unit has also coordinated audits prescribed by the Department of Epidemiology of Regional Health Service of the Lazio Region on 'Mortality within 30 days after surgery for malignant tumors of lung and colon' based on the findings of the P.Re.Val.E.

Additional Epidemiology

Narrative Medicine

The Unit promoted research activities on the application of narration and arts in medicine and has been involved in several initiatives such as: oral presentations at training courses, meetings and conferences; contribution to the AIOM monography on cancer care and narrations during the COVID-19 pandemic; contribution to the production of videos on projects results. Trials aiming at validating methodologies for the application of narration and arts in oncological clinical practice, targeting different populations and settings, have been carried out.

The Unit has continued monitoring, collecting and evaluating data concerning the studies started in previous years: EPIMENAT (application of narrative medicine in patients with tumoral epilepsy); AMENAS (application of narrative medicine in patients with sarcoma); TARPEA (a multicentric pilot study involving a three-dimensional evaluation of

aromatase inhibitor toxicity - expected, detected and perceived - in early breast cancer patients).

Telemedicine

The Unit, has been involved in the IFO Task Force of the 'Specialization and Telemedicine' group in collaboration with DNM Srl (the social start-up supplier of the DNMLAB platform) since 2020. The activities, in accordance to the operational protocol, have been: monitoring of telemedicine activities, surveys addressing the health care professionals, and a final report describing the whole process. The survey aims at exploring - for each outpatients' virtual room - the characteristics of the population involved, the methods employed in using the platform, the potential applications outside the pandemic period and the barriers or limits encountered. The final report describes the IFO telemedicine activities, starting at the beginning (March 2020), and provides the results from the survey, involving over 3400 patients and 179 health care professionals from the 28 IRE outpatients' virtual rooms.

Gender medicine

Participation in the IRCCS working table, which contributed to the preparation of the document of the Ministry of Health on the relationship between COVID 19 and gender health.

Partecipations in Commission, Committees, Working Groups

- HB-HTA. IFO (Health Technology Assessment) commission.
- CC-CICA. Control Committee of Infections Related to the CC-CICA - IFO.
- LIMeNar Steering Committee. ISS research project ("Use and application contexts of the guidelines for the use of NARRATIVE MEDICINE in clinical care and associations area)

Editorial Board

V. Ferraresi, MC Cercato, C. Zoccali Editors. Special Issue "Bone and Soft Tissue Sarcomas: A "Big" Family of "Rare" Tumors. A Multidisciplinary Targeted Approach and Emerging Topics". A special issue of Journal of Clinical Medicine (ISSN 2077-0383). This special issue belongs to the section "Oncology".

https://www.mdpi.com/journal/jcm/special_issues/Bone_and_Soft_Tissue_Sarcomas

Oral Presentations at courses, meeting and Webinar

- MC Cercato. "Tools for a more Personalized Oncological Care: from Digital Narrative Diaries to a Community Sharing Digital Space" OECI Oncology Day. Promoting innovation and quality for patients. Milano, 16 giugno 2021 (virtual meeting).
- MC Cercato. "Epidemiologia e prevenzione in oncologia". 22° Corso biennale in Psicologia Oncologia IFO Modulo II, 20 luglio 2021.
- MC Cercato. "Medicina narrativa: applicazione nella pratica clinica oncologica". Incontro pubblico: "NON di SOLO COVID" Curare, umanizzare, narrare ...Dall'esperienza della medicina narrativa, ai progetti di telemedicina. Cittadinanzattiva Regione Liguria ODV, IRCCS Istituto Nazionale Tumori Regina Elena IFO, ASL 5 Liguria. Lerici (SP), 10 settembre 2021.
- MC Cercato. "Drammaterapia Integrata: applicazione delle arti nella pratica clinica (studio DIPSO)". RIDAIT SEMINARS, 5° ciclo, primo modulo. IFO, 21 settembre 2021.
- MC Cercato. "Il diario narrativo digitale in oncologia". Virtual meeting ECM: Laboratorio di Medicina Narrativa. SIMEN, 22 settembre 2021.
- MC Cercato. "L'impatto sull'operatore nell'applicazione della medicina narrativa: risultati dello studio IMPERO". RIDAIT SEMINARS, 5° ciclo, secondo modulo. IFO, 30 novembre 2021
- MC Cercato. "Approccio metodologico alla rarità: dall'epidemiologia alla umanizzazione delle cure" al corso "Tumori Rari e networking: le basi per l'applicazione delle evidenze cliniche. Focus on: sarcomi e tumori cerebrali". Centro Bastianelli, 2 dicembre 2021
- V Ramazzotti. "Epidemiologia ICA internazionale e nazionale". La prevenzione e la gestione delle infezioni correlate all'aassistenza (ICA). IFO, 13 dicembre 2021.

Oncogenomic and Epigenetic Unit

Head: Dr. Giovanni Blandino, MD, PhD

Staff

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Mr. Roberto Bernardi, Administrative collaborator
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Sara Donzelli, PhD, Senior Researcher
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Fabio Valenti, PhD, Senior Researcher
Giulia Fontemaggi, Senior Researcher

Mission

Developing more precise diagnostic approaches to predict cancer progression and prognosis is the key to precision medicine. The mission of the Oncogenomic and Epigenetic Unit mirrors at specific genomic and epigenetic alterations in both solid and hematopoietic malignancies that hold the potential to represent novel cancer biomarkers or druggable targets. This is pursued through genome wide approaches applied to cell systems, animal models, tissues and biological fluids ctDNA and non-coding RNAs of cancer patients.

Clinical and Research Activities

The Oncogenomic and Epigenetic Unit actively contributes to the clinical research activity of Regina Elena National Cancer Institute through:

The generation of molecularly and clinically annotated databases of specific types of tumors. This also includes the collection and the storage of DNA, RNA and proteins from both tissues and biological fluids from cancer patients.

The establishment of datasets of raw data from genome wide analysis coding and con-coding RNA profiles, RNA-Seq and DNA mutational analysis of matched cancer lesions.

The establishment of early passage culture from melanoma, breast, lung, ovary, endometrial, brain, head and neck cancer lesions.

The research objectives of the Oncogenomic and Epigenetic Unit are pursued through the integrated experimental work of the following groups:

Blandino's group is actively pursuing the identification of molecular biomarkers non-coding RNAs whose association with the TP53 status may predict recurrence of head and neck cancers.

Biroccio's group is actively investigating the extra-telomeric role of TRF2 in oncogenesis with the aim to identify novel therapeutic targets for antitumoral therapies in colon cancer.

Giacomini's group is actively developing and optimizing nanoparticles for cancer therapeutics, and assays to detect circulating tumor DNA ctDNA in real-life Liquid Biopsy LB studies.

Rizzo's group is actively investigating the role of extracellular circulating miRNAs in hematopoietic malignancies and brain tumors as promising biomarkers for disease classification and outcome prediction.

The Segatto's group has generated genetically defined mouse models of intrahepatic cholangiocarcinoma iCCA driven by FGFR2 fusion proteins FFP. These models are being used to identify iCCA vulnerabilities associated to oncogenic dependence from FFPs.

Immunology and Immunotherapy Unit

Head: Dr. Paola Nistico', MD

Staff

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Anna Maria Mileo, PhD, Group Leader
Aldo Venuti, MD, Group Leader
Silvia Baldari, PhD, Senior Researcher
Anna Di Carlo, PhD, Senior Researcher
Roberta Melchionna, PhD, Senior Researcher
Belinda Palermo, PhD, Senior Researcher
Francesca Paolini, PhD, Senior Researcher
Gabriele Toietta, PhD, Group Leader
Paola Trono, PhD, Senior Researcher
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Erica Di Bernardo, Junior Researcher, PhD Student
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Maria Vincenza Sarcone, Administrative collaborator
Flavio Di Michele, Student
Beatrice Pinci, Student
Michela Lupo, Student
Paola Trono, Senior Reseracher (CNR)

Mission

This Unit is focused on understanding the immune response against tumor in patients, focusing on non-small cell lung cancer (NSCLC). The principal aim is to study the biological processes and signaling pathways involved in the complex interaction between tumor cells, extracellular matrix (ECM), cancer associated fibroblasts (CAFs) and immune cells in the tumor immune microenvironment (TIME). From a clinical point of view, our aim is to identify novel criteria to stratify patients that may benefit or not from immunotherapy treatment with immune checkpoint inhibitors (ICI). Final aim is to provide the rationale for designing novel immunotherapeutic treatment including CAR-T cells suitable for solid tumors.

The mission is: to develop and standardize methodologies of immune-monitoring also at single cell level; to establish preclinical models of patient-derived organotypic cultures of tumors; identify surrogate biological markers of clinical response, focusing on ICI treatment; to identify novel targets related to the tumor microenvironment, suitable for developing CAR T cells able to infiltrate solid tumors also exploring oncolytic virus activity. In cooperation with the HPV Unit we participate in programs of cancer prevention on HPV vaccination for males and we are defining new formulations of DNA vaccines against HPV oncoproteins. Close cooperation with the clinical departments is a cornerstone of our Unit to define immune landscape in patients treated with ICI and during radiotherapy and to design combined immunotherapeutic clinical trials.

Clinical and Research Activities

PINISTICO'

The group activity was focused in identifying mechanisms involved in the role of hMENA splicing as crucial regulator at the crossroad of tumor-stroma communication and immune response in NSCLC patients.

- We highlighted hMENA isoforms as crucial in the communication among tumor cells, cancer associated fibroblasts (CAF), T and B cells. We demonstrated that in non-small cell lung-cancer (NSCLC) cells hMENA11a increases the expression of the Tertiary Lymphoid Structure (TLS) regulator LTbetaR, reduces fibronectin and favors CXCL13

production by tissue resident T cells. Conversely in CAFs, hMENA/hMENA Δ 6 favor fibronectin production, inhibit LTbetaR-related NF-kB pathway and CXCL13 secretion. Consistently, NSCLC tumors with hMENA11a high expression, paucity of hMENA positive CAFs and stromal fibronectin low have intratumoral TLS (TLS-IT), which associate with memory B cells in tumor tissues and are predictive of longer survival in NO NSCLC patients. In ICI treated patients, hMENA isoform pattern, fibronectin and LTbetaR expression may discriminate responding or not-responding NSCLC patients.

- We established a novel role for hMENA11a in controlling Type I IFN signalling. At the molecular level, we found that depletion of hMENA11a induces the production of inflammatory mediators including IFNbeta via RIG-I, and this sustains the increase of cancer cell PD-L1 levels and favors a pro-tumor behavior of macrophages. We derived a gene signature that identifies a unique subset of macrophages associated to poor survival in Lung Adenocarcinoma (LUAD) patients. Notably, high expression of hMENA11a and low expression of IFN target genes discriminate patients responding to ICI-based therapy. These data enforce the role of hMENA splicing in modulating tumor microenvironment, and in turn mechanisms of resistance to ICI in NSCLC (Paola Trono and Annalisa Tocci major contributors).

- hMENA expression is enriched in a CAF cluster with epithelial-mesenchymal transition (EMT) traits enrichment, an extensive repertoire of ECM proteins and TGF-beta-associated genes. We found that TGF-beta1 treatment of primary CAFs up-regulates hMENA/hMENA Δ 6. The knockdown of hMENA/hMENA Δ 6 expression in CAFs: 1) reduces the TGF-betaRI and II mRNA levels; 2) inhibits the TGF-beta1-induced CAF proliferation, ECM remodeling and chemokine/cytokine secretion. hMENA expression in CAFs regulates TGF-beta1-mediated PD-L1 up-regulation. CAFs secretoma affects PD-L1 expression in NSCLC cell lines, which is regulated by hMENA through SMAD2 phosphorylation. hMENA knockdown in CAF inhibits, via a paracrine mechanism, surface expression of PD-1 checkpoint inhibitor in T lymphocytes (Roberta Melchionna, major contributor).

- We have evaluated frequency, phenotype and functionality of CD8+ T cells isolated from 46 NSCLC patients according to their expression of PD-1 and/or CD28 and how these molecules change from periphery to the tumor, impacting on an effective antitumor response. Polyfunctionality of CD28- or CD28+ T cells depends from presence/absence of relevant inhibitory immune receptors (IR) such as TIGIT, TIM-3, LAG-3 and CTLA-4. Analysis at single-cell level by matched surface proteins and transcripts of CD8+ T-lymphocytes from peripheral blood, adjacent non-tumor tissue and tumor site revealed that PD-1+CD28- and PD-1+CD28+ T cell subsets clustered into 10 different groups characterized by distinctive transcriptional profiles and heterogeneously represented within the different districts. Different clusters were significantly associated with poor or improved clinical outcome in LUAD patients. (Belinda Palermo, major contributor).

- We conducted a pilot study on peripheral blood cells of 18 PCa patients treated with various fractionation schedules and volumes at 5 longitudinal time points. We in-depth analyzed: frequency of T cells (alpha/beta and gamma/delta), Treg, B cells and NK cells; maturative differentiation phenotype; expression of IR. SBRT is the treatment that induces less toxicity and is less suppressive, favouring anti-tumor immune response. A significant increase of VISTA in both CD8+ and CD4+ T-cells of SBRT treated patients at the end of RT was found, indicating that VISTA could represent a new therapeutic target for combined immunotherapy and RT in this clinical setting (Belinda Palermo and Mariangela Panetta, major contributors)

- In the framework of the CAR-T project (Ministero della Salute and Lazio Innova project) the Unit focused on the identification of stroma-derived targets for chimeric antigen receptor-modified T cells (CAR-T) and bispecific T-cell engagers (BiTE). Thanks to the contribution of bioinformaticians Lorenzo D'Ambrosio and Eleonora Sperandio, a hypothesis-driven biocomputational analysis of NSCLC RNA-seq transcriptomic datasets from The Cancer Genome Atlas (TCGA), integrated with machine learning methods was performed and we identified novel TME-derived targets.

Paola Nisticò as National coordinator of the WG Immunotherapy of Alleanza Contro il Cancro contributes through an integrated experimental and clinical work in projects aimed at identifying biomarkers of resistance to ICB in NSCLC by multiomic approaches.

New Machines and Techniques

Several technological improvements have been made: 1) the acquisition of the GeoMx Digital Spatial Profiler for digital

spatial transcriptomics and proteomics of tumor tissues; 2) The purchase of Leica VT1200 S fully automated vibrating blade microtome for the preparation of organotypic tissue slice culture from tumor specimens; 3) the up-grade of BD FACSMelody instrument, from two to four sorting channels; 4) the purchase of BD Rhapsody, high-throughput technology linked to single cell sequencing.

PI DI MODUGNO

Among the targets specific of CAF subtypes involved in T cell exclusion as potential stromal target of CAR-T therapy, we identified C-type mannose receptor 2 (MRC2). MRC2 expression is induced by TGF β and is higher in CAF from NSCLC with respect to normal fibroblasts. We demonstrated that MRC2 activates CAFs, remodels ECM and increases TGF β production and PD-L1 and PD-L2 expression in CAFs. In NSCLC primary tumors, we found that MRC2 is highly expressed in the stroma and heterogeneously expressed in tumor cells. We suggest that MRC2 could contribute to a hostile immunosuppressive tumor microenvironment and may have a potential role as CAR-T target in solid tumors (with the contribution of Beatrice Pinci and Anna Di Carlo).

- We found a paracrine mechanism of hMENA11a expressing tumor cells that induce the expression of CXCL13, a key cytokine in TLS formation, by CD8⁺ and CD4⁺ tumor-resident T cells. Conversely, the expression of hMENADv6 isoform in CAF inhibits the secretion of CXCL13, indicating that the cytoskeleton regulatory protein hMENA might differently affect the TME depending on the cell type and the isoform expressed (with the contribution of Anna Di Carlo and Belinda Palermo).

- To investigate the effects of radiotherapy (RT) on the immunoregulatory properties of CAFs we have explored the effects of different radiation regimens on the secretoma of freshly explanted NSCLC derived CAFs, focusing on a panel of cytokines and chemokines (co-PI Roberta Melchionna).

- We set-up RNA-scope approach to visualize the expression of hMENA splice variants in tumor tissues and multiplex immunofluorescence to visualize the respective localization of hMENA isoforms with markers of tumor cells, stroma and immune cells. We are also setting-up digital spatial transcriptomic by the use of GeoMx Digital Spatial Profiler (NanoString Technologies, Seattle, WA, USA) to characterize the transcripts expression of tumor cells, CAFs and lymphocytes in different NSCLC regions.

- Finally, we are standardizing the culture of organotypic tissue slices from surgical resections of NSCLC, as an ex vivo experimental model that maintain the physiological conditions of the tissues of each single patient.

PI VENUTI

In collaboration with the HPV Unit we participate in male vaccination programs for prevention of HPV-associated cancer and we are a coordinating Center of a large multicentric (V503-049) study on HPV vaccine for prevention of oral cancer. Enrollment was concluded reaching the assigned number of patients and a three-year follow-up is underway. Furthermore, recently a clinical trial on circulating HPV DNA in oropharyngeal cancer started. We have been funded to conduct an observational study on HPV-associated oropharyngeal cancer to evaluate the presence of HPV16 E5 oncogene as progression marker. Our group settled a specific assay to evaluate E5 expression and developed a new micro-structured substrate for a sensitive ELISA for anti-HPV16 E7. We also demonstrated, in collaboration with HPV-Unit, the association between HPV infection and middle ear squamous cell carcinoma and its prognostic role. Regarding HPV-specific new immunotherapies, we produced and validated in collaboration with ISS new intrabodies targeting HPV16 E6 and E7 oncoproteins. These intrabodies, by intratumor delivering, are able to decrease tumor growth in pre-clinical model of HPV-associated cancer. Finally, during SARS-CoV2 pandemic, our group was involved in analyzing data of health worker immunological response to vaccines (Francesca Paolini major contributor).

PI MILEO

Tumor evolution is driven and regulated by reciprocal interaction between cancer and microenvironment non-cancerous cells via autocrine and paracrine signaling. We focused our study on the characterization of the autophagic process and its potential role on the crosstalk between cancer cells and CAFs in NSCLC. Although autophagy is conventionally considered a degradation pathway, emerging evidence supports a role of this process in contributing to the export of

cytokines and/or proteins by unconventional secretion mechanisms. We demonstrated that the specific “silencing” of the hMENA expression in a subtype of CAF population determines a significant inhibition of autophagic flux that in turn may affect, through the secretoma modification, the cross talk between CAFs and tumor cells. These findings suggest a direct link between cytoskeletal dynamics regulated by hMENA and secretory mechanisms autophagy-dependent in CAFs. Studies are in progress to characterize the role of autophagic flux on EMT process and invasive ability of NSCLC cells promoted by CAFs soluble factors, with the aim of identifying autophagic inhibitors that may improve and/or synergize current cancer therapy, including immunotherapy (with the contribution of Annalisa Tocci).

PI TOIETTA

We focused on the evaluation of innovative immunotherapeutic strategies using CAR-T and BiTE for specifically targeting immunosuppressive TME. Taking advantage of data obtained *in silico* we validated a number of targets using qRT-PCR and immunoblotting analysis in a collection of CAFs freshly explanted from primary lung tumor tissues, and by immunohistochemical analysis of tissue microarrays. In particular, we focused on Ephrin type-A receptor 3 (EphA3), C-type mannose receptor 2 (MRC2), Leucine Rich Repeat containing 15 (LRRC15), and fibroblast activation protein (FAP); we collected data that provide the proof concept for the subsequent generation of BiTEs and CAR-T cells against two of these targets. Notably, we performed *ex vivo* and *in vivo* studies in models of head and neck cancer to evaluate whether oncolytic virotherapy may be instrumental in converting the TME from immunosuppressive to immunostimulatory, thus rendering solid tumors more permissive to CAR-T therapy (Silvia Baldari and Francesca Paolini major contributors).

Preclinical Model and New Therapeutic Agents Unit Head: Dr. Anna Bagnato, PhD

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Mission

Despite a rapidly increasing scenario of cancer treatments, the development of resistance remains one of the most important problems of modern cancer research. To overcome this challenge and to increase efficacy, therapies are frequently given in combination. However, it is not always clear which treatments should be combined or the schedule to maximise response whilst reducing toxicity and overcoming resistance.

The aim of this Unit is to define the determinants of adaptive mechanism to escape therapeutic response in pertinent pre-clinical models, including patient-derived xenografts, and organoid/tumoroid technology of ovarian, lung, colon cancer, melanoma, mesothelioma, to develop novel combinatorial approaches for their translation to the clinic. In these models we investigate the critical pathways i.e. endothelin-1, estrogen, or bcl2/bcl-xL signaling, that regulate cell plasticity and the interactions between tumour microenvironment (TME) and neighboring tumor cells. Cell plasticity occurs in response to environmental stresses and therapeutic pressure to engage finely tuned and graded adaptive mechanism to escape therapy. In this Unit we aim to decipher how microenvironmental and tumor determinants interact to highlight the importance of deciphering clinically actionable vulnerabilities in tumours for designing more effective therapies in patients. Tumor cells may develop dependencies on critical survival signals, the disruption of which can result in the blockade of dangerous interactions likely to provide novel therapeutic options. In a broader scenario, these adaptive dependencies can involve functional patterns at various levels, including signals within the same pathway, or within parallel compensatory pathways, or other pathways that functionally cooperate for the drug escape. Recent studies on these interdependencies and on the dynamic of tumor ecosystem, including tumor-stroma interactions, have provided valuable biological insights into the mechanisms of drug resistance that could be used to rationally and effectively design combined regimens. Novel 3D technologies have led to the development of more physiological preclinical models - tumour organoids or tumoroids - which rely on self organisation of tumour tissues into organotypic cultures following embedment into a 3D dense matrix. Patient-derived tumoroids can be established from patient's tumours and have been demonstrated to retain the genetic features and drug responsiveness of the patient donors. The ultimate goal of this Unit is to characterize the repertoire of molecular determinants and the signalling networks that impact on the drug response and can be exploited in patient-derived preclinical models as a means to discover pharmacologically actionable pathways and to screen combinatorial regimen optimization that would enable clinicians to predict how tumours respond to treatment. The activity of the Unit concerns patient-centred research, learning from every patient the complexity of tumor evolution to combat resistance.

Clinical and Research Activities

PI Anna Bagnato

The group of Dr. Bagnato is aimed at discovering sequential drug treatment protocols in which new vulnerabilities can be targeted. This objective will be tackled by differential analysis of responder versus non-responder tumours. Among the typical features of solid tumors in the malignant progression, we focused on hypoxia, which, stabilizing the transcription factor hypoxia inducible factor-1alpha (HIF-1alpha), can activate the expression of genes involved in tumor vascularization, metastasis, and drug resistance. Notably, the activity of HIF-1alpha can be induced by different signaling, including endothelin-1 (ET-1), irrespective of oxygen tension or in synergism with hypoxia. It has been reported that the ET-1 receptors (ET-1R), ETAR and ETBR, activation promotes cancer progression through a network of cellular pathways and interactions with the TME, emerging as key targets for cancer therapy. The deep knowledge of the ET-1-guided interconnected routes represents a substantial therapeutic challenge to improve patient survival. In this regard, we recently disclose the interplay between ET-1R axis, YAP and mutant TP53 (mutp53) in patient-derived high-grade serous ovarian cancer (HG-SOC) cells, opening new prospects on the regulation of YAP/mutp53 interplay. Our hypothesis is that ET-1R-driven transcriptional 'interactome', that includes YAP and other novel partners, can modulate the cross-talk with the TME elements impacting cancer plasticity and drug response. To clarify this point, we analyzed, by RNA-seq, the effect of ET-1 on the overall transcriptome of patient-derived HG-SOC cells and the effect of the dual ETAR/ETBR antagonist macitentan. ET-1 markedly influences the overall profile of the cellular transcriptome and in particular the hypoxia pathway, which were inhibited by macitentan. Deciphering the nuances of these interactions guided by ET-1R/hypoxia will be critical for advancing our ability to improve therapeutic options for tumors harboring TP53 mutations. During 2021, we dissected the ET-1R/hypoxia-mediated mechanisms that contribute to cancer metastasis and therapeutic escape, including the signal integration of tumor and microenvironmental niche and the formation of unexplored transcriptional complexes, as a vulnerability node that could be therapeutically exploited by the effective combination of the ET-1R antagonist with other drugs, as PARP inhibitors (PARPi). We investigated the role of the ET-1-guided mutp53/HIF-1alpha/YAP signaling between tumor and stromal elements to regulate malignant progression and drug response. ET-1R blockade, interrupting tumor-stroma communication inhibits the YAP/mutp53/HIF1alpha-driven therapeutic escape pathway of PARPi, sensitizing HG-SOC cells to olaparib by using clinically relevant patient-derived preclinical models, that include engineered 3D systems (tumoroids) alongside PDX. The anti-metastatic effect was more pronounced in mice treated with the combinatorial treatment schedule of macitentan and olaparib. These findings provide strong *in vivo* evidence of how macitentan, suppressing simultaneously YAP and HIF-1alpha intertwined pathways, sensitizes to olaparib, showing a greater anti-metastatic potential in a combinatorial regimen, contributing to hamper the permissive TME. These findings, in compliance with previous studies demonstrating that macitentan, blocking the ET-1R expressed in tumor (ETAR) and stromal cells (ETBR), inhibits vascularization in different tumor models, disclose ET-1R as mechanistic determinants in the regulation of HG-SOC/TME crosstalk and indicate the combination of macitentan with PARPi as a promising therapy.

In a search for transcriptional circuits responsible for cell plasticity and metastatic progression, we demonstrated that a reciprocal network integrates ET-1/ETAR and YAP/ZEB1 axes in a regulatory circuit to promote the acquisition of aggressive traits and foster progression to metastasis. We reported that ET-1/ETAR axis, through ILK, promoted the direct physical ZEB1/YAP interaction. Moreover, ET-1 directed their engagement in a functional transcriptional complex with the AP-1 factor JUN. This led to the aberrant activation of common target genes regulating cellular plasticity, invasion and EMT, creating a persistent ET-1/ZEB1 signaling. Our findings add greater relevance to the above results demonstrating that ET-1R-driven mediators support the ability of HG-SOC to acquire metastatic traits through the cooperation of ET-1R and YAP-mediated regulatory signaling and that the drug repositioning of macitentan, can improve the current treatments for HG-SOC. Moreover, unraveling the cooperative interaction between HG-SOC and host components, in collaboration with Dr. L. Rosanò, we focused on the tumor-associated mesothelial cells (MC), demonstrating that ET-1R/beta-arr1 activation elicits a mesothelial-to-mesenchymal transition program, triggering the enhanced secretion of cancer-related proteins, MC migration and invasion, and tumor cell transmesothelial migration. In this context, we recently demonstrated that, ETAR/ILK/Rac3 signaling supports the communication between HG-SOC and MC, favouring invadopodia formation.

Our future studies will be aimed to clarify the role of wider factors, including age-related stromal changes, mechanobiology and tissue architecture, integrate with hypoxia sensing, in cancer progression. Greater understanding

of these factors may allow us to move towards personalized therapeutic approaches to target tumor and its TME in HG-SOC. On the basis of these results, Rosanna Sestito has been awarded as Best Scoring E-Posters at EACR Virtual Congress, 9-12 Giugno 2021; Piera Tocci has been awarded as best oral presentation at the SIC Virtual Meeting, 27-28 October 2021, and with the prestigious Premio RECTI EQUES Paladini Italiani della Salute, October 26, 2021, and with Premio 100 eccellenze Italiane, December 16, 2021. This research work was supported by AIRC and Italian Ministry of Health to A Bagnato and by IFO funding to P Tocci and R Sestito.

PI Donatella Del Bufalo

Inhibition of the anti-apoptotic protein bcl-2 has emerged as a highly effective treatment for different tumors and global translational efforts investigating bcl-2 inhibitor combinations are rapidly transforming the clinical treatment paradigm, that leads to higher response rates, longer durations of remission and, ultimately, significantly improved overall survival. During 2021, the studies of Dr. Del Bufalo were carried out in order to understand the mechanism of action through which the antiapoptotic proteins, belonging to the bcl-2 family, are able to affect the progression of melanoma, and establish a crosstalk with the microenvironment, and in particular with the immune system cells, endothelial cells and fibroblasts. As previously reported for Bcl-2, by using both mice and zebrafish preclinical melanoma models, we demonstrated the capability of melanoma cells overexpressing Bcl-xL antiapoptotic protein to affect the recruitment and polarization of tumor-associated macrophages establishing tumor microenvironmental conditions that favour melanoma development. Several factors have been identified to be released primarily by melanoma cells overexpressing Bcl-xL, including Interleukin-8, Interleukin 1BETA and C-C Motif Chemokine Ligand 5, which could contribute to polarization and migration of macrophages.

The collaboration with the Sapienza University of Rome was particularly intense, involving i) Prof. Rino Ragno for both the virtual screening analysis conducted in order to identify new inhibitors of antiapoptotic proteins with antitumor activity in vitro and in mouse models, and for the study of some essential oils able to enhance the antitumor activity of target therapy in melanoma models; ii) Prof. Dante Rotili, with whom we demonstrated the antitumor activity of some inhibitors of MINA53, an oxygenase that catalyses ribosomal hydroxylation, and iii) Prof. Ada Maria Tata for the study of inhibitors of muscarinic receptors to overcome drug resistance in glioblastoma stem cells.

Given the experience in the field of melanoma, some reviews of the literature were produced in 2021 regarding the role of antiapoptotic proteins, semaphorins and hypoxia in the progression and therapy of melanoma. AIRC has allowed the realization of these studies through the funding of a research project to Donatella Del Bufalo, the assignment of two three-year scholarships for Italy to Marta Di Martile and Martina Chiacchiarini and a two-year scholarship abroad to Anna Maria Lucianò. These studies were also carried out thanks to IFO funding to Simona D'Aguanno.

PI Rossella Galati

Malignant pleural mesothelioma (MPM) is a tumor of the pleura caused mainly by exposure to asbestos, which after a long period of latency (20-40 years) manifests itself in advanced stages. Because of this, it responds poorly to therapies with median survival of about 12 months. Therefore, many efforts are made to define sensitive biomarkers for monitoring people exposed to asbestos at risk of mesothelioma in order to make an early diagnosis (stage I) and to intervene promptly with a therapy that would improve the response. The previous studies of Dr. Galati highlighted a new COX2/CYP19A1 axis and recognized a role of 17-beta-estradiol in the pathogenesis of MPM. The aim of the research is to translate into the clinic, our previous evidences, we assume that asbestos-induced inflammation in professionally exposed individuals can increase 17-beta-estradiol levels and identify individuals at risk of pleural disease. To this end, the ongoing study investigates the serum levels of 17-beta-estradiol and its metabolites in healthy subjects not exposed to asbestos, healthy subjects exposed to asbestos and patients with MPM. In addition the group is actively investigating the 17-beta-estradiol role in oncogenesis with the aim to identify novel targets for antitumoral therapies in mesothelioma.

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Mission

Cellular networks and new therapeutic targets are key areas of innovation in the field of cancer therapy. The potential targeted pathways for personalized cancer therapies consist in oncogenic signals and in the events generated by biochemical and/or genetic alterations that characterize cancer cells. Our mission is to develop and to sustain sound expertise in these areas to understand the hierarchy of therapeutic targets and the molecular mechanisms underpinning the pharmacological action of innovative therapies. This Unit has a dual function. On one hand, it aids researchers and clinicians to plan preclinical and clinical research activities, as well as to conduct, stimulate and support research programs integrated into innovative investigator-driven clinical trials. On the other hand, it assists other researchers who aim to discover and plan the development of novel biomarkers and therapeutic agents. In addition, part of the activity of this Unit concerns pharmacological repositioning, the discipline that identifies new applications for drugs whose clinical use is already approved by the regulatory Agencies, even if for other pathologies.

Clinical and Research Activities

The following research objectives have been pursued by the Unit “Cellular Networks and Molecular Therapeutic Targets” through the integrated work of the staff researchers with intra- and extra-mural collaborators.

Role of SEMA6A in BRAF-mut metastatic melanoma. In the context of BRAF-mut melanomas, Drs. Loria and Bon have identified Semaphorin 6A (SEMA6A) both as a mediator of the response to the combined treatment with dabrafenib + trametinib and as a prognostic factor. Low SEMA6A expression correlates with a longer response to therapy and improved progression free survival and overall survival. Mechanistically, they have found that in BRAF-mutant melanoma, a SEMA6A/RhoA/YAP axis mediates tumor-stroma interactions and prevents tumor response to treatment with BRAF/MEK double inhibition.

Exploring molecular traits and immunogenicity of osteosarcoma for new therapeutic approaches. Unlike other solid tumors, in which the introduction of molecular target therapies and immunotherapy has led to an improvement in terms of survival, the therapeutic armamentarium of osteosarcoma is still mainly constituted by antiproliferative drugs. This results in a poor improvement in overall survival and indicate that further translational research studies are crucial to identify new therapeutic approaches to improve the treatment and, consequently, the prognosis of osteosarcoma patients. About that, the main purpose of this study, funded by the “ALE CON NOI” Association, is to identify new therapeutic targets, such as membrane antigens or proteins with kinase activity, selectively expressed in osteosarcoma lesions. The evaluation of gene expression modulation during neoplastic progression is carried out through RNA-seq experiments by comparing tumor tissue samples with normal bone samples. During 2021, in collaboration with the BBIRE and the bioinformatic Unit, Dr Loria has collected tumor and normal bone specimens and begun preliminary

bioinformatics analyses.

HIPK2 as a prognostic biomarker in colorectal cancer. In the past decades, survival for colorectal cancer (CRC) has increased substantially mainly thanks to significant improvements in screening processes, diagnosis, and therapy. Still, a considerable portion of CRC patients has a high risk of disease recurrence after treatment and CRC remains a leading cause of death among cancer patients. HIPK2 is a member of a conserved family of kinases which modulates different biological processes and that has recently gained attention as a fine tuner of multiple signaling pathways, among which those commonly altered in CRC. In collaboration with the Pathology Unit, Dr Verdina identified HIPK2 as a potential predictive marker of a favorable response for adjuvant chemotherapy in stage II colorectal cancer, while Drs Viridia and Di Segni, in the group led by Dr Di Rocco, identified HIPK2 as a prognostic biomarker candidate in CRC patients and underscored a previously unknown functional link between HIPK2 and the KRAS pathway. In particular, they provided evidence that HIPK2 contributes to KRAS signaling activation by physically participating in the active RAS complexes, contributing to the RAS/MAPK pathway cascade, and sustains the growth of mutant KRAS CRC tumors.

Classification of ATM variants of uncertain significance (VUS) by functional test. Due to its complex genomic organization, the large number of polymorphisms, and the presence of mutations without hot-spots, gene sequencing is not sufficient to classify rare variants with uncertain significance. In the past few years, the Unit chief has employed a functional test based on p53 mitotic centrosomal localization (p53-MCL) in peripheral blood mononuclear cells (PBMCs) to improve our ability to identify pathogenic variants of the ATM gene. Based on the data collected, two main projects have been undertaken together with Dr Federici. The first one in collaboration with the Departments of Human Neuroscience at Sapienza University in Rome and Carlo Bo University in Urbino, has applied the p53-MCL test to evaluate the pathogenicity of ATM variants present in patients affected by atypical, mild variants of Ataxia-Telangiectasia. This project has been awarded by a grant from “Associazione Nazionale Ataxia-Telangiectasia” to Giulia Federici. The second project is the genetic validation of the p53-MCL for ATM variant classification. To this aim, Dr Federici is designing and applying the CRISPR/Cas9 technology to generate several Knock-INs cell clones, each carrying a different ATM variant. The analysis of each single cell clone will depict the functional consequences of individual ATM variants and, from the translational point of view, will allow an accurate classification of currently clinically neglected ATM variants of uncertain significance to be used as risk factors and therapeutic response markers. This project has been awarded by a grant from “Fondazione AIRC per la Ricerca sul Cancro” to the Unit chief.

Drug repositioning in glioblastoma. Studies by Dr Paggi and collaborators are focusing on glioblastoma, a tumor extremely aggressive and substantially refractory to therapy. In this context, they have highlighted the efficacy of the neuroleptic drug chlorpromazine in inhibiting key functions in glioblastoma cells, thus setting the basis for a Phase II multicenter clinical trial in which this drug is added to the first-line therapy of patients diagnosed with glioblastoma with unmethylated MGMT gene promoter.

Unfolded protein response (UPR) in resistance to chemotherapy. The activity of Prof D’Orazi is mainly focused on the role played by the endoplasmic reticulum stress, the unfolded protein response (UPR), and the autophagy in cancer cell sensitivity to chemotherapy. Pre-clinical experiments were performed by using conventional anticancer drugs (e.g., doxorubicin, cisplatin, PARP inhibitors) and novel zinc-curcumin compounds. The main target of the studies is the inhibition of mutant p53 and re-activation of wild-type p53. To prove the role of UPR in increasing cancer cell resistance to drugs and the involvement of mutant p53, specific genetic or pharmacologic manipulations were applied for the main molecules involved. The main results showed the survival role for UPR whose inhibition could be exploited to increase cancer cell sensitivity to the cytotoxic effect of chemotherapeutic drug, in clinical trials. This research was conducted in collaboration with scientists at Sapienza University of Rome and at University of Calabria (for zinc compounds) and it was partially supported by Grants from the University G. D’Annunzio of Chieti.

DNA damage accumulation for diagnostic procedures. In collaboration with the Radiology and Medical Physic Units, Dr Verdina is evaluating the potential risk due to diagnostic radiological tests and nuclear medicine, despite the low doses of radiation used in the individual diagnostic procedures. During 2021, DNA damage measured by 53BP1/gammaH2Ax double stained foci was evaluated in nontumor cells grown in culture and subjected to repeated Computed Tomography (CT) scans over short time intervals. We observed an accumulation of damage following repeated CT scans that increases from about 0.7 foci/cell before the first CT scan to 1.2 after the second, 1.3 after the third, and 1.8 foci/cell after the fourth CT scan. The study will be next carried out on peripheral blood mononuclear cells from a selected population of cancer patients undergoing CT scans repeated every three months in our Institute for therapy monitoring.

SAFU Unit

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Mission

The mission of the SAFU UOSD focuses on the establishment of innovative mouse models of human cancer including implantation of tumor specimens into immunocompromised mice at the heterotopic and orthotopic sites and genetically engineered mouse models. All mouse models are devoted to study cancer initiation, immune system roles, tumor angiogenesis, environmental carcinogenesis, invasion as well as response to novel anticancer strategy. Currently, several models are being designed to allow in vivo imaging of tumor development from earlier stages and to follow tumor response to therapeutics. Besides to the research activities, this UOSD has the responsibility for day-to-day management of the Institute animal house. In agreement, this structure coordinates the activity of Animal Welfare Body (D.Lgs. n.26/2014), evaluating scientific projects in which are involved animal experimentations.

Alongside these activities, SAFU unit carries out an intense development and validation of NGS technologies in exploratory research, also contributing to the generation of specific software for analyzing the data produced. In fact, in the light of the scientific knowledge acquired, it is clear that molecular analysis of the genome is not sufficient to improve diagnosis and therapy, as the response of a neoplasm to therapeutic treatment does not depend only on the characteristics of its genome, but also on the transcriptome and the epigenome. RNA analysis provides important information on transcriptional variations related to the tumor phenotype, identifying aberrations in the regulation of gene expression and also pathogenic gene fusions. Of absolute importance, by associating these analyses with exome sequencing, it is possible to identify specific neoantigens present in tumor cells, as well as fusion proteins generated in the tumor. In addition, RNA-seq analyses are carried out to analyze the composition of the immune infiltrate within the tumors, while exomic analysis is often used to evaluate the mutational load of a single tumor. More recently, the NGS methodology has also been used to analyze the expression variations of miRNAs and long noncoding RNA in various tumor forms. Unlike the genome, the epigenome is not a static entity: an epigenetic variation can precede or be a consequence of the onset of a disease, environmental exposure, or reflect specific factors and lifestyles. This makes the epigenome attractive as a field of investigation for the identification and transfer to the clinic of biomarkers of very different pathologies and of specific predisposing conditions such as tumors. Through these analyses it is possible to determine how chromatin conformation changes affect neoplastic transformation, altering the access to specific DNA regions by transcription factors or RNA polymerase.

Clinical and Research Activities

NGS facility is a research infrastructure, and its goal is to offer users state-of-the-art, next-generation DNA and RNA sequencing technology and to provide high-quality raw data and analysis to collaborators. The staff offers comprehensive support throughout the whole next-gen project including initial consulting service. The facility is equipped with several instruments and throughput capacities ranging from a MiSeq (1-25 million read-pairs) to a NextSeq 500 (130-400 million read-pairs), up to a NovaSeq 6000 instrument acquired in the 2021 (0.8 - 20 billion read-pairs per run). A nCounter platform from Nanostring provides a simple and cost-effective solution for multiplex analysis of up to 800 RNA, DNA, or protein targets. Other instrumentation includes a complete a GeoMX instrument, a DEPAArray station, Agilent Tape station and Bioanalyzer for estimating nucleic acid samples integrity. During 2021, two 10X Genomics Chromium stations for single cell libraries production have been acquired.

The NGS activity during 2021 included the following analyses:

- RNA sequencing: 389 samples
- DNA exome sequencing: 185 samples
- Epigenetic assays: 110 samples
- Target DNA-seq library prep: 14 samples
- COVID sequencing: 6204 samples
- Single Cell sequencing: 18 samples
- Nanostring platform: 60 samples
- GeoMX instrument: 24 samples

In addition to the institutional activity, the Unit conducted several research activities during the year:

Multiple Myeloma (MM) is a haematological neoplasm characterized by proliferation of clonal plasma cells in the bone marrow and overproduction of immunoglobulins. During this year the SAFU team has developed an optimized protocol to collect and store viable CD138+ cells (plasma cells selected for the expression of CD138 marker) from patients, and through the collaboration with the Hematological Unit CD138+ plasma cells from bone marrow of ~ 80 MM patients enrolled in clinical monitoring have been collected. In addition, we have collected CD138+ plasma cells from healthy samples, M_{gus} and smoldering patients, relapse, and post transplantations patients. This dataset includes 22 first onset and therapy matched samples of patients. The chromatin organization profiles of several healthy and pre-treated patients have been produced by ATAC-seq experiments, while those related to post-treatments patients will be profiled as samples are collected according to clinical treatment plan of each patient. The ATAC-seq experiments carried out so far have produced analysable results from 4 healthy donors and 64 MM samples. The peaks generated showed a high heterogeneity although containing numerous regions shared among the different patients (sharing peaks). The accessible regions were analyzed for the presence of binding motifs for transcriptional factors (Foot printing), also characterizing the latter for their degree of sharing. In the meantime, we performed studies by using two primary cell lines MM217 and MM196, derived from 2 newly diagnosed MM patients and made resistant to Bortezomib. Drug -sensitive and -resistant cells were utilized for preliminary analyses, and experiments of western blot revealed a strong increase of the Unfolded Protein Response and DNA damage, in both resistant lines. ATAC-seq experiments from sensitive and resistant MM196 cells, revealing that resistant cells exhibit a dramatic reduction in chromatin opening with a closure of more than 40% of the accessible sites, balanced by less than 5 % of new open regions.

Dr. Piaggio models have investigated the macro-environment before tumor appearance by using preclinical mice. Her group identified spatio-temporally early steps of tumor transformation, involving waves of systemic proliferation and metabolic activation when molecular events necessary for successful tumor growth could take place. Moreover, using human bio banked specimens she conducted a retrospective analysis on tissues and liquid biopsies to evaluate the presence of NETosis features in EC and their potential usefulness for diagnosis and/or prognosis providing evidence on the possible involvement of NETosis formation in tumor-induced systemic effects.

Dr. Strano focused her efforts on the identification of circulating miRNAs as predictive biomarkers of the development of oral mucositis in patients with HNSCC tumors, undergoing radio/chemotherapy treatment. To mimic the inflammatory process “in vitro”, primary lines of gingival keratinocytes and epidermis (HEKa) were treated with different classes of antineoplastic agents used in the treatment of patients suffering from HNSCC tumors and known

to induce mucosal lesions of various degrees in the patient. Total circulating RNA was extracted from the treated gingival keratinocyte media, which was used as a probe to hybridize Agilent slides containing specific oligos of 2549 microRNAs. With this approach it was possible to identify six commonly deregulated microRNAs between the different groups with respect to control. MiR-18b-3p levels were commonly upregulated in culture media tested regardless of the type of treatment carried out. We conducted a bioinformatics analysis on miRNA seq data from the TCGA of miR18b-3p expression levels in normal versus tumor tissues. The data included miR18b-3p expression levels in tumor samples of colorectal cancer, lung, breast, head-neck. Such an analysis did not show an involvement of miR18b-3p in the tumor process. This reinforces our initial hypothesis of the specificity of miR18b-3p as a biomarker of the mucosal inflammatory process secondary to iatrogenic damage.

Dr. Fattore's research activities stem from a comprehensive analysis of the entire miRNome using in vitro models of acquired resistance to targeted therapies in melanoma which underscored a general dysregulation of miRNAs at the basis of this phenomenon. This discovery is the object of a patent application: IT 102018000004384 (11/04/2018) internationally extended in 2019. The main focus has been directed to 4 miRNAs, two oncosuppressor miRs, i.e., miR-199b-5p and miR-204-5p, and two novel oncomiRs, namely miR-4443 and miR-4488. The firsts have been investigated as novel therapeutics for melanoma using Lipid Nanoparticles (LNPs) to conduct in vitro and in vivo efficacy studies. Results have demonstrated the capability of LNPs carrying oncosuppressive miRs to reduce melanoma cell growth and to potentiate targeted therapies. As to study of the molecular function of miR-4443 and miR-4488 in melanoma drug resistance, in silico predictions of their molecular targets have suggested an impact on pathways belonging to migration and invasion behaviors. Furthermore, the transient overexpression of both miR-4443 and miR-4488 in sensitive melanoma cells can recapitulate such biological effects. These studies have been supported by a two-years grant won as PI by Dr.Fattore (LILT Call 2020-21) entitled: "Therapeutic and diagnostic implications of miR-4488 and miR-4443 to fight resistance to targeted therapy in metastatic melanoma". Finally, his activities are also directed to develop circulating miRNA signatures able to predict therapy response in melanoma before starting treatments.

To understand the molecular mechanisms of miRNA deregulation in CRC, Drs. Gurtner, obtained data demonstrating an inhibitory activity of mutant p53 on the activity of Dicer, a key enzyme in the miRNA's biogenesis. She identified 20 deregulated miRNAs in a cohort of 80 cancer patients with TP53 hot spot mutations. The KEGG pathway and GO analyses of their target genes identified several pathways related to cancer and druggable genes. Finally, she characterized the functional role of the mutantp53/NF-Y complex on miRNA regulation during the epithelial mesenchymal transition on colon cancer primary tumor and metastasis.

In addition to these activities, SAFU unit has focused numerous efforts on the study of Covid 19. In collaboration with the microbiology unit of the San Gallicano Institute and with the Oncogenomic and Epigenetic and Bioinformatics units, more than 6000 sequences of virus-positive patients were carried out, monitoring the variants present in the Lazio region. Drs. Piaggio measured and compared the impact of the pandemic on the access of cancer and immunocompromised patients to therapies in three Italian regions; She assessed how reorganizational measures put in place in these different institutions have impacted on specific metrics of performance; she established a COVID-19 Biobank of biological samples from SARS-Cov-2 infected patients to be used to study immunological alterations in patients with immune frailty.

Dr. De Marco contributed to develop a quantitative method to assess both circulating and secretory SARS-CoV-2 anti S1 IgA. Studies are in progress to assess the actual risk for severe COVID-19 outcomes, associated with current or past neoplastic diseases, hematologic malignancies, or treatments with immune response modifying drugs. In addition, he worked to assess the long-term durability of COVID specific serological and T cell responses, either following natural infection, or BNT162b2 vaccination, or in subjects experiencing both exposures in either way. He observed that vaccination stimulates a RBD-specific antibody response several fold stronger than natural infection, raising the possibility that vaccine-mediated immunity might be more protective than immunity at preventing reinfection and limiting morbidity upon reinfection in frail patients. Finally, antibodies are the presumed surrogate for protection against infection with most viral infections but the surrogate for protection for SARS-CoV-2 has not yet been established. If antibodies are not the correlate of protection for SARS-CoV-2, the impact of malignancies or immune modifying treatments on vaccine-specific T-cell responses and durability may turn out as the factor associated with the ultimate success of BNT162b2 vaccine in these frail populations.

