Transition to an industrial scale of human stem cell production for therapeutic use by Bruno JARRY, Jean-François STOLTZ and Raymond ARDAILLOU on behalf of a working group joining Academy of Technologies and National Academy of medicine

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The production of stem cells for the treatment of human diseases, initiated in research laboratories and in university hospitals, is developing in startups and is being taken over by the pharmaceutical industry with the aim of developing innovative therapeutic medicines (ITMs) that are homogeneous, reproducible, effective, reasonably priced and in sufficient amount to perform therapeutic trials.

Stem cells for therapeutic use

The initial resource of human stem cells is free according to the ethical principle depriving the human body of any financial value. As regards biotechnologies, "bio" remains free, while "technologies" are innovative practices in the industrial and commercial field. Therapeutic use of stem cells started with multipotent stem cells, mainly human hematopoietic stem cells (HSC) that are found in bone marrow, cord blood and placenta. These stem cells are utilized for allogeneic transplantation in aplasia, leukemia and hematologic genetic diseases. Bone marrow stem cells come from volunteer donors listed in a registry under the control of the French “Agence Française de la Biomédecine “(Biomedicine Agency, BMA). The autologous grafts for the treatment of genetic diseases consist in correcting the mutation in vitro and then reinjecting the cells to the patient. Mesenchymal stem cells (MSC), also multipotent, are present in very small quantities in the bone marrow and the cord, but also in other tissues, and are used after isolation and culture to multiply them. They are not very immunogenic. Therapeutic successes have been obtained in various cardiac and cutaneous affections through their paracrine secretory properties of growth factors rather than by the colonization of the injured tissues. A big step has been made with the use of embryonic (ESC) or induced pluripotent (iPS) stem cells. The use of the first obtained by culture of cells of embryo blastocysts is governed by the French laws of bioethics and requires the authorization of the

BMA. ESCs are differentiated by appropriate medium culture in most mature cell varieties. Not very immunogenic, but potentially carcinogenic, they have been used only in therapeutic trials limited to a small number of patients with myocardial infarction or age-related macular degeneration. ESCs are also, after introduction of mutations, a modeling tool for genetic diseases and thus are used for the *in vitro* screening of drugs. IPS are produced from adult cells after reprogramming into stem cells and then differentiating into mature cells from all tissues. They can be used in an autologous fashion in genetic diseases after correction of the mutation in the donor cells and reinjection. Because of their unlimited production capacity and the absence of ethical questioning, they represent the material of the industrial manufacture of stem cells for therapeutic use despite the "double disadvantage" of being genetically unstable and immunogenic. They are therefore widely used in regenerative therapy trials, particularly in age-related macular degeneration. Their *in vitro* uses are numerous: modeling of human diseases from patients' skin cells and obtaining of control cells by correction of the mutation in order to screen drugs, creation of 3-dimensional organoids as a new route to organ transplantation, generation of red blood cells very useful in alloimmunized patients or carriers of a rare phenotype.

The transition to industrial production

The work initiated in the hospitals and in the academic research laboratories has developed in startups often created by researchers benefiting from the possibility opened by the French Law N ° 99-587 of July 12, 1999 which allows them the temporary passage to a private activity. Industrial production of the most promising products is the next step. It is restricted to the pharmaceutical industry, the blood transfusion establishments and the hospitals that have created an economic interest group and requires the authorization of the "Agence nationale de la sécurité du médicament et des produits de santé" (National Agency for the Safety of Medicines, NASM). The conditions to be fulfilled in order to proceed to the industrial stage are numerous:

1. to have bioreactors ensuring mass production and to master the final techniques of preparation of the product, verifying its homogeneity and the reproducibility of its qualities;
2- to standardize the raw materials used to prepare the culture media;
3- to obtain a patent guaranteeing the precedence of the production processes;
4- to control the cost of manufacturing to keep it within reasonable limits;

5- to develop industrial processes compliant with the European regulation concerning "Advanced therapy medicinal products" and to respect good manufacturing practices applicable to medicinal products for human use by a pharmaceutical establishment.

Small organizations facing these difficulties may use public or private multi-partnership platforms such as, in France, "Cell for cure" set up by LFB, a state-owned company, and Ypo-Skesi created by I-Stem (AFM-Telethon). These platforms can select patients, reprogram and immortalize iPS, produce isogenic control lines, create differentiated cell banks, all available on catalog, and provide advice on the preparation of regulatory files.

The development of stem cells for therapeutic use in our country is based on one hundred academic teams, a dozen startups, and to a lesser extent on the pharmaceutical industry still at the planning stage. Only the L'Oréal group is actively working in the field of skin stem cells, mainly with the Episkin company that it has created. ITMs obtained in France have been the subject of a limited number of therapeutic trials up to phase II / III, each trial involving about thirty patients. The situation in other countries highlights our backwardness. Ten "stem cell" products Ten "stem cell" products are currently on the market, including none in France and around 20 tissue engineering products, two of which are marketed in France but not reimbursed by the Health Insurance. Note that to date are registered in https://clinicaltrials.gov 142 clinical trials using MSC in the United States, 147 in Europe and 230 in China. The market in the world is changing rapidly. Of $ 8.5 billion in 2016, it is expected to reach more than $ 60 billion in 2020.

Stem cell production and research in the field raise ethical issues that the International Society for stem cell research has tried to answer. In addition to the questions posed by the use of ESC submitted in France to the regulation of the latest bioethics law, other directives concern the industrial phase, including the obligation to declare all therapeutic trials, convincing or not, in a register searchable by all and the demand for scientists and the media to present complete reports of trials including failures and complications.

Regulatory constraints on cell therapy drugs in France

Law N ° 2011-302 introduces into the Public Health Code a new type of product, the ITM. In fact, there are four types of usable products, each within a specific regulatory framework:

1- the usual ITMs covering somatic and genetic cell therapy drugs, those derived from tissue and cell engineering and those associated with a medical device when these products have

undergone substantial manipulation (cell culture, differentiation) or are used regardless of their origin (for example, MSC injection into the heart);

2 - therapy medicinal products that are punctually prepared (ITM-PP) and intended for the treatment of one patient in a hospital environment;

3- experimental advanced therapy medicinal products prepared for clinical trials in establishments approved by the NASM;

4- preparations of allogeneic or autologous cells or tissues that have not been manipulated and have a therapeutic purpose.

The use of these products is subject to a set of European and French regulatory texts. We will only mention the main ones. The European Union has confirmed the drug status with its inherent obligations for ITMs (N ° 1394/2007). Directive N ° 2004/23 / EC sets quality and safety standards at the different stages of ITM preparation. French law has introduced European directives into national legislation and has supplemented them, often making them even more restrictive. Thus, Law N ° 2011-302 introduced the ITM in the Public Health Code (CSP) and decrees N ° 2012/136 and 2016/1536 completed the Law. France has enacted the laws of bioethics, of which the last of August 6, 2013 amending the law No. 2011-814 regulates the use of ESC.

The creator of an ITM must, in accordance with this regulation, go through 3 steps to introduce it on the market and obtain its reimbursement. The first is the authorization to launch therapeutic trials that follows a national process. A double authorization is necessary. It is given independently by 2 bodies, the “Comité de protection des personnes” (Committee for the Protection of Persons, CPP) suitable for Biomedical Research and the NASM. The first verifies that all the requirements of the Law on the Protection of these persons, including the informed consent of the subjects, have been respected. The second takes the opinion of the BMA and, in case of genetic manipulation, of the “Haut conseil des biotechnologies” (High Council of Biotechnology). It also uses external experts. The final decision is known after about 6 months. The second stage of marketing authorization depends on the European Medicines Agency, which takes advice from the Committee for Advanced Therapies. With regard to reimbursement, we return to a national process that falls under the “Commission de la transparence de la Haute Autorité de Santé, HAS (Transparency Commission of the High Health Authority). The latter takes the opinion of the “Union nationale des caisses d’assurance maladie”(National Union of Health Insurance Funds) and the “Comité économique des produits de santé” (Economic Committee of Health Products), then decides on the price and the rate of care.

Recommendations

At the end of this report, the two academies formulate a series of recommendations concerning the legislation and the support of startups.

Simplify the legislation with the following aims:

1- To extend to preclinical and clinical fields of application, studies preliminary to the use of human embryonic cells for the production of ITMs that the French Bioethics Law actually limits to basic research;
2-To allow the French Blood Establishment ("Etablissement français du sang") and cord blood banks to provide the industrial cells with the necessary cells to manufacture an ITM;
3- To alleviate the regulatory constraints relative to the protection of personal data while preserving the traceability of the cells used;
4- To facilitate the import and export of biological cells and raw materials necessary for the production of ITMs in accordance with the traceability rules;
5- To make it possible for NASM to issue authorization to manufacture pharmaceutical raw materials used in the manufacture of ITMs;
6- To assist authorized institutions to prepare experimental ITM-PPs and ITMs to undertake phase I / II clinical trials in agreement with the pharmaceutical industry that will take over the research;
7-To open to the ITMs the legislation of the temporary authorizations of use, thus allowing the placing on the market of these very innovating products for a limited and controlled period of time as soon as phase III of the clinical trials has been completed;
8-To request HAS to expedite review of files and improve repayment terms for ITMs that have demonstrated effectiveness.

Support startups with the following aims:

9- To promote the development of existing platforms and the creation of new platforms to provide the necessary assistance in terms of industrialization of manufacturing processes, preparation of batches meeting the conditions for placing on the market and advice to present files necessary for obtaining them for the small structures of production of stem cells with therapeutic aim;

10- To reinforce the training of the corresponding technologies in the university framework or engineering schools;
11- To ask the industry to launch calls for tenders to academic laboratories targeting the axes of work for which they favor to develop collaborations.
12- To create financial conditions in France allowing companies to go to phase III clinical studies to facilitate the emergence of new pharmaceutical groups specialized in this axis of regenerative medicine.

Pour copie certifiée conforme :

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