Organoid based tissue manufacturing: designing high-precision functional living implants.

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ABSTRACT

The field of Regenerative Medicine and Tissue Engineering seeks to build functional tissues ultimately replacing failing organs, thereby curing the patient. The lack of living building blocks is a major hurdle in the manufacturing of human scale functional living implants. The ability to produce large populations of small functional tissue niches that could be used for bottom-up engineering of larger tissues would constitute a major step towards addressing this bottleneck.

In this presentation, as a case study, a developmental engineering process yielding autonomous 'callus organoids' will be provided. These organoids appeared to undergo developmental processes *in vitro* mimicking those encountered in the embryonic growth plate and during fracture healing *in vivo*. Upon reaching a degree of "autonomy", as defined by genomic comparison to developmental controls, these organoid modules were able to continue their biological program upon implantation, resulting in the formation of bone organs. This capacity was robustly exhibited either when implanted as single modules or in larger self-assembled multimodular tissues, independent of the implantation site. Strikingly critical size murine long bone defects were also healed within natural physiological time scales while in all cases abundant implanted cells were present, demonstrating their critical role in the regenerative process.

With these advancements, we believe that we contribute towards an era were multimodular tissue implants possessing 'design specifications' could be produced at a scalable and robust manner. This paves the way for the mitigation of unmet clinical challenges of large non healing tissue defects such as critical size bone non-unions. The µtissues could be viewed as a living 'bioink' allowing bottom up manufacturing of multimodular tissues with intricate geometric features and inbuilt quality attributes.