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Lung/liver-on-a-chip system

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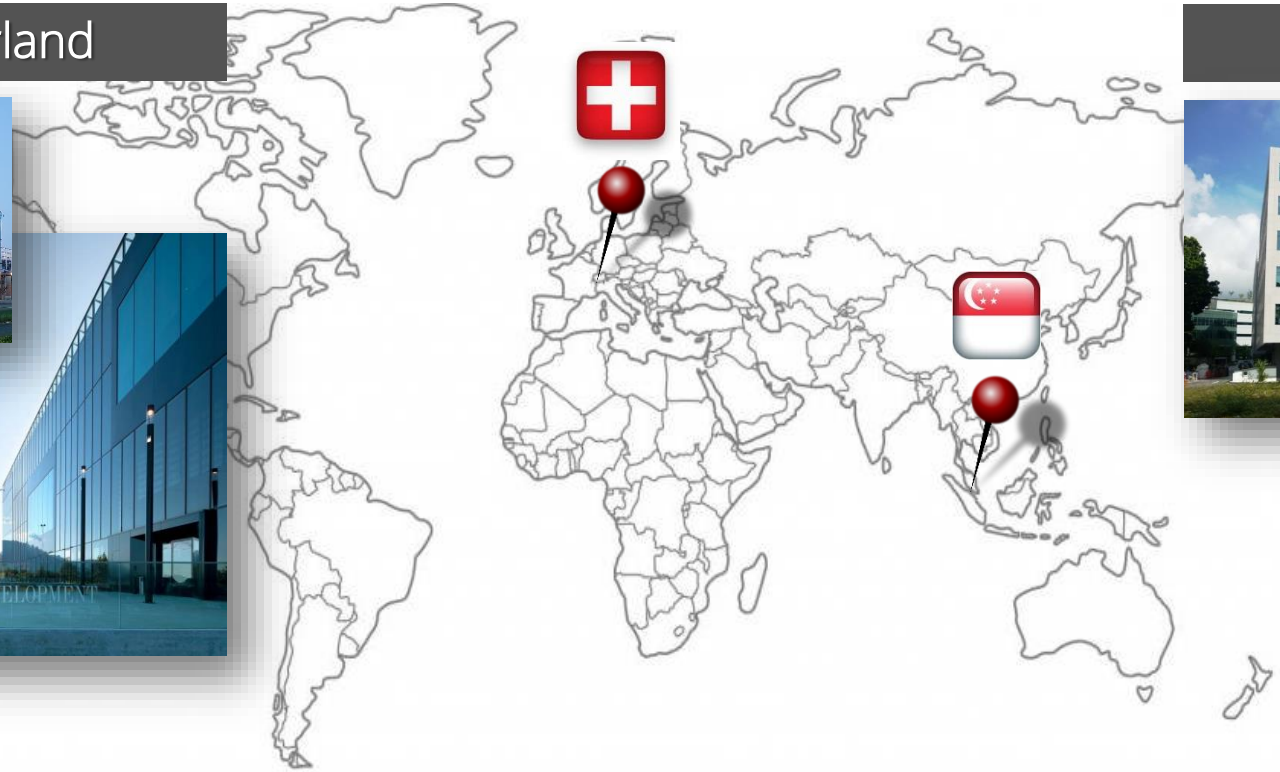
Philip Morris International R&D facilities

Neuchatel, Switzerland



Singapore

- 200+ world-class scientists, engineers, and medical directors (40+ nationalities)
- 30+ disciplines, including material science, consumer electronics, *in vitro* and *in vivo* research, computer science, and clinical science

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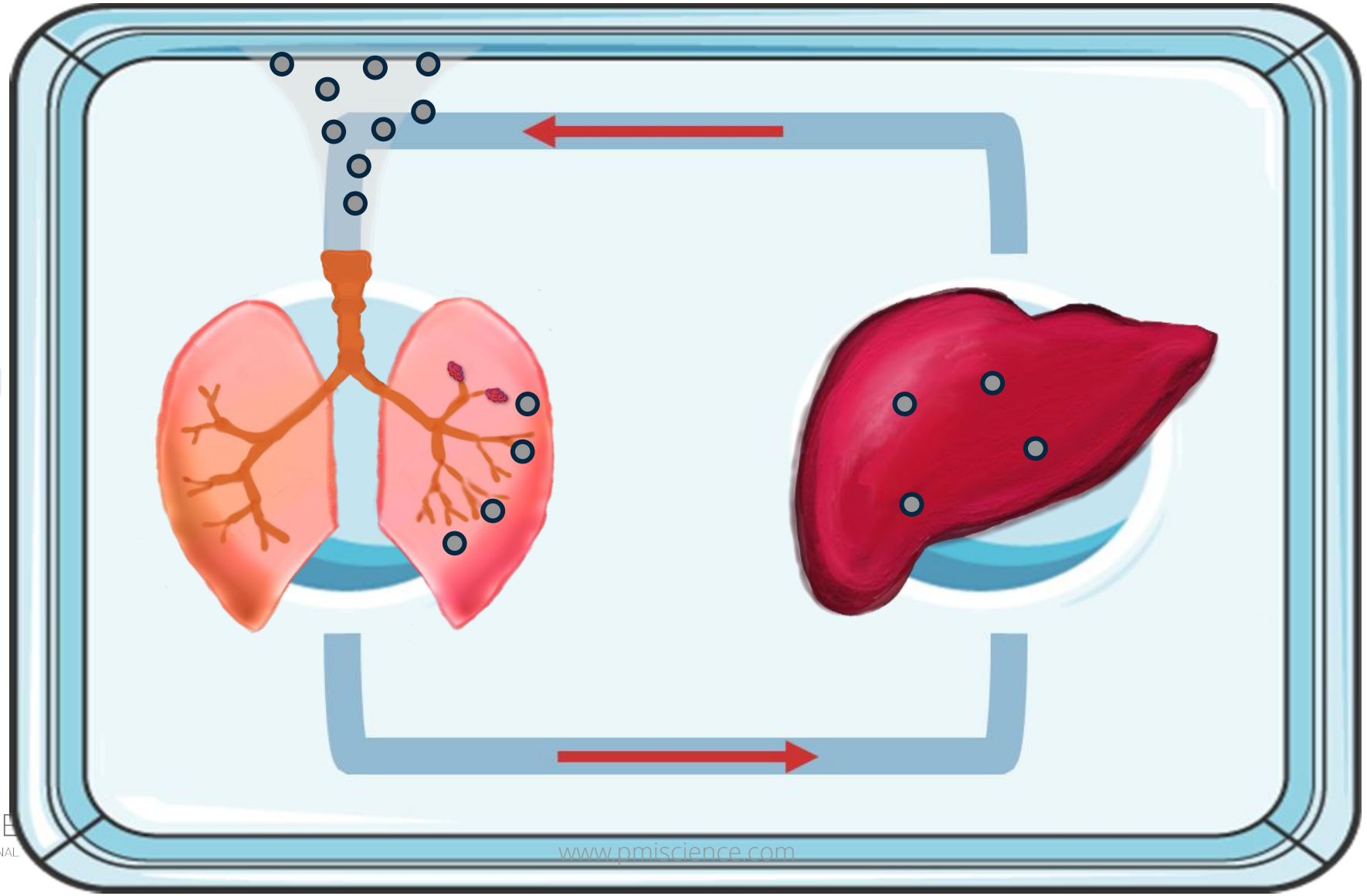
Aerosol absorption

Lung

- CYP 1A1/1B1
- CYP 2B6
- CYP 2E1
- CYP 2J2
- CYP 3A5



Liver

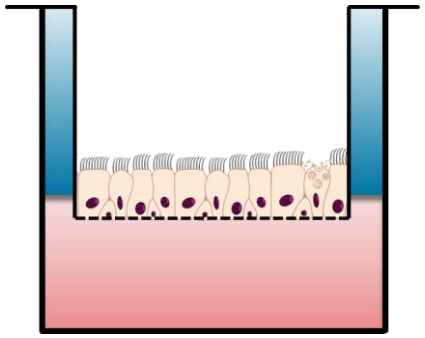
- CYP 1A2
- CYP 2E1
- CYP 2C8
- CYP 2C9
- CYP 3A4

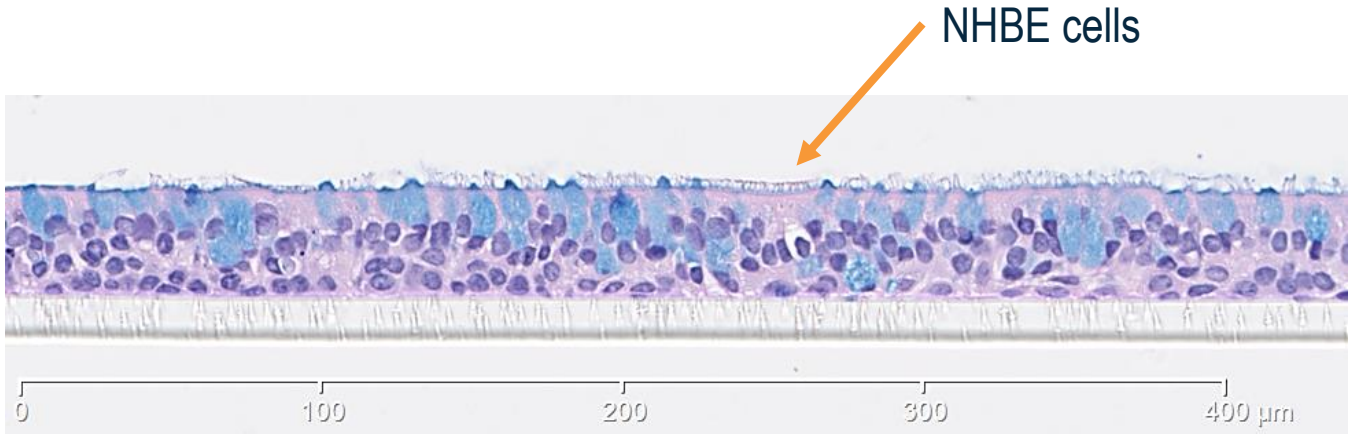
Key features of the platform

- Air-liquid interface (ALI) bronchial model
- Liver spheroid model

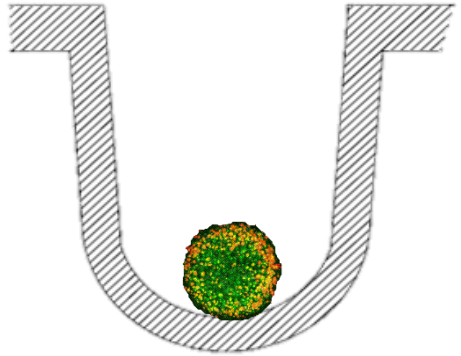
Lung and liver models

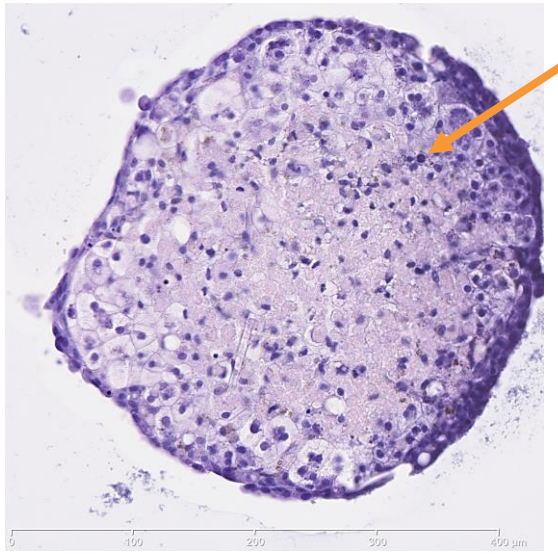
Bronchial ALI model





Liver spheroid model





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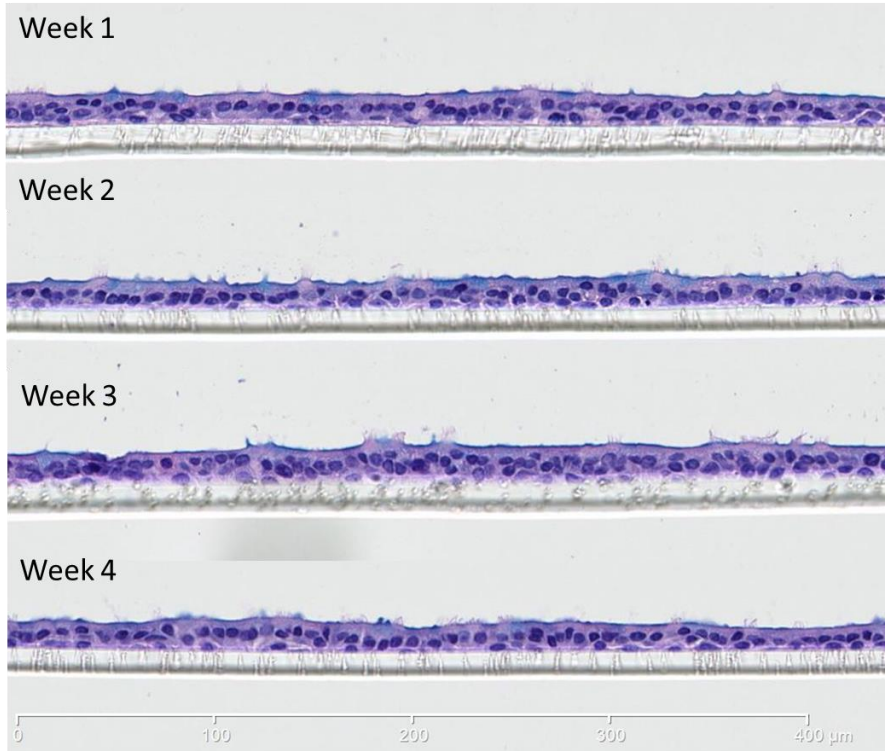
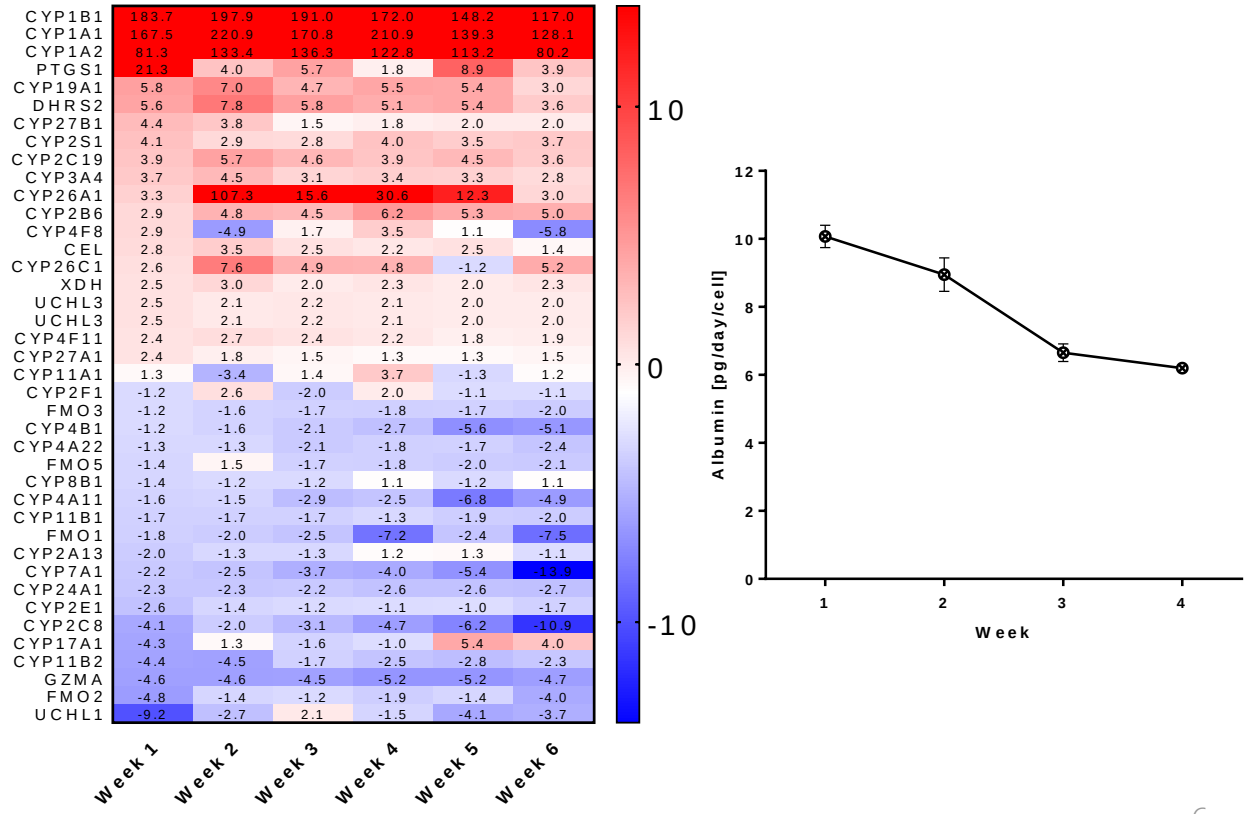
Model stability

- Key tissue characteristics were assessed over a six-week period

Bronchial ALI model



Liver spheroid model



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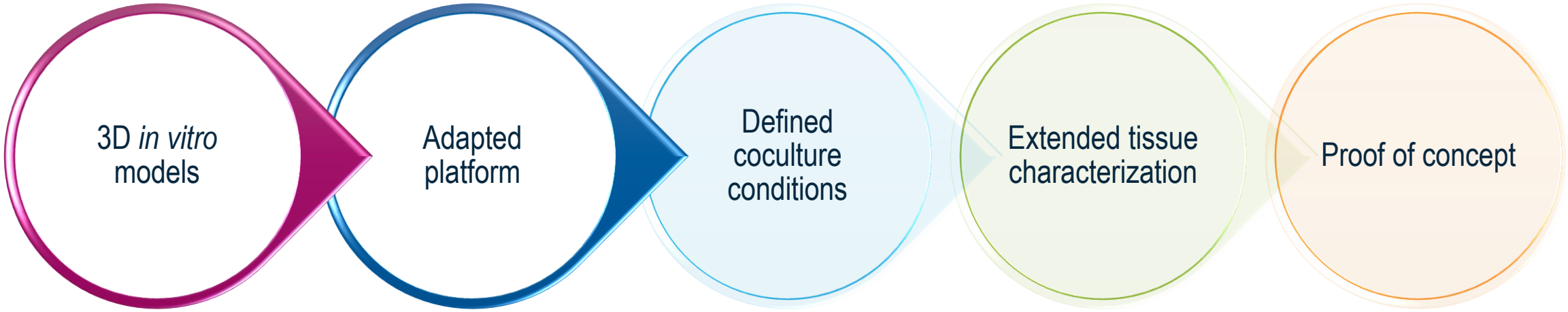
Key features of the platform



- ALI bronchial model
- Liver spheroid model

- Air-exposed
- Adapted for 3D tissues
- Biocompatible
- Easy to use

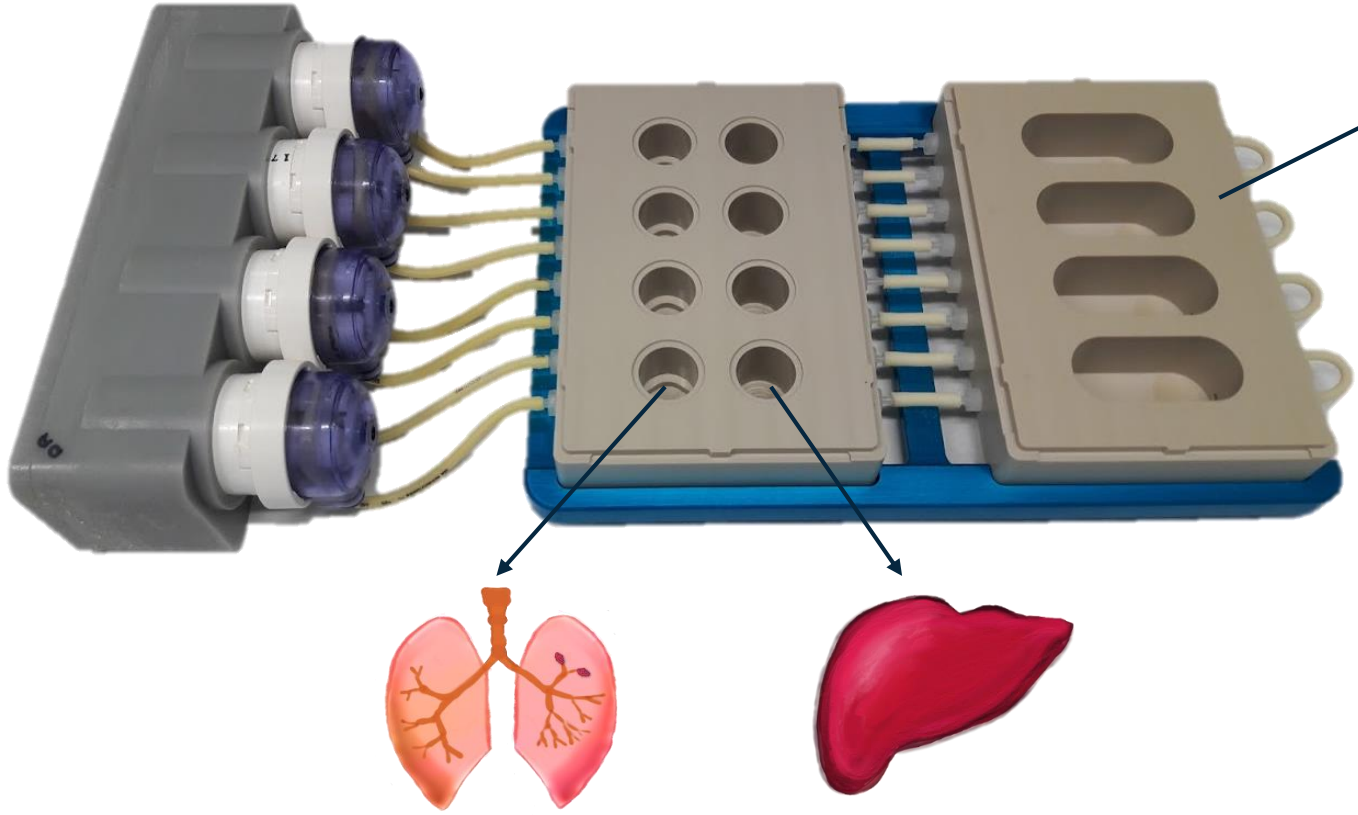
Lung/liver-on-a-chip platform

Pump controller

Pump main unit

Chip

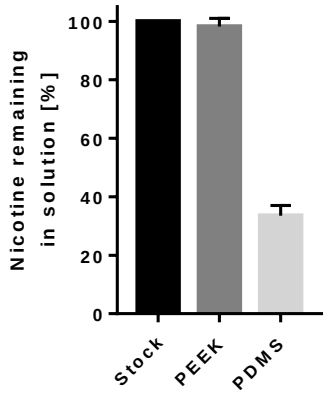
Reservoir plate



Bronchial ALI model

Liver spheroid model

Polyetheretherketone: Biocompatible and nonabsorbent material



After eight hours of incubation, nicotine concentration remained stable in the PEEK chip but not in the PDMS chip.

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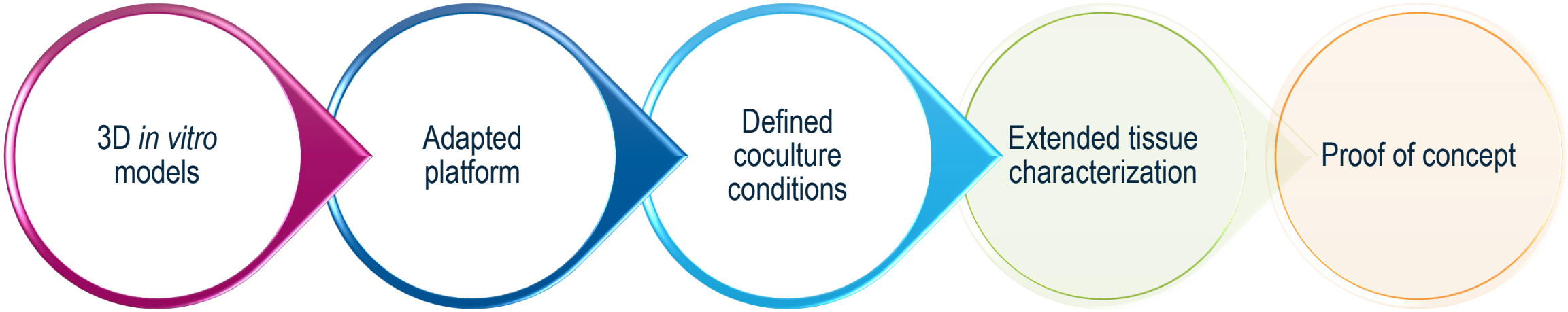
Key features of the platform



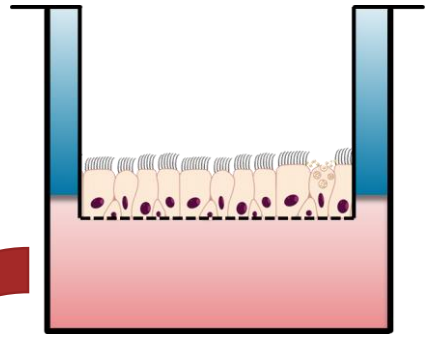
- ALI bronchial model
- Liver spheroid model

- Air-exposed
- Adapted for 3D tissues
- Biocompatible
- Easy to use

- Impact of the bronchial medium on the liver spheroids was assessed

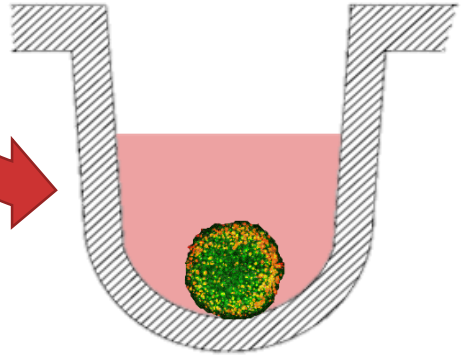
Defined coculture medium

Bronchial ALI model

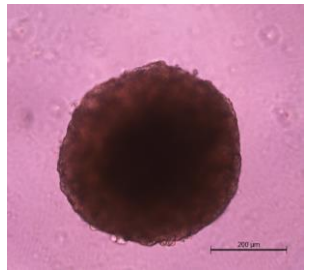


10 days

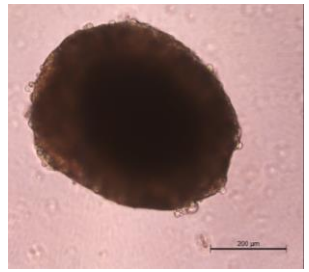
Liver spheroid model



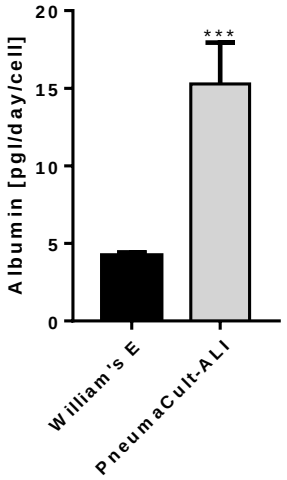
William's E Medium

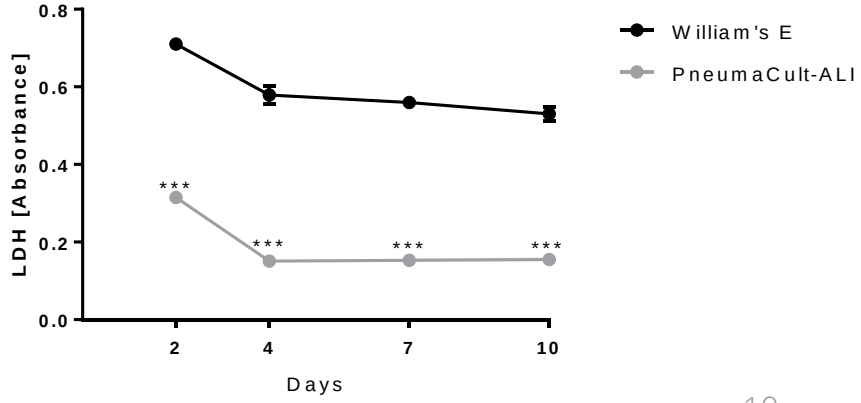


PneumaCult™-ALI Medium



	24 h	48 h	72 h	96 h	168 h	240 h
CYP3A4	18.1 ***	47.0 ***	19.7 **	53.1 ***	31.5 ***	18.2 ***
CYP3A43	6.9 *	33.8 *	9.3 *	8.5 ***	2.8	5.5 *
CYP2B6	3.9 *	4.8 *	2.0	4.6 **	4.3 *	16.7 **
CYP7A1	3.2 **	3.3 **	1.7 *	2.5 **	1.1	1.1
CYP2C8	3.1 **	1.6	2.1 ***	2.3 *	2.7 ***	1.1
CYP2A13	3.0 *	1.9 *	1.7	8.5 *	6.0 **	3.8 *
ADH7	2.4	-1.4	-1.9	-1.4 *	-2.2	-6.8
CYP7B1	1.9 **	6.1 **	1.2	3.3 ***	2.6 **	-1.3
CYP2C9	1.8 *	2.9 **	1.3	4.3 **	2.6 ***	-4.2
ADH1A	1.8	1.4	1.1	2.7 *	1.3	-1.5
CYP2F1	1.8 *	1.1	-1.4	1.9	-1.0	1.4
CYP4F12	-1.8 *	-2.1 **	-2.3 **	1.3	-1.7 **	1.1
AADAC	-1.8 **	1.3	-2.2 **	1.2	-1.6	-2.7 **
ALDH5A1	-1.9	-2.7 **	-6.5	1.5	-1.7	2.5 *
CYP27A1	-1.9 *	-1.1 *	-2.0 *	1.8 **	1.1	-1.1
CYP4A22	-2.0	-3.3 *	-3.6	-1.1	-1.4	-1.7 *
CYP1B1	-2.1 *	-2.0 *	-2.7 **	1.3	-1.3	-1.0
CYP27B1	-2.3	1.8	-1.8	5.2 *	1.1	-1.7
CYP26B1	-2.8 **	-2.5 *	-5.8 **	1.0	-1.0	1.2
CYP1A1	-3.2 ***	-3.6 ***	-5.0 ***	-2.7 *	-1.4	1.8
CYP19A1	-3.7 *	-1.9	-3.0 *	-1.9	-3.3 **	-2.1 *
ALDH3A1	-4.1	-4.6 **	-7.0 *	1.1	1.1	1.1
CYP4A11	-4.9 ***	-4.8 ***	-9.0 **	-1.8 *	-4.9 ***	-3.2 **
ALDH1A3	-10.1 *	1.1	-5.9	1.3	-1.6	1.2





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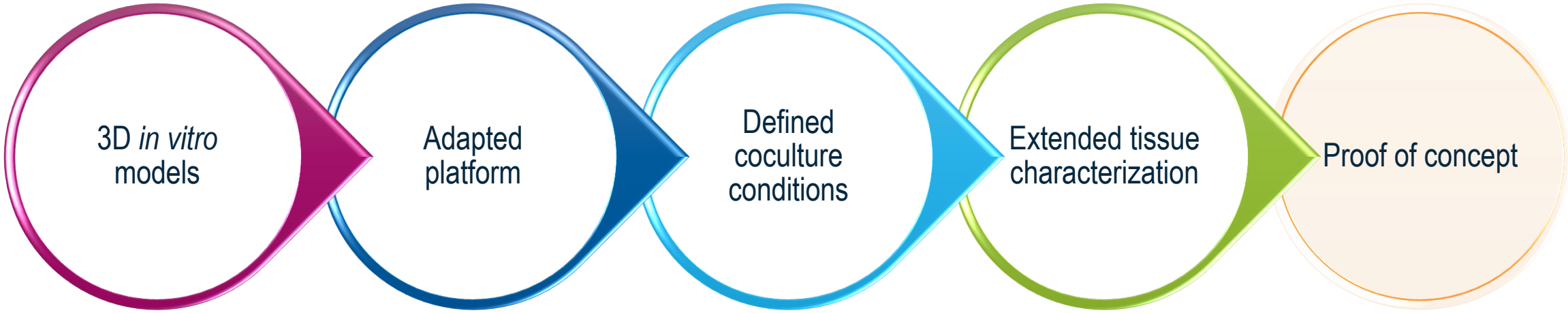
Key features of the platform



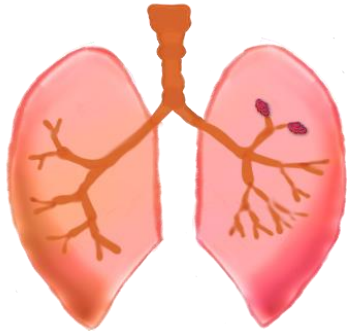
- ALI bronchial model
- Liver spheroid model

- Air-exposed
- Adapted for 3D tissues
- Biocompatible
- Easy to use

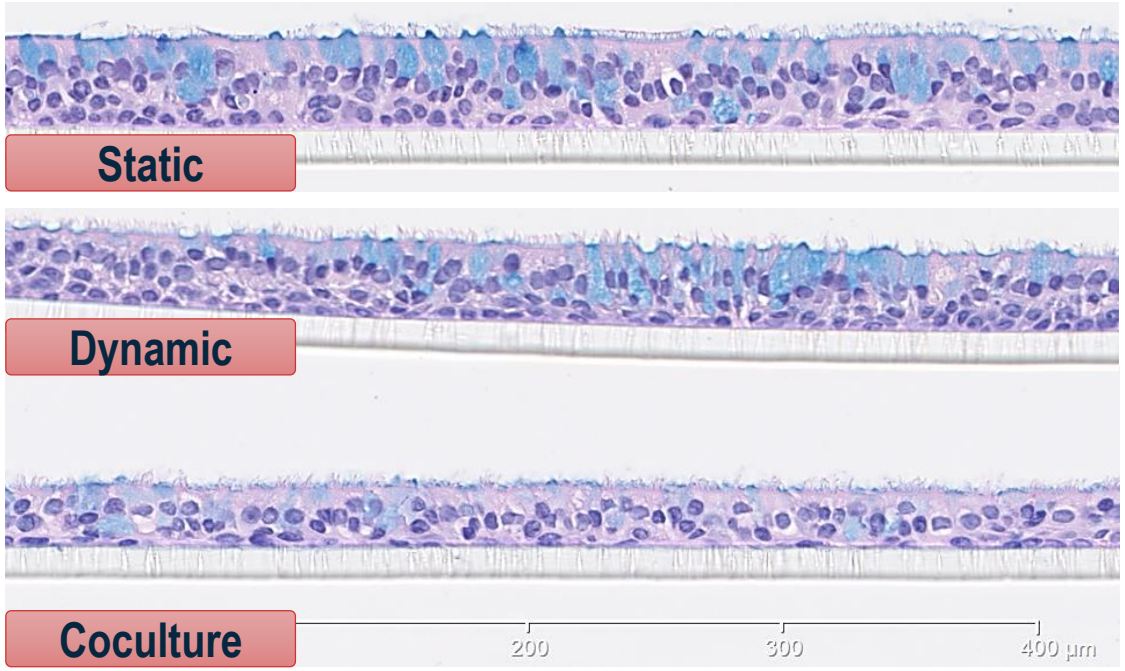
- Impact of the bronchial medium on the liver spheroids was assessed

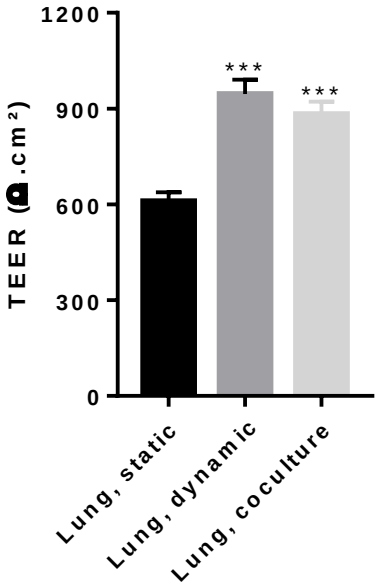
- Maintenance of both tissues in monoculture and coculture conditions for 28 days

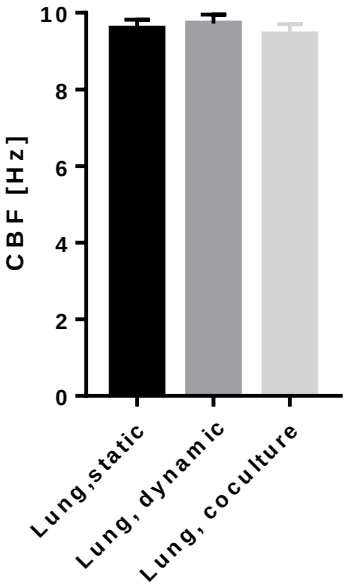
Lung-liver coculture



- Tissues were maintained for 28 days in either
  - Static (monoculture, in standard 24-well plate)
  - Dynamic (monoculture, in the chip with medium flow)
  - Coculture (coculture with liver spheroids)







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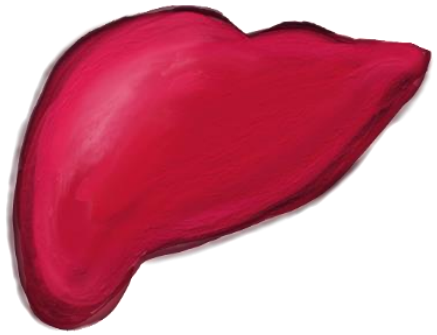
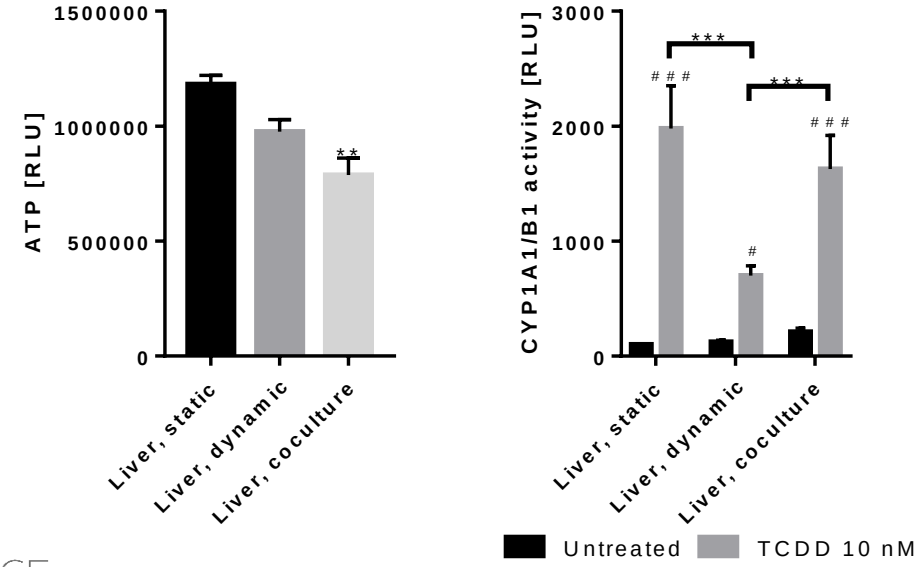
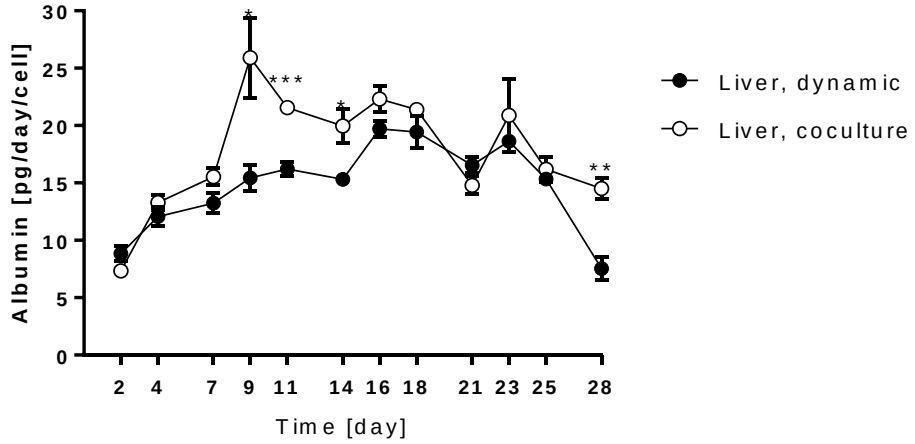
Lung-liver coculture



- Tissues were maintained for 28 days in either
  - Static (monoculture, in standard 96-well plate)
  - Dynamic (monoculture, in the chip with medium flow)
  - Coculture (coculture with bronchial ALI tissues)





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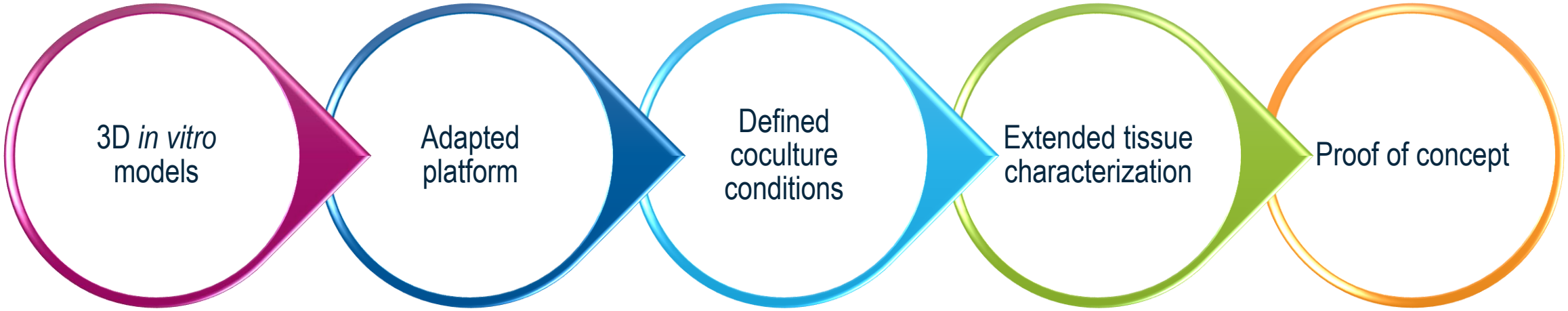
Key features of the platform



- ALI bronchial model
- Liver spheroid model

- Air-exposed
- Adapted for 3D tissues
- Biocompatible
- Easy to use

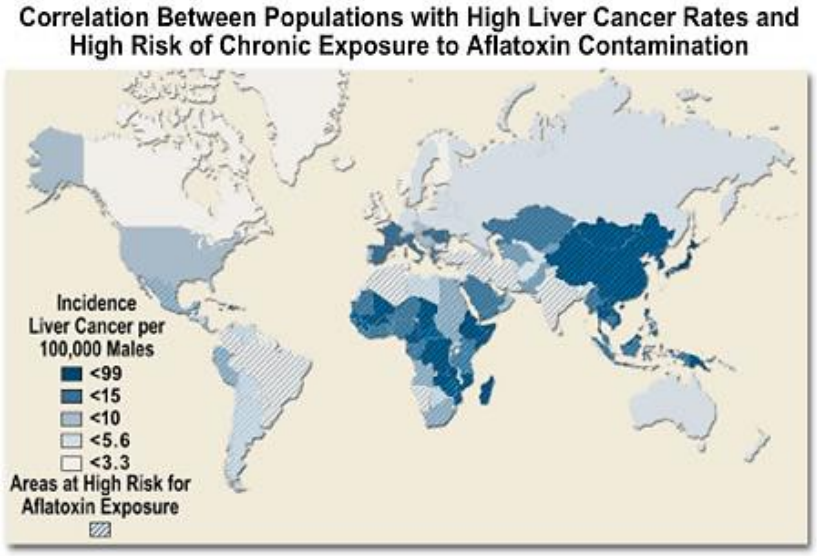
- Impact of the bronchial medium on the liver spheroids was assessed

- Maintenance of both tissues in monoculture and coculture conditions for 28 days

- Lung-liver crosstalk demonstrated with aflatoxin B1 (AFB1)

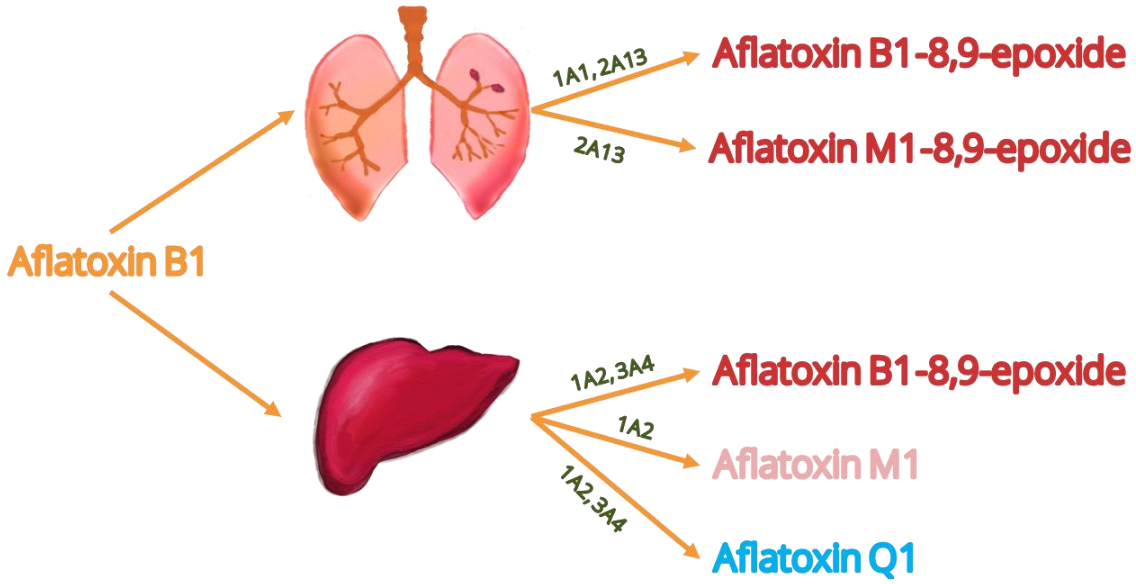
AFB1

- Produced by *Aspergillus flavus*
- Common food contaminant
- Causes hepatocellular carcinoma



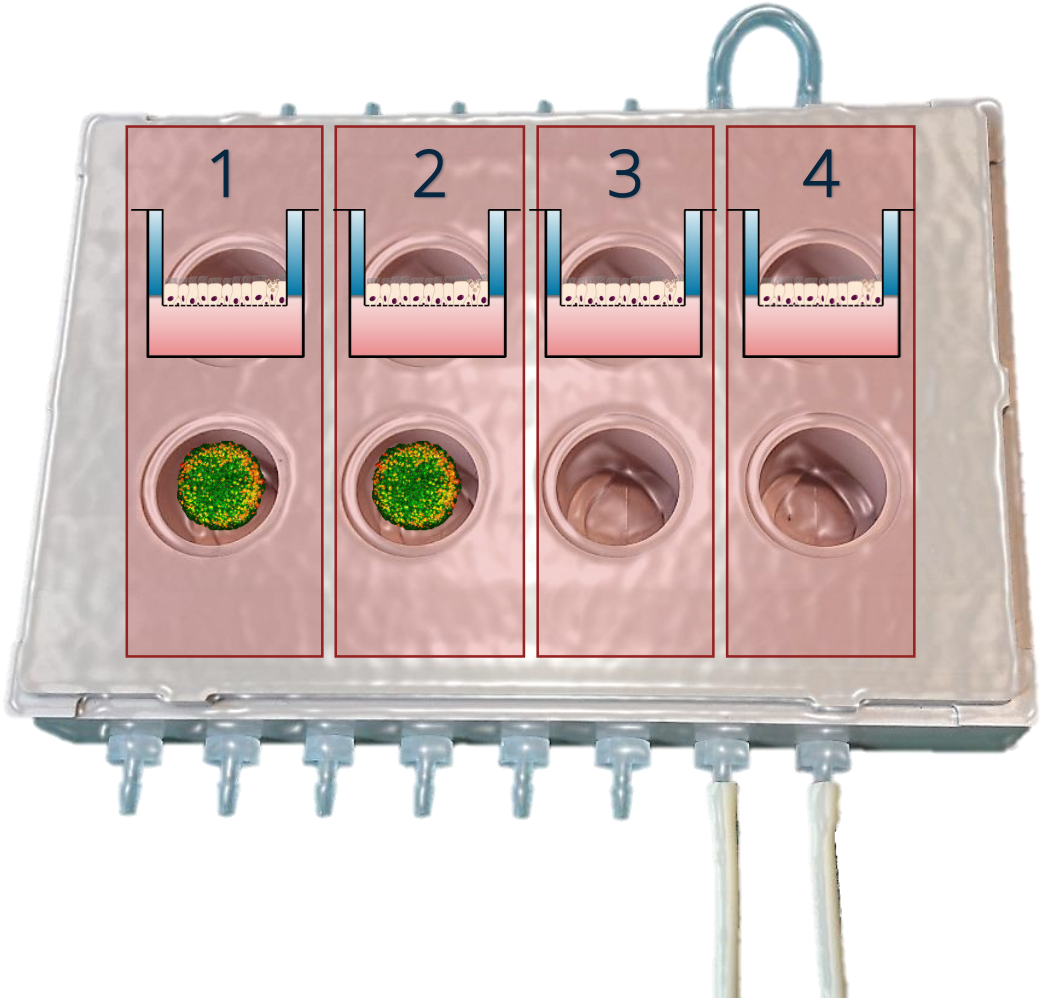
Liver cancer data from the GLOBOCAN 2002 database (http://www-dep.iarc.fr/GLOBOCAN_frame.htm)

Aflatoxin data from Williams et al., Human Aflatoxicosis in Developing Countries, Am J Clin Nutr 80:1106–22, 2004.



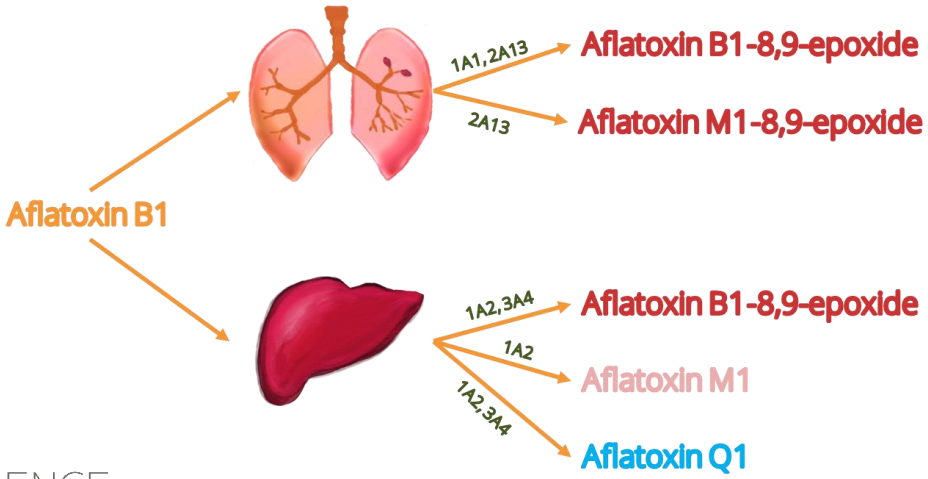
AFB1 in the chip

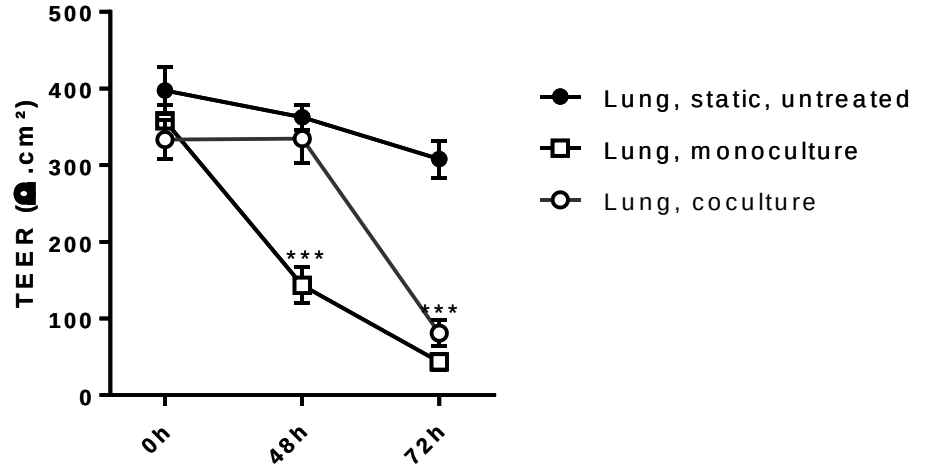
- AFB1: 100 uM
- Compound diluted in medium
- 48-hour exposure

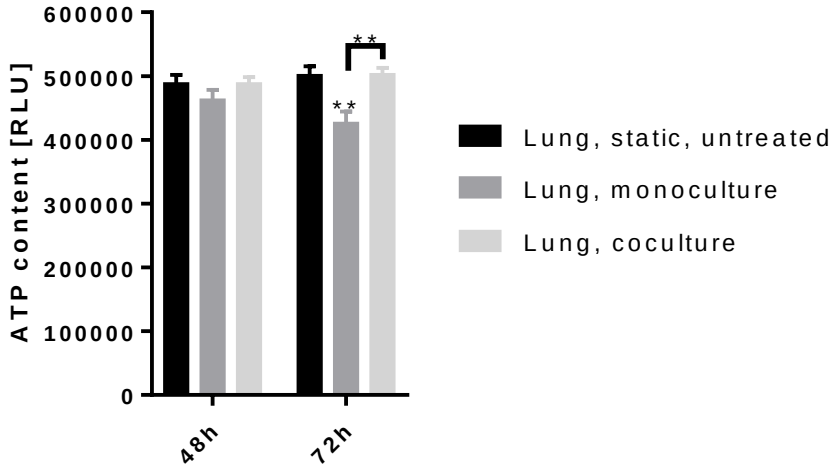


AFB1 in the chip

- Results:
  - AFB1 caused strong cytotoxicity to the bronchial ALI tissues
  - ABF1 cytotoxicity to the ALI bronchial cultures was decreased by the presence of liver spheroids in the chip







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Conclusion & perspectives

- A two-organ chip has been developed using a biocompatible and nonabsorbent material
- Lung and liver tissues can be maintained for 28 days in coculture in the chip
- The lung-liver crosstalk was demonstrated using AFB1

- **The lung-liver-on-a-chip platform allows for chronic and acute toxicity testing**

- Using the current platform, several aspects will be optimized:
  - Higher throughput
  - Increased tissue complexity (cell type composition)
  - Connection of additional “organs”

Thank you for your attention !!