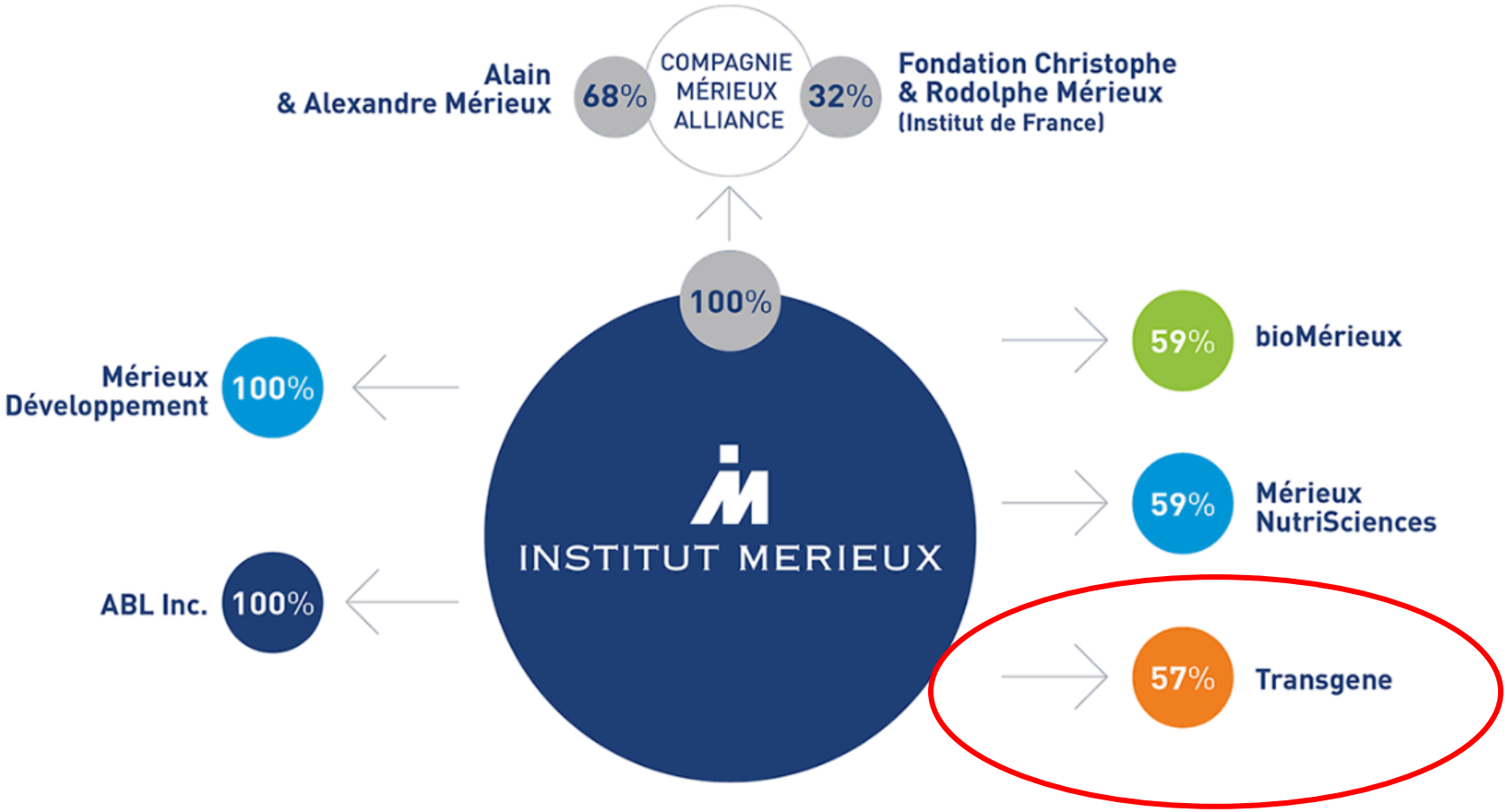
In vitro Systems
Towards a Personalized medicine approach

Workshop: « Systèmes modèles précliniques en cancérologie »
15 Novembre 2019

Institut Mérieux



Transgene |Company overview

- **150** employees
- Operations in **Strasbourg, Lyon** and in the **US**
- Listed on **the Paris stock exchange**
- Part of the **Mérieux Group**

Strasbourg (HQ)

Lyon

Player of the global healthcare ecosystem

Orchestrating a brighter world NEC · AstraZeneca · Bristol-Myers Squibb · MERCK · Pfizer · BioInvent · SERVIER

- Clinical trials active in **Europe** and in **the US**
- **>60** peer-reviewed publications and **>100** presentations in international/ national conferences in 5 years

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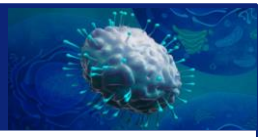
Current pipeline

Product	Indication	Partner	Preclinical	Clinical Phase		Next-steps
				Phase 1	Phase 2	
THERAPEUTIC VACCINES						
TG4010	Non-small cell lung cancer – 1st line	Bristol-Myers Squibb *	+ nivolumab (ICI) + CT			6-month efficacy readout in Dec. 2019
TG4001	Recurrent HPV positive cancers	MERCK Pfizer *	+ avelumab (ICI)			1st efficacy readout @ESMO 2019
TG4050	Ovarian cancer	myvac *				FPI in 4Q 2019
	HPV- Head & Neck cancers	Orchestrating a brighter world NEC				FPI in 4Q 2019
ONCOLYTIC VIRUSES						
TG6002	Colorectal cancer – IV Route	*				Safety data in 4Q 2019
	Colorectal cancer – IHA Route	*				FPI in 4Q 2019
VV-α-CTLA-4	Solid tumors	invir io BioInvent *				IND filing in 1Q 2020
5 OVs	Confidential targets	AstraZeneca *				

* Research or clinical collaboration / ** Chinese rights sold to Tasly Biopharmaceuticals

Experience driven innovation to develop virus-based immunotherapeutics

Therapeutic Vaccines

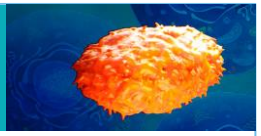


myvac

- Individualized immunotherapy based on patient's own tumor mutations called neoantigens
- Expected to induce broader and stronger T cell response for better treatment outcomes
- Ability to prime/boost patient's immune system to overcome the immunosuppressive environment of the tumor sites
- The advantages of personalized treatment without the drawbacks of autologous approaches
- Integrates Artificial Intelligence with NEC's prediction systems

Lead candidate TG4050 to enter the clinic in 2019

Oncolytic Viruses

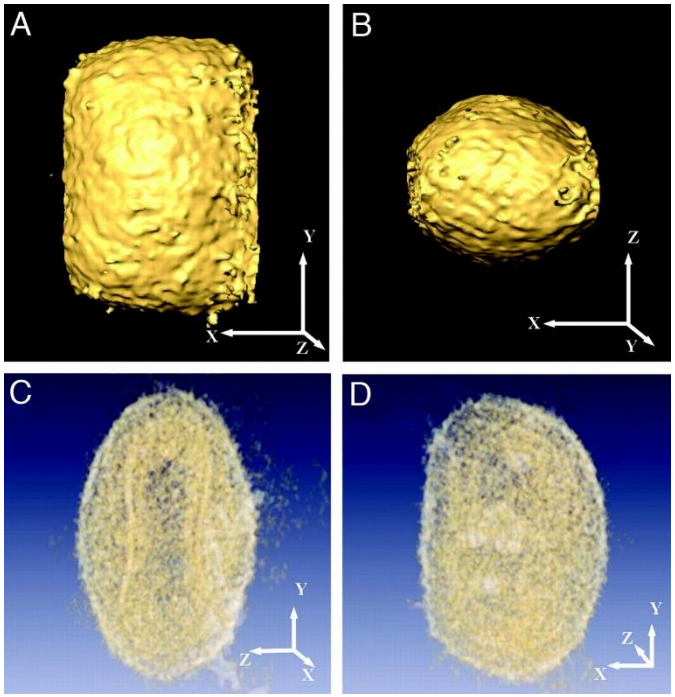


invir io

- Novel platform for multifunctional oncolytic viruses based on a proprietary virus (VV_{Cop} TK-RR-)
- Express a range of anti-cancer weapons to better modulate the Tumor Micro Environment (TME)
- Sustained anti-tumor response via immunogenic cell death boosting innate and adaptive immune responses
- Large genome capacity to accommodate multiple transgenes
- TG6002 is paving the way for Invir.IO®
- Research collaboration with AstraZeneca

First Invir.IO® candidate (VV-α-CTLA-4) in the clinic in 2020

VACV Transgene Platform: Copenhagen Strain based



Cyrklaff M et al. PNAS 2005;102:2772-2777

- Vaccinia Particles are Live Nanometric Autoreplicative objects (~400x200 nm).
- Large genome ~200Kb, allowing introduction of large genetic inserts ~20Kb.

- Metabolic restriction with improve therapeutic index:
  - J2R kinase deletion
  - I4L Ribonucleoside-diphosphate reductase deletion

COP*TK-RR-*

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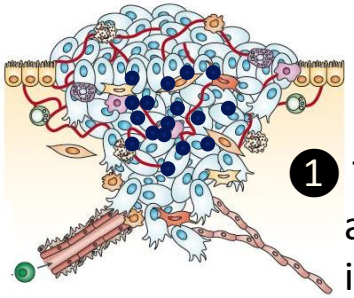
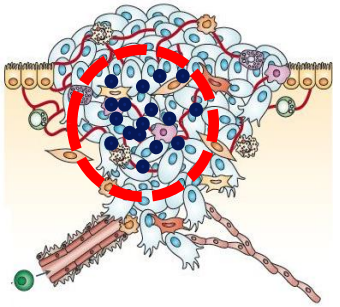
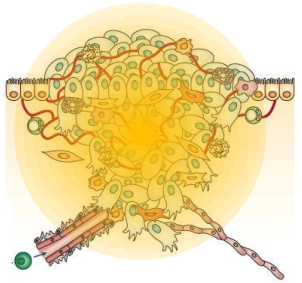
COP*TK-RR-*: Concepts and mechanisms of action



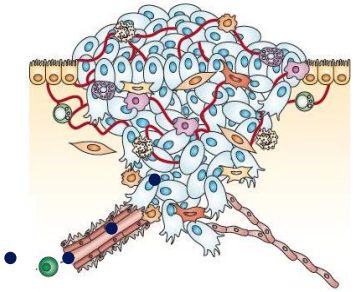
1 Tumor cell lysis induced after specific viral replication in tumor cells



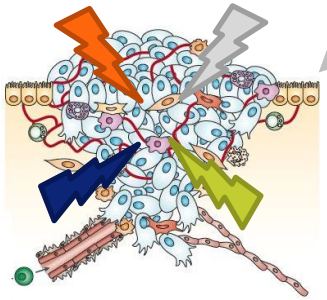
2 Immunogenic cell death, proinflammato response and induction of both immune innate & adaptive responses



3 Local release of active payload in the TME



Suitable for either IT or IV routes



3 complementary ways to tackle solid Tumors

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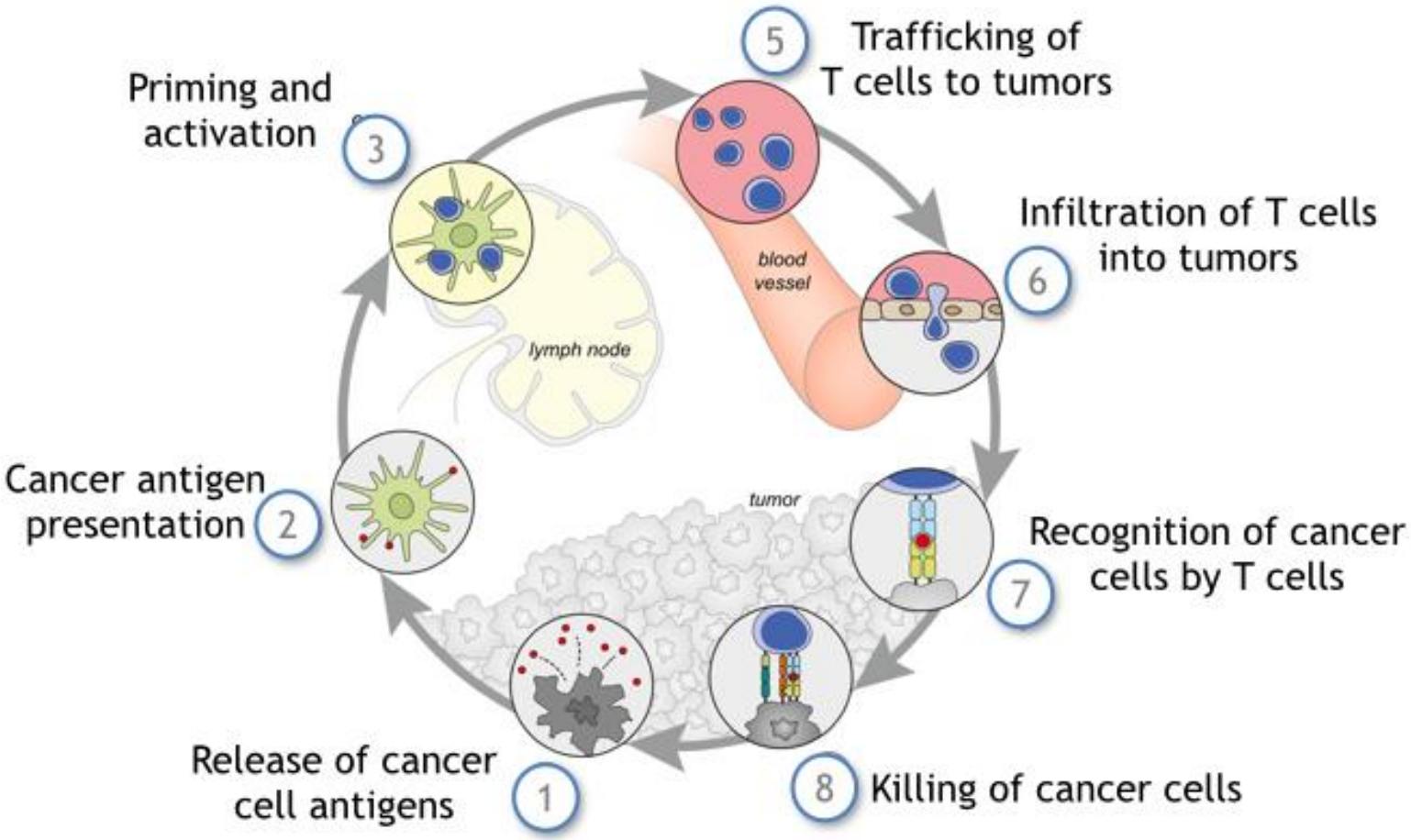
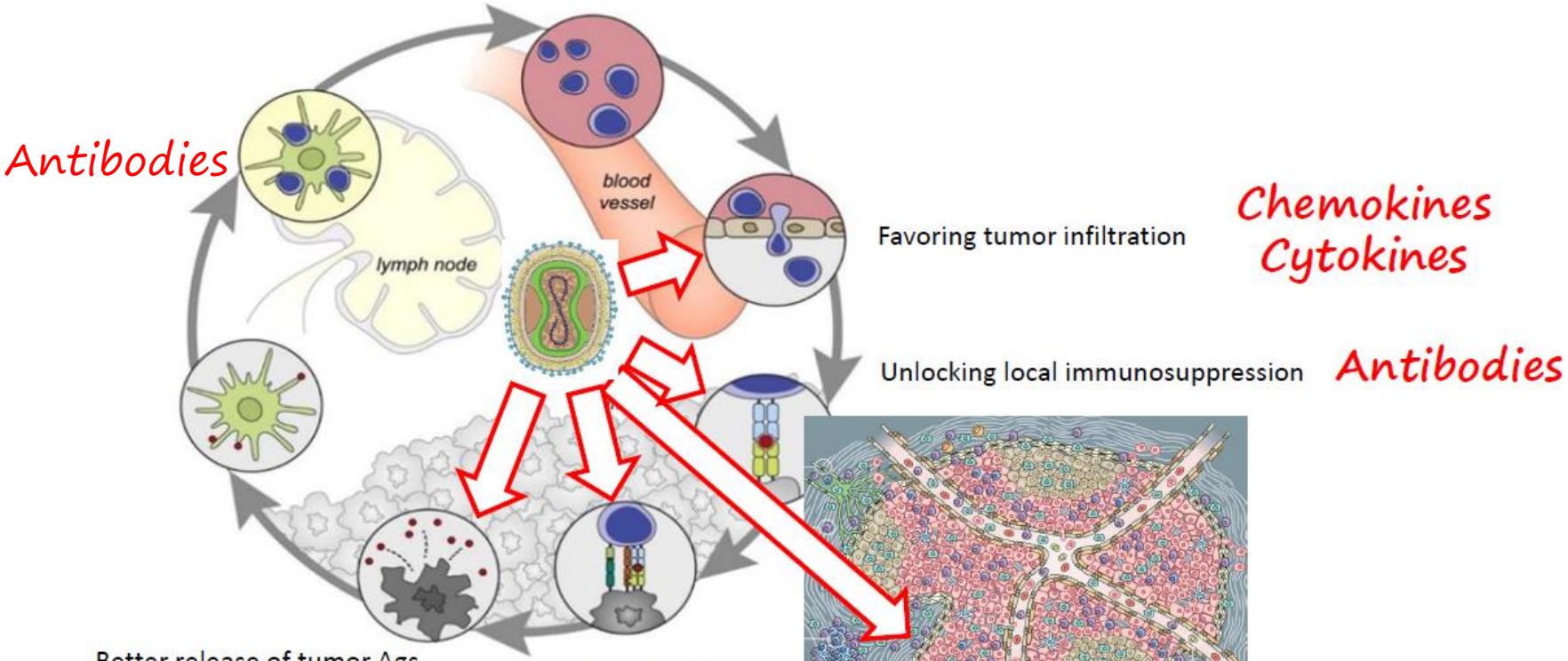
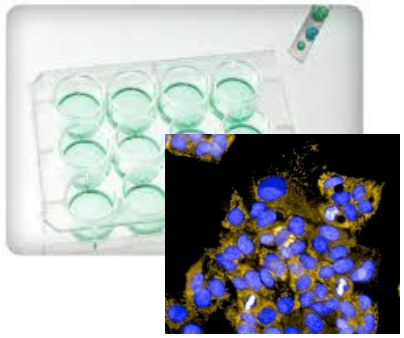
The cancer immunity cycle



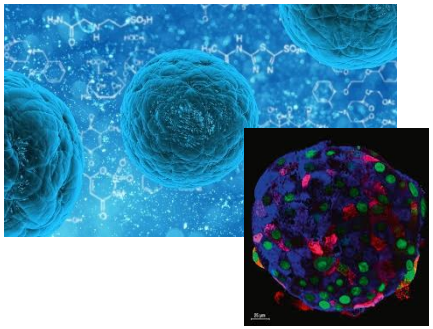
A versatile platform for engineering innovative immuno-armed OVs



Today *In Vitro-In vivo* Pre-clinical Models



2D culture cells, static

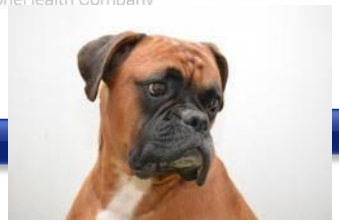


3D Spheroids, static

Nude Mice,

Immuno-competente mice

NOD.CgPrkdcscid Il2rgtm1Wjl/SzJ NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (to be humanized by engraftment of human CD34+ hematopoietic stem cells (HSC), peripheral blood mononuclear cells (PBMC), patient derived xenografts (PDX), or adult stem cells and tissues)



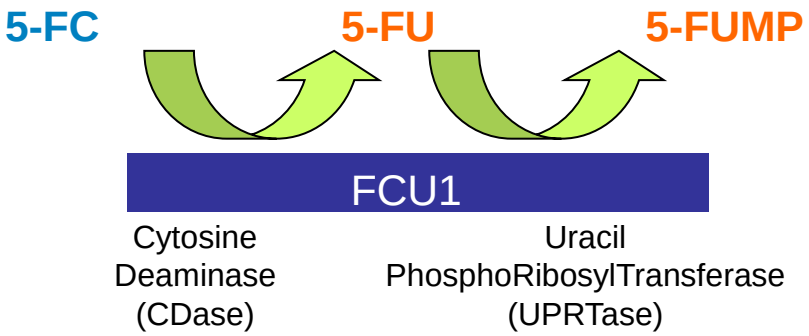
Spontaneous cancer (glioblastona, osteosarcoma, ...)

Regulatory Toxicology

COP *TK-RR-* is "ARMED "with FCU1: Molecular Chemotherapy

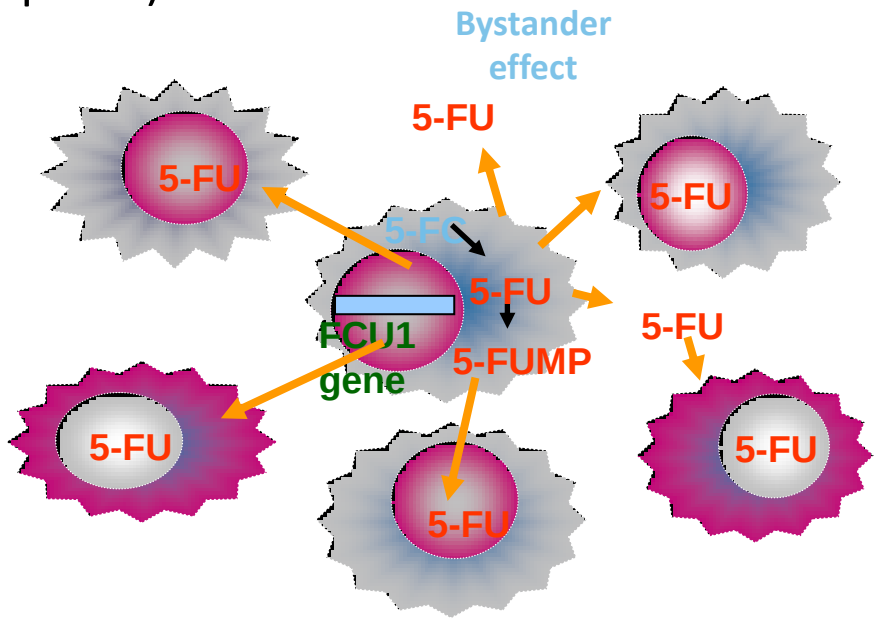
FCU1 = Bifunctional chimeric protein

Conversion of non-cytotoxic flucytosine (5-FC) into cytotoxic 5-FU (5-fluorouracil) and 5-FUMP (5-fluorouridine 5'-monophosphate)



5-FC: 5-Fluorocytosine 5-FU: 5-Fluorouracil

Erbs P et al. 2000, 2008; Foloppe J et al. 2008



TG6002 therapy combines the destruction of cancer cells by viral oncolysis and molecular chemotherapy

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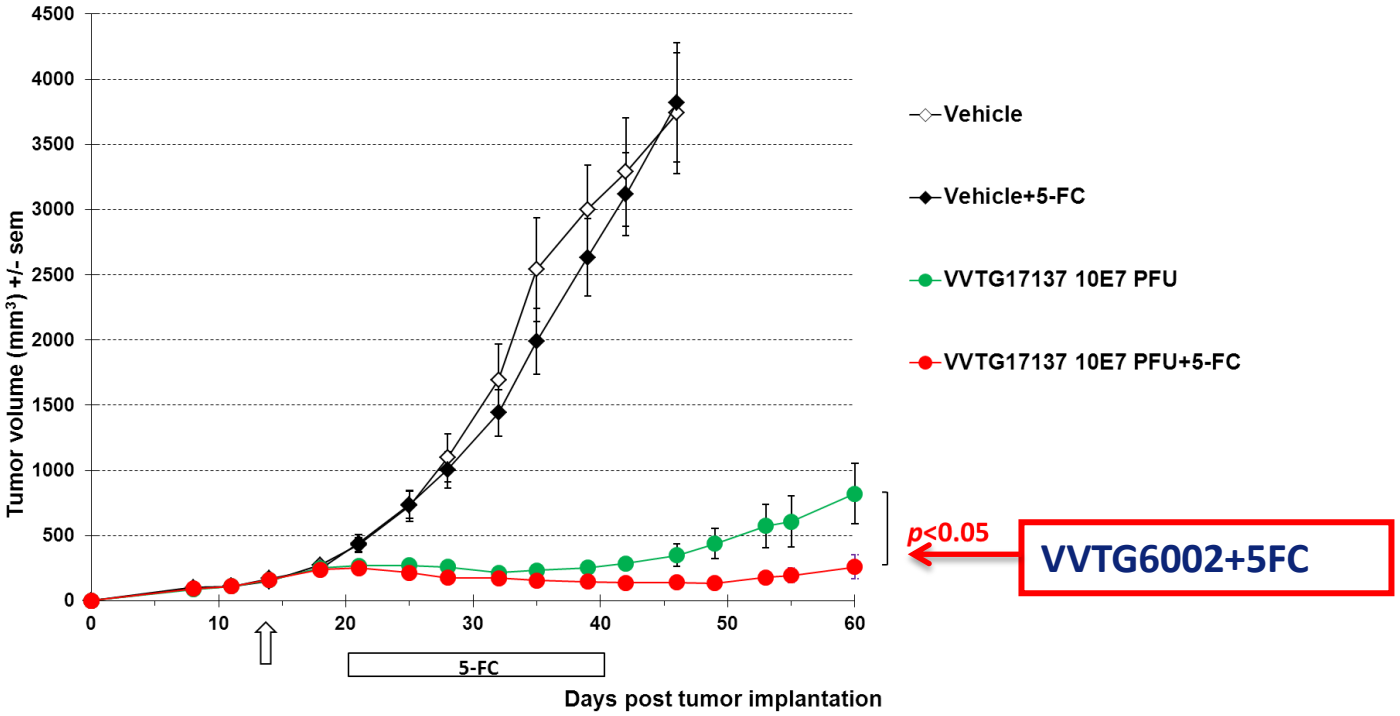
Example: In vivo anti-tumor activity of COP *TK-RR-* FCU1 *(VVTG6002)*

Human esophageal cancer model



- Mice: n=12

Significant anti-tumor activity by viral oncolysis, increased by the combination of *FCU1* gene expression and 5-FC pro-drug administration

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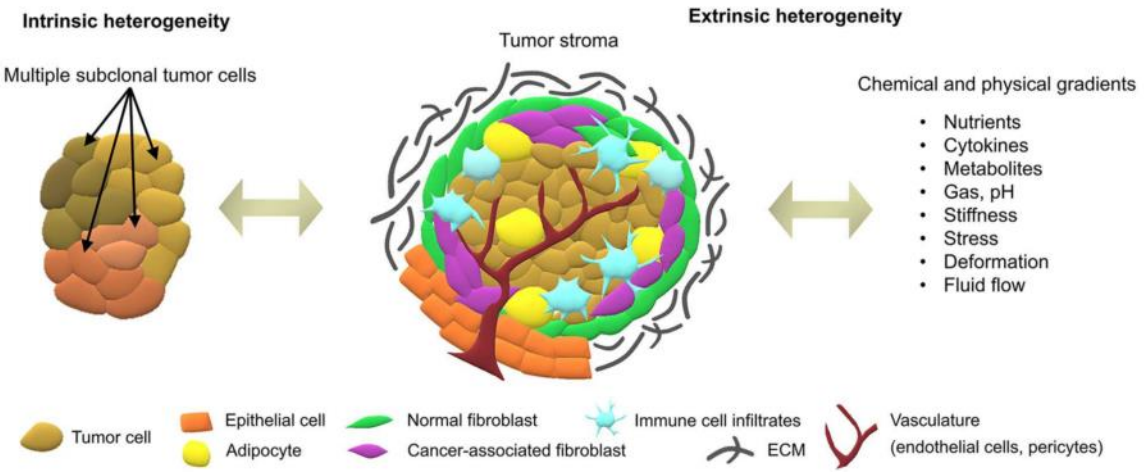
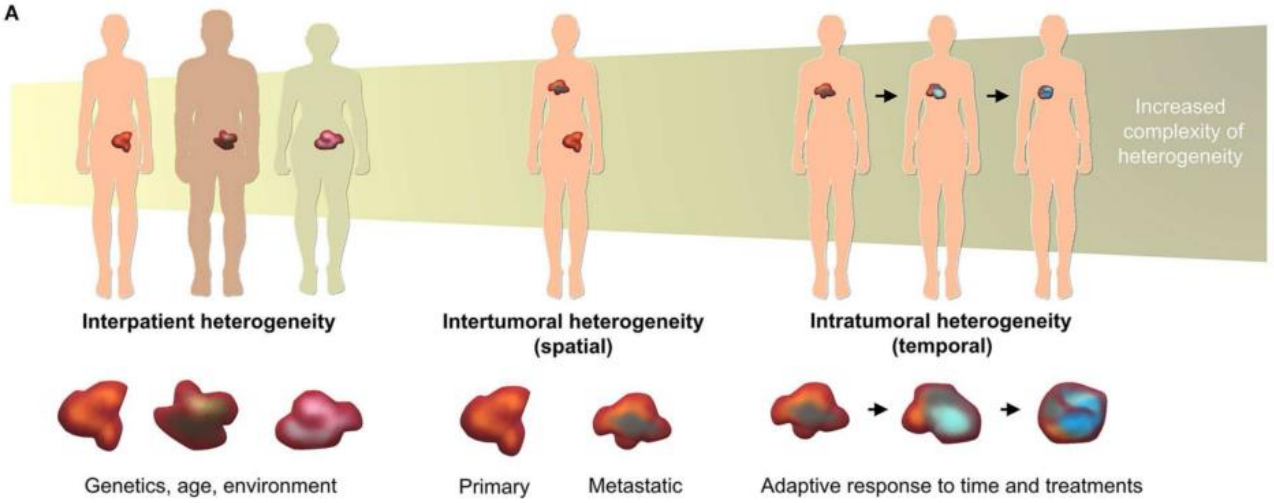
Cancer heterogeneity:



Tumors are composed of various cell types.

Tumors vary according to patients, location in the body, along with time and treatments.



Necessity to include patient-derived samples : tumoral cells + stroma cells + extra cellular matrix

L. J. Bray, D. W. Hutmacher, N. Bock,. Front Bioeng Biotechnol 7, 217 (2019)

Tomorrow needs

- Urgent need to better understand inherent risks of innovative therapeutics for Immuno-Oncology and Immuno-Inflammatory disease indications
  - e.g. cytokine release syndrome, infection, malignancy, autoimmunity

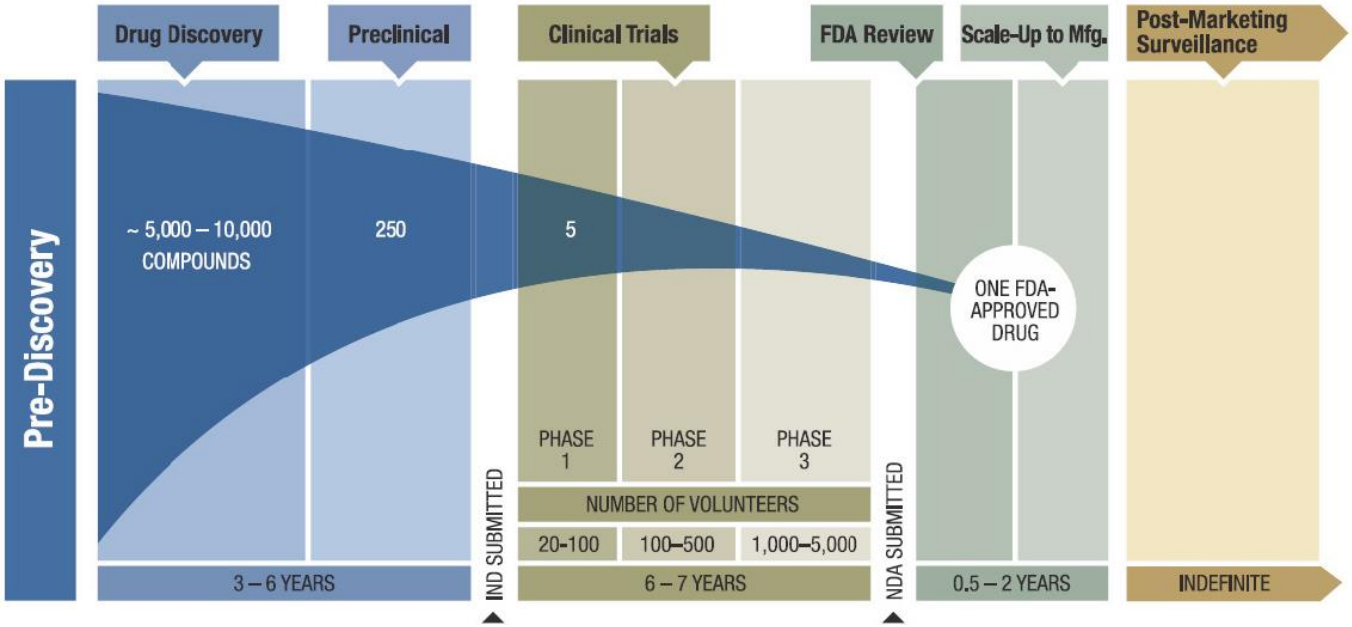
- Toxicities induced by immunomodulatory therapeutics in patients are often not detected in traditional animal models
  - e.g. lack of expression of appropriate targets/pathways in young healthy animals
  - differential target genetics/expression/functions in animals versus intended patient populations

Non-Animal approach: why ? (1)

- Animals are still necessary to understand basic physiology and pathophysiology, and to reproduce cause and biology of disease
- But there are significant concerns over how animal research is designed and how data is Analysed
- Some analysis shows that experimental animals have no or very low predictive power of drug effects in humans

https://ec.europa.eu/environment/chemicals/lab_animals/3r/pdf/scientific_conference/concluding_remarks.pdf

Non-Animal approach: why ? (2)



- 80 to 90% failure of clinical trials
- Relevance of preclinical models ??

FDA = Food and Drug Administration; IND = investigational new drug; Mfg. = manufacturing; NDA = New Drug Application.

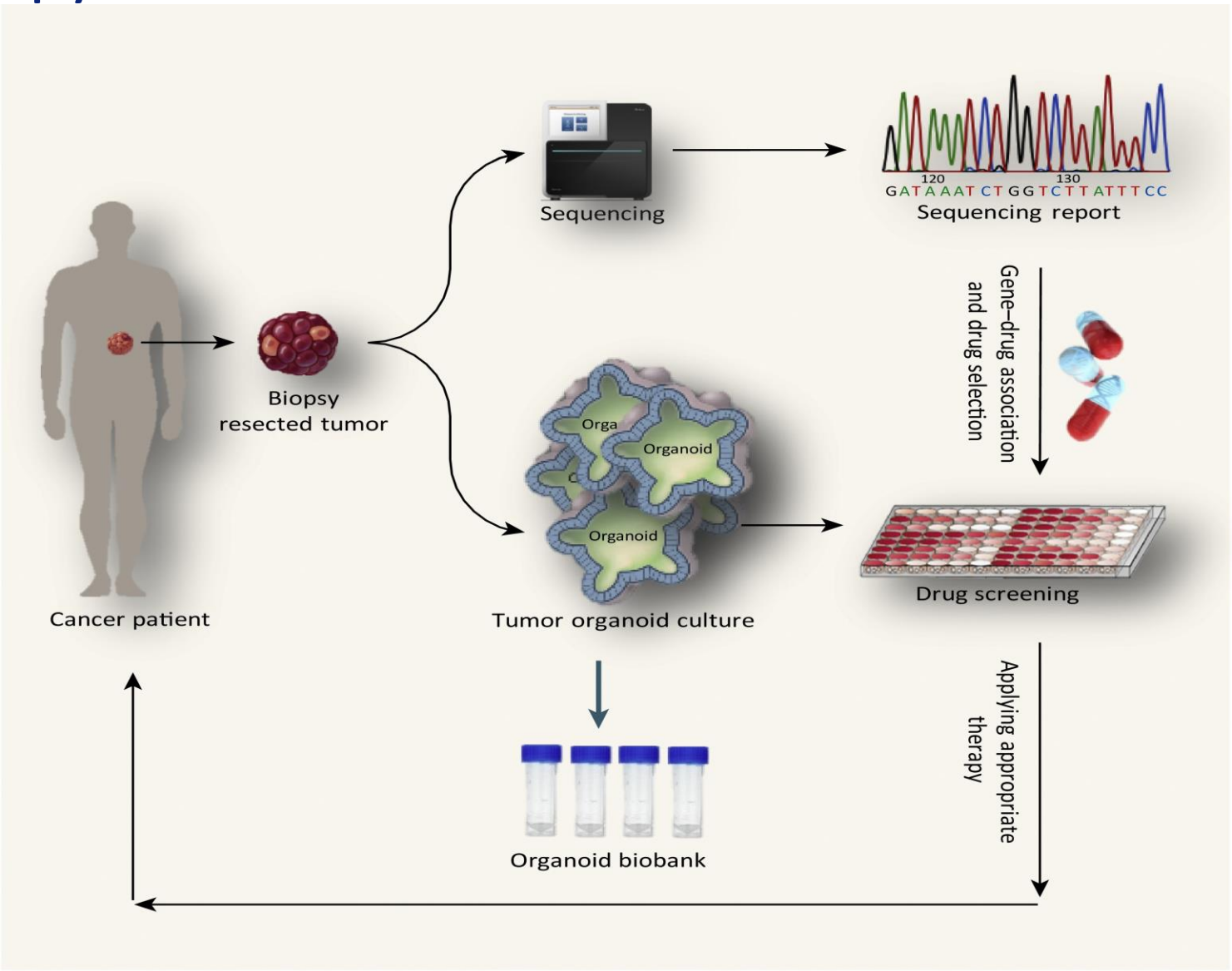
SOURCES: Sigal presentation, December 12, 2016; AACR, 2011.

Non-Animal approach: why ? (3)

- Human cell-based models and organs on a chip have great potential, but still need an in vivo test to confirm if 3D – cell simulation reflects in vivo
- Repeated dose toxicity and repro – or developmental toxicity still a challenge
- Human genomics helps to use animal models wisely, and reduce use of larger species. Targeted gene editing of animal helps to exactly model a human disease
- Safety studies to investigate severe adverse effects could be replaced by in vitro methods
- Metabolism info and computer modelling can help bridge differences between species

https://ec.europa.eu/environment/chemicals/lab_animals/3r/pdf/scientific_conference/concluding_remarks.pdf

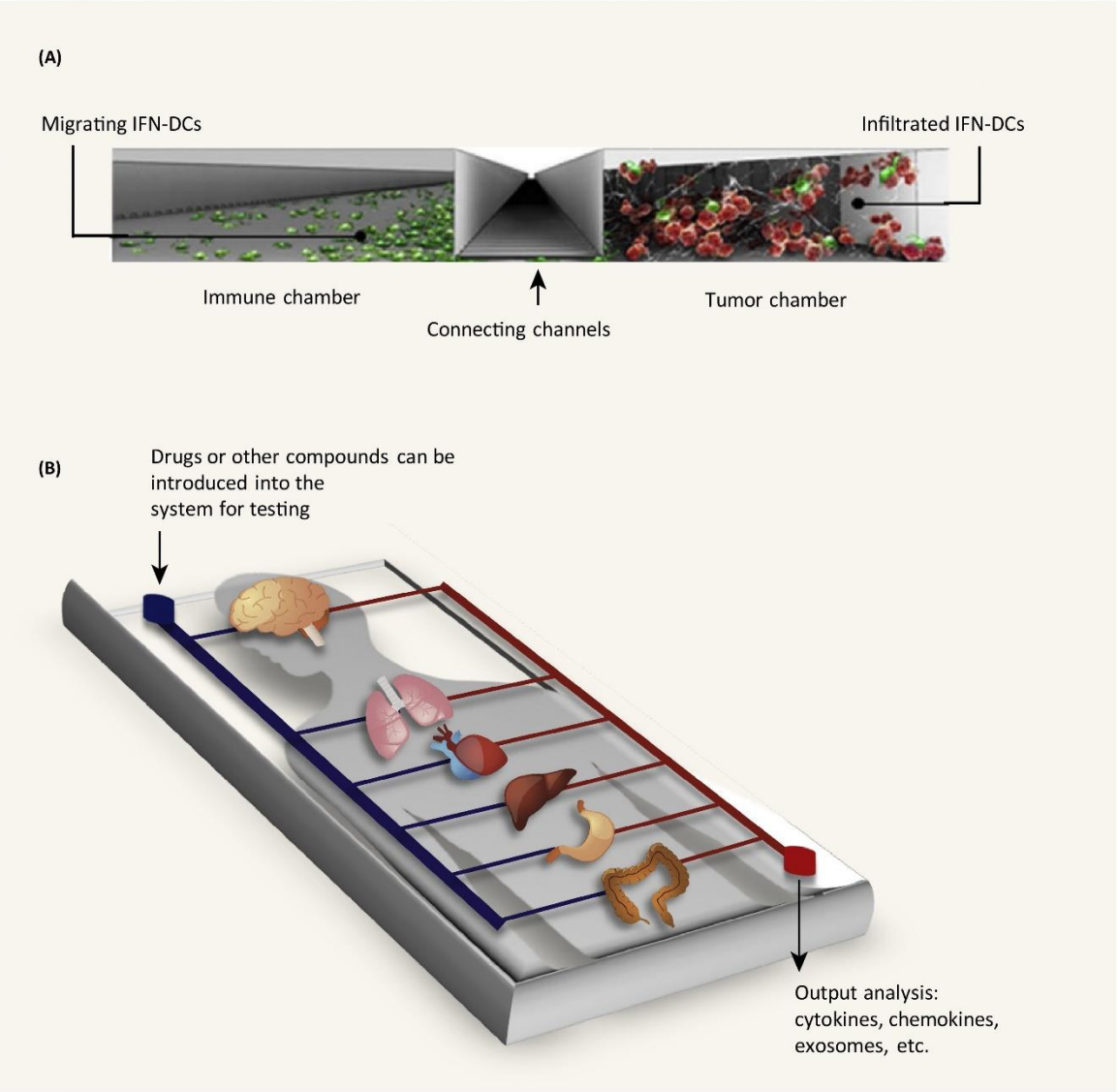
Schema of Organoid-Based Personalized Cancer Therapy



Trends in Biotechnology 2018 36, 358-371DOI: (10.1016/j.tibtech.2017.12.005)

Trends in Biotechnology

Application of Microfluidic Technology in Cancer–Immune Interaction and Organ-On-Chip Concepts



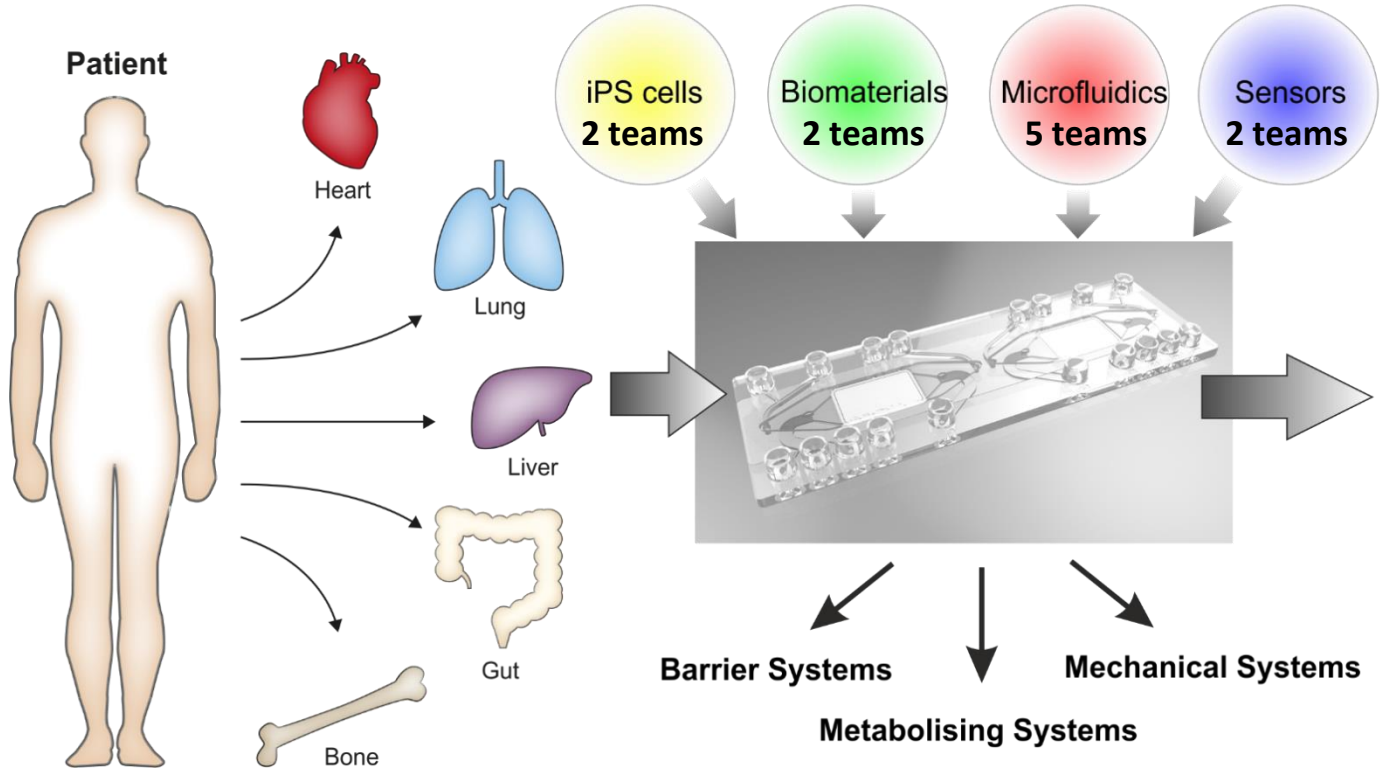
Trends in Biotechnology 2018 36, 358-371DOI: (10.1016/j.tibtech.2017.12.005)

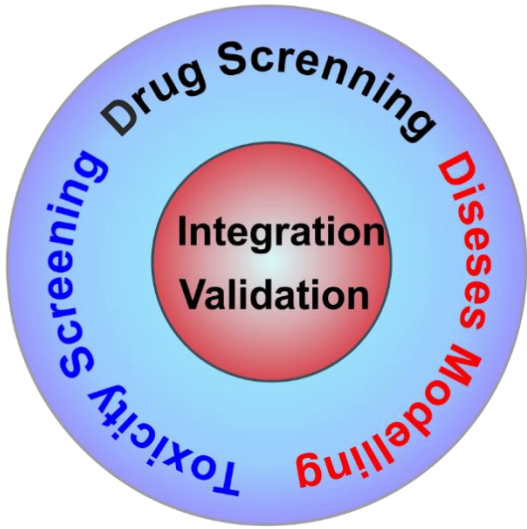
Trends in Biotechnology

H2020-MSCA-ITN-2018:

Marie Sklodowsk-Curie Actions , ***Innovative Training Network***

To support innovative research projects, which together target the development of advanced Organ-on-a-chip systems with higher physiological significance and that directly integrate endpoint analysis





End-users: **3 companies**

Regulatory Agencies: **4 agencies**

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Transgene' Project Objectives

- Making personalized organs-on-chips from tissues of specific patients in order to select best therapeutic (High Content Low Throughput):
  - MOA
  - Tox
- Bio design principles
- Tissue-Tissue Interface
  - Human tissue human cancer cell and Healthy tissues
  - Endothelial cell (Vasculature Model, Lymph circuit, …)
  - Immune compartment (Synthetic LN, PBMC, …)
- Dynamic Flow
- Nanomaterial selection
- Biosensors/analytics (MS, microscopy, PCR, sample recovery for titration, immunoprofiling)

Thank you for your attention

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