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Bridging bench to bedside: The evolution and impact of translational research in oncology. The experience of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)

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Abstract

The Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) is Italy's first cooperative oncology research group, evolving to conduct academic clinical trials since 1985. With 167 publications and collaborations with national and international partners, GOIRC has significantly impacted clinical practices. The group emphasizes training and has developed robust internal standard operative procedures (SOPs) to enhance data quality. GOIRC is poised to tackle future challenges in translational research, focusing on innovative trial designs, precision medicine, and leveraging different laboratory resources across its 42 units.

Keywords

Breast oncology, gynecologic oncology, molecular oncology

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Introduction

The Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) was the first cooperative oncology research group in Italy.[1] Born with a simple basic structure, it has grown into a systematized and organized group that conducts academic oncology clinical trials. Over time, collaboration has been built with other national and international research groups and significant results have been achieved with 167 publications in peer-reviewed journals from 1985 to 2023. Furthermore, GOIRC is among the founders of the Breast International Group (BIG), collaborating on several trials that have changed clinical practice. Advances in clinical research guidelines have increased the quality of clinical data collection and the concomitant professional growth of the actors involved in conducting clinical trials.[2] The GOIRC structure has grown by constantly improving internal organization over the years. The development of internal standard operating procedures (SOPs), necessary for a correct management of clinical studies, was conducted according to national and

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international regulatory requirements allowing for participation of high scientific value. The training activity also represented one of the cornerstones of GOIRC, aiming at the training of clinical investigators, data managers, clinical study coordinators, clinical project managers as well as at specific seminars dedicated to the training of young researchers. Recent changes observed in molecular biology, research methodology and privacy regulation have addressed GOIRC's future research activity with the aim of increasing expertise in all these areas.

Advancements and innovations in translational research: The revolution in cancer treatment methodologies

In oncology, translational research is a pivotal discipline that establishes a systematic and effective approach for leveraging advanced knowledge and technologies from preclinical and clinical biology to enhance cancer treatment methodologies. At its core, this field involves a deep understanding of the biological attributes of cancer, translating molecular biological evidence into clinical anticancer strategies. Essentially, 'translational research' represents a methodological process where treatment decisions are exclusively guided by discerned molecular biological characteristics.[3]

In this context the studies adopt a multidisciplinary approach, seamlessly bridging the gap between scientific research and practical applications to advance human health.[4] The translation of laboratory findings into clinical applications and public health interventions is a key objective, with diverse types of interventions focusing on specific goals.[5]

One category of translational research is devoted to researching and developing new therapies for medical scenarios, emphasizing the pivotal translation from laboratory discoveries to clinical trials and eventual implementation in practice.[6] Another category focuses on unravelling the evolutionary dynamics of tumors, particularly in cancer biology. Recent strides in mathematical and computational models have substantially contributed to the understanding of tumor biology, thereby steering the development of personalized treatment strategies. These models offer valuable insights into tumor heterogeneity, clonal evolution and drug resistance, guiding the formulation of more effective therapeutic approaches.[7]

The origins of translational studies can be traced back to the final decades of the 20th century when it emerged as a distinct discipline bridging the gap between basic research and clinical practice by focusing on molecular and cellular response endpoints.

Furthermore, initial translational efforts concentrated on discovering and characterizing the molecular underpinnings of pathological mechanisms across various diseases. This involved seeking potential therapeutic targets and expanding endpoints to evaluate tumor response and pharmacokinetics.

Moreover, advancements in genomics and 'omics' technologies have played a transformative role, allowing a deeper understanding of the molecular foundations of diseases and paving the way for precision medicine.

In the realm of precision medicine, translational studies actively engage in identifying predictive biomarkers to tailor therapies, thereby enhancing treatment efficacy. The incorporation of the progression-free survival (PFS) end point signifies commitment to a personalized approach.

Moreover, the identification of specific molecular targets has driven the development of targeted therapies, including biological drugs and immunotherapies. The inclusion of immune response endpoints reflects ongoing advancements in this domain. Translational research continues to evolve as an indispensable force that seamlessly integrates scientific knowledge with clinical applications to propel advancements in cancer treatment methodologies.

In the era of precision oncology, novel trial designs are changing traditional phase I, II and III protocols, driven by advancements in high-throughput diagnostic technologies.[8] The advent of these innovative designs is fostered by the increase in the number of actionable biomarkers and the reduction in the target population size.[9] The primary goal is to expedite drug investigation and approval by minimizing study timelines and associated costs. Three notable trial designs are as follows:

1. Basket Trial: Enabling treatment with a single drug across different diseases sharing a common actionable target in distinct trial cohorts (the basket).
2. Umbrella Trial: Enrolling patients with a specific tumor type for treatment with various drugs based on molecular alterations into subtrials.
3. Platform Trial: Randomizing patients with one or multiple tumor types into different experimental arms versus a standard control arm, with adaptive changes guided by Bayesian statistical methods.

Adaptive elements that allow trial modifications based on accumulating evidence are incorporated into the study protocol. These adaptations encompass the randomization treatment arm and end point selection, target sample size adjustment and responses to ongoing research findings. Innovative trials may employ unique endpoints such as overall response rate and duration of response, facilitating rapid evaluation and safety assessment for potential drug approval.

These trials may serve as confirmatory trials rigorously following the methodology in the presence of a control arm. Advantages of innovative trials include accelerated drug development, parallel testing of multiple drugs on the same tumor type, efficient achievement of primary endpoints and adaptation to changes in clinical practice.

However, challenges arise, including an increased risk of false-positive findings, potential regulatory withdrawal due to inconclusive results in expansion phases, slow accrual due to condition rarity, and the need for appropriate infrastructure and trained physicians with a strong biological background, capable of managing diverse tumor types and complex drug schedules/toxicities. The transformative potential of innovative clinical trials in oncology is evident, balancing advantages with potential challenges to enhance the efficiency and efficacy of drug development and approval processes.

Multiarm multistage (MAMS) trials represent an innovative approach to clinical research, revolutionizing the evaluation of new treatments across diverse medical conditions.[10] This methodology involves simultaneous assessment of multiple treatment arms against a common control arm, enabling efficient and accelerated evaluation of potential therapies. Successfully applied in oncology, infectious diseases, and postpartum hemorrhage, MAMS trials demonstrate versatility and broad applicability.[11]

A key advantage of MAMS trials lies in their adaptive nature, allowing prespecified interim analyses to assess activity in different treatment arms. This adaptability empowers researchers to make informed decisions regarding arm continuation or early termination, thereby optimizing resource allocation and expediting effective treatment identification.[12]

Incorporating biomarker stratification into MAMS trials enhances precision and personalization, especially in precision medicine and conditions such as prostatic neoplasms.[13] Leveraging biomarker data enables tailored treatment strategies for specific patient subgroups, maximizing therapeutic success potential.

Statistical considerations in MAMS trials are crucial, focusing on controlling family wise error rates and addressing challenges related to multiple testing.[14,15] This research emphasizes efficient determination of optimized MAMS experimental designs with control of generalized error rates, underscoring the importance of robust statistical methodologies in trial design and analysis.[16]

Furthermore, MAMS trials offer a promising framework for the evaluation of new agents and treatment regimens, providing a flexible and adaptive platform for efficient clinical research. By incorporating adaptive interim analyses, biomarker stratification, and rigorous statistical control, MAMS trials can significantly influence drug development, ultimately enhancing the delivery of effective therapies to patients.

The informed consent issues

The requirement that researchers obtain informed consent from potential participants before research commences is a fundamental principle of medical research, included in the Declaration of Helsinki and in the subsequent Universal Declaration on Bioethics and Human Rights released by UNESCO.[17,18] The requirement for consent is supported by ethical principles of respect and individual autonomy. Consent is also the basis for data protection and privacy law in the EU countries.[19] In this regard, it is fundamental to underline that the legal consent, devoted to the protection of people's personal data, and the ethical one have two different meanings. For this reason, when the former is not required, for example when the data are managed in a completely anonymized form, the latter is in any case mandatory, following the right granted to each individual to approve the use of their clinical data for research purposes.

However, in the last two decades biomedical research has been transformed through the application of information technologies that allow ever greater amounts of data to be collected on an unusual scale, and, at the same time, we have observed a huge proliferation of biobanks, that are a reference point for multiple researchers and research projects. In this scenario the study design is very often based on a retrospective sampling, making it difficult to obtain the required informed consent.

For this reason, the static, paper-based procedure for recording consent can no longer be considered adequate, and new approaches are needed to meet ethical and legal requirements.[20]

In this context, *dynamic consent* may address the changing nature of biomedical research, allowing researchers to overcome the limitations of static consent. In this case the consent process is based on a technology platform that permits participants to express agreement to a broad range of uses of their samples and data, or opt to be approached on a case-by-case basis, or set different preferences for different types of research. Moreover, it should be point out that the term 'dynamic' means that the preferences originally expressed can be modified at any time by each subject. In this way a permanent channel of communication is open between researchers and people, that can also receive different kind of information, of personal or general interest, according to the preferred format.

Implementing a dynamic consent model requires cultural change for both health-care professionals and individuals, and many challenges must be addressed. However, the opportunities that this model can provide, in terms of respect for the recognized rights of human beings and recruitment capability, are substantial.

Laboratory resources and techniques in Italian oncology units: A survey of GOIRC

As the largest cooperative oncology group in Italy, GOIRC (Gruppo Oncologico Italiano di Ricerca Clinica) consists of 42 units. To assess the laboratory resources available in each unit, we conducted a survey. This survey, consisting

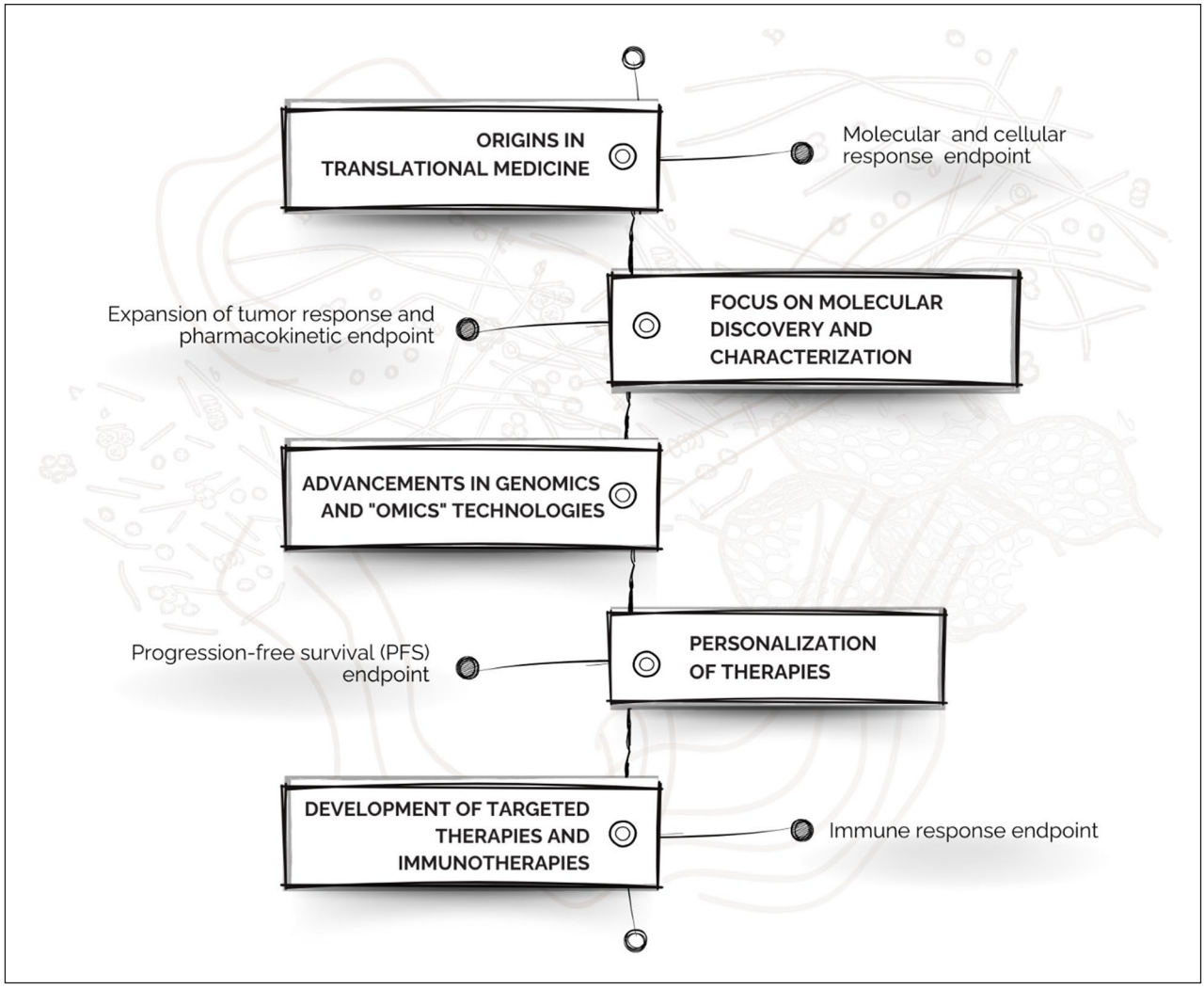

Figure 1. Survey of GOIRC Oncology Units focused on the resources directly controlled by the center. It was distributed to the representatives of each GOIRC unit.

of 17 questions, focused on the resources directly controlled by the center. It was distributed to the representatives of each GOIRC unit (Figure 1).

Out of the total 42 GOIRC units, 13 (31%) responded to the survey. All 13 units reported the ability to store biological samples at -20°C, while all but one unit had the capability to store samples at -80°C. Additionally, all freezers were equipped with temperature detection systems and/or alarms.

Regarding specific laboratory techniques, immunohistochemistry tests were conducted in 61.5% of GOIRC units, and the FISH technique was used in 69% of units. Eight out of 13 units (61%) were able to extract and analyze both DNA and RNA, while only four units analyzed cfDNA. Protein extraction and analysis were performed in four out of 13 (31%) centers, and the ELISA assay was carried out in five out of 13 (38%) centers. Six (46%) GOIRC units utilized flow cytometry.

In terms of cell culture capabilities, 69% of our centers were equipped with cell culture hoods/incubators. Our survey revealed that a greater number of centers were able to perform Next Generation Sequencing (NGS) tests compared to PCR/quantitative PCR/digital droplet PCR tests, with 69% and 54% respectively. Among the nine centers performing NGS, all used commercial panels, while two centers also utilized custom panels. Illumina platform was used by all nine centers, except one which used the ThermoFisher platform. One center had two NGS instruments, and another center had four instruments. Only five out of 13 centers (38%) had a bio-computer scientist, and only two centers had server/cloud infrastructure for data backup. Lastly, two centers participated in the regional Molecular Tumor Board (MTB).

Discussion

Our paper highlights the advancements and innovations in translational research, specifically in the field of cancer treatment methodologies, achieved by the Gruppo

Oncologico Italiano di Ricerca Clinica (GOIRC). It is the first cooperative oncology research group in Italy, it has grown over time and has achieved significant results through collaboration with other national and international research groups, leading to numerous publications in peer-reviewed journals. The group has also played a role in changing clinical practice through its collaboration with the Breast International Group (BIG).

Translational research aims to bridge the gap between scientific research and practical applications, with a focus on translating molecular biological evidence into clinical anticancer strategies. It encompasses multidisciplinary approaches and the translation of laboratory findings into clinical applications and public health interventions. In recent years, molecular biology has revealed the complexity of cancer initiation and evolution, enlightening the presence of rare tumors in the context of each tumor type (i.e. breast cancer, lung cancer). This scenario dramatically modified the methodology of conducting clinical trials, highlighting the usefulness of academic cooperative groups in leading translational studies.

To emphasize the key role of academic research groups (i.e. GOIRC) in promoting translational research, we present the results of a survey conducted on the laboratory resources available in each GOIRC unit. The survey focused on resources directly controlled by the center and included questions on sample storage, immunohistochemistry tests, DNA and RNA analysis, protein analysis, ELISA assay, flow cytometry, NGS tests, and computational resources. The survey revealed the availability of various technologies and expertise across different GOIRC centers.

Based on our findings, we can state that GOIRC, as the first and one of the biggest Italian academic cooperative groups, will be key in facing the following challenges in conducting translational research:

1) Increasing sample size in the era of precision medicine. GOIRC aims to conduct umbrella trials, which involve enrolling patients with different diseases but sharing a common molecular target. By including a larger sample size, GOIRC can gather more robust data to support precision medicine approaches, like MAMS trials.
2) Conducting basket trials for different diseases. Considering its broad multidisciplinary, in the approaching future, GOIRC will focus on basket trials, where a single drug is tested across different diseases that have a common actionable target. This approach allows for a dipper evaluation of the drug's efficacy and potential benefits in multiple disease types.
3) Enhancing the possibility of being awarded with research grants. The collaboration of GOIRC with national and international research groups, as well as its track record of significant results and publications, increases its chances of receiving grants for further research and clinical trials both from public and private/pharma sponsors.
4) Availability of different technologies and expertise from different centers. GOIRC comprises 42 units, each with its own laboratory resources and expertise. This allows for a wide range of technologies and knowledge to be implemented, enhancing the group's ability to conduct comprehensive research and clinical trials.
5) Infrastructure. GOIRC has established infrastructure such as a Clinical Research Organization (CRO) and data management systems. These resources facilitate the efficient management and coordination of clinical studies, ensuring high-quality data collection and analysis.
6) GOIRC tumor board participation. Finally, GOIRC has all the components to build its own MTB. It will allow for interdisciplinary discussions and collaboration among experts in different fields, leading to improved decision-making and personalized treatment strategies for patients.

To pursue these goals, we have recently established a new GOIRC group, the Translational GOIRC Group. It aims to advance oncology research and clinical practice by conducting innovative trials, leveraging diverse technologies and expertise, and actively engaging in collaborations and knowledge sharing with GOIRC pathology groups (i.e. Breast Cancer Group, Thoracic Group).

Declaration of conflicting interests

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