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Product in a Patient: *In Vivo* Surgical Manufacturing

We envision a paradigm shift in surgery where operating rooms will become manufacturing facilities. Products will be produced in the operating room and in the patient to regenerate multiple tissue types to support reconstructive surgeries. This paradigm shift will leverage advances in tissue engineering, biomaterials, regenerative medicine, robotics, 3D printing, and imaging.

Current approaches in reconstructive surgery use tissues from the patient's body, tissues harvested from cadavers or animals, and man-made materials to rebuild and repair a patient's body in the operating room. A surgeon sculpts and positions these materials to restore the structure and function of the defective tissues. For example, jaw defects can be reconstructed using bone pieces harvested from the leg and held in place with supporting metallic structures. While reasonable outcomes can be achieved, such reconstructive materials are not purpose built in composition and structure for their use, can prolong healing times, and outcomes are highly varying with surgical skills. Tissue engineering aims to improve these processes by providing purpose-built tissues for each surgery.

Tissue engineering's early promise was of manufacturing tissues *in vitro* within bioreactors and laboratories. While the *in vitro* approach remains feasible, the field has realized the potential of *in vivo* tissue engineering. Here, a template for regeneration is placed within the body and enhances the body's innate regenerative capacity. We believe this *in vivo* regenerative approach will be leveraged in the future towards *in vivo* surgical manufacturing.

Our long-term vision is a new paradigm of reconstructive surgery where purpose-built tissue regeneration templates are manufactured within the operating room and within the patient. Rapid prototyping and scaffold manufacturing technologies will be used by the surgical team to produce the tissue regeneration template. Real-time measurements such as 3D scanning, imaging, and spectroscopy will guide and evaluate the manufacturing processes. The flexible manufacturing system will allow for the composition and structure of the regeneration templates to be tuned for each patient and each tissue. For example, a jaw defect would have a bone regeneration template 3D printed into the defect. The composition of the template would be designed to promote bone regeneration while providing required structural stability. The structure of the manufactured bone would be guided by medical imaging and real-time optical sensors. We expect this suite of tools will enable less invasive surgeries while improving outcomes.

This new paradigm of *in vivo* surgical manufacturing will leverage innovations in the fields of bioengineering, biomaterials, surgery, medicine, robotics, and imaging. However, further innovations and collaboration are required to bridge these disparate fields. *In vivo* surgical manufacturing will require new ways of thinking about manufacturing as well as patient care. These products will be inherently customized for each patient but must also meet stringent regulatory and quality criteria. Surgical staff will guide the processes and will require training and experience with manufacturing approaches. *In vivo* surgical manufacturing is a needed next step for treating patients.