

# Translational research on advanced therapies

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**Summary.** Fostering translational research of advanced therapies has become a major priority of both scientific community and national governments. Advanced therapy medicinal products (ATMP) are a new medicinal product category comprising gene therapy and cell-based medicinal products as well as tissue engineered medicinal products. ATMP development opens novel avenues for therapeutic approaches in numerous diseases, including cancer and neurodegenerative and cardiovascular diseases. However, there are important bottlenecks for their development due to the complexity of the regulatory framework, the high costs and the needs for good manufacturing practice (GMP) facilities and new end-points for clinical experimentation. Thus, a strategic cooperation between different stakeholders (academia, industry and experts in regulatory issues) is strongly needed. Recently, a great importance has been given to research infrastructures dedicated to foster translational medicine of advanced therapies. Some ongoing European initiatives in this field are presented and their potential impact is discussed.

*Key words:* translational research, advanced therapy medicinal products, research infrastructures.

**Riassunto** (*La ricerca traslazionale sulle terapie avanzate*). La promozione della ricerca traslazionale nel campo delle terapie avanzate è avvertita sempre di più come una priorità sia dalla comunità scientifica che dai governi nazionali. I prodotti medicinali per terapie avanzate (PMTA) sono una nuova categoria di farmaci e comprendono tre tipologie di prodotti: prodotti per terapia cellulare somatica, prodotti per terapia genica e prodotti di ingegneria tissutale. Lo sviluppo dei PMTA apre nuove strade per approcci terapeutici a varie malattie incluso il cancro, le malattie neurodegenerative e le malattie cardiovascolari. Tuttavia questo processo è ostacolato dalla complessità della cornice regolatoria, dai costi elevati e dalla necessità di produzione GMP (*good manufacturing practice*, buona pratica di fabbricazione) e di nuovi *end-point* per la sperimentazione clinica. Quindi è necessario che si stabilisca una cooperazione strategica tra i differenti “stakeholders” (mondo accademico, industria ed esperti in campo regolatorio). Recentemente ha assunto una grande importanza lo sviluppo di infrastrutture di ricerca dedicate alla promozione della ricerca traslazionale nel campo delle terapie avanzate. In questo lavoro vengono presentate alcune iniziative europee in questo ambito e viene discusso il loro impatto potenziale.

*Parole chiave:* ricerca traslazionale, prodotti medicinali per terapie avanzate, infrastrutture di ricerca.

## INTRODUCTION

The recent advances of biomedical research and biotechnologies have opened new challenges and promising perspectives for the development of advanced therapies for human diseases, which may potentially have a great beneficial impact on patients' expectation of cure and quality of life as well as on public health. However, it is commonly felt that the new discoveries generally fail to be efficiently translated into clinical research and ultimately into clinical practice [1]. This concern has recently become a major issue raised by scientists, clinicians, policy-makers and patients' organizations. Possible strategies and initiatives to foster translational research have recently been debated [2-7].

The term “advanced therapies” includes a variety of novel therapeutic strategies, which are based on

the cutting-edge progress of biomedical research and on the use of novel and sophisticated technologies progressively aiming at patient-tailored interventions and at discovering novel and reliable biomarkers for predicting and monitoring the clinical response [8]. However, the regulatory issues to be addressed for the clinical development of these new therapies are much more complex as compared to traditional drugs [9]. As a consequence, the translational process of advanced therapies into clinical studies and medical practice is currently greatly delayed.

In this article, we will address and discuss the major bottlenecks currently impairing the full preclinical and clinical development of advanced therapy medicinal products (ATMP), as they currently represent the most challenging category of novel pharmaceutical products.

## ATMP: NEW PRODUCTS DESIGNED FOR DIFFERENT THERAPEUTIC PURPOSES

ATMP are a new medicinal product category comprising gene therapy and cell-based medicinal products as well as tissue engineered medicinal products. Their development opens new avenues for novel therapeutic approaches in numerous diseases, such as cancer, neurodegenerative diseases or cardiovascular diseases. They hold a huge potential in terms of possible impact on patients, public health and industry. Many public and private research institutions are currently involved in the development of ATMP. Moreover, there is also a current trend of increase of potential industrial market for ATMP development. ATMP include the three types of products described in the following paragraphs (see also *Table 1*).

### Gene therapy medicinal products

Gene therapy medicinal products (GTMPs) work by transferring genetic sequences (DNA, RNA) into cells by using various methods, including viral or bacterial plasmid vectors. The genetic sequences are engineered to modify, control, inhibit, or express a specific target. By using these vectors, *in vivo* genetic modification of somatic cells can be achieved [10].

**Table 1** | Main types of ATMP under current development and their potential medical use

<b>Immunotherapies (e.g. cancer vaccines)</b>
Dendritic cells
T Lymphocytes
Cell lines
Genetically modified primary cells
<b>Adult stem cells</b>
<b>Chondrocytes</b>
Repair of cartilage/articulations
<b>Haematopoietic/mesenchymal cells</b>
Modulation of GVHD
Bone regeneration
Muscular and myocardial regeneration
Nervous tissue and glia
<b>Pancreatic cells</b>
Pancreatic islet regeneration
<b>Endothelial cells</b>
Regeneration of microcirculation in ischemic tissues
<b>Epithelial cells</b>
Artificial skin
Corneal repair
<b>Hepatic cells</b>
Bio-artificial livers (BAL)
<b>Neuronal cells</b>
<b>Gene therapy products</b>
Viral vectors
Non-viral vectors
Genetically modified cells
<i>ATMP: advanced therapy medicinal products.</i>

The modification of germ line cells is strictly forbidden. Somatic cells may also be modified *ex vivo* or *in vitro* prior to administration to the patient. These cells can be intended for use in the same patient who donated the starting cells (autologous use) or can be obtained from a tightly-matched (allogeneic) donor. When the new gene is integrated into a stem cell's chromosome, the cell produces or stops the production of a protein in all the daughter cells which may help slow down or cure inherited diseases. Other application in non genetic diseases such as cancer can also be envisaged. GTMP are complex medicinal products whose clinical effects (both in terms of safety and efficacy) result from the combined action of vectors and transgenes (as in GTMP containing viral or non viral vectors) or of vectors, transgenes and cells (as in GTMP containing genetically modified cells).

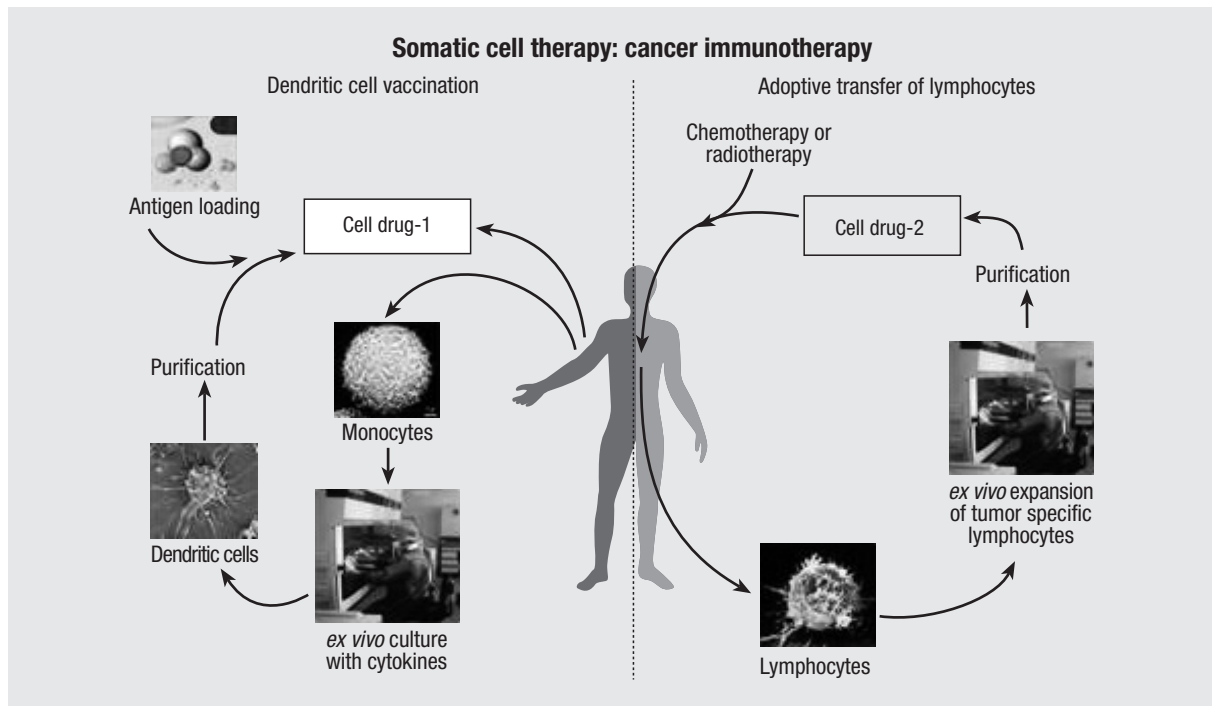
### Cell therapy medicinal products

Human cell therapy medicinal products (CTMP) are heterogeneous with respect to origin and type of the cells and to the complexity of the manipulations which leads to the final product. Cells may be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells, manipulated or expanded *in vitro* in order to exert a specific defined physiological function. Cells may be of autologous, allogeneic or xenogeneic origin. In addition, the cells may also be genetically modified (then classified as GTMP). The cells may be used alone, associated with biomolecules and chemical substances, or combined with structural materials that alone might be classified as medical devices (combination products). Furthermore, their administration might require dedicated medical device or specific surgical procedure. CTMP are therefore complex medicinal products whose clinical effects (both in terms of safety and efficacy) result from the pharmacological action of cells alone or in combination with other substances resulting in the therapeutic, diagnostic or preventive effect.

*Figure 1* illustrates some examples on the use of CTMP for studies of cancer immunotherapy, which have become of major interest for several research institutions in the field of cancer biotherapy in Italy and other European countries [11, 12].

### Tissue engineered products

Human tissue engineered products (TEP) combine various aspects of medicine, cell and molecular biology, materials science and engineering, for the purpose of regenerating, repairing or replacing diseased or missing tissues. Current applications of this nascent field of "regenerative medicine" include treatment for skin, cartilage and bone diseases or injuries. More complex, three-dimensional products – such as heart valves, blood vessels or heart muscle tissue – are currently in development, and could reach clinical application in a near future. Their mode of action is based on the replacement of miss-



**Fig. 1** | Two examples on the use of CTMP in trials of cancer immunotherapy. CTMP: cell therapy medicinal products.

ing tissue, or on the restoring of tissue function, or on the replacement of diseased tissue. They are often characterized by a three-dimensional structural complexity.

### MAJOR BOTTLENECKS AND CRITICAL ISSUES FOR ATMP DEVELOPMENT

The clinical development of ATMP raises several critical issues related to the specific nature of these new products [9]. In the case, for instance, of CTMP, we are dealing with different types of cells (often autologous cells), modified *in vitro* in order to induce defined functions, which are potentially beneficial for the patients after injection. Thus, there are major uncertainties for their development including the animal models, if any, to be used in preclinical studies, the mode of administration and the dose of cells to be injected. The requirement of certified good manufacturing practice (GMP) facilities for the production of ATMP to be used in clinical studies has recently caused major difficulties for the activation of clinical trials in Italy as well as in other European countries, especially for academia and public research institutions. These non profit organizations are usually unable to support the costs necessary for the preclinical and clinical development of ATMP and to meet the current complex regulatory framework needed for clinical experimentation with these new cell products. In an extensive survey conducted in the context of the EUROCAN+PLUS project coordinated by the International Agency for Research

on Cancer (IARC) [13], we could reveal that a major concern of cancer research institutes involved in ATMP development was the lack of help-desk on regulatory issues and of public support for GMP production of ATMP. In addition, the clinical development of ATMP requires special attention to critical issues in designing and performing clinical trials, due to the particular nature of these new products. They include the safety endpoints, the efficacy end-points and the time of patient's follow-up. An additional issue is how these new therapies can be combined with conventional treatments, since we are currently learning that this is often desirable, however it may pose specific regulatory issues. As an example, for studies in the field of immunotherapy (e.g. cancer vaccines) based on the use of dendritic cells or lymphocytes, there is an emerging interest today to move to studies where conventional drugs, such as chemotherapy, are used in combination with immune-based interventions [14, 15]. In addition, the importance of possible surrogate end-points of clinical efficacy is currently discussed and platforms for defining and identifying categories of responding patients are under development. All this may raise special regulatory issues and uncertainties for approval of clinical protocols, which need to be positively addressed in order to promote clinical experimentation in standardized and controlled conditions.

There are relevant quality criteria necessary for ATMP development, which differ depending on the specific product [9]. For instance, ATMP may often

comprise viral vectors and/or living cells; thus, they cannot be sterilized by heat without detrimental effects and are highly susceptible to environmental conditions (e.g. nutrients, temperature) as well as to microbial contamination (e.g. adventitious viruses, bacteria, mycoplasmas and moulds). ATMP are highly regulated also because they may carry not well defined biological risks for health workers, especially if they contain or have been exposed to xenogenic cells or biological fluids and for the environment, in the case of genetically modified products. As a consequence, producing and administering ATMP requires highly controlled conditions and specialised expertise. When the ATMP contain cells, even though cryopreservation is possible, highly controlled storage arrangements are required; for some type of products, especially complex tissue engineered structures, cryopreservation is not feasible as this process is likely to compromise their clinical efficacy. This results in a very short shelf-life, ranging from hours to few days, requiring production sites to be relatively close to the patient's bed in a highly specialised environment. It can be concluded that ATMP are generally more difficult to handle as compared to chemical drugs or "classical" biologicals like monoclonal antibodies and recombinant proteins.

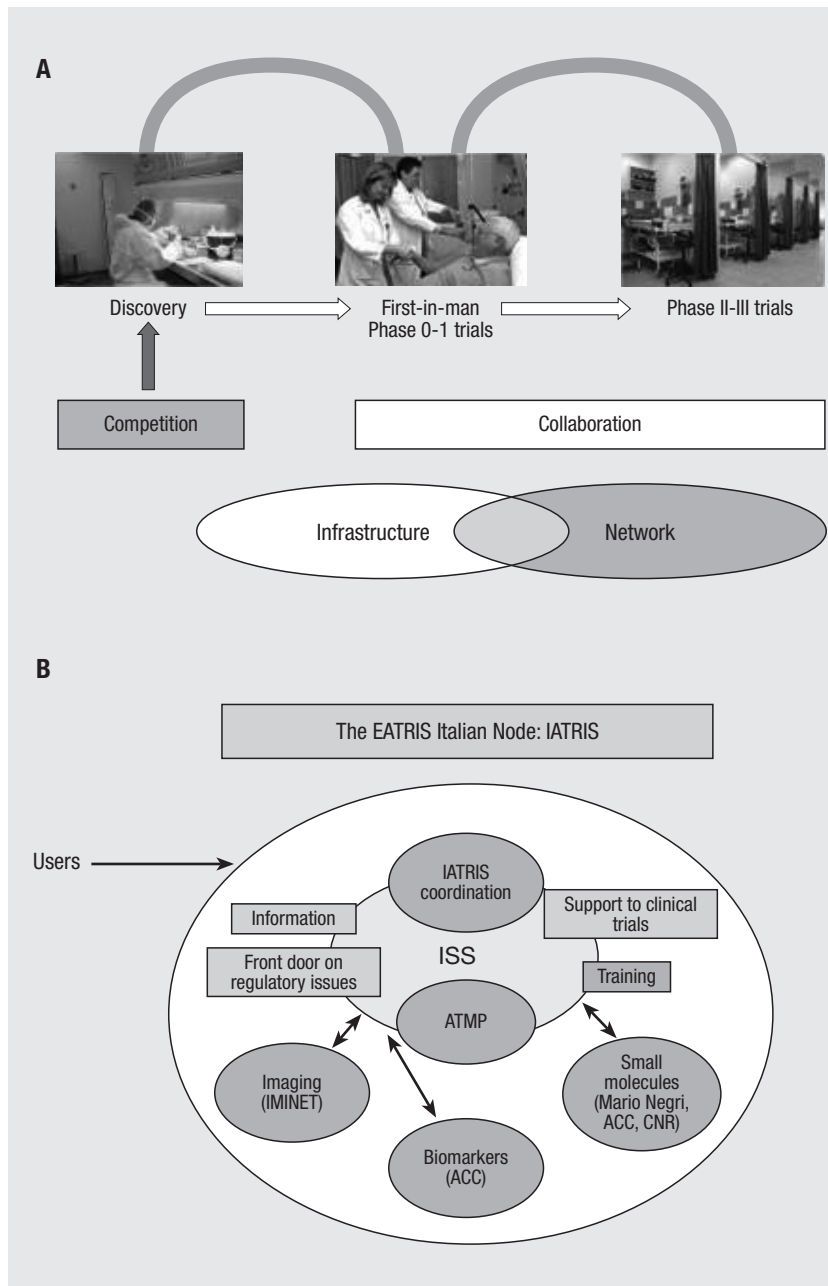
While it is important to promote clinical experimentation with ATMP in view of the great expectations of patients for their potential efficacy, there is a particular moral duty to pay attention to patient's safety and quality standards of the experimental medicinal products. Notably, it is particularly important to convey a correct information to patients to be enrolled in clinical trials. Phase I studies are mainly aimed at testing toxicity of a new drug, including ATMP, and the potential clinical benefit for the patient is still unknown. Thus, the potential efficacy of the new ATMP should not be excessively emphasised at this early stage of clinical development, since only results from subsequent and randomised Phase II/Phase III trials can give relevant information on potential efficacy.

#### **THE NEED OF NATIONAL AND EUROPEAN RESEARCH INFRASTRUCTURES: POTENTIAL ROLE FOR THE DEVELOPMENT OF ADVANCED THERAPIES**

In Europe, the activation of Phase I clinical studies with ATMP encounters highly specific and critical bottlenecks, due to the complexity of the regulatory framework, the lack of harmonisation among the different National Competent Authorities involved in clinical trials authorization and the current needs of both good laboratory practice (GLP) laboratories for safety preclinical studies and GMP facilities for ATMP production. Such bottlenecks are of especially crucial impact for academia and various research groups that, although highly interested in the development of these promising new therapies, suffer from the current lack of strong expertise/initiatives from both private and public partners in this field.

Recently, the European Strategy Forum on Research Infrastructures (ESFRI) released the European Roadmap for Research Infrastructures with the aim of structuring and fostering the European Research Area [16]. In particular, in 2008 the preparatory phases for the construction of some European Research Infrastructures (RIs) particularly relevant for the promotion of biomedical translational research of advanced therapies have been started. Among them, the European Advanced Translational Research Infrastructure in Medicine (EATRIS) is of special potential importance for the development of advanced therapies. EATRIS is finalised to fill the gap between basic research and clinical experimentation (from the bench to the bedside) by providing high quality services necessary for European researchers (users) interested in the transfer of their discoveries into clinical studies (up to the early Phase II trials). Currently, there are ten European countries participating in the EATRIS preparatory phase, which will end by December 2010. Each country is represented by one or more research institutions or national networks, which constitute a national node ([www.eatris.eu](http://www.eatris.eu)). The Istituto Superiore di Sanità (ISS) represents the national scientific partner with a European leadership on the regulatory and ethical issues for translational research, while the Italian Ministry of Health is the national governmental partner in the EATRIS consortium. During the last two years, with the valuable collaboration of additional experts also from other departments of our institute, we have finalised important *consensus* documents related to the regulatory issues for translational research, including a first-in-man manual for clinical studies, aimed at guiding the researchers to initiate and conduct Phase I clinical trials, as well as reports on animal experimentation and ethical issues in the different EATRIS countries. An extensive work has recently been devoted to the characterization of the specific gaps, needs and components of services necessary for the development of different types of products, including ATMP, small molecules, vaccines, tracers for *in vivo* imaging and biomarkers. In this context, we have played a leading role in EATRIS as for the ATMP field. In addition, we have promoted the participation of other Italian institutions and networks in the EATRIS projects, creating the initial national node of EATRIS, named IATRIS (Italian Advanced Translational Research Infrastructures in Medicine). IATRIS' main objective is to overcome the bottlenecks which delay both the transfer of basic research results into clinical applications and the feedback of clinical observations to the basic investigation. In the IATRIS, the governmental institutions (the Italian Ministry of Health in cooperation with the Ministry of Education, University and Research and with the Regions) will form an unique body with the academic institutions and the research entities, for organizing open multidisciplinary laboratories and centralized facilities under a national coor-





**Fig. 2** | Importance of the cooperation and research infrastructures for translational research (A) and the potential role of the IATRIS, coordinated by the ISS, to provide services to the users for the development of new products (B). EATRIS: European Advanced Translational Research Infrastructure in Medicine; IATRIS: Italian Advanced Translational Research Infrastructures in Medicine.

dination. All this is expected to ensure an effective and rapid transfer of the scientific knowledge to prevention, diagnosis and treatment of diseases. IATRIS will represent the infrastructure system of our country in the next steps of EATRIS project. All this will be realized through the contribution of the other main institutions or networks participating in the EATRIS project (the Italian network for molecular imaging, IMINET; the Mario Negri Institute for Pharmacological Research, Alliance against Cancer, and the Department of Experimental Medicine of the National Research Council), as originally suggested by the Italian Ministry of Education, University and Research.

The IATRIS activities will be mainly focused on three main areas: cancer, neurodegenerative and rare

diseases. In particular, cancer is an area of primary current IATRIS focus, since a strong national coordination effort on translational research has already been launched and positively tested in the context of the ISS project for Alliance against Cancer (Alleanza Contro il Cancro, ACC), promoted by the Italian Ministry of Health in 2006. In fact, the current active participation of ACC (which is the Italian network on national cancer institutes and associated centres), in the context of the ISS coordination, in the EATRIS project can ensure a highly relevant critical mass for providing qualified services, including clinical facilities, for activating and performing Phase I-II trials with ATMP in cancer patients. Thus, cancer will represent an area where highly qualified services for translational research could be

already provided, in an integrated manner, in the first Phase of IATRIS and EATRIS implementation.

The principal areas of action which will characterize the IATRIS activities will be: i) the development of ATMP; ii) the development of methods and tracers for imaging for translational research; iii) the developments of small molecules; iv) the development of biomarkers.

Figure 2 illustrates the importance of the cooperation and research infrastructures for translational research (A) and the potential role of the IATRIS, under the ISS coordination, to provide services to the users for the development of new products (B).

In Italy, several scientific institutes for research and care (Istituti di Ricovero e Cura a Carattere Scientifico, IRCCS) and public research institutes, including the ISS, are involved in the research and development of ATMP. Some of them cover specific fields, such as cells immunotherapy or skin transplants or tissue engineering.

In the context of the "ISS for ACC" project, we have performed training courses on ATMP GMP production aimed at informing representatives from IRCCS and other institutions on the complexity of the regulatory framework for the development of these new products. In addition, our department has recently activated a website devoted to explain to both the users and patients the specific nature of these products, the critical regulatory issues for their development and their potential medical impact for patients ([www.iss.it/pmta](http://www.iss.it/pmta)).

The global analysis of the studies with ATMP proposed by the different institutions in Italy reveals a complex situation, the difficulties in activating programmed clinical studies and the need of a coordination action. Thus, the creation of a national centre for the coordination, but also for providing solutions to bottlenecks in ATMP-focused translational research, is urgently needed. In this context, we have recently established a network of other national institutions, including the ISS, actively involved in the developments of ATMP in Italy, composed of Centro di Medicina Rigenerativa, Modena; Fondazione San Raffaele del Monte Tabor, Milan; Istituto Dermopatico dell'Immacolata, Rome; Istituto Ortopedico Rizzoli, Bologna; Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione, Palermo.

Additional institutions and laboratories will be subsequently included in this ATMP network belonging to IATRIS on the basis of their expertise and added value, with the purpose of increasing cooperation and avoiding useless competition and fragmentation.

In 2011, EATRIS is expected to start the transitional phase towards the European Research Infrastructure Consortium (ERIC). Some pilot projects of translational research will be started where ISS plays a special role in the development of products and clinical trials in the field of ATMP.

The translation of advanced therapies into the clinical practice to ensure patients' benefits requires multiple initiatives in addition to those, such as EATRIS, designed to promote Phase I-II clinical studies. As an example,

in order to take full advantage of the recent progress on functional genomics and biotechnologies, it is important to pay special attentions to the collection of biological samples with their related clinical data in high quality biobanks by an integrated and comprehensive Italian and European strategy, in view of their possible use for the development of new molecular predictive markers of diagnosis and prognosis of human diseases as well as of response to new therapies. Likewise, great importance should be given to promote high quality services and infrastructures dedicated to not-for-profit Phase II-III clinical trials in fields with major public health impact. Very often, in fact, promising results emerging from Phase I-II studies performed by public institutions cannot be tested in advanced Phase II and III trials because of lack of funds, coordination and service support. Thus, additional research infrastructures specifically focused on biobanks and advanced clinical trials are strongly needed. In this regard, it is worth mentioning that our department is also actively involved in the final stages of the preparatory phases of two other ESFRI Research Infrastructure (RI) preparatory phase projects, namely Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) and European Clinical Research Infrastructures Network (ECRIN). Information on the participants, mission and current activities of these important European projects can be found on the specific websites ([www.ecrin.org/](http://www.ecrin.org/), [www.bbmri.eu/](http://www.bbmri.eu/)).

## CONCLUSIONS

We are currently facing major bottlenecks for the translation of the novel findings stemming from the recent progress of basic research into advanced therapies of potential impact for patients and public health. While competition is the driving force for basic research, cooperation, coordination and infrastructures are essential for translational research, especially in the field of advanced therapies, where the regulatory framework is still somehow in progress and both public health issues and industrial interests need to be addressed in a comprehensive manner. ATMP represent novel therapeutic principles and may have a complex identity and mode of action making it difficult to define quality and potency assays. Moreover, the species-specificity linked to physiologic differences and tissue histo-compatibility makes the development of adequate animal models very difficult and the design of first-in-man clinical trials complicated by the uncertainties in identifying a safe and efficacious dose. A strategic cooperation between all the main stakeholders (academia, clinicians, experts on regulatory issues, patients representative and industry) is strongly needed in order to promote translation of ATMP into clinical interventions and, ultimately, clinical practice, for the benefit of patients and public health. Lastly, ongoing initiatives for the implementation of national and European RIs highly relevant in this field (EATRIS, ECRIN, BBMRI) are expected to lead to an important advance of translation of advanced therapies in Italy and worldwide.

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### Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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