

Biotherapy of cancer. Break the barriers to foster translation of knowledge

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ABSTRACT

Biotherapy of cancer holds great promise for its potential to lead to the identification of novel, selective, and effective treatments against cancer. However, the clinical development of biopharmaceuticals and biotherapy products is hampered by several and diverse barriers.

Herein, we will address some of the critical issues identified both at the national and European level as the major obstacles for the translation of knowledge into clinical applications in the field of biotherapy and immunotherapy of cancer. We will also illustrate specific initiatives undertaken both in Europe and in Italy in order to support the translational and clinical research and that are expected to have a favorable impact on the process of clinical development of novel and more effective therapeutic interventions against cancer.

The contents of this article are directly referred to the event "International Clinical Trials' Day on Biotherapy of Cancer" organized in the context of the OEIC Genova 2008, with the sponsorship of Alliance Against Cancer and the Istituto Superiore di Sanità (the Italian National Institute of Health), and under the auspices of the European Clinical Research Infrastructures Network (ECRIN). This event sees the active participation of representatives of the ISS and of the Italian Network for Tumor Biotherapy, both involved in a project recently funded by ACC and aimed at the promotion of clinical research in the field of cancer biotherapy and immunotherapy, through the creation of a national network of clinical cancer research centers and GMP facilities dedicated to the production of biological drugs and advanced medicinal products.

Introduction

The recent advances in tumor immunology and biotechnologies have opened new perspectives for cancer biotherapy. Today, these perspectives hold great promise for the development of up to date effective cancer treatment strategies. However, a number of critical issues need to be solved and barriers have to be overcome in order to give biotherapy and immunotherapy of cancer the chance of fully demonstrating its potential of becoming one of the standard approaches for the management of neoplastic diseases.

Specific initiatives are being undertaken in Europe for supporting the translational and clinical research driven by academic institutions. It is expected that these actions will foster the pre-clinical and clinical development of novel biological drugs and biotherapy approaches for cancer treatment. It is of utmost importance that national programs parallel the European initiatives, particularly concerning the realization of research infrastructures.

Alliance Against Cancer (ACC) and the Istituto Superiore di Sanità (ISS), within the framework of the programs provided for in Art. 3 of the National Program for Cancer Research launched by the Italian Ministry of Health in July 2006, have recently funded a project aimed at the promotion of clinical research in the field of cancer biother-

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apy and immunotherapy, through the creation of a national network of clinical cancer research centers and GMP facilities dedicated to the production of biological drugs and advanced medicinal products. This project involves the Italian Network for Tumor Biotherapy (NIB-IT)¹ as well as representatives of the ISS.

The recent entry of the ISS as a partner in the preparatory phase of the pan-European ECRIN – Infrastructure for Clinical Trials and Biotherapy has prompted the initiative of a satellite celebration of the International Clinical Trials' Day dedicated to biotherapy of cancer. The International Clinical Trials' Day is a traditional yearly appointment for ECRIN partners, dedicated to the celebration of what can be considered the first documented randomized clinical trial in the history of medicine. In fact, on 20th May 1747, James Lind, while serving as naval surgeon on HMS Salisbury, carried out the first comparative trial on 12 sailors afflicted by scurvy. Lind gave the sailors in each group different additions to their basic diet: cider; seawater; a mixture of garlic; mustard and horseradish; and, spoonfuls of vinegar. The last group received oranges and lemons. Only the sailors fed citrus fruits experienced a remarkable recovery. Although the antiscorbutic effect of citrus fruits had been known at least since 1600, by conducting this clinical trial, Lind had definitively established the superiority of citrus fruits above all other 'remedies' and proved that citrus fruits cure scurvy. Lind's recommendation on the inclusion of fresh citrus fruits and lemon juice in the diet of seamen eventually resulted in the eradication of scurvy from the British Navy.

Nowadays, randomized clinical trials are used worldwide to identify and validate novel diagnostic and therapeutic interventions.

The great expectations for the impact of biological and immunological interventions against cancer can only be met through the application of a clinical development paradigm best suited to address the peculiar and unique characteristics of biologics, and particularly of cancer vaccines and immunotherapeutic agents.

The "OECD 2008 Cancer Week" represented an ideal forum for debating among scientists and with representatives of patients' associations and of industry on the state of art and perspectives of cancer biotherapies, as well as on critical regulatory, ethical, and clinical development issues pertaining to these innovative therapeutic strategies.

Promotion of biotherapy of cancer at the European level

Lessons from the EUROCAN+PLUS project

Europe, thanks to the presence of several top-level laboratories, hospitals and institutions with a long-standing record of excellent preclinical and clinical re-

search in cancer biotherapy, has a great potential in playing a leading role in the progress of the research in this field and in the translation of the new knowledge into the clinical management of cancer. However, some steps need to be taken in order to promote clinical research, remove barriers, avoid excessive fragmentation and duplication, harmonize rules and requirements for clinical experimentation in the different member states, and to foster cooperation on critical issues of special importance.

In the context of the project EUROCAN+PLUS "Feasibility Study for Coordination of National Cancer Research Activities", funded within the EC 6th Framework Programme (FP) and coordinated by the International Agency for Research on Cancer (IARC), the ISS has realized, in its capacity of Italian partner, a series of activities to identify bottlenecks and possible solutions for promoting the translational and clinical research in oncology, with particular regard to the field of biotherapy and immunotherapy of cancer. These activities have resulted in recommendations concerning specific initiatives to be undertaken in the context of the EC FP7. These recommendations have been delivered to the EC and are summarized in the following paragraphs.

A clearly urgent need is the definition of a new paradigm for the clinical development of cancer vaccines and biopharmaceuticals, as single agents or in combination with other therapeutic interventions, in consideration of their peculiar characteristics and differences with respect to conventional drugs and therapies. The debate on this important issue has been prompted by the publication of the *consensus* document prepared by the Cancer Vaccine Clinical Trial Working Group (CVCTWG)². The paradigm proposed in the CVCTWG document suggests investigating cancer vaccines in two phases: proof-of-principle (exploratory trials) and efficacy trials, with early and informed decision making through prospectively defined "go" or "no go" decision points, use of biologic end points, adjusted clinical end points, early use of randomized trials and, when possible, adaptive design components. In Europe, the comprehensive cancer centers and their networks would represent the ideal entities for the development and "validation" of the new paradigm, and coordination between cancer centers would be instrumental to reach these objectives. However, a prerequisite is that the new paradigm finds acceptance by the national regulatory authorities and by EMEA. Therefore, the crucial initiatives to be undertaken are those promoting the discussion between laboratory and clinical investigators and experts of regulatory bodies, aimed at the definition of a shared and highly agreeable set of rules for the developmental process for clinical investigation of cancer vaccines and related biologics. These rules should obviously warrant the safety of the patients and at the same time allows a more efficient and adequate evaluation of the biological and clinical efficacy of cancer vaccines,

biopharmaceuticals, immunotherapy and combination therapy strategies.

The second important recommendation is based on the *consensus* registered on the need and importance of fostering academy-driven clinical and related laboratory investigation aimed at acquiring new knowledge, in cancer patients, on the tumor-immune system interactions and on the mechanisms underlying tumor response or non-response to immunological interventions. Exploitation of this knowledge will allow to optimize the design and clinical development of new drugs and therapeutic strategies against cancer based on the manipulation of the immune system.

The third recommendation concerns the launch of an European initiative for the development, validation and standardization of immunomonitoring assays for assessing the biological response and predicting the clinical response to cancer vaccines and immunotherapy. Of note, this initiative can take advantage from the existence of immune monitoring platforms in different European countries, that, however, need to be better connected and integrated among themselves and with other platforms outside the EU, particularly in the USA.

The fourth recommendation stems from the absolute need, in order to facilitate the running of multi-center clinical studies between different European member states, of harmonization of rules for standardization and characterization of cancer vaccines and reagents for cancer biotherapy, and of facilitation of the access of public research institutions to GMP reagents. Of note, one of the major goals of two ESFRI infrastructures, namely the ECRIN³ - Infrastructure for Clinical Trials and Biotherapy and the EATRIS⁴ (European Advanced Translational Research Infrastructure in Medicine) (see below), is to perform a survey on needs and existing resources in terms of GMP facilities for biopharmaceuticals and biotherapy products. The outcome of the survey will then be used for the design and planning of the construction of the necessary GMP facilities.

A final recommendation concerns the identification of instruments and policies for establishing a partnership between academy and industry in the field of cancer biotherapy. It is absolutely necessary to join forces, sources and knowledge, both private and governmental ones, in order to develop a solid biotech sector throughout Europe, transforming needs and problems into opportunities. To this regard, both the participation of SMEs in EC projects and the establishment of a public-private partnership within the Innovative Medicine Initiative in the field of cancer immunotherapy should be fostered.

The above mentioned proposals have been included in the framework of the more general recommendations that the EUROCAN+PLUS has forwarded to the EC concerning initiatives to be undertaken at the European level in the context of the FP7. These recommendations include the establishment of a Network of Comprehen-

sive Cancer Centers and the launch of an ERA-Net for the translational research in oncology.

The opportunities offered by the European infrastructures

The European Strategy Forum for Research Infrastructure (ESFRI)⁵ published in late 2006 a Roadmap⁵ which identifies 35 large scale infrastructure projects, at various stages of development, in seven key research areas including Biomedical and Life Sciences. In this area, two infrastructures appear of particular relevance for the field of cancer biotherapy, namely the Infrastructure for Clinical Trials and Biotherapy and the European Advanced Translational Research Infrastructure in Medicine (EATRIS). The preparatory phase of both infrastructures has started in 2008, and with specific regard to the Infrastructure for Clinical Trials and Biotherapy this phase represents the third phase of the European Clinical Research Infrastructures Network program³, previously funded in the context of the EC FP6.

The ECRIN program is aimed at building an integrated, pan-European infrastructure able to provide support to clinical research in any medical field, and for any type of clinical research, and to the conduct of multinational studies in Europe⁶. ECRIN is designed to bridge the fragmentation of clinical research in Europe through the interconnection of national networks of clinical research centers and clinical trial units. A first phase of the ECRIN program helped identify bottlenecks to multinational cooperation. In the current second phase, transnational working groups are in charge of defining procedures and guidelines for multinational studies in the EU. The third phase of the program will consist of building the infrastructure for EU-wide clinical trials and biotherapy described in the ESFRI Roadmap. This distributed infrastructure, based on the integration of competence centers coupled to data centers and biotherapy facilities, will provide access to clinical research projects through a set of flexible services offered by ECRIN. These services are particularly relevant for academic clinical research and for clinical trials sponsored by biotechnology, drug, and device enterprises that may lack the capacity to conduct EU-wide studies. In addition, ECRIN will enable efficient implementation of the Innovative Medicines Initiative (IMI) strategic research agenda, providing support and infrastructure for public-private partnership in EU-wide studies. Ultimately, ECRIN will stimulate EU research on prevention, diagnosis and treatment, hence improving healthcare delivery to patients and citizens.

The EATRIS preparatory phase is aimed at the realization of a distributed pan-European infrastructure consisting of a network of biomedical translation research centers across Europe⁵. The ultimate goal of EATRIS is to support a faster and more efficient translation of research findings into the development of innovative

strategies for the prevention, diagnosis and treatment of diseases which are of particular relevance for European member states and that have a high medical and economic burden.

The need of a EU-wide infrastructures supporting translational research stems from the observation that in Europe the translation of basic research discoveries into industrial applications has been hampered by diverse barriers and represents a major challenge for the European Research Area. A major bottleneck is the fragmented nature of basic and clinical research infrastructure, leading to unnecessary delays and difficulties in drug development or the implementation of new diagnostic strategies.

The EATRIS program will be focused initially on the disease areas of cancer, metabolic diseases, neurological disorders, cardiovascular diseases and infectious diseases. The EATRIS infrastructure will provide access to preclinical and clinical research infrastructures, comprising a number of physical such as animal facilities for preclinical validation studies, small molecule screening facilities to identify and characterize new drug targets, disease specific patient and population cohorts to develop and validate new hypothesis for innovative diagnostic and therapeutic strategies, centralized GMP facilities for bioprocess development and manufacturing, and facilities to carry out clinical phase I studies. In addition, the EATRIS infrastructure will offer to its users (laboratory biomedical investigators and clinical scientists, acting in the context of public institutions or SMEs, and industrial partners) consulting services, in order to support an efficient and well-controlled development process from the discovery to the preclinical and clinical stage. The consulting services will include scientific assessment, intellectual property issues, advise on regulatory issues, benchmarking with regard to existing technologies, potential risks, market potential, cost, medical need and ethical issues. Importantly, EATRIS will dedicate a particular attention to the development of programs of education and training of the next generation of translation researchers, a major bottleneck also identified by the European technology platform IMI (Innovative Medicine Initiative).

Promotion of biotherapy of cancer at the Italian and European level.

The role of the Istituto Superiore di Sanità and Alliance against Cancer

The commitment of the ISS in promoting the field of biotherapy and immunotherapy of cancer in Italy dates back to 1999, when the first of a series of international conferences dedicated to this sector was organized by this institution⁷⁻¹⁰. In the recent years, the ISS has devoted an increasing attention to the internationalization of the Italian biomedical research, particularly in the on-

cology field. In addition to its role in the EUROCAN+PLUS project, the ISS is presently involved in the preparatory phases of pan-European infrastructures in the biomedicine area. In fact, the Italian Ministry of Education, University and Research, in agreement with the Italian Ministry of Health, has charged the ISS with the role of coordinating the organization of the Italian participation to the construction of the EATRIS infrastructures. This assignment has determined the involvement of the ISS in the present preparatory phase of EATRIS. In this context, taking advantage of the co-existence within the same institution of expertise in various research fields as well as in the regulatory and ethical fields, the ISS participates with the leadership and responsibility of the activities aimed at developing, in agreement with the other EATRIS member states, a *consensus* regulatory and ethical framework for the construction and operation of the EATRIS infrastructure. The contemporary participation of the ISS in the preparatory phases of the infrastructures EATRIS, ECRIN, as illustrated below, and BBMRI (Biobanking and Biomolecular Resources Research Infrastructure), should represent an advantage for an efficient and harmonized coordination in the biomedicine area.

Of relevance for the field of cancer biotherapy is the involvement of the ISS in the ECRIN preparatory phase with the responsibility of defining, in close coordination with the EATRIS project, the existing resources and needs, on both the academic and the biotechnology industry sides, regarding the GMP compliant manufacturing facilities for clinical batches of biopharmaceuticals/biotherapy products, and of deciding on the connection or construction of such facilities under the umbrella of either ECRIN or EATRIS.

As pointed out also in the context of the EUROCAN+PLUS project, the access to GMP-compliant manufacturing facilities providing clinical grade batches of medicinal products often represents a bottleneck for academic institutions and biotechnology SMEs acting in the field of biotechnology and biotherapy. In particular, there is a clear need for flexible academic GMP facilities providing, in a non-commercial context, small amounts of biopharmaceuticals and advanced medicinal products for phase I-II “proof-of-concept” trials. For this reason both the ECRIN and the EATRIS projects included the development of GMP manufacturing facilities accessible to the users for the clinical proof of concept and, if relevant, subsequent clinical development on innovative biotherapy and biopharmaceutical products.

The role of the ISS in the European context can be paralleled at the national level. In fact, the Italian Ministry of Health, as provided for in Art. 3 of the National Program for Cancer Research launched in July 2006, has assigned to the ISS the role of coordinating the network activities of the Italian Comprehensive Cancer Centers (IRCCS) and thus of establishing a synergy with Alliance

against Cancer (ACC), that represents the network of the IRCCS. The Art. 3 is entitled “National solidary network and international collaborations” and identifies, among the four programs indicated as priorities to be funded in the oncology field and in the context of ACC, the integration of the research activities through the realization of national networks (Program 2) and the promotion of the international collaboration with preferential reference to Europe (Program 4).

The ISS, in its capacity of coordinator of the ACC activities included in Art. 3, has taken the commitment to realize national networks considered of primary importance by ACC and to promote their entry in the European context (Figure 1). In this context, the “National Network for Clinical Studies and GMP facilities” is aimed at the implementation of infrastructural activities supporting the clinical research in the field of bioterapy and immunotherapy of cancer, including the facilitation of access to GMP facilities certified for the preparation of biopharmaceuticals and advanced medicinal products. The priority given to the realization of this national network, among the others, is motivated by the notable delay and inefficiency that is registered in Italy in the process of translation of knowledge into clinical experimentation of advanced therapies against cancer. In this context, it is to be hoped that this Italian network will connect to the ECRIN and EATRIS infrastructures, in agreement with the other partners of the respective preparatory phases. To this regard it is worth pointing out that the ISS is committed to play a role in fostering at the national and European level the synergy and cooperation of all the components that are necessary for promoting the process of translational research and, thus, the development of more efficacious and safe drugs and therapies (Figure 2).

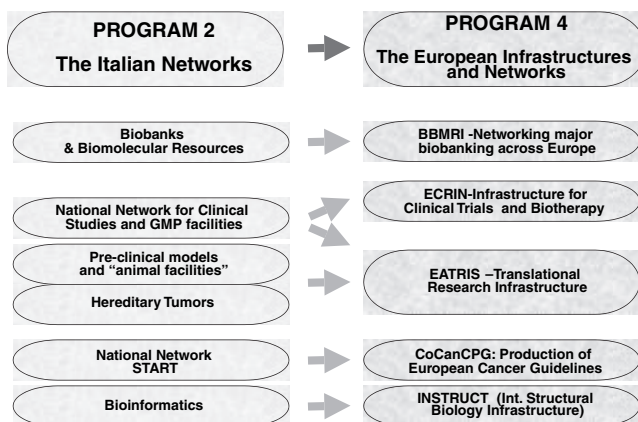


Figure 1 - Parallelism between the Italian ISS-ACC networks and the ESFRI pan-European infrastructures of the Biomedical and Life Sciences area.

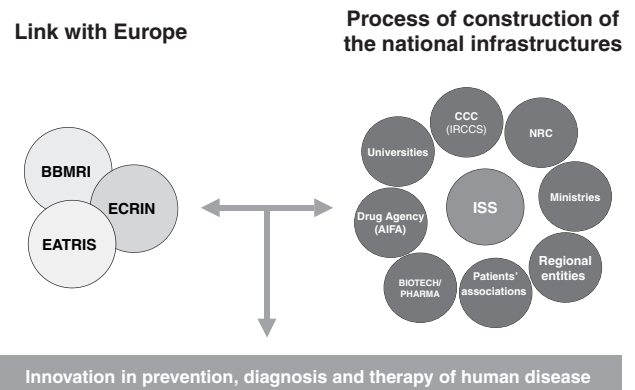


Figure 2 - Role of the ISS in the process of integration of the national networks in the construction of the pan-European infrastructures for translational and clinical research.

Concluding remarks

In the conclusion of this article, we would like to add a few considerations. First, we would like to stress the urgent need in translational medicine of fostering the formation of interdisciplinary teams comprising laboratory scientists, clinical practitioners, and professionals dedicated to solving the regulatory and logistical problems. This type of institutional infrastructure support has a general importance, but more specifically in the field of cancer bioterapy in consideration of the complexity of the regulatory and clinical experimentation issues.

Secondly, the availability of a database containing the blueprints and the results of the clinical research in cancer bioterapy would greatly contribute to overcome the fragmentation and duplication existing in Europe in this sector.

Finally, we believe that it would be beneficial, for rendering the European research on cancer immunotherapy more competitive, avoiding unnecessary fragmentation and duplication and favouring cooperation, to work towards the establishment of a European network for immunotherapy. This network should include: public institutions (academic, governmental, clinical centers), private institutions (foundations, organizations), industries, representatives of EMEA, and patients’ organizations for adequately addressing quality of life and of care issues. This may be a long route; defined EC instruments in the context of the FP7 can be used for paving the way, in the context of more comprehensive coordination initiatives at the EU level.

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