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Stem cell roadmap – The industrial point of view

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Abstract. CELL*for*CURE is a French Contract Development and Manufacturing Organization (CDMO) dedicated to industrialization and process development for routine manufacturing, GMP manufacturing for clinical and commercial batches and regulatory services and associated logistics. CELL*for*CURE is a subsidiary of LFB Group.

Stem cells fields of application gather cell and gene therapy as well as tissue engineering. According to VisionGain survey, cell therapy medicinal products will remain predominant in the future.

Clinical trials are sponsored either by universities or private companies. Most of clinical trials are performed in oncology (53%). More than 100 clinical trials are currently performed in France, involving 36 products in clinical phases II or II/III.

Tomorrow's regenerative medicine will be organ reconstruction using scaffolds and bioprinting technologies. The expected applications in the near future could be skin, cornea, blood vessels, retina, urethra and trachea. There are still important issues to overcome: create the vasculature and neuron connection.

Solutions are expected regarding I) fundamental biology, in particular better understanding of IPS behavior and metabolism, precursor differentiation conditions, sustainability of induced genetic changes, II) technical approaches which involves injectable preservation medium, high density cells and centrifugation system.

Keywords: LFB, CELL*for*CURE, gene therapy, cell therapy, Contract Development and Manufacturing Organization

1. Introduction

LFB is a French state owned group LFB specialized in biopharmaceuticals which develops, manufactures and markets biological medicines for serious, often rare diseases in its therapeutic areas of excellence in Immunology, Hemostasis and Perinatal & Intensive Care. CELL*for*CURE is a subsidiary of the French group. It is a Contract Development and Manufacturing Organization (CDMO) located at les Ulis (France), dedicated to Industrialization and process development for routine manufacturing, GMP manufacturing for clinical and marketing batches and Regulatory services and associated logistics. It is one of the largest production capacities in Europe for cell and gene therapy.

2. Stem cells fields of application

The stem cells fields of application could be neural, pancreatic, blood, liver or cardiac. These cells could be from different origins; embryonic or induced pluripotent cells (IPS). IPS are still the less mature ones. Embryonic stem cells are in emergent phase. Adult stem cells and hematopoietic stem cells are in a more mature phase.

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Cell therapy, gene therapy and tissue engineering approaches face different advantages or constraints. Cell therapy could be embryonic stem cells or adult mesenchymal stem cells. Embryonic stem cells are totipotent but cope with high legal and ethical constraints which can be solved thanks to derived cells bank. Cell therapy could also be derived from adult mesenchymal stem cells (MSCs), hematopoietic stem cells (HSC) or other precursors. In gene therapy, cells could be modified in-vivo or ex-vivo. Ex-vivo modifications use IPS or adult stem cells (i.e. CAR-T cells). Originally, In-vivo modifications use viral recombinant vectors as Adeno virus but now prioritize the use of bacculoviruses based constructs. Tissue engineering consists in organ reconstruction or organoid development. Organ reconstruction could be an alternative to transplantation using stem cells and a scaffold with a 2D or 3D approach. Organoid development could be used as predictive models to test medicinal products toxicity.

3. The cell and gene therapy market analysis

3.1. The cell and gene therapy future market size

In 2016, European sale price of Glybera® was €1.2 million in adults with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis and the average price in the EU countries where reimbursement is granted, €18.000 for Chondroselect® indicated for the repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults. Meanwhile the US sale price of Provenge® in prostate cancer was $93.000 and $65.000 for Imlygic® in oncolytic virus in melanoma.

VisionGain 2016 has predicted a potential market size of $19.5 billion for cell therapy, $9.3 million for tissue engineering and $2.1 million for gene therapy in 2026.

3.2. Top ten world leaders in gene & cell therapy

The number of clinical trials is a good indicator for gene & cell therapy developments comparison. The main players are the universities (Baylor College of medicine and National cancer Institute). Many startups and big pharma companies invested in cell or gene therapy programs. For example, Baylor College of medicine, Houston–Texas, is currently running 78 clinical trials and Novartis AG 46. The cell and gene therapy clinical applications are split into 20 different domains of which 53% are developed in oncology. The remaining 50% concerning immunology, cardiovascular system, central nervous system, infectious diseases and ophthalmology.

3.3. Regenerative medicine world market

More than 100 clinical trials are currently under a development status in France. These developments involve 36 products, mostly in Phase III or II/III. For example, Zalmoxis – MOLMED is developed in high-risk haematological malignancies in patients receiving haplo-identical haematopoietic stem cell transplantation and Cx-601 – TIGENIX in Expanded adipose tissue-derived mesenchymal cells – treatment of complex perianal fistulas in patients with Crohn's disease.

Four ATMPs are available in France: Glybera – UniQure, ChondroCelect – Tigenix, Holoclar – Chiesi and Strimvelis – GSK. Due to price, unfavorable opinion of HAS[1] or reimbursement conditions, there is a limited prescription of these products.

[1] Haute Autorité de Santé.

3.4. French academic teams, startups and industrial companies

Most of the French players are academic including 14 university hospitals, Inserm,[2] CEA,[3] Institut Pasteur, EFS.[4]

Almost 30 companies share the French market, mainly small and mid-size enterprises but also large industrial (Sanofi, Servier and LFB Group).

Fourteen pharmaceutical establishments are located in France, mainly in the Paris CELLforCURE, AGEPS, THERAVECTYS, Genethon Bioprod, EFS Creteil) and in the Lyon (Erythec, Bio Elpida) regions.

3.5. International competition: The South Korean model

The Samsung Medical Center opened in 1994 in South Korea and was "patient-centered" and dedicated to "customer satisfaction."

The Samsung Medical Center plans to achieve medical innovation in the future to promote the happiness of patients and will develop into a global hub of biohealth care study and link the industry by connecting to hospital–R&D Center–school and enterprises.

Then, the Stem Cell & Regenerative Medicine institute was launched to develop novel medical technologies to restore impaired tissues or organs damaged due to aging, diseases or accidents. The institute has mainly focused on translational researches and the development of novel medical therapeutics for incurable and refractory diseases.

The main target diseases and research fields are musculoskeletal and joint diseases, stroke, dementia and degenerative brain disease, incurable diseases of preterm infants, hematopoietic stem cell transplantation, peripheral nerve disorders, hepatocyte regeneration, blood vessel disease, intractable diabetes, kidney disease, spinal cord damage, brain tumor, transplantation immunity, and hair loss and skin regeneration.

The new regulation regarding innovative medicine addressing unmet medical need, established in 2014, allows end of phase II marketing based on good clinical results. This advantage is provided without reimbursement, and with, in parallel, the obligation to perform a phase III trial to support further market authorization and reimbursement in a defined timeline.

This private dual model (research and patient treatment) must question our French system and its benefits.

4. Organ reconstruction: Tomorrow's regenerative medicine

The biomedical market of organ reconstruction could reach $5 Billion in 2020 mainly dominated by Implants and organoids.

An increasing unmet medical need is observed in transplantation due to the low availability of organs. The organs most lacking are liver and kidney.

The investigated technology is based on synthetic or de-cellularized organ scaffold covered with cells obtained from stem cells culture.

[2] Institut National de la Santé et de la Recherche Médicale.

[3] Commissariat à l'Energie Atomique et aux Energies Alternatives.

[4] Etablissement Français du Sang.

Applications could be bladder, trachea, auricle (Wake Forest Institute), thyroid gland (Mironov, 3DBioscience) or skin (L'Oréal/Poiëtis, L'Oréal/Organovo). Bioprinting is the promising technology to build the organ structure similar to the human model.

The expected applications in the near future are skin, cornea, blood vessels, urethra and trachea. A main issue is still to overcome, the vasculature creation.

5. What are the manufacturing issues?

5.1. Manufacturing in a GMP environment

The main issues related to manufacturing in a GMP[5] environment are to avoid using as possible animal material or serums, to create a GMP precursor bank, to use a GMP grade for growth factors and required molecules during the precursor's differentiation and secure supplies with sourcing backups. The issue difficulty level is mainly medium or high.

5.2. Stem cells properties

The stem cells properties are quite easy to characterize by surface markers, with a capacity to be amplified but in a controlled and limited way. In addition other properties are of high interest. For gene therapy it is the ability for gene transduction and modification. Regarding precursor's pluripotence, it is the capacity to control orientation and form organized cell structures. Other issues are the capacity of activation in-vitro or in-vivo (immunotherapy) and to releases active molecules like cytokines, to be removable in-vivo if needed (suicide gene approach), to support cryopreservation in an injectable excipient, to allow the 2 and 3D construction and to demonstrate the therapeutic efficacy.

5.3. Intellectual property

Early filing of Intellectual Property is essential, like any other discovery and early verification of "Freedom To Operate" regarding the process and the raw material (i.e. sorting on magnetic beads, Retronectine® . . .) is crucial.

For IPS cells, management of licenses with IPS Japan Academia should be done at the earliest possible stage of development considering potential amount of royalties to be paid for future market use.

Even if gene and cell therapies are promising new entities, there are still many remaining issues to be solved related to fundamental biology and industrial processes. A better understanding of IPS behavior and metabolism should be explored by research teams. The precursor's differentiation conditions should be detailed and the sustainability of induced genetic changes analyzed. *Inter alia*, three main technical issues should be prioritized: 1) to develop an injectable preservation medium, DMSO[6] free, GMP grade, up to 72 h fresh or cryo-frozen, for biological starting material (cells) and the final product, 2) for high density cells, reduce the volume and concentration used effectors especially during differ-

[5] Good Manufacturing Process.
[6] Dimethyl sulfoxide.

entiation amplification steps, 3) to develop efficient GMP compliant closed continuous centrifugation systems.

Conflict of interest

The authors have no conflict of interest to report.