Companies start to sell ad hoc stem cells and material to the researchers.

The business of the stem cells is growing.

The States is feeling the competition in the area of stem cell research, of which the stake is the development of regenerative medicine. Since five years, small companies were born in this sector that is yet to open up. They developed lines of cells and the tools to work with. But the lack of scientific and financial visibility makes their start up a delicate one.

After five years of waiting, the French government authorized, on 16 February, the import, the conservation and the use of embryonic stem cells for the purpose of research.

The team of Professor Marc Peschanski, director in Inserm, is the first to be benefit from this authorization. Two weeks before, the British authorities granted to Ian Wilmut, researcher of Roslin Institute of Edinburgh and "father" of the ewe Dolly, the authorization to proceed on the cloning of human embryos for therapeutic ends. At the same time, the Swedish Parliament gave its green light to the therapeutic cloning and to the creation of new lines of stem cells. Sweden is now in a situation comparable with that of Great Britain, the European country which until now disposes of the most favourable legislative context for the research of embryonic stem cells. “Currently, the competition in the field of embryonic stem cells is not found as much at the level of companies, still very few, as it is found at the country level due to the regulatory environment and the financial backing for this research” reckon Pascal Brandys, president of BioBank that invests in the early stages of biotechnology. So and in spite of a very restrictive American ruling, California, that envisaged to invest 3 billion dollars over tens years, will certainly be among the regions that will count on the matter.

"The emergence of Asia, in particular South Korea, who has succeeded in the first therapeutic human cloning, should be mentioned as a first in the history of biotechnologies, where the major advances have, until now, always come from the Unites States", Pascal Brandys continues. The embryonic stem cells are indeed the category of stem cells which, at the same time, raise the most hopes and remains the least known and the least well-controlled. In fact, today, 90% of the research programmes are based on adult stem cells.

The stem cells are undifferentiated cells which are characterized by their capacity of auto-renewal and of differentiation to generate cells of various fabrics (to read following page). Present in the embryo, the adult and the foetus, they can be cultured with the goal of using them for various applications ranging from fundamental research to regenerative medicine (replacement of the defective cells, reconstitution of the damaged organs), to the identification of new drugs.

Patchy Knowledge

Regenerative medicine causes obviously the strongest passion, because it provides an alternative – as yet theoretical - to the traditional approach in the treatment of the degenerative diseases (Parkinson’s, Alzheimer’s) or involving the fabric destruction (heart diseases, diabetes, osteoporosis, osteoarthritis, leukaemias...). However, the cellular therapies represent also the field of application for which the prospects are most distant, if one excludes the use of the blood stem cells, which became almost a routine for the medical community.

For all the other applications, basic scientific knowledge is only very compartmental. "Until a recent date, it was thought that the cells stocks existed only in the embryo, and it is only into 1998 that one succeeded in isolating and cultivating the first human embryonic stem cells, recalls Jason Loveridge, manager of Capital BioPharma, subsidiary company of IT Asset Management. When we know that it took fifteen years for the first monoclonal therapeutic anti-bodies to arrive on the market, it is probable that there will be no cellular therapy

treatment before the next ten years." Many fundamental problems must indeed still be solved (to read below). "Currently, there are technologies and intellectual property, Jason Loveridge continues. Some try to build companies on this basis, but as long as there will are no products, the venture capital will balk to invest.

An analysis shared by Peter Mountford, chairman of the Scottish company Stem Cell Sciences

"I am convinced that there is a gulf between the need for financing in the life sciences and the concerns of the investors", he reckons.

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From here, we see an original business-model. The company, specialized in the utilization of research results on the embryonic stem cells, is organized in network, grouped under a holding company based in Edinburgh. This holding company ensures the coordination of the research tasks undertaken in the various subsidiary companies located in Scotland, in Australia, in Japan (and perhaps soon in France) beside the best academic laboratories. The company carries out research under contract and grants licenses on technologies thus developed (cellular culture, genetic engineering, in vitro differentiation...).

Sale of cell lines

"We can thus benefit from the contribution of the best specialists in the field", assures Peter Mountford. Since 2001, Stem Cell Sciences has thus succeeded in generating 5 million euros of contracts from industrialists like Pfizer, Aventis, GSK, BioTransplant or Genentech. "This type of organization is completely relevant at the very early stage of acquisition of the scientific bases, observe Jason Loveridge. But it is not appropriate for more advanced degrees of maturity of technology, because the researchers think in terms of knowledge and not of products. One is then obliged to return to a more traditional structure.

This "traditional" structure, the majority of the companies operating in the field besides already adopted it. But, while waiting for treatments to be close enough to be marketed, the choice of the businesses-models remains problematic. The sale of products and technologies around the stem cells is not in any case sufficient, at the present stage, to be profitable.

For this reason, the Australian-listed company CyGenics owns 2 other companies, CordLife, based in Singapore and specialized in the storage of cord blood (source of stem cells), and Cytomatrix, in Boston, that invented a three-dimensional matrix allowing the culture of stem cells in 3D, an essential process so that the cells preserve all their functions. "We are not waiting for extraordinary performances in the short and medium term, underlined a recent study of Australian Elixir Securities, specialized in the life sciences. And, in the long term, the valuation of the company will depend very largely on the success of the Cytomatrix technology.

To market lines of embryonic cells stocks is another way of developing a commercial activity. It is the path chosen by Swedish company CellArtis, created in 2001 by a group of scientists of the university of Gothenburg and university hospital of Sahlgrenska. Employing 20 people, it is today the most important source in the world of lines of embryonic stem cells. It proposes 30 lines, including three eligible for American public financing.

The embryonic cells stocks are first and foremost an unparalleled tool of research for everything from fecundation, embryogenesis, genetic diseases, etc. "However, this market currently does not exceed 50 million euros per annum, estimates Boo Edgar, person in charge for the business development of CellArtis. The cellular tests for the search for new drugs weigh about four times more ", it continues. The pharmaceutical groups are indeed of the

biggest users of these tests, as well for the identification of the targets as for the studies of toxicology. "To have human cells is then more considerable, observe Boo Edgar. That will make it possible to considerably decrease the use of tests on animals ", which we recognize as being of a mediocre predictive character.

How do we industrialize?

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But it is of course in the long term the market of the cellular therapies which CellArtis targets. A very ambitious objective, if one believes the list of the conditions to fulfill to reach a status of pharmaceutical product, drawn up by Eric Halioua, director at Arthur D. Little, in its study "Stem cells and cellular therapy". In addition to the conditions of purity, of viability and stability of the lines, difficulties related to industrialization will arise: validation of the scaling process of multiplication and extraction, access to growth factors based on GMP ("good manufacturing practices") standards, installation of a quality control... All stringent constraints to respect with living matter.

Depending on whether the company chooses a therapy autologist (individual treatment starting from the very cells of the patient) or allogenic (standardized treatment), the organization of the production will also be completely different. "The autologists therapies will avoid the problems of rejection, but they will be much heavier and expensive to implement than the allogenic therapies in the absence of any economy of scale ", explain Eric Halioua. It then remains to define standard surgical or medical procedures, as well as evaluation and control procedures.

The Swedish company NeuroNova chose to turn the difficulty around while remaining faithful to the current pharmaceutical model of administration of standardized drugs. It seeks to develop proteins already used in other indications to stimulate the growth of the adult stem cells present in the brain. "We currently have three molecules in pre-clinic phase and we should be able to start a first clinical trial on Parkinson's disease in 2006", explain Ulf Ljungberg, new president of the company. But a more urgent expiry awaits it: to raise money imperatively before next June, date where the bank account will dry up. For the pioneering stem cell companies, indeed, the lack of visibility is an at the same time scientific and financial.

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