3-D bioprinting of living structures with built-in chemical sensors

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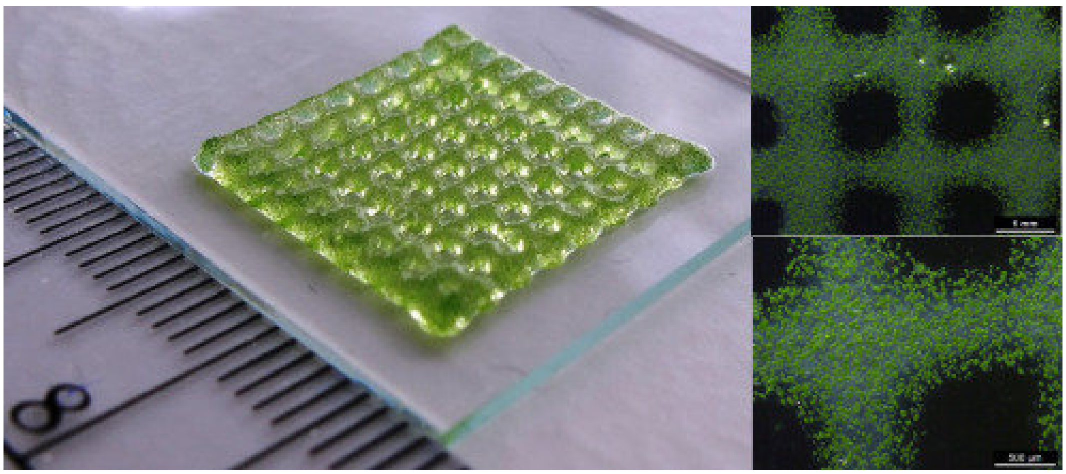

3D bioprinted structure containing green algae (Chlamydomonas) in a hydrogel. Credit: Anja Lode, TU Dresden

A new method enables non-invasive monitoring of oxygen metabolism in cells that are 3-D bioprinted into complex living structures. This could contribute to studies of cell growth and interactions under tissue-like conditions, as well as for the design of 3-D printed constructs facilitating higher productivity of microalgae in biofilms or better oxygen supply for stem cells used in bone and tissue reconstruction efforts.

An international team of researchers led by Professor Michael Kühl at the Department of Biology, University of Copenhagen, has just published a breakthrough in 3-D bioprinting. Together with German colleagues at the Technical University of Dresden, Professor Kühl's group implemented oxygen sensitive nanoparticles into a gel material that can be used for 3-D printing of complex, biofilm and tissue-like structures harboring living cells as well as built-in chemical sensors. The work has just been published in *Advanced Functional Materials*.

Kühl explains: "3-D printing is a widespread technique for producing objects in plastic, metal and other abiotic materials. Likewise, living cells can be 3-D printed in biocompatible gel materials (bioinks) and such 3-D bioprinting is a rapidly developing field, e.g. in biomedical studies, where stem cells are cultivated in 3-D printed constructs mimicking the complex structure of tissue and bones. Such attempts lack online monitoring of the metabolic activity of cells growing in bioprinted constructs; currently, such measurements largely rely on destructive sampling. We have developed a patent pending solution to this problem."

The group developed a functionalized bioink by implementing luminescent oxygen-sensitive nanoparticles into the print matrix. When blue light excites the nanoparticles, they emit red luminescent light in proportion to the local oxygen concentration—the more oxygen, the less red luminescence. The distribution of red luminescence and thus oxygen across bioprinted living structures can be imaged with a camera system. This allows for online, non-invasive monitoring of oxygen distribution and dynamics that can be mapped to the growth and distribution of cells in the 3-D bioprinted constructs without the need for destructive sampling.

Kühl says, "It is important that the addition of nanoparticles doesn't change the mechanical properties of the bioink, e.g. to avoid cell stress and death during the printing process. Furthermore, the nanoparticles should not inhibit or interfere with the cells. We have solved these challenges, as our method shows good biocompatibility and can be used with microalgae as well as sensitive human cell lines."

The recently published study demonstrates how bioinks functionalized with sensor nanoparticles can be calibrated and used, e.g., for monitoring algal photosynthesis and respiration, as well as stem cell respiration in bioprinted structures with one or several cell types.

"This is a breakthrough in 3-D bioprinting. It is now possible to monitor the oxygen metabolism and microenvironment of cells online, and non-invasively in intact 3-D printed living structures," says Prof. Kühl. "A key challenge in growing stem cells in larger tissue- or bone-like structures is to ensure a sufficient oxygen supply for the cells. With our development, it is now possible to visualize the oxygen conditions in 3-D bioprinted structures, which e.g. enables rapid testing and optimization of stem cell growth in differently designed constructs."

The team is interested in exploring new collaborations and applications of their developments. Kühl says, "3-D bioprinting with functionalized bioinks is a powerful new technology that can be applied in many other research fields than biomedicine. It is extremely inspiring to combine such advanced materials, science and sensor technology with my research in microbiology and biophotonics, where we currently employ 3-D bioprinting to study microbial interactions and photobiology."

More information: Erik Trampe et al, Functionalized Bioink with Optical Sensor Nanoparticles for O2 Imaging in 3D-Bioprinted Constructs, *Advanced Functional Materials* (2018). DOI: 10.1002/adfm.201804411

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