Automated Tissue Engineering on Demand

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The system is intended for the fully automatic production of skin models ready for shipping. © Fraunhofer

(PhysOrg.com) -- There is an increasing demand for skin. Manufacturers of pharmaceuticals, chemicals, cosmetics and medical engineering products need it in order to test the compatibility of their products with human skin. At the 2009 BIO International Convention in Atlanta from May 18 to 21, Fraunhofer researchers will be demonstrating how artificial skin can be manufactured in a fully automatic process.

Skin from a factory - this has long been the dream of pharmacologists, chemists and doctors. Research has an urgent need for large quantities of 'skin models', which can be used to determine if products such as creams

and soaps, cleaning agents, medicines and adhesive bandages are compatible with skin, or if they instead will lead to irritation or allergic reactions for the consumer. Such test results are seen as more meaningful than those from animal experiments, and can even make such experiments largely superfluous.

But artificial skin is rare. “The production is complex and involves a great deal of manual work. At this time, even the market's established international companies cannot produce more than 2,000 tiny skinpieces a month. With annual requirements of more than 6.5 million units in the EU area alone, however, the industrial demand far exceeds all currently available production capacities,” reports Jörg Saxler. Together with Prof. Heike Mertsching, he is coordinating the “Automated Tissue Engineering on Demand” project within the Fraunhofer-Gesellschaft.

Tissue engineering is still in its infancy. “Until now, the offer was limited predominantly to single-layer skin models that consist of a single cell type,” explains Mertsching, who heads the Cell Systems Department at the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB. “Thanks to developments at our institute, the project team has access to a patent-protected skin model that consists of two layers with different cell types. This gives us an almost perfect copy of human skin, and one that provides more information than any system currently available on the market.”

An interdisciplinary team of Fraunhofer researchers is currently developing the first fully automatic production system for two-layer skin models. “Our engineers and biologists are the only ones who have succeeded in fully automating the entire process chain for manufacturing two-layer skin models,” explains Saxler, who is from the Fraunhofer Institute for Production Technology IPT where he is responsible for technology management and heads the “Life Science Engineering” business unit. In a multi-stage process, first small pieces of skin are

sterilized. Then they are cut into small pieces, modified with specific enzymes, and isolated into two cell fractions, which are then propagated separately on cell culture surfaces. The next step in the process combines the two cell types into a two-layer model, with collagen added to the cells that are to form the flexible lower layer, or dermis. This gives the tissue natural elasticity. In a humid incubator kept at body temperature, it takes the cell fractions less than three weeks to grow together and form a finished skin model with a diameter of roughly one centimeter. The technique has already proven its use in practice, but until now it has been too expensive and complicated for mass production. Mertsching explains, “The production is associated with a great deal of manual work, and this reduces the method's efficiency.”

The project team, in which engineers, scientists and technicians from four Fraunhofer institutes are cooperating, is currently working at full speed to automate the work steps. The researchers at the IGB and the Fraunhofer Institute for Cell Therapy and Immunology IZI are handling the development of the biological fundamentals and validation of the machine and its sub-modules. Experts from the Fraunhofer Institute for Manufacturing and Automation IPA and the Fraunhofer Institute for Production Technology IPT are taking care of prototype development, automation and integration of the machine into a complete functional system. “At the beginning, our greatest challenge was to overcome existing barriers, because each discipline had its own very different approach,” Saxler remembers. “Meanwhile, the four institutes are working together very smoothly - everyone knows that progress is impossible without input from the others.” After working together for one year, the project team has already initiated eight patent procedures.

At a collective Fraunhofer-Gesellschaft booth at the 2009 BIO in Atlanta, the researchers are presenting a computer model of the overall system, along with the three fundamental sub-modules. The first module prepares the tissue samples and isolates the two cell types; the second

proliferates them. The finished skin models are built up and cultivated in the third, and then packed by a robot.
The researchers still have a lot of meticulous work ahead before the machine will be finished. The difference between success and failure often depends on details, such as the quality of the skin pieces, processing times of enzymes, and liquid viscosities. Furthermore, the cell cultures must be monitored throughout the entire manufacturing process in order to provide optimal process control and to allow timely detection of any contamination with fungi or bacteria. The skin factory is expected to be finished in two years. “Our goal is a monthly production of 5,000 skin models with perfect quality, and a unit price under 34 euros. These are levels that are attractive for industry,” Saxler continues.

But chemical, cosmetic, pharmaceutical, and medical technology companies who have to test the reaction of skin to their products are not the only ones interested in Automated Tissue Engineering. In transplantation medicine, surgeons require healthy tissue in order to replace destroyed skin sections when burn injuries cover large portions of the body. The two-layer models that the new machine is intended to produce are not yet suitable for this purpose, however. “They don't have a blood supply, and are consequently rejected by the body after some time,” Saxler explains.

But IGB researchers are already working on a full-skin model that will even include blood vessels. Once the research has been completed, fully automatic production of the transplants should also be possible. “We have designed the production system in such a way that it satisfies the high standards for good manufacturing practices (GMP) for the manufacture of products used in medicine,” Mertsching explains. “And so they are also suitable for producing artificial skin for transplants.”

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