

# CELLINK

A BICO COMPANY

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BIOLOGY + TECHNOLOGY

Bio Convergence is  
the future of health.



# The BICO Group



**14**  
companies



**37**  
offices



**1,000+**  
employees



**25,000+**  
Instruments  
in 65+ countries



**9,500+**  
Publications

## Business Area Bioprinting

**CELLINK** >>  
A BICO COMPANY

**MATTEK** >>  
A BICO COMPANY

**VISIKOL** >>  
A BICO COMPANY

**nano scribe**  
A BICO COMPANY

**ADVANCED  
BIOMATRIX** >>  
A BICO COMPANY

## Business Area Biosciences

**CYTENA** >>  
A BICO COMPANY

**CYTENA BPS** >>  
A BICO COMPANY

**DISPENDIX** >>  
A BICO COMPANY

**ECHO** >>  
A BICO COMPANY

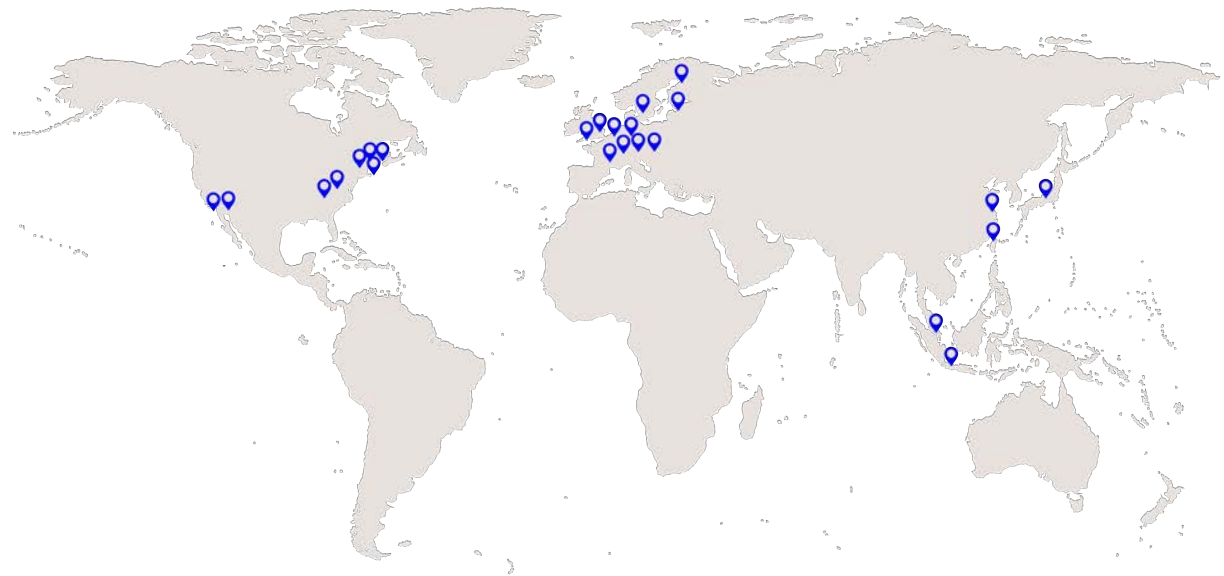
## Business Area Bioautomation

**SCIENION** >>  
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**CELLENION** >>  
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**GYNOLIS** >>  
A BICO COMPANY

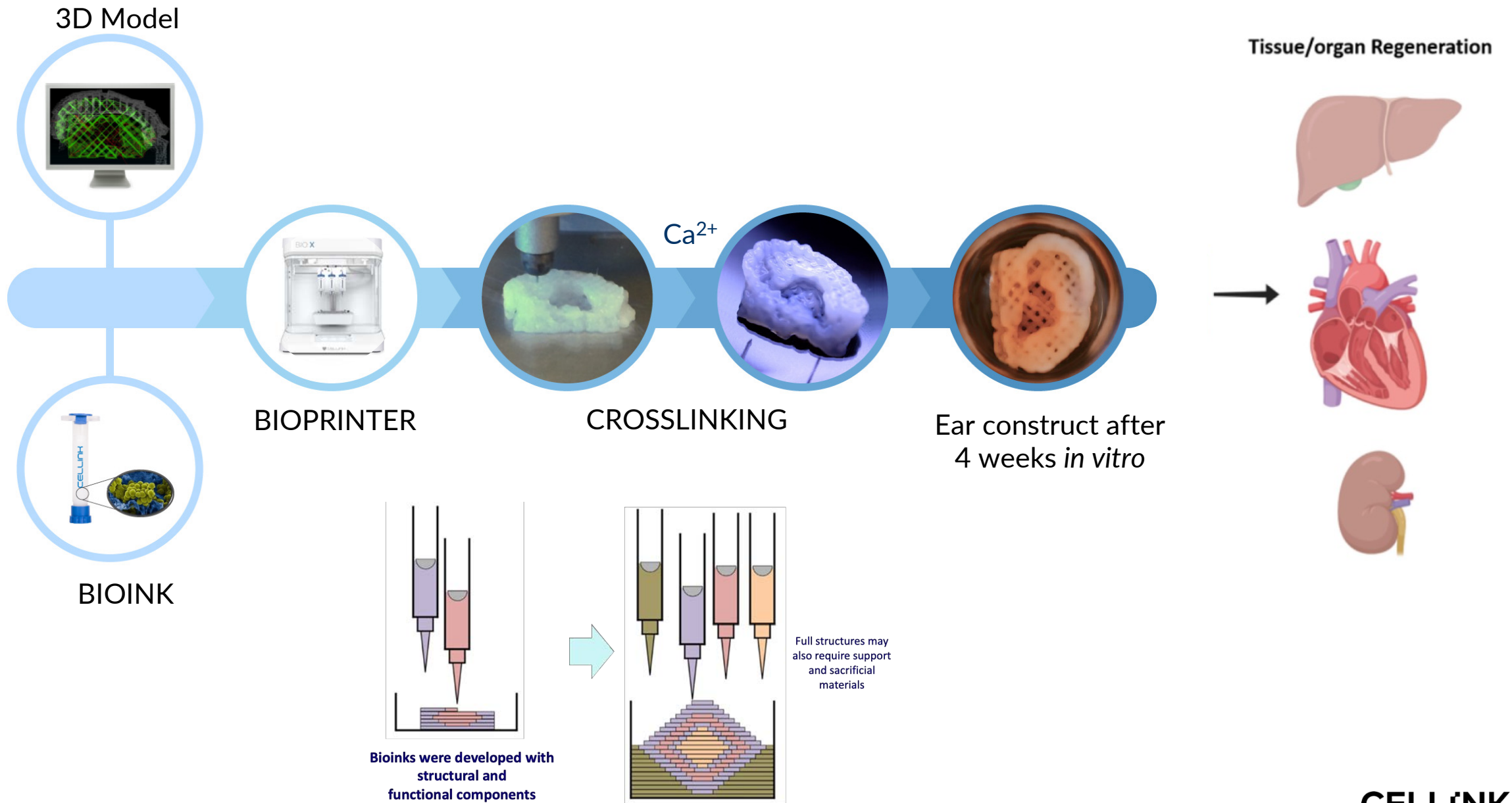
**QINSTRUMENTS**  
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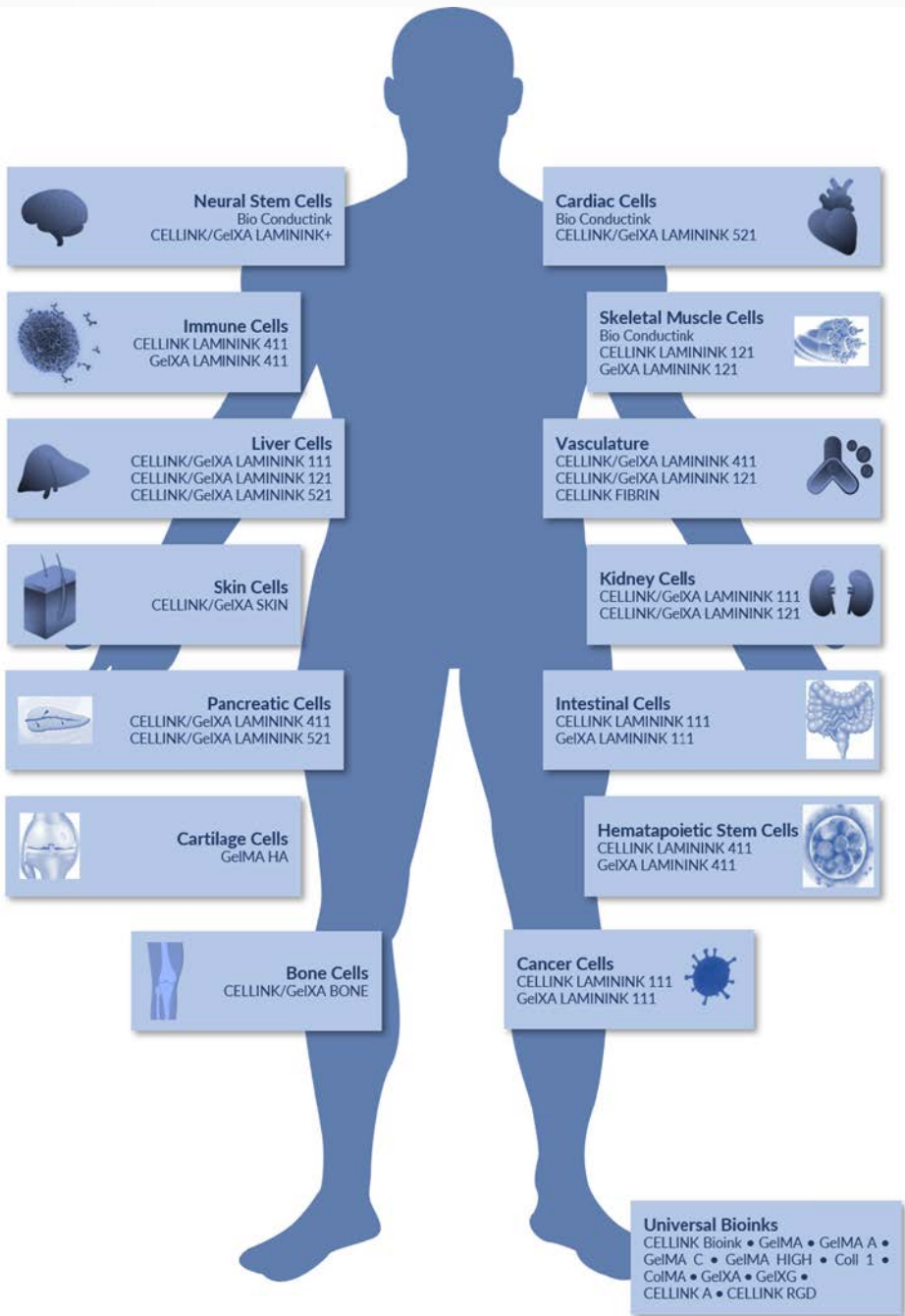




# BIOPRINTING







**Tissue Engineering Kits**  
Direct application, consistent models

**Advanced Bioinks**  
Tissue-specific biomaterials, case studies

**Standard Bioinks**  
Basic bioinks, ready-to-use products

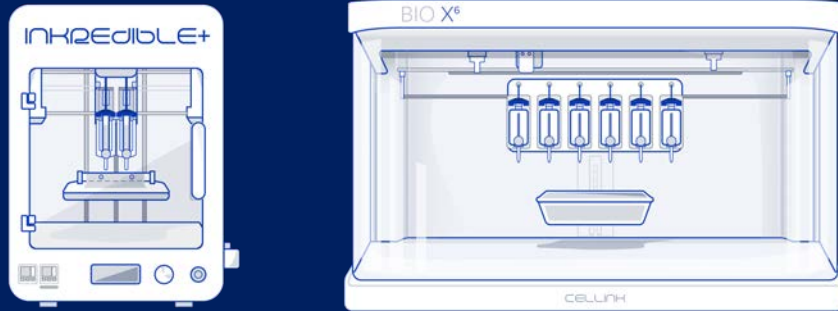
**Stock Solutions**  
Consistent stock solutions, defined properties

**Concentrated Components**  
Raw materials, accessories, basic tools



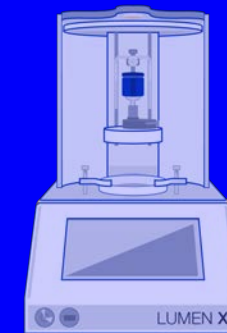
# OUR BIOPRINTING TECHNOLOGIES

## EXTRUSION-BASED



- Pressure-based prints
- Cartridge and syringe dispensing
- Successive filaments/droplets
- Crosslinking post-bioprinting

## LIGHT-BASED



- Optics-based prints (UV)
- Resin bath
- Successive layers/points
- Crosslinking while bioprinting



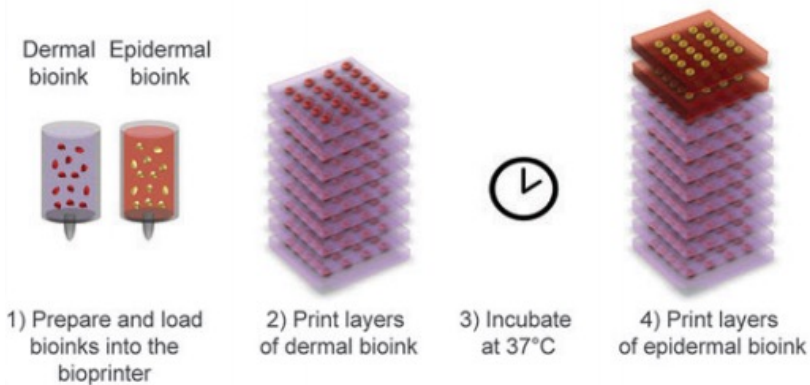




# 3D BIOPRINTING OF VASCULARIZED SKIN

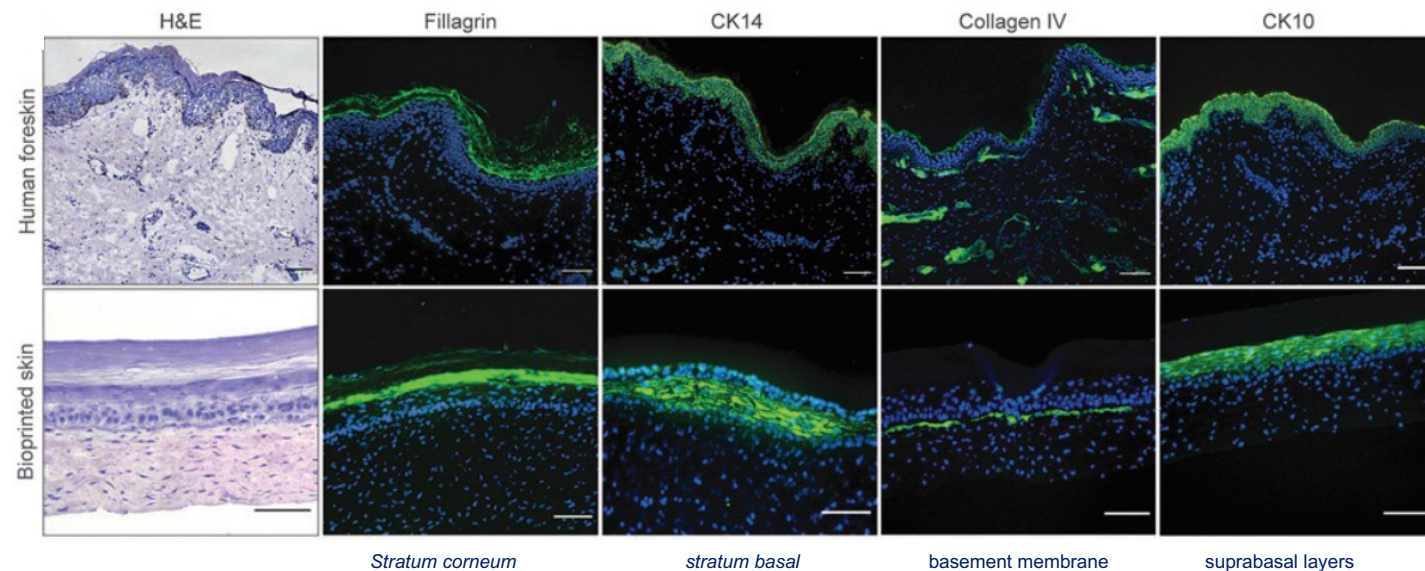
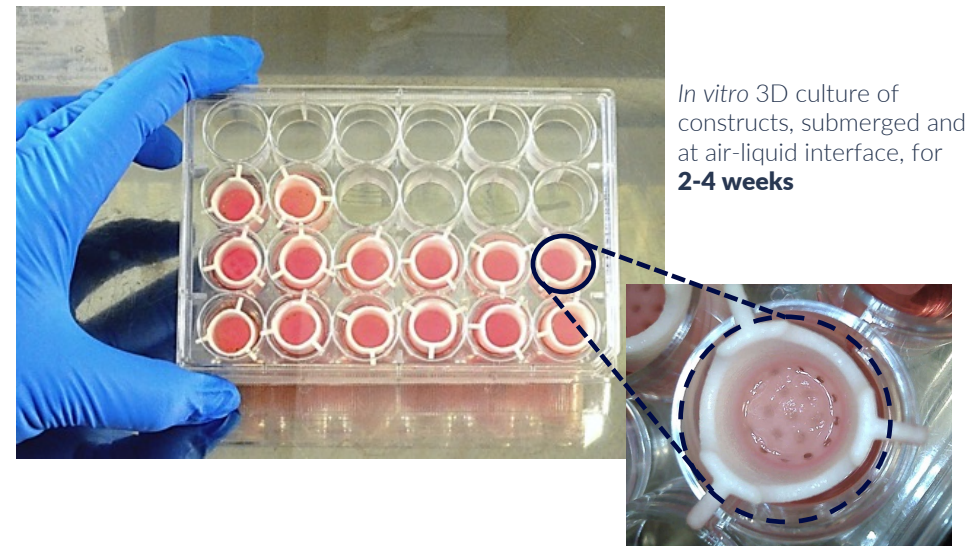
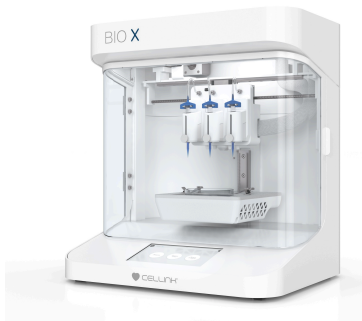
## Three Dimensional Bioprinting of a Vascularized and Perfusable Skin Graft Using Human Keratinocytes, Fibroblasts, Pericytes, and Endothelial Cells

Tânia Baltazar, PhD,<sup>1</sup> Jonathan Merola, MD, PhD,<sup>2</sup> Carolina Catarino, MS,<sup>3,4</sup> Catherine B. Xie, MS,<sup>1</sup> Nancy C. Kirkiles-Smith, PhD,<sup>1</sup> Vivian Lee, PhD,<sup>5</sup> Stephanie Hotta, MS,<sup>6</sup> Guohao Dai, PhD,<sup>5</sup> Xiaowei Xu, MD, PhD,<sup>7</sup> Frederico C. Ferreira, MBA, PhD,<sup>8</sup> W. Mark Saltzman, PhD,<sup>9</sup> Jordan S. Pober, MD, PhD,<sup>1</sup> and Pankaj Karande, PhD<sup>3,4</sup>



**Model 1: Non-vascularization**  
Dermis: Fibroblasts (FB)  
Epidermis: Keratinocytes (KC)

**Model 2: Vascularization**  
Dermis: FB + Endothelial cells (EC) + Pericytes (PC)  
Epidermis: Keratinocytes (KC)







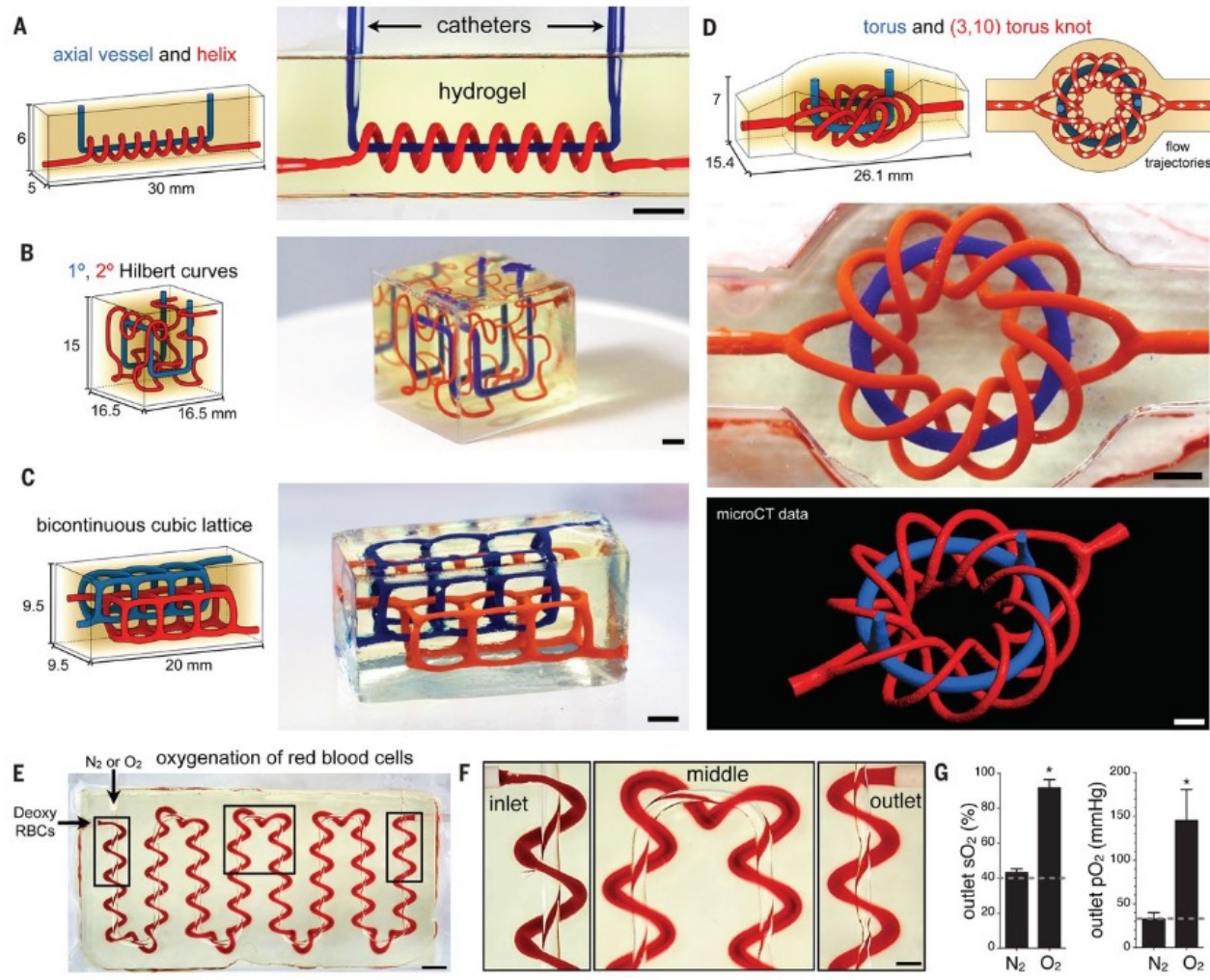
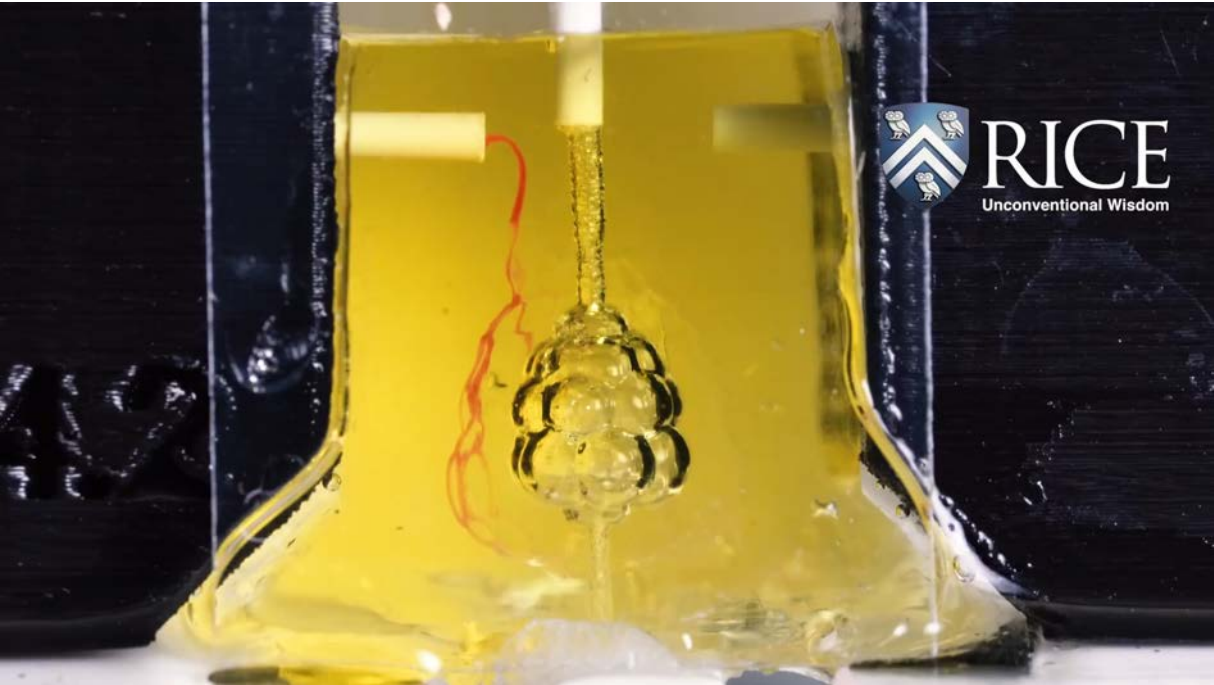
# LUMEN X+ : HIGH RESOLUTION DLP-SLA



BIOMEDICINE

## Multivascular networks and functional intravascular topologies within biocompatible hydrogels

Bagrat Grigoryan<sup>1\*</sup>, Samantha J. Paulsen<sup>1\*</sup>, Daniel C. Corbett<sup>2,3\*</sup>, Daniel W. Sazer<sup>1</sup>, Chelsea L. Fortin<sup>3,4</sup>, Alexander J. Zaita<sup>1</sup>, Paul T. Greenfield<sup>1</sup>, Nicholas J. Calafat<sup>1</sup>, John P. Gounley<sup>5,†</sup>, Anderson H. Ta<sup>1</sup>, Fredrik Johansson<sup>2,3</sup>, Amanda Randles<sup>5</sup>, Jessica E. Rosenkrantz<sup>6</sup>, Jesse D. Louis-Rosenberg<sup>6</sup>, Peter A. Galie<sup>7</sup>, Kelly R. Stevens<sup>2,3,4,†</sup>, Jordan S. Miller<sup>1,†</sup>



# APPLICATION Notes TECHNICAL Notes

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## A 3D Bioprinted Model to Study Osteogenic Differentiation of Primary Mesenchymal Stem Cells

APPLICATION NOTE

### Abstract

Primary cells from bone biology and developing mesenchymal stem cell and the bioprinting process in biofabrication for its potential to differentiate rigidity and support to the in vivo microenvironment to study osteogenic differentiation by Alizarin red staining after 21 days of culturing in differentiation by Alizarin red staining.

### Introduction

Mesenchymal stem cells (MSCs) are stromal cells that have self-renewal and differentiate into different lineages: osteogenic, chondrogenic, adipogenic, and neural (Figure 1). MSCs are recommended for regenerative medicine because they are able to differentiate into bone, cartilage, and adipose tissue. MSCs are characterized by the expression of several markers including CD29, CD44, CD105, and CD133. However, MSCs are heterogeneous and may have different origins, including bone marrow and adipose tissue. MSCs are characterized by the expression of several markers including CD29, CD44, CD105, and CD133. However, MSCs are heterogeneous and may have different origins, including bone marrow and adipose tissue.

### Abstract

Lung cancer is one of the most common causes of death worldwide. It is a complex disease that requires a better understanding of its biology and mechanisms. In this study, we developed a 3D bioprinted lung cancer model to study the expression of junctional proteins in 3D cultures.

### Introduction

The vital function of the lung is to exchange gases between the atmosphere and the blood. The system is put under a high pressure and a high flow rate. Lung cancer is the disease that requires a better understanding of its biology and mechanisms. In this study, we developed a 3D bioprinted lung cancer model to study the expression of junctional proteins in 3D cultures.

Cancer cells often form spheroid-like structures in 2D cultures using (Figure 1).

β-catenin pattern in Drosophila the nucle activation structure of the cell

## In Vitro 3D Lung Cancer Model Presents a More Relevant Expression of Junctional Proteins than 2D Cultures

APPLICATION NOTE

## Printing Alginate Beads: A Technical Note

TECHNICAL NOTE

## Evaluating Liver Toxicity in Bioprinted Mini Livers

APPLICATION NOTE

Priyanka Koti, MEng, Shubhankar Nath, PhD, Himjyot Jaiswal, PhD, Christen Boyer, PhD, Josefin Bleil, MSc, and Itedale Namro Redwan, PhD  
CELLINK LLC, Boston, MA, USA

### Abstract

Drug-induced liver injury (DILI) affects the liver's ability to metabolize and detoxify substances, but its underlying mechanisms are largely unknown. To accurately and reproducibly predict DILI in humans, there is a significant need for *in vitro* liver models that replace costly and low-throughput 2D cell culture systems, animal studies and lab-on-a-chip models. Here, we present a new method of "droplet in droplet" (DID) bioprinting to produce physiologically relevant liver models for hepatotoxicity studies. These models, or mini livers, were produced using a BIO X to droplet-print hepatic (HepG2 and LX2) and nonhepatic (HUVEC) cells encapsulated in type I collagen. After 7 days of culture, mini livers were exposed to acute and high doses of acetaminophen or flutamide, then evaluated for changes in cell viability, albumin secretion, alanine aminotransferase (ALT) activity and lipid accumulation. Increased ALT activity and low albumin and lipid production in mini livers suggested a cytotoxic response to both drugs. The results of this study further validate 3D bioprinting as a viable and medium- to high-throughput solution for modeling hepatic tissue and screening idiosyncratic drug reactions.

### Introduction

Drug-induced liver injury (DILI) is a leading cause of liver disease and acute liver failure (ALF). The risk factors for DILI are elusive, but drug properties and disposition can affect DILI development and play a major role in drug attrition and withdrawal from market. In fact, preclinical studies in 2015 showed that 50% of drug candidates failed due to liver toxicity, justifying the need for a model that can predict drug toxicity and mirror abnormalities associated with DILI (Chen, 2015). Recently, abnormalities like upregulated alanine aminotransferase (ALT) and reduced albumin production have been studied in 3D models like hanging droplets and spheroids (Shah, 2018). These models, however, are unrepresentative and low-throughput. As an alternative, bioprinted tissue models can be used for medium- to high-throughput drug screenings, to reduce drug attrition and fast-track preclinical phases of drug development (Ramaiahgari, 2014).

This study evaluates the effects of two drugs on mini livers that were produced using a new method of "droplet in droplet" (DID) bioprinting. DID bioprinting allowed for controlled cellular arrangements and cell-matrix interactions, and provided unique multi-layered models to study drug penetration and response. The compounds used in this study, acetaminophen (APAP) and flutamide (FLU), are frequently used to evaluate liver toxicity. These compounds are categorized by severity, for which Category 1 is considered "Severe Clinical DILI," Category 2 is "High Clinical DILI," and Category 3 is "Low Clinical DILI Concern" (Proctor, 2017). FLU and APAP fit into Categories 1 and 3, respectively. FLU is an antiandrogen used to treat prostate cancer; and APAP is a widely used analgesic and COX-3 inhibitor. At high doses, both drugs have been linked to hepatic toxicity, oxidative stress, ALF and DILI, which makes them ideal for evaluating the efficacy and functionality of bioprinted liver models (Behrendts, 2019; Zhang, 2018).

Crosslinked alginates calcium ions, which help to form a gel structure, as less reactive phosphate supplements linked alginates (Lee due to the lack of en

BIOX-06082020V1



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