Autologous skin cells from the factory.

First-class conditions for cell biologists, physicians and patients in the 'Centre de production cellulaire' at the CHUV.

How does one get the idea to put a class A isolator into a cleanroom class D?

Dr. Jean-François Brunet: Basically, it is important for the CHUV to further develop the hitherto gained expertise in cell therapy in various applied disciplines: neuroscience, dermatology, cardiology, and other application areas. The CHUV provides a cell production for patients with severe burns for more than 25 years but we had to deal with legal quality requirements, we needed the accreditation of Swissmedic. The challenge of building a facility that meets the GMP requirements is that the actual standard for Laboratories in cell production, to work with an isolator class A within a clean room of class B, is not only very expensive, but also time-consuming and troublesome for the staff. That in short was the starting point for our intention, to place as many of the instruments which are linked to the production process on the smallest possible area. The work with a glove box, a container which is hermetically sealed and gas-tight from the surrounding working room, was therefore an obvious choice. In cell production, it's all about, to protect the product according to Class A directives and still to guarantee the manual handling, the visual observation and the control of cell cultures. Because the process has to be carried out always at a relative humidity of 37 ° C body temperature and at constant CO_2 regulation, the placement of an incubator in this environment is an imperative. For this reason, the idea was born.

Do you still remember when and where you first thought of it as a possibility?

Dr. Jean-François Brunet: I always wanted to find a new and easier way how to place the necessary working tools so that everything is as close as possible to each other and still corresponds to the highest quality and purity procedural requirements. One day, when I was in the clean room where human skin is grown, a possible arrangement arose before my inner eye and I immediately brought this wishful thinking on paper. We have discussed the sketch with the specialists of Sysmex in order to search for ways and means to implement the plan into reality as faithfully as possible, what we now have achieved three years later. The goal to build a GMP-compliant production facility for working with the body's own (autologous) cells was provided in a previous year’s strategy paper for the period 2009-2013 by the CHUV. In so far this important strategy goal could definitely be realized with this project. Nevertheless, research is one thing, production & distribution another. Cultivation of autologous skin cells in the CHUV had to make a shift from the research laboratory culture through to a GMP-qualified manufacturing facility with regard to implementation processes. There is no plan B if one wants to guarantee all patients in Switzerland with severe burns (> 40% of the skin surface) a standardized transplantation approach to skin regeneration within the required time gaps also in the future.

The concept is recognized by Swiss authorities, what were the conditions for it?

Dr. Jean-François Brunet: The experts from Swissmedic carefully checked the concept, the individual modules isolator with integrated incubator and the production system as a whole during three days and found it to be good. In addition, these specialists were extremely impressed by wealth and scope of our documentation. It has been found that with the help of dedicated project management and thanks to a constructive cooperation with the participating delivery works, a complete overview of all major aspects: components, work processes, quality control units and risks created, a systematic analysis and transparent assessment will be possible at any time. The well-functioning network of expertise CHUV, Sysmex, Euro Clone and Swissmedic was undoubtedly an essential key factor for this groundbreaking success.

Back to medicine, the plant is used in the treatment of severe burns -, how it came about that the CHUV has become the reference center for such patients in Switzerland?

Dr. Jean-François Brunet: The story begins in 1983 with the first therapeutic use of laboratory-grown human keratinocytes and fibroblasts, as Howard Green, a founding father of regenerative medicine and professor of cell biology at Harvard Medical School, performed the world's first transplant of epidermal stem cells to burn wounds third degree. The event attracted researchers and clinicians from around the world and among them was also a representative of the CHUV, Dr. Sébastien Déglise, who returned, animated and committed to form a partnership with a cell biologist, Dr. Messod Benathan, what turned into a success story in the field of autologous cell therapy, which is still continuing. Because the production of autologous skin cells lasts three weeks and the burn patients must be supplied with special interactive wound dressings meanwhile, logistical and technical challenges are at the core of this treatment regimen and hence limit the number of patients. This led to a selection pressure in the past, so that only the most difficult cases, third-degree burns, more than 40% of the skin surface, for which there is no alternative, could be treated in this manner. Artificial skin is expensive to produce and therefore also a rare commodity.

How many people get seriously burned every year in Switzerland and what is the capacity of the plant?

Dr. Jean-François Brunet: I can only say something about the numbers at the CHUV: we treat each year 15 up to 20 patients and to give you an idea of our capacity; in 2012 we cultivated 9m2 artificial skin for transplantation purposes in our "Tissue Factory".

Will the plant at the CHUV also be used for research purposes?

Dr. Jean-François Brunet: What we do are more clinical trials and not research in the original sense. Research in the field of applied cell therapy, regardless of whether the cultured autologous cells are subsequently used for dermatological, cardiac or neurological purposes would be held under the aegis of cell biologists. In our case, the goal is clearly to provide a GMP production facility for the needs of cell transplant physicians who already have a precise idea of what kind of cells should be prepared for what application in regenerative medicine. The

difference between research and clinical studies is that in our situation, the basic idea and observation which led to the systematic search for new insights and documentation, already exists and therefore we are focusing on the "recipe" for the production according to standard procedures in line with the GMP rules. We translate the original process into a checklist that is used to ensure and document a constant process level, what is a real challenge given the high degree of complex handling steps in the production of autologous stem cells.

Where do you stand with the Center in a global comparison?

Dr. Jean-François Brunet: There are some places in the world where similar projects have been started and the bar is set pretty high everywhere. To guarantee a process chain from the extraction to cell proliferation up to three-dimensional tissue structure in accordance with GMP criteria is a steep path with huge hurdles, here and there. Technical and economical standards of the pharmaceutical industry are not directly transferable to the cultivation methods of autologous stem cells, there are big differences. The single fact that we have to work with H_2O always carries a high risk of contamination. We also maintain close professional exchange across national boundaries with colleagues from around the world, e.g. in Montpellier, Lyon, Paris, Boston, Montreal, Toronto but our approach is to correspond to the guidelines of Swissmedic in the first instance and to guarantee a close and good relationship with the patient.

This is our top priority.

Lousanne, June 2015