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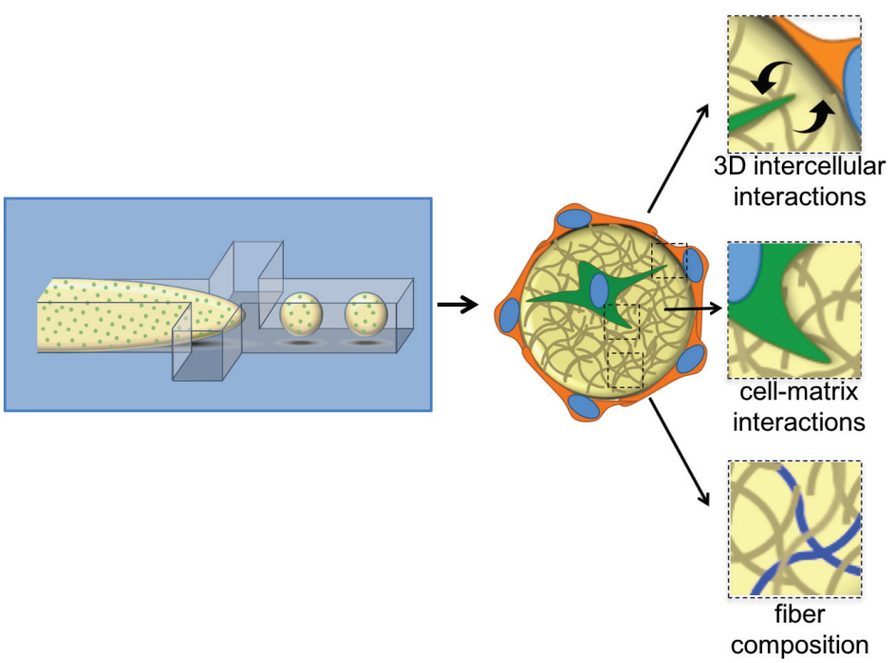
# PRESS RELEASE

## Rapid generation of collagen-based microtissues to study cell-matrix interactions

May 2, 2016 — Novel and simple method to rapidly generate microscale tissue constructs that can be used as a high throughput platform to probe 3D cell-matrix and cell-cell interactions and for drug screening.




*Collagen-based droplets are rapidly generated using a microfluidic flow focusing device. Cells can be encapsulated within the collagen matrix, and they can be cultured on the surface of the microtissues. These cell-laden protein-based microtissues can be used as a high throughput 3D culture platform to study cellular responses to cell-cell and cell-matrix interactions.*

A team of researchers from the Living Devices Lab at the University of Minnesota in Minneapolis, MN have developed a method to fabricate microscale tissue constructs using only naturally occurring proteins, and demonstrated the use of these "microtissues" as a high throughput 3D tissue culture platform. Three-dimensional tissue culture models with protein-based scaffolds are commonly used to capture the complex interplay between drugs, cell mechanics, and matrix interactions. However, most fabrication methods for 3D culture platforms have significant throughput limitations and

limited analysis modalities. The novel method presented in a forthcoming 2016 issue of the journal *TECHNOLOGY* allows thousands of microtissues to be produced every minute, and the collagen composition allows cells to directly interact with and manipulate the matrix, unlike synthetic hydrogel scaffolds. In this report, the team demonstrates the ability to quantify cell contraction in the microtissues, and they demonstrate a novel 3D cell patterning method.

"There are lots of methods to fabricate 3D tissue constructs, but few of them are suitable for high throughput applications because they are too slow and labor intensive to fabricate. We wanted to make a truly high throughput 3D tissue culture platform, and we wanted to develop a fabrication method that would be easy enough for anyone to implement," said Professor David K. Wood, Ph.D., who led the study.

The team focused on collagen to build the microtissues because it is the most abundant fibrillar protein in the body, it creates a neutral (not pro-inflammatory) environment to study cell behavior, and it is a common material for 3D tissue culture. Microfluidic technology provides a powerful tool to rapidly generate monodisperse emulsions of aqueous solutions such as collagen, but it is challenging to control the collagen polymerization process to make microtissues. *In vitro* collagen hydrogel fabrication relies on thermal polymerization — the gels are liquid when they are cold, and they self-organize into a lattice as the temperature increases. Thermal polymerization typically requires 10 to 30 minutes to complete, which is lengthy compared to the fractions of a second required to create the collagen droplets. "The key was to use global temperature control to prevent polymerization of the collagen during droplet formation. Then the temperature of the entire emulsion could be raised to controllably polymerize the collagen," said Alexandra L. Crampton, a doctoral student at the University of Minnesota.

Once the fabrication method was optimized, the researchers focused on cellular functions that could be quantified within the microtissues. Cell contractility was chosen to highlight the ability of this platform to quantify cell-matrix interactions. There are several bulk gel methods to assay cell contractility, but the assays are time consuming, require large volumes of collagen, and the gels are difficult to image. These parameters contribute to small sample sizes typically reported, which are usually between three and five gels for each treatment group. "We knew that translating this assay to microtissues would resolve many of the issues related to bulk gel fabrication and analysis as well as increase the statistical power of the assay," said Marie-Elena Brett, Ph.D., a postdoctoral fellow at the University of Minnesota. In this study, the average sample size contained 100 microtissues, which could be generated at speeds in excess of 45,000 microtissues per hour. Not only is this less hands-on work for the researcher, but also creates three orders of magnitude more microtissues for the same amount of materials required for bulk gel analysis. The team used automated imaging and analysis to rapidly analyze the microtissues, and reported quantification of gel contraction with cells either encapsulated inside the collagen or coated on the collagen surface, which has not previously been demonstrated.

The Living Devices Lab team is now working on applications of this microtissue platform that explore cell-matrix interactions in 3D as well as cell-cell interactions using the novel ability to pattern co-cultures of varying cell types within and around the microtissues. Currently, they are investigating the influence of extracellular matrix composition on cancer cell migration, and they are using 3D co-cultures to study cell interactions that lead to pathologies such as fibrosis. "We believe the platform we have developed can be easily disseminated to other groups, and we ultimately envision this as a powerful new tool for screening drugs in more physiologically relevant microenvironments," said Wood.

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