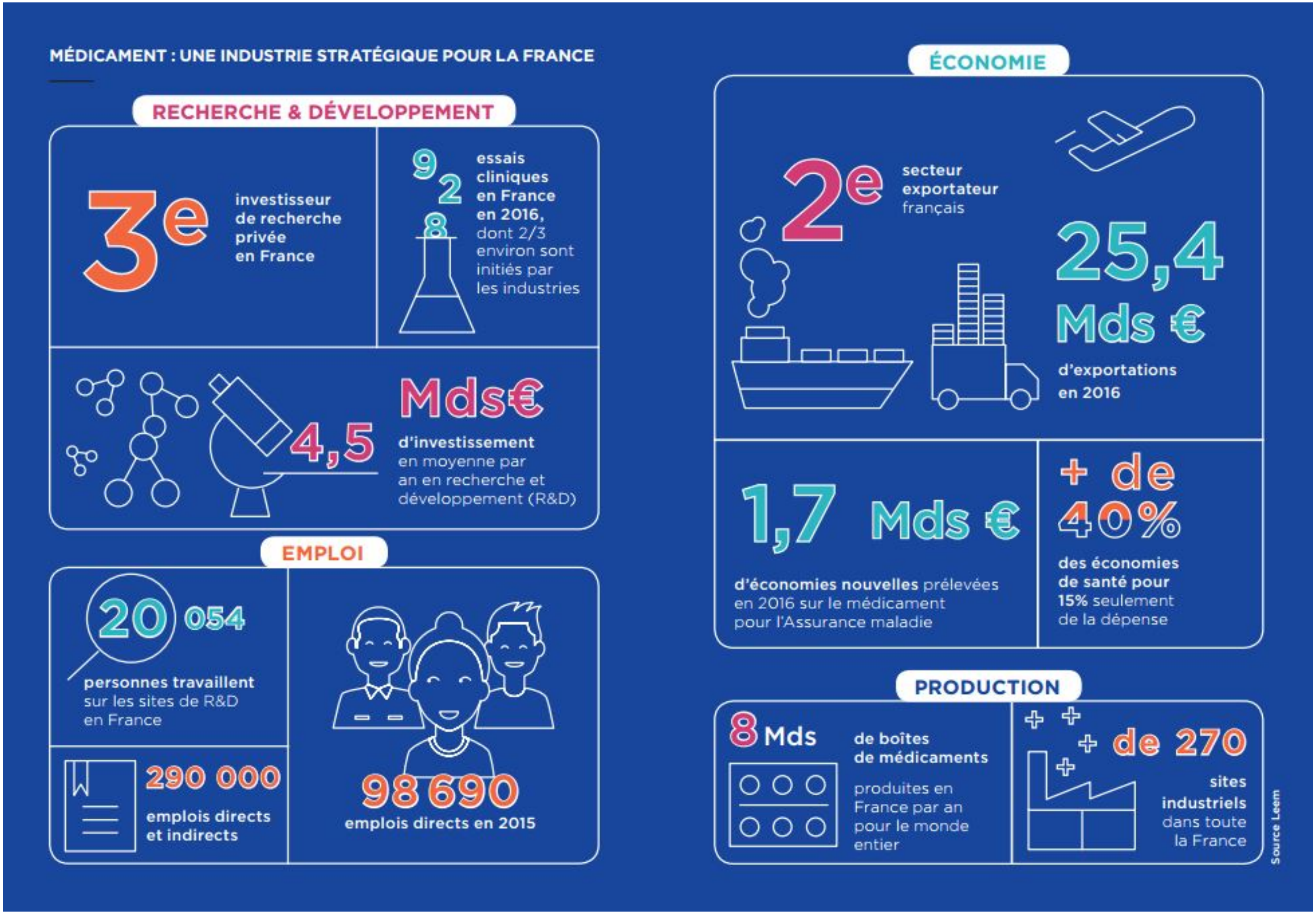
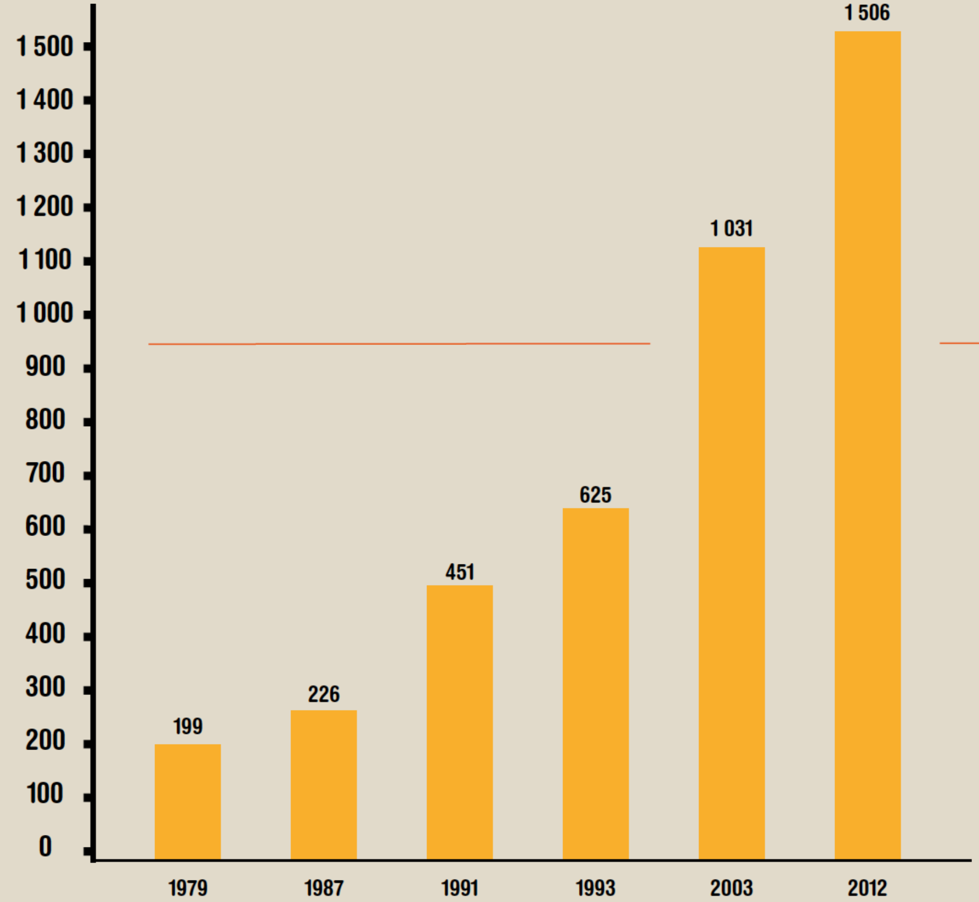
Le point sur le domaine du développement du médicament

Jean-Luc Galzi
CNRS et université de Strasbourg


MÉDICAMENT : UNE INDUSTRIE STRATÉGIQUE POUR LA FRANCE
RECHERCHE & DÉVELOPPEMENT
3e
investisseur de recherche privée en France
928
essais cliniques en France en 2016, dont 2/3 environ sont initiés par les industries
4,5 Mds€
d'investissement en moyenne par an en recherche et développement (R&D)
EMPLOI
20 054
personnes travaillent sur les sites de R&D en France
290 000
emplois directs et indirects
98 690
emplois directs en 2015
ÉCONOMIE
2e
secteur exportateur français
25,4 Mds €
d'exportations en 2016
1,7 Mds €
d'économies nouvelles prélevées en 2016 sur le médicament pour l'Assurance maladie
+ de 40%
des économies de santé pour 15% seulement de la dépense
PRODUCTION
8 Mds
de boîtes de médicaments produites en France par an pour le monde entier
+ de 270
sites industriels dans toute la France
Source Leem

LEEM

COÛT TOTAL DE RECHERCHE ET DÉVELOPPEMENT D'UN MÉDICAMENT CHIMIQUE OU BIOLOGIQUE JUSQU'À SA MISE SUR LE MARCHÉ (EN MILLIONS DE $. BASE 2011)

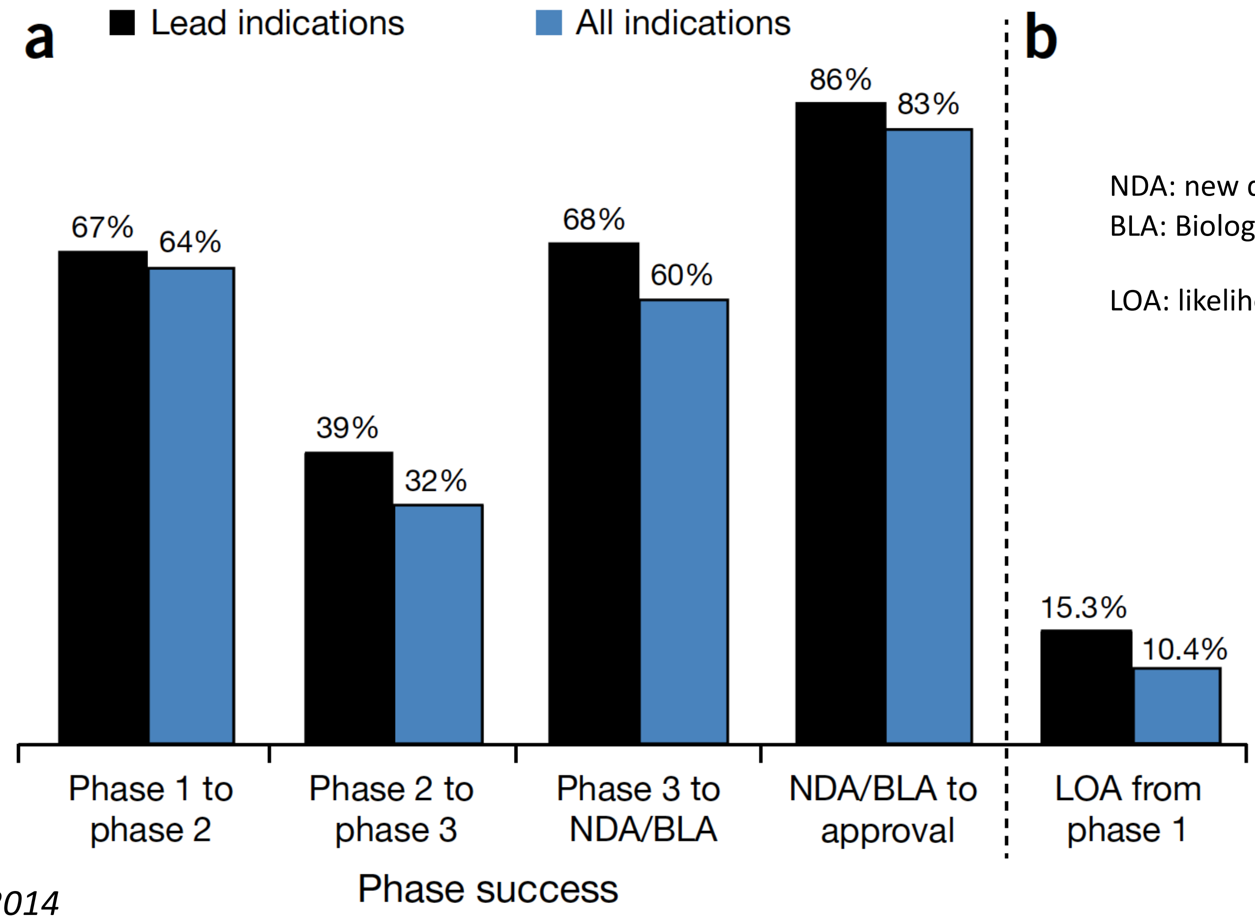


0,78 Mrd€

C'est le coût moyen de développement d'un médicament[1]

Attrition importante

Taux de succès du développement d'un médicament



NDA: new drug application
BLA: Biologic license application

LOA: likelihood of approval

Hay et al. Nat Biotech 2014

Etudes

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE

Physicochimie des molécules

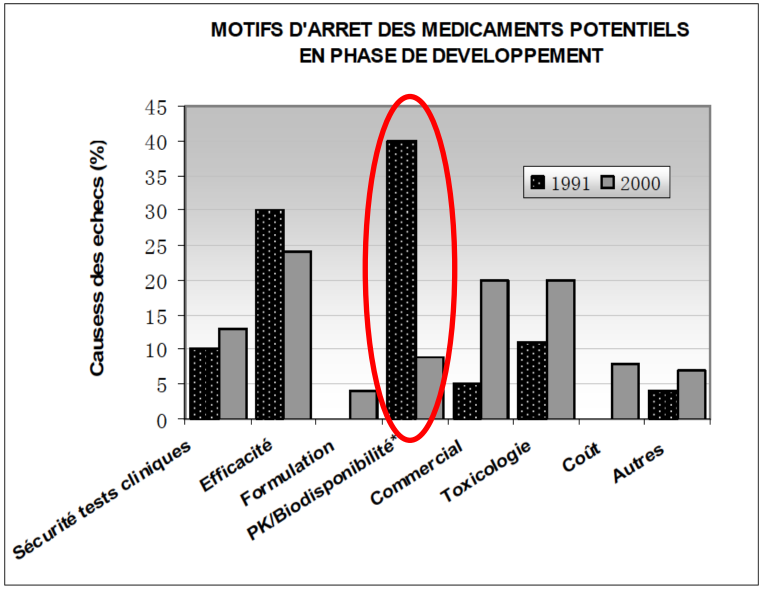
Règles de Lipinski (2001) (MW, LogP, accept-donneur liaison…)

Règle des 3/75 (2015) (LogP/TSA)

R&D des compagnies pharmaceutiques :

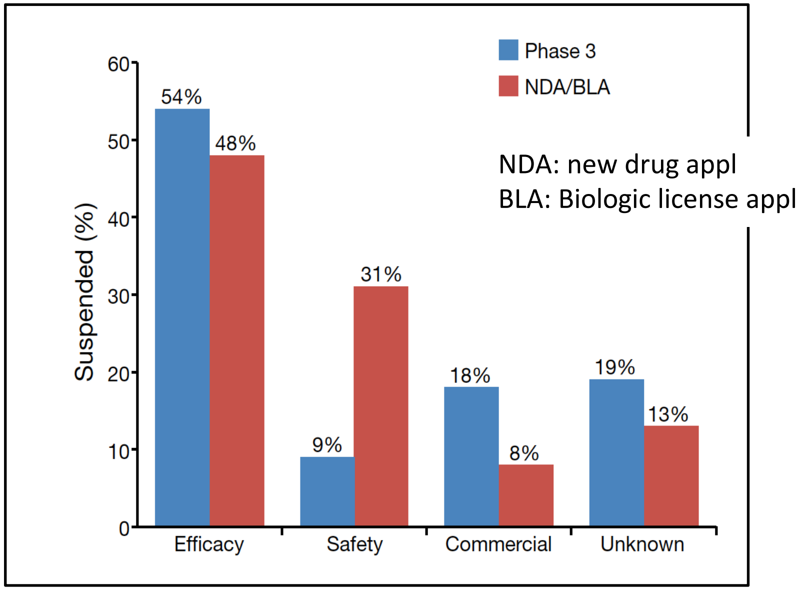
Ruptures et mutations

1990 -> 2000



2008, Nelly Weinmann

2010-2015



2014, Michael Hay, Nat Biotech 2014

Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13

Courtney Davis,[1] Huseyin Naci,[2] Evrim Gurpinar,[2] Elita Poplavska,[3] Ashlyn Pinto,[2] Ajay Aggarwal[4,5]

ABSTRACT

OBJECTIVE
To determine the availability of data on overall survival and quality of life benefits of cancer drugs approved in Europe.

Design
Retrospective cohort study.

Setting
Publicly accessible regulatory and scientific reports on cancer approvals by the European Medicines Agency (EMA) from 2009 to 2013.

Main outcome measures

WHAT THIS STUDY ADDS

Most new oncology drugs authorised by the EMA in 2009-13 came onto the market without clear evidence that they improved the quality or quantity of patients' lives

After market entry, cancer drugs rarely show benefits on overall survival or quality of life in randomised trials

When survival gains over available treatment alternatives are shown, they are not always clinically meaningful

the bmj | BMJ 2017;359:j4530 | doi: 10.1136/bmj.j4530

Etude sur 48 cancers et 68 indications.
Augmentation d'espérance de vie dans 35% des études / durée de l'augmentation de 1 à 6 mois (valeur moyenne 2,7 mois)
Augmentation de la qualité de vie dans 10% des études

Progrès récents et faits remarquables Année 2016-2017:

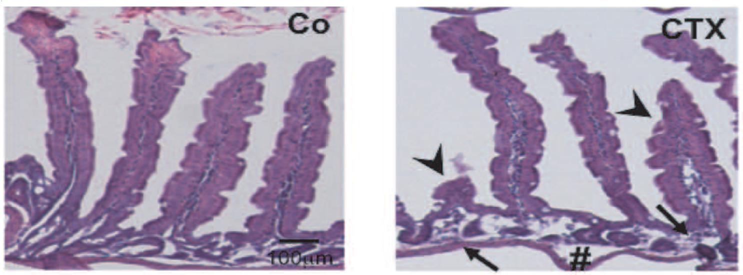
Importance du microbiote dans l'action des médicaments
(Efficacité ; PK/PD ; groupes de patients …)

Développement des méthodes de substitution des modèles animaux
Organoides, sphéroides, Organ on chip, human on chip
(prédictivité chez l'homme, modèles de pathologies humaines, médecine de précision,
métabolisme chez l'homme, toxicité)

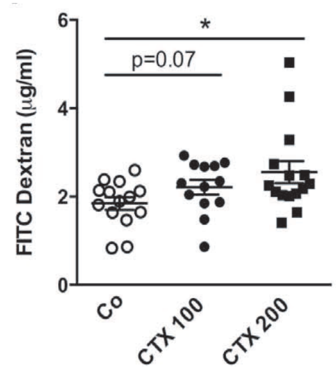
Autres faits remarquables: perméabilité des barrières, maladies génétiques

The Intestinal Microbiota Modulates the Anticancer Immune Effects of Cyclophosphamide
Sophie Viaud *et al.*
Science **342**, 971 (2013);

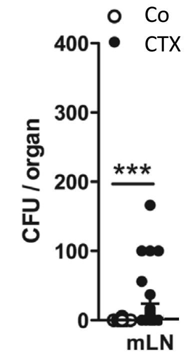
Contrôle cyclophosphamide



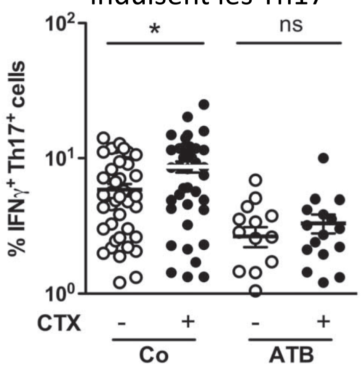
Affaiblissement de la barrière intestinale:
p.o. FITC-dextran dans le sang



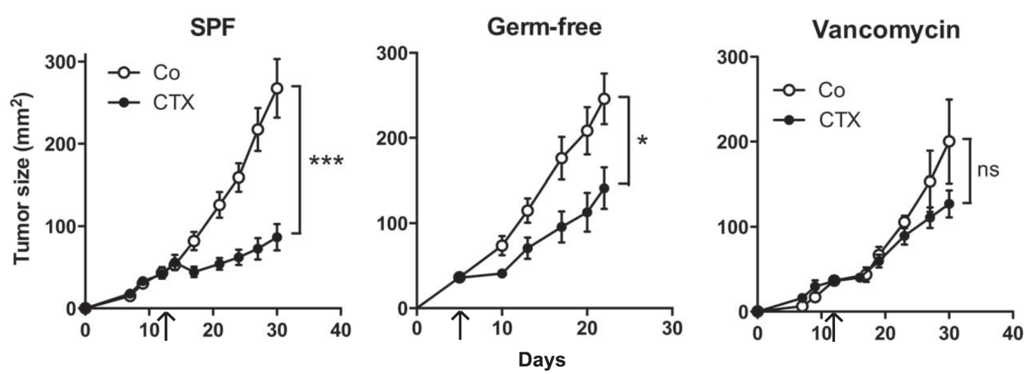
Bactéries dans les ganglions myentériques (Gram +)



Les bactéries Gram$^+$ induisent les Th17



Souris inoculées avec un sarcome

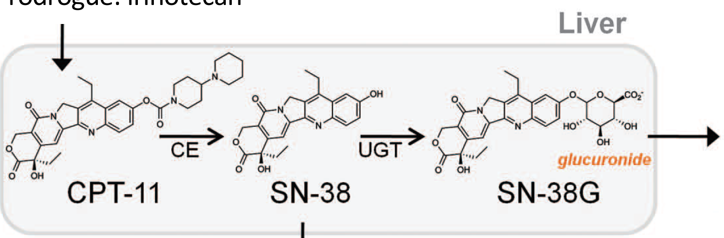


Δ gram$^+$

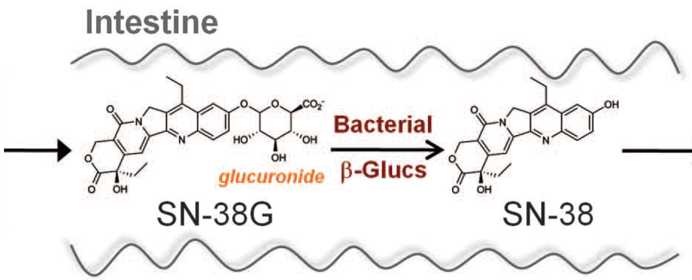
ATB = colistin, ampicillin, streptomycin

Microbiote et toxicité

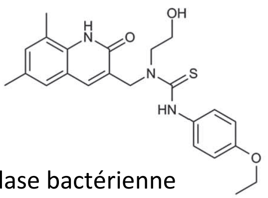
Administration i.v.
Prodrogue: irinotécan



Poison de topoisomérase I



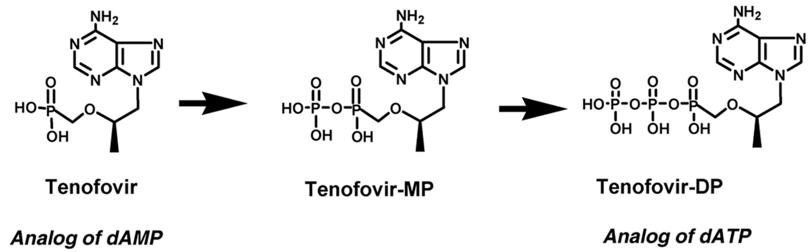
Diarrhées
Limite le Traitement chez 40% des patients



Inhibiteur de
β-glucuronidase bactérienne
-> NDE pour phase I (Symberix)

Wallace et al
Science 330, 831-835

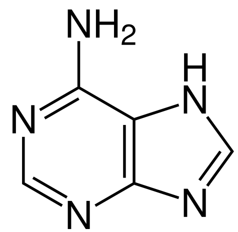
Microbiote et efficacité



Gardnerella vaginalis

Inhibits HIV or HBV reverse transcriptase

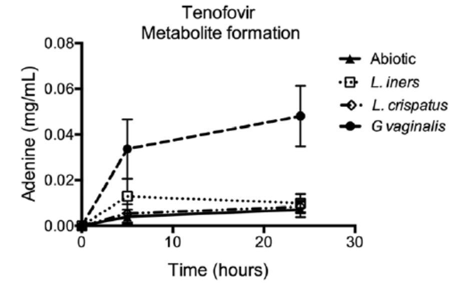
- Competes with dATP
- Incorporates into viral DNA
- Causes viral DNA chain termination
- Prevents viral replication



Analogue inactif
(adénine)

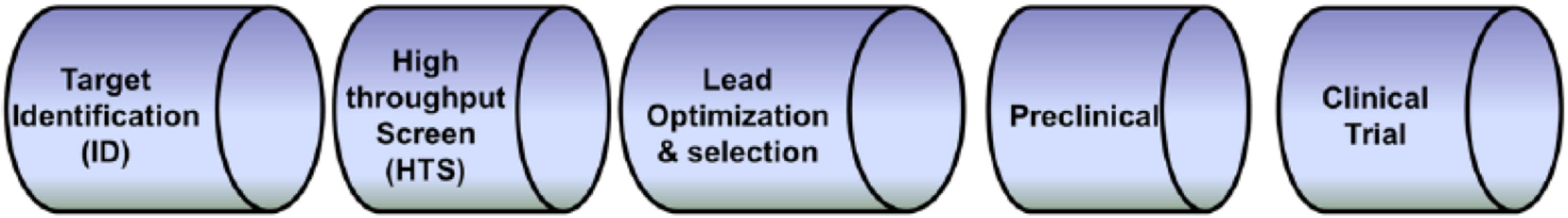
Klatt et al
Science 356, 938-945

G.v présente dans la flore de 40% des femmes
Efficacité : 18 % contre 61%



Modèles in vitro: Sphéroides, organoïdes, organ-on-chip, human-on-chip

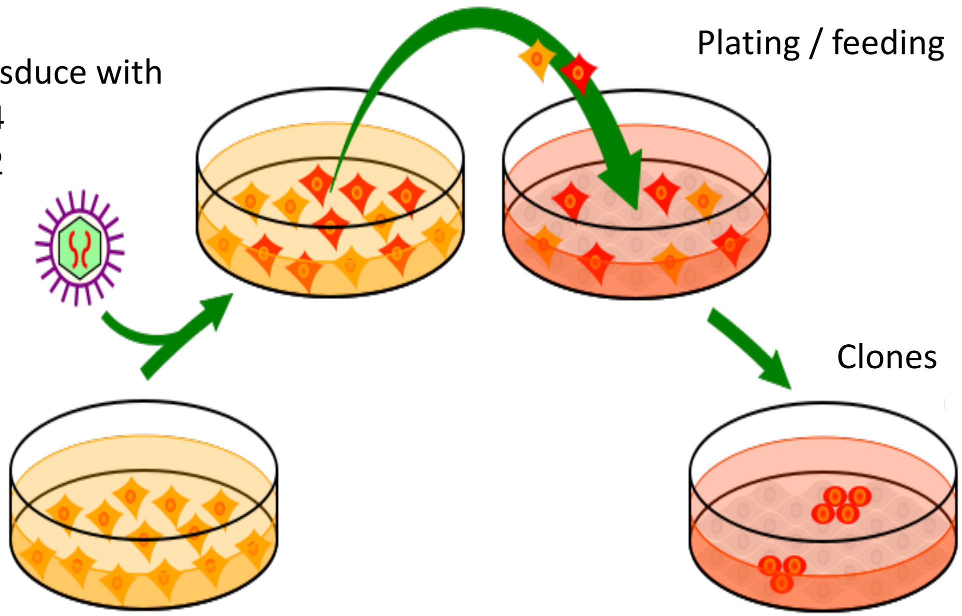
hSCs, hES, hMSC, primary cells, iPSCs → Organoïdes, organs-on-chip



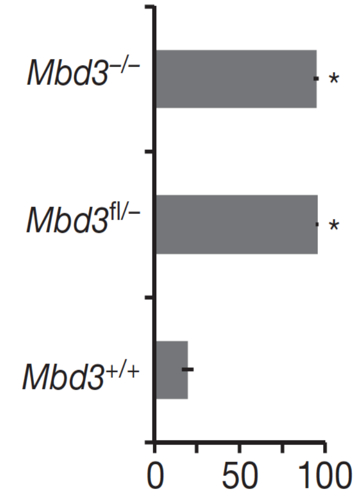
Modèles humains
- d'organes
- de pathologie
- De PK/PD
- Toxicité
- métabolisme

Médecine de précision
Médecine régénérative
Pharmacogénomique
Identification de cible
Candidats médicaments

Induced pluripotent stem cells

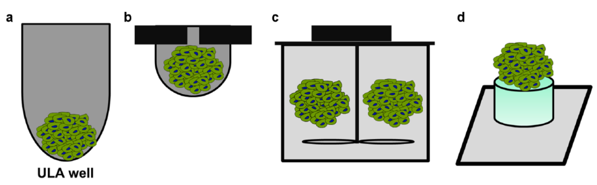


Yamanaka & coll. 2006



Rais et al. Nature (2013) 502, 65-70

Differentiation
3D culture



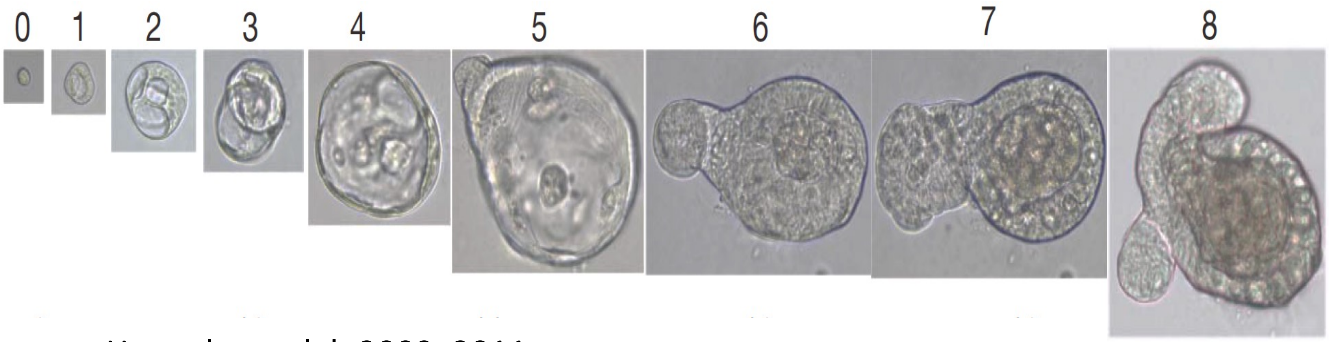
C-~~myc~~ -> Glis1 or valproic acid (iHDAC)

Sox2 -> BIX-01294 (iHMT)

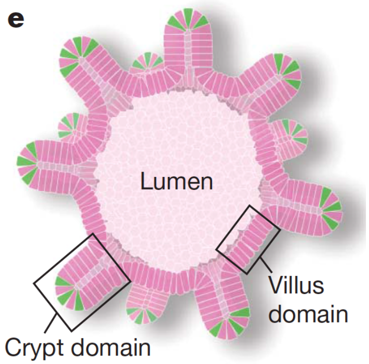
Picollet-D'hahan et al
Trends Biotechnol 2017

production d'organoïdes et interêt

- Intestin: (biopsies cryptes / cell souche Lrg5^{+}) + R-spondin1 + EGF + Noggin+ laminin/matrigel)



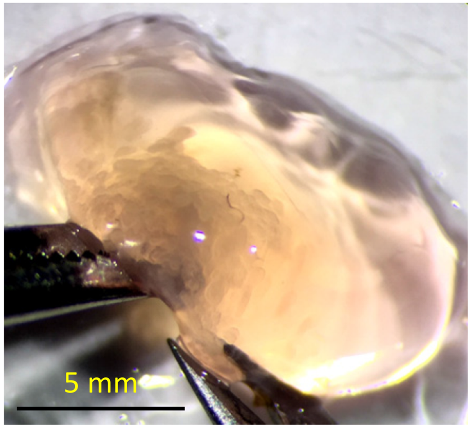
Hans clevers lab 2009, 2011 …



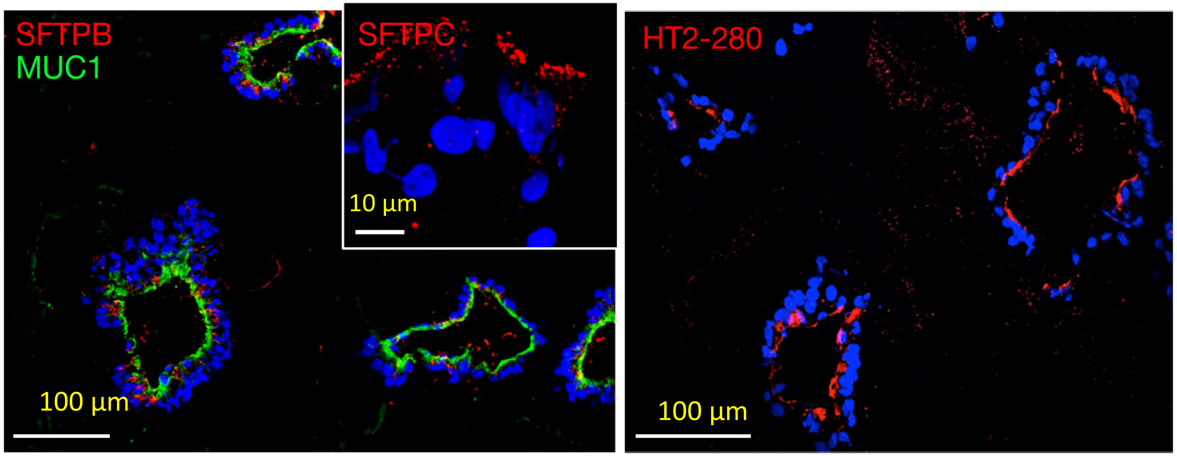
- ➢ études de biodisponibilité
- ➢ Incorporation de microbiote / métabolisme - efficacité
- ➢ modèles de pathologies

production d'organoïdes et interêt

- Poumon ESCs and iPSCs

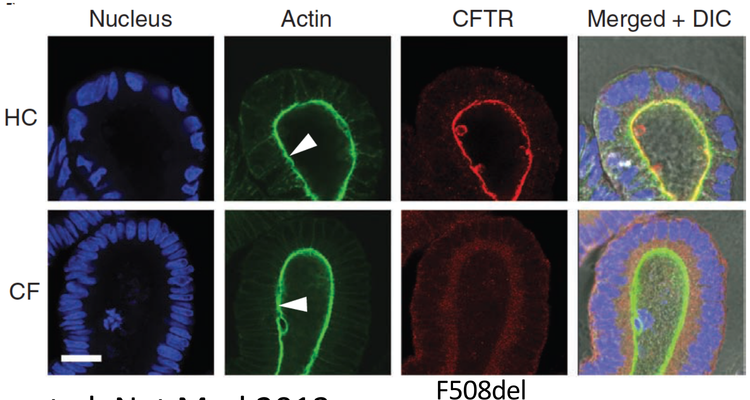


Chen et al. Nat Cell biol 2017



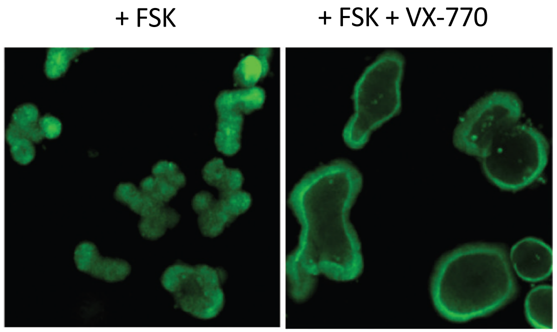
Mucine / Surfactant protein / alveolar type 2 lung cells

Médecine de précision



Dekkers et al. Nat Med 2013

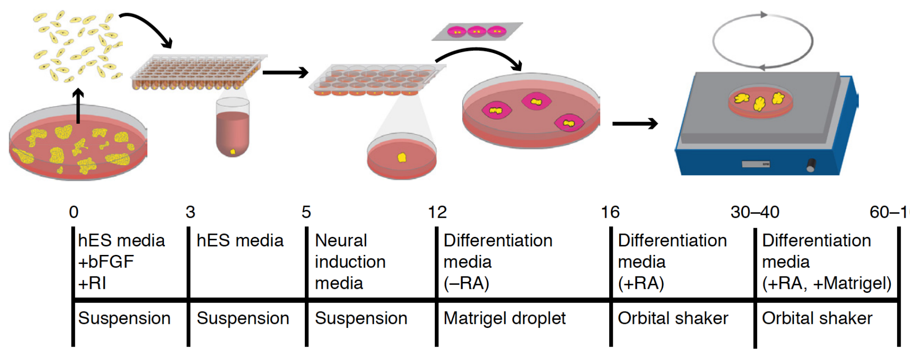
1 patient avec
mutation rare
CFTR
G1249R

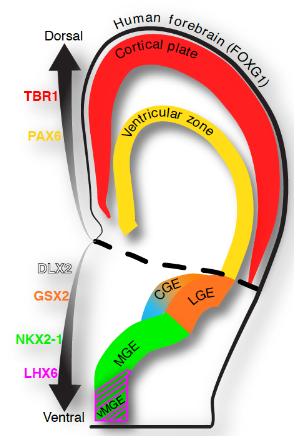


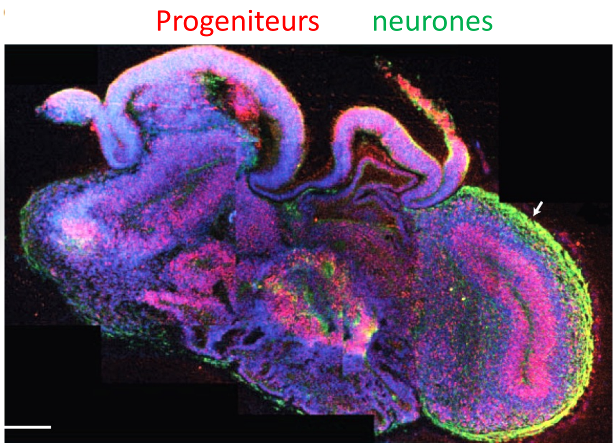
Phenotype rescue with ivacaftor (VX-770)
Marketed for G551D -> patient treated successfully

aviesan
alliance nationale pour les sciences de la vie et de la santé

Institut Thématique Multi-Organismes
Technologies pour la santé



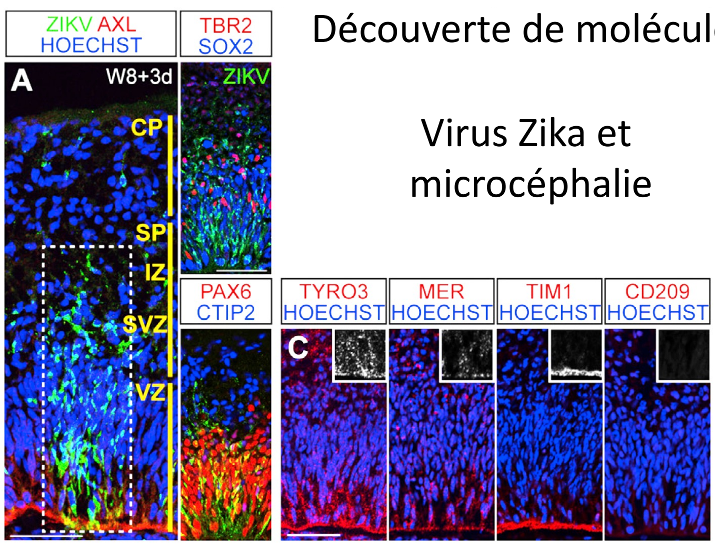


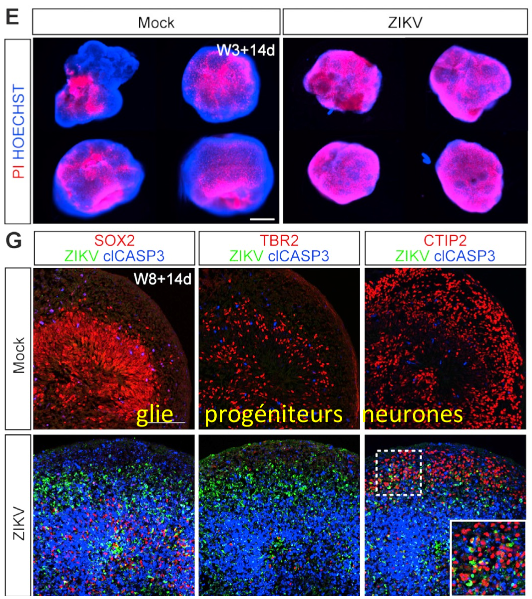


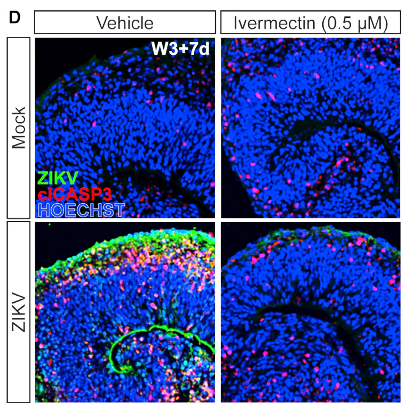
Knoblich group 2013-2017

Validation de cible
Découverte de molécules

Virus Zika et microcéphalie



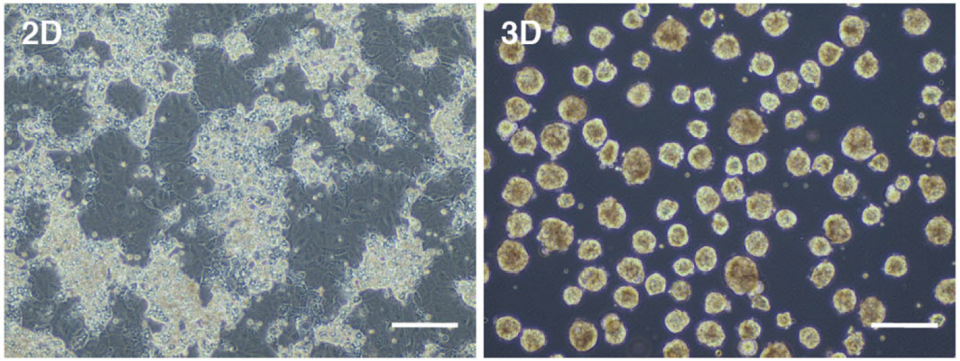


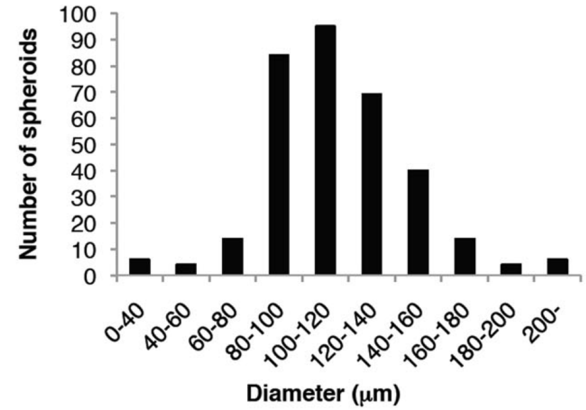


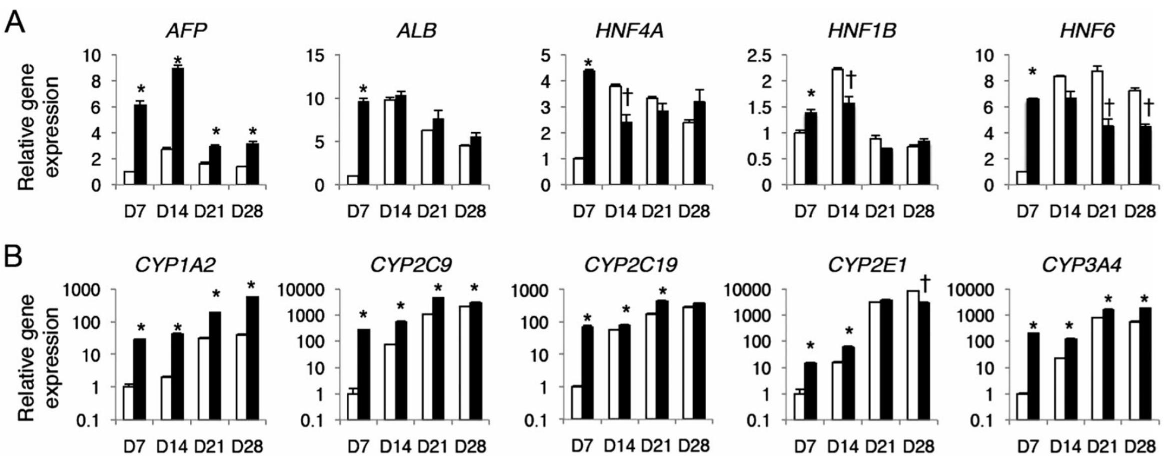
Watanabe cell rep 2017

FOIE

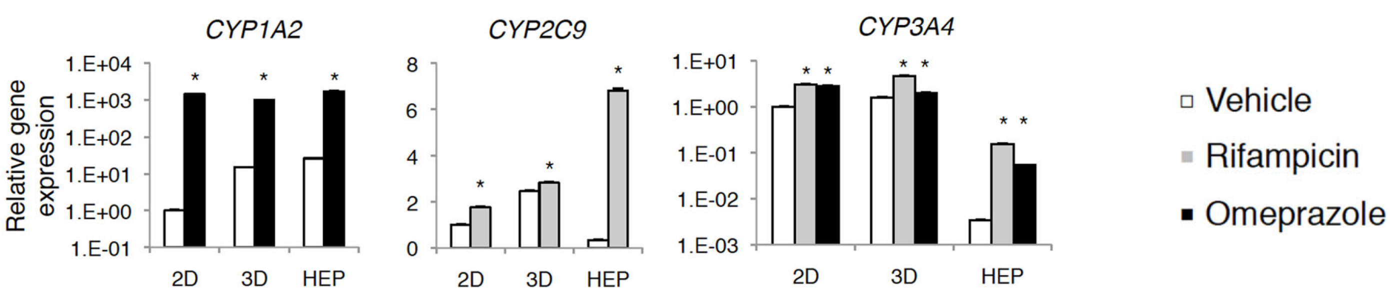
Lignée HepaRG





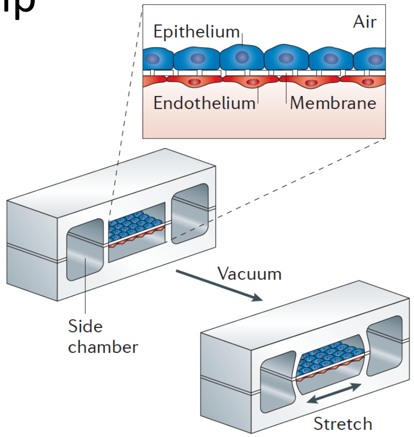


□ 2D
■ 3D



Interfaçage avec micromécanique et microélectronique

Lung-on-a-chip



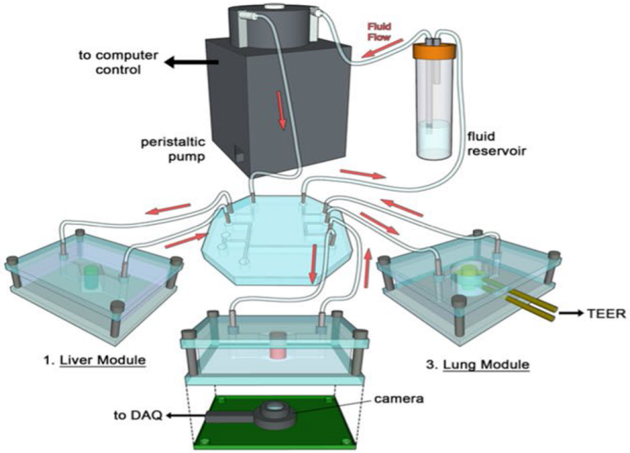
Organoïde

Organoïde « vascularisé »

body-on-a-chip

complexité

Organoïde « immunocompétent »



Organoïdes interconnectés

Les espoirs:

Modèles humains (3R)

Médecine personnalisée / connaissance des groupes de patients

Modèles pour maladies génétiques et rares

Pathologies du SNC

Les défis:

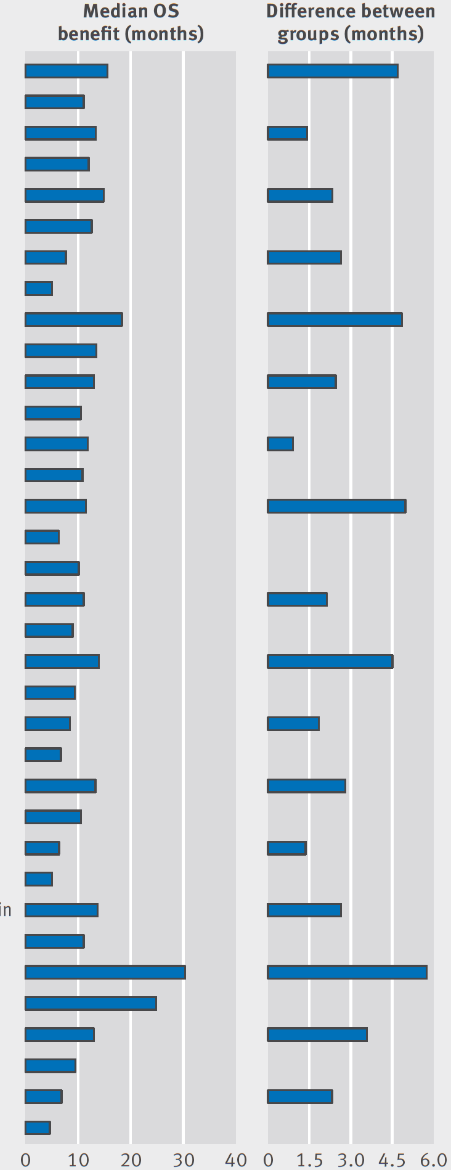
Validation physiologique des modèles
Ex: Profil d'expression des transporteurs et cytochromes dans foie

Transport/Microbiote dans un organoïde intestinal

Fonctions complexes: Connexion entre organoides / Système immunitaire

……

Agent	Cancer site	Indication	Intervention and control groups	Hazard ratio (95% CI)
Abiraterone acetate	Prostate	After chemo mCRPC (+pred)	Group 1: Abiraterone acetate + pred	0.74 (0.64 to 0.86)
			Group 2: PBO + pred	
Aflibercept	Colorectal	2nd line mCRC (+FOLFIRI)	Group 1: Aflibercept followed by FOLFIRI	0.82 (0.71 to 0.94)
			Group 2: PBO followed by FOLFIRI	
Cabazitaxel	Prostate	Hormone refractory mPC (+pred) previously treated with docetaxel	Group 1: Cabazitaxel + pred	0.70 (0.59 to 0.83)
			Group 2: Mitoxantrone + pred	
Decitabine	Haematological	1st line AML in chemo ineligible adults aged ≥65	Group 1: Decitabine and/or supportive care	0.82 (0.68 to 0.99)
			Group 2: Cytarabine and/or supportive care	
Enzalutamide	Prostate	mCRPC previously treated with docetaxel	Group 1:MDV3100 – enzlutamide	0.63 (0.53 to 0.75)
			Group 2: PBO	
Eribulin	Breast	3rd line mBC	Group 1: Eribulin	0.81 (0.66 to 0.99)
			Group 2: Physician's choice	
Erlotinib	Lung	Maintenance therapy in mNSCLC (previously platinum based chemo)	Group 1: Platinum based chemo + erlotinib	0.81 (0.70 to 0.95)
			Group 2: Platinum based chemo + PBO	
Ipilimumab	Haematological	2nd line unresectable or metastatic melanoma	Group 1: Ipilimumab + gp 100	0.68 (0.55 to 0.85)
			Group 2: gp 100 + PBO	0.66 (0.51 to 0.87)
			Group 3: Ipilimumab + PBO	
Ipilimumab	Haematological	1st line unresectable or metastatic melanoma	Group 1: Dacarbazine + ipilimumab	0.72 (0.59 to 0.87)
			Group 2: Dacarbazine + PBO	
Lapatinib	Breast	HER2+ HR- mBC (+trastuzumab) Previous trastuzumab + chemo	Group 1: Lapatinib + trastuzumab	0.74 (0.57 to 0.97)
			Group 2: Lapatinib	
Paclitaxel (nab-paclitaxel)	Pancreas	1st line (+gemcitabine) metastatic pancreatic adenoca	Group 1: Abraxane (paclitaxel) + gemcitabine	0.72 (0.62 to 0.84)
			Group 2: Gemcitabine	
Pemetrexed	Lung	Maintenance for mNSCLC (non-squam) after platinum based doublet chemo (with gemcitabine or taxane)	Group 1: Pemetrexed + BSC	0.79 (0.65 to 0.95)
			Group 2: Placebo + BSC	
Regorafenib	Colorectal	mCRC either after previous therapy with or eligible for 5-FU based chemo or VEGFi or EGFRi therapy	Group 1: Regorafenib + BSC	0.79 (0.66 to 0.93)
			Group 2: PBO + BSC	
Trastuzumab	Stomach	1st line HER2+ mGC or mGOJ adenoca	Group 1: Trastuzumab + (5-FU or capecatebine) and cisplatin	0.74 (0.60 to 0.91)
			Group 2: (5-FU or capecatebine) and cisplatin	
Trastuzumab emtansine	Breast	HER2+ unresectable or mBC after trastuzumab and/or taxane therapy	Group 1: Trastuzumab emtansine	0.68 (0.55 to 0.85)
			Group 2: Lapatinib + capecatebine	
Vemurafenib	Haematological	Unresectable or metastatic melanoma (BRAF V600 mut)	Group 1: Vemurafenib	0.62 (0.49 to 0.77)
			Group 2: Dacarbazine	
Vinflunine	Urinary	Advanced or metastatic TCC or urothelial tract previous platinum regimen	Group 1: Vinflunine + BSC	0.78 (0.61 to 0.96)
			Group 2: BSC	



Agent	Indication
Degarelix	Advanced PC
Rituximab	1st line CLL (+chemo)
Mifamurtide	Resectable non-metastatic osteosarcoma after complete resection (+chemo)
Imatinib	Adjuvant treatment for high risk GIST
Gefitinib	EGFR mut+mNSCLC
Pemetrexed	Maintenance for mNSCLC (non-squam) after platinum based doublet chemo (w/gemcitabine or taxane)
Bevacizumab	1st line mBC (+docetaxel)
Everolimus	Advanced RCC after VEGF targeted treatment
Rituximab	Relapsed/refractory CLL (+chemo)
Vinflunine	Advanced or metastatic TCC of urethral tract. Previous platinum regimen
Temsirolimus	Relapsed or refractory MCL
Trabectedin	Relapsed (platinum sensitive) ovarian cancer (+PLD)
Trastuzumab	1st line HER2+mGC or mGOJ adenoCa
Ofatumumab	CLL refractory to fludarabine and alemtuzumab
Erlotinib	Maintenance therapy in mNSCLC (previous platinum based chemo)
Lapatinib	HER2+HR+mBC (+aromatase inhibitor). No previous chemo, trastuzumab, or AI)
Pazopanib	1st line advanced RCC
Pazopanib	2nd line advance RCC (previous cytokine)
Docetaxel	Adjuvant treatment of operable node negative BC (+doxorubicin and cyclosphamide)
Rituximab	Maintenance therapy for follicular lymphoma after induction
Sunitinib	2nd line unresectable or metastatic well differentiated PNET
Dasatinib	1st line Ph+CML (CP)
Nilotinib	Newly diagnosed adult Ph+CML (CP)
Tegafur/gimeracil/oteracil	Advanced GC (+cisplatin)
Cabazitaxel	Hormone refractory mPC (+pred) previously treated with docetaxel
Eribulin	3rd line mBC
Trastuzumab	HER2+BC (+taxane) after adjuvant chemo
Trastuzumab	HER2+BC (+ adjuvant chemo)
Bevacizumab	1st line mBC (+capecitabine). No previous taxanes or anthracyclines
Ipilimumab	2nd line unresectable or metastatic melanoma
Erlotinib	1st line EGFR mut+mNSCLC
Everolimus	Unresectable or metastatic well or moderately differentiated PNET
Abiraterone acetate	mCRPC (+pred) after chemo
Pemetrexed	Maintenance for mNSCLC (non-squam) after platinum based chemo
Panitumumab	1st line KRAS WT mCRC (+FOLFOX)
Panitumumab	2nd line KRAS WT mCRC (+FOLFIRI)
Bevacizumab	1st line (+carboplatin and paclitaxel) in stage IIIB ovarian, fallopian, or primary peritoneal cancer
Trastuzumab	HER2+ locally advanced BC (+neoadjuvant chemo and as monotherapy adjuvantly)
Cetuximab	1st line KRAS WT mCRC (+FOLFOX)
Vandetanib	Unresectable or metastatic medullary TC
Vemurafenib	Unresectable of metastatic melanoma (BRAF V600 mit)
Pixantrone	Multiple relapsed or refractory NHL (B cell)
Everolimus	2nd line HER2/nue-negative BC (+exemetane)
Pazopanib	Advanced STS (after chemo or progressed within 12 months after neo-adjuvant therapy)
Axitinib	2nd line advanced RCC
Decitabine	1st line AML in adults aged ≥65 ineligible for chemo
Crizotinib	2nd line ALK+advanced NSCLC
Bevacizumab	2nd line (+carboplatin and gemcitabine) platinum sensitive ovarian, fallopian, or primary peritoneal cancer. No previous VEGFi
Brentuximab vedotin	Relapsed or refractory CD30+HL after ASCT or 3rd line if ineligible for ASCT
Brentuximab vedotin	Relapsed or refractory systemic ALCL
Abiraterone acetate	mCRPC (+pred) before chemo
Aflibercept	2nd line mCRC (+FOLFIRI)
Pertuzumab	1st line HER2+mBC
Bosutinib	2nd or 3rd line CP, AP, BP, Ph+, or CML
Enzalutamide	mCRPC previously treated with docetaxel
Ponatinib	CML (CP, AP, BP) resistant or intolerant to dasatinib or nilotinib or with T3151 mutation or ineligible for imatinib
Ponatinib	Ph+ALL resistant or intolerant to dasatinib or with T3151 mutation or ineligible for imatinib
Vismodegib	mBCC
Lapatinib	HER2+HR- mBC (+trastuzumab). Previous trastuzumab+chemo
Bortezomib	1st line multiple myeloma eligible for SCT (+dexamethasone or dexamethasone+thalidomide)
Pomalidomide	3rd line (+dexamethasone) relapsed and refractory multiple myeloma
Dabrafenib	Unresectable or metastatic melanoma w/ BRAF V600 mut
Regorafenib	mCRC either after previous treatment with/ or ineligible for 5FU based chemo or VEGFi or EGFRi treatment
Afatinib	TKI naive EGFR mut+mNSCLC
Ipilimumab	1st line unresectable or metastatic melanoma
Trastuzumab emtansine	HER2+ unresectable or mBC after trastuzumab and/or taxane treatment
Nab-paclitaxel	1st line (+gemcitabine) metastatic pancreatic adenoca
Bortezomib	2nd line multiple myeloma ineligible for SCT (monotherapy or +doxorubicin or dexamethasone)

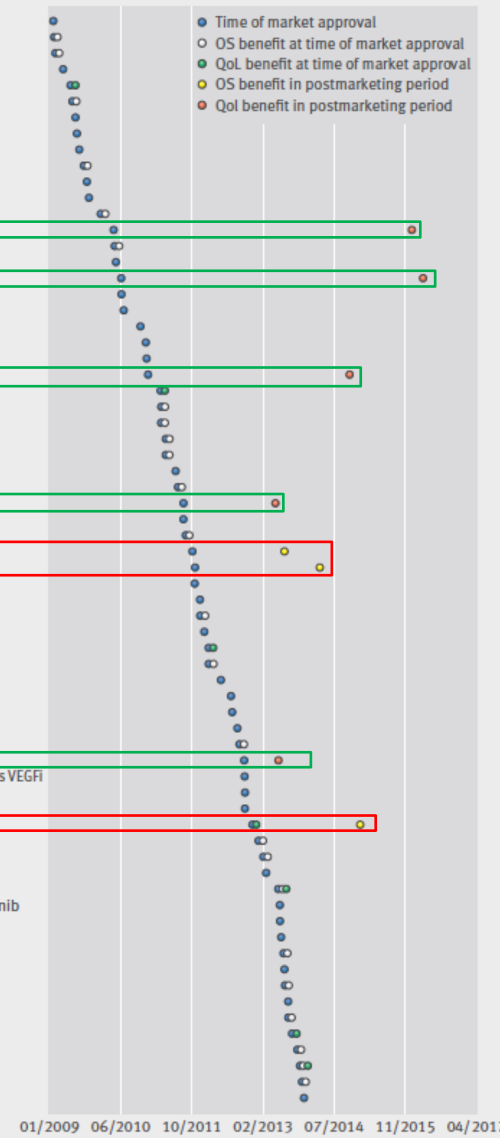


Fig 2 | Availability of benefits on overall survival and quality of life of cancer drugs approved 2009-13. Box 1 shows abbreviations used

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