

Clinical Translation of Stem Cell Therapies: A Bridgeable Gap

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Stem cell scientists trying to reach patients often lack the multidisciplinary skills needed to overcome complex regulatory barriers and may feel deterred from pursuing clinical implementation. In order to help bridge this gap, we offer a European perspective based on our hands-on experience at the Andalusian Initiative for Advanced Therapies.

Advanced therapies constitute one of the most complex organizational and regulatory areas currently approached by clinical research in order to explore new therapeutic applications. Basic scientists and clinicians trying to implement stem cell science into clinical practice may feel overwhelmed by the apparently endless regulatory requirements that apply. In this article we review, from a European perspective, practical issues that must be confronted in order to move from “proof of concept” studies in animal models into human subjects. In trying to answer what steps are needed to move stem cells into clinical practice, several review articles, including a recent series on stem cell “roadmap to the clinic” (Daley, 2010), have taken different approaches in covering the topic (i.e., define appropriate cell source, best expansion, purification, and delivery methods, etc.). Others have thoroughly reviewed good manufacturing practice (GMP) as applied to stem cells and their derivatives (Ahrlund-Richter et al., 2009). We offer a complementary perspective by sharing our experience at the Andalusian Initiative for Advanced Therapies in Spain, a publicly funded entity that has been established to bridge the gap between academic and clinical researchers and the translation of their findings to widely distributed therapeutic interventions. We briefly outline the basic definitions for cell products and clinical protocols, followed by a focused discussion of the relevant organizational actions to be undertaken by interested research institutions.

Definition of Advanced Therapy Medicinal Products

Advanced therapies were classified as such by two European Directives (2003/63/EC and 2009/120/EC) and Regulation (EC) No. 1394/2007 of the European Parliament and of the Council. They defined “advanced therapy medicinal products” (ATMPs) into three main types: (1) gene therapy, (2) somatic cell therapy, and (3) tissue engineered products. Cells or tissues shall be considered “engineered” if they fulfill at least one of the following conditions: (a) the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair, or replacement are achieved. For these purposes, the manipulations listed in Annex I to the Regulation, in particular, shall not be considered as substantial manipulations (e.g., cell separation, concentration, or purification); or (b) the cells or tissues are not intended to be used for the same essential function in the recipient as in the donor (Figure S1 available online).

Importantly, it can be ascertained from the definitions above that not all cells that go into patients will be classified as ATMPs: uncultured cells used for the same essential function in the recipient as in the donor, will be regulated in a different manner, i.e., as a cellular transplant (Directives 2004/23/EC and 2006/17/EC).

Cells as Medicinal Products: Manufacturing Aspects

Once we have determined that a particular cellular product lies within the ATMP cate-

gory, regardless of it being investigational (i.e., a drug to be used in clinical trials and not yet authorized for marketing as such), production of the cells that will go into patients must comply with good manufacturing practice (GMP) for medicinal products. Implementation of GMP in cell manufacturing processes substantially increases production costs. However, regulatory agencies are unlikely to be dissuaded from requiring GMP implementation on the basis of monetary arguments, because patient safety and law enforcement are, and should be, their primary considerations. It is therefore important that stem cell scientists are aware of the intricacies of GMP implementation before initiating full-fledged translational programs.

Typical regulatory concerns surrounding the application of cellular components are product safety, characterization of the cells, and characterization and control of their manufacturing process. With regard to safety, cell donors must be carefully screened and the cellular product, once expanded in the GMP production facilities through master and working cell banks, must be checked by several standardized tests (viability, sterility, adventitious agents, genetic stability/tumorigenicity, pyrogenicity, mycoplasma infection, etc.). Cell products will usually have to be defined as for identity, purity, potency, stability, and viability.

Clinical Research with ATMPs

Before administration into humans, both biological activity and toxicity of the investigational medicinal product must be tested in a relevant animal model

according to good laboratory practice (GLP). Researchers must then seek approval of an institutional review board (IRB) for all centers involved in the clinical trial as well as an authorization from the national regulatory agencies of the countries where patients will be recruited, irrespective of their nationalities. In order to guarantee respect for human subject rights, ensure data quality, and steer clear of avoidable errors, European Directives 2001/20/EC and 2005/28/EC on good clinical practice (GCP) and associated guidelines (e.g., CPMP/ICH/135/95) must be followed. Likewise, and specifically for the clinical translation of stem cells, the ISSCR Guidelines offer a good starting point (Hyun et al., 2008). Once the clinical trial is authorized and patient recruitment has started, the sponsor has a legal requirement to communicate to the regulatory authorities any suspected unexpected serious adverse reactions. The sponsor's duties also include ensuring that there is an insurance policy in place to cover any liability, that recruitment of subjects is done after appropriate informed consent, and that approval of medicinal product batches for release conforms to specifications.

End of the Road: Marketing Authorization, Distribution, and Pharmacovigilance of ATMPs

If the regulatory bodies determine that quality, safety, and efficacy of an ATMP are sufficiently established through successful clinical phases, then the next step is to apply for marketing authorization. This step must be done through a centralized procedure at the European Medicines Agency (EMA), and approval would bestow Europe-wide commercialization rights. For this reason, the set requirements are usually even more stringent than those expected of clinical trial applications, because the number of candidate patients may be enormous, especially in the case of highly prevalent conditions. The requisites and procedure for commercialization of ATMPs are beyond the scope of this review and are primarily relevant for pharmaceutical companies. At the moment only one ATMP has been granted marketing authorization at the EMA, an industrial product based on autologous chondrocytes expanded for cartilage regeneration. Of note, some European countries permit

exceptions to this authorization rule depending on the nature of the medicinal product, be it industrial or otherwise. This exemption is based on the exclusion defined by Regulation 1394/2007 for ATMPs that are prepared on a nonroutine basis and only as a custom-made product for an individual patient. We would like to encourage national authorities to consider a more flexible procedure than the marketing authorization process that would allow certain nonindustrially manufactured medicinal products to be introduced into clinical practice. Such products would include those that can't be commercialized because they are more similar to a service than to a product, and would still need to meet requirements for quality, safety, and efficacy. On the other hand, and in order to give small and medium-sized enterprises (SMEs) an incentive to conduct quality and nonclinical studies on ATMPs, a recent regulation has come into force (No. 668/2009). Accordingly, the EMA Committee for Advanced Therapies (CAT) has published a related guideline on the minimum quality and nonclinical data required for certification of ATMPs (EMA/CAT/486831/2008/corr). Even though the certification provided is not legally binding, this system aims at facilitating the evaluation of any future application for clinical trials and marketing authorization application based on the same data. In our view, it would be of great help to allow a similar certification to hospitals and academic researchers at nonprofit institutions, irrespective of the size of their workforce (be it SME or not).

Finally, the safety oversight of investigational medicinal products and pharmacovigilance is a key aspect of all research with ATMPs. These products are considered relatively "high risk" and regulatory authorities will require tight safety follow-up of ATMP-treated patients, both in clinical trials and after marketing authorization (Directive 2004/27/EC).

ATMP Development from Scratch

Medicinal product development, from discovery to marketing authorization, is thus a costly, lengthy, highly regulated, and high-risk process (Figure 1). As such, it is difficult to approach this goal and achieve a reasonable success rate in reaching the market, leaving medicinal product development predominantly in

the hands of big pharmaceutical companies that have the financial and human capacities to invest the enormous resources required (Kola and Landis, 2004). Unfortunately, stem cell science has attracted relatively little interest from big pharma to date (McKernan et al., 2010, this issue of *Cell Stem Cell*). Oft-quoted reasons are general uncertainties with regard to therapeutic promise of ATMPs, high production costs, and extreme logistical complexity because of specific characteristics of these products, such as their generally short shelf life, relatively long-term investment revenues, and differing international regulatory climates.

It is therefore compulsory to implement some sort of bridge between promising basic stem cell science results and the pharmaceutical industry (Trounson et al., 2010, this issue of *Cell Stem Cell*). Such a bridge will probably involve solid management of intellectual property rights, demonstration of success through early-phase clinical trials, and technological transfer to interested third parties. Several small biotech companies are filling this gap world-wide with varying success (Lysaght et al., 2008).

Bridging the Gap in Andalusia

As a publicly funded alternative, in 2008 the Andalusian Government created what is now known as the Andalusian Initiative for Advanced Therapies. Andalusia is the biggest region in Spain, with nearly 8.5 million inhabitants. With an autonomous government since 1981 and a 100% publicly funded healthcare system, with universal coverage, Andalusia has pioneered stem cell legislation in Spain (Law 7/2003 on research with embryonic stem cells and Law 1/2007 on cellular reprogramming). The Initiative draws up plans and tailors the resources to promote research in the field of advanced therapies in Andalusia and to transfer basic research into clinical practice through the forging of alliances among academia, research institutions, hospitals, patient associations, and the biotech and pharmaceutical industries. Although mainly financed at a regional level, with 84M€ allocated to projects and research infrastructures in advanced therapies in the last 6 years, the Initiative is also supported by Spanish National funding agencies. The budget allocated for the next 6 year strategic plan

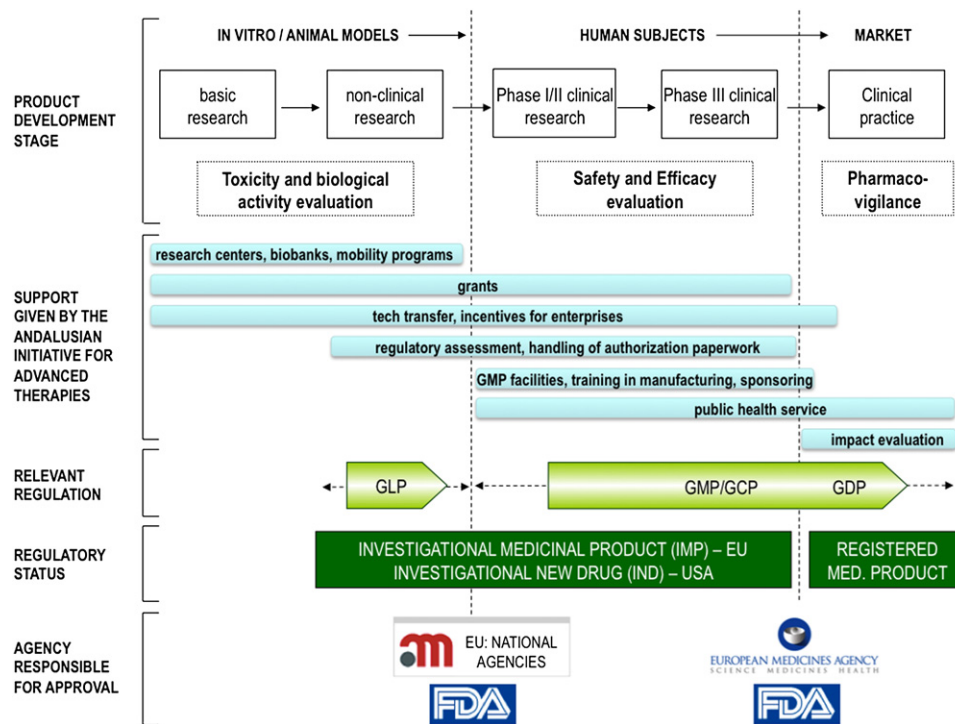


Figure 1. Andalusian Initiative Support for ATMP Development and Relevant Regulatory Facts for Each Stage

The scheme depicts the five stages of typical medicinal product development and the specific support given by the Andalusian Initiative. It starts with basic in vitro studies, followed by nonclinical research in animal models to understand toxicity and biological activity of the medicinal product. The latter should be performed by following good laboratory practice (GLP). From this early phase throughout clinical trials to evaluate safety and efficacy, the investigational medicinal product should be produced under good manufacturing practice (GMP) and infused to patients under good clinical practice (GCP). In Europe, national regulatory agencies will be responsible for approval of all these stages. In an ideal situation, the final step of marketing authorization will be done through a centralized procedure at the European Medicines Agency and the registered medicinal product will be ready for commercialization under good distribution practice (GDP).

(2010–2015) is 90M€ (operational costs not included within these figures).

Although other countries such as Brazil and Korea have committed public funds to clinical trials of stem cell treatments and multiple US states, led by California, are also working in that direction, the Andalusian Initiative offers a distinct, major translational focus. That is, in addition to building research centers and funding basic research grants for advanced therapies, as other regional administrations have done elsewhere in the world (Daniels et al., 2006), our organization provides all the support required by basic and clinical researchers for translating research, acting as sponsors of noncommercial clinical trials driven by investigators based at the local research institutions and hospitals. This model was designed with the intention to facilitate clinical research and innovation within the public health system.

Some cellular therapies that have no manufacturing process involved (and specifically those “nonsubstantially manipu-

lated” cell protocols that do not fit into the “transplant” classification) do not attract significant commercial interest, and it is therefore difficult to develop a business model around them. As a publicly funded Initiative especially accountable to our Regional Health Ministry and focused on population health improvement and innovation within the healthcare system, our particular interest is to develop new therapeutic approaches and make them available to the general population. Based on this mandate, our efforts aim to promote the development of new advanced therapies not only out of commercial interests but also purely as a service. Likewise, when manufactured cells that lie within ATMP category are developed, intellectual property will be handed to interested companies through transparent licensing or partnership agreements, although some of the reimbursement will be handed back to the regional government under different formulae as legislated (Andalusian Science and Knowledge Law 16/2007).

Furthermore, support comes not only in the form of financing, but also with implementation of complementary expertise. Success of this organizational model is evidenced by the construction of multiple public GMP facilities for cell production within Andalusia and the authorization of several Phase I/II clinical trials by Spanish regulatory authorities in the areas of cardiology, neurology, immunology, peripheral vascular disease, and hepatic regeneration (more information available at <http://www.juntadeandalucia.es/terapiasavanzadas/>).

A Model to Support Researchers Interested in Therapeutic Development

As an Initiative promoted by the Regional Government of Andalusia, our work comprises all the steps between the generation of knowledge and knowledge transfer with a special emphasis on the development of new therapies. For that reason, over the last few years we have pushed to build a cluster of research centers, biobanks, and GMP facilities.

Table 1. Main Support Activities of the Andalusian Initiative for Advanced Therapies Related to Clinical Research

Assessment on the Regulatory Agencies' Requirements
Nonclinical experimental design: pharmacodynamic proof of concept, biodistribution, dose, toxicity, immunogenicity, tumorigenicity studies
Product safety, characterization of the cells (identity, purity, potency, stability, and viability), and characterization and control of their manufacturing process
Design and Implementation of GMP-Compliant Cell Production Laboratories
Design technical installations and equipment according to homogenous standards
Supervise the construction, development, and maintenance of GMP facilities
Prepare relevant documentation for regulatory approval of GMP facilities, quality management systems, validation of equipment and installations, audits of the National Medicines Agency
Hire and train laboratory personnel
Promotion and Development of Investigational Medicinal Products
Encourage collaboration between basic and clinical researchers to help design clinical trials
Negotiate insurance policies and agreements with hospitals and clinicians: zero cost for researchers involved
Prepare IMPDs and handle authorization paperwork required by IRBs and National Medicines Agency
Advise on product characterization and quality controls
Perform the administrative release of medicinal batches
Supervise monitoring process and results analysis
Perform safety vigilance of the IMP (in agreement with Andalusian Centre for Pharmacovigilance)
Financial Support
Help with grant applications and direct financial support

We have implemented a human resources policy that includes direct recruitment of researchers through competitive calls, training and return programs, and mobility programs. We have also designed our own training program for manufacturing and clinical research on advanced therapies that includes practical training modules held under real conditions at a GMP facility built for training purposes. This modular training program covers materials intended for all personnel involved in translational work, including technical directors, heads of manufacturing, quality control and quality assurance workers, technicians, and clinical researchers.

Moreover, the Initiative was set up as a comprehensive support hub to develop clinical research, and in particular to promote noncommercial clinical trials. To that end, we act as sponsors, providing the support that our researchers and clinicians need and that would usually be provided by the pharmaceutical industry. Our organization has built GMP facilities in multiple research centers and hospitals. Most of the clinicians work for our health service, but an increasing number

of clinicians based at other health services collaborate with us in multicenter clinical trials. In summary, we currently support the construction and accreditation of a network of clean rooms, the development of investigational medicinal products, and the design and implementation of clinical trials (Table 1). In the case of the latter, our support begins with a regulatory assessment during preclinical development, followed by promotion of collaborations between basic and clinical researchers, and extends all the way to monitoring the safety of the resulting investigational medicinal products.

Concluding Remarks

Our experience dealing with regulatory authorities in order to authorize clinical trials with ATMPs has been quite remarkable: in the last few years, we have moved from a do-it-yourself approach, where almost no one was in a position to issue specific recommendations for a particular ATMP application, to a fast-moving field with a constantly evolving regulatory landscape that scientists and regulators alike find difficult to navigate. Several of the

regulatory advances, including the establishment of the regulatory agencies themselves (Wax, 1995), have come about in response to unintended side effects of novel therapies. We are also aware of how adverse events in early gene therapy clinical trials caused a major setback in the field (Wilson, 2009). However, the pitfalls encountered because of insertional mutagenesis do not actually reflect the predominantly successful record of these therapies to date, which indicates that gene therapy has a favorable risk-benefit profile (Aiuti and Roncarolo, 2009). For obvious reasons, every clinical trial will carry an associated risk, because of the investigational nature of these efforts. However, it is in everybody's interest to ensure that the field avoids any major setbacks that arise from novel ATMP clinical trials. We can only encourage researchers and clinicians to contact regulators at an early stage of ATMP development (as early as possible) and to make use of regulatory mechanisms such as orphan drug designation (if pertinent) that will help alleviate the high costs associated to medicinal product development.

Our intention has been to convey that although seemingly complicated, the gap between stem cell science and therapies is certainly bridgeable. Only through concerted effort with regulators can publicly financed nonprofit institutions shoulder the enormous logistical and monetary burden required for full-fledged ATMP development. However, only by applying the highest quality, safety, and efficacy standards, can we anticipate that the stem cell field will move toward clinical translation at a steady pace.

In showing here the efforts made to design a unique model in a public health system to help the translation of research into clinics, our particular interest was to collaborate in the development of new therapeutic approaches, to find alternatives for diseases for which there is currently no cure, and to make them available to the general population.

Other research institutions might want to follow our organizational model, acting as sponsors of clinical trials and giving comprehensive support to both researchers and clinicians where needed. In doing so, we hope to expand the notion that this particular bridge may and should be crossed more often. Rather than

just focusing on financial support of researchers, in our experience it is a worthwhile investment to build a multidisciplinary and skilled support team, as appropriate to develop this special sort of medicinal product and convert them into therapies.

SUPPLEMENTAL INFORMATION

Supplemental Information includes one figure and can be found with this article online at [doi:10.1016/j.stem.2010.05.005](https://doi.org/10.1016/j.stem.2010.05.005).

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