Paper-Based Biomaterials for Personalized Medicine and Regenerative Engineering

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Statement of Purpose: Major limitations in conventional tissue engineering models include the inability to provide physiologically relevant size structures without mass transport limitations, the need for extensive optimization procedures, and the requirement of sophisticated instrumentation or costly set-ups for fabrication of 3D scaffolds. Therefore, it is challenging to fabricate biocompatible scaffolds for personalized medicine. To tackle these hurdles, we developed paper-based biomaterials for a range of applications that involve the use of different types of cells (e.g. stem cells, primary cells, cells from patient biopsies, immune cells, fibroblasts, osteoblasts, epithelial cells, tumor cells, bacteria, fungi, plant cells)[1-4].

Methods: Paper-based biomaterial platforms are flexible, tunable, simple, inexpensive, and amenable to high-throughput sample preparation and analysis. In this work, we used paper-based scaffolds as matrices to support cells and/or hydrogels in 3D. After the desired cell culture period, we monitored and characterized the behavior of cells through standard analytical assays such as cytotoxicity, metabolic activity, proliferation, DNA content, protein content, apoptosis, immunostaining, high-resolution imaging, or mechanical tests. Whatman filter paper was used due to its large pore size (25-30 micron) and thickness (190 micron) for cellular migration. After sterilizing the constructs, they were seeded with cells at a density of 5-20x10^6 cell/mL in hydrogel matrices. The samples were cultured for the desired period of time and cell behavior was monitored using colorimetric assays, immunocytochemistry, high-resolution imaging (SEM), and micro-computed tomography (micro-CT). *In vivo* experiments were carried out to explore the immune response as well as integration and vascularization of the paper-based constructs.

Results:
We fabricated paper-based scaffolds for different applications in personalized medicine and regenerative engineering (Figure 1). For example, we investigated migration of primary human tumor cells that were isolated from patient biopsies in a multilayered paper-based cell culture platform. This approach can be adapted to screen different doses of chemotherapeutics or radiation in a patient-specific fashion. We also used paper scaffolds to induce template-guided biomineralization in origami-inspired structures. This method can be used to fabricate constructs for patients who have irregular size and shape bone defects. In addition, we generated wax-printed patterns in paper scaffolds that are for high-throughput sample preparation and analysis of osteoblast cultures. We have shown that we can form and control gradients of oxygen, nutrients, and other biological molecules in paper-based cell culture platforms. We also used these platforms to culture bacteria, fungi, and plant cells and developed in vitro disease models. Our results demonstrated that the paper scaffolds enable patterning from micron- to cm-scale, adapt modular configurations, and can provide physiologically relevant tissue models. Paper scaffolds can also be used for origami-inspired tissue engineering.

Conclusions: We developed paper-based biomaterials to obtain multicellular and compartmentalized tissue-mimetics for clinical applications. To overcome the major limitations of the traditional tissue models, we adapted a layer-by layer strategy to assemble tissue-like structures from low-cost and biocompatible paper-based materials. We also have performed *in vivo* implantation experiments in animal models and showed that paper-based scaffolds are biocompatible materials and rapidly vascularize and integrate with the host. This approach offers unique opportunities from understanding fundamental biology to developing disease models for personalized medicine, and assembling different tissues for organ-on-paper configurations. Paper has great potential to tackle the limitations of traditional scaffolds including cost, availability, accessibility, porosity, flexibility, rigidity, and ease of fabrication. In the future, paper-based scaffolds could possibly guide and/or accelerate bone repair using patient specific cells.

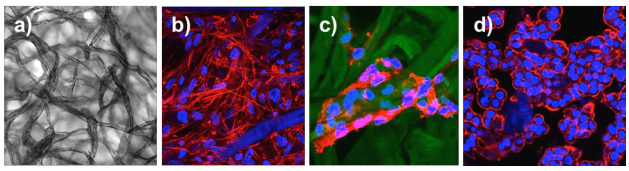

Figure 1. a) Fibrous structure of filter paper, b-d) patient-derived tumor fibroblasts, mouse fibroblasts, and patient-derived lung tumor cells, respectively cultured in paper.

References:
[1]Wu, X., Suvarnapathaki, S., Walsh, K., Camci-Unal, G., "Paper as a Scaffold for Cell Cultures: Teaching an Old Material New Tricks", DOI:10.1557/mrc.2018.8, MRS Communications, 1-14, 2018.
[2]Lantigua, D., Kelly, Y.N., Unal, B., Camci-Unal, G., "Engineered Paper-Based Cell Culture Platforms", Advanced Healthcare Materials, 6(22): DOI: 10.1002/adhm.20, 2017.
[3]Camci-Unal, G., Laromaine, A., Hong, E., Derda, R., Whitesides, G.M., "Biomineralization guided by paper templates", Scientific Reports (Nature Publishing Group), 6, 27693, 2016.
[4]Camci-Unal, G., Newsome, D., Eustace, B., Whitesides, G.M., "Fibroblasts enhance migration of human lung cancer cells in a paper-based co-culture system", Advanced Healthcare Materials, 5(6): 641-647, 2016.