H2020-FETOPEN-2018-2019-2020-01- 828931

Work Package Number	**5**	**Task Number**	**N/A**	**Deliverable Number**	**5.1**	**Lead Beneficiary**	**IBEC**
Deliverable Title	**REPORT OF KICK-OOF MEETING**						
Contractual Delivery Date	**M1**	**Nature**	**Report**		**Dissemination Level**		**PU**
Actual Delivery Date	**23/07/2019**	**Contributors**	**IBEC**				

Overview/Abstract* *Delete as appropriate*

Minutes of the kick-off meeting including the agenda, list of participants, presentations of the participants and minutes from the meeting

Explanation for large delay in submitting deliverable

N/A

Led by

Name	Elena Martínez	**Partner**	IBEC	**Date**	**23/07/2019**

Reviewed by

Name	Javier Selva	**Partner**	IBEC	**Date**	**23/07/2019**

Document Control

Issue #	Date	Changed Pages	Cause of Change	Implemented by

BRIGHTER Kick-Off Meeting

Date: 04-05 July, Barcelona, Spain
Place: Institute for Bioengineering of Catalonia (IBEC), c/ Baldiri Reixac 4-8, Tower I floor 11.
Travel: See "How to get to IBEC.pdf" attached file.

Attendees:

IBEC: Elena Martínez, Javier Selva, Nuria Torras, Vanessa Fernández y Jordi Comelles.
GUF: Francesco Pampaloni.
CELLENDES: Helmut Wurst, Brigitte Angres, Gabriele Di Napoli.
MYCRONIC: Gustaf Mårtensson, Robert Eklund.
TECHNION: Ruby Shalom Feuerstein.

Thursday 4thth July

Day 1	**Consortium Management**	
10:00-10:30	Welcoming Coffee	
10:30-10:45	Roundtable introductions and Meeting Agenda.	All
10:45-12:30	Roles and Responsibilities: • Co-ordinator (15 min): IBEC. • Beneficiaries (15 min each): GUF, CELLENDES, MYCRONIC and TECHNION. Questions and doubts.	All
12:30-14:00	Lunch	
14:00 – 14:20	Overview of the research project.	IBEC
14:20-15:00	WP1 - Development of the light-sheet bioprinter: • Planning for the next 6 months: task review, deliverables and experimental work plan. Questions and doubts.	GUF
15:00-15:40	WP2 - Photopolymerizable hydrogels.: • Planning for the next 6 months: task review, deliverables and experimental work plan. Questions and doubts.	CELLENDES
15:40-16:15	Coffee break	
16:15-16:50	WP3 - Demonstration of light-sheet bioprinting: • Planning for the next 6 months: task review, deliverables and experimental work plan Questions and doubts.	IBEC
16:50-17:30	WP4 - Engineered skin tissues: • Planning for the next 6 months: task review, deliverables and experimental work plan Questions and doubts.	TECHNION
17:30	Closing Remarks from first day.	IBEC
20:00	Dinner – El Com Restaurant Address: Carrer Progrés, 9-11, L'Hospitalet de Llobregat,	

Friday 5th July

Day 2	Consortium Management	
09:15-09:30	Welcoming Coffee	
09:30-10:30	Work Package 5 - Project Management & Dissemination: • General aspects (Rights & obligations, amendments, reporting, CFS, DLs and MLs). • Upcoming deliverables (M0-M7). • Scheduling project meetings. Questions and doubts.	IBEC
10:30-11:30	Work Package 6 – Dissemination, Exploitation and Communication • Dissemination actions • Exploitation strategy • IPR roadmap (MYCRONIC) • Consortium Agreement Questions and doubts.	IBEC MYCRONIC
11:30 – 13:00	Visit IBEC laboratories (optional).	IBEC
13:00-14:00	Lunch	
14:00- 14:10	Group Picture	
14:10-15:00	AOB and Closing Remarks.	IBEC

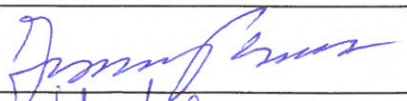
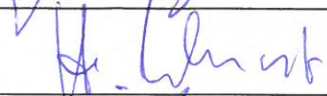
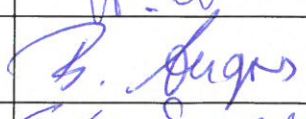
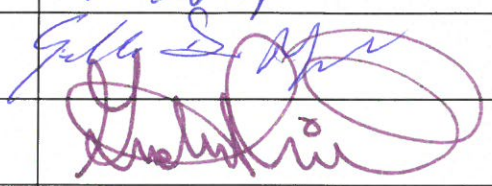
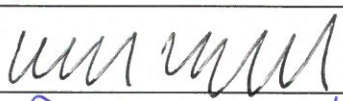
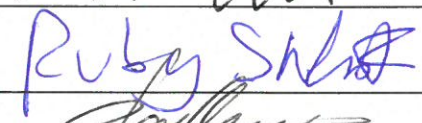
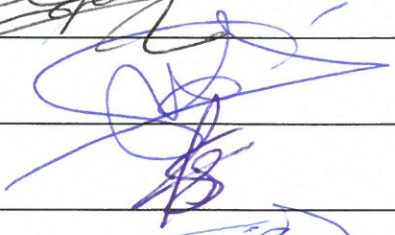
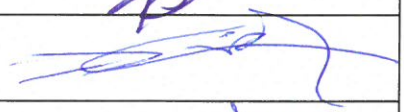
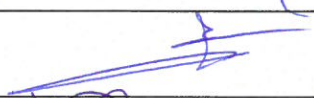
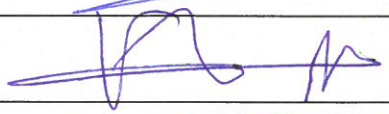
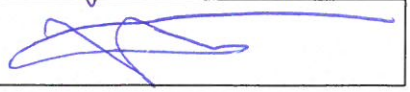
BRIGHTER Kick-Off Meeting

Date: 04-05 July, Barcelona, Spain
Place: Institute for Bioengineering of Catalonia (IBEC), c/ Baldiri Reixac 4-8, Tower I floor 11.

Thursday 4thth July from 2019

NAME	ENTITY	SIGNATURE
Francesco Pampaloni	GUF	
Helmut Wurst	CELLENDES	
Brigitte Angres	CELLENDES	
Gabriele Di Napoli	CELLENDES	
Gustaf Mårtensson	MYCRONIC	
Robert Eklund	MYCRONIC	
Ruby Shalom Feuerstein	TECHNION	
Elena Martínez	IBEC	
Núria Torras	IBEC	
Javier Selva	IBEC	
Vanessa Fernández	IBEC	
Jordi Comelles	IBEC	

Friday 5th July from 2019

NAME	ENTITY	SIGNATURE
Francesco Pampaloni	GUF	
Helmut Wurst	CELLENDES	
Brigitte Angres	CELLENDES	
Gabriele Di Napoli	CELLENDES	
Gustaf Mårtensson	MYCRONIC	
Robert Eklund	MYCRONIC	
Ruby Shalom Feuerstein	TECHNION	
Elena Martínez	IBEC	
Núria Torras	IBEC	
Javier Selva	IBEC	
Xavier Puñet	IBEC	
Xavier Rúbies	IBEC	
Vanessa Fernández	IBEC	
Jordi Comelles	IBEC	

BRIGHTER Kick-Off Meeting

Date: 04-05 July, Barcelona, Spain
Place: Institute for Bioengineering of Catalonia (IBEC), c/ Baldiri Reixac 4-8, Tower I floor 11.
Travel: See "How to get to IBEC.pdf" attached file.

Attendees:

IBEC: Elena Martínez (EM), Javier Selva (JS), Núria Torras (NT), Vanessa Fernández (VF) y Jordi Comelles (JC).
GUF: Francesco Pampaloni (FP).
CELLENDES: Helmut Wurst (HW), Brigitte Angres (BA), Gabriele Di Napoli (GN).
MYCRONIC: Gustaf Mårtensson (GM), Robert Eklund (RE).
TECHNION: Ruby Shalom-Feuerstein (RSF).

Thursday 4thth July

Day 1 **Consortium Management**

10:00-10:30 **Welcoming Coffee**

10:30-10:45 **Roundtable introductions and Meeting Agenda.**

10:45-12:30

Roles and Responsibilities:

- **Co-ordinator (15 min): IBEC.**

  E. Martínez introduces IBEC to the partners: the origins of the institution, its main research activities and the groups.

- **Beneficiaries (15 min each): GUF, CELLENDES, MYCRONIC and TECHNION.**

GUF (Francesco Pampaloni): Brief introduction about himself (trajectory and research experience). He works at the Buchmann Institute for Molecular Life Sciences Then he talks about his two main research lines in the group: tissue models using (*i*) spheroids for mimicking tumours, and (*ii*) pancreatic organoids. He currently has another EU project in which Cellendes is also involved developing synthetic gels for replacing the widely used (an expensive) Matrigel® for organoids cultures.

He also introduces part of his team which be involved on Brighter: Mr. Prateek Gupta (optical engineer, master student), in charge of prototyping and optical design, who will interact with MYCRONIC and Mrs. Sanam Saeifar (biologist, PhD student), in charge of 3D cell culture and microscopy, who will interact with IBEC, GUF and CELLENDES.

CELLENDES (Helmunt Wurst): Brief introduction about the company, located in Reuthingen, Germany (foundation, mission and expertise). Their main working lines lie in the development of (*i*) synthetic hydrogels, (*ii*) reagents for 3D cell cultures and (*iii*) 3D testing systems for soft polymers.

Examples of their knowledge:

They use to work with two-components systems:
(a) Thio-reactive polymers (e.g. PVA, dextrans, MMA, etc.)
(b) Thiol-functionalized polymers (e.g. PEG, Hyaluronic acid, MMP-cleavable.)

Basically, they use the Michael addition method (which is cell-compatible) for the crosslinking reaction of the polymers. They also have experience in the incorporation of RGD-dextran peptides within the polymer chains to make the scaffolds more cell-friendly (adding cell adhesion motives).

They show several examples of their applications (neurosphere outgrowth and differentiation, tumour-stroma model, etc.). They work with cell lines and primary cells.

In addition to the work developed together with GUF, they have a collaboration with Tecan Schweiz AG and the Zürich University of Applied sciences for the development of an automatic system for cells culture based on 96-wells plates, covering the whole process.

MYCRONIC (Gustaf Mårtensson and Robert Eklund): Brief introduction about themselves (background, research experience) and the main production and research lines of Mycronic: future electronics for deposition of fluids, melting compounds and microlithography. The company basically sales highly precise machinery for large scale photolithography and electronic components assembly (bonding). Then, they explain to the rest of the consortium members which their suggestions for the optical part of Brighter project are, including optical elements such as DOE (beam splitters), AOM (acoustic modulators) and AOD (optical deflectors). They will be interacting very much with GUF. MYCRONIC will be adding the laser technology in the scanner technology from GUF. Time signal is going to be a challenging point.

Basically, the system will read data in vector format and later rasterized using grey scale, to maintain the resolution (200 nm pixel size) while being able to adjust the precision for printing.

Mainly, Robert (application specialists, microlithography specialist) is the one that will be involved in Brighter project; Gustaf (physics and fluid mechanics) will do the supervision.

TECHNION (Ruby Shalom-Feuerstein): Brief description about his laboratory in Israel (Laboratory of Epithelial Stem Cells & Pathophysiology). They mainly work with corneal and skin stem cells, but also using induced pluripotent stem cells (IPSCs).
He also introduces part of his team which be involved on Brighter: Mrs. Anna Altshuler (PhD student) and Mrs. Aya Amitai-Lange (lab manager).
Ruby shares the idea of trying to model the niche of the stem cells with the light sheet microscopy.

12:30-14:00 Lunch

14:00 – 14:20 Overview of the research project.

Javier Selva (IBEC) makes a short overview of the research project, pointing out (or reminding) the:

- The general aim and specific objectives of the project.
- The work plan the project.
- The deliverables rearrangement during the acceptation process. Those appearing at the Document of Action (DoA), have changed with respect the initial project proposal submitted (they have increased). A deep overview of the deliverables of the first 6 months, and more slightly on the next deliverables (from M12 to M36).
- Before preparing them, it is very important to be sure about their nature (public or confidential). We must be aware of what we include and how we explain things (data protection?).
- It is very important that we refer to the achieved milestones within the deliverables.

- The WP leaders will be in charge of assembly the contributions of the different partners from their WP, to their corresponding tasks in one single document (deliverable) and send it to the project coordinator team (IBEC).
- Coordinators (IBEC) should have a complete version of the deliverables, at least, one month before their due date, in order to check them and prepare the final version to be uploaded into the participants portal.
- J.S. (IBEC) will provide all partners with the templates for that purpose.

14:20-15:00 WP1 - Development of the light-sheet bioprinter:

- **Planning for the next 6 months: task review, deliverables and experimental work plan.**

WP1 leader (GUF) describes the first tasks to be done within the first six months regarding the development of the Light-sheet bioprinter. First, GUF proposes two different light sheet (LS) configurations: 90º or inverted (will require V-shaped well plates). GUF has experience working on that inverted configuration and developed the protocols for customizing the bottom part of IBIDI culture plates (they buy bottom-less plates, create by thermo-conforming thin polymeric films the desired shapes and stick them to the culture plate with double-side adhesive).

GUF has experience using different types of polymeric films, but the ones working better are the ones that have the refractive index closer to the one of water (Ri=1.33), as for example LUMOX (Teflon®, Ri=1.34 and thickness of 12.5 – 25 – 50 – 125 µm) and GRILAMIDTR (Polyamide, Ri=1.54, not available as foils).

Their current LS microscope has the following characteristics:

- Lasers with 405, 488, 561 and 647 nm of wavelength. In Brighter we have two different possibilities regarding the light sources: a permanent illumination or a switching mode. This should be decided in the following months as function of the dose of energy that the polymers developed by Cellendes will require to properly photopolymerize.
- Piezo-based X-Y-Z stages with long travelling distances (able to completely move a 96-wells plate).
- Culture chamber with temperature and CO_2 control (as an incubator). They do not have humidity control.
- Light-sheet slices (working plane) ~2µm.

GUF, together with Mycronic, have identified a list of potential system requirements and provide some possible technical solutions. These requirements are the followings:

  - Dual left and right illumination/imaging
  - High NA/Large field of view /long working distance objective lenses
  - Multiple laser sources
  - The possibility to tune energy to change ligand
  - 3D geometric structure to create the hydrogel
  - Mask type
  - Light sheet forming
  - LSFM opto-mechanical arrangement
  - Cuvette
  - Double side illumination
    - Light sheet tiling
  - Imaging FOV
  - Time to scan/polymerize the volume

Questions and doubts.

Consortium needs to decide which type of LS configuration want.

Here appears a discussion about the scalability of the system. Brigitte Angres (Cellendes) asks about the size of the specimens we can achieve (1 cm^2) and

15:00-15:40 WP2 - Photopolymerizable hydrogels:

- **Planning for the next 6 months: task review, deliverables and experimental work plan.**

WP2 leader (Cellendes) describes two different material strategies they have planned to work in during the the project.

First strategy:

Gel system 1

Reversable gelation: Will act as sacrificial hydrogel. Its main function will be to maintain cells suspended within the gel avoiding precipitation.

Examples and comments:

- Polyoxamers (block co-polymers): react with temperature.
- N-isopropylacryamide (poly (NIPAAM)): not transparent at all but maybe at low concentrations.
- Dextran-PEG: click-chemistry (cyclooctyne-azide),
- Gelatine: temperature, proteases,

\+

Gel system 2

Light-triggered gel formation:
The hydrogel will polymerize upon illumination trapping the cells on it.

Examples and comments:

- Michael Addition reaction (pH 5.5-7.5) and Thiol-ene reaction (radical initiators –light-, as MMP, PEG, etc.).
- Narborene-functionalized PVA.
- Possible photoinitiators to be used: LAP, VA-086, Eosin-Y (need to be chosen and define the working concentrations –to be optimized-).
- Characterization: functionalization, biocompatibility, kinetics, stiffness, etc.

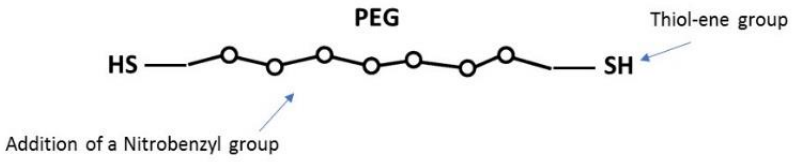
\+

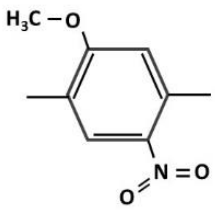
Cells suspension

Second strategy (in case the first one fails):

Use photodegradable polymers instead of photopolymerizable hydrogels. By using this strategy, we will start with a block of material (bulk) that will be shaped with the laser by degradation (opposite concept than the previous one).

In this approach a hydrogel and a crosslinker with the following groups will be required:





-

15:40-16:15 Coffee break

16:15-16:50 WP3 - Demonstration of light-sheet bioprinting:

- **Planning for the next 6 months: task review, deliverables and experimental work plan**

As the work related to WP3 does not started until M5, WP3 leader (IBEC) uses the most part of its time to explain to the other consortium members the expertise of the group regarding hydrogels, their preparation, the photopolymerization dynamics and how can them be microstructured using, mainly, two different approaches: (*i*) UV light with a 365 nm wavelength filter (to minimize cell damage) through a physical, patterned photomask (photolithography-based method), and (*ii*) visible light through a digital photomask by means of a customized 3D printing machine.

E.M. (IBEC) presents some results of its group regarding those hydrogels applied to the development of an in vitro model of the small intestine mucosa, including proper formation of an epithelial cell monolayer growing on top of the hydrogels and stromal cells embedded in.

16:50-17:30 WP4 - Engineered skin tissues:

- **Planning for the next 6 months: task review, deliverables and experimental work plan**

WP4 leader (Technion) makes a nice introduction about the different skin components: (*i*) epidermis (epithelial cells), (*ii*) dermis (sebaceous and sweat glands, hair follicles, dermal cells such as fibroblasts, immune cells, blood vessels, neurons and dermal papilla, collagen and elastin fibres, etc.), and (*iii*) hypodermis (vasculature); showing the complexity of putting all the elements together in one single model (it would be of great interest if the consortiums manages to mimic, at least, two or three skin components). Hair follicle and sebaceous gland are complex structures.

Ruby Shalom (Technion) pointed out that there are stem cells niches at every one of the skin components and that collagen IV and laminin fibres are present to the epithelial basement membrane to support the epithelial stem cells layer.

Cellendes points out that they have experience on adding peptides for Collagen I and IV (basal membrane proteins) to their polymers. This would be a possibility for our system to increase the cell interaction with the material, by achieving a proper ECM.

Questions and doubts.

Consortium needs to decide if we will use human or mouse cells. IBEC and Technion decide to start directly with human cells; Technion can provide IBEC with HaCaT cell line and also with foreskin cells, to start doing some tests with their current hydrogels and setups.

Vanesa Fernandez (IBEC) asks Ruby Shalom (Technion) about the culture time of the HaCaT cells (human cell line). Usually culture time of those cells is 3 weeks, as other epithelial cells; however, 2 weeks will be also OK. Technical aspects regarding cell markers, immunostaining protocols, etc. will be discussed in near future between IBEC and Technion.

Cellendes is afraid of the possible unreacted thiol-ene groups remaining on the hydrogel (may cause cell damage). These groups can be blocked in somehow (chemistry involved need to be checked).

Will be, then, regions with different crosslinking (polymerization) degree? This is a question that should be addressed when materials provided by Cellendes can be tested with the light-sheet setup.

Mycronic tells that the power of the lasers they currently use is about 600 mW. Power will be a concern that should be carefully stablished to determine the requirements and the final configuration of the light-sheet setup.

17:40 Closing Remarks from first day.

- Laser dose will be an issue with the current photo initiator. Is something to consider that we might be limiting.
- 3D distribution of the cell in the organoids will be challenging.
- Thiols from the hydrogels, could be toxic for the cell afterwards, work on that. Maybe we can vary the gels.

20:00 Dinner – El Com Restaurant

Friday 5th July

Day 2 Consortium Management

09:15-09:30 Welcoming Coffee

09:30-10:30 Work Package 5 - Project Management & Dissemination:

Javier Selva (IBEC) exposes to the other members of the consortium some managerial questions regarding:

- The three main documents the consortium must follow: DoA, C.A and G.A.
- The rights and obligations regarding: keeping information; Informing the Commission and coordinator; Submission of deliverables; Reporting; Protection, exploitation and dissemination of results; information on EU funding and the consortium agreement contents.
- The information regarding amendment procedures.
- reporting periods: There are 2 reporting periods in Brighter project
  RP1: from M1 to M12
  RP2: from M13 to M36

The reports should be uploaded to the participants portal by the coordinator (IBEC) up to 60 days after the end of each reporting period.

- Financial periods: It is very important that in those documents all the members include all the deviations of the plan. Moreover, is compulsory to perform an external audit to obtain a 'certificate on the financial statements' if the beneficiary requests a total contribution of 325.000 € or more.

-Payment process: with the pre-financing at the beginning of the project, the interim payment after approved intermediate reporting and the payment of balance at the end of the project. The concept of the 5% of the Guarantee Fund has also been introduced.

- continuous reporting: there is an opened space in the participants portal to upload all the info
  - Deliverables
  - Publications, communication activities, IPRs, etc.
  - Gender balance modifications, SME, impact, etc.

Javier Selva (IBEC) will send to all the consortium members, in the management presentation a link to a web page where there is the embargo period of each journal (http://sherpa.ac.uk/romeo/index.php). We must be aware of that when uploading publications on the portal.

It is also very important to include ALWAYS on the Acknowledge section the name and grant agreement of the project.

- Meetings calendar: all the consortium members agree with the following calendar.

Month	Location, Hosting institution
M6	Germany (GUT, Frankfurt)
M14	Brussels (EU commission, scientific review)
M18	Sweden (Mycronic)
M24	Israel (Technion) (meeting + PhD students workshop)
M30	Germany (Cellendes)
M37	Brussels (EU commission, scientific review)

All the partners agree that intermediate meetings within WP members and WP leaders will be necessary to discuss technical aspects. We are free arrange the meetings when necessary. Javier Selva (IBEC) insists on the importance of preparing the agenda and minutes of all meetings (even informal ones) to keep recording.

10:30-11:30 Work Package 6 – Dissemination, Exploitation and Communication

- Disseminaiton:
Even previously mentioned, Javier Selva (IBEC) reinforces the importance of gather evidences (include ALWAYS on the project logo, name, grant agreement and the Webpage address of the project.

Due to the IPR protection (under consideration) it is very important to communicate every action to be taken in advance regarding dissemination to the rest of the consortium members to avoid misunderstandings and infringe confidentiality.

It is very important, from the dissemination point of view, to advertise the project and the related activities to the different social networks (Twitter, LinkedIn, etc.).

Keep in mind that when attending to conferences, even invited, we need evidences to be able to pay the expenses with the budget of the project. We must ask for a poster, short talk, etc. In case of attending to fairs (Mycronic and Cellendes), it would be necessary to take picture of the stand with visible Brighter advertising.

- Exploitation:
Xavier Rubies (from tech transfer department at IBEC) joints the meeting and exposes at which point the negotiations between the different consortium members are regarding the Agreement document. It seems that there are some discrepancies between Technion and GUF regarding liability. They are close to the agreement.

There is a short discussion between Gustaf (Mycronic) and Xavier Rubies (IBEC) regarding the licencing rights from Brighter project. Mycronic wants to have all the rights (equipment and optical system). Others, like materials, can be patented separately if considered. The idea can be patentable, we must decide the time to patent and to who can be this IPR licensed after the project.

Questions and doubts.

Cellendes asks some questions regarding which expenses can be assumed by the project budget (attending to conferences, meetings, fairs, etc.)

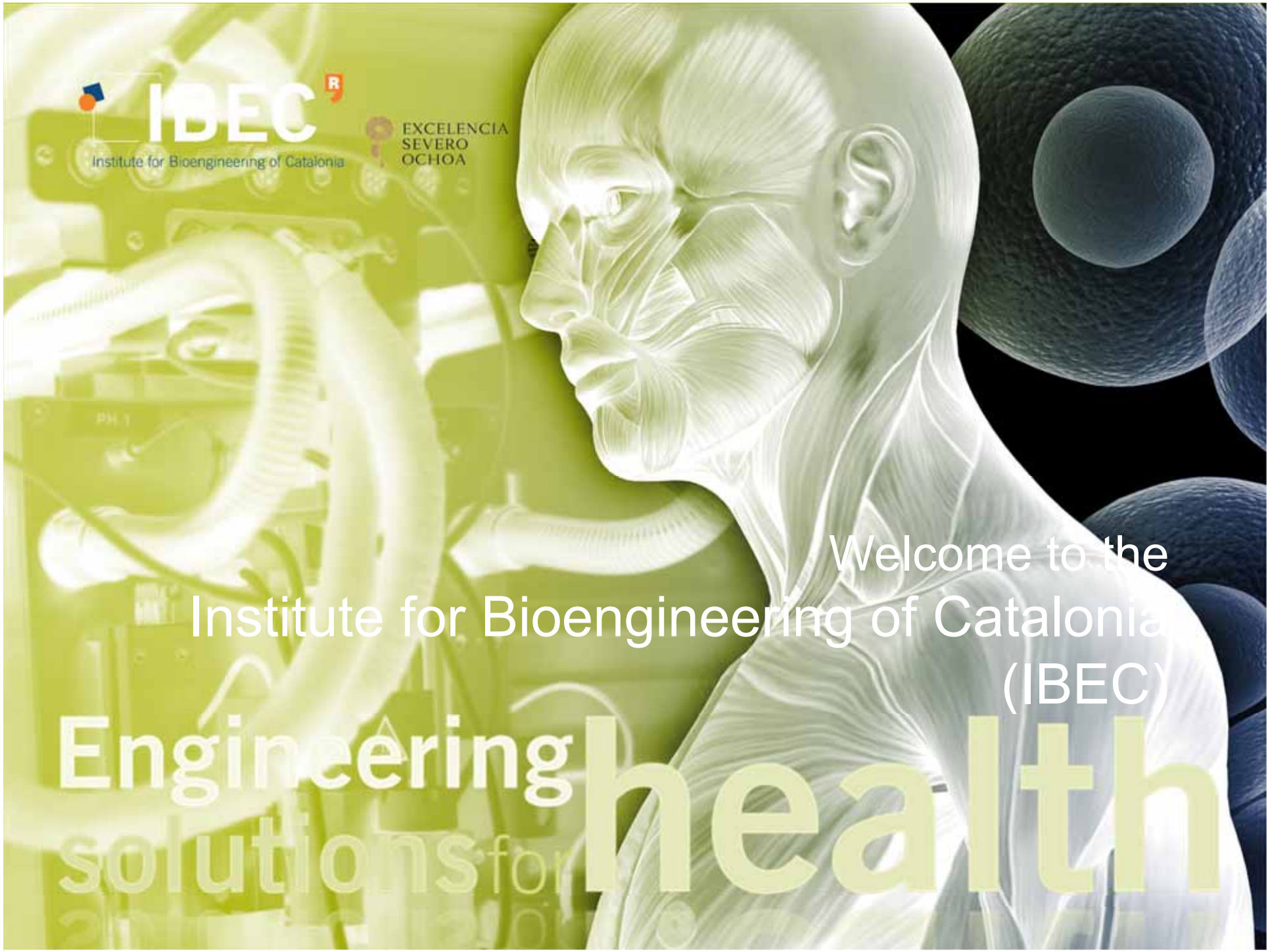
11:30 – 13:00 Visit IBEC laboratories (optional).

13:00-14:00 Lunch

14:00- 14:10 Group Picture

From left to right: R.S.F (Technion), H.W. (Cellendes), G.M. (Mycronic). E.M. (IBEC), F.P. (GUF), B.A. (Cellendes), J.C. (IBEC). N.T. (IBEC). R.E. (Mycronic). V.F. (IBEC) and G.N. (Cellendes).

14:10-15:00 AOB and Closing Remarks.


IBEC
Institute for Bioengineering of Catalonia
EXCELENCIA
SEVERO
OCHOA
Welcome to the
Institute for Bioengineering of Catalonia
(IBEC)
Engineering
solutions for
health

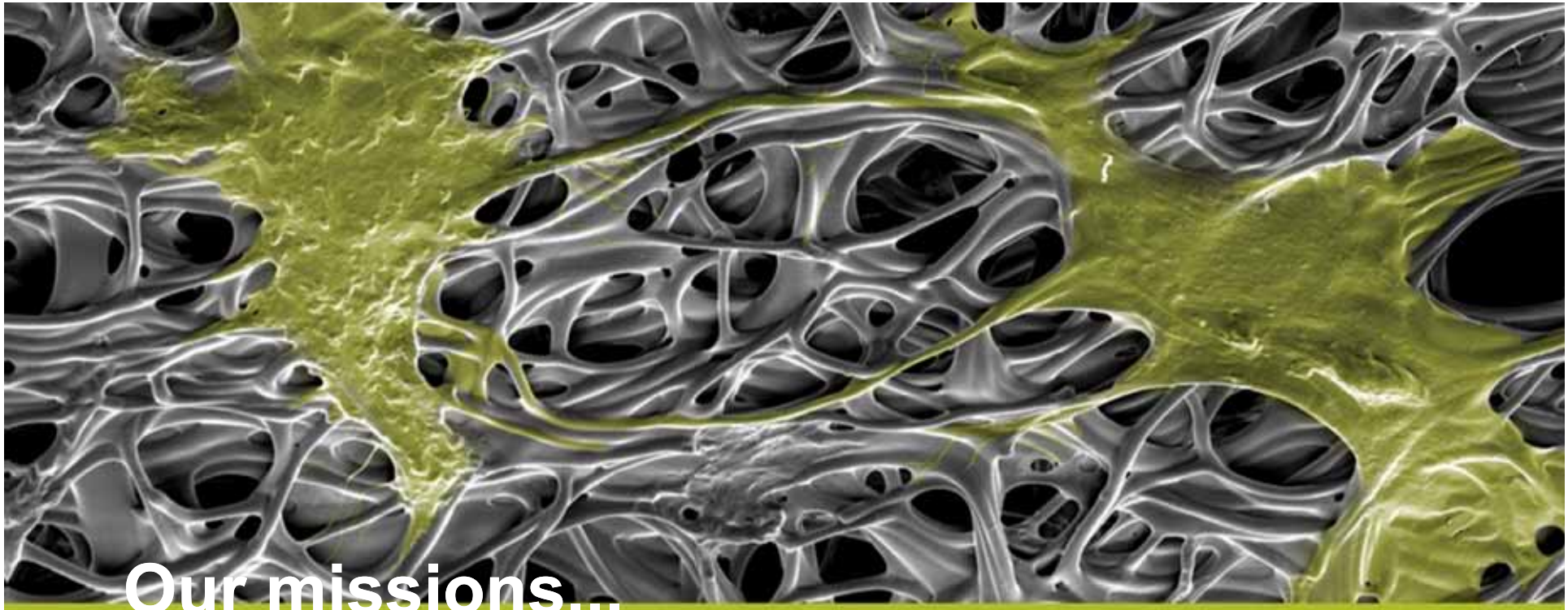
IBEC
Institute for Bioengineering of Catalonia
EXCELENCIA SEVERO OCHOA

Who are we?

The Institute for Bioengineering of Catalonia (IBEC) is a **multidisciplinary research centre** in **bioengineering** and **nanomedicine**

Where we are?

- In black: current locations
- In white: new locations



Our missions...

Basic and interdisciplinary research in bioengineering and nanomedicine

Knowledge and technology transfer to the biomedical sector

Collaborations with international academia, hospitals and industry

Training the next generation of experts in healthcare technology

Improving health and quality of life

A brief history of how IBEC was born

2002 2003 2004 2005 2006

2002-2003
Biomedical Engineering Research Center (CREB)

CREB Centre de Recerca en Enginyeria Biomèdica
UNIVERSITAT POLITÈCNICA DE CATALUNYA

Bioelectronics & Nanomedicine Center (CBEN)

cben

2003-2005
Reference Center for Bioengineering of Catalonia (CREBEC)

CREBEC
CENTRE DE REFERÈNCIA EN BIOENGINYERIA DE CATALUNYA

2006
IBEC is born

UNIVERSITAT DE BARCELONA

UNIVERSITAT POLITÈCNICA DE CATALUNYA BARCELONATECH

Generalitat de Catalunya
Departament de Salut

Generalitat de Catalunya
Departament d'Innovació, Universitats i Empresa

Who are we?

7 ICREA

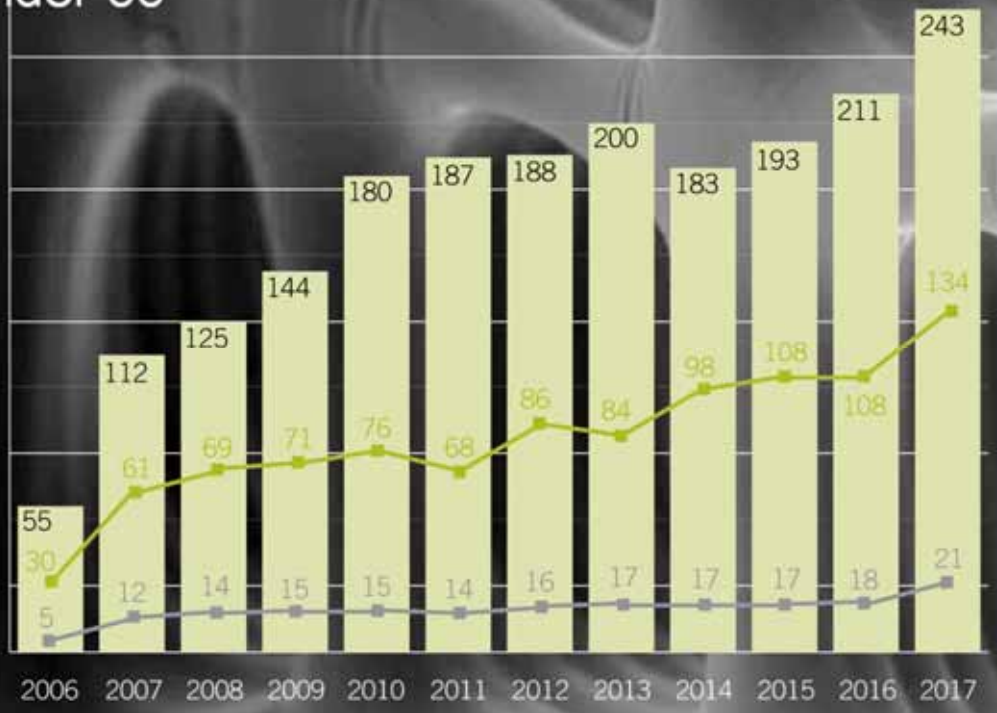
We're MANY!
341 personnel in 2019

We're INTERNATIONAL!
28 countries represented in 2019

We're YOUNG!
59% of personnel in 2017 were under 35

We're BALANCED!
51% of personnel in 2017 were women

14 erc
European Research Council
Established by the European Commission



74%
of IBEC's indexed journal papers in 2017 were in the first quartile

IBEC's staff from 2007 to 2016 came from 38 countries

Canada
Czech Republic
Iraq
Morocco
Russia
South Africa
Switzerland
Ukraine
Australia
Greece
Iran
Philippines
South Korea

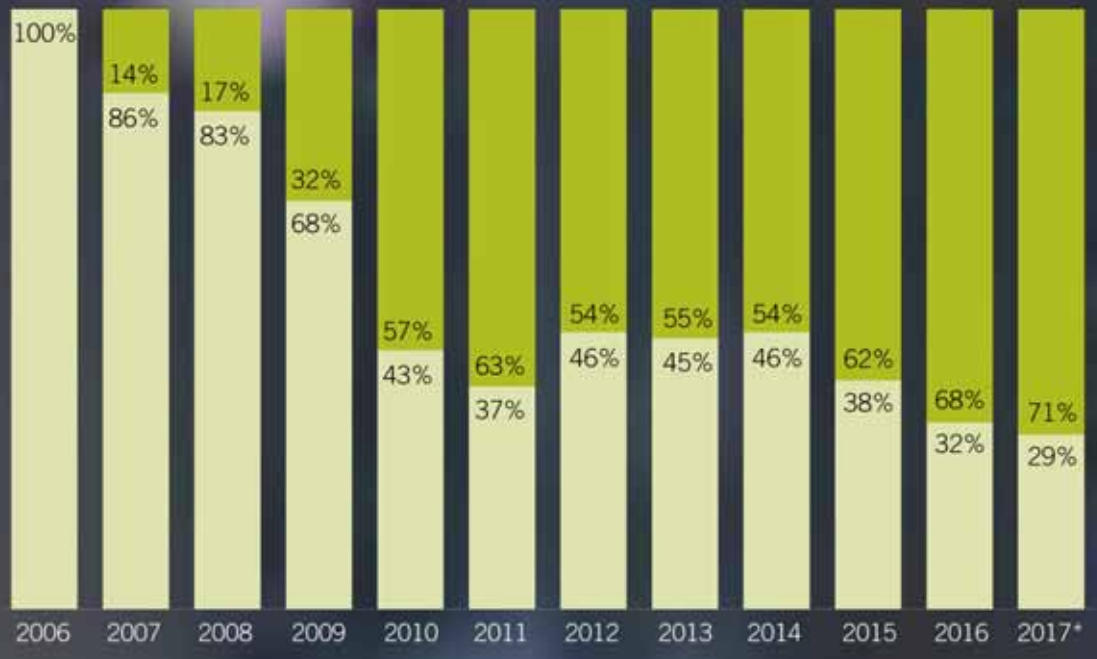
Netherlands
Austria
China
Panama
Uruguay
Ecuador
Brazil
Sweden
USA
Poland
India
Venezuela

Argentina
Chile
Turkey
UK
Bulgaria
Cuba
Colombia
Germany
Portugal
Mexico
France
Italy
Spain

We have MoUs with organisations all over the world

And **107** IBEC researchers have spent research stays in labs throughout the world

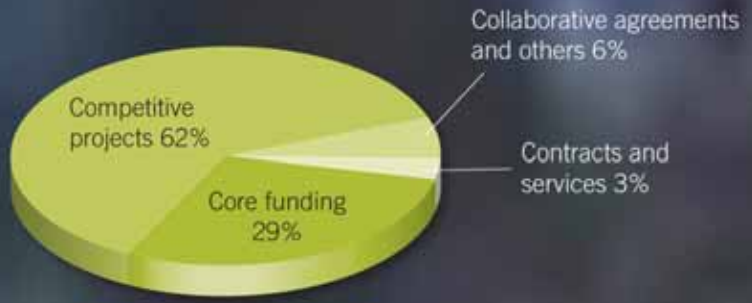
How are we funded?



Graph: Percentage of funding from core v. competitive sources. Core funding is funding from trustees. Soft funding includes competitive projects (funded by sources such as the EU's H2020 programme, the Spanish Ministry of Science or the Catalan Ministry of Research), Industry contracts, funding from private institutions.

Pie chart: Different sources of funding in 2017, broken down into types.

** Figures for 2017 are provisional, pending audit*



Our supporters

Our founders…

Generalitat de Catalunya

UNIVERSITAT DE BARCELONA

UNIVERSITAT POLITÈCNICA DE CATALUNYA

Our local supporters…

Obra Social "la Caixa"

Fundació Privada CELLEX

ICREA

Fibrosi Quística

FCRI Fundació Catalana per a la Recerca i la Innovació

CERCA

FECYT Fundación Española para la Ciencia y la Tecnología

Fundació Catalunya La Pedrera

Gobierno de España – Ministerio de Economía y Competitividad

Excelencia Severo Ochoa

Fundación Botín

ACCIÓ Generalitat de Catalunya

ciber isciii

Parc Científic de Barcelona – Universitat de Barcelona

FPdGi Fundació Fundación Princesa de Girona

biocat

La Marató TV3

And further afield…

erc

elt Health

AXA Research Fund – Through Research, Protection

Horizon 2020

Seventh Framework Programme

NIH

Unió Europea – Fons europeu de desenvolupament regional – Una manera de fer Europa

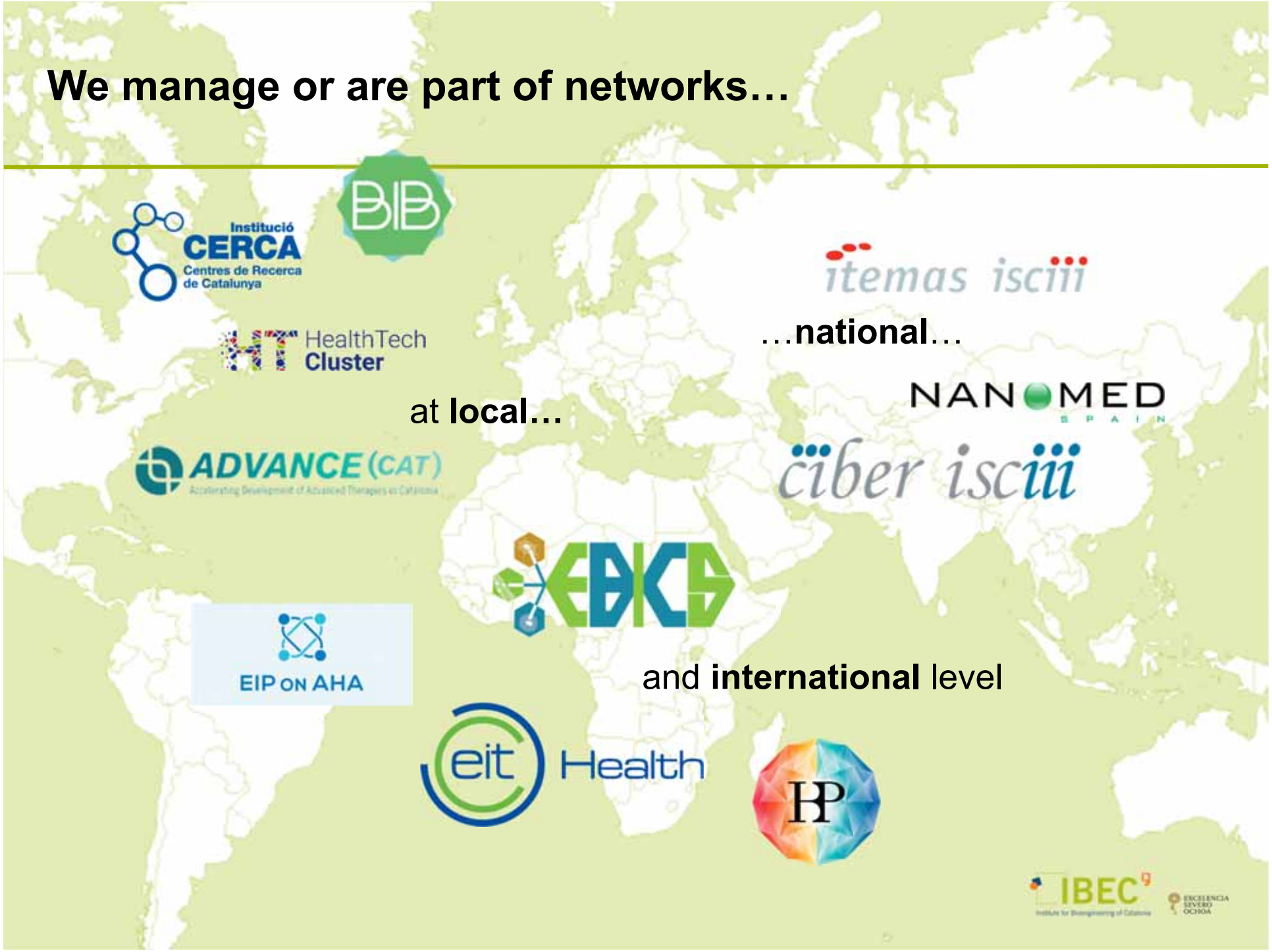
fondazione cariplo

HFSP Human Frontier Science Program

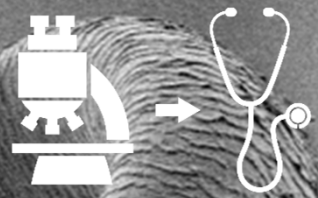
EMBO excellence in life sciences

EF Clif – European Foundation for the Study of Chronic Liver Failure

We manage or are part of networks…



Clinical and translational collaborations



- VHIR-IBEC alliance on infectious diseases
- VHIR-IBEC alliance on 3D in vitro model of the human intestine
- Fetal surgery and research into prenatal diseases with the Cellex Foundation and the ”la Caixa” Banking Foundation
- Kidney and iPS collaborations with Hospital Clinic
- Working with Bellvitge on CJD…

...and many more examples

Bellvitge Hospital Universitari

Vall d'Hebron Institut de Recerca

Radboudumc

BCNATAL

Fundació Privada CELLEX

fetal iD

CLÍNIC BARCELONA Hospital Universitari

Sant Joan de Déu Hospital Materninfantil Universitat de Barcelona

Clínica CEMTRO

Technology transfer

2009: 3 patents
2010: 5 patents
2011: 1 patent
2012: 3 patents
2013: 3 patents
2014: 3 patents
2015: 1 patent
2016: 4 patents
2017: 2 patents

Post-surgery ischemia control system

Novel wound healing angiogenic particles

3D Bioprinting research with companies

Microfluidics in point of care diagnostics

Clean tech nanorobots

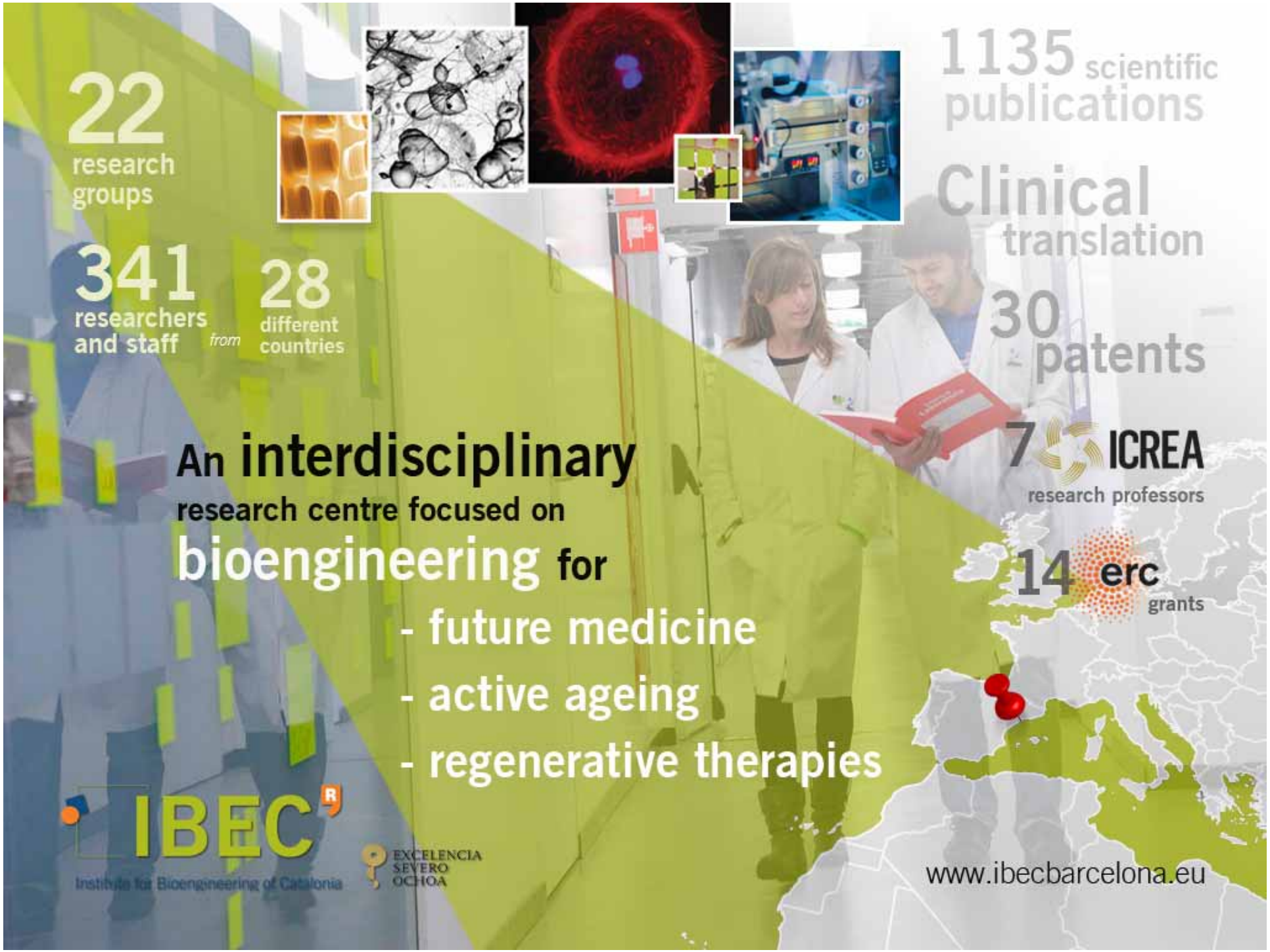
New strategies against bacterial biofilm formation

New pancreatic cancer molecules

Contract research with local and international companies

IBEC

High-impact papers


22
research groups
341
researchers and staff
from
28
different countries
1135 scientific publications
Clinical translation
30 patents
7 ICREA
research professors
14 erc grants
An interdisciplinary
research centre focused on
bioengineering for
- future medicine
- active ageing
- regenerative therapies
IBEC
Institute for Bioengineering of Catalonia
EXCELENCIA SEVERO OCHOA
www.ibecbarcelona.eu

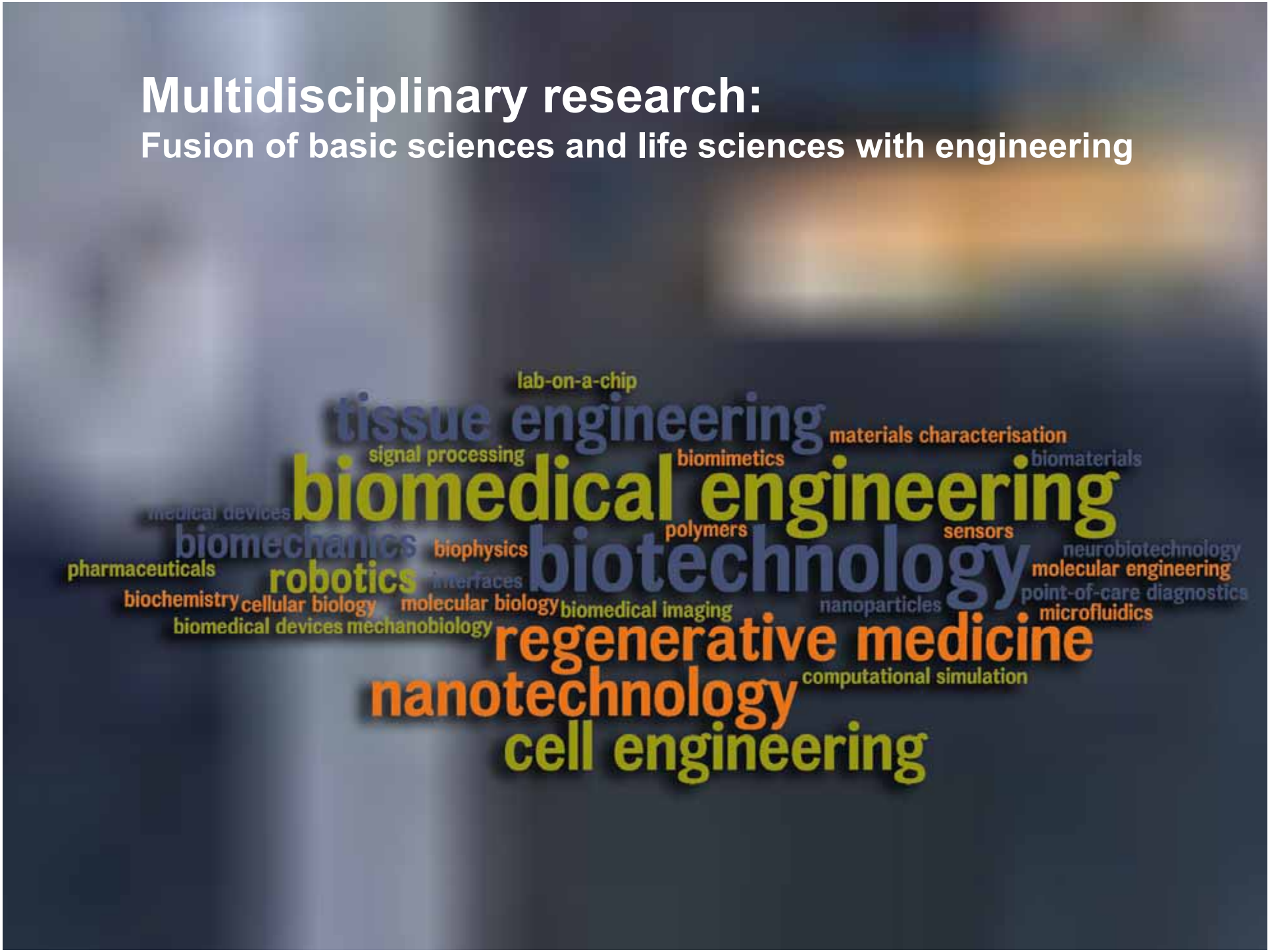
EXCELENCIA
SEVERO
OCHOA

Allocated by an international panel of more than 70 judges, MINECO's Severo Ochoa Excellence Awards identify and promote research centres in Spain that stand out as international references in their specialized fields.

Of the 19 other awarded organisations in the country, IBEC is the third youngest centre to receive it.

Multidisciplinary research:

Fusion of basic sciences and life sciences with engineering

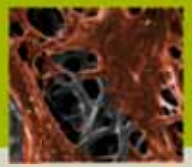


…plus
5 Associated Researchers, university professors seconded to IBEC who are working on topics that are of interest or complementary to our research areas

IBEC: Engineering Solutions for Health

Bioengineering for Active Ageing

- Telehealth
- Telecare
- Non-invasive sensing systems
- Age-related disease
- Antibiotic resistance
- Neuroengineering



Bioengineering for Regenerative Therapies

- 3D bioprinting
- Stem cell engineering
- Intelligent scaffolds
- Cell/tissue interactions with biomaterials
- Cell niches

Bioengineering for Future Medicine

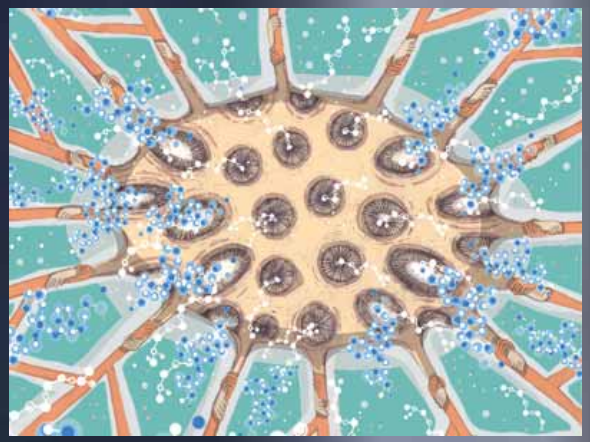
- Precision medicine
- Cross-disciplinary technologies
- Photopharmacology
- Organ on chip
- Mechanobiology
- Nanorobotics
- Nano drug delivery

Selected research highlights...

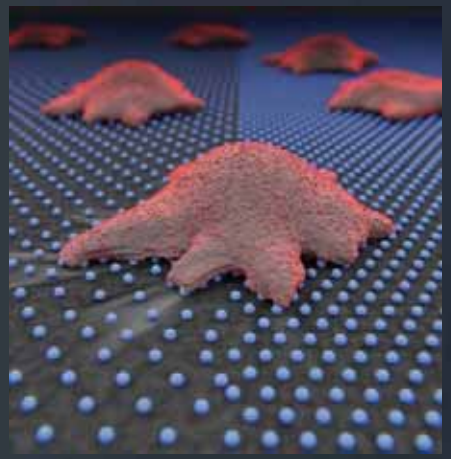
Cell mechanobiology

Mechanical forces affect the links and conformation of a network of molecules connecting cells to the extracellular matrix.

We unravel the mechanisms that these molecules use to detect and respond to mechanical stimuli like forces or tissue rigidity, triggering downstream cell responses. Ultimately, we want to understand how forces determine development when things go right, and tumor formation when they go wrong.



Cartoon depicting how force transmission to the nucleus affects nuclear pores, leading to nuclear protein import (from Elosegui-Artola et al. 2017, *Cell*).



Artistic rendering of a cell attaching to a substrate coated with a gold nano-pattern array, used to study how cells detect spatial cues (From Oria et al. 2017, *Nature*).

@ibecbarcelona

@IBECBarcelona

www.ibecbarcelona.eu

Generalitat de Catalunya

UNIVERSITAT DE BARCELONA

UNIVERSITAT POLITÈCNICA DE CATALUNYA

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Goethe University Frankfurt, BMLS (GUF)
PI Francesco Pampaloni

Kick off meeting
4th July 2019

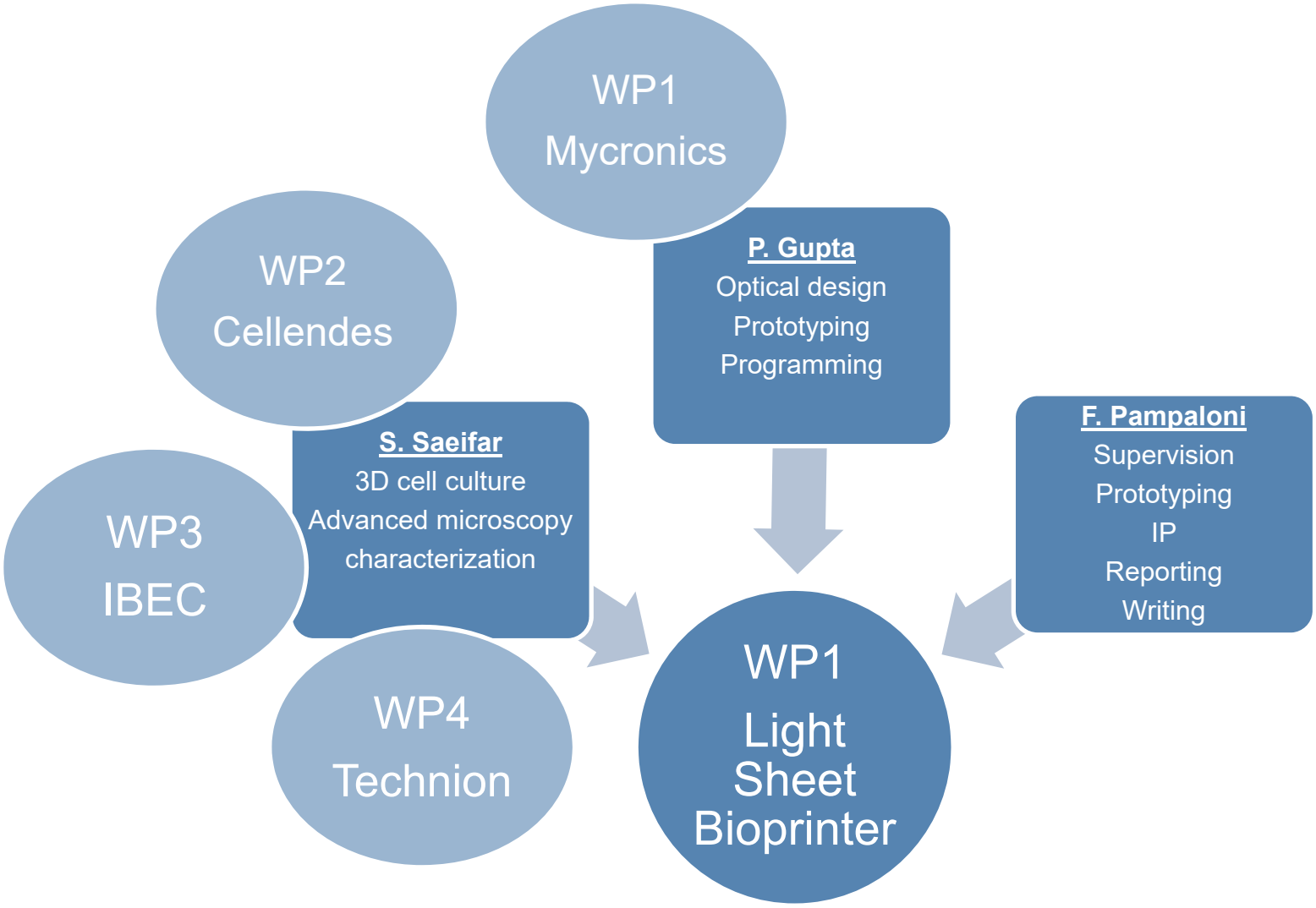
GUF – Goethe University Frankfurt, Campus Riedberg

GUF – Goethe University Frankfurt, BMLS

Team members BRIGHTER

- Prateek Gupta, Optical Engineer,
  Karlsruhe Institute of Technology (KIT)

- Sanam Saeifar, MSc Biologist,
  Goethe University Frankfurt


WP1
Mycronics
WP2
Cellendes
WP3
IBEC
WP4
Technion
P. Gupta
Optical design
Prototyping
Programming
S. Saeifar
3D cell culture
Advanced microscopy
characterization
F. Pampaloni
Supervision
Prototyping
IP
Reporting
Writing
WP1
Light
Sheet
Bioprinter

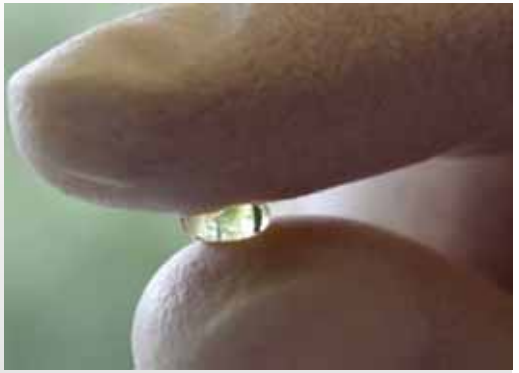
Cellendes GmbH:

Designing the Environment of Cells

Helmut Wurst
BRIGHTER Kickoff Meeting
Barcelona, July 4, 2019

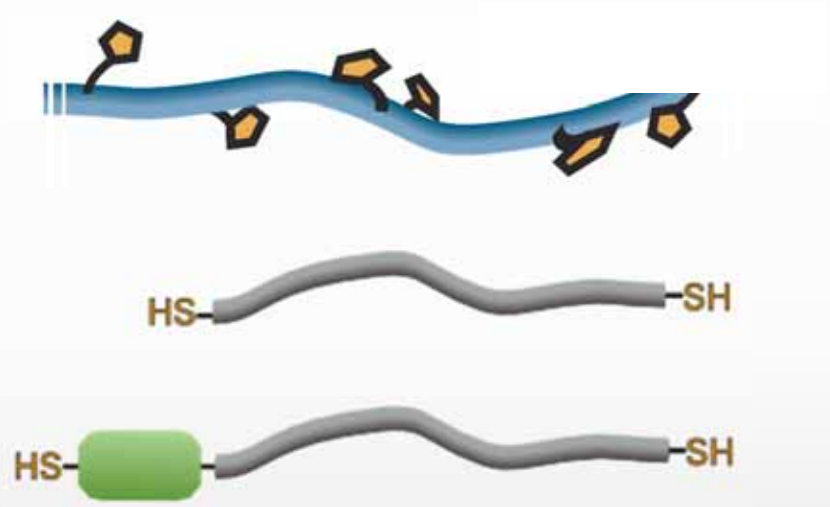
Cellendes GmbH

- Founded in 2009
- Located in Reutlingen, Germany
- 3 FTE
- Reagents for 3-D cell cultures
- Development of 3-D test systems
- *3-D Life* catalog product line
- Distribution partners

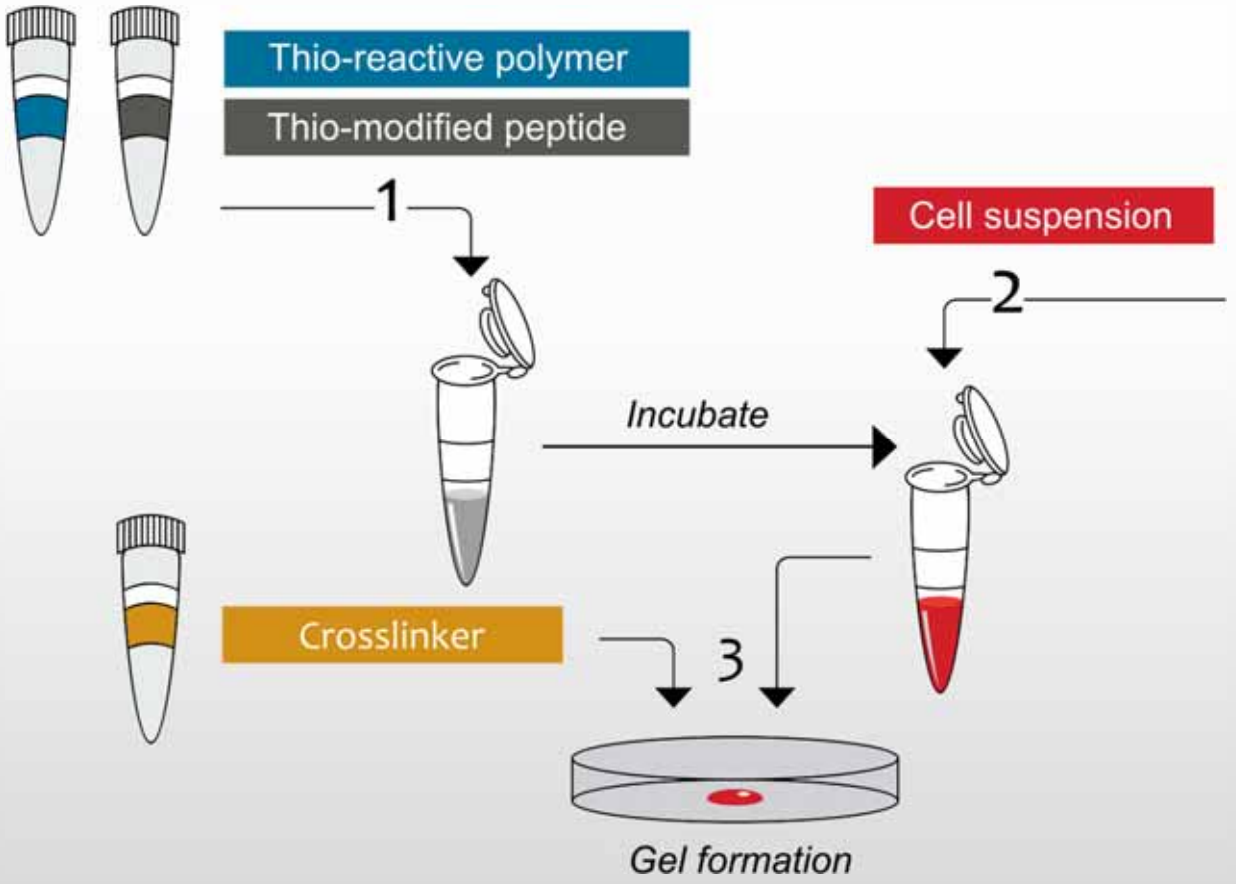


The Hydrogel System

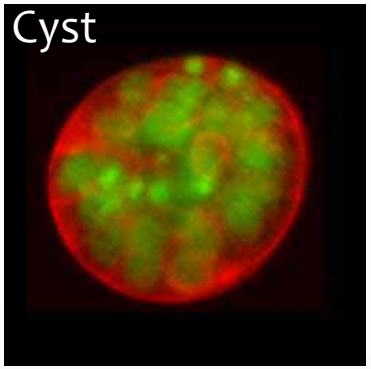
- Two-component system
  - Thio-reactive polymers:
    - PVA, Dextran, Albumin
  - Thiol-functionalized crosslinkers:
    - PEG, hyaluronic acid, MMP-cleavable
- Peptide-mediated cell adhesion
- Control of gel stiffness
- Cell-compatible crosslinking
- Chemically defined reagents
- User-controlled degradation

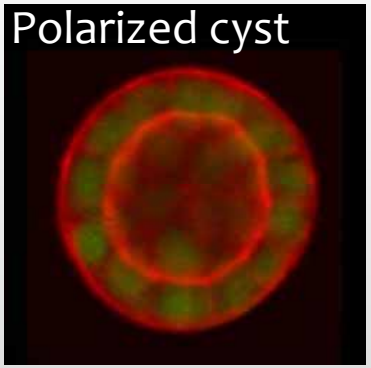


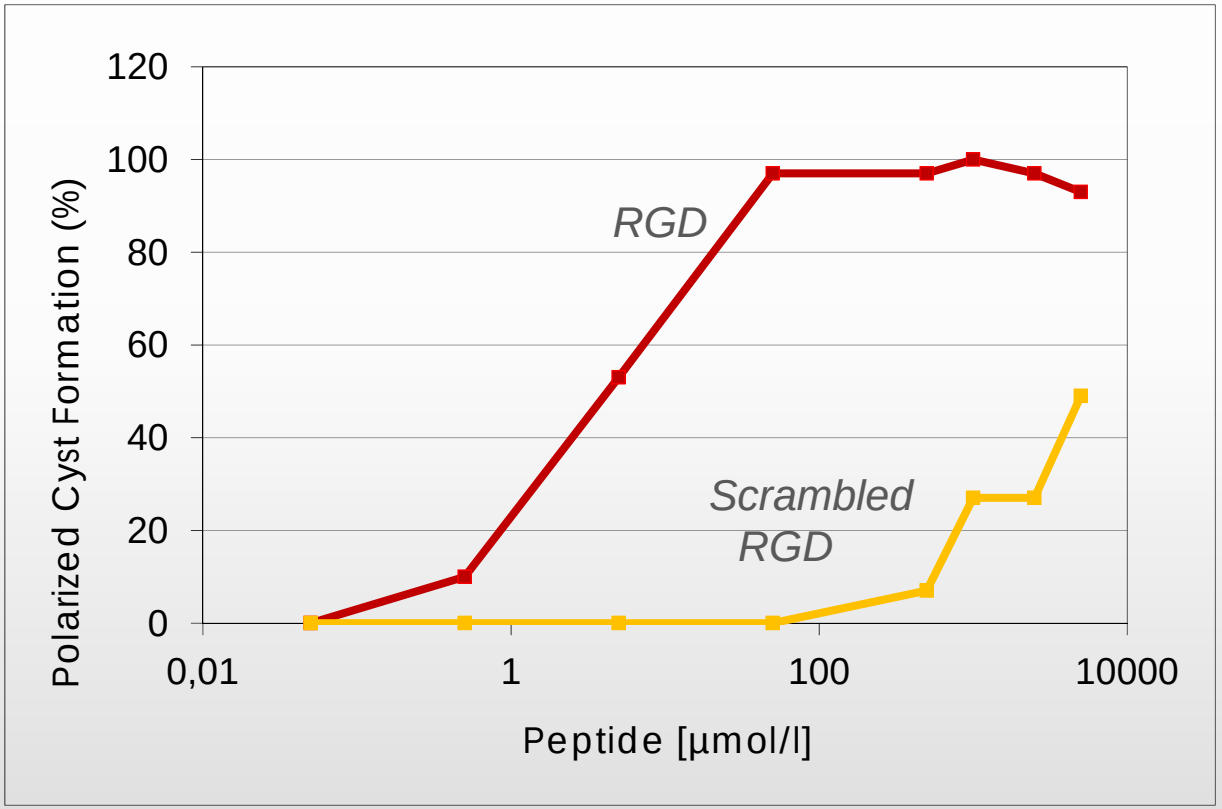
Setup of Hydrogels



Polarization of Epithelial Cells





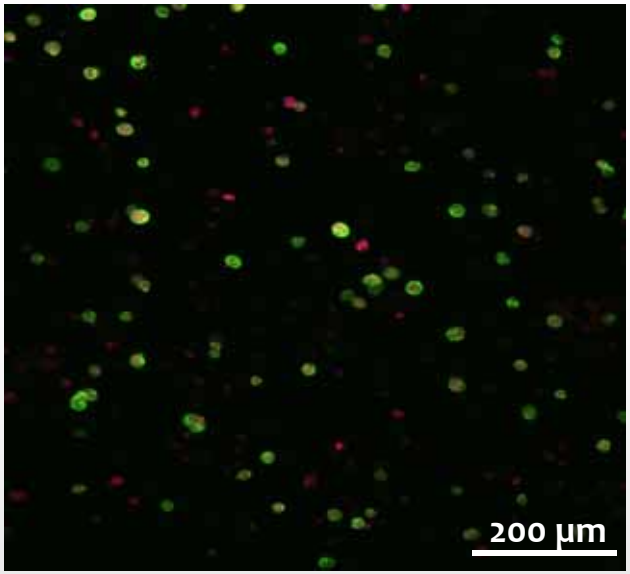


Cultivation time: 15 days
Gel composition: PVA-PEG hydrogel
Red: filamentous actin (phalloidin)
Green: nuclei

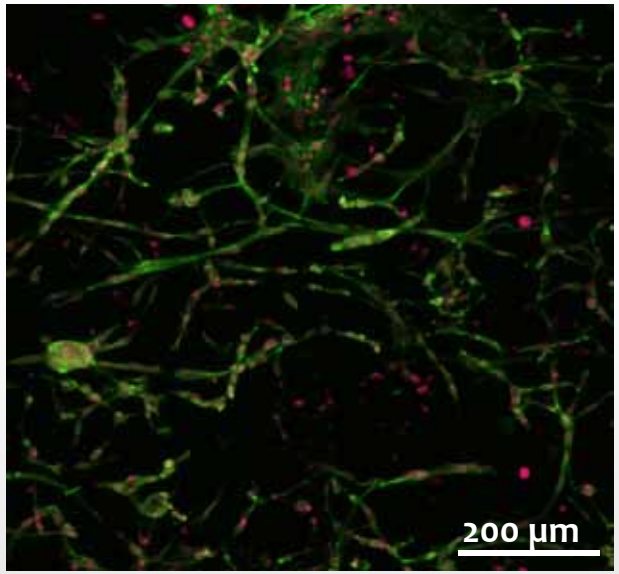
Spreading of Fibroblasts

CELLENDES
Cell • Environment • Design

Without MMP-sensitive sites

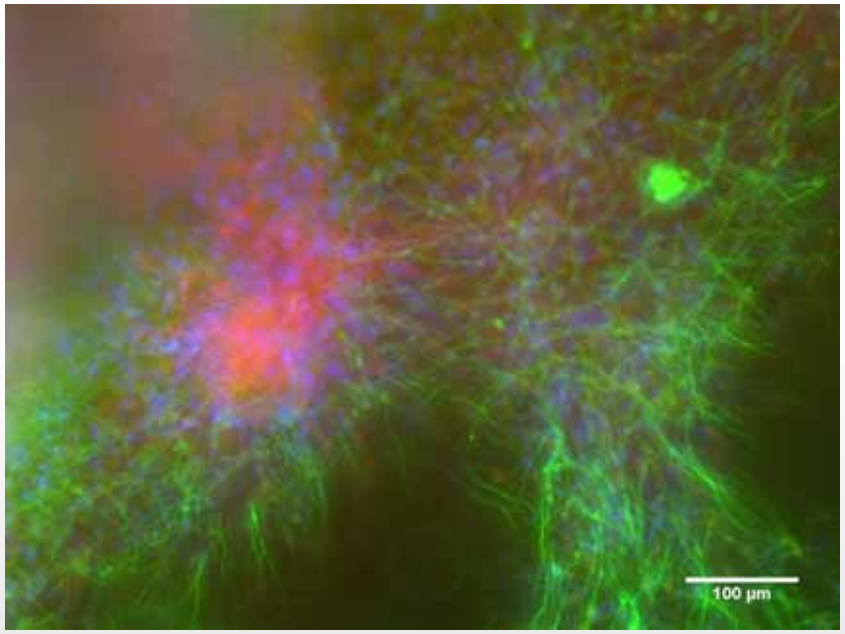


With MMP-sensitive sites



Cultivation time: 5 days
Gel composition: RGD-functionalized Dextran hydrogel
Green: actin
Red: nuclei

Neurosphere outgrowth and cell differentiation

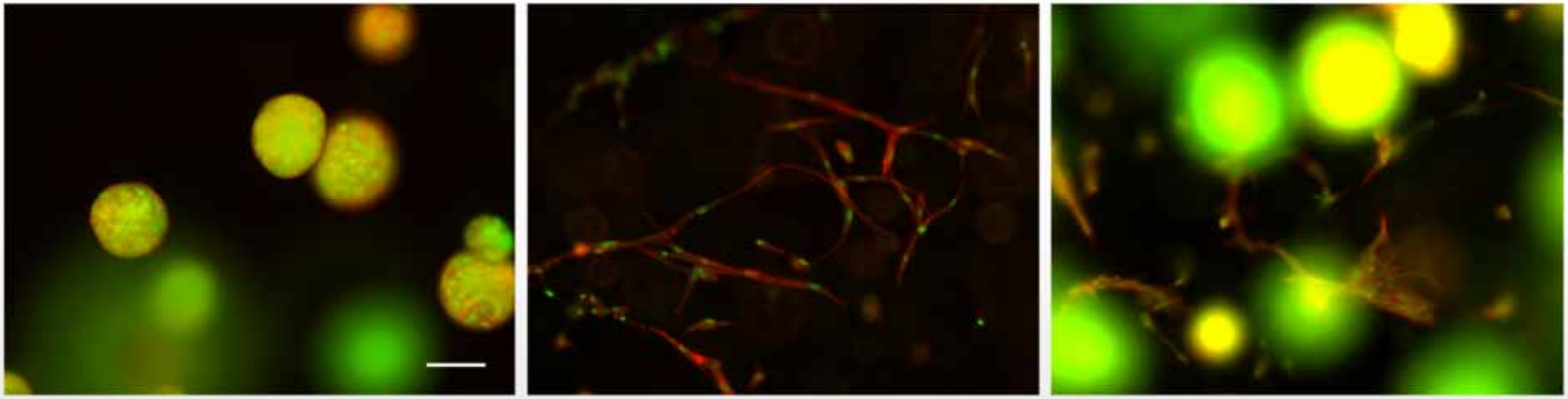


Cultivation time: 25 days
Gel composition: PVA-CD hydrogel with IKVAV peptide,
Red: filamentous actin (phalloidin)
Green: ß(III) tubulin (immunostaining)
Blue: nuclei (Hoechst)

Data courtesy of E. Fritsche, J. Baumann and C. Hellwig, Heinrich-Heine-Universität Düsseldorf, Germany

Tumor-Stroma Model

MCF-7 | Fibroblasts | MCF-7 and Fibroblasts



Cultivation time: 14 days
Gel composition: Dextran-CD Hydrogel with RGD Peptide
Actin: red
Nuclei: green
Size bar: 100 µm

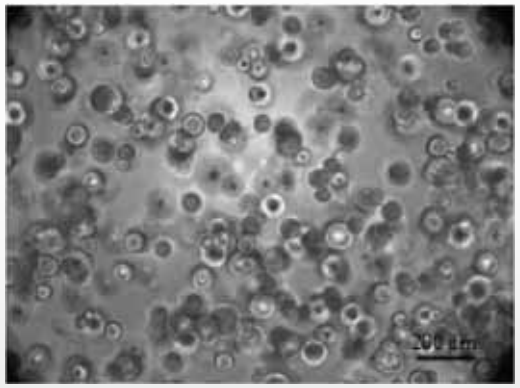
Automation of 3-D Life Hydrogel cultures

CELLENDES
Cell • Environment • Design

Culture set-up

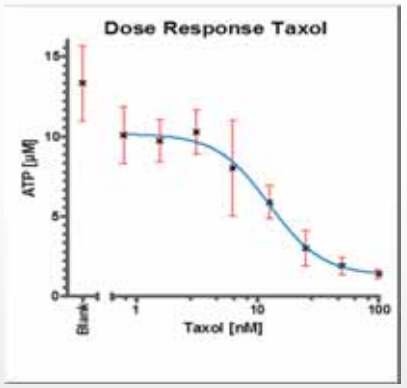
Automated pipetting of hydrogel reagents and cells

Growth of tumor spheroids, day 8



Automated medium changes, drug addition

Drug response and screening



Automated gel dissolution, cell lysis, viability analysis

In collaboration with Tecan Schweiz AG and Zurich University of Applied Sciences.
J Lab Autom. 2014 Apr;19(2):191-7.

Cell Types cultivated so far…

CELLENDES
Cell • Environment • Design

Cell lines

- Epithelial: MDCK (kidney epithelial cells), T47D, MCF 7, MCF 10A (normal and tumor breast epithelial cells)
- Fibroblasts (3T3)
- Carcinoma cells (HCT-116, A549)
- Endothelial cells (EA.hy926)

Primary cells

- Mesenchymal stem cells
- T-lymphocytes
- Chondrocytes
- Human dermal fibroblasts
- HUVEC
- Embryonal heart muscle cells
- Neuronal progenitor cells
- Organoids (pancreatic, liver)

Thank you very much !

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Mycronic AB
Gustaf Mårtensson
Robert Eklund

MYCRONIC

When passion meets innovation

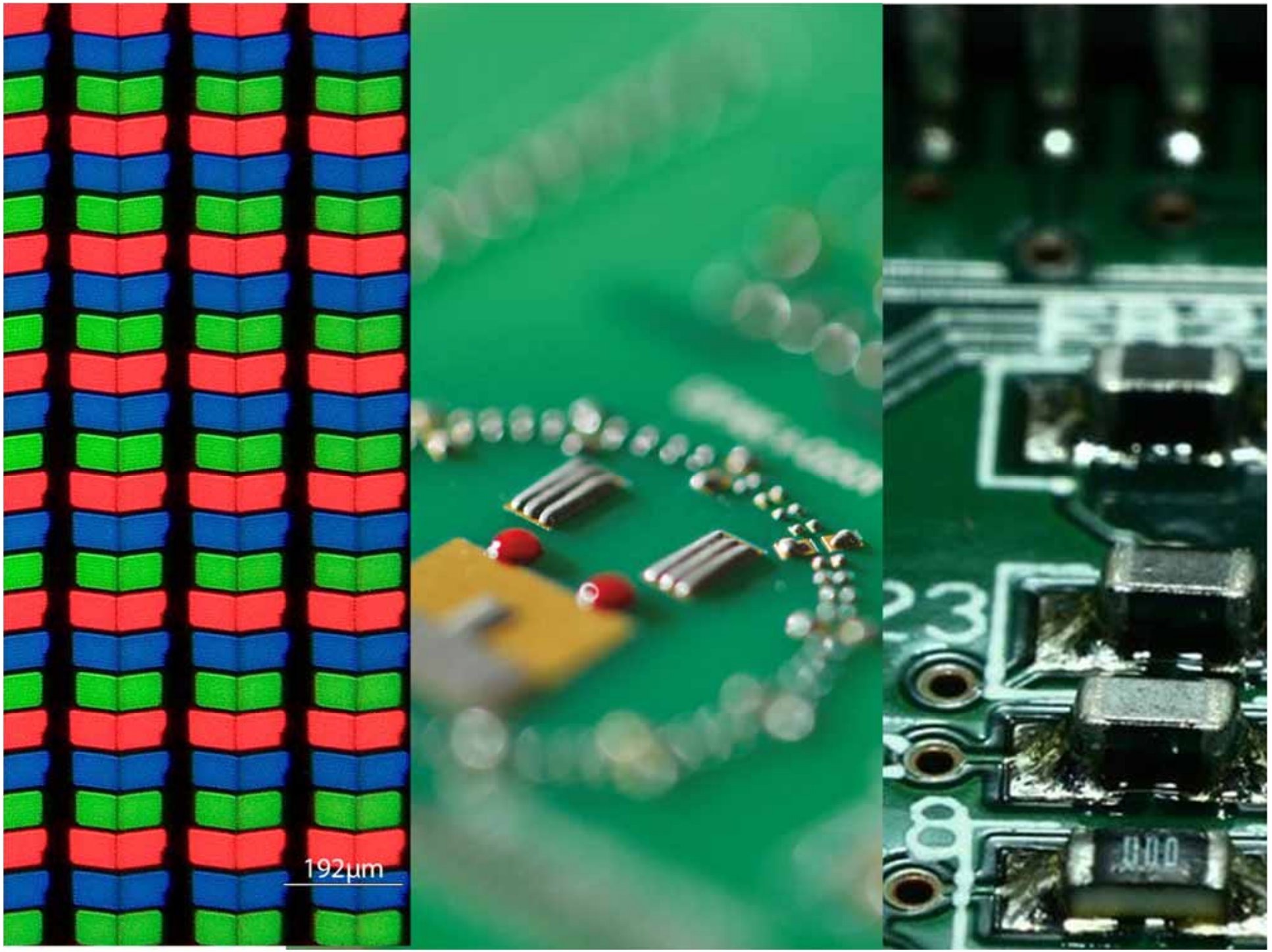
Kick off meeting
4th July 2019

Mycronic representatives

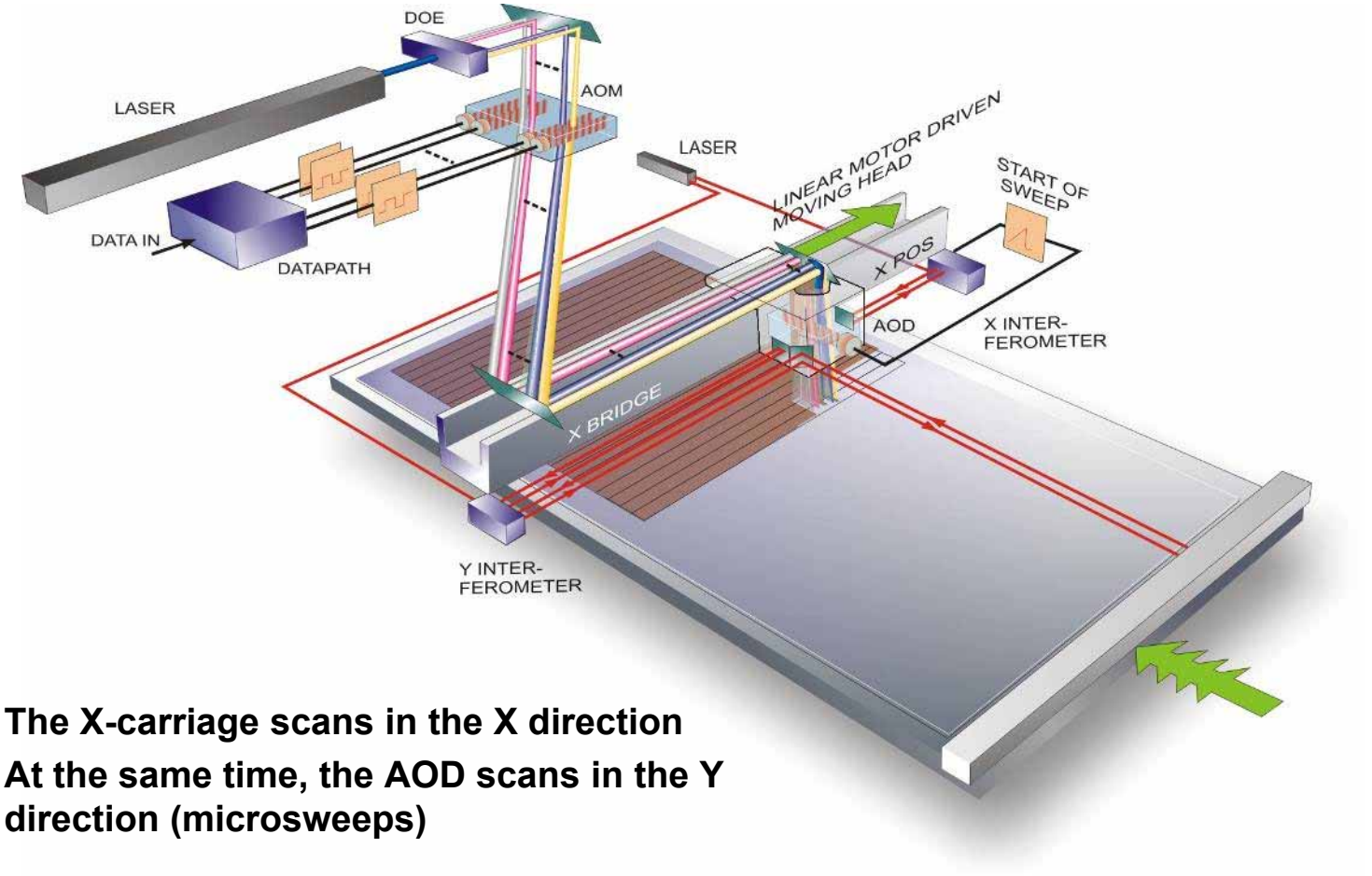
- Gustaf Mårtensson, Mycronic responsible and coordinator

- Robert Eklund, Application specialist

MYCRONIC
When passion meets innovation


192µm

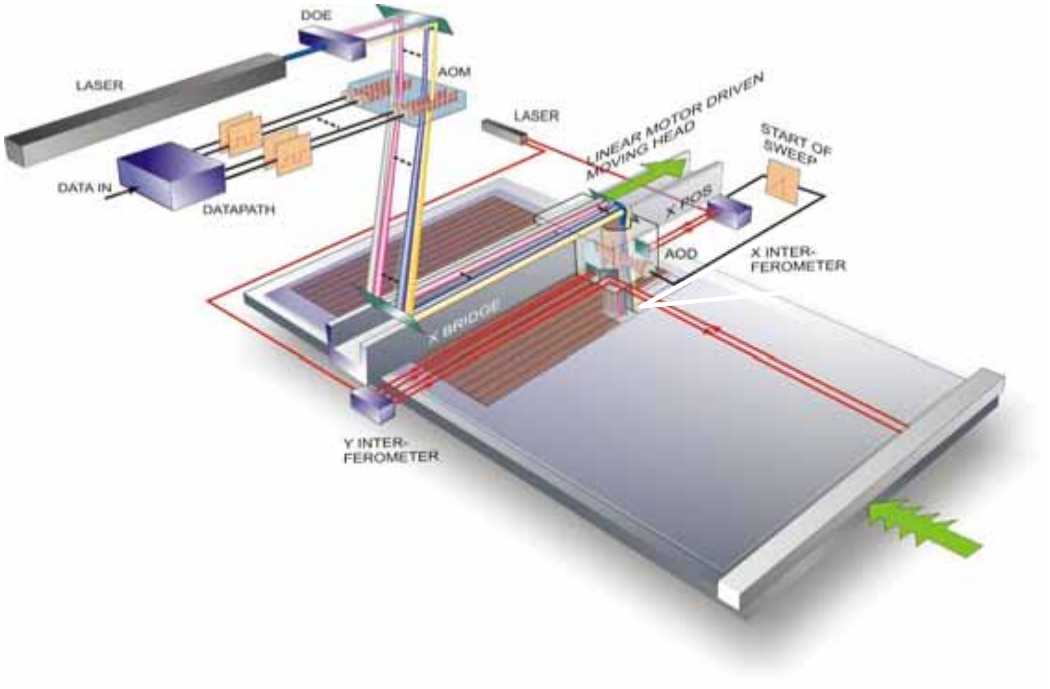
Principle of operation – 1/2

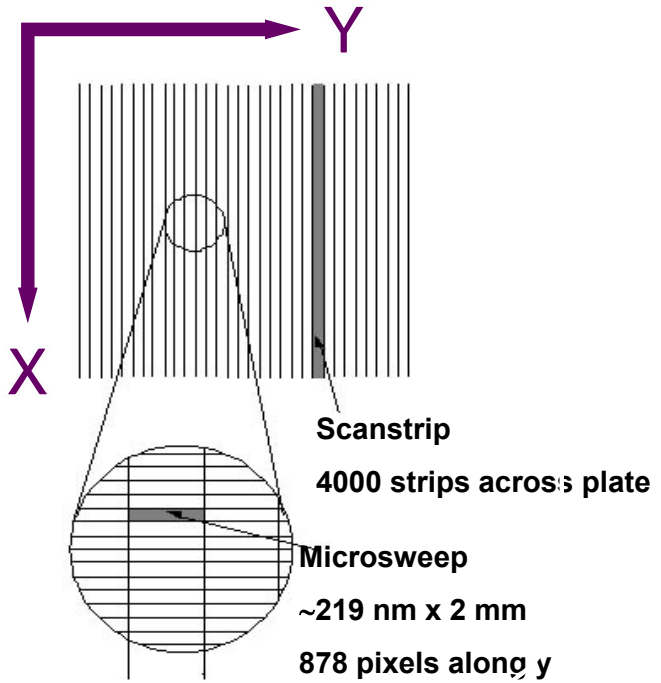


- **The X-carriage scans in the X direction**
- **At the same time, the AOD scans in the Y direction (microsweeps)**

Principle of operation – 2/2

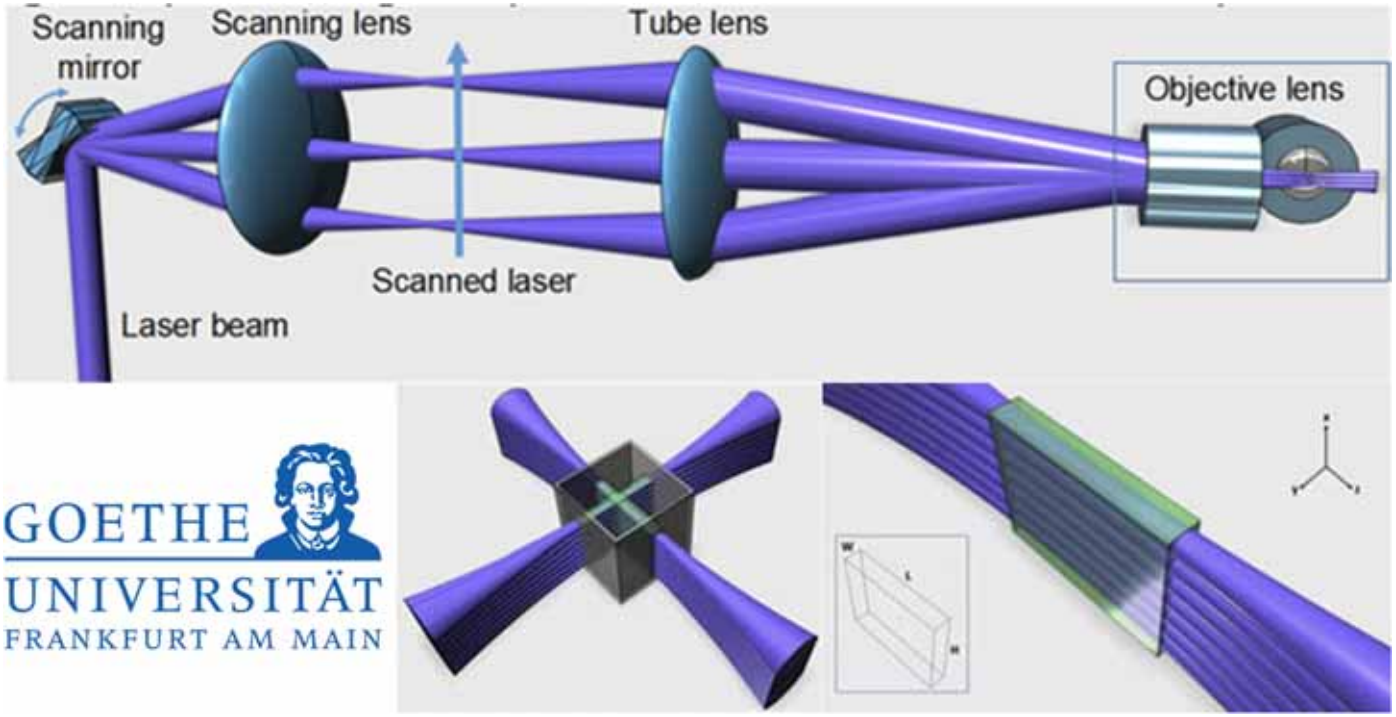
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY





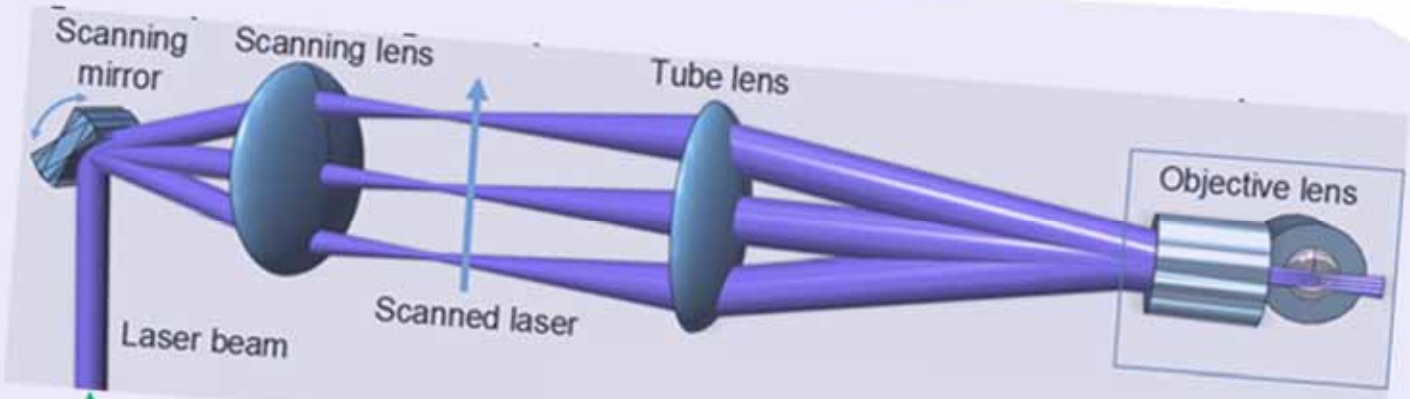
- The exposure is made by writing several micro sweeps in one scan strip.
- During the X-carriage return stroke, the Y-stage moves one step length (scan strip width)
- 30 pixel overlap between strips in y direction to reduce stitching effects

Where do we fit in?



MYCRONIC
When passion meets innovation

GU



T1.3. Coupling light-sheet with a pattern generator (UMYCRONICU, GUF).

T3.3. Production of 3D structures by light-sheet illumination (UMYCRONICU, GUF, IBEC).

MY

MYCRONIC
When passion meets innovation

BRIGHTER

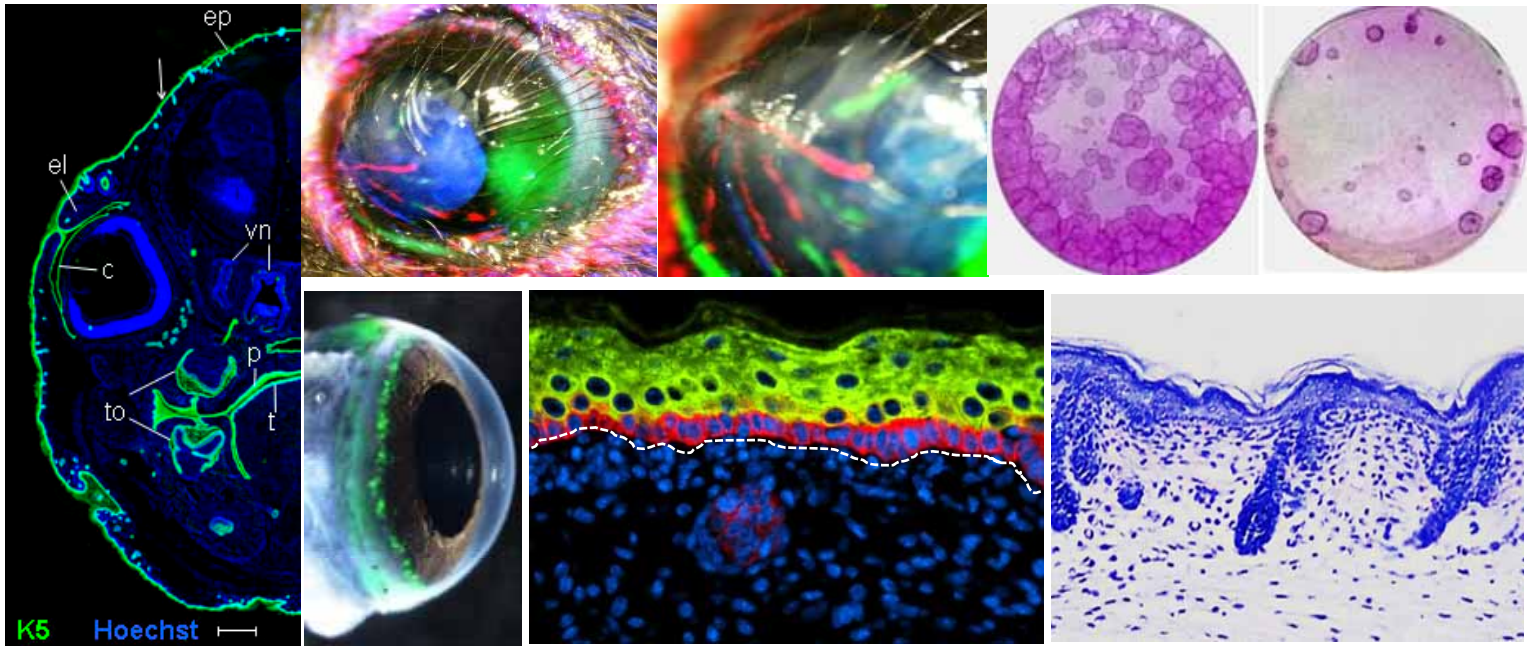
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Partner Name:
Ruby Shalom-Feuerstein

Kick off meeting
4th July 2019

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Lab of Epithelial Stem Cells & Pathophysiology



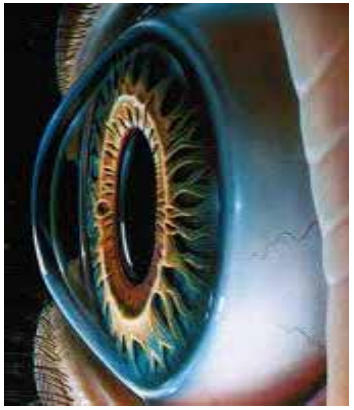
Ruby Shalom-Feuerstein, Associate Professor

Technion
Israel Institute of
Technology

Technion - Israel Institute of Technology
The Ruth and Bruce Rappaport Faculty of Medicine

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Corneal SCs

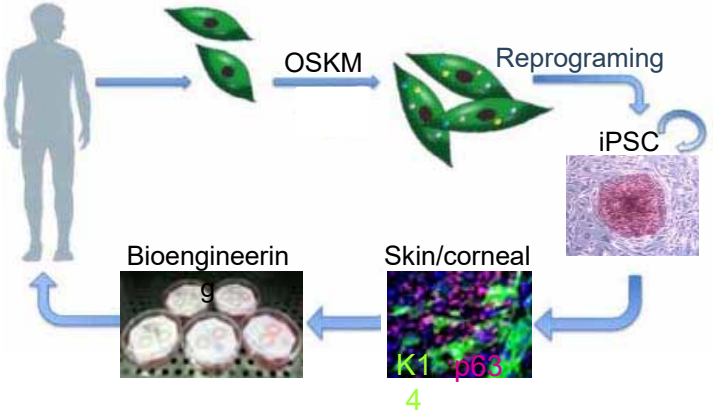


- ✓ **Identification of SC location**
  Amitai-Lange et al, Stem Cells 2015
- ✓ **Recovery of entire SC pool & boundary by committed cells**
  Nasser et al, Cell reports 2018
- ✓ **SC regulation by SOX2**
  Bhattacharya et al, Stem Cells 2019

Skin SCs

- ✓ **Differentiation switch by miR-184**
  Nagosa et al, Stem Cell Reports, 2017

Pluripotent SCs



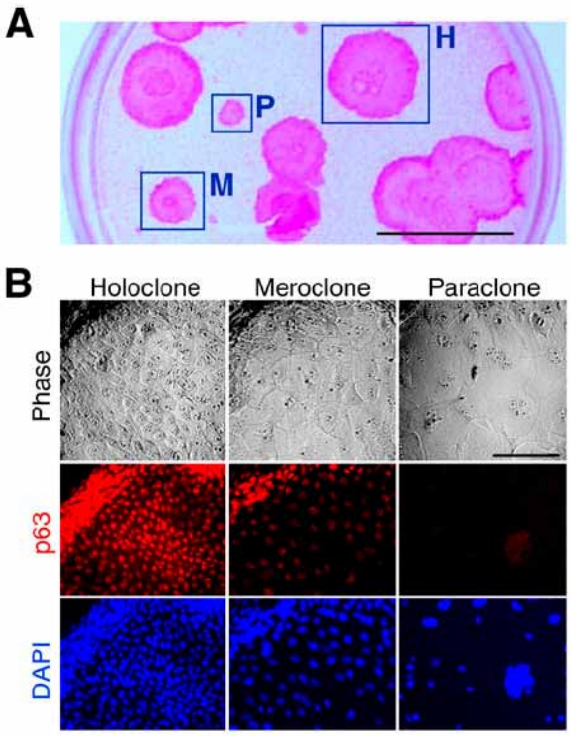
- ✓ **Pluripotent SC priming to differentiation by RAS oncogenes**
  Altshuler et al, Stem Cell Reports, 2018

Technion
Israel Institute of Technology

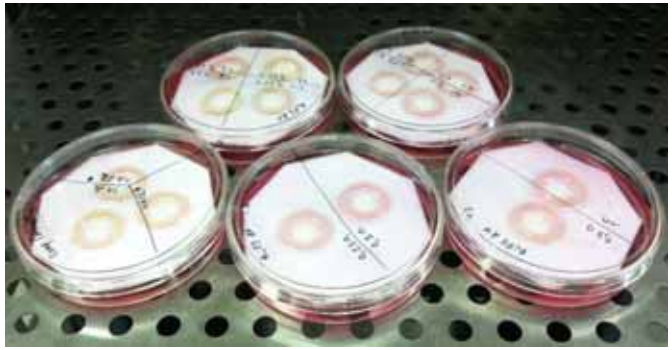
Technion - Israel Institute of Technology
The Ruth and Bruce Rappaport Faculty of Medicine

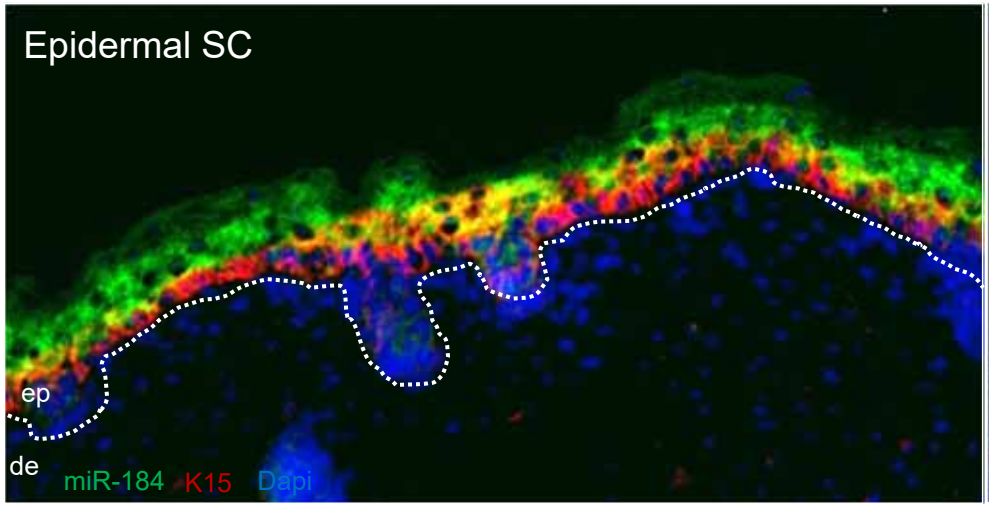
Genetic mouse models

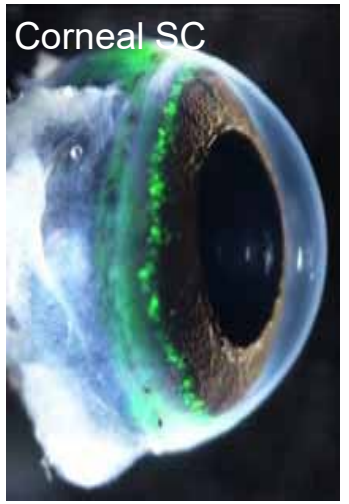
Skin/cornea SC culture, iPS

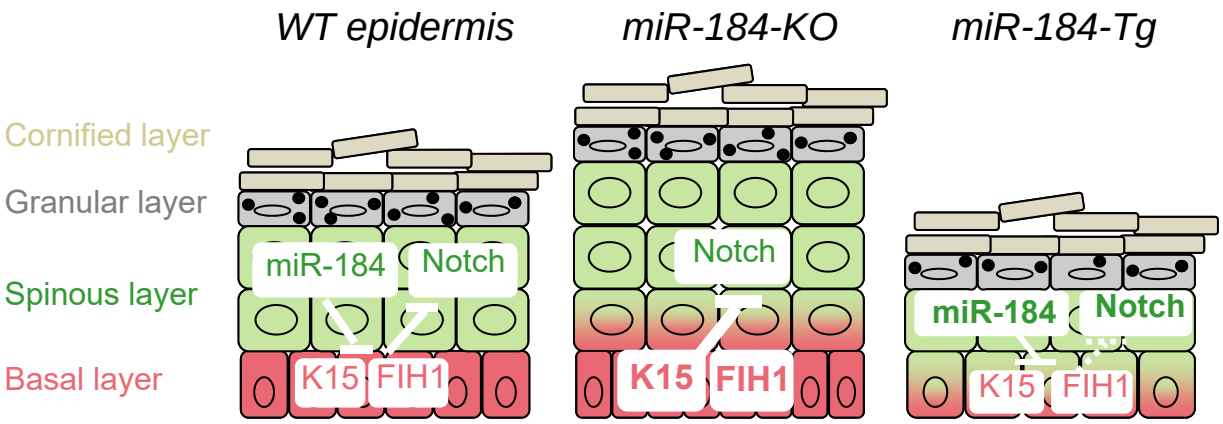


Organotypic culture









Technion
Israel Institute of Technology

Technion - Israel Institute of Technology
The Ruth and Bruce Rappaport Faculty of Medicine

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

This project has received funding from the European Union's Horizon 2020 Research & Innovation Programme Under Grant Agreement No. 828931

European Commission

ISRAEL SCIENCE FOUNDATION

משרד המדע, הטכנולוגיה והחלל
Ministry of Science, Technology & Space

RAPPAPORT INSTITUTE
The Rappaport Family Institute for Research in the Medical Sciences

BRIGHTER

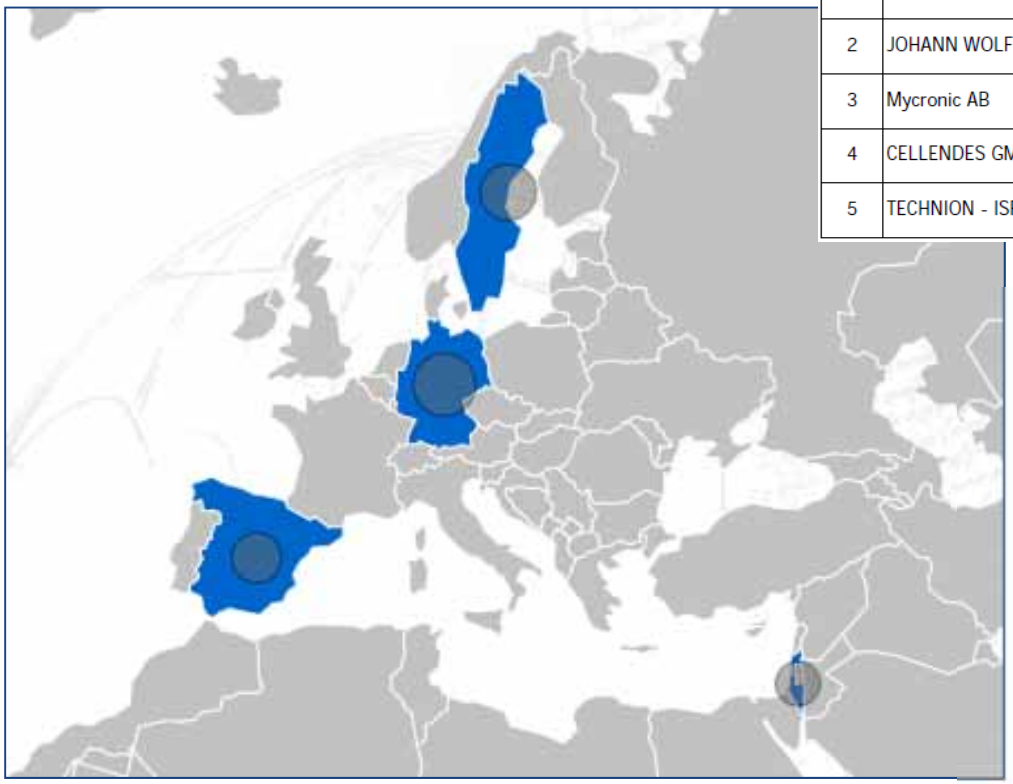
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Objectives and WP

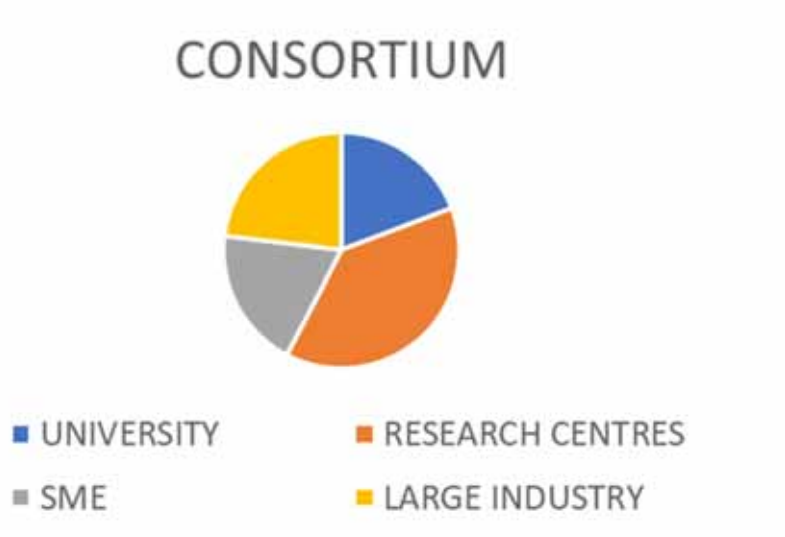
Kick off meeting

4th July 2019

Consortium



#	Participant Legal Name	Country
1	FUNDACIO INSTITUT DE BIOENGINYERIA DE CATALUNYA	ES
2	JOHANN WOLFGANG GOETHE-UNIVERSITATFRANKFURT AM MAIN	DE
3	Mycronic AB	Sweden
4	CELLENDES GMBH	DE
5	TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY	Israel



"The consortium is well balanced with one large Partner, a high-tech SME as a new actor in the FET Programe and three academic partners."

Objectives

General Aim:

- To develop a **bioprinting technology able to produce 3D complex tissue structures at unprecedented high speed and spatial resolution**.

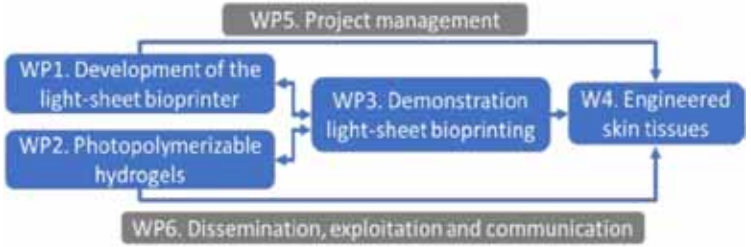
Specific objectives:

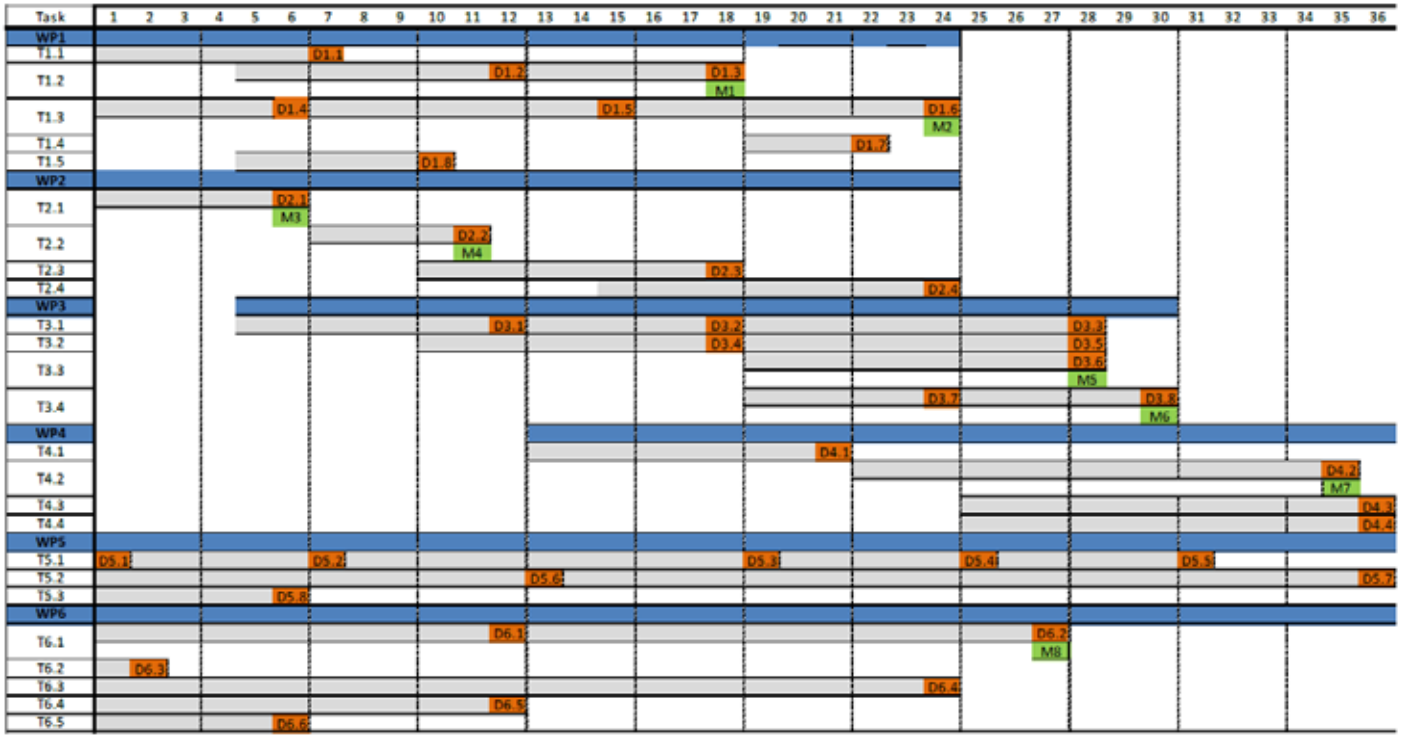
- Development of the high-resolution, high-speed bioprinting system.
- Building 3D complex structures in cell-laden hydrogels.
- Proof-of-concept: engineering complex skin tissue models.

Work Plan

WP		Task	1		2		3	
1	Development of the light-sheet bioprinter	T1.1. Generation of the light-sheet						
		T1.2. Development of a system including two light-sheet illumination sources						
		T1.3. Coupling light-sheet with a pattern generator						
		T1.4. Development of the imaging system.						
		T1.5. Development of the bioprinting chamber						
2	Photopolymerizable hydrogels	T2.1. Fabrication and characterization of photopolymerizable polymers						
		T2.2. Polymer functionalization and biocompatibility evaluation						
		T2.3. Development of reversibly crosslinkable hydrogels						
		T2.4. Formation and characterization of IPNs including reversibly crosslinkable polymers						
3	Demonstration of light-sheet bioprinting	T3.1. Calibration of the crosslinking density and stiffness of hydrogels						
		T3.2. Cell viability on hydrogels crosslinked with light-sheet energy						
		T3.3. Production of 3D structures by light-sheet illumination						
		T3.4. Production of niches with varying stiffness by light-sheet illumination						
4	Engineered skin tissues	T4.1. Isolation and characterization or relevant skin cells						
		T4.2. Reconstitution of epidermis and underlying dermis						
		T4.3. Bioprinting of hair follicles with associated sebaceous gland unit						
		T4.4. Bioprinting of sweat glands						
5	Project management	T5.1. Management of financial, administrative and contractual aspects						
		T5.2. Scientific management and progress monitoring						
		T5.3. Risk management						
6	Dissemination, exploitation and communication	T6.1. Scientific dissemination activities and exploitation plan						
		T6.2. Public communication and engagement activities						
		T6.3. Educational and training activities						
		T6.4. Networking activities						
		T6.5. IPR handling strategy						

Work Plan





Remember: deliverables from the Work Plan (DoA) were modified from the initial proposal

Deliverables 2019 (M1-M6)

Deliverable	Deliverable name	WP nº	LP	Type	Dissemination level	Delivery month	Delivery date
D1.1	Light-sheet generation	1	GUF	Report	CO	**7**	**31/01/2020**
D1.4	Initial specifications of the pattern generator	1	MYCRONIC	Report	PU	6	**31/12/2019**
D2.1	First batch of photopolymerizable polymers available	2	CELLENDES	Report	CO	**6**	**31/12/2019**
D5.1	Report of kick-off meeting.	5	IBEC	Report	PU	1	**31/07/2019**
D5.2	6M Meeting organization, and internal progress report	5	IBEC	Report	CO	7	**31/01/2020**
D5.8	Risk management plan	5	IBEC	Report	CO	6	**31/12/2019**
D6.3	BRIGHTER web site and logo	5	IBEC	Report	PU	2	**30/08/2019**
D6.6	IPR Guidance Plan	1	MYCRONIC	Report	CO	6	**31/12/2019**

Deliverables 2019 (M1-M6)

Del. (No)	Deliverable name	Description	WP No	Lead part.	Type	Diss. level	Del. date
D1.1	Light-sheet generation	Description of the technical set up to allow spatially and temporally structured light-sheet illumination	1	GUF	R	CO	M7
D1.4	Initial specifications of the pattern generator	Description of the requirements and technical specifications of the pattern generator to be applied to the light-sheet bioprinting system	1	MYCRONIC	R	PU	M6
D2.1	First batch of photopolymerizable polymers available	Synthesis and physicochemical characterization of on-purpose made photopolymers.	2	CED	R	CO	M6
D5.1	Report of kick-off meeting	Minutes of the kick-off meeting including the agenda, list of participants with their affiliations and roles, and presentations of participants	5	IBEC	R	PU	M1
D5.2	6M Meeting organization, and internal progress report	Minutes of the periodic project meetings, internal reporting and project monitoring	5	IBEC	R	CO	M7
D5.8	Risk management plan	Detailed analysis of the foreseen risks including monitoring and steering actions. It is a living document.	5	IBEC	R	CO	M6
D6.3	BRIGHTER web site and logo	It will include basic project information, logo, news and events, downloadable e-newsletters, and links to social media accounts (tweeter, Facebook and LinkedIn). It is a living document.	6	IBEC	R	PU	M2
D6.6	IPR Guidance Plan	A document describing the roadmap on how to protect IPR within relevant BRIGHTER results	6	MYCRONIC	R	CO	M6

Deliverables 2020 (M7-M18)

Deliverable	Deliverable name	WP nº	LP	Type	Dissemination level	Delivery month	Delivery date
D1.8	Bioprinting chambers	1	GUF	Report	CO	10	30/04/2020
D2.2	Photopolymerizable polymers Biocompatibility	2	IBEC	Report	PU	11	31/05/2020
D1.2	Initial specifications of the light-sheet Bioprinter	1	GUF	Report	CO	12	30/06/2020
D3.1	Characterization of first batch of hydrogels	3	IBEC	Report	PU	12	30/06/2020
D6.1	Dissemination and exploitation plan	6	IBEC	Report	CO	12	30/06/2020
D6.5	Report on networking activities	6	IBEC	Report	PU	12	30/06/2020
D5.6	Technical/scientific review meeting documents	5	IBEC	Report	CO	13	31/07/2020
D1.5	First prototype of the high-resolution digital photomask system	1	MYCRONIC	Report	CO	15	30/09/2020
D1.3	First prototype of the light-sheet bioprinter	1	GUF	Report	CO	18	31/12/2020
D2.3	First batch of polymer formulations for IPNs	2	CELLENDES	Report	CO	18	31/12/2020
D3.2	Characterization of reversible crosslinked IPNs hydrogels	3	IBEC	Report	PU	18	31/12/2020
D3.4	Cell viability on cell-laden hydrogels	3	IBEC	Report	PU	18	31/12/2020
D5.3	18M Meeting organization, and internal progress reports	5	IBEC	Report	CO	19	30/01/2021

Deliverables 2021 (M19-M30)

Deliverable	Deliverable name	WP nº	LP	Type	Dissemination level	Delivery month	Delivery date
D4.1	Protocols to isolate, culture and characterize relevant skin cells	4	TECHNION	Report	PU	21	31/03/2021
D1.7	Light-imaging system	1	GUF	Report	CO	22	30/04/2021
D1.6	Improved light-sheet bioprinter prototype and technical specifications	1	GUF	Report	CO	24	30/06/2021
D2.4	Optimized polymer formulation of IPNs for light-sheet polymerization	2	CELLENDES	Report	CO	24	30/06/2021
D3.7	Calibration of stiffnessvarying substrates	3	IBEC	Report	CO	24	30/06/2021
D6.4	Project Workshop	6	IBEC	Other	PU	24	30/06/2021
D5.4	24M Meeting organization, and internal progress reports	5	IBEC	Report	CO	25	30/07/2021
D6.2	Report on patent applications	6	IBEC	Report	CO	27	30/09/2021
D3.3	Report on the lightsheet bioprinter process characteristics	3	IBEC	Report	PU	28	30/10/2021
D3.5	Cell viability on IPNs cell-laden hydrogels	3	IBEC	Report	PU	28	30/10/2021
D3.6	Protocols to produce 3D structures	3	MYCRONIC	Report	CO	28	30/10/2021
D3.8	Protocols to produce stiffness-varying substrates	3	IBEC	Report	CO	30	31/12/2021
D5.5	30M Meeting organization, and internal progress reports	5	IBEC	Report	CO	31	31/01/2022

Deliverables 2022 (M31-M36)

Deliverable	Deliverable name	WP nº	LP	Type	Dissemination level	Delivery month	Delivery date
D4.2	Reconstitution of epidermis and dermis	4	TECHNION	Report	CO	35	30/05/2022
D4.3	Bioprinted skin with hair follicles	4	TECHNION	Report	PU	36	30/06/2022
D4.4	Improved characteristics of the engineered skin tissues	4	TECHNION	Report	PU	36	30/06/2022
D5.7	Technical/scientific final review meeting documents	5	IBEC	Report	CO	36	30/06/2022

List of Milestones

Milestone number[18]	Milestone title	WP number[9]	Lead beneficiary	Due Date (in months)[17]	Means of verification
MS1	Light-sheet illumination successfully integrated with digital photomasks	WP1	2 - GUF	18	Deliverable D1.3
MS2	Operative prototype of the light-sheet bioprinter available	WP1	2 - GUF	24	Deliverable D1.6
MS3	Light-sheet energy dose is suitable to crosslink thiol-ene chemistry	WP2	4 - CELLENDES	6	Deliverable D2.1
MS4	Custom-made hydrogels support cell adhesion and growth	WP2	4 - CELLENDES	11	Deliverable D2.2
MS5	Light-sheet lithography can produce 3D geometries	WP3	1 - IBEC	28	Deliverable D3.6
MS6	Light-sheet bioprinting can produce structures with varying stiffness	WP3	1 - IBEC	30	Deliverable D3.8
MS7	Relevant skin cells and structures can be printed with BRIGHTER	WP4	5 - TECHNION	35	Deliverable D4.2
MS8	Patent application	WP6	1 - IBEC	27	Deliverable D6.2

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Work Package 1

Kick off meeting

4th July 2019

Task review

- TASKS:
- **T1.1. Generation of the light-sheet**
- **T1.2. Development of a system including two light-sheet illumination sources**
- T1.3. Development of a system to shape light sheet illumination
- **T1.4. Development of the imaging system**
- **T1.5. Development of the bioprinting chamber**
- T3.3. Production of 3D structures by light-sheet illumination
- T3.4. Production of niches with varying stiffness by light-sheet illumination
- T4.2. Reconstitution of epidermis and underlying dermis
- T4.3. Bioprinting of hair follicles with associated sebaceous gland unit
- T4.4. Bioprinting of sweat glands

Deliverables

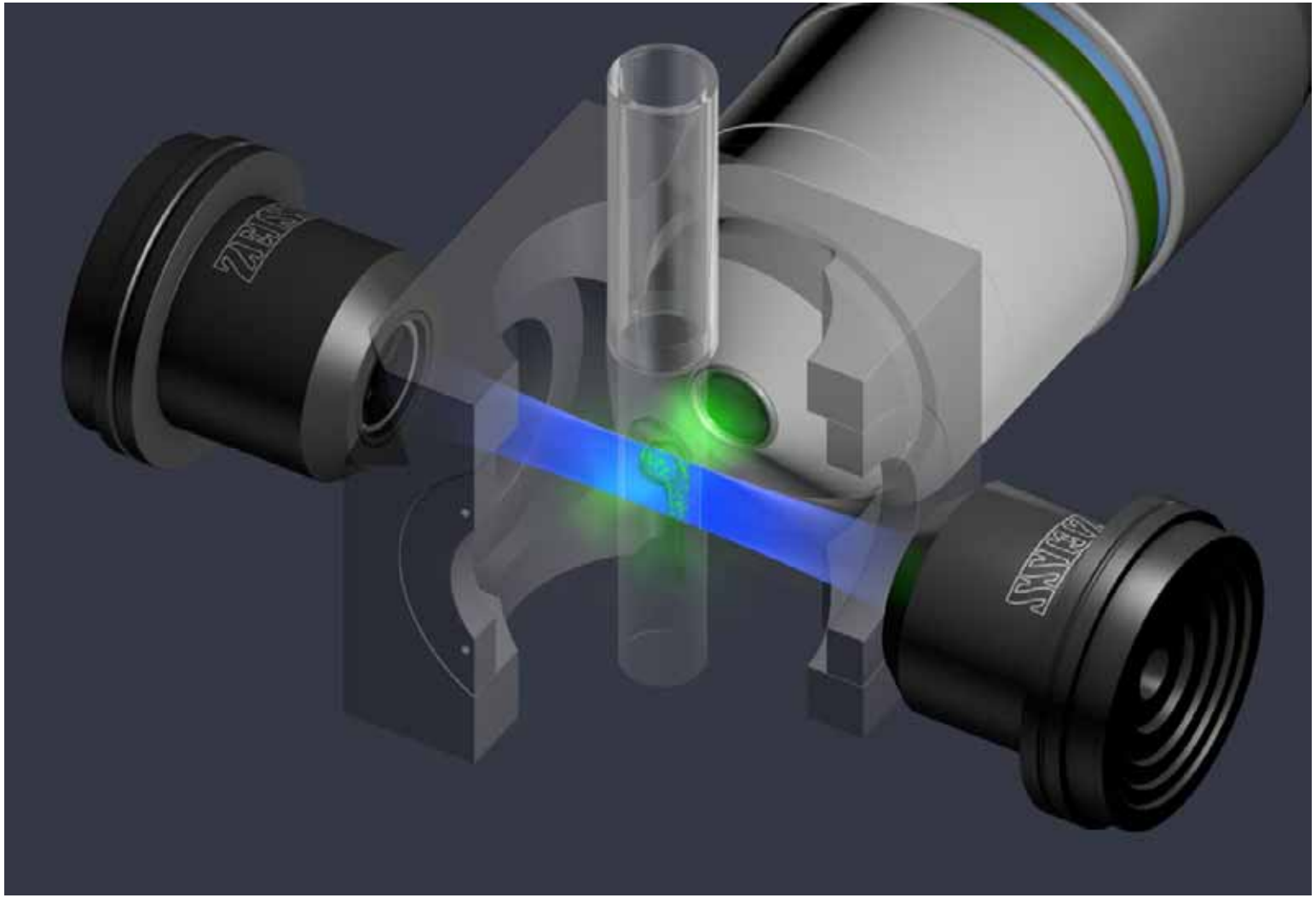
D1.1. First prototype of the light sheet bioprinter

D1.2. Bioprinting chambers

Experimental Work Plan

Setup Light Sheet Microscope

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

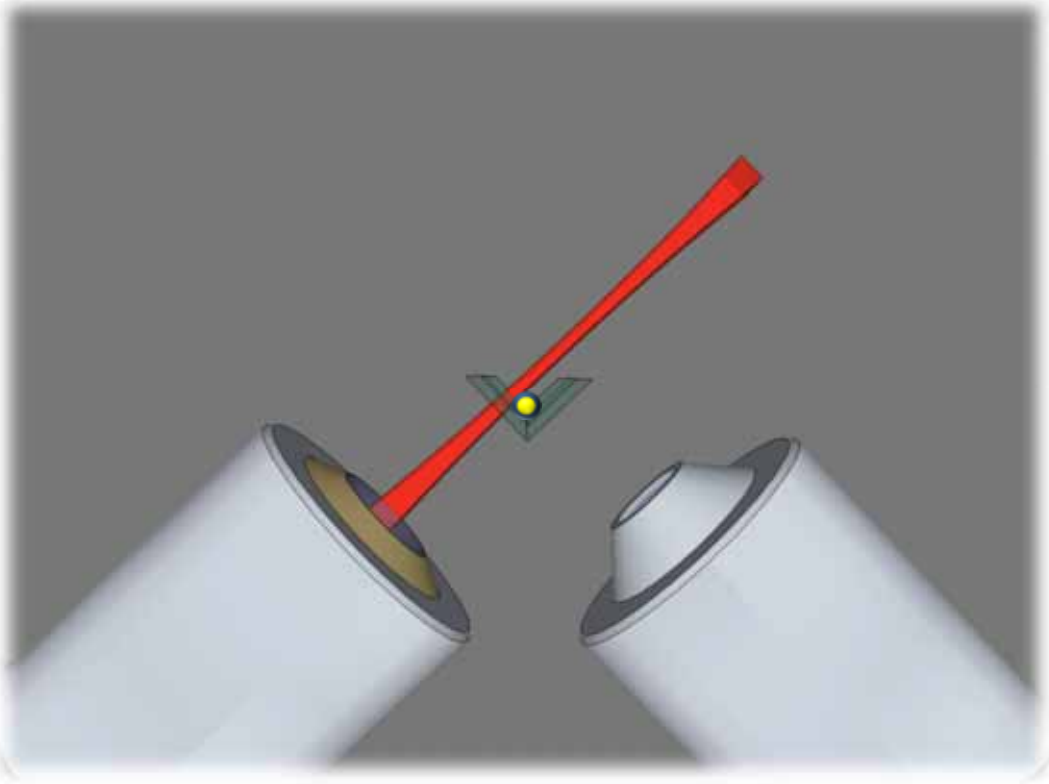


Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

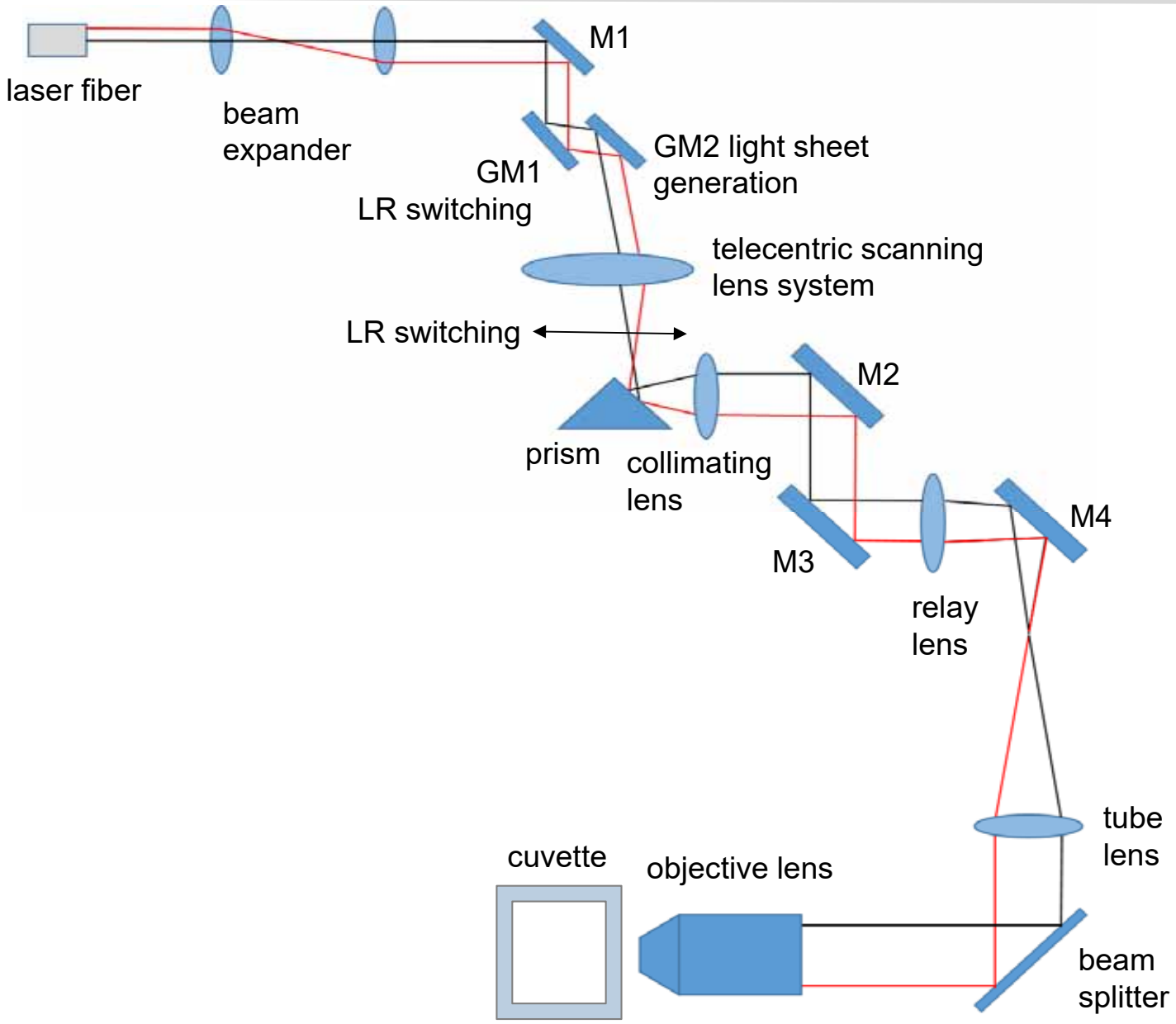
Well geometry for the inverted HT-LSFM

- V-shaped wells
- Pyramidal wells
- Use of both air and water immersion objective lenses.
- Double-side illumination and detection



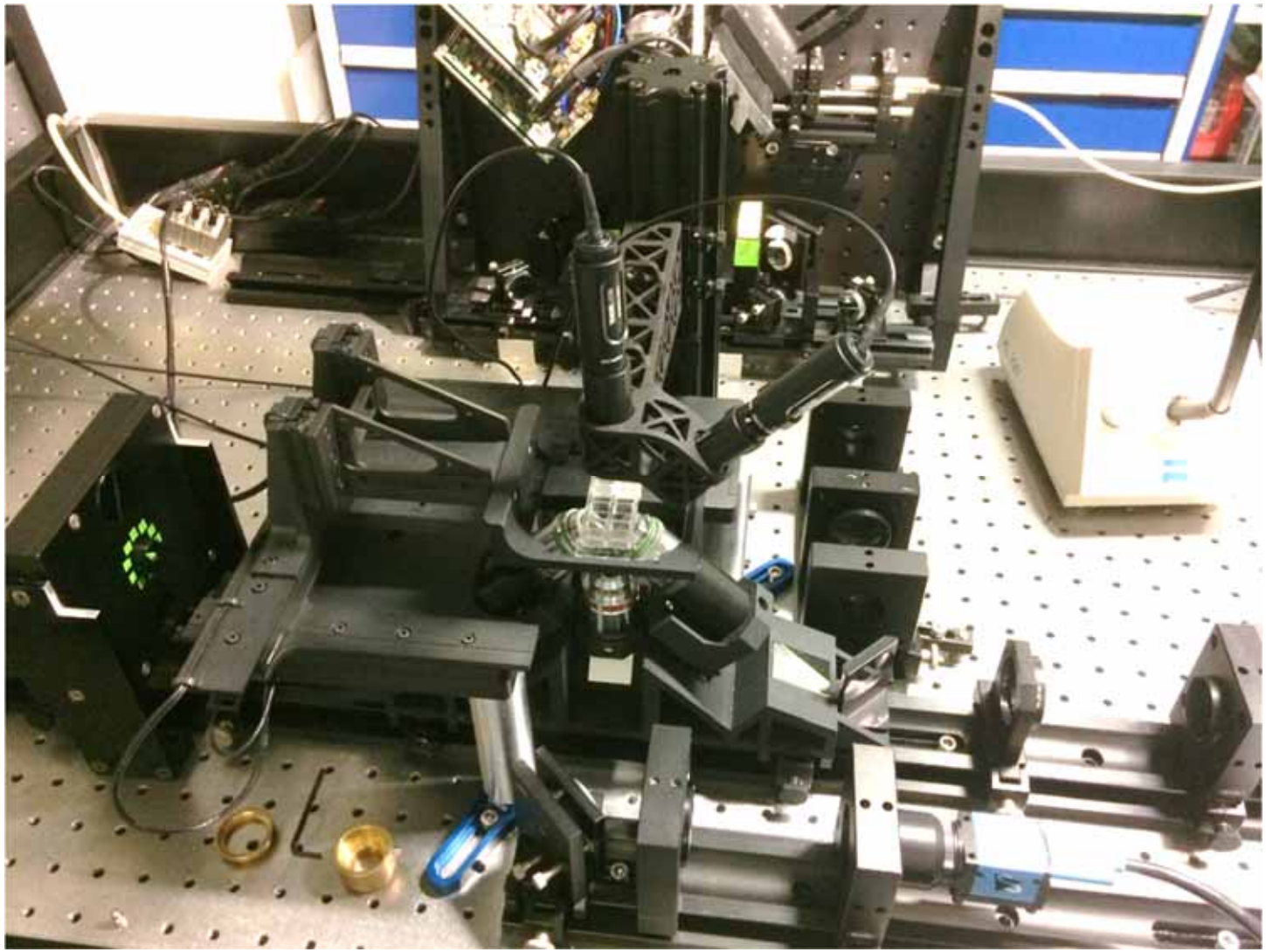
Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



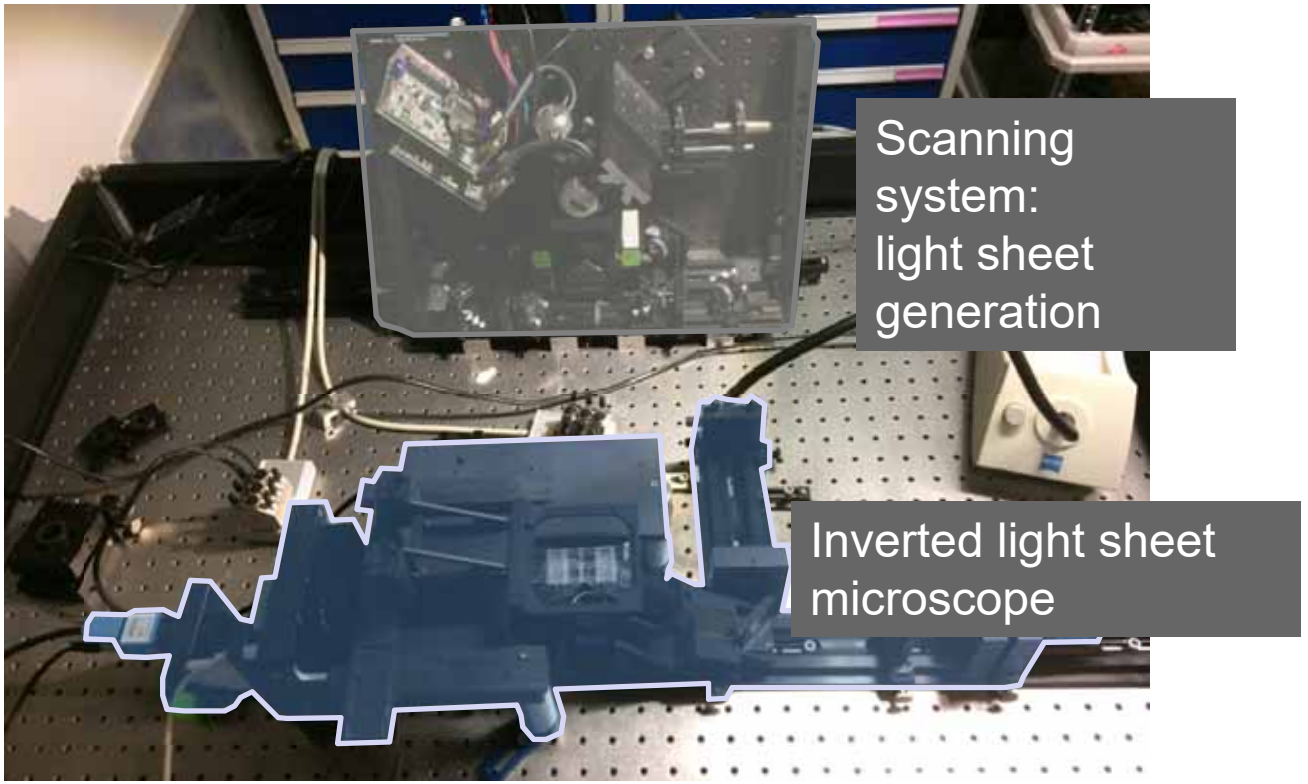
Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



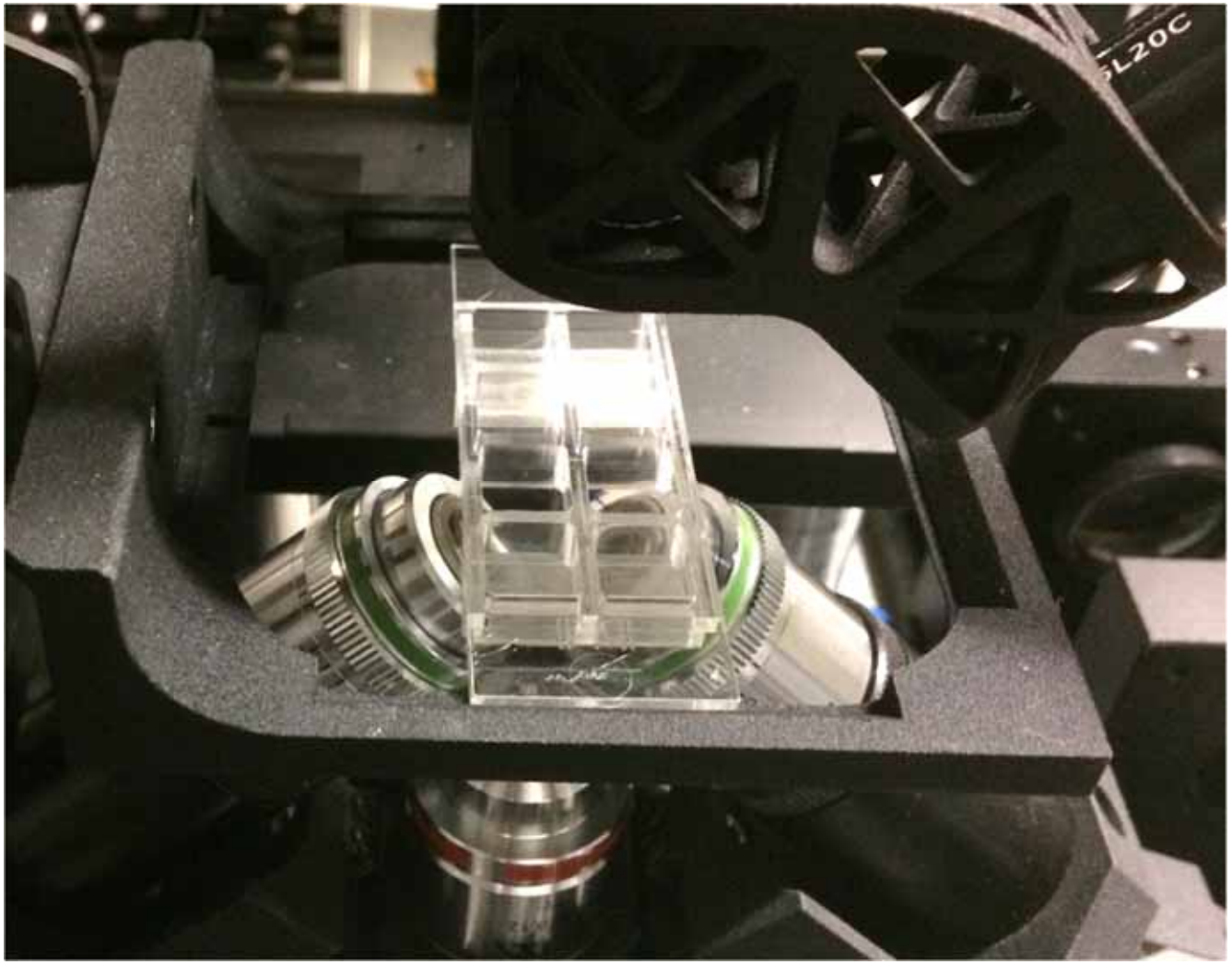
Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

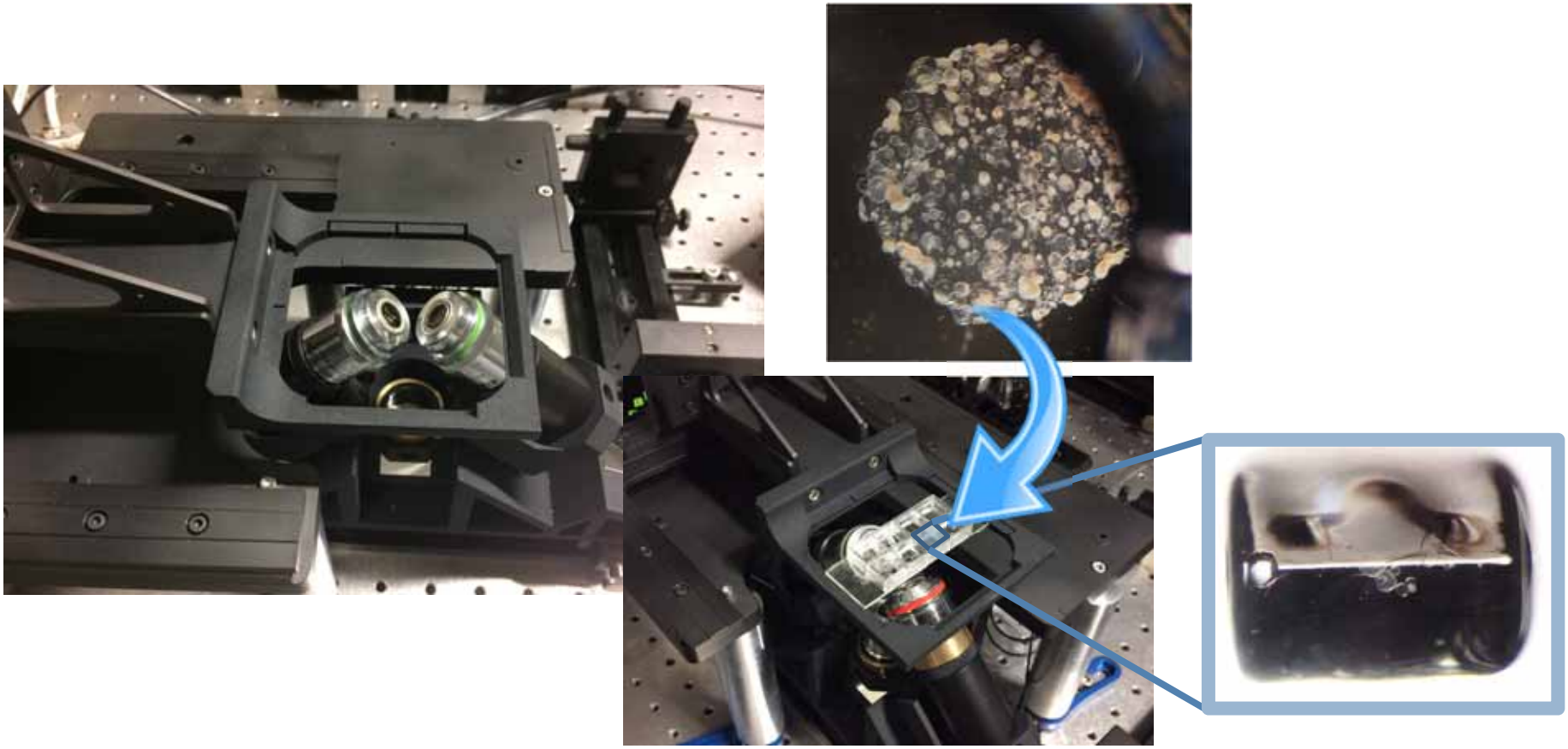


Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Setup HT-LSFM

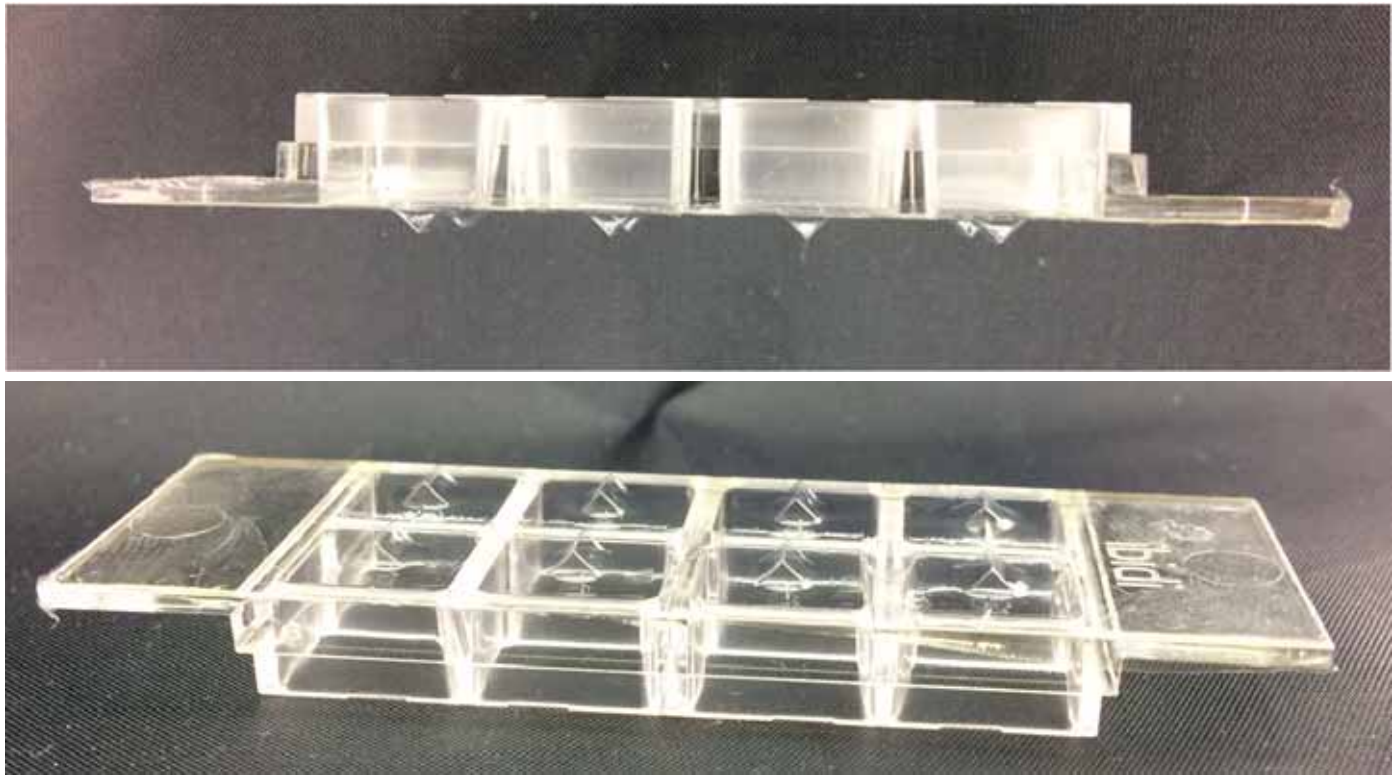
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

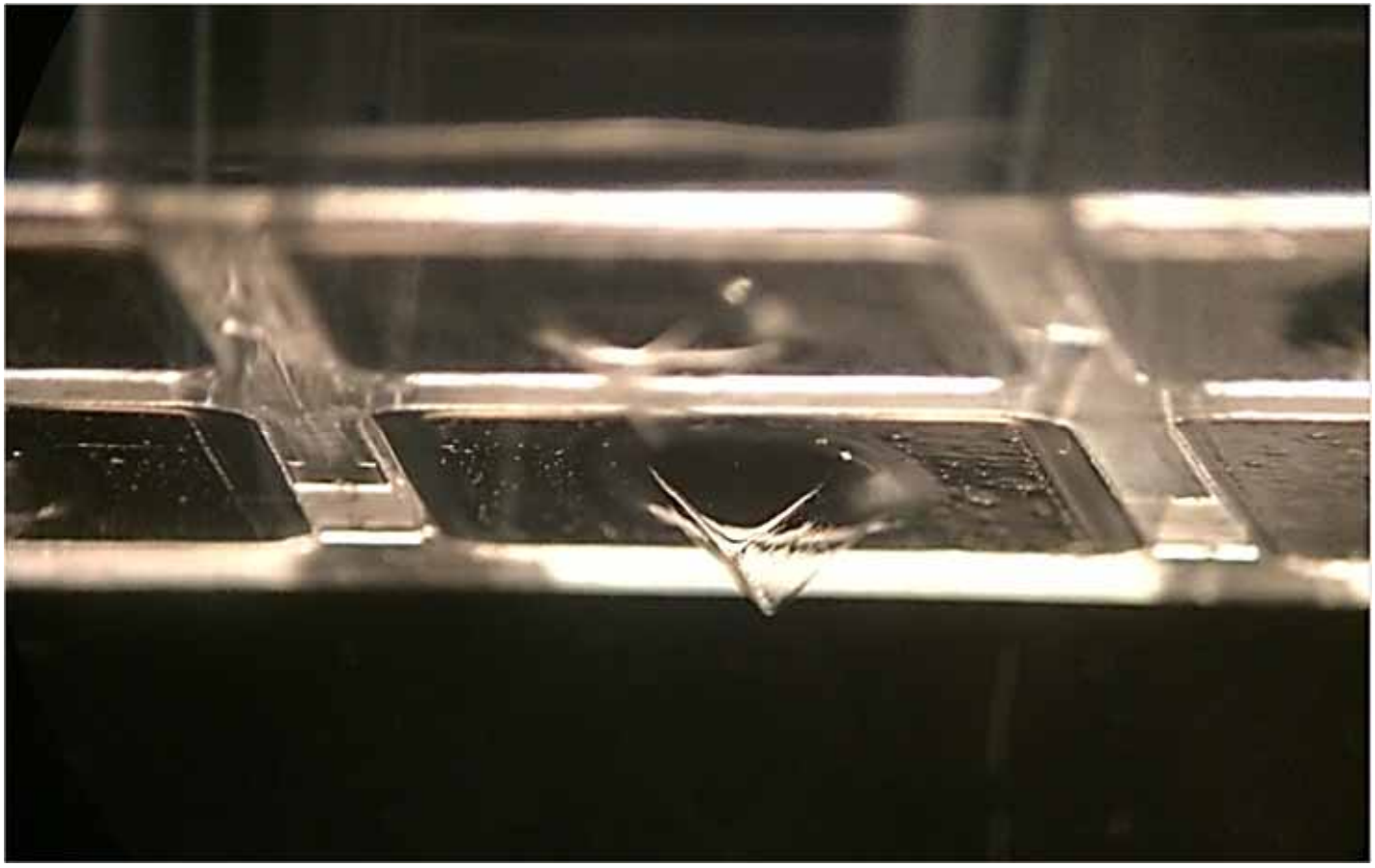
FEP V-shaped multiwell plates for the HT-LSFM based on Ibidi-slide



Pampaloni, Stelzer, WO2015036589 A1

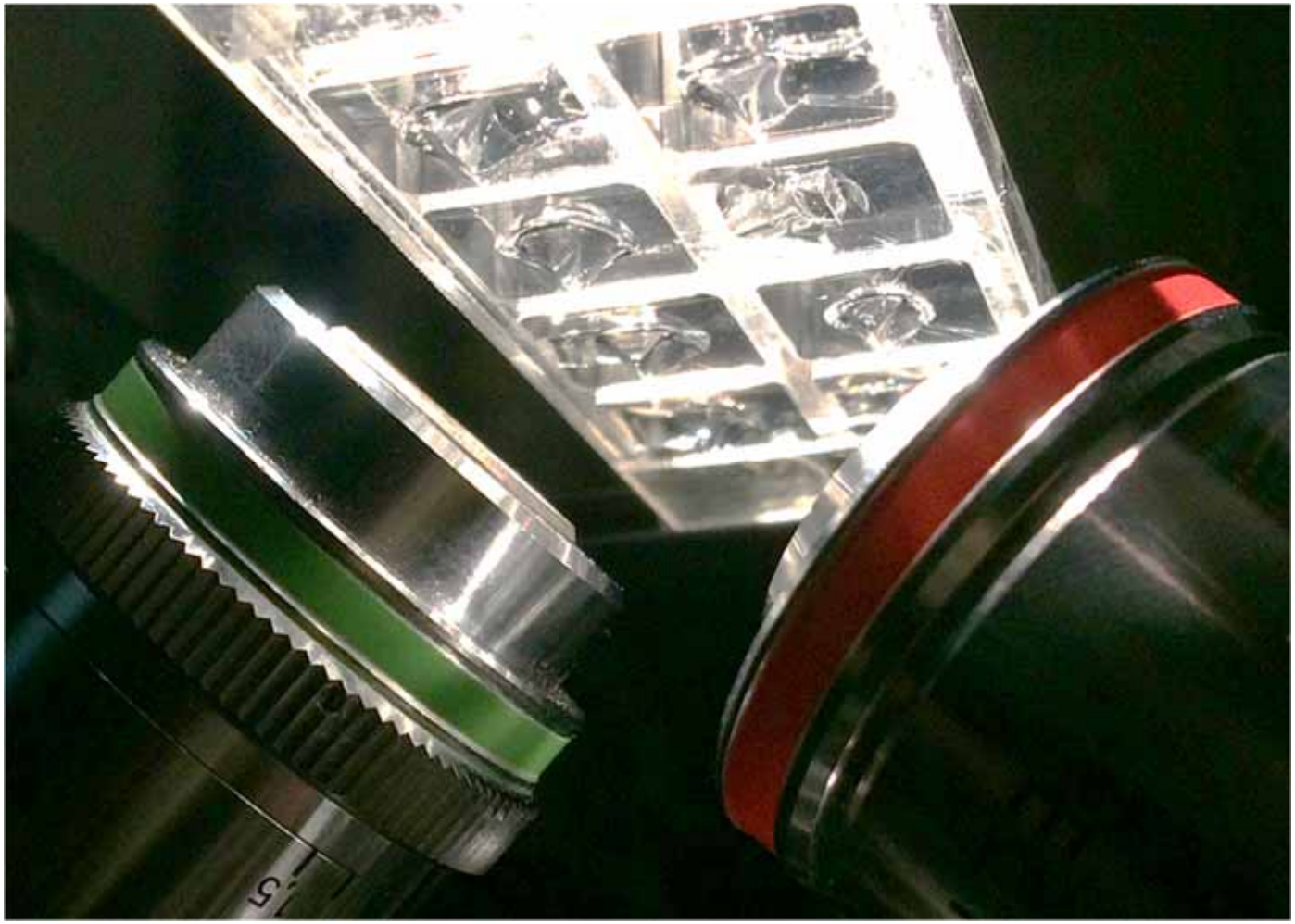
Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Setup HT-LSFM

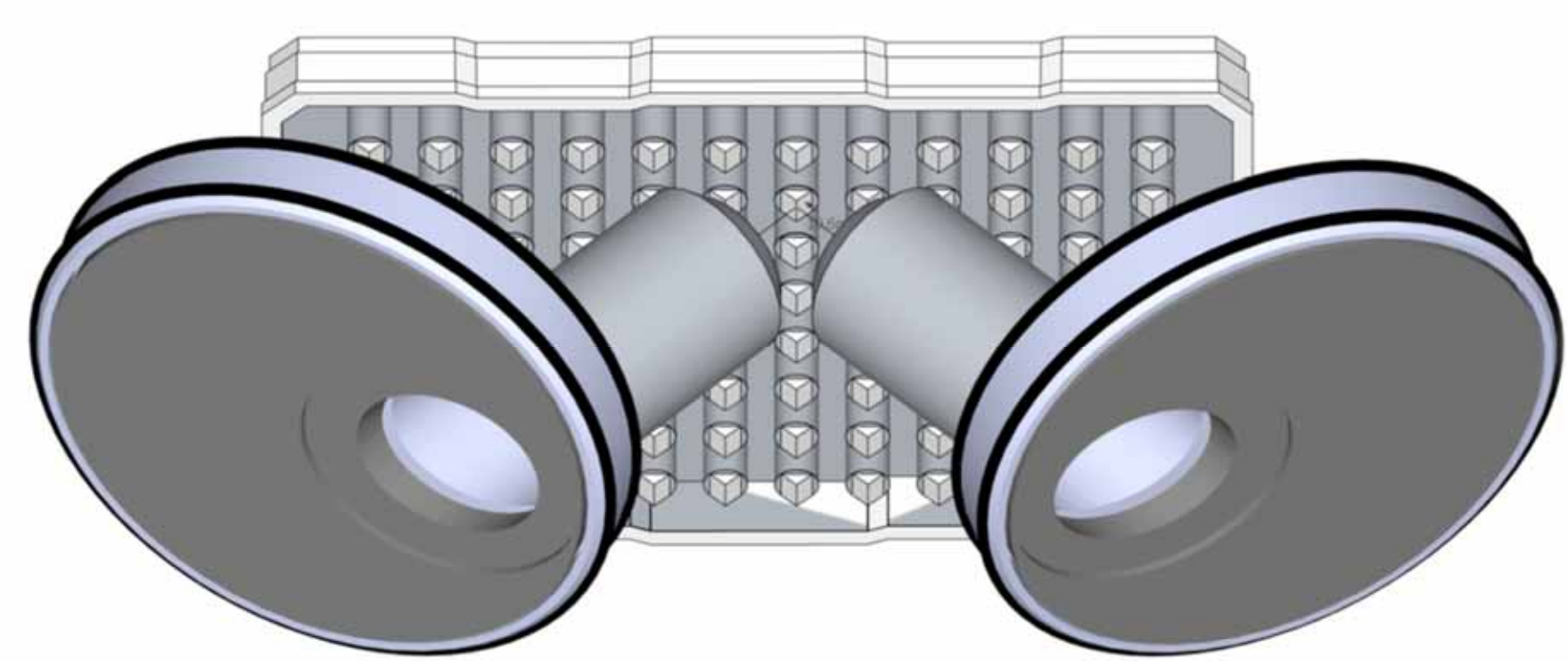
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Setup HT-LSFM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

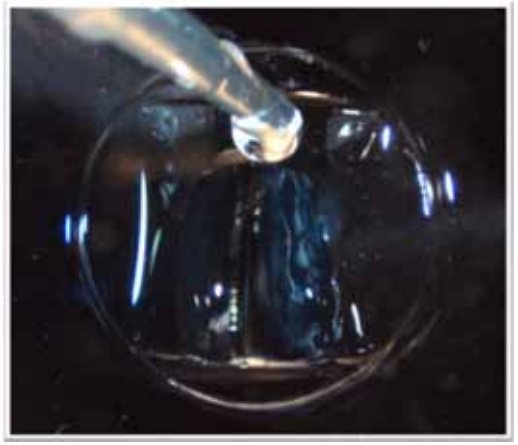
Multiwell plate configuration

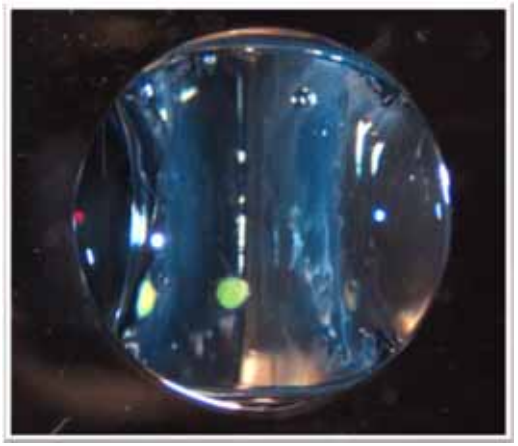


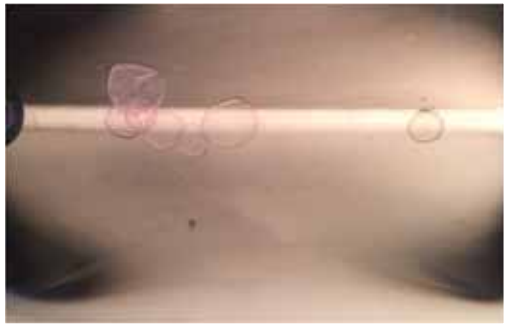
Imaging

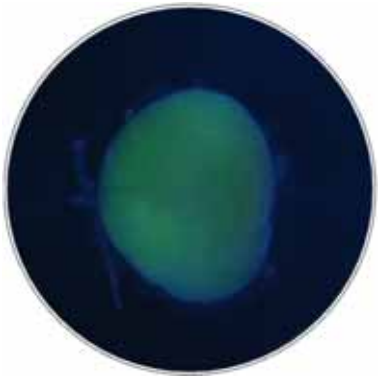
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

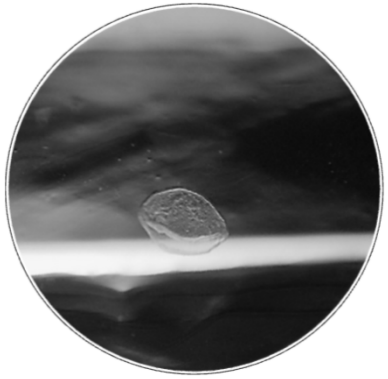
The specimens (spheroids, organoids) are simply pipetted in the wells











Pampaloni, Stelzer, WO2015036589 A1

Imaging

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

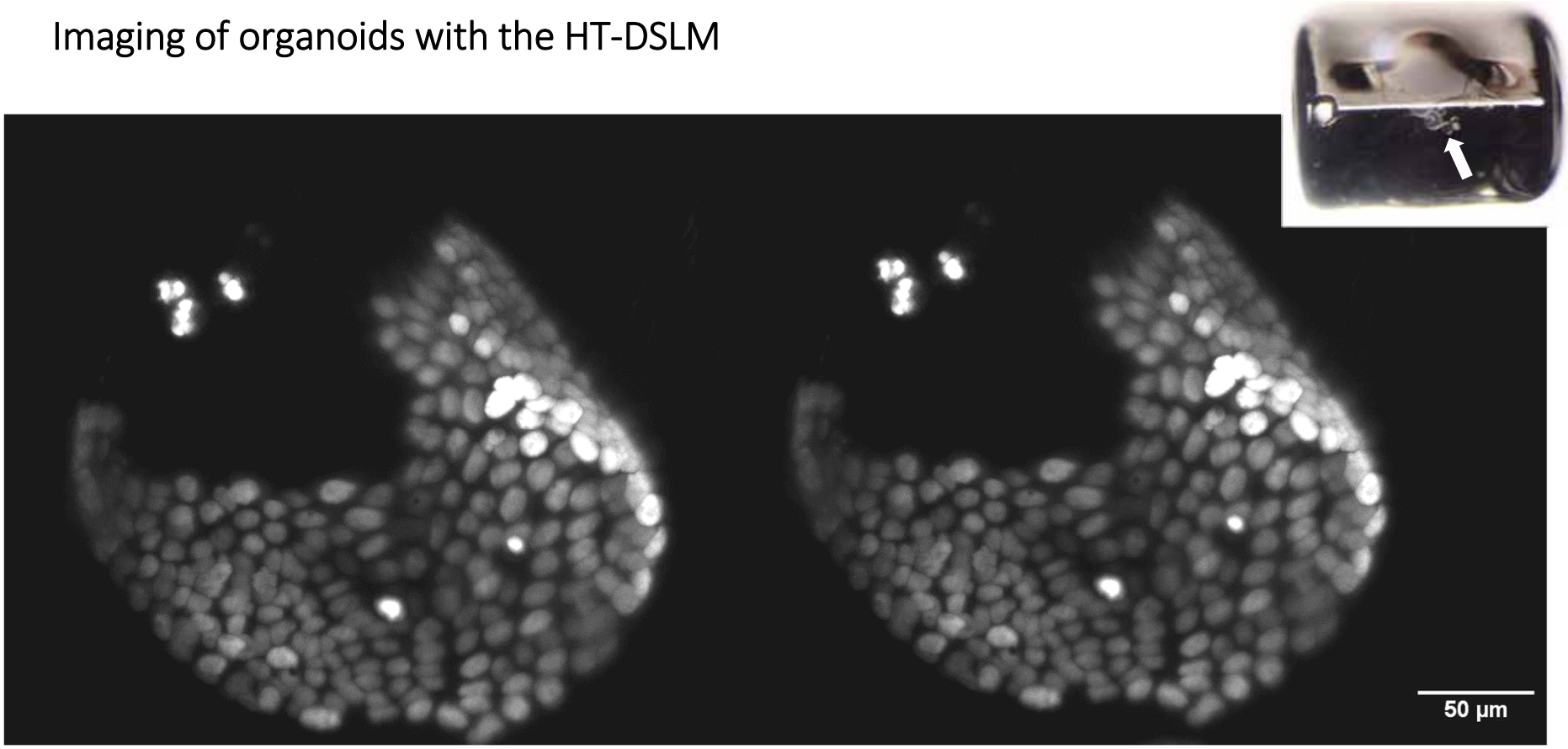
Imaging of organoids with the HT-DSLM

Specimen:
Pancreas organoids
Marker: Phalloidin Alexa-488
Objective lens: Detec.: LD A-plan 10x/0.25
Illum.: Epiplan-Neofluar 5/0.06
Illumination: 488 nm Scale bar: 100 µm

Imaging

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Imaging of organoids with the HT-DSLM

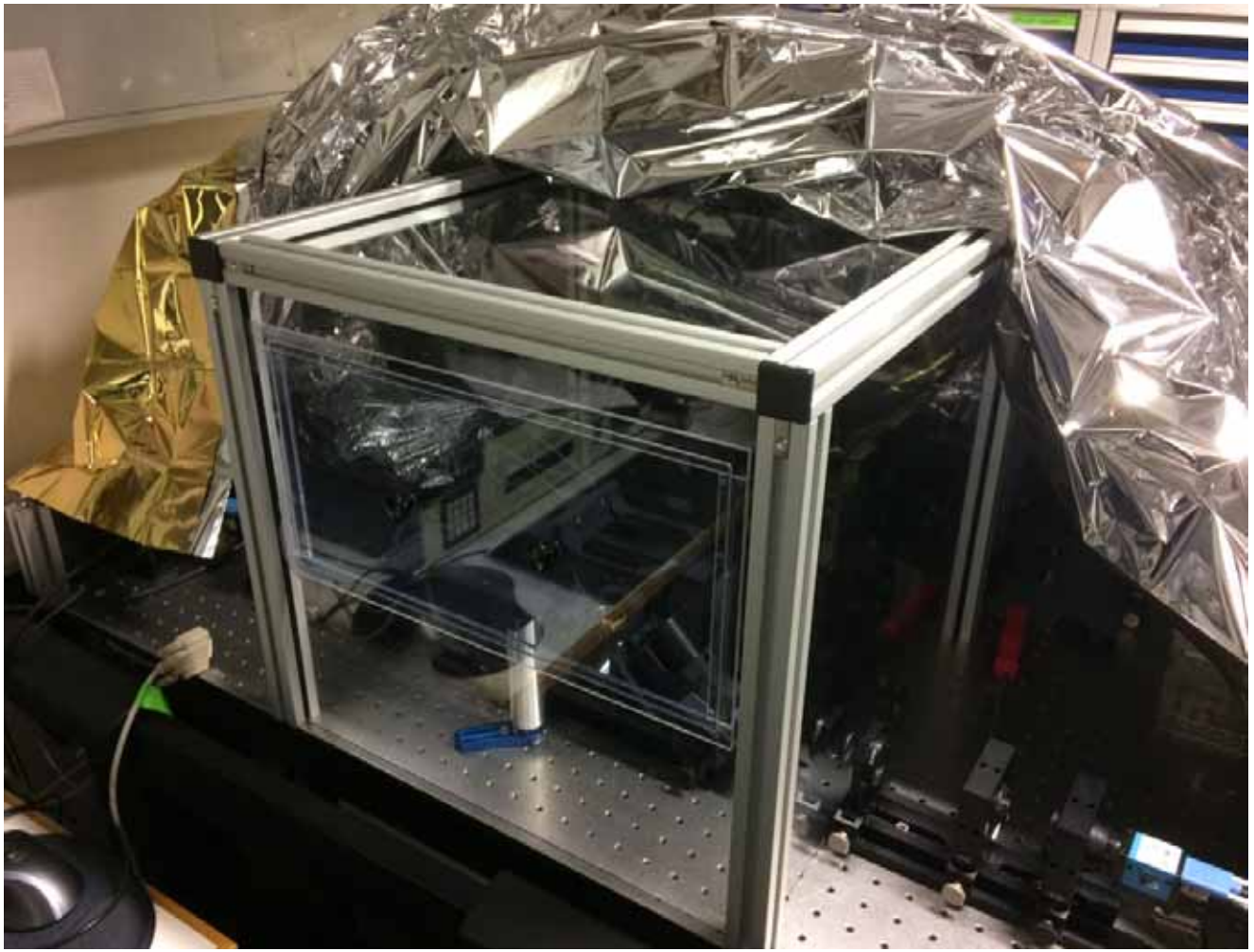


Human liver organoid (huLO) in a V-shaped FEP-well imaged with the HT-DSLM
Illumination objective lens CZ 5x NA 0.6
Illumination and detection objective lens CZ LD achroplan 20x / NA 0.40 wd = 10.2 mm
Exc. wavelengths: 488 nm (H2B-GFP). Maximum projection of 150 planes, spacing 1 µm

Imaging

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Incubator box for live imaging on the HT-LSFM

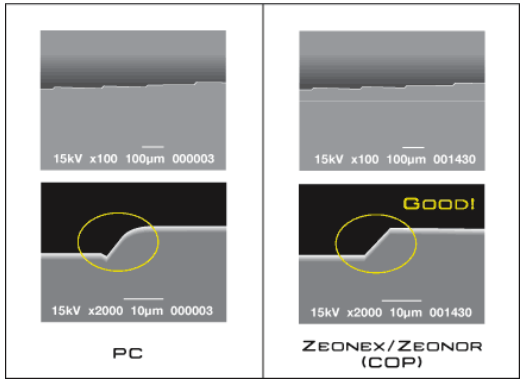


Specimen chamber

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Ultra-thin FEP foil: a versatile specimen mounting technique for LSFM

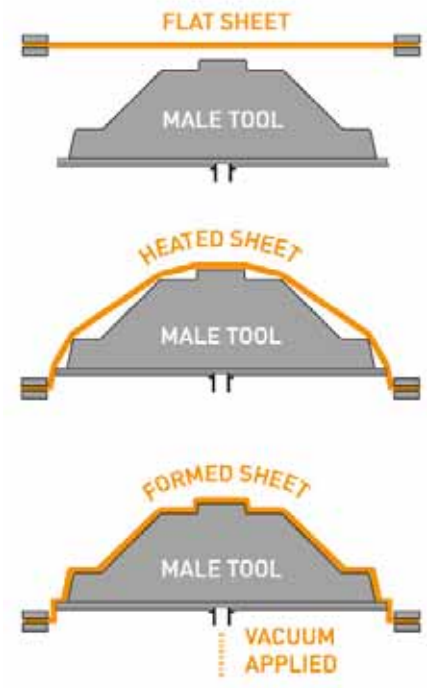
Material	Commercial name	Refractive index	Available foil thickness
Cycloolefin polymer	ZEONEX, ZEONOR	1.52	40 µm - 188 µm
Tetrafluorethylene, perfluorpropylene, FEP	LUMOX, Teflon	1.34	12.5 µm, 25 µm, 50 µm, 125 µm
Polyamide	GRILAMID TR	1.54	not available as foil off-the-shelf
Polyimide	KAPTON	1.66	from 7.9 µm to 152 µm

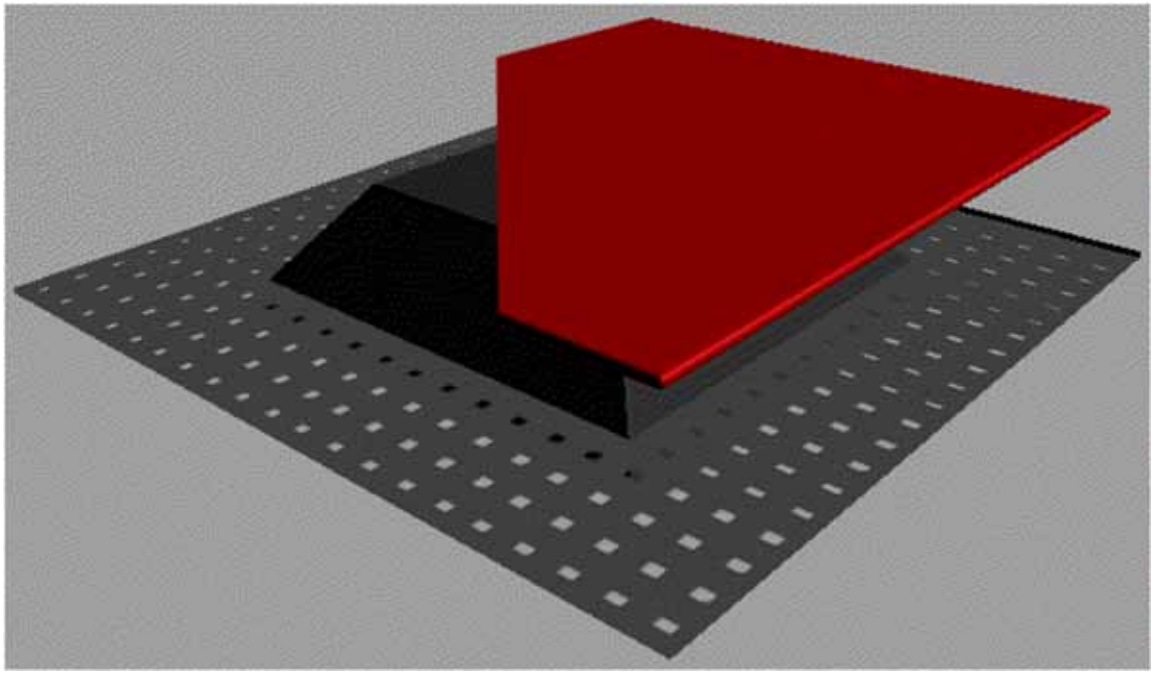


Specimen chamber

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Fabrication of LSFM specimen holders with **vacuum forming** of FEP foil





System requirements

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Main features

- Dual left and right illumination/imaging
  Allows for optimal sheet penetrationacross wide specimens and avoidance of opaque structures that may be present on one side but not the other

- High NA/Large field of view / long working distance objective lenses
  Macro lenses at 1x/0.25NA and 1.5/0.37 NA

- Piezo stage driving multiple sample chambers
  Sub-micron resolution stage allows precise positioning of the specimen.

System requirements

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

System requirements		
Requirement	Technical solution	Comments
Multiple laser sources	Power density (consider Beer-Lambert law to take into account the cuvette thickness) Wavelenghts (365nm, 405nm, 488nm, 543nm, 647nm, 780nm)	wl depends on the photo-initiator (UV range standard). Initiator that work in the visible range could be available. Further wavelengths for imaging.
Possibility to tune the energy in order to change ligand number within the hydrogel	Control of laser power, Control of exposure time	
3D geometric structure to create in the hydrogel. Include structures that cannot be realized with the state of the art systems.	Digital programming of the mask.	Tunnels for vascularization, invaginations, cavities.
Mask type	SLM, AOM+AOD (frequency 15 MHz) Patterns created with a sophisticated processing unit.	
Light sheet forming	Scanning with galvo-mirrors (DSLM)	
LSFM opto-mechanical arrangement	Monolithic	
Cuvette	FEP foil (to be tested for gas permeability, i.e. whether the anoxic conditions for polymerization are achieved within the cuvette)	
Double side illumination	Galvo-mirror + prism	Ensure the uniformity of the illumination
Imaging FOV	SLM, AOM+AOD	Highly flexible with light sheet tiling.
Time to scan/polymerize the volume	Depending on polymerization time at a given laser energy	

Light sheet tiling to extend the FOV

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

How Tiling Works

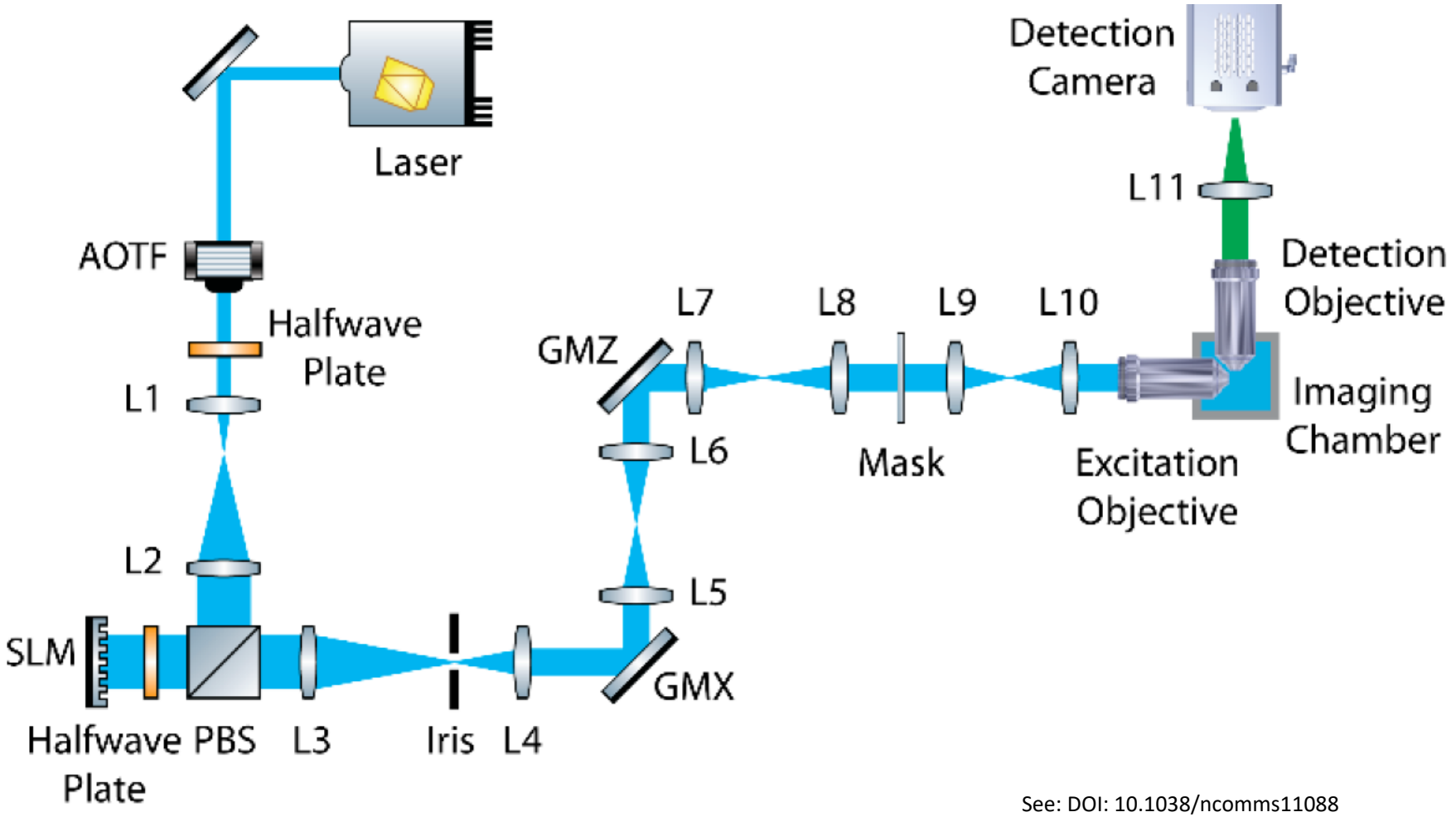
The optical sectioning ability of a light sheet is dependent on the thickness of the waist of the focused beam used to create the sheet. The thickness of the waist is directly proportional to the beam length. A thinner waist is generally required for better optical sectioning, but the thinner the waist the shorter the usable length of the beam. Imaging large cleared specimens with a light sheet requires a beam with a long waist matched to the large field of view. The long waist has a correspondingly high thickness, and the result is often poor optical sectioning.

To dramatically improve on this limitation, CTLS uses a spatial light modulator to create a sharply focused beam with a thin waist much shorter than the detector's field of view. The beam waist is tiled along the axis of propagation and the camera is synchronized to capture one image per tile. The optimal region of each capture is selected and stitched together forming a continuously optimized image. The resulting data has an excellent axial resolution compared to a non-translated focused beam.

See: DOI: 10.1038/ncomms11088

Prior art SLM-based tiling

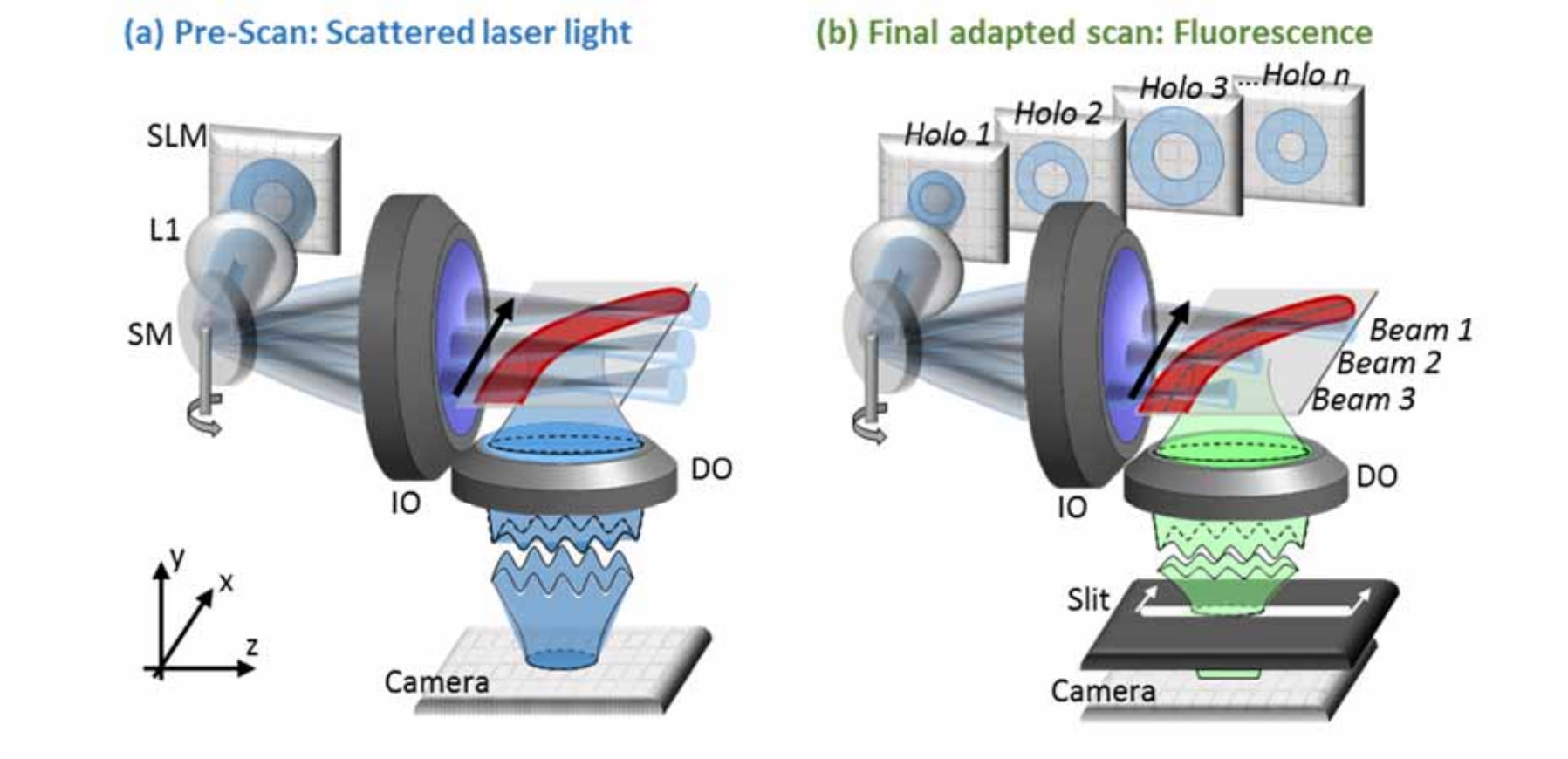
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



See: DOI: 10.1038/ncomms11088

Prior art SLM-based tiling

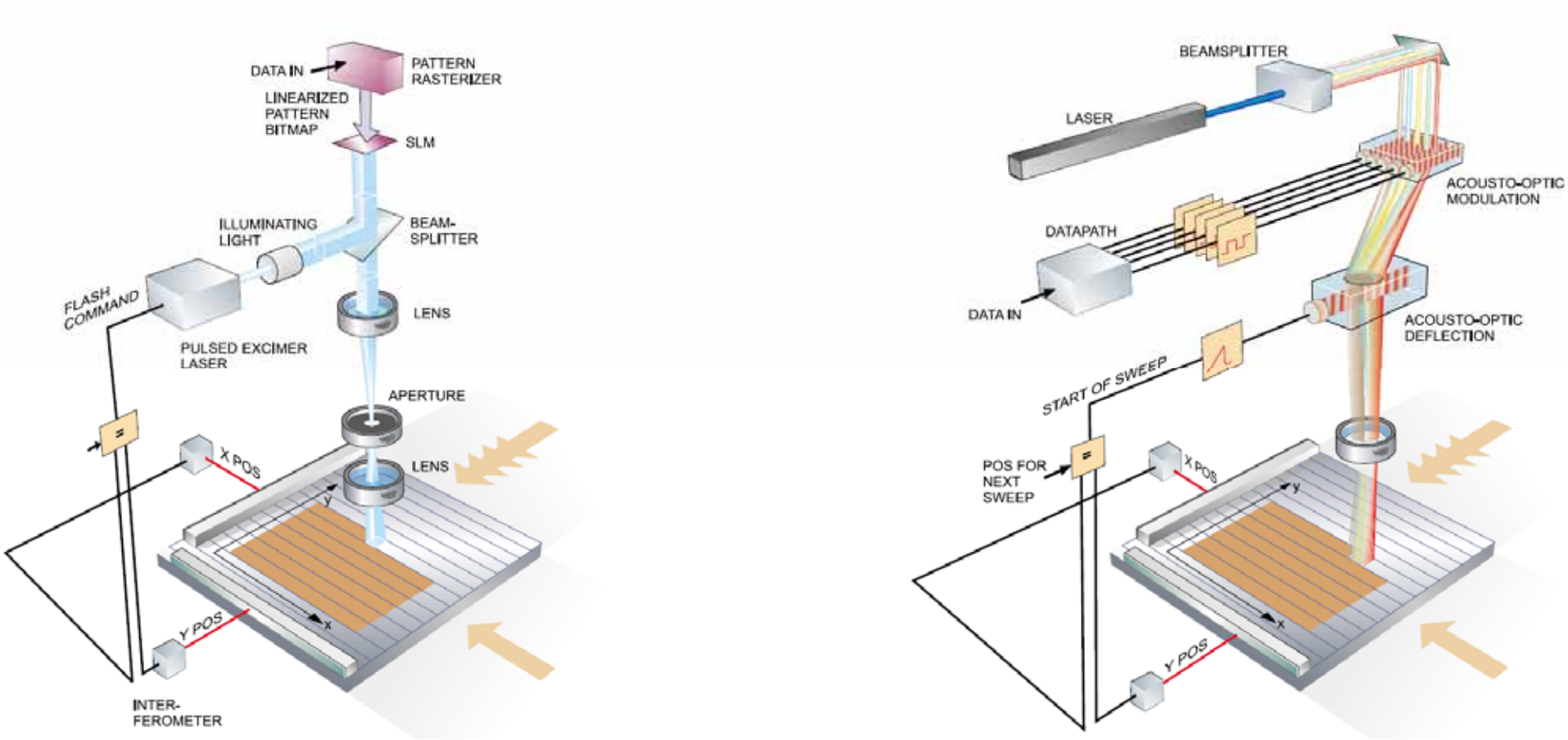
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Citation
Tobias Meinert, Alexander Rohrbach, "Light-sheet microscopy with length-adaptive Bessel beams," Biomed. Opt. Express **10,** 670-681 (2019);
https://www.osapublishing.org/boe/abstract.cfm?uri=boe-10-2-670

Light sheet shaping options

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Source: Mycronics

Prior art volumetric fabrication

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

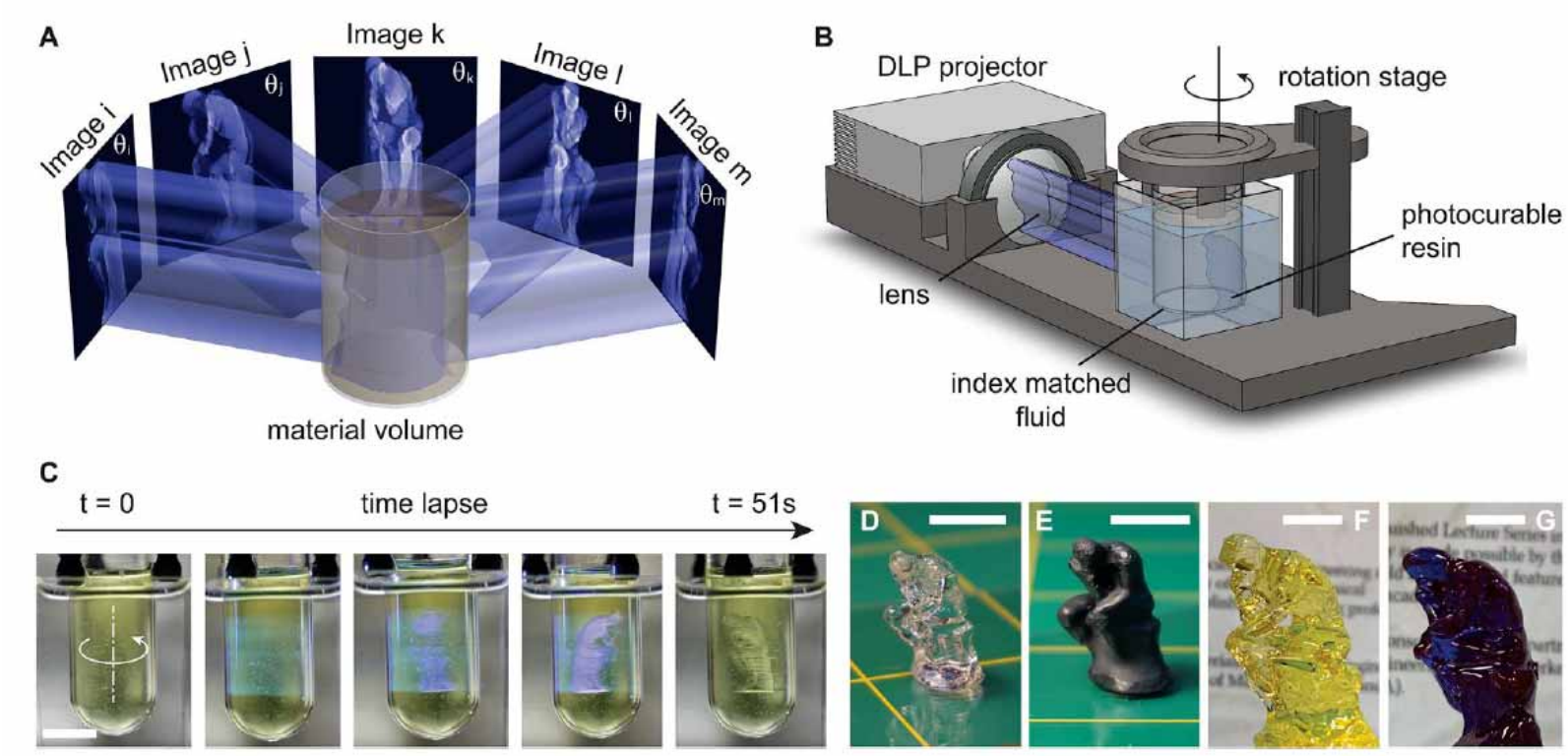


Fig. 1. CAL volumetric fabrication. (**A**) Underlying concept: patterned illumination from many directions delivers a computed 3D exposure dose to a photoresponsive material. (**B**) Schematic of CAL system used in this work. (**C**) Sequential view of the build volume during a CAL print. A 3D geometry is formed in the material in less than a minute. (**D**) The 3D part shown in (C) after rinsing away uncured material. (**E**) The part from (D) painted for clarity. (**F**) A larger (40 mm-tall) version of the same geometry. (**G**) Opaque version of the geometry in (F), using crystal violet dye in the resin. Scale bars: 10 mm.

DOI: 10.1126/science.aau7114 (2019)

Thank you for your attention!

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

Kick off meeting
4th July 2019

Hydrogel Development – Tasks and Milestones

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

Tasks

T2.1. Fabrication and characterization of photo-polymerizable polymers

T2.2. Polymer functionalization and biocompatibility evaluation

T2.3. Development of reversibly crosslinkable hydrogels

T2.4. Formation and characterization of IPNs including reversibly crosslinkable polymers

T3.1. Calibration of the crosslinking density and stiffness of hydrogel

Deliverables

D2.1. First batch of photo-polymerizable polymers under light-sheet (M6)

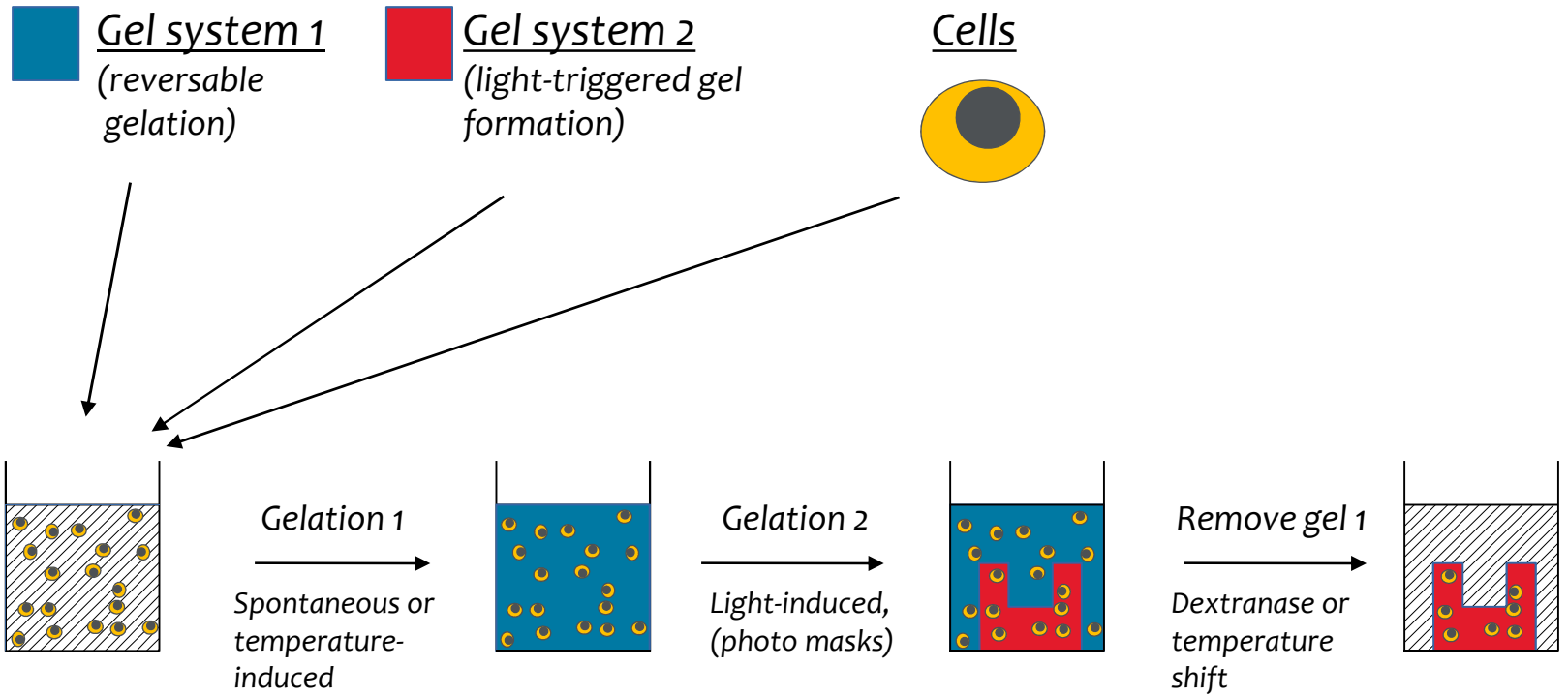
D2.2. First batch of polymer formulations for IPNs (M15)

D2.3. Optimized polymer formulation of IPNs for light sheet polymerization (M24)

T2.4. Formation and characterization of interpenetrating networks including reversibly crosslinkable polymers

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design



T2.3. Development of reversibly crosslinkable hydrogels (Gel System 1)

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

- Requirements:
  - Cell compatibility (short term exposure)
  - Reversable gelation
  - Compatibility with gel system 2

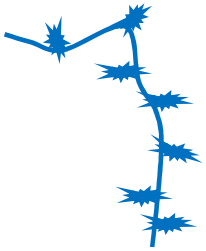
- Examples:

Hydrogel	Gel fomation	Gel dissolution
Polyoxamers; e.g. Pluronics F-127)	Increase temperature	Lower temperature
N-Isopropylacryamide (poly(NIPAAM))	Increase temperature	Lower temperature
Dextran-PEG	Click chemistry (Cyclooctyne-azide)	Dextranase
Gelatine	Lower temperature	Increase temperature, protease

Cellendes Hydrogel System

Thiol-reactive (e.g. maleimide) Polymer

(Dextran, Polyvinyl alcohol)

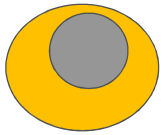


Thiol-modified Peptide

(RDG, IKVAV, YIGSR, GFOGER...)

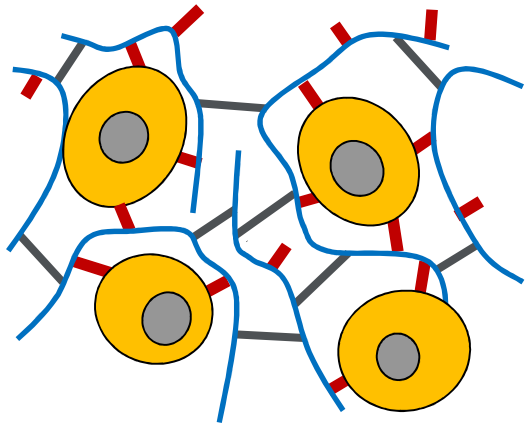
Cells

(Provided by user)



Thiol-modified Crosslinker

(PEG, MMP-cleavable PEG, Hyaluronic acid)

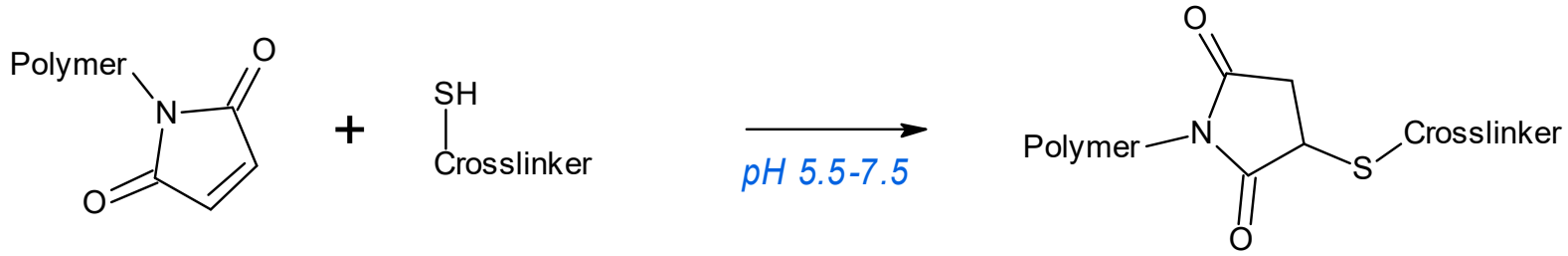


Michael Addition vs Thiol-ene Reaction

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

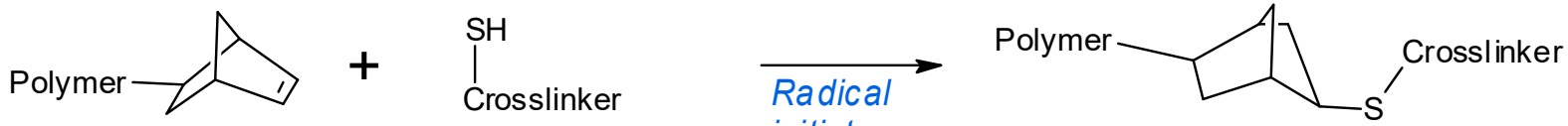
CELLENDES
Cell • Environment • Design

- Michael Addition (current Cellendes product):



Maleimide

- Thiol-ene Reaction (light-induced gel formation):



Norbornene

6-Month Work Plan

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

Development of Norbornene-functionalized PVA

- Acquisition of materials (Chemicals, UV pen…)
- Quantitative assay for Norbornene groups
- Chemical conversion
- Purification procedure

Characterization of Norbornene-PVA preparations

- Solubility
- Purity
- Degree of substitution
- Gel formation ability with thiol-functionalized crosslinker
- Stability of Norbornene group

T2.2. Selection of initiator for light-induced gel formation

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

Initiator	Peak absorbance
LAP (Lithium phenyl-2,4,6-trimethylbenzoylphosphinate)	375 nm
VA-086 (2,2'-azobis[2-methyl-N-(2-hydroxyethyl)propionamide])	375 nm
Eosine Y (Tetrabromfluorescein)	518 nm

T2.2. Polymer functionalization and biocompatibility evaluation

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

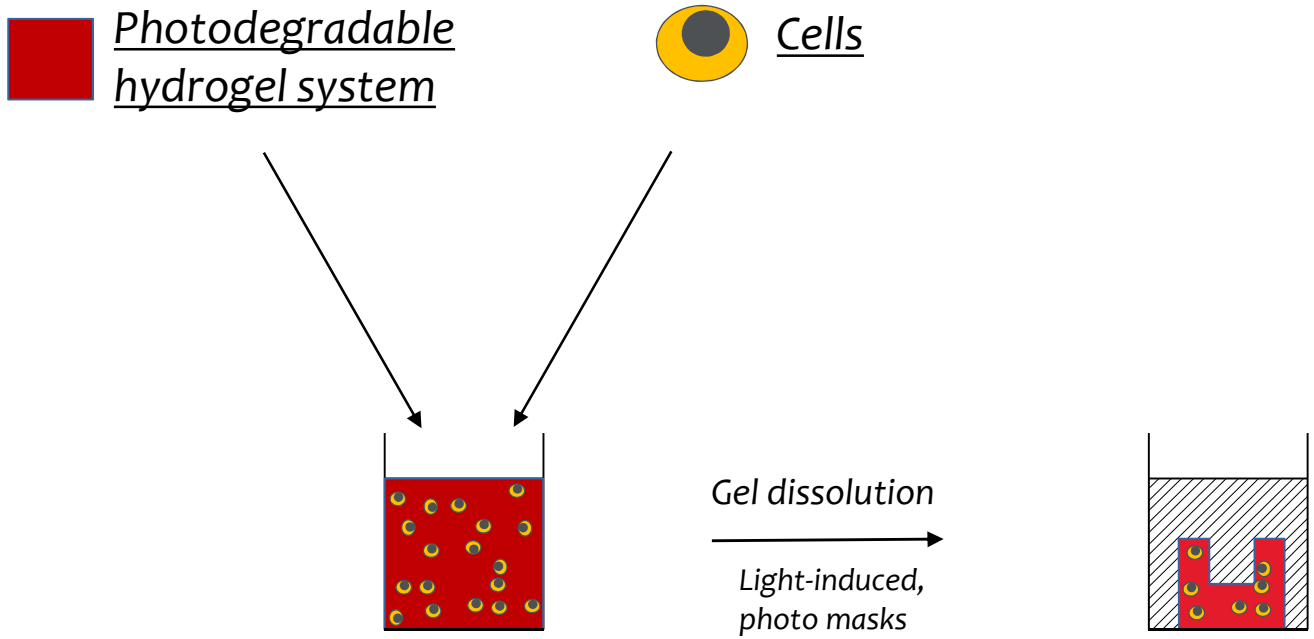
Functionalization with thiol-modified peptides and cell degradation signals

- Attachment efficiency
- Biological functionality

Characterization of hydrogels

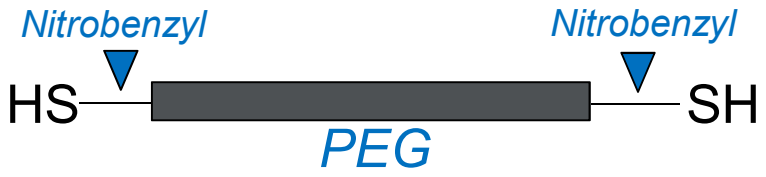
- Initiator selection and formulation
- Components formulation
- Kinetics of light-induced gel formation
- Control of gel stiffness
- Cell survival and vitality after gel formation

Plan B: Photodegradable hydrogel

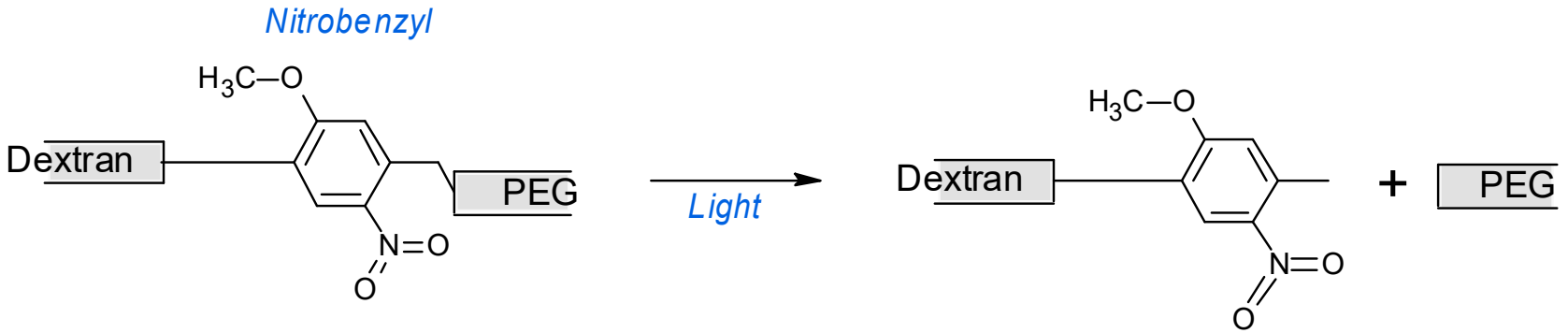


Plan B: Chemistry of photodegradable hydrogel

Photodegradable crosslinker:



Photodegradable hydrogel:



Summary

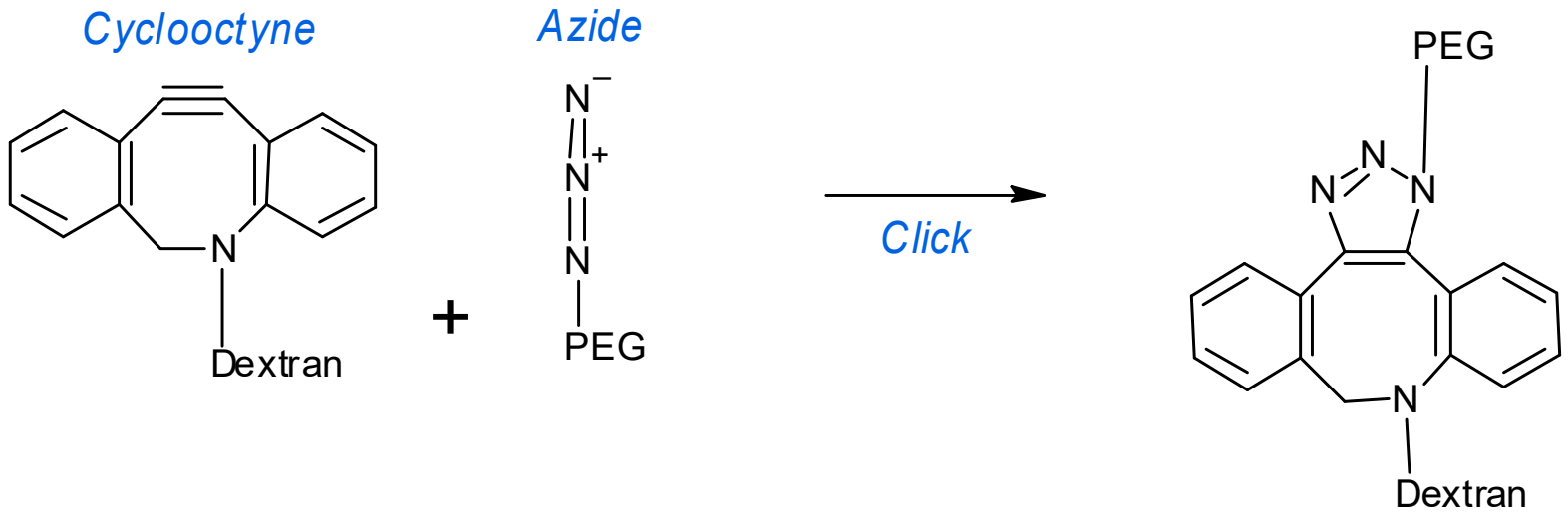
- Reversable gel system (Gel System 1)
  - Reverse thermoresponsive or enzyme-degradable
    - Cell compatibility (short term exposure)
    - Compatibility with gel system 2
- Photopolymerizable gel system (Gel System 2)
  - Thiol-ene-based photo reaction
    - Selection of photo initators (LAP, VA-086, Eosin Y)
  - Controlable biological functions
    - Gel stiffness, adhesion sites, cell degradable)
- Plan B: photodegradable hydrogel
  - Functions
    - Gel stiffness, adhesion sites, cell degradable, user degradable)

T2.3. Development of reversibly crosslinkable hydrogels: Dextran-PEG

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

Copper-free Click reaction:



T2.3. Fabrication and characterization of clickable polymers

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

CELLENDES
Cell • Environment • Design

Development of Cyclooctyne-functionalized Dextran

- Acquisition of materials (chemicals, UV pen…)
- Quantitative assay for Cyclooctyne groups
- Chemical conversion
- Purification procedure

Characterization of Cyclooctyne-Dextran preparations

- Purity
- Degree of substitution
- Gel formation ability with azide-functionalized crosslinker
- Stability of Norbornene group
- Solubility

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

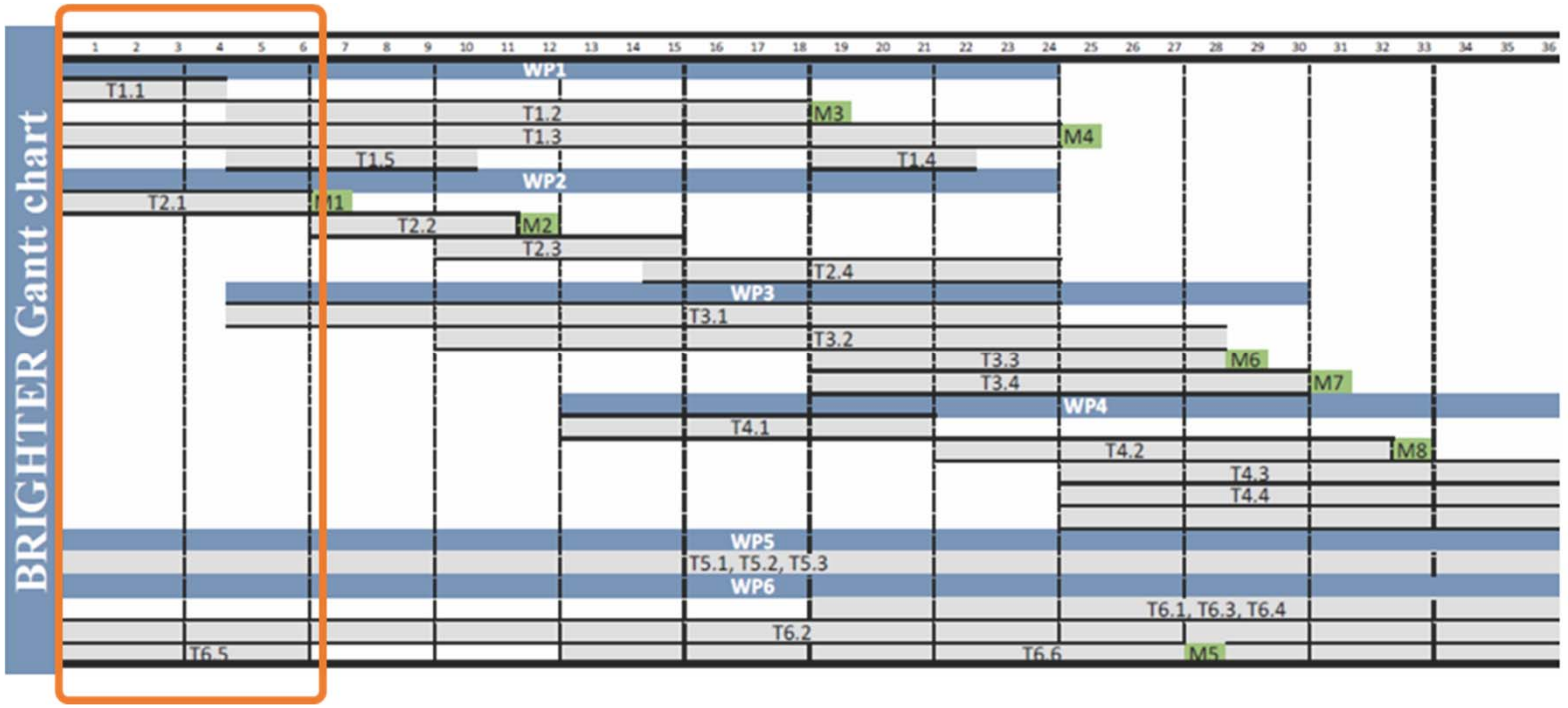
Institute for Bioengineering of Catalonia (IBEC)

Kick off meeting

4th July 2019

Work plan up to M6

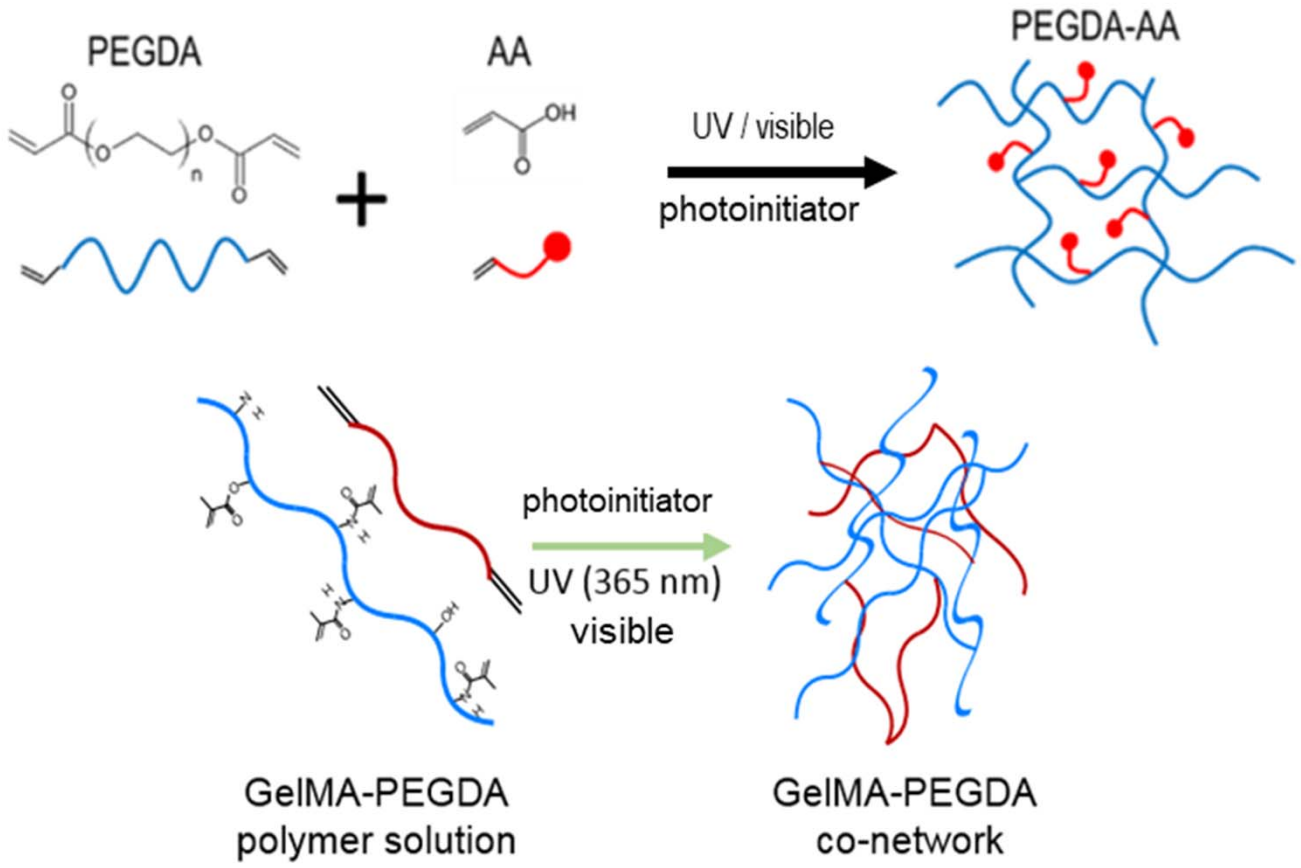
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Task 3.1. Calibration of the crosslinking density and stiffness of hydrogels (M5-M28)

Previous experience

Photopolymerization of acrylate-based hydrogels by **UV** (365 nm) and **visible** light (white and 405 nm).



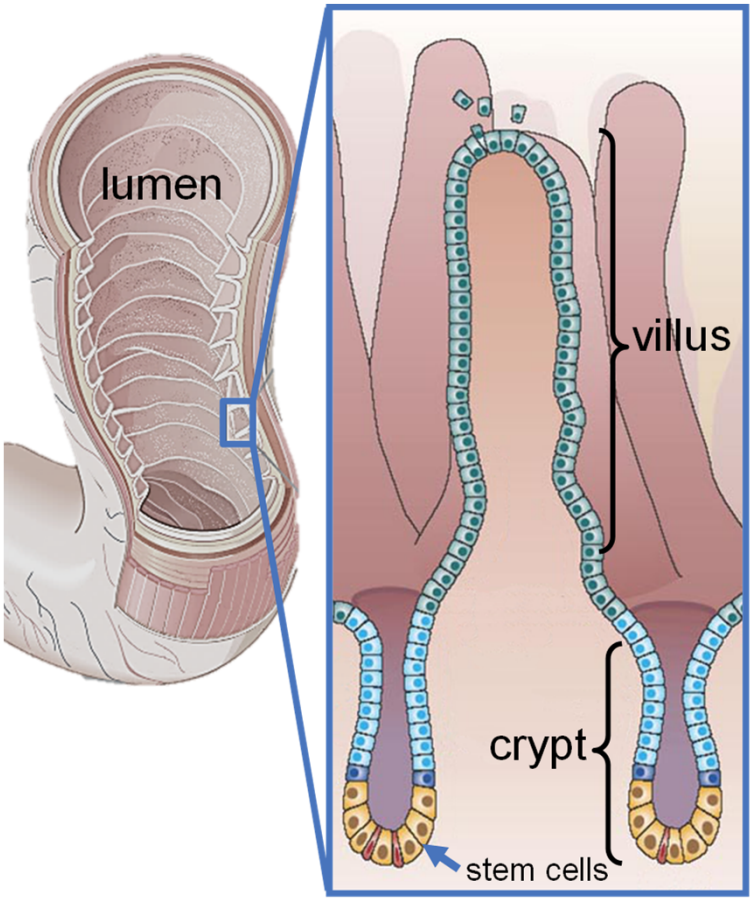
Oxygen and free radical photopolymerization

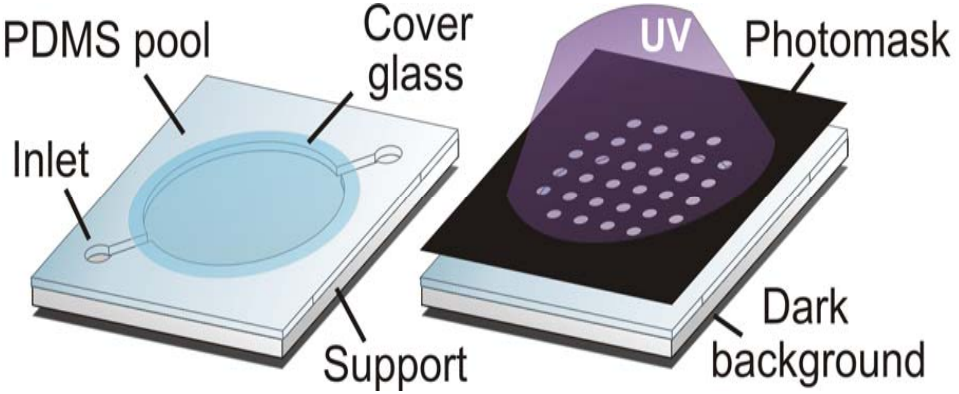
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

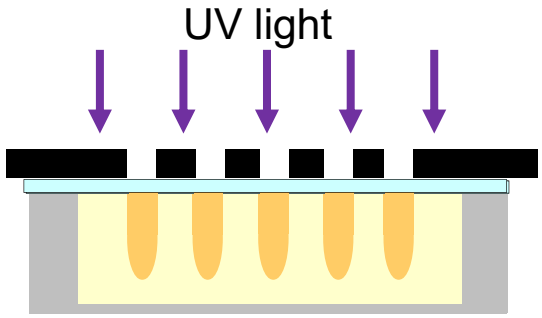
$PI + h\nu \rightarrow R^*$	Photoinitiator photolysis
$R^* + M \rightarrow RM^*$	Chain initiation
$RM^*_n + M \rightarrow RM^*_{n+1}$	Chain propagation
$RM^*_n + RM^*_m \rightarrow RM_nM_m$	Chain termination
$RM^*_n + O_2 \rightarrow RM_nOO$	Oxygen inhibition

Biofabrication methods – small intestine

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

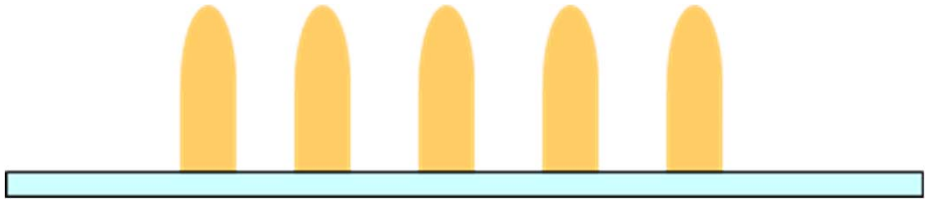


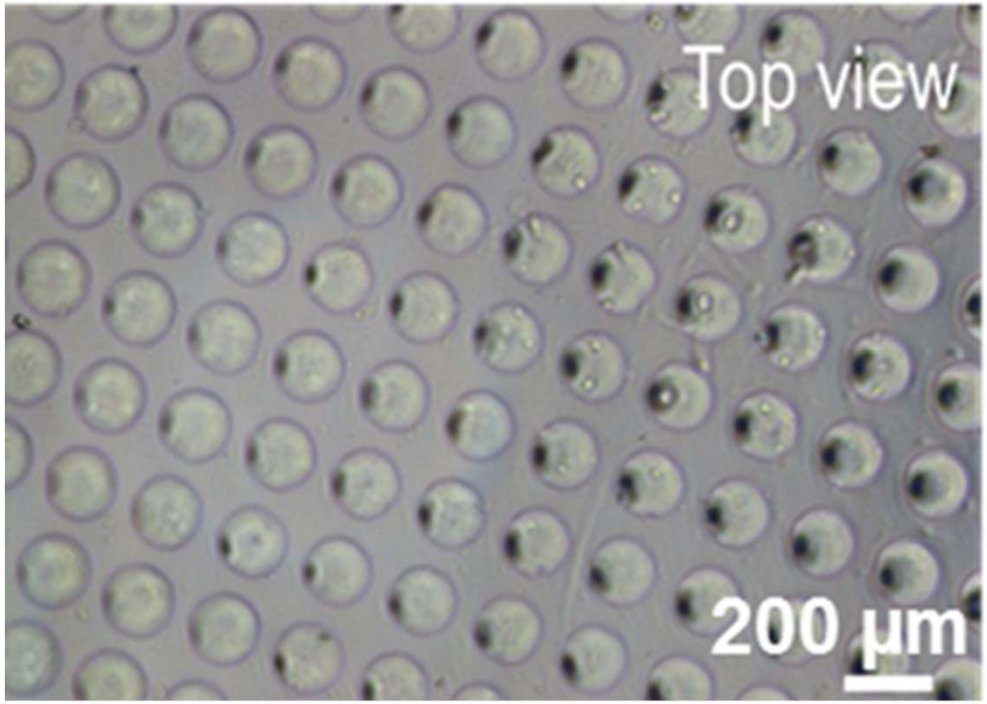


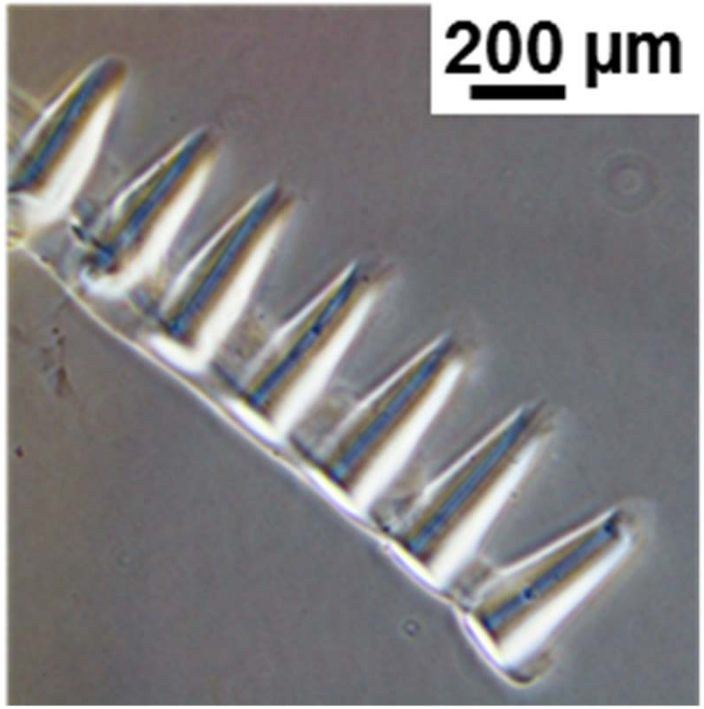


Photolithography produces 3D structures

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

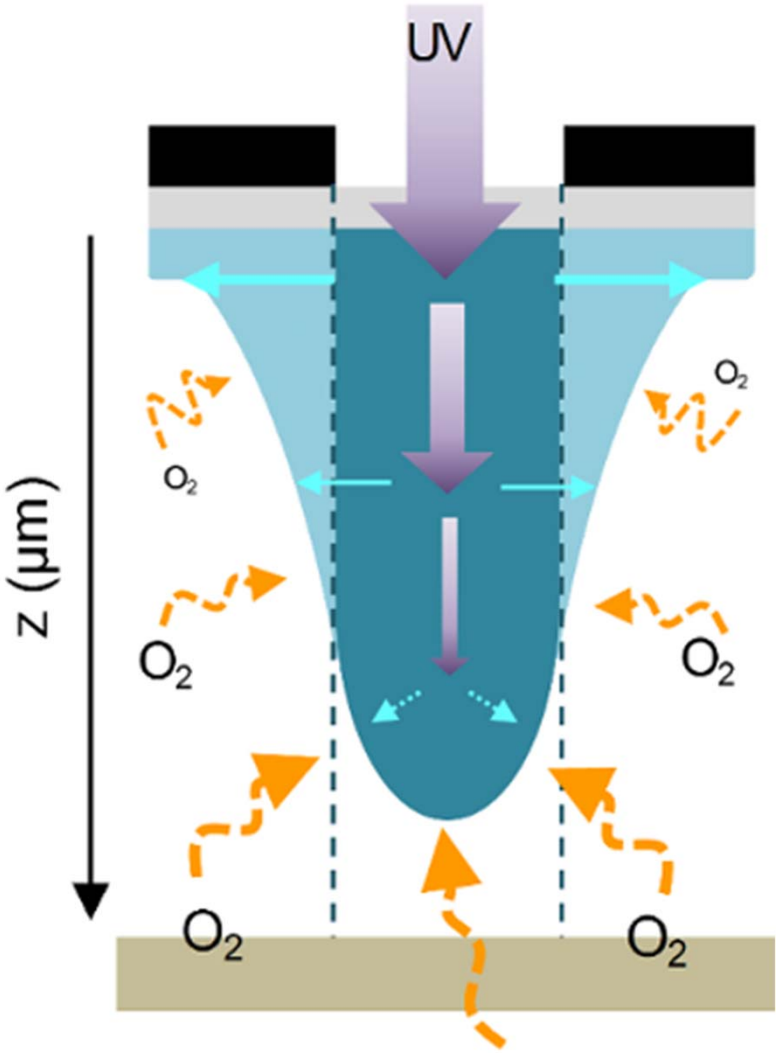






Complex microstructures can be generated

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Damköhler number

$$Da = \frac{\tau_{diff}}{\tau_{depl}} = \frac{R^2/D_0}{[O_2]_0/\varphi\,\varepsilon[PI]I}$$

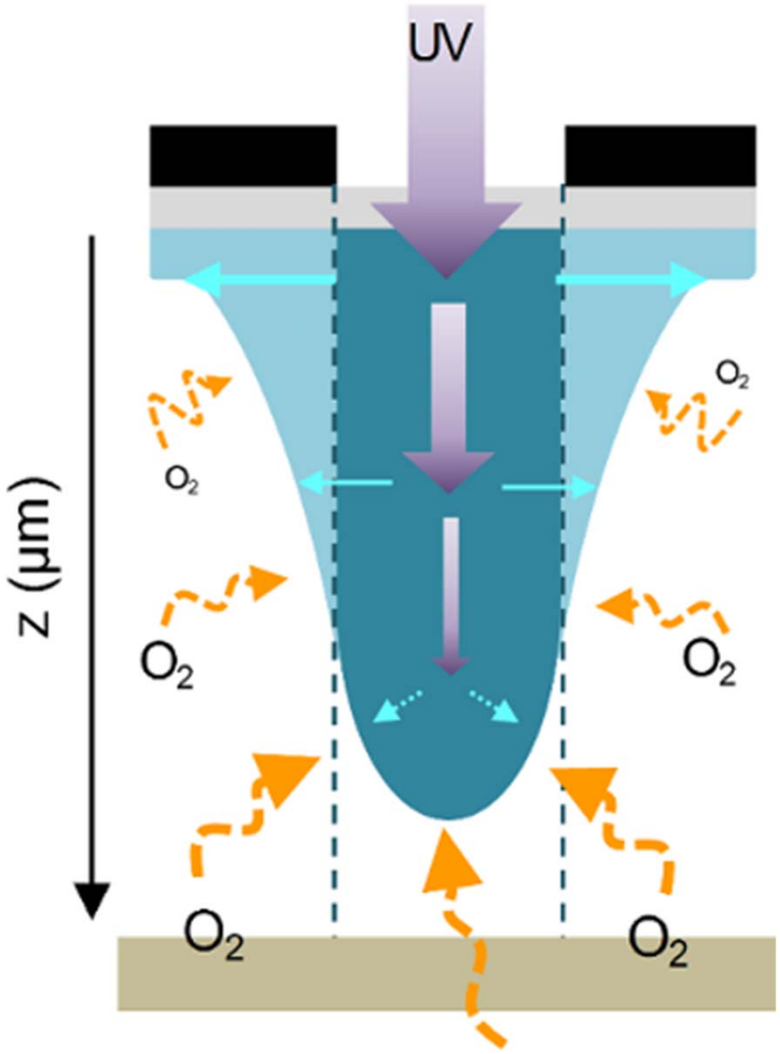
Da << 1 No polymerization

Da >> 1 Fast polymerization

Da ~ 1 Oxygen gradient

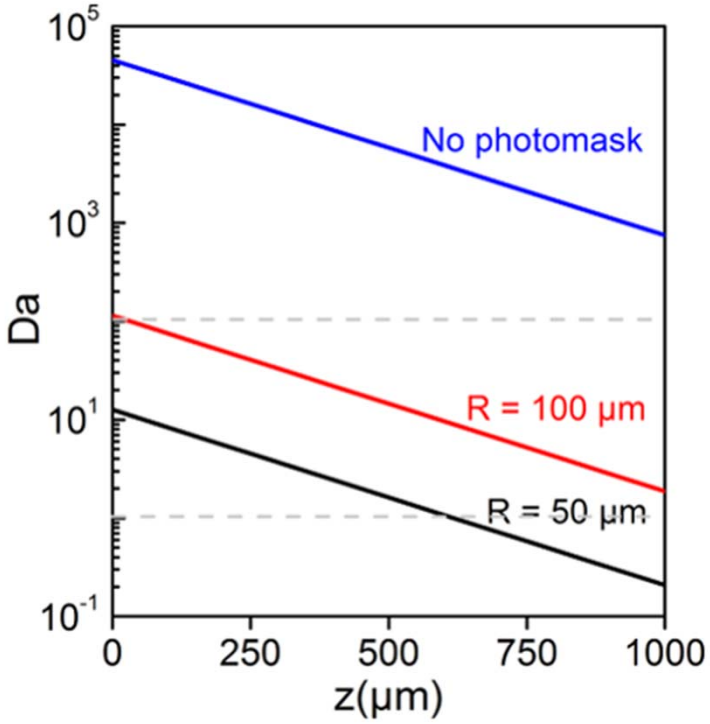
Complex microstructures can be generated

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



$$Da = \frac{\tau_{diff}}{\tau_{depl}} = \frac{R^2/D_0}{[O_2]_0/\varphi\,\varepsilon[PI]I} \rightarrow I(z)$$

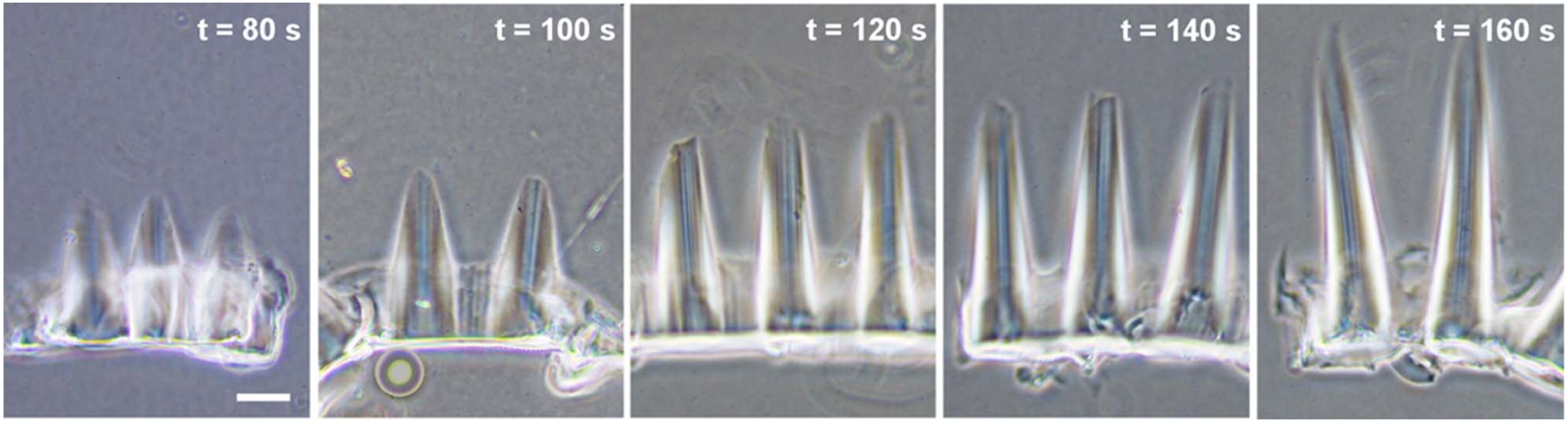
$$Da\,(z) = \frac{R^2/D_0}{[O_2]_0/\varphi\varepsilon[PI]I\ \cdot exp(-2.303\varepsilon[PI]z)}$$



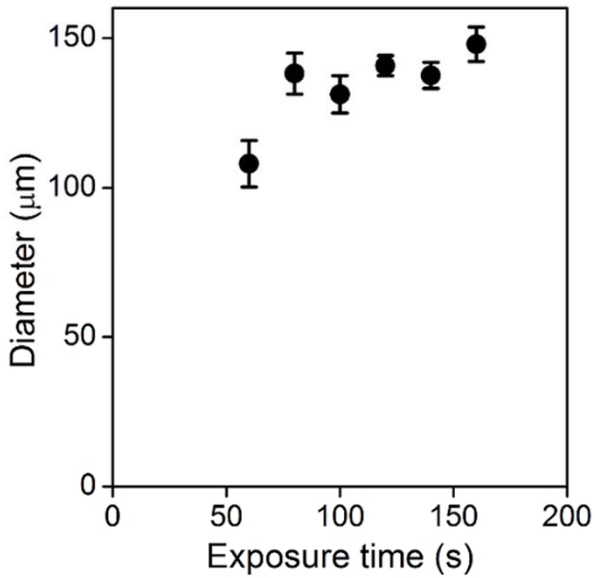
Precise control of feature size

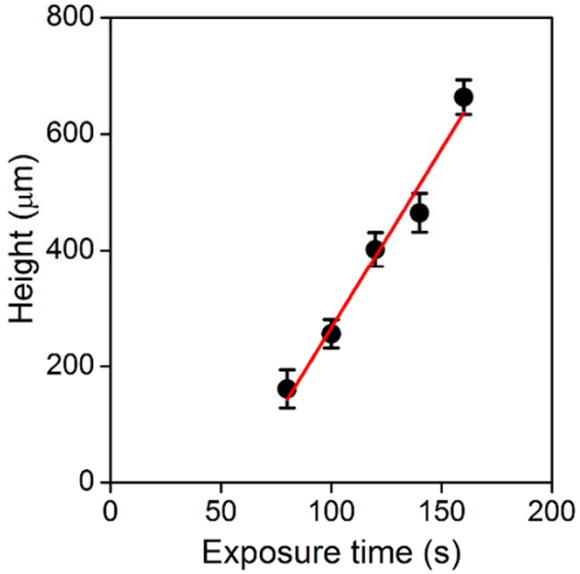
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

$PEGDA_{6000}$ 6.5% (w/v) + AA 0.3% (w/v) + 1% PI



Scale bar = 100 μm



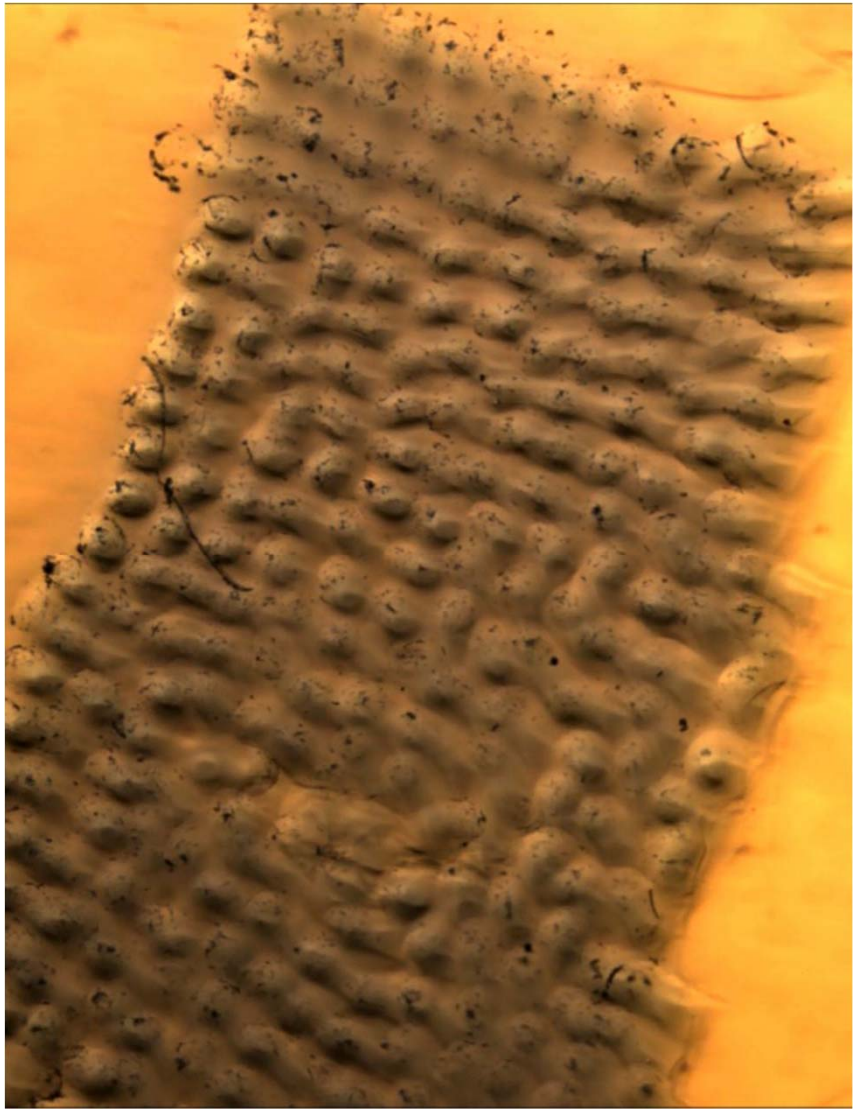


Aspect ratio 1:6

Castaño et al. *Biofabrication* (2019)

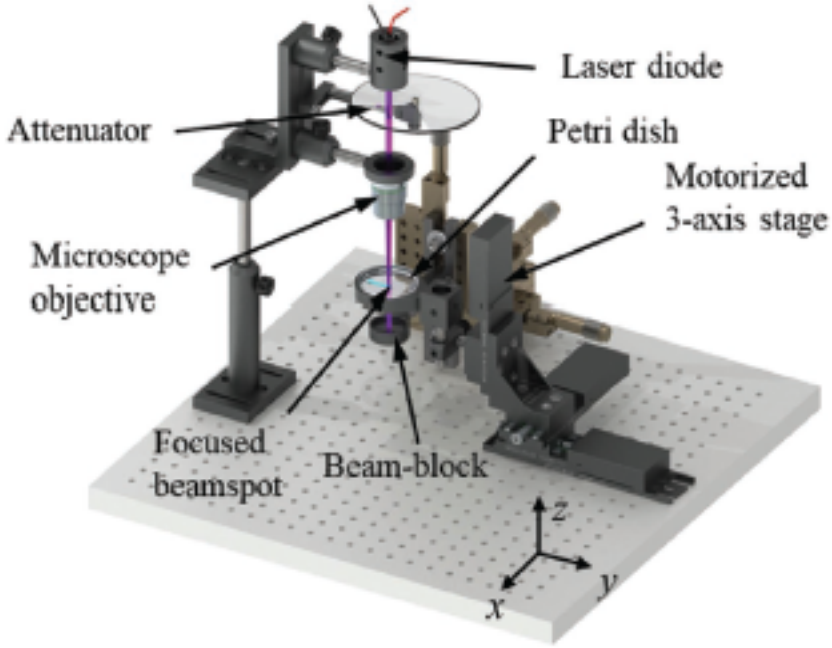
In vivo vs. In vitro

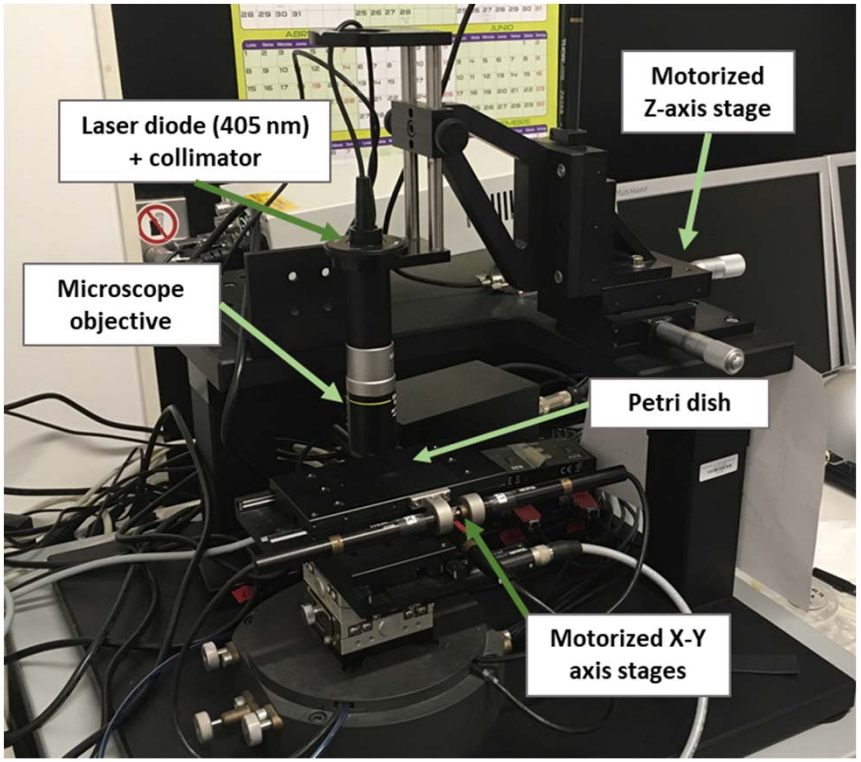
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

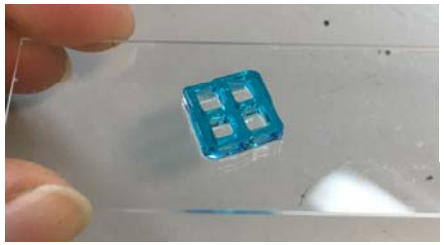


Direct-laser photopolymerization

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



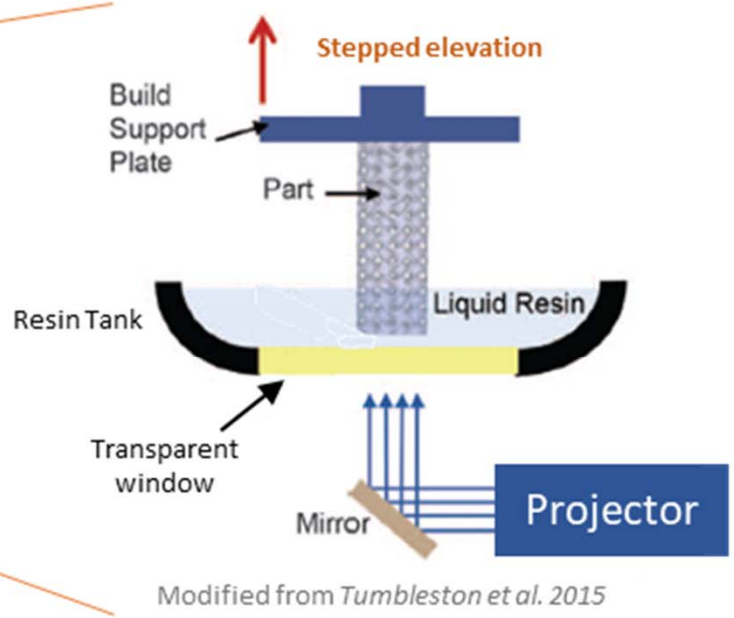




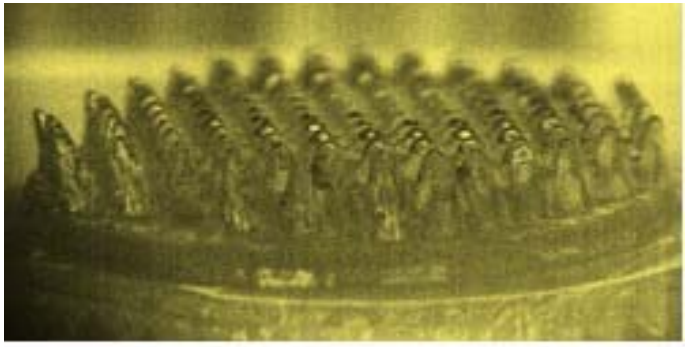
CLIP-based 3D printing

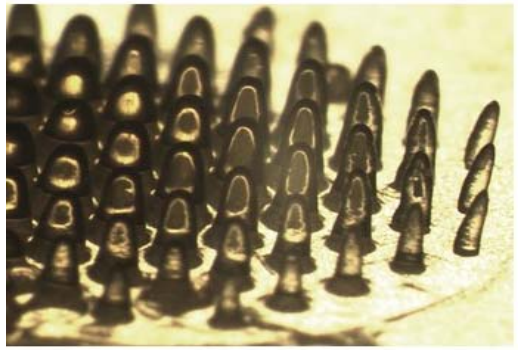
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

3D SOLUS system
(IBEC cleanroom)



Modified from *Tumbleston et al. 2015*





Photoinitiators

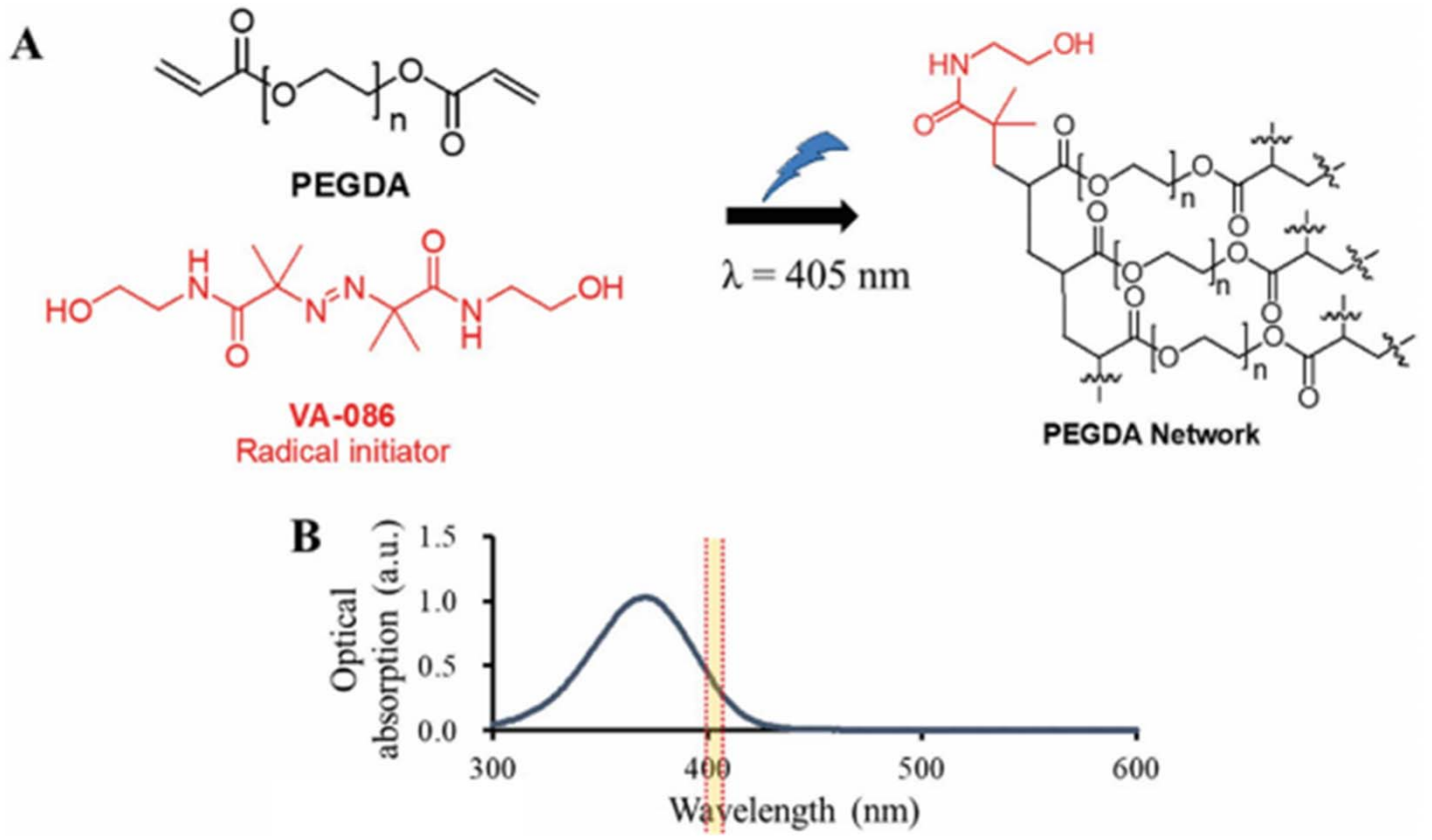
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Table 1. Comparison of Widely Used Photoinitiators in Tissue Engineering

chemical name	abbreviation	absorbing peak (nm)	hydrogel monomers
1-[4-(2-hydroxyethoxy)-phenyl]-2-hydroxy-2-methyl-1-propanone	Irgacure 2959	257	PEGDA, GelMA, hyaluronic acid (HA), etc.
lithium phenyl-2,4,6-trimethylbenzoylphosphinate	LAP	375	PEGDA, GelMA, HA
2,2′-azobis[2-methyl-*n*-(2-hydroxyethyl)propionamide]	VA-086	385	PEGDA, GelMA
2′,4′,5′,7′-tetrabromofluorescein disodium salt	eosin Y	514	PEGDA, PEGDA–GelMA

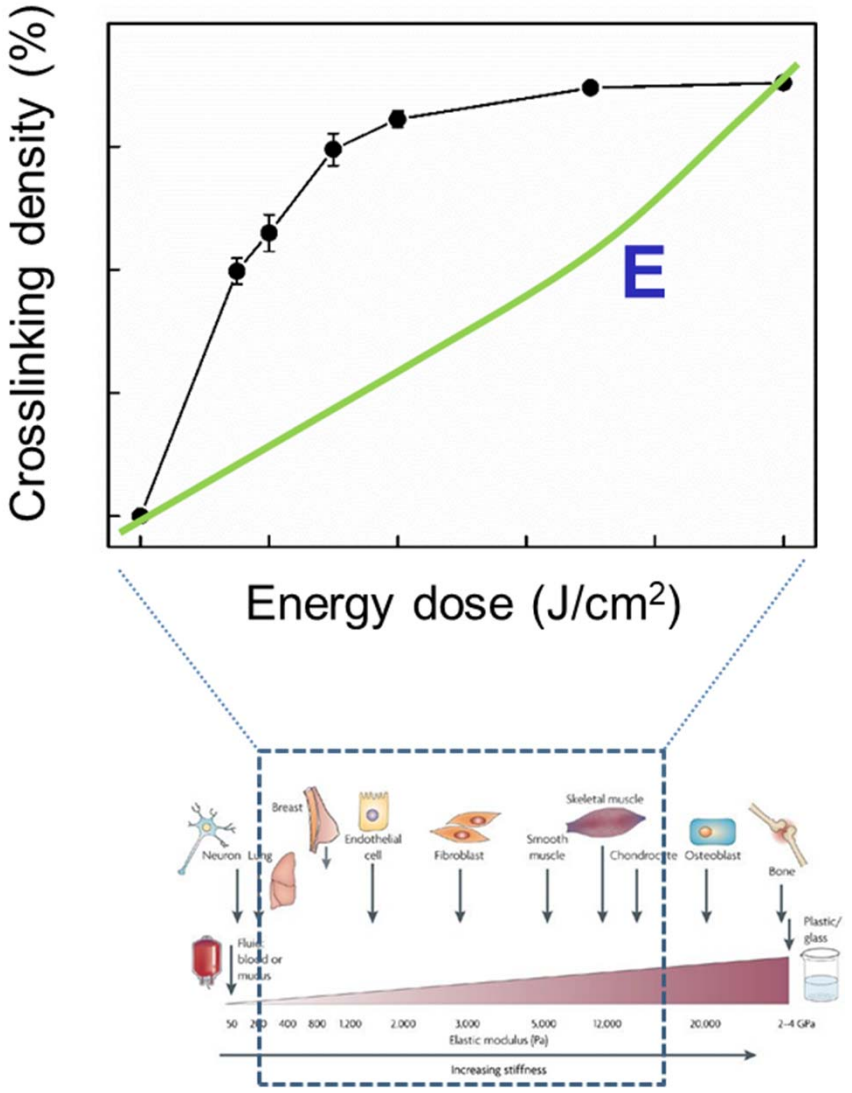
Our experience: Irgacure 2959
LAP

In the Project we considered VA-086


A
PEGDA
VA-086
Radical initiator
λ = 405 nm
PEGDA Network
B
Optical absorption (a.u.)
1.5
1.0
0.5
0.0
300
400
500
600
Wavelength (nm)

Photopolymerization controls crosslinking degree

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

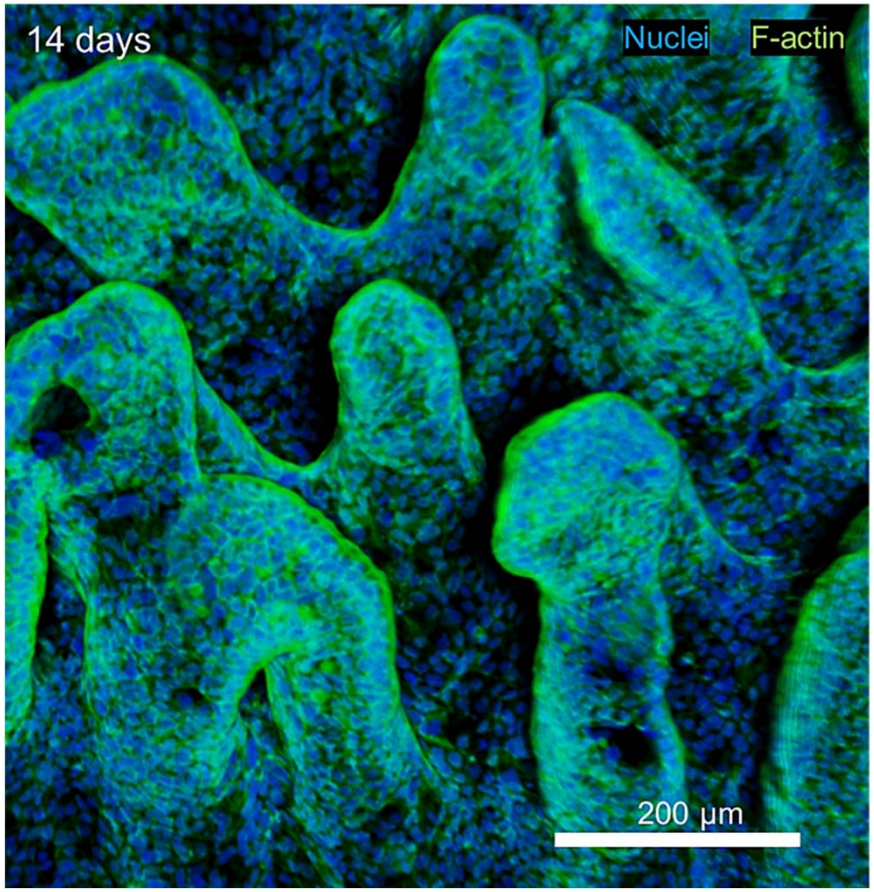


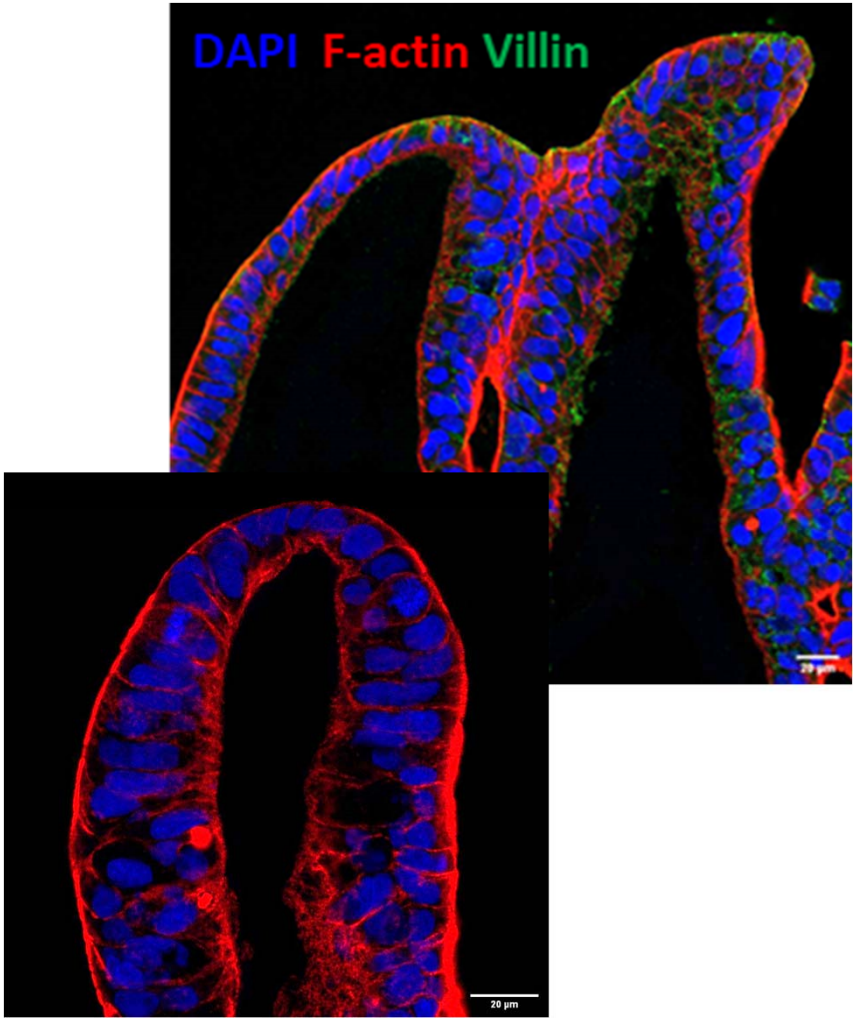
- Mechanical properties
- Swelling behavior
- Pore size and mesh characteristics

Butcher et al. *Nat Rev Cancer* (2009)

Process is compatible with cell culture

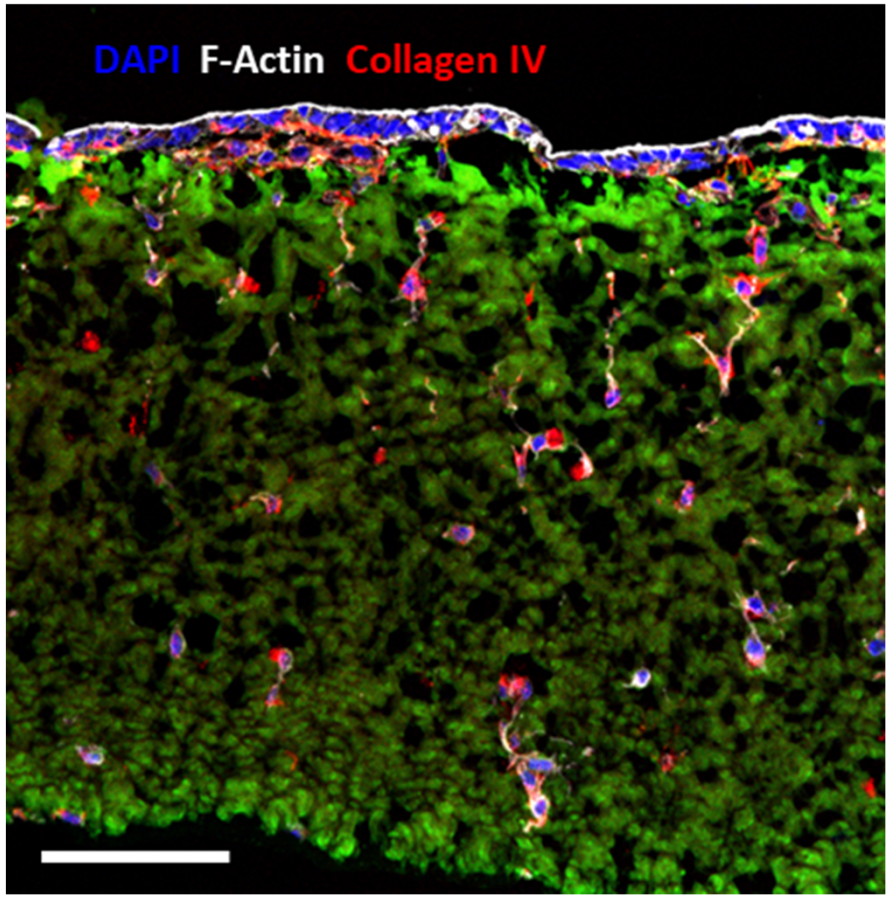
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

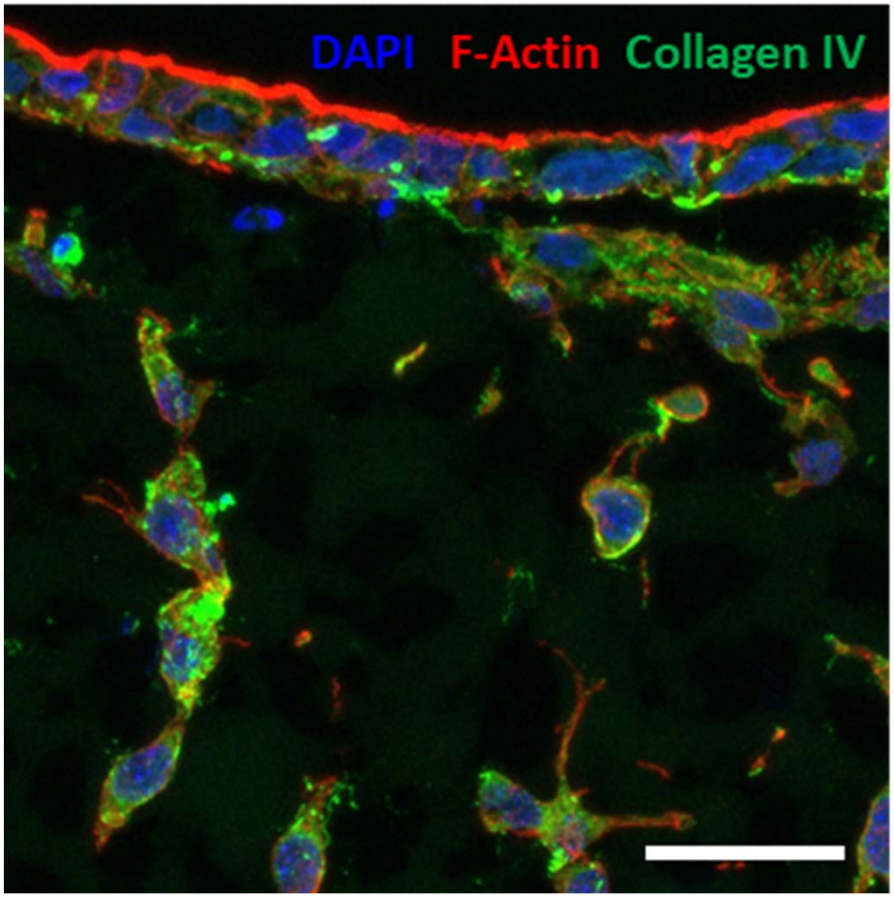




Process is compatible with cell culture

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY





BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

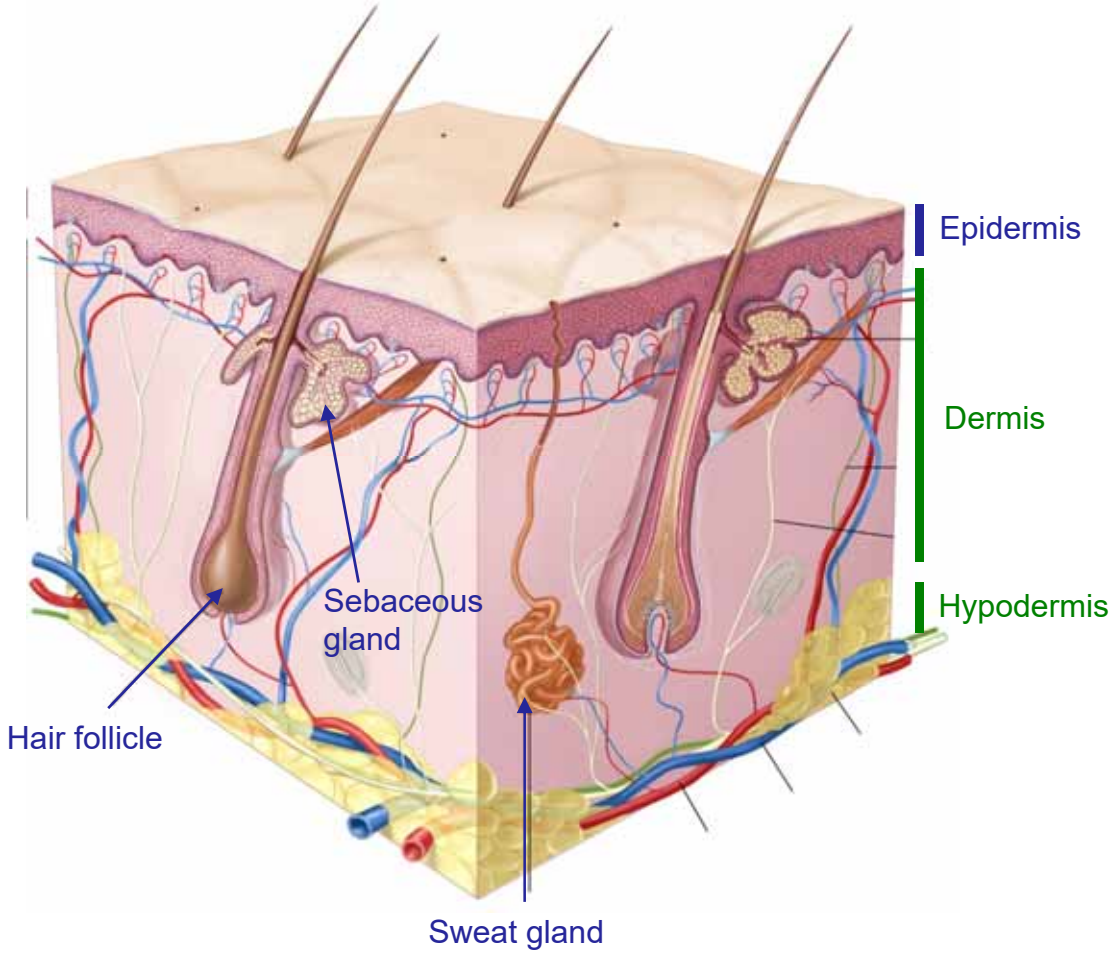
Work Package 4 : Engineered skin tissues

TECHNION
Ruby Shalom-Feuerstein

Kick off meeting
4th July 2019

WP4: Engineered skin tissues

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



WP4

4.1 SC isolation/characterization

4.2 Reconstituted epidermis/dermis

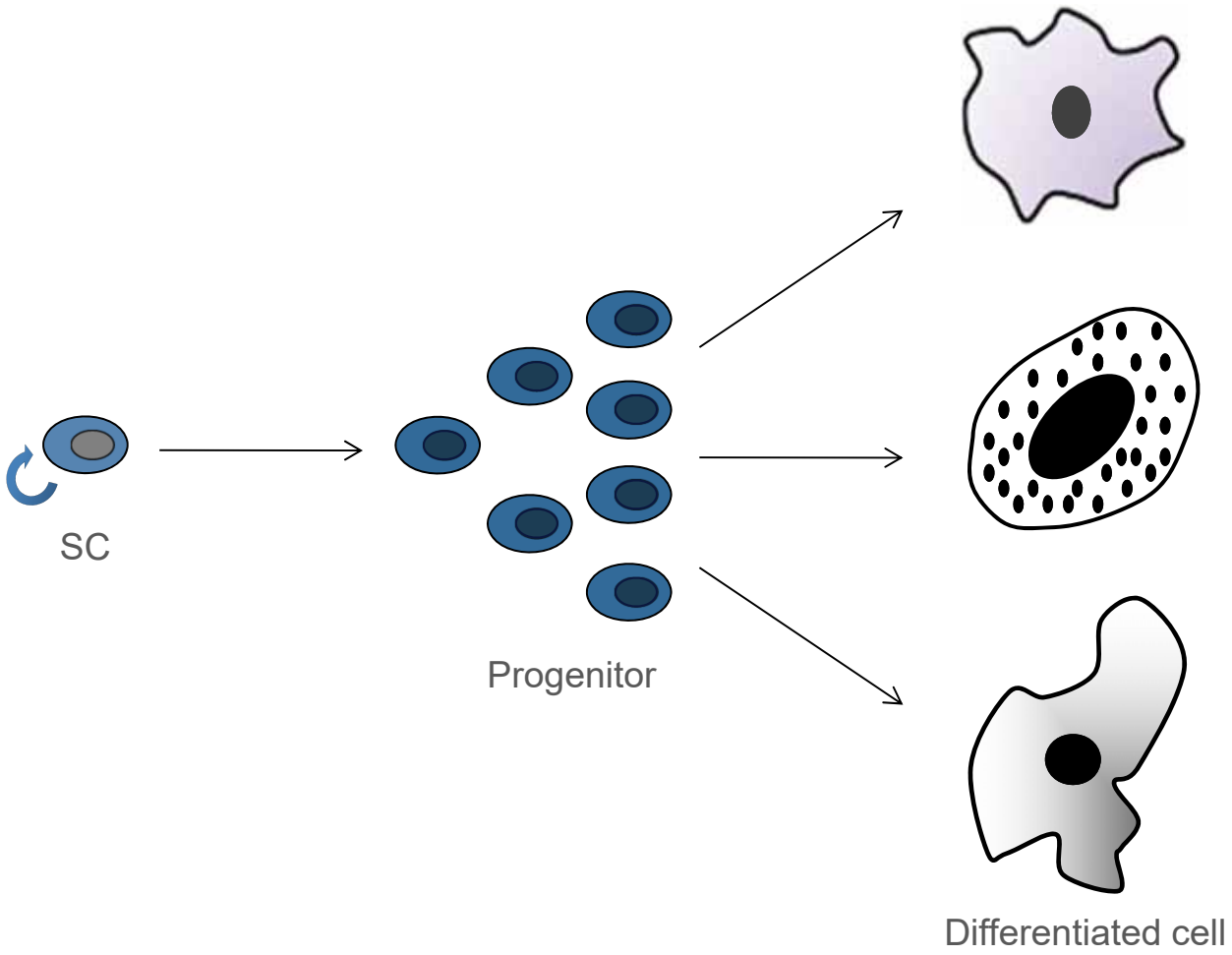
4.3 Reconstituted hair follicle/Seb. gland

4.4 Reconstituted sweat gland

Kick off meeting
4th July 2019

SC self-renewal and differentiation

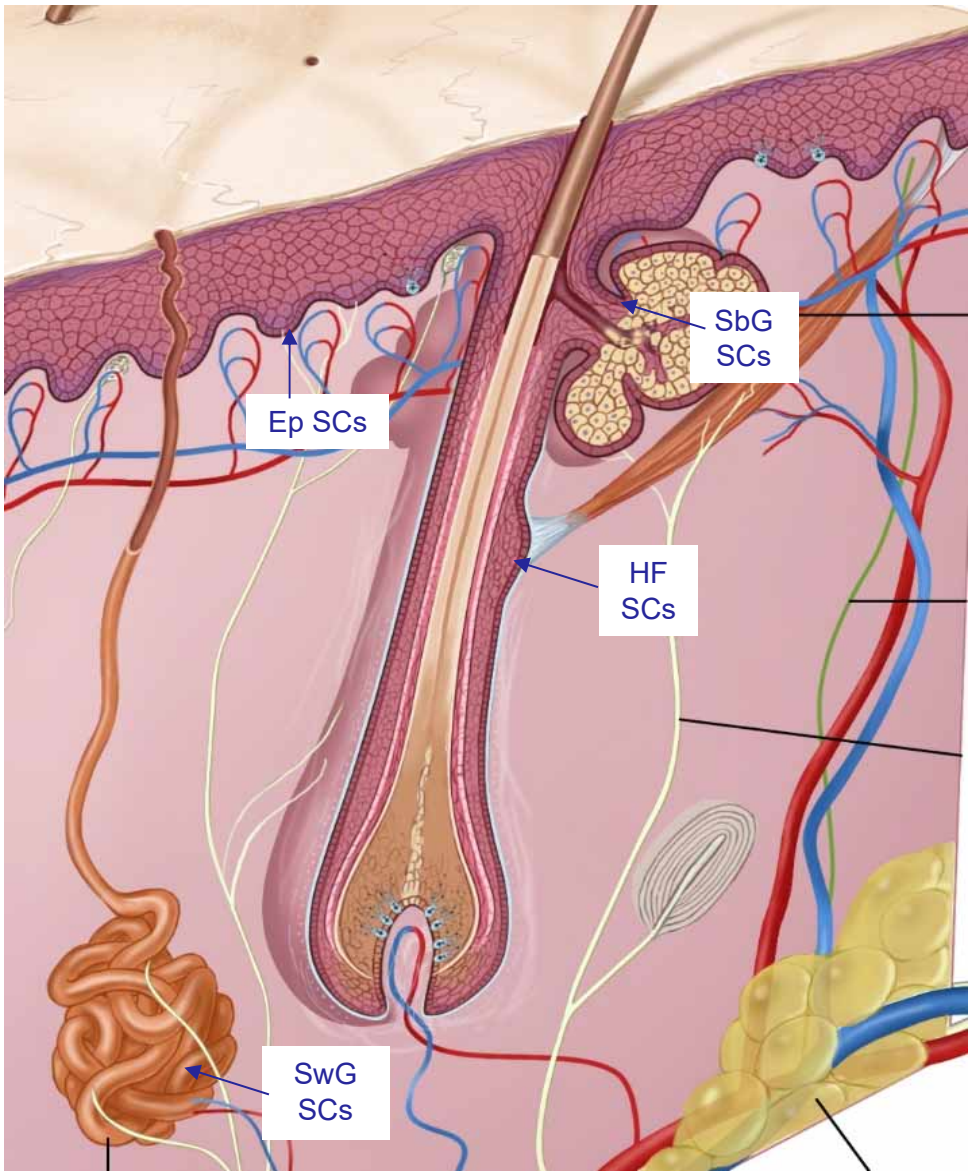
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Kick off meeting
4th July 2019

Stem cells & compartments

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY



Epidermis

Dermis

Epidermal SCs
Sca1+/Itga6+

Hair follicle SCs
CD34+

Sebaceous gland SCs
Blimp1-YFP+

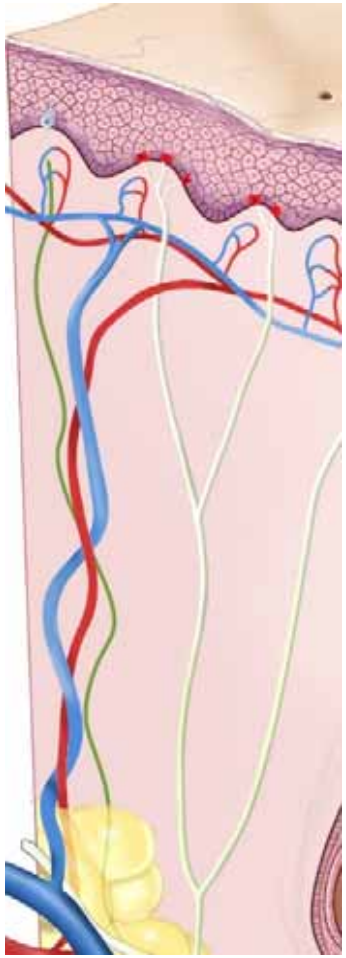
Sweat gland SCs
Itga6+/itgb1+

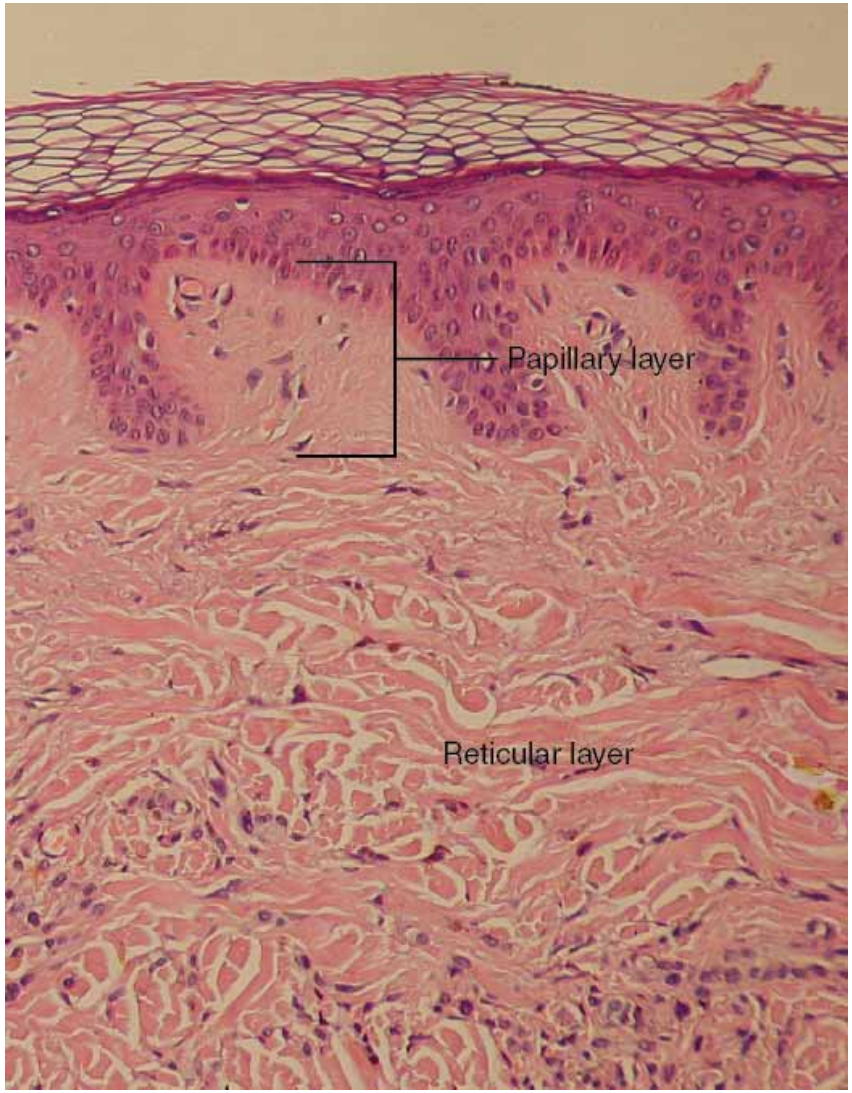
Dermal cells
Fibroblasts
Immune cells (T, B, MΦ)
Blood vessels
Neurons
Dermal papilla Sox2-GFP+

Kick off meeting
4th July 2019

ECM

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY





Epidermis

Papillary Dermis

Reticular Dermis

Kick off meeting
4th July 2019

4.1 SC isolation & characterization (TECHNION)

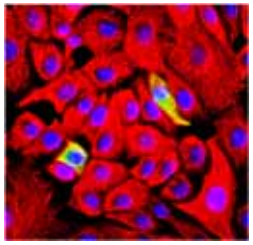
BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

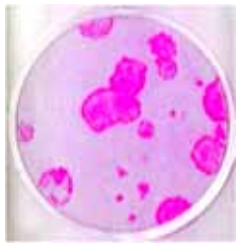
Experimental workplan

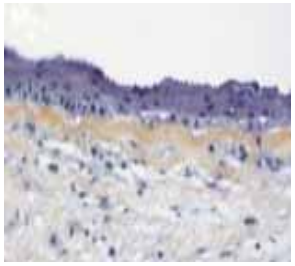
SC isolation

Concerns:

- Markers? Death? Proliferation
- Clonogenic?
- Stratify? Barrier?


Staining


Colony formation


Organotypic culture

Mouse or Human

Epidermal SCs
HaCaT, hForeskin, mouse epidermis
Sca1+/Itga6+

Hair follicle SCs
CD34+

Sebaceous gland SCs
Blimp1-YFP+

Sweat gland SCs
Itga6+/itgb1+

Dermal cells
Fibroblasts
Immune cells (T, B, MΦ)
Blood vessels
Neurons
Dermal papilla Sox2-GFP+

Kick off meeting
4th July 2019

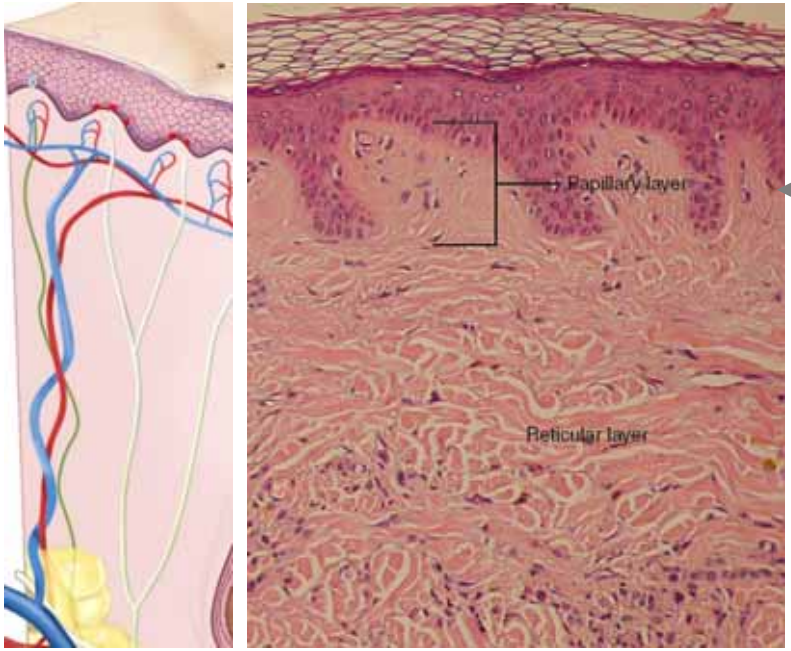
4.2 Reconstituted epidermis & underlying dermis (TECHNION, GUF, IBEC)

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Experimental workplan

Cells: Epidermal SCs, native dermal cells

Specific structural considerations:
Rete ridge, basement menbrane, papillary dermis and reticular dermis



Epidermis
Epidermal SCs

Basement membrane

Papillary Dermis
ECM (collagen, elastin)
Fibroblasts
Immune cells (T, B, Macrophages etc)
Blood vessels
Neural structures

Reticular Dermis
Stiffer ECM

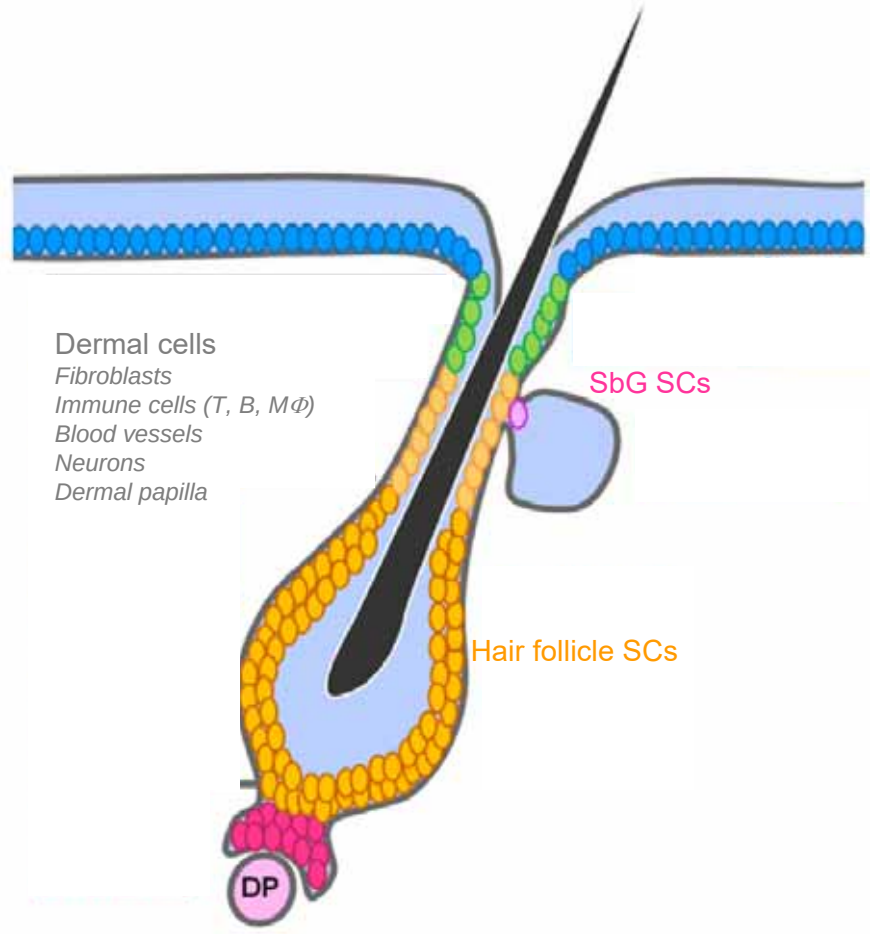
4.3 Bioprinting hair follicle (TECHNION, GUF CELLENDES)

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Experimental workplan

Cells: HF SCs, SbG SCs, native dermal cells

Specific structural considerations:
Basement menbrane, papillary dermis and reticular dermis



Epidermis
Epithelial SCs

Basement membrane

Papillary Dermis
ECM (collagen, elastin)
Fibroblasts
Immune cells (T, B, Macrophages etc)
Blood vessels
Neural structures

Reticular Dermis
Stiffer ECM

Kick off meeting
4th July 2019

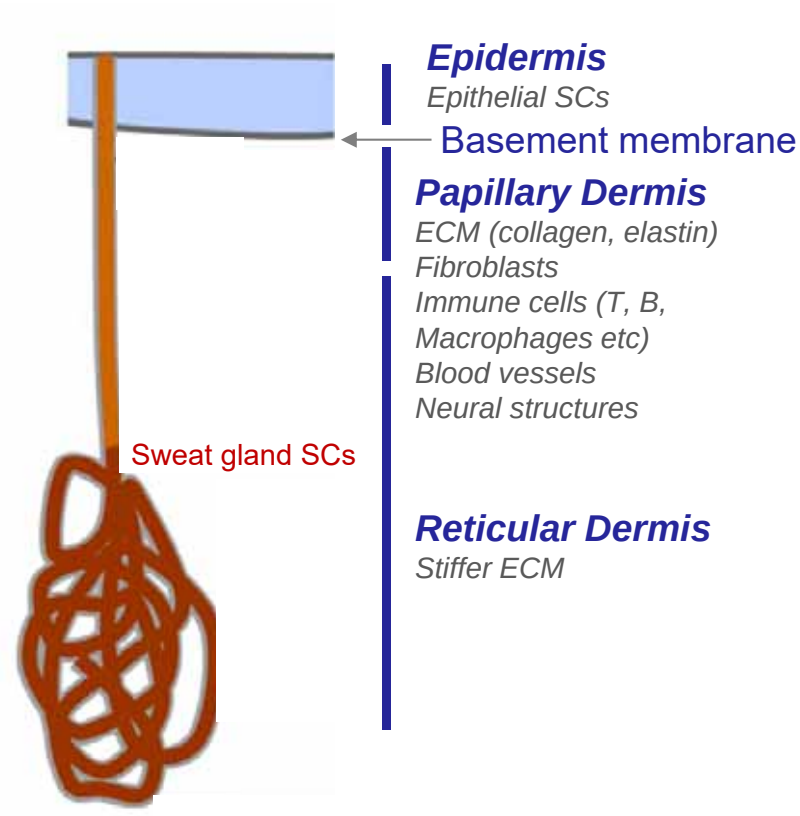
4.3 Bioprinting hair follicle (TECHNION, GUF CELLENDES)

BRIGHTER
BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Experimental workplan

Cells: Sweat Gland SCs, native dermal cells

Specific structural considerations:
Basement menbrane, papillary dermis and reticular dermis



Kick off meeting
4th July 2019

Deliverables

4.1 Protocols to isolate, culture & characterize relevant skin SCs

4.2 Reconstitution of epidermis/dermis

4.3 Reconstitution of hair follicle/Seb. Gland & Sweat gland

4.4 Improved characteristics of engineered skin

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Grant Management

Kick off meeting

4-5th July 2019

General Information

TITLE: Bioprinting by light-sheet lithography: engineering complex tissues with high resolution at high speed

ACRONYM: BRIGHTER

DURATION: 01/07/2019 – 30/06/2022 (3 year project)

PROJECT ID: 828931

FUNDED UNDER: H2020-FETOPEN-2018-2020 (FET Open – Challenging Current Thinking)

TOPIC: FETOPEN-01-2018-2019-2020

USEFUL WEBSITES:

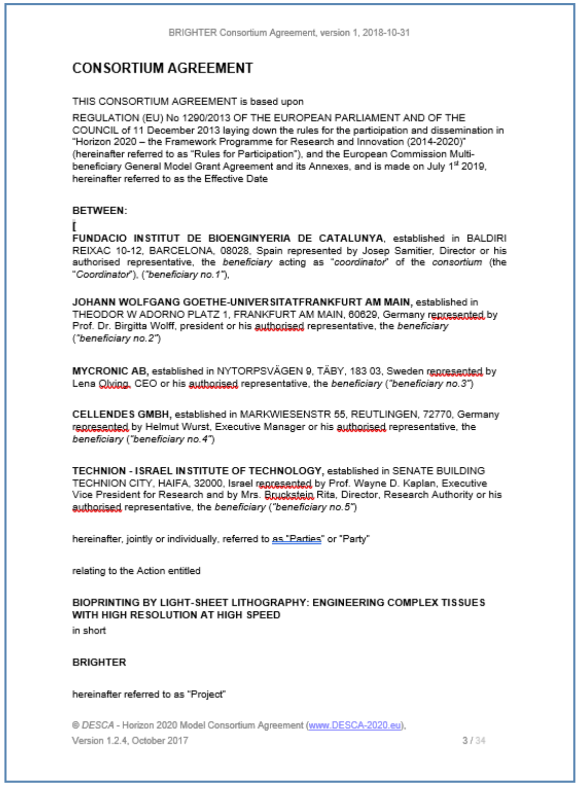
- CORDIS Web: https://cordis.europa.eu/project/rcn/220538/factsheet/en
- BRIGHTER Web: under construction
- BRIGHTER Intranet: under construction (CONFIDENTIAL FILES)
  - GRANT AGREEMENT (GA, Declaration, Data sheet, etc.)
  - CONSORTIUM AGREEMENT
  - MEETING MINUTES
  - DELIVERABLES

Three main documents to follow:

GRANT AGREEMENT

NUMBER 828931 — BRIGHTER

Grant Agreement (GA)



BRIGHTER Consortium Agreement, version 1, 2018-10-31

CONSORTIUM AGREEMENT

THIS CONSORTIUM AGREEMENT is based upon

REGULATION (EU) No 1290/2013 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2013 laying down the rules for the participation and dissemination in "Horizon 2020 – the Framework Programme for Research and Innovation (2014-2020)" (hereinafter referred to as "Rules for Participation"), and the European Commission Multi-beneficiary General Model Grant Agreement and its Annexes, and is made on July 1st 2019, hereinafter referred to as the Effective Date

BETWEEN:

FUNDACIO INSTITUT DE BIOENGINYERIA DE CATALUNYA, established in BALDIRI REIXAC 10-12, BARCELONA, 08028, Spain represented by Josep Samitier, Director or his authorised representative, the *beneficiary* acting as *"coordinator"* of the *consortium* (the *"Coordinator"*), *("beneficiary no.1")*,

JOHANN WOLFGANG GOETHE-UNIVERSITATFRANKFURT AM MAIN, established in THEODOR W ADORNO PLATZ 1, FRANKFURT AM MAIN, 60629, Germany represented by Prof. Dr. Birgitta Wolff, president or his authorised representative, the *beneficiary ("beneficiary no.2")*

MYCRONIC AB, established in NYTORPSVÄGEN 9, TÄBY, 183 03, Sweden represented by Lena Olving, CEO or his authorised representative, the *beneficiary ("beneficiary no.3")*

CELLENDES GMBH, established in MARKWIESENSTR 55, REUTLINGEN, 72770, Germany represented by Helmut Wurst, Executive Manager or his authorised representative, the *beneficiary ("beneficiary no.4")*

TECHNION - ISRAEL INSTITUTE OF TECHNOLOGY, established in SENATE BUILDING TECHNION CITY, HAIFA, 32000, Israel represented by Prof. Wayne D. Kaplan, Executive Vice President for Research and by Mrs. Bruckstein Rita, Director, Research Authority or his authorised representative, the *beneficiary ("beneficiary no.5")*

hereinafter, jointly or individually, referred to as "Parties" or "Party"

relating to the Action entitled

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY: ENGINEERING COMPLEX TISSUES WITH HIGH RESOLUTION AT HIGH SPEED

in short

BRIGHTER

hereinafter referred to as "Project"

© *DESCA* - Horizon 2020 Model Consortium Agreement (www.DESCA-2020.eu), Version 1.2.4, October 2017 3 / 34

Consortium Agreement (CA)

1. Excellence

1.1 Radical vision of a science-enabled technology

Document of Action (DoA)

GA: Rights and Obligations

- **Keep information** in Beneficiary Register up to date
- **Inform** Coordinator/Commission of events likely to affect or **delay** implementation
- Keep **records** and supporting documents **for 5 years** after the final payment (To learn more about keeping records, please read Article 18 of the H2020 Annotated Model Grant Agreement).Examples:
  - contracts, subcontracts, invoices and accounting records.
  - Time records (except for persons working exclusively on the action if the beneficiary signs a declaration confirming that the persons concerned have worked exclusively on the action.)
- **Submission of deliverables**
  - Coordinator will provide a deliverable template.
  - WP leaders are responsible of their elaboration within the rest of the WP partners.
  - WP leaders must send them to the coordination from review (**1 month before**).
  - Coordinator will submit it, to the European Commission.
- **Reporting** – see further
- Protection, exploitation and dissemination of results (**prior notice**)
- Information on **EU funding** (logo + specific text)

GA: Rights and Obligations

- The Consortium Agreement (CA) to be approved and signed by all partners soon.
- The CA provides the **basis for the management** of the project
- **Governance** structure, roles & **procedures**
- **Financial** provisions
- **IPR**: Ownership & access rights
- **Confidential information**: to be marked as such confidentiality until 5 years after end of project

All partners are urged to "read and understand" both agreements

Amendments

Under what circumstances must the Grant Agreement be amended?

- If there are any changes to:
  - its **terms & conditions**
  - its **annexes**.
- For H2020 policy on amendments, see Article 55 of the Annotated Model Grant Agreement.

Prior consultation with the Project Officer through the coordinator

- Amendments are NOT necessary
  - for certain budget transfers
  - if the name or address of a beneficiary, linked third party or coordinator changes
  - if a universal takeover results in a change of beneficiary
  - if there is a change in the name of the bank or the address of the branch where the coordinator has an account

Reporting

- Under Article 20 of the grant agreement (GA), the **coordinator must submit** to the Commission technical and financial reports, including requests for payment - specifically:
  - a **periodic report** (both technical and financial) **within 60 days** of the end of each reporting **period** (including the final one)
  - a **final report** at the **end** of the project ('action')

- The consortium shall submit a final report to the Commission **within 60 days** after the end of the project.

Reporting

- **Reporting periods**
  - RP1: from month 1 to **month 12**
  - RP2: from month 13 to **month 36**

- **Technical report**:
  - Explanation of the **work carried out**
  - Overview of **progress** + **exploitation/dissemination** of results
  - Public summary

- **Financial report**:
  - Detailed **individual financial statement** for each beneficiary
  - Explanation of **use of resources**
  - **Summary** financial statement

Certificate on the financial statements

A ‘certificate on the financial statements’ for each beneficiary , if it requests a **total contribution of EUR 325.000 or more**, as reimbursement of actual costs and unit costs calculated on the basis of its usual cost accounting practices (see Article 5.2 and Article 6.2, Point A).

To be included in the Final Financial Report

Maximum Payments:

Pre-financing: 80% of maximum grant amount

- 75% of max grant amount (**proportional to budget agreed**)
- 5% of max grant amount (**Guarantee Fund**)

Interim payment: Up to 10% of maximum grant amount

- **Reimburse** the eligible **costs** incurred for the implementation of the action.
- **Subject to the approval** of the periodic report.
- **Limit to 90%** of the maximum grant amount.

Payment of the Balance

- The payment owed to the consortium **based on the final accepted costs**.
- Payment is made **based on the information in the submitted** periodic report (technical report & financial report) and final report.
- Payment is capped at the maximum amount in the grant agreement and **any amounts exceeding this will not be reimbursed**,
- Payment of negative balance (i.e. **recovery**) is processed in the same way.
- **After** payment of the balance, the **Guarantee Fund** will be released

Continuous reporting

- As a beneficiary, you can and should **use the continuous reporting**. This includes:
  - **deliverables**
  - progress in achieving milestones
  - updates to the **publishable summary**
  - response to critical risks, **publications**, **communication** activities, **IPRs**
  - your answers to the questionnaire about the **economic and social impact** of the project.
  - Questionnaires:
    - **Gender**
    - **SME impact**
- Preparing your periodic report
  - Once the periodic reporting function is **activated at the end of each reporting period**, you can start preparing your next report in the grant management system:
    - **Participant Portal -> My Projects -> MP (Manage Projects) action button**

Deliverables & Milestones

- **Deliverables** are additional outputs (*e.g. information, special report, a technical diagram brochure, list, a software milestone or other building block of the project*) that must be produced at a given moment during the action.
  - **The coordinator must submit the deliverables** identified in Annex 1 of the grant agreement.
  - **All deliverables** will be also uploaded on the **intranet**.
  - **Template** will be available on the **intranet**

  - To learn more about deliverables, please read Article 19 of the H2020 Annotated Model Grant Agreement.

- **Milestones** are, by contrast, control points in the project that help to chart progress. They may correspond to the completion of a key deliverable, allowing the next phase of the work to begin or be needed at intermediary points.
  - If milestone not achieved review **contingency plans & alternatives**.

Meetings calendar

- Decide meeting dates and venue

Meeting	Organization	Month
Kick off Meeting	IBEC	1
Progress meeting	GUF	6
Technical/scientific review meeting	Brussels (European Commission)	14
Progress meeting	MYCRONIC	18
Progress meeting	TECHNION	24
Progress meeting	CELLENDES	30
Final technical/scientific meeting	Brussels (European Commission)	37

- Additional meetings can be held on consortium request

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

Dissemination and Exploitation

Kick off meeting

4-5th July 2019

Dissemination

- Dissemination activities (led by IBEC)
  - Scientific **publications** in high-impact journals.
  - Participation in **conferences** (TERMIS, MasMEDIC).
  - Dissemination material (leaflets, brochures and roll-ups).
  - Gather **evidences** (with the proper logo + grant number).
  - **Communicate every action** to the coordinator/consortium
- Communication activities (IBEC and all)
  - Project **Website** → under construction
  - **Social networks** (Twitter, Facebook, Linkedin)
  - Communication **material** (leaflets, brochures and posters).
  - Communication **events to society**
    - School events
    - Open Days
    - Regional workshops

Dissemination

- Educational and training activities (led by IBEC)
  - Organize a **Project Workshop** (M24) – Hosting institution?
  - **PhD short visits** among partners.

- Networking activities (led by MYCRONIC)
  - Participation in **trade fairs and exhibitions** (BIOMEDevice, MEDICA)
  - Workshops and **EU events** (EuroScience, Open Forum ESOF, CONCORDI, European Researcher's Night).

Dissemination

- Scientific Publications:
  - **No partner** shall have the right to **publish** or allow the publishing of any data which constitutes Foreground, Background or **Confidential Information of another Partner**.
  - Always ask for **formal permission** (by e-mail) from partners **before** submission.
  - **Be aware** to not publish any R+D development if it is **patentable**.
  - Send always a **copy** of the final submission **to all partners**.

- According to CA (8.4.1) "*Prior notice of any planned publication shall be given to the other Parties **at least 45 calendar days before the publication**. Any objection to the planned publication shall be made in accordance with the Grant Agreement in writing to the Coordinator and to the Party or Parties proposing the dissemination within **30 calendar days** after receipt of the notice. If no objection is made within the time limit stated above, the publication is permitted.*"

Acknowledgement of EU Funding

Use **EU emblem**:

- High-resolution emblems are available here
  http://europa.eu/about-eu/basic-information/symbols/flag/

Use **text** as indicated in GA:

This project has received funding from the European Union's Horizon 2020 research and innovation programme under No. 828931. The results presented here reflect only the views of the authors; the European Commission is not responsible for any use that may be made of the information it contains.

Web page to search the embargo months of a journals in 'Green Way' Open Access:

http://sherpa.ac.uk/romeo/index.php

Dissemination & Exploitation of results

- Dissemination of results - Article 29 of H2020 annotated model grant agreement
- Exploitation of results - Article 28 of the H2020 annotated model grant agreement
- Fact Sheet - the Plan for the Exploitation and Dissemination of Results in Horizon 2020

Responsible Research and Innovation (RRI):

Implementation of RRI actions:

- http://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation

- Public engagement
- Open access
- Gender
- Ethics
- Science education

Inter- & transdisciplinary actions will be taken in BRIGHTER to promote RRI application

Exploitation

- **Exploitation activities** (led by IBEC)
  - Business model (valorisation strategy, time-to-market, barriers affecting the exploitation, etc.).
- **IPR handling strategy** (led by MYCRONIC)
  - Information on IPR
  - IPR Guidance Plan
  - Patent application (IBEC) – Deliverable 6.2 (M27)
- **BRIGHTER's Tech-transfer Strategy**
- **Consortium Agreement**
  - update of the situation

BRIGHTER

BIOPRINTING BY LIGHT-SHEET LITHOGRAPHY

IPR

- T6.4. Networking activities (MYCRONIC, All).
  - Tradeshows/conferences
- T6.5. IPR handling strategy (MYCRONIC, All).
  - Technology
  - Process
  - Jenny Blidefalk
- T6.6. Exploitation plan (MYCRONIC, All).
  - Academic
  - Stakeholders
  - Society
  - Business