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European Paediatric Translational Research Infrastructure

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 777554

Novel preclinical models as platform for drug discovery for paediatric diseases

Mikros Emmanuel

ATHENA Research Center

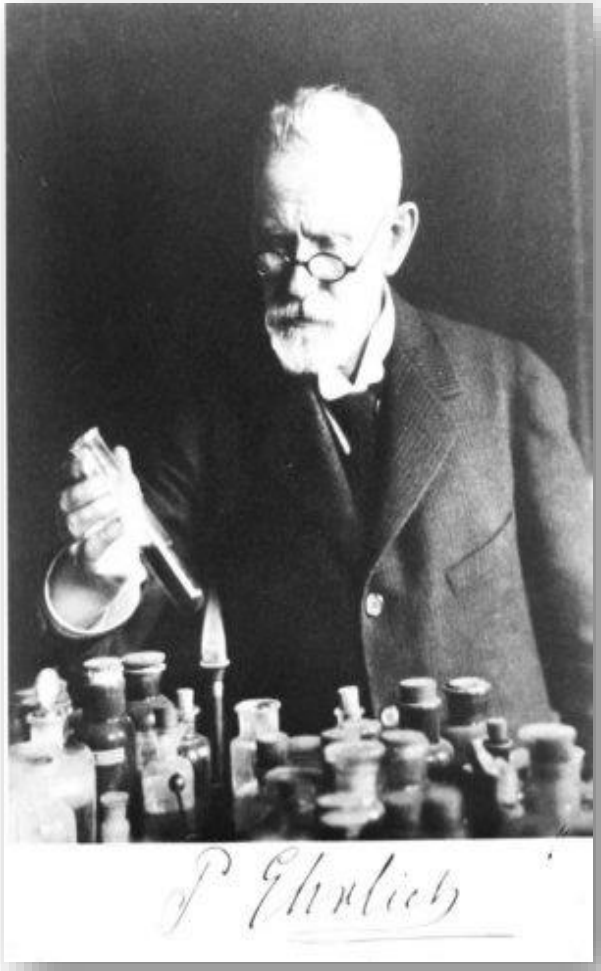
EPTRI webinar: biotechnology to bring innovation in the paediatric drug development

The event is part of the European Biotech Week 2020

PART OF EUROPEAN BIOTECH WEEK

INNOVATION IS IN OUR GENES

Rational drug design



"…..This approach is not only of great importance for a real understanding of the life processes but also the basis of the of a truly rational use of medicinal substances…."

Paul Ehrlich, Nobel Lecture

December 11, 1908

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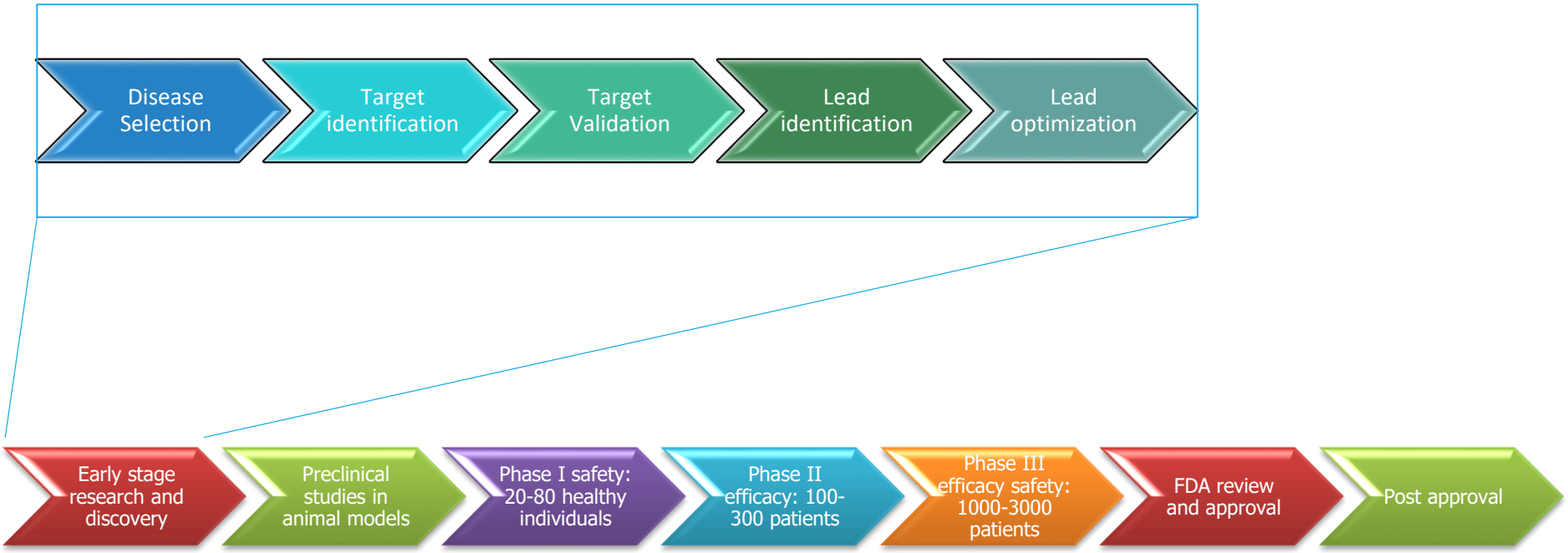
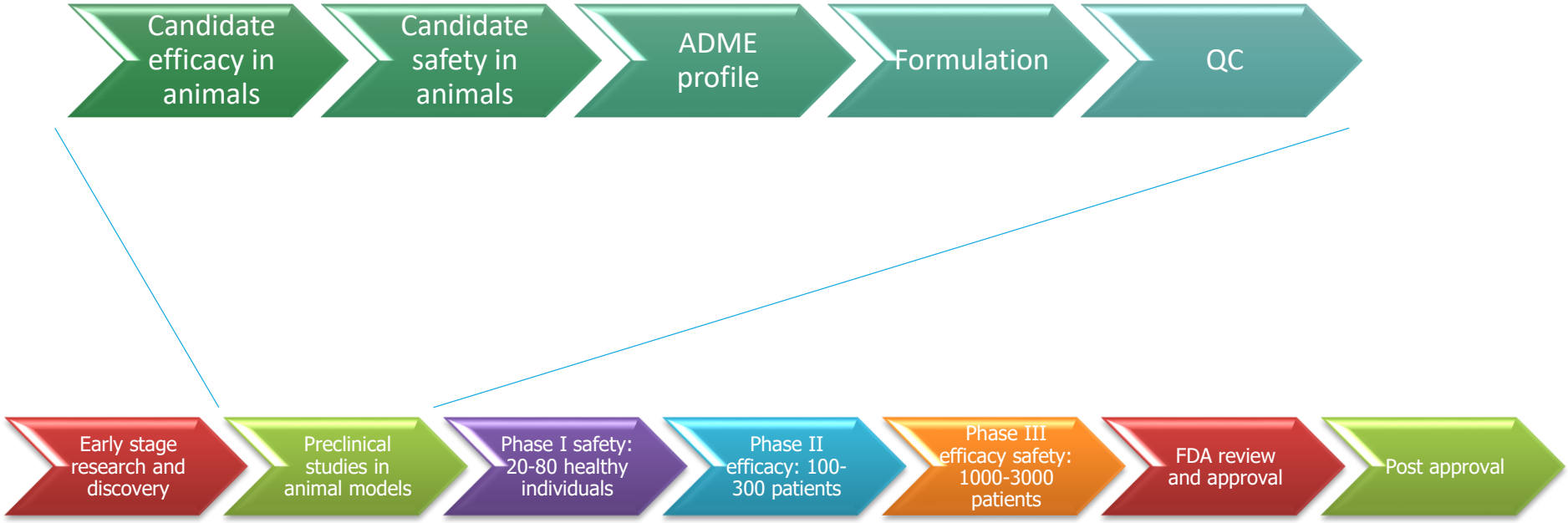
Drug Discovery pipeline



Drug Discovery pipeline



Cost

Contents lists available at ScienceDirect

Journal of Health Economics

journal homepage: www.elsevier.com/locate/econbase

Innovation in the pharmaceutical industry: New estimates of R&D costs☆

Joseph A. DiMasi[a,*], Henry G. Grabowski[b], Ronald W. Hansen[c]

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[c] Simon Business School, University of Rochester, United States

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O31

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Innovation

ABSTRACT

The research and development costs of 106 randomly selected new drugs were obtained from a survey of 10 pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug and biologics development. The costs of compounds abandoned during testing were linked to the costs of compounds that obtained marketing approval. The estimated average out-of-pocket cost per approved new compound is $1395 million (2013 dollars). Capitalizing out-of-pocket costs to the point of marketing approval at a real discount rate of 10.5% yields a total pre-approval cost estimate of $2558 million (2013 dollars). When compared to the results of the previous study in this series, total capitalized costs were shown to have increased at an annual rate of 8.5% above general price inflation. Adding an estimate of post-approval R&D costs increases the cost estimate to $2870 million (2013 dollars).

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nature REVIEWS DRUG DISCOVERY

The molecular pharmacopoeia

The human targets of FDA-approved oral drugs

John P. Overington*, Bissan Al-Lazikani* and Andrew L. Hopkins‡

The molecular pharmacopoeia of 166 human protein drug targets for FDA-approved oral drugs. The drug targets are grouped into target subfamilies where there are multiple related drug targets. The size of the icons represents the number of drugs approved for that target or target subfamily. The horizontal axis illustrates the cellular location of a drug target. The vertical axis illustrates an approximate timeline depicting when the first drug for a target or target subfamily was approved (older drug targets are at the top of the chart). The dates next to the targets illustrate the year in which the first USAN (United States Adopted Name) was assigned for the first drug against that target or any target in the subfamily (which usually occurs in the late stages of clinical development). The availability of protein structural information for the targets or targets subfamily is illustrated by the coloured dot next to the target name. The shapes of the icons represent the general functional classes of drug targets and related groups within a functional class are coloured the same.

inpharmatica

Pfizer

FDA-approved drugs (2016):
667 human targets

Secreted | Plasma and vesicle membrane | Cytoplasm | Organelle membrane | Nucleus

Central functional classes (by shape): GPCR | Enzyme | Ion channel | Nuclear receptor | Transporter/transducer | Other

Number of drugs approved (by size): Small icons: 1–10 | Medium icons: 11–50 | Large icons: >50

Protein structure information: Low | Medium | High | Null

Founded in 1849, Pfizer is the world's largest research-based pharmaceutical company, taking on the toughest challenges to better health. We discover and develop innovative medicines to treat and help prevent disease for both people and animals. Through consistent, high-quality manufacturing and distribution operations, our medicines reach patients in 150 nations. We also partner with healthcare providers, governments and local communities around the world to expand access to our medicines and to provide better quality healthcare and health system support. At Pfizer, our colleagues work every day to help people stay healthier and live longer and to make the best use of the economic burden of diseases worldwide.

Produced with support from Inpharmatica and Pfizer

Inpharmatica Ltd, 1 New Oxford Street, London, WC1A 1NU, UK
www.inpharmatica.co.uk

‡Pfizer Global Research and Development, Sandwich, Kent, CT13 9NJ, UK
www.pfizer.com

Drug Targets

- **Known targets**
  893 human and pathogen-derived biomolecules
- **Known drugs**
  1,578 US FDA-approved drugs

Table 1 | **Molecular targets of FDA-approved drugs**

Drug target class	Targets			Drugs		
	Total targets	Small-molecule drug targets	Biologic drug targets	Total drugs	Small molecules	Biologics
Human protein	667	549	146	1,194	999	195
Pathogen protein	189	184	7	220	215	5
Other human biomolecules	28	9	22	98	63	35
Other pathogen biomolecules	9	7	4	79	71	8

The list also includes antimalarial drugs approved elsewhere in the world.

2006	324
2016	667

Santos etal Nature Reviews Drug Discovery v16, 19–34 (2017)

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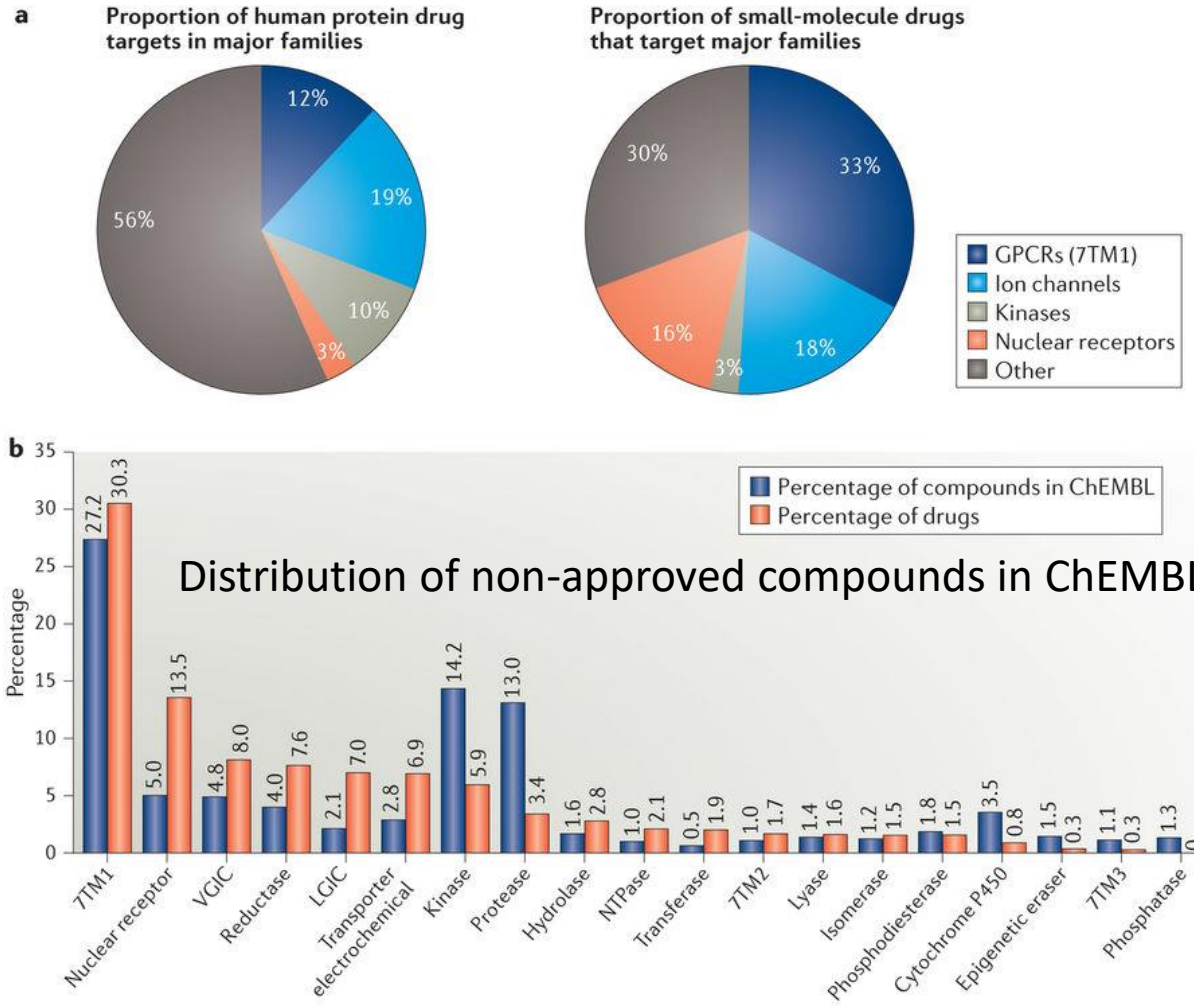
Drug targets

Major protein families as drug targets.

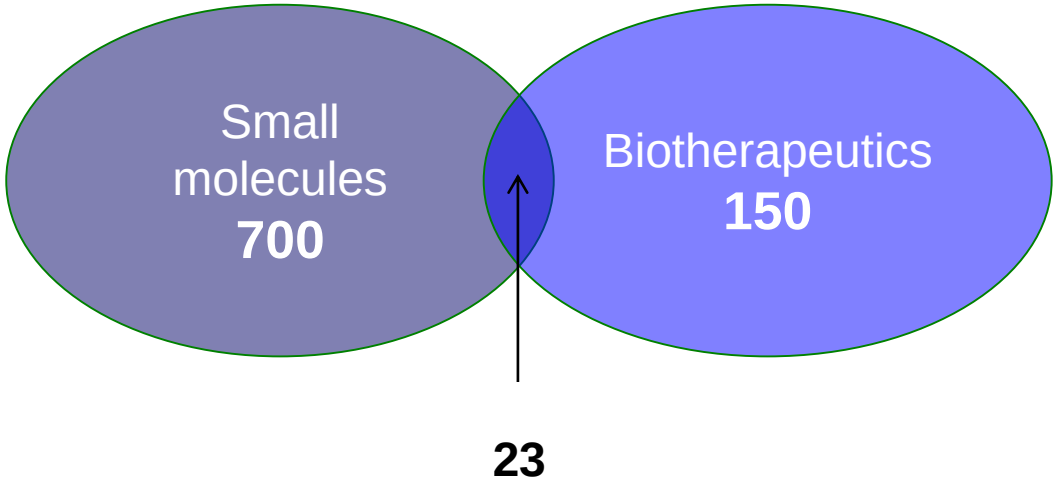
Dominance of privileged target families



Santos etal Nature Reviews Drug Discovery v16, 19–34 (2017)

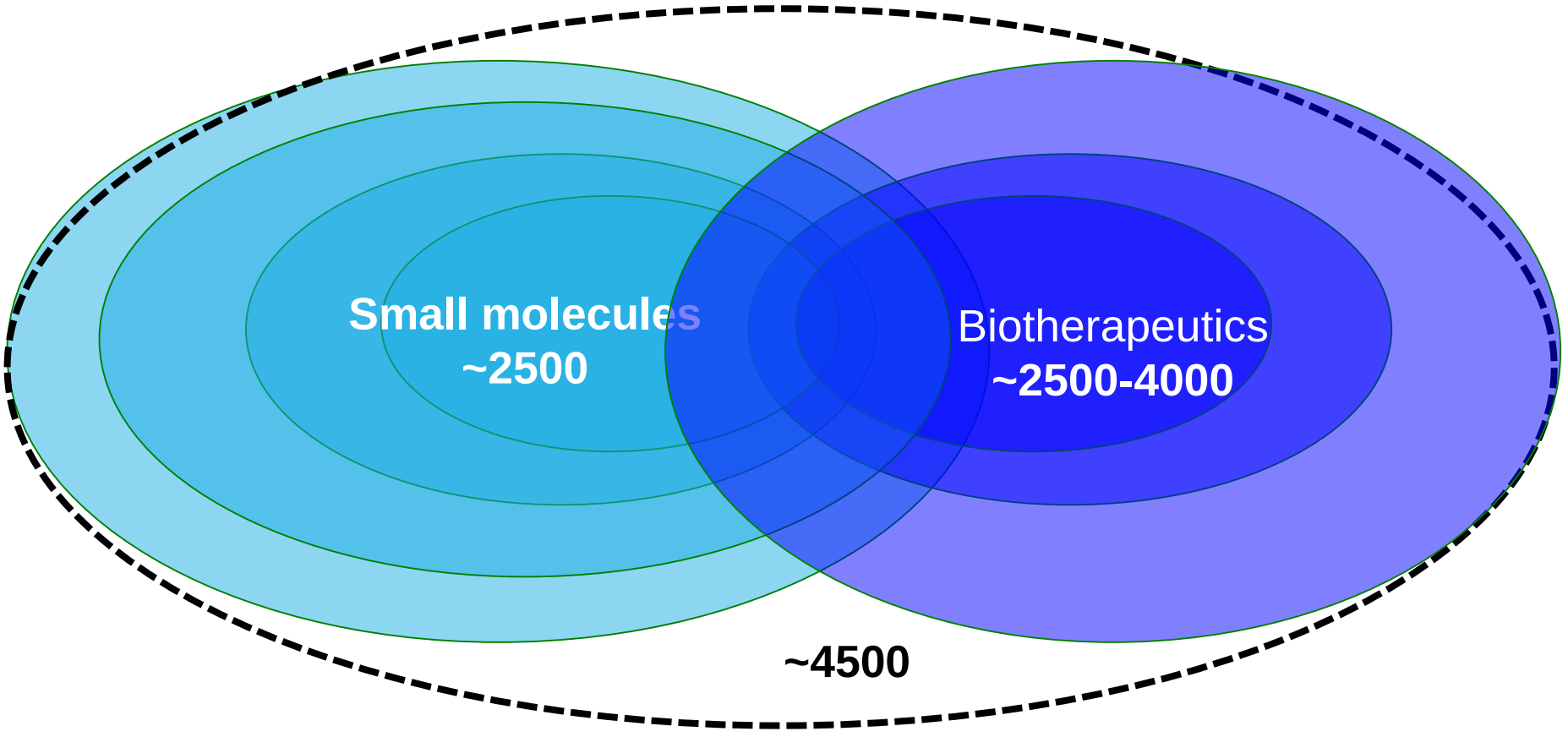
The druggable genome

- Targets of approved drugs



Anna Gaulton The Druggable Genome EMBL - EBI, ChEMBL Group

The druggable genome



Anna Gaulton The Druggable Genome EMBL - EBI, ChEMBL Group

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Target validation

Druggability

- The amenability of a molecular target (within the context of a cell, tissue, or whole organism) to pharmacologically useful functional modulation by synthetic compound(s) with drug-like properties.

Ligandability

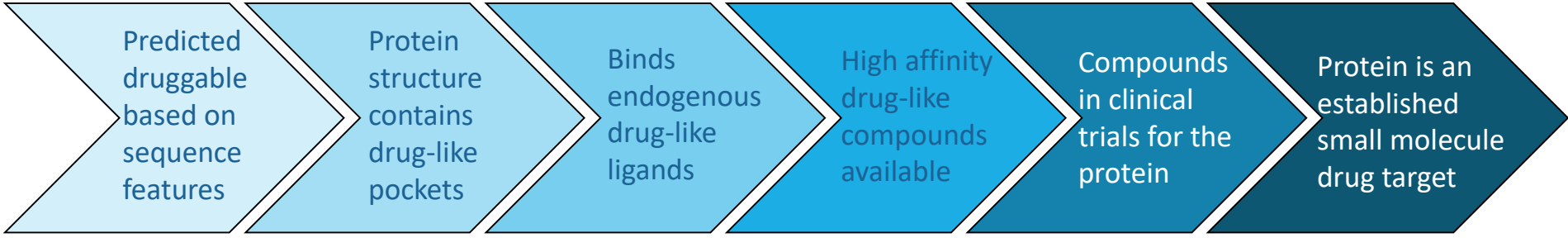
- the propensity of the target to bind small-molecule compounds with high-affinity

Target validation

- the process of gathering evidence to provide confidence that modulation of a target has the potential to treat a disease.

U. Bauer A.L. Breeze in Lead Generation-Methods and Principles in Medicinal Chemistry 2016 Wiley

Assessing druggability



Sequence analysis	Structural analysis	Metabolite/ligand databases	Pharmacology databases	Clinical trial databases	Drug databases
e.g., Machine-learning algorithms	Protein Data Bank	ChEBI, HMDB, KEGG, IUPHAR	ChEMBL, PubChem, BindingDB	ClinicalTrials.gov	DrugBank, TTD, DailyMed, ChEMBL

Increasing confidence in druggability

Anna Gaulton The Druggable Genome EMBL - EBI, ChEMBL Group

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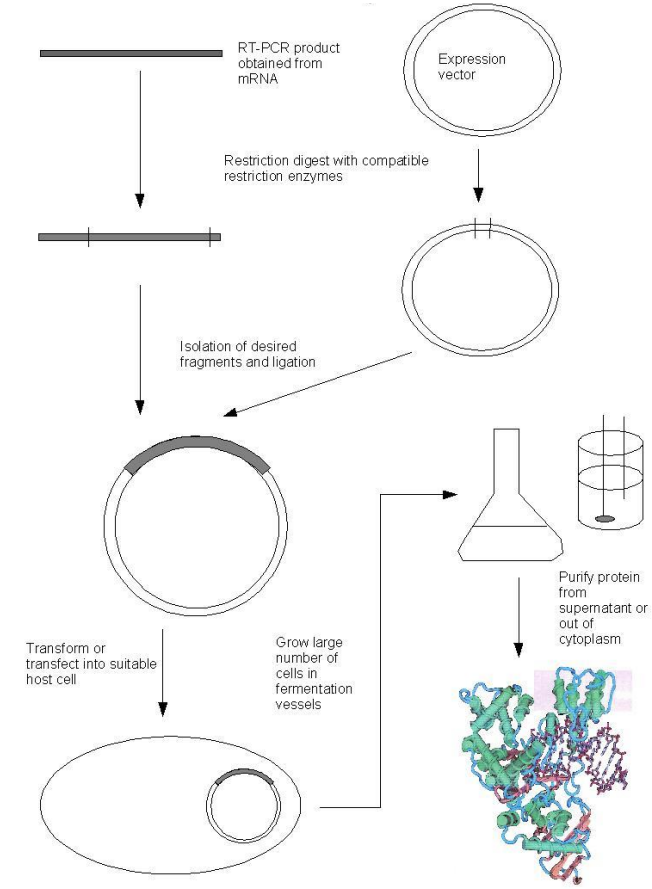
Technologies

Recombinant Proteins



www.technoscop.ch

http://www.biotechnet-mps.de/track_project.html

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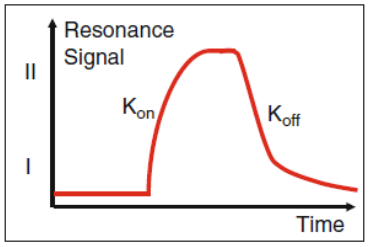
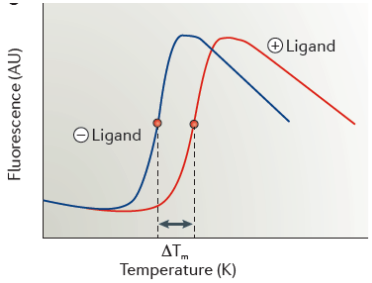
High Throughput Screening

SPR

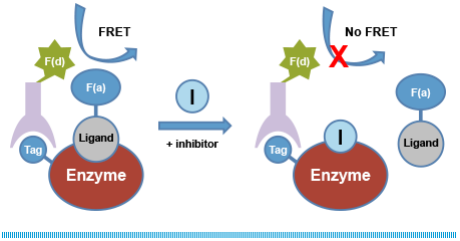


Sensorgram

DSF

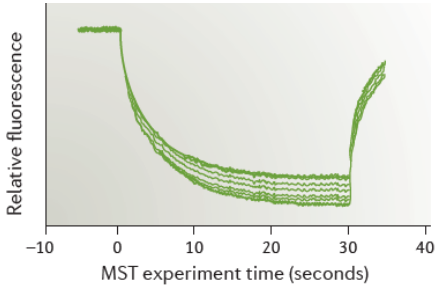


FRET

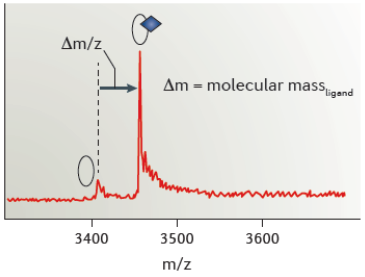


http://www.selcia.com/

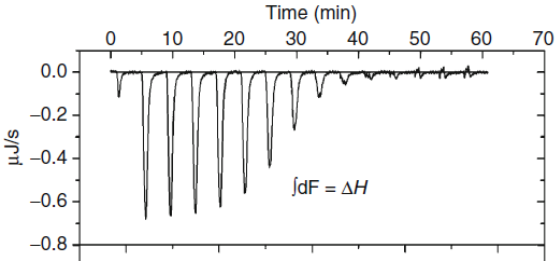
MST



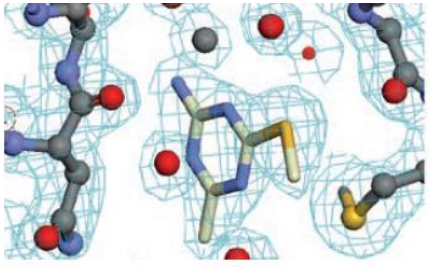
MS



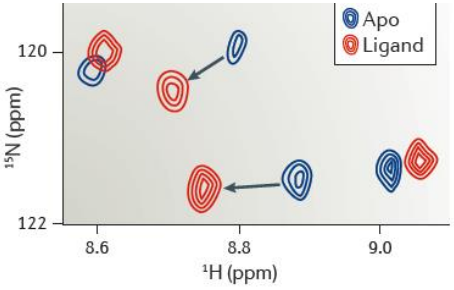
ITC

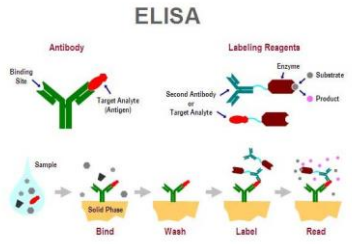


X-ray



NMR





Nat Rev Drug Discov **15,** 679–698 (2016).

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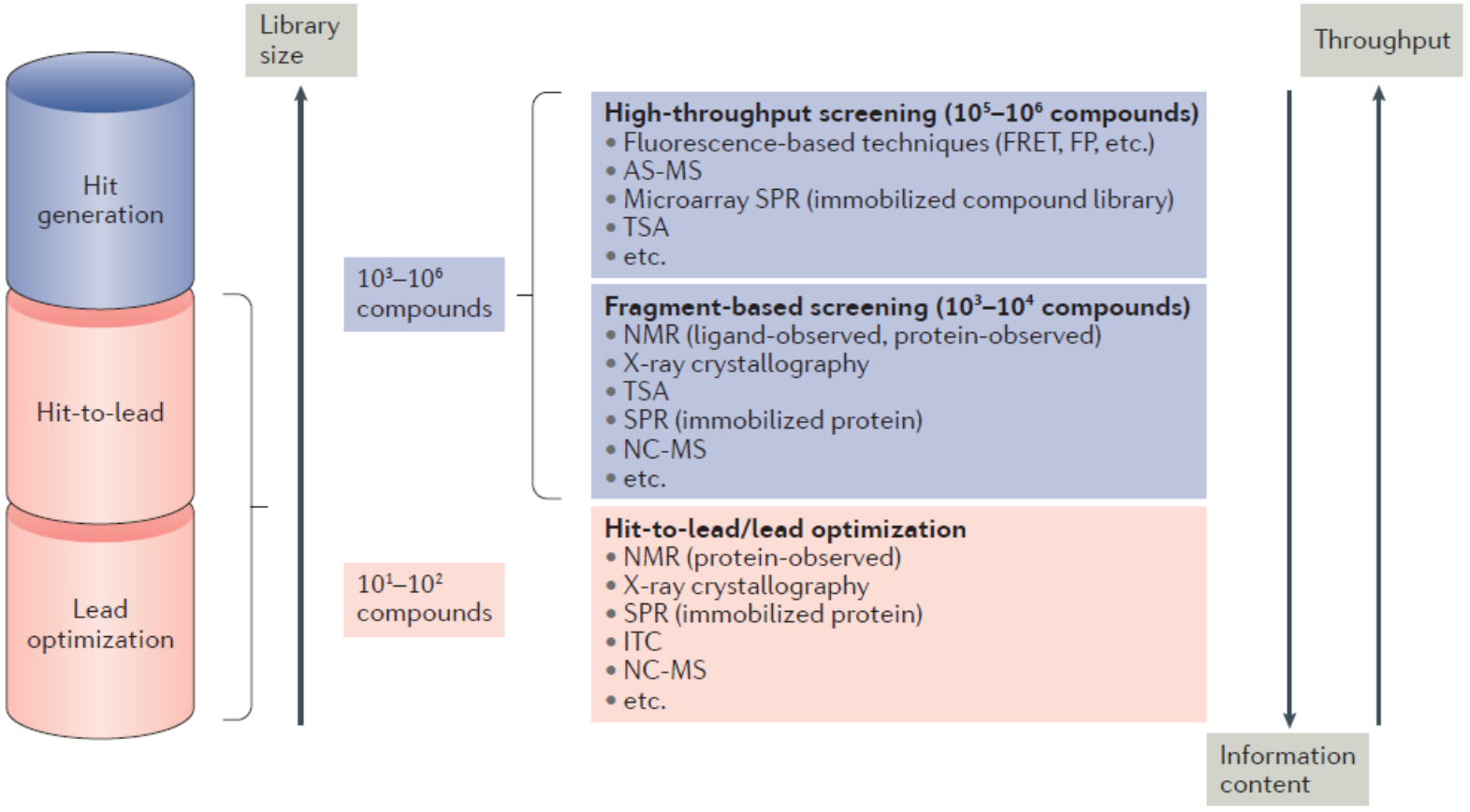
Hit to Lead



Nat Rev Drug Discov **15,** 679–698 (2016).

Screening for active compounds

The chemical space

The actual space:

10^{60} drug-like molecules

"Space is big. You just won't believe how vastly, hugely, mind-bogglingly big it is"

Douglas Adams

Chemical Libraries

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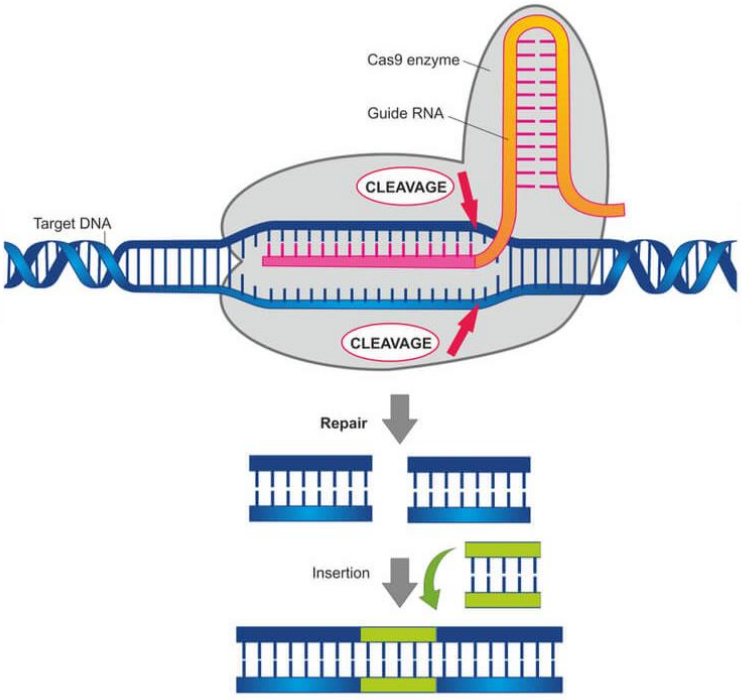
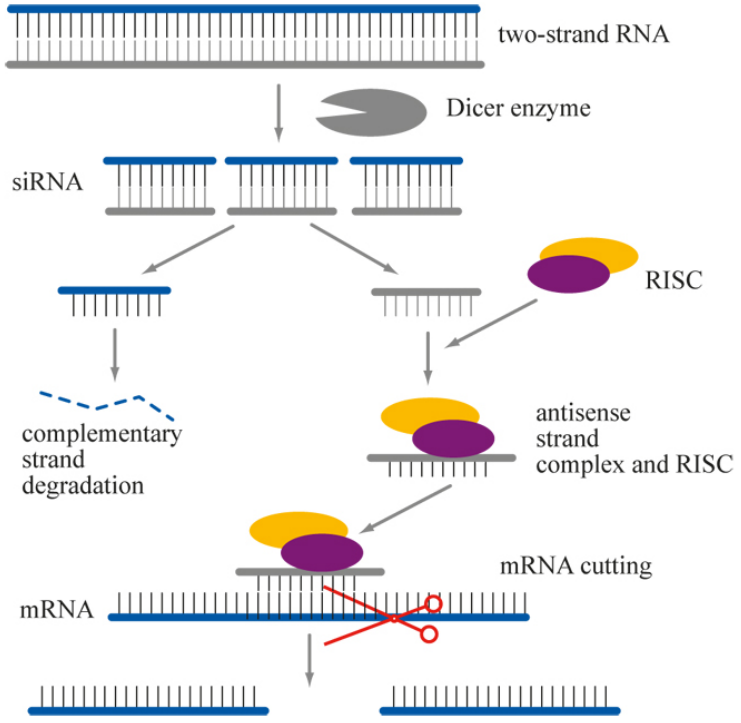
New Technologies

Gene editing



https://labiotech.eu/crispr-cas9-review-gene-editing-tool/

Silencing Genes



http://eng.thesaurus.rusnano.com/wiki/article3699

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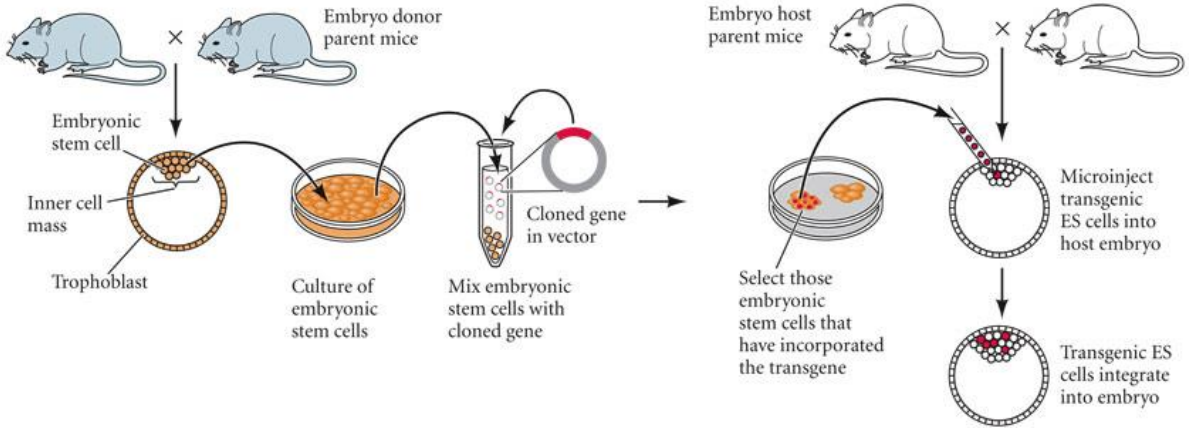
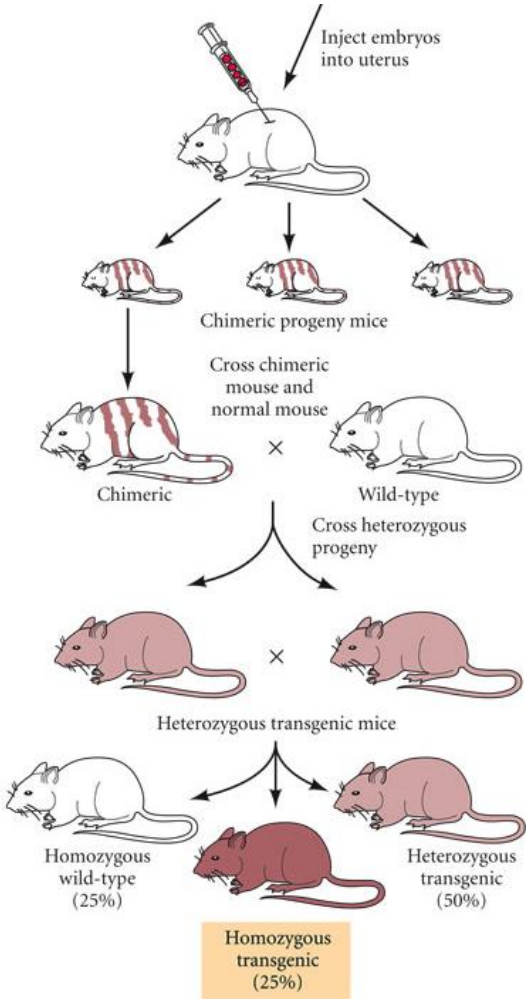
Transgenic animals





http://11e.devbio.com/wt0

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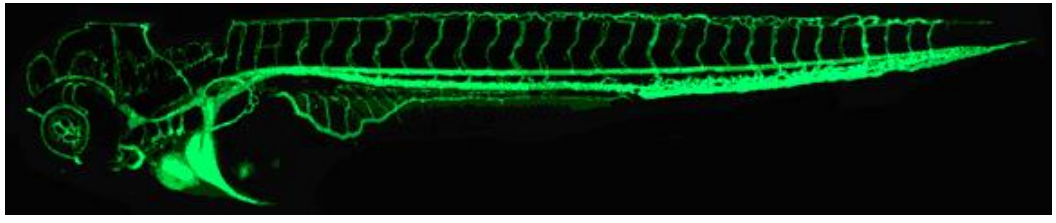
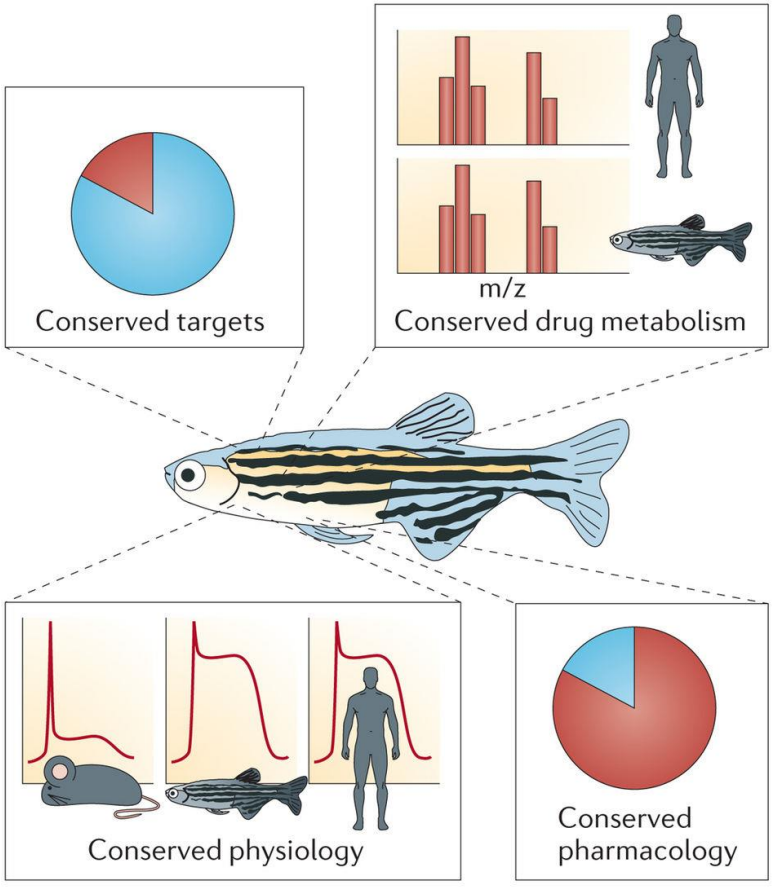
Zebrafish





Nature Reviews | Drug Discovery

https://www.nature.com/scitable/topicpage/mapping-genes-to-chromosomes-linkage-and-genetic-377

Nature Reviews Drug Discovery **14**, 721–731 (2015)

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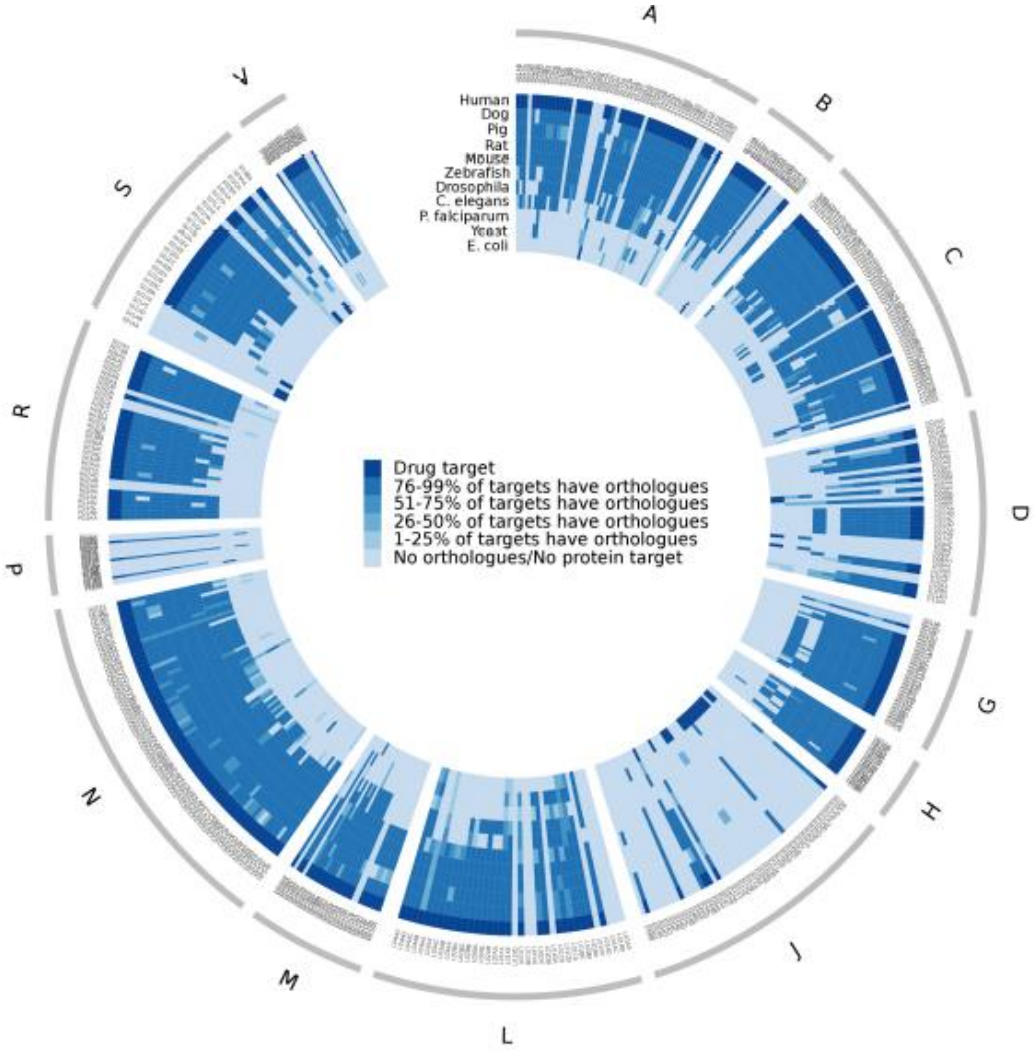
Animal models - Humans



Santos etal Nature Reviews Drug Discovery v16, 19–34 (2017)

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New technologies

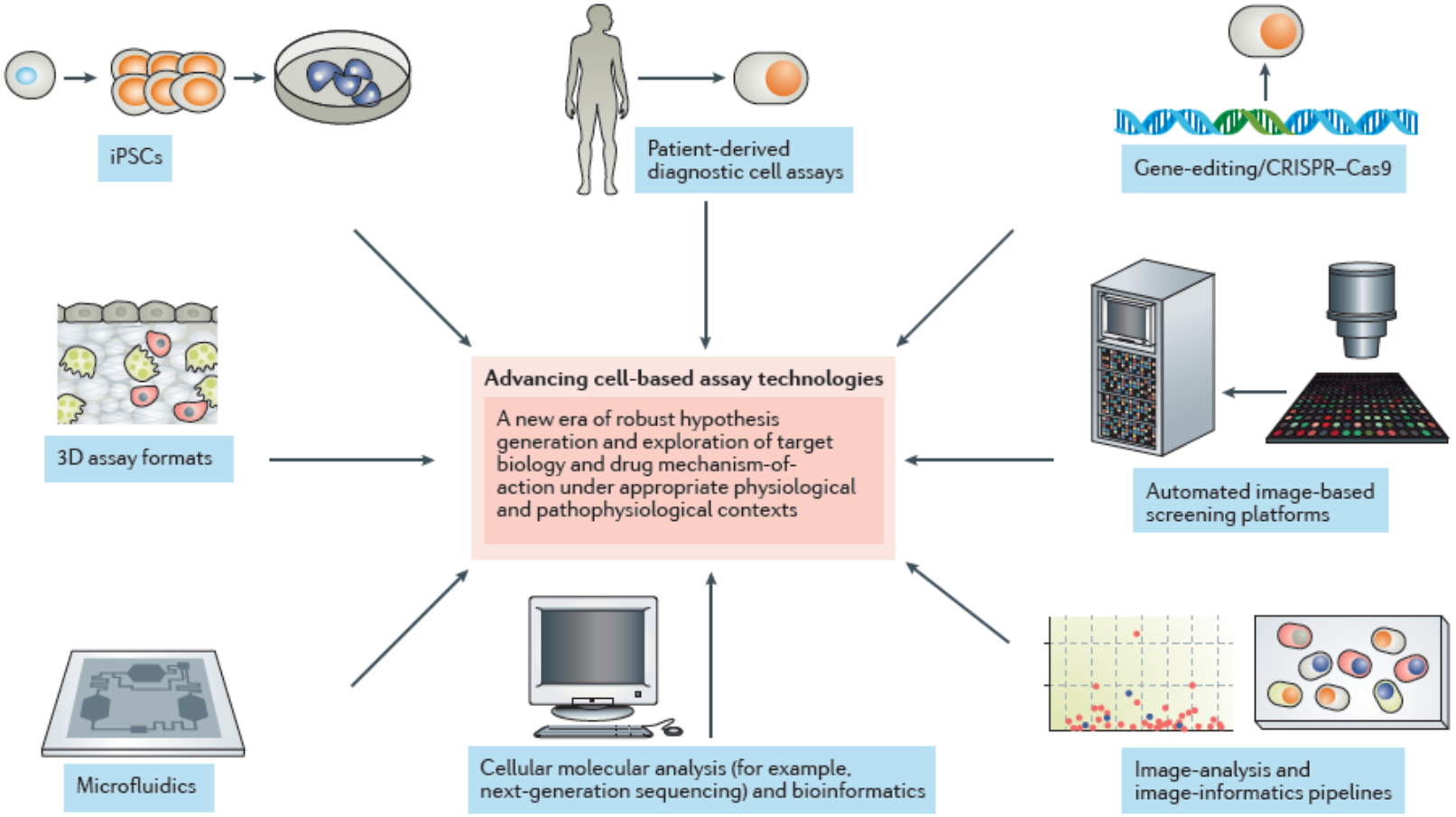
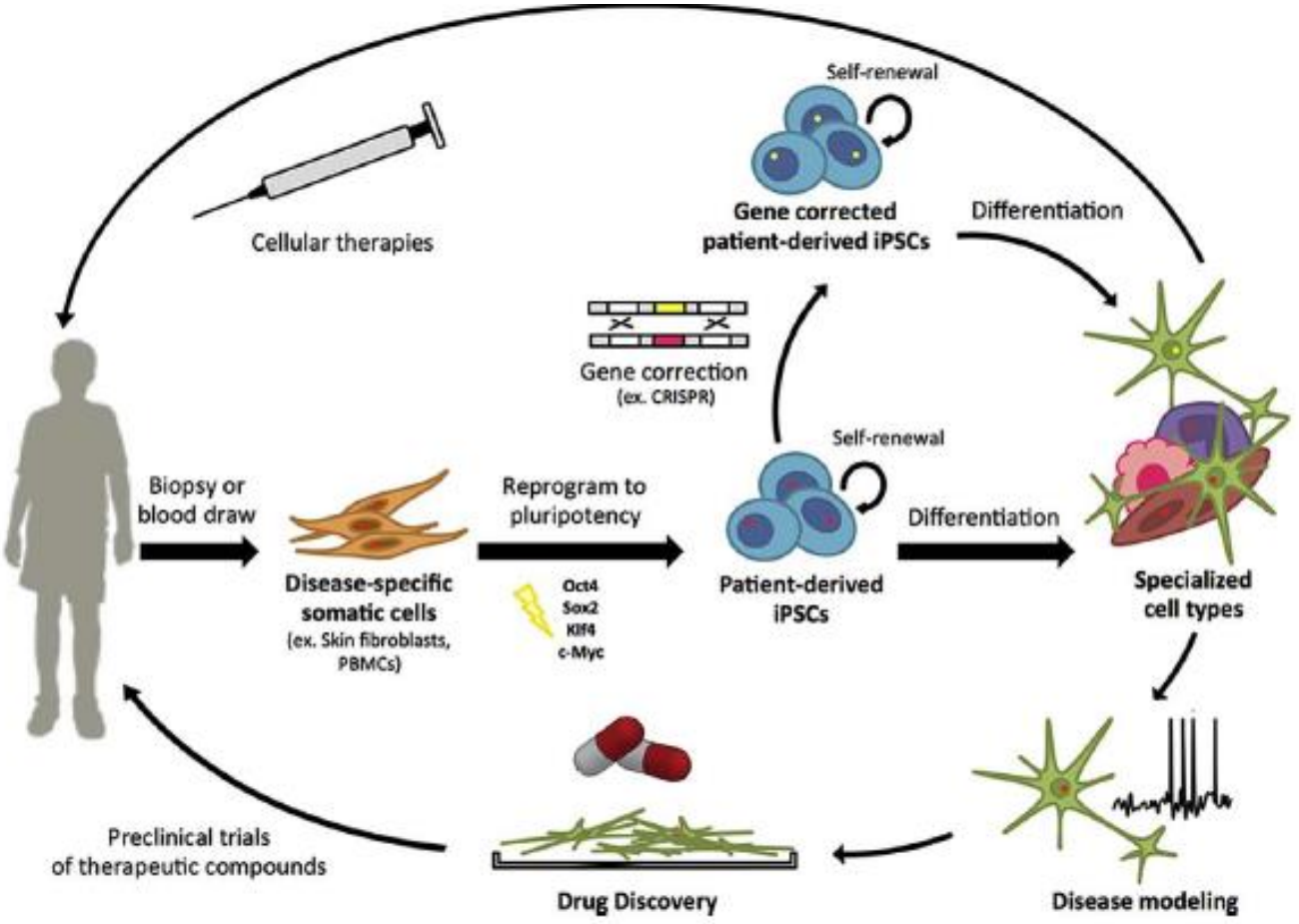


Figure 1 | **Novel assay technologies and their integration.** Advances in patient-derived primary cell models; induced pluripotent stem cell (iPSC) technology; three-dimensional (3D) *ex vivo* and multicellular models, and microfluidic devices; CRISPR–Cas9 gene-editing; automated imaging and image analysis platforms; and molecular cell profiling technologies, including advanced proteomic and genomic methodology (such as next-generation sequencing and bioinformatics) individually and together present new opportunities for incorporating more relevant physiological models into drug discovery.

iPSC



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R.H. Anderson, K.R. Francis Molecular and Cellular Probes 40 (2018) 52–59

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Autism spectrum disorders (ASDs)

LETTER

doi:10.1038/nature12618

SHANK3 and IGF1 restore synaptic deficits in neurons from 22q13 deletion syndrome patients

Aleksandr Shcheglovitov[1], Olesya Shcheglovitova[1], Masayuki Yazawa[1], Thomas Portmann[1], Rui Shu[1], Vittorio Sebastiano[2,3], Anna Krawisz[1], Wendy Froehlich[4,5], Jonathan A. Bernstein[4], Joachim F. Hallmayer[5] & Ricardo E. Dolmetsch[6]

Kolevzon *et al. Molecular Autism* 2014, **5**:54
http://www.molecularautism.com/content/5/1/54

Molecular Autism

RESEARCH Open Access

A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome

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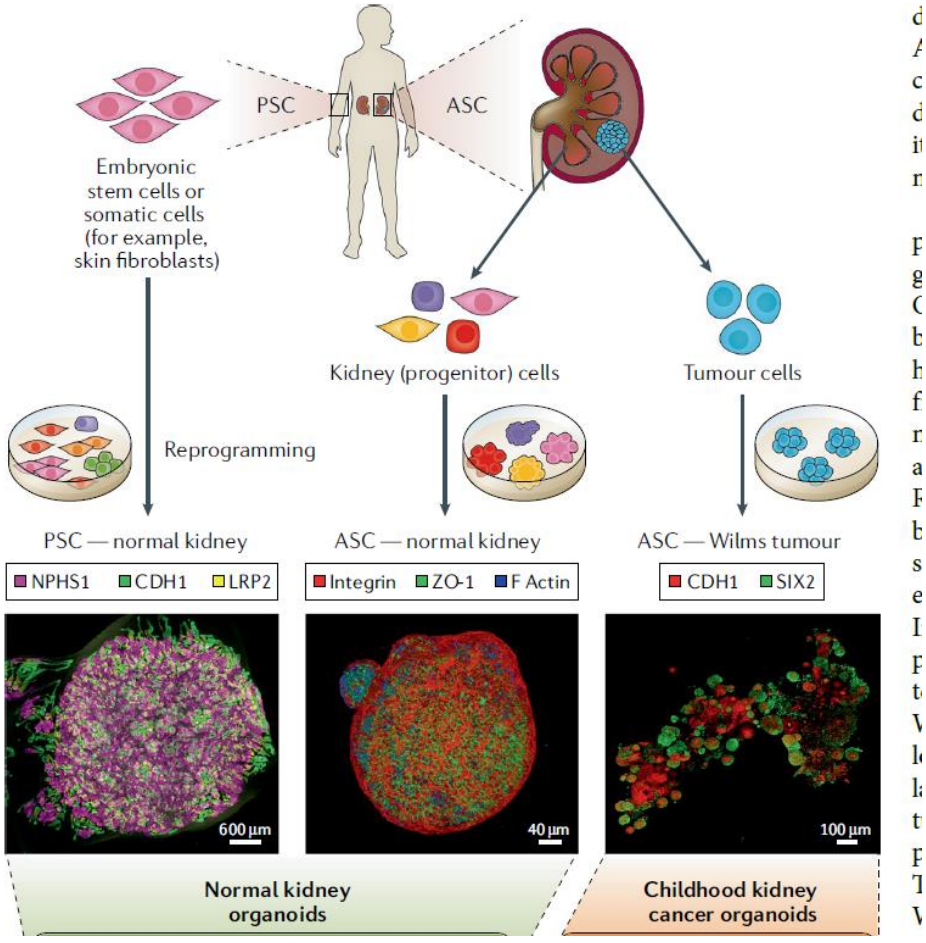
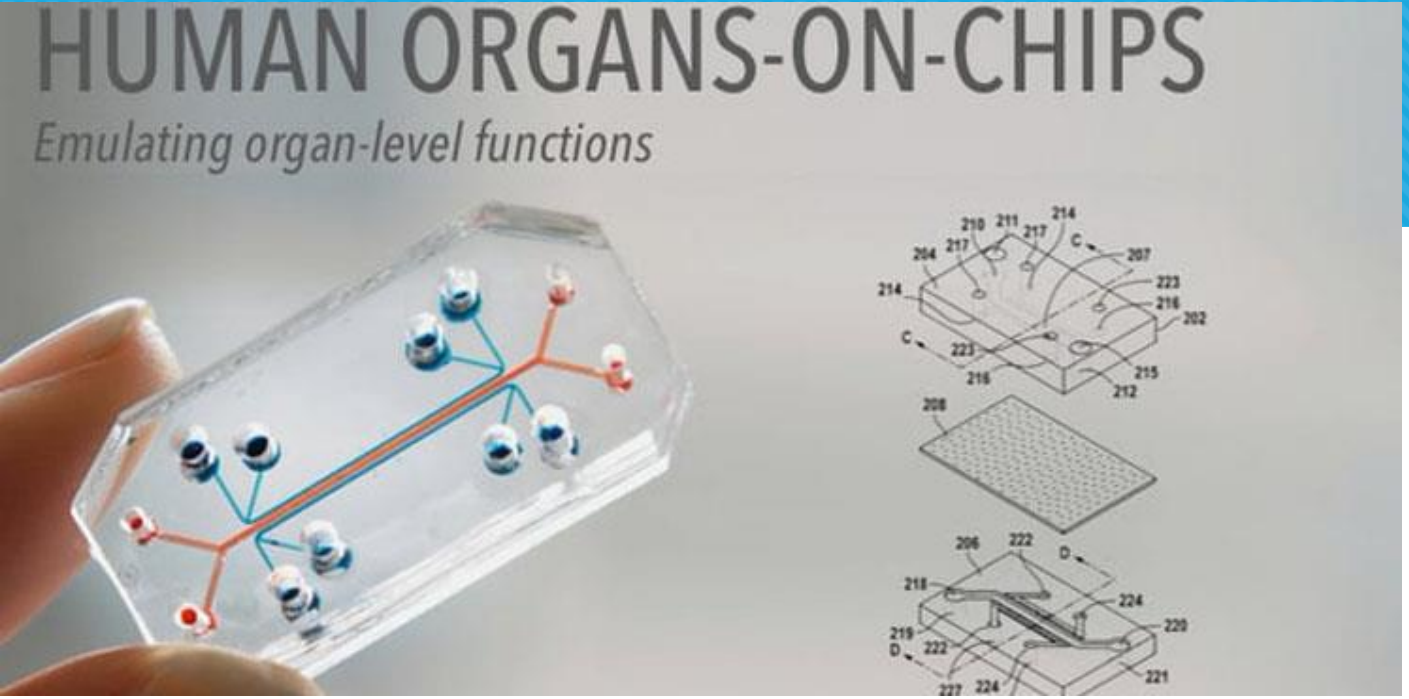
Organoid models of childhood kidney tumours

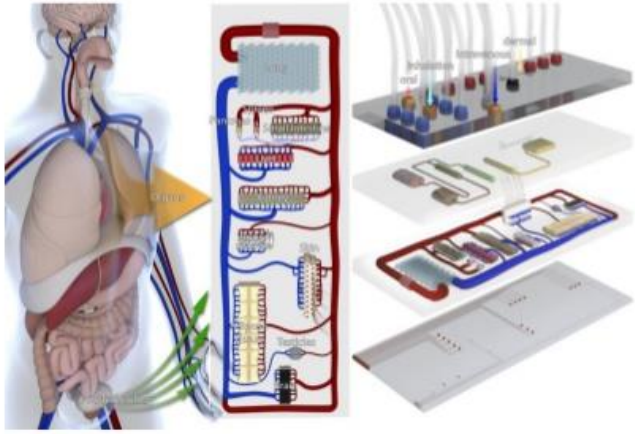
Ariadne H. A. G. Ooms[1,2,4], Camilla Calandrini[1,2,4], Ronald R. de Krijger[1,3] and Jarno Drost[1,2] ✉





https://wyss.harvard.edu/technology/human-organs-on-chips/

Concept of Multi-Organ-Chip



Materne etal Lab Chip, 2013,13, 3481-3495

Genomics

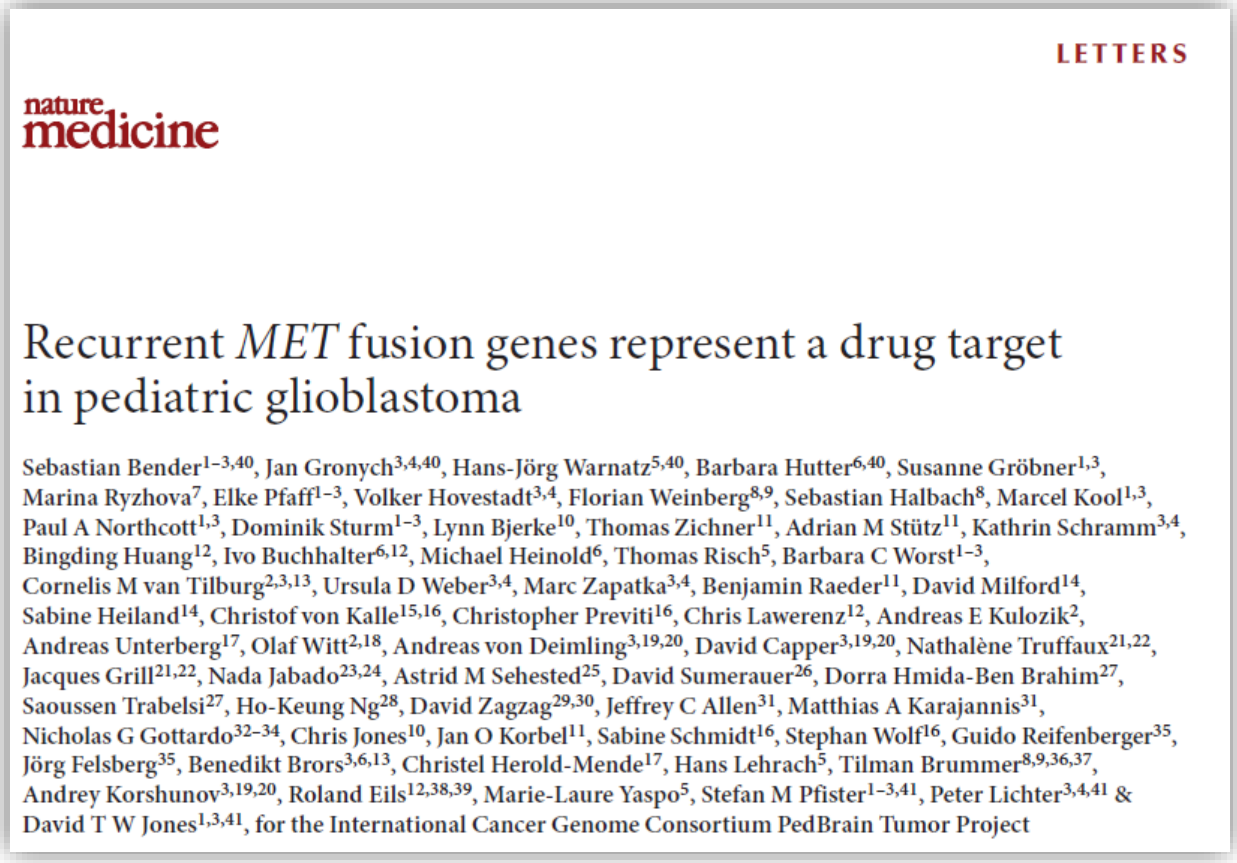
Target

Paediatric glioblastoma:

- Deadly childhood tumor
- Standard treatment with marginal clinical benefit
- No molecularly targeted therapy is currently used

Approach

1. **Whole-genome sequencing.**
2. **RNA-sequencing.**
3. **Target validation – *in vitro/in vivo*.**
4. **Translation into the clinic.**



LETTERS

nature medicine

Recurrent *MET* fusion genes represent a drug target in pediatric glioblastoma

Sebastian Bender[1–3,40], Jan Gronych[3,4,40], Hans-Jörg Warnatz[5,40], Barbara Hutter[6,40], Susanne Gröbner[1,3], Marina Ryzhova[7], Elke Pfaff[1–3], Volker Hovestadt[3,4], Florian Weinberg[8,9], Sebastian Halbach[8], Marcel Kool[1,3], Paul A Northcott[1,3], Dominik Sturm[1–3], Lynn Bjerke[10], Thomas Zichner[11], Adrian M Stütz[11], Kathrin Schramm[3,4], Bingding Huang[12], Ivo Buchhalter[6,12], Michael Heinold[6], Thomas Risch[5], Barbara C Worst[1–3], Cornelis M van Tilburg[2,3,13], Ursula D Weber[3,4], Marc Zapatka[3,4], Benjamin Raeder[11], David Milford[14], Sabine Heiland[14], Christof von Kalle[15,16], Christopher Previti[16], Chris Lawerenz[12], Andreas E Kulozik[2], Andreas Unterberg[17], Olaf Witt[2,18], Andreas von Deimling[3,19,20], David Capper[3,19,20], Nathalène Truffaux[21,22], Jacques Grill[21,22], Nada Jabado[23,24], Astrid M Sehested[25], David Sumerauer[26], Dorra Hmida-Ben Brahim[27], Saoussen Trabelsi[27], Ho-Keung Ng[28], David Zagzag[29,30], Jeffrey C Allen[31], Matthias A Karajannis[31], Nicholas G Gottardo[32–34], Chris Jones[10], Jan O Korbel[11], Sabine Schmidt[16], Stephan Wolf[16], Guido Reifenberger[35], Jörg Felsberg[35], Benedikt Brors[3,6,13], Christel Herold-Mende[17], Hans Lehrach[5], Tilman Brummer[8,9,36,37], Andrey Korshunov[3,19,20], Roland Eils[12,38,39], Marie-Laure Yaspo[5], Stefan M Pfister[1–3,41], Peter Lichter[3,4,41] & David T W Jones[1,3,41], for the International Cancer Genome Consortium PedBrain Tumor Project

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Target

Paediatric glioblastoma:

- Deadly childhood tumor
- Standard treatment with marginal clinical benefit
- No molecularly targeted therapy is currently used

Approach

1. Whole-genome sequencing.

2. RNA-sequencing.

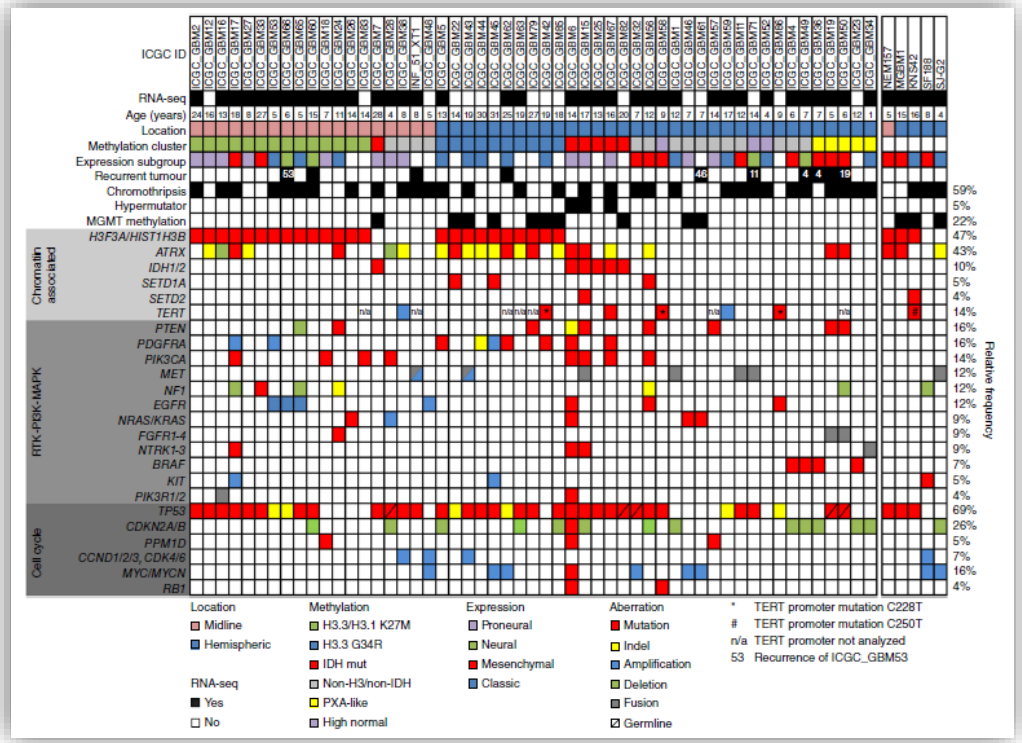
3. Target validation – *in vitro/in vivo*.

4. Translation into the clinic.

1. Whole-genome sequencing.

Identification of critical genetic alterations

- Mutations in cell cycle regulatory genes (*TP53*)
- Aberrant activation of RTKs and PI3K-MAPK signaling
- Amplification of EGFR, PDGFR and MET



Target

Paediatric glioblastoma:

- Deadly childhood tumor
- Standard treatment with marginal clinical benefit
- No molecularly targeted therapy is currently used

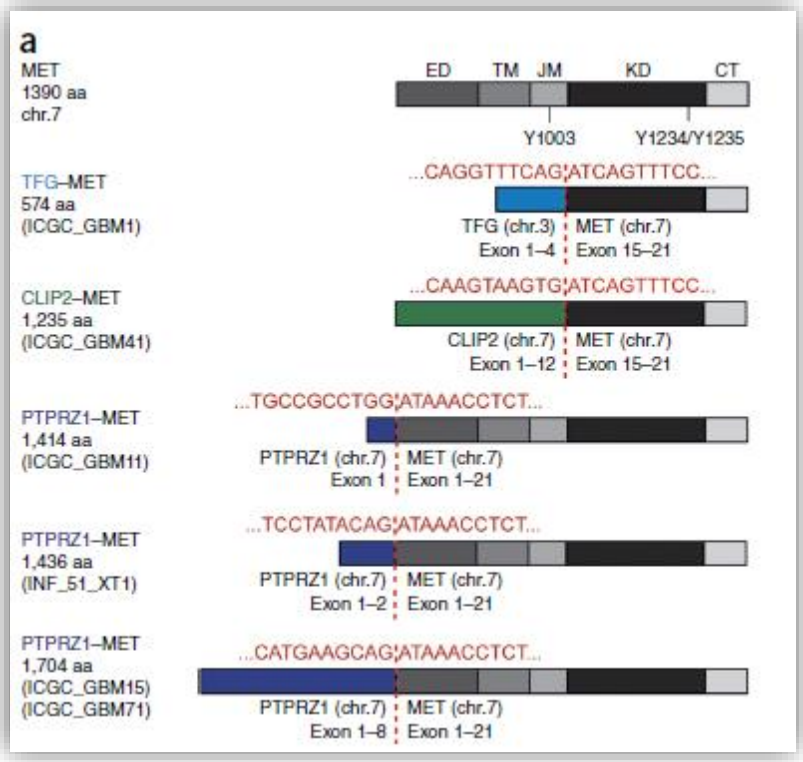
Approach

1. Whole-genome sequencing.
2. **RNA-sequencing.**
3. Target validation – *in vitro/in vivo.*
4. Translation into the clinic.

2. RNA-sequencing.

Identification of fusion transcripts

- Most frequently affected gene was *MET*
- Various oncogenic MET fusions determined



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3. Target validation – in vitro/in vivo

Pharmacological MET inhibition *in vitro*.

- Use of MET inhibitors **foretinib**, **SGX523** or **crizotinib**
- Inhibitors abrogated MET-fusion-induced MAPK activation in TFG-MET-overexpressing cells
- **Foretinib** reduced viability in SJ-G2 cells

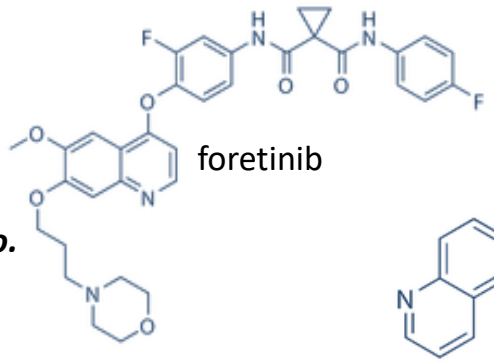
Pharmacological MET inhibition *in vivo.*

Allografts: mouse tumor cells allografted in mice

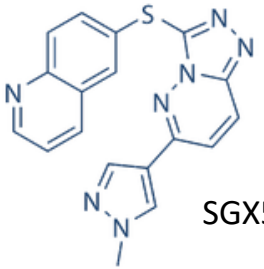
- **foretinib** significantly decelerated MET-fusion-driven tumor growth

Xenografts: SJ-G2 cells endogenously harboring *CLIP2-MET* fusion

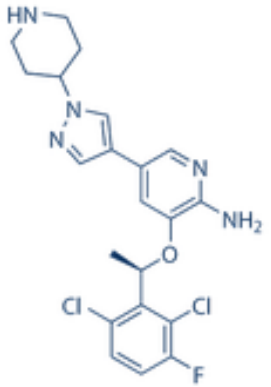
- Prolonged survival of **foretinib**-treated mice determined - key downstream signaling reduced



foretinib



SGX523



Crizotinib (Xalkori®)

Target

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- Standard treatment with marginal clinical benefit
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Approach

1. Whole-genome sequencing.
2. RNA-sequencing.
3. **Target validation – *in vitro/in vivo.***
4. Translation into the clinic.

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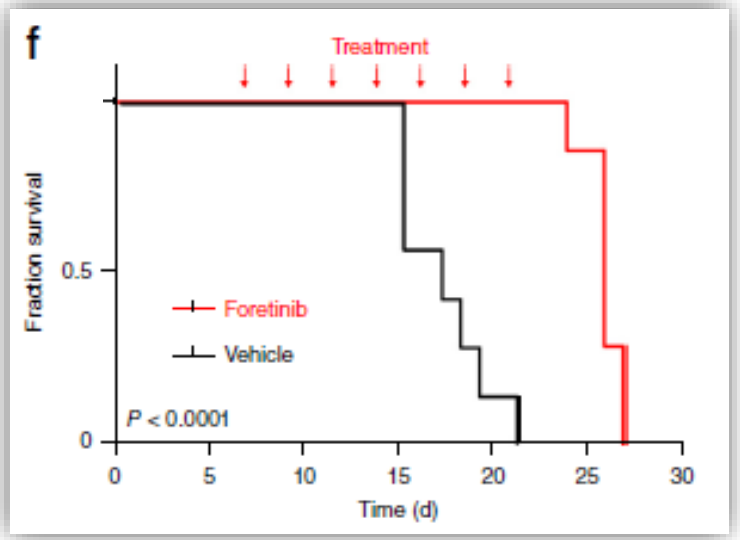

Target

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Approach

1. Whole-genome sequencing.
2. RNA-sequencing.
3. Target validation – *in vitro/in vivo.*
4. **Translation into the clinic.**

Approach

4. Translation of findings into the clinic

Pilot phase of the INFORM personalized oncology program

- Patient received treatment with **crizotinib** (FDA–approved kinase inhibitor with activity against MET)

- Partial response of the primary lesion with concomitant relief of symptoms
- However, several new treatment-resistant lesions observed

Results:

- highlight new recurrent mechanism of tumorigenesis in pediatric glioblastoma
- underline importance of individualized molecular diagnosis for cancer patients as basis for optimal personalized therapy
- provide strong rationale for systematic analysis of MET inhibitors in future pediatric glioblastoma clinical trials.


LETTERS

nature medicine

Recurrent *MET* fusion genes represent a drug target in pediatric glioblastoma

Sebastian Bender[1–3,40], Jan Gronych[3,4,40], Hans-Jörg Warnatz[5,40], Barbara Hutter[6,40], Susanne Gröbner[1,3], Marina Ryzhova[7], Elke Pfaff[1–3], Volker Hovestadt[3,4], Florian Weinberg[8,9], Sebastian Halbach[8], Marcel Kool[1,3], Paul A Northcott[1,3], Dominik Sturm[1–3], Lynn Bjerke[10], Thomas Zichner[11], Adrian M Stütz[11], Kathrin Schramm[3,4], Bingding Huang[12], Ivo Buchhalter[6,12], Michael Heinold[6], Thomas Risch[5], Barbara C Worst[1–3], Cornelis M van Tilburg[2,3,13], Ursula D Weber[3,4], Marc Zapatka[3,4], Benjamin Raeder[11], David Milford[14], Sabine Heiland[14], Christof von Kalle[15,16], Christopher Previti[16], Chris Lawerenz[12], Andreas E Kulozik[2], Andreas Unterberg[17], Olaf Witt[2,18], Andreas von Deimling[3,19,20], David Capper[3,19,20], Nathalène Truffaux[21,22], Jacques Grill[21,22], Nada Jabado[23,24], Astrid M Sehested[25], David Sumerauer[26], Dorra Hmida-Ben Brahim[27], Saoussen Trabelsi[27], Ho-Keung Ng[28], David Zagzag[29,30], Jeffrey C Allen[31], Matthias A Karajannis[31], Nicholas G Gottardo[32–34], Chris Jones[10], Jan O Korbel[11], Sabine Schmidt[16], Stephan Wolf[16], Guido Reifenberger[35], Jörg Felsberg[35], Benedikt Brors[3,6,13], Christel Herold-Mende[17], Hans Lehrach[5], Tilman Brummer[8,9,36,37], Andrey Korshunov[3,19,20], Roland Eils[12,38,39], Marie-Laure Yaspo[5], Stefan M Pfister[1–3,41], Peter Lichter[3,4,41] & David T W Jones[1,3,41], for the International Cancer Genome Consortium PedBrain Tumor Project

doi:10.1038/nm.4204

EPTRI

Paediatric Medicines Discovery Platform

Aim:

Offer access to academic drug discovery facilities specialized to paediatric diseases,
Provide integrated services, coordinating efforts among European Centres of Excellence,
Implement cutting edge technologies, to accelerate discovery and preclinical drug development in paediatrics

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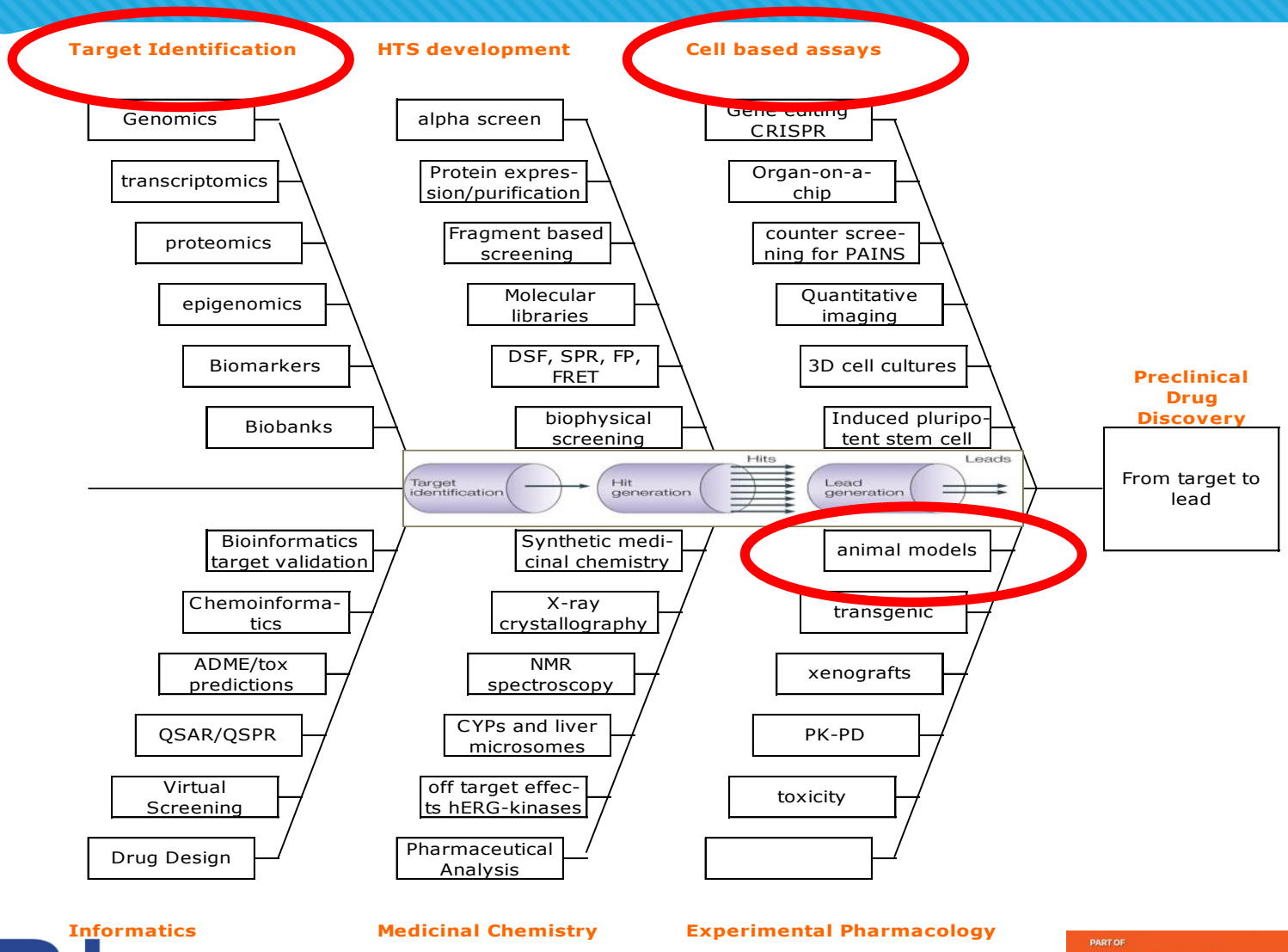
Part of European Biotech Week
Innovation is in our genes

Preclinical Drug Discovery



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EPTRI unique collection

Cell models

Disease specific cell models for

- ***muscular dystrophies,***
- ***brain injury,***
- ***apoptosis,***
- ***cancer etc***

Specialised cell models

- ***3-dimensional cell cultures,***
- ***microtissue products, nano-culture spheroid plates, micropattern plates,***
- ***Patient derived disease models (oncology,) on the basis of biobank samples.***
- ***Stem cells***

EPTRI unique collection

Animal models

Paediatric diseases animal models

Mouse model of premature ageing (Hutchinson-Gilford Progeria)

Drosophila model for Congenital disorders of glycosylation (CDGs);

Mouse model for Duchenne Muscular Dystrophy (mdx)

Mouse, rat, hypoxia

Transgenic mice, xenografts

Drosophila model of motor neuon disease in particular hereditary spastic paraplegia genes

Periventricular leukomalacia, cerebral ischemia

Mouse models of primary immunodeficiency

Mice ADPKD model; juvenile rabbit BPD model; rabbit CDH model; PREPL mice model;

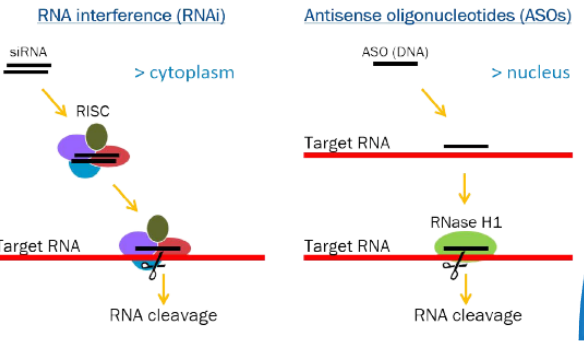
Zebrafish Dravet model

Murine medulloblastoma model.

Mouse model of PCD with hydrocephalus and infertility

Areas of services

Target validation

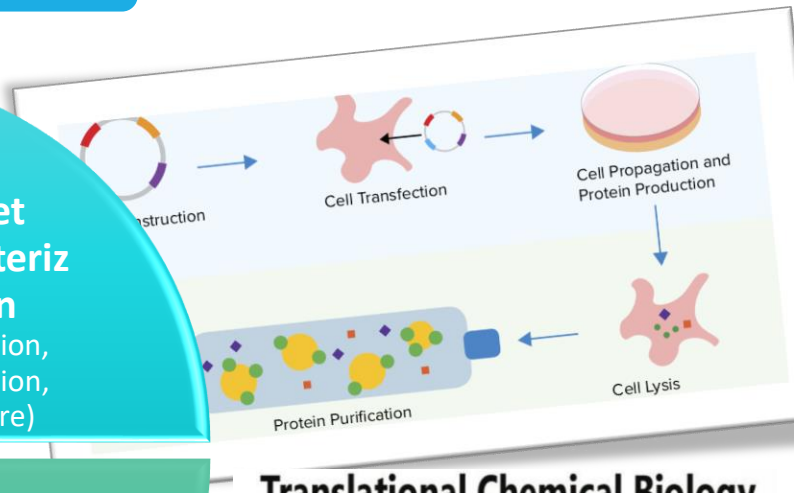


Genetic Approaches (knock-out, si-RNA, antisence

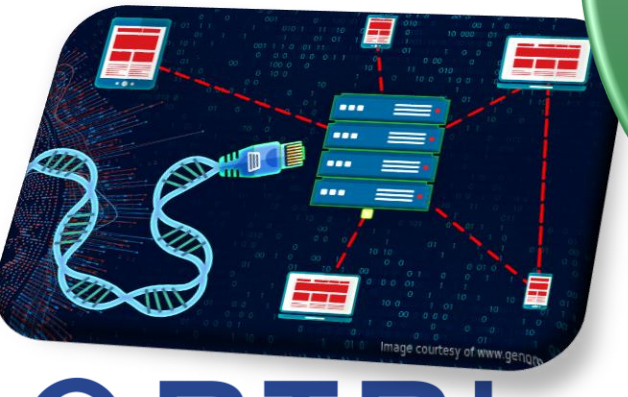
Target Characterization (expression, purification, structure)

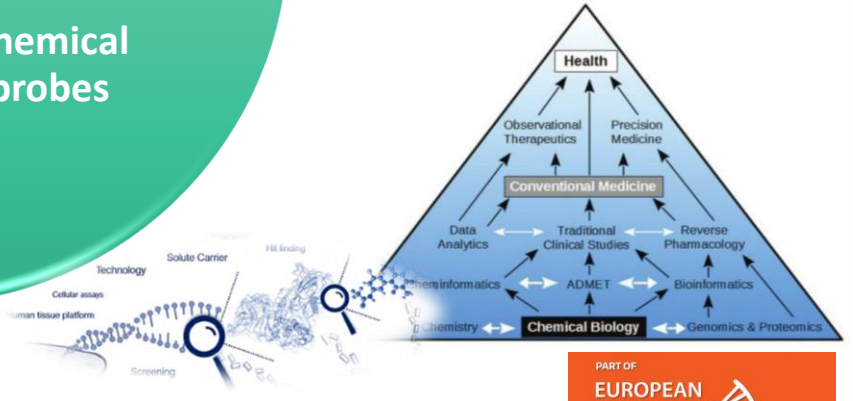
Bio informatics

Chemical probes



Translational Chemical Biology





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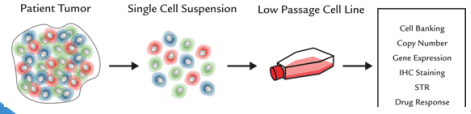
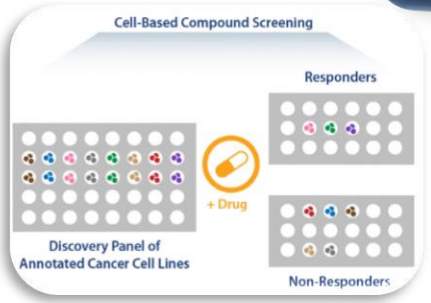
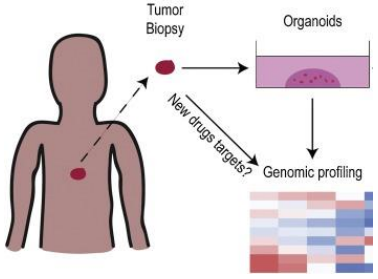
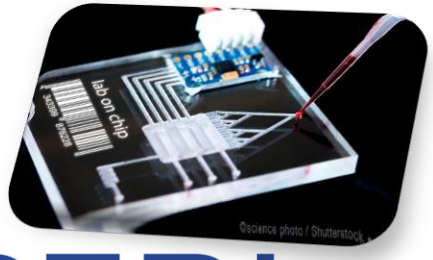
Areas of services

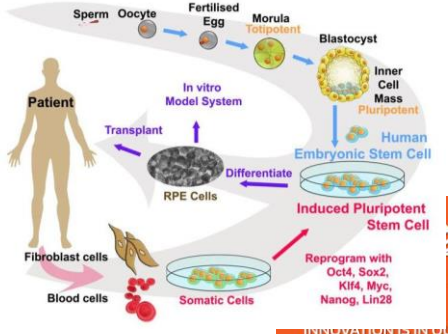
Paediatric disease specific cell models

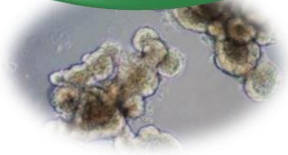












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Areas of services

ANIMAL MODELS

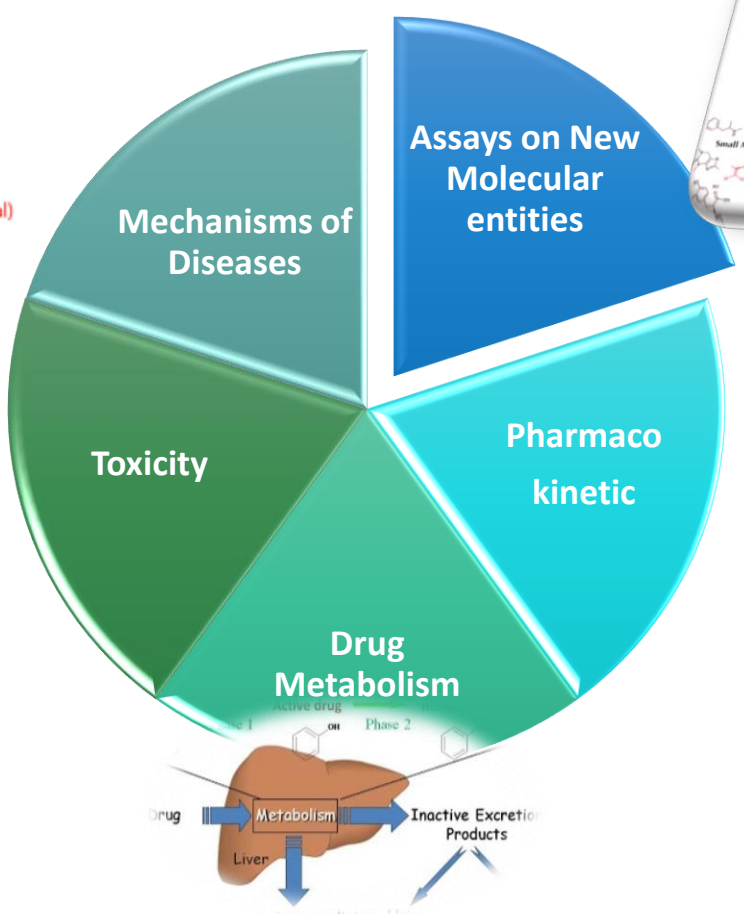
Zebrafish models	•Phenotypic characterization of novel genes identified in paediatric disease •Generation of zebrafish mutant lines for modelling paediatric diseases •Generation of zebrafish xenogeneic tumour models •Chemical screening in Zebrafish models
Rabbit Bronchopulmonary Dysplasia model	•Assessment of the neurotoxicity following perinatal exposure •Assessment of the mechanisms and effects of therapeutic interventions in the juvenile bronchopulmonary dysplasia model.
Göttingen Minipig model	•Safety assessment of paediatric drugs in development in healthy juvenile Göttingen Minipigs •Study of the effect of cooling therapy on the PK of several drugs used in NICU in a neonatal Göttingen Minipig asphyxia model
Rodent models of Rett syndrome and *MECP2* or *CDKL5* related disorders	•Preclinical studies, by testing the efficacy of therapeutic strategies, starting from the young age of P5
Rodents model of hereditary paediatrics disease.	•Metabolic profile and Behavioural phenotyping •Preclinical studies of new compounds
Rodent models of paediatric neurodevelopmental disorders	•Analysis of the effects of acute or chronic drug administration on molecular, biochemical and morphological features •Resuscitation and neuroprotection studies with different levels of oxygen and drugs
Rodent models of paediatric neurodevelopmental disability related to schizophrenia, epilepsy and ASD	•Behavioural and physiological phenotyping analysis to test paediatric drugs' efficacy in vivo

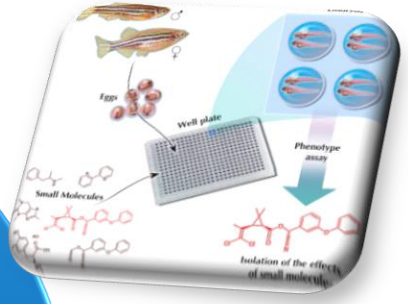
Areas of services

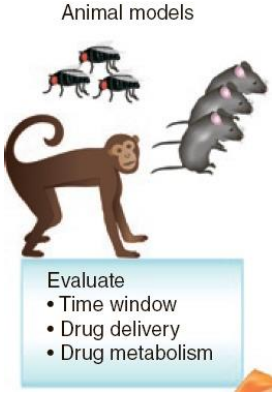
Paediatric disease specific animal models

With gene
(wild-type animal)

Without gene
(knockout animal)







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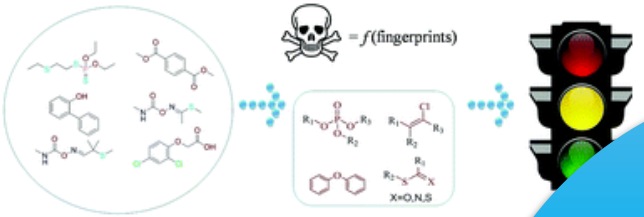
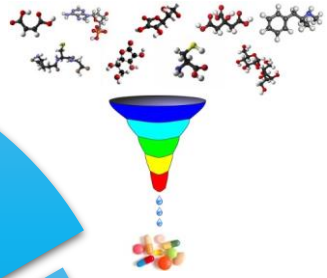
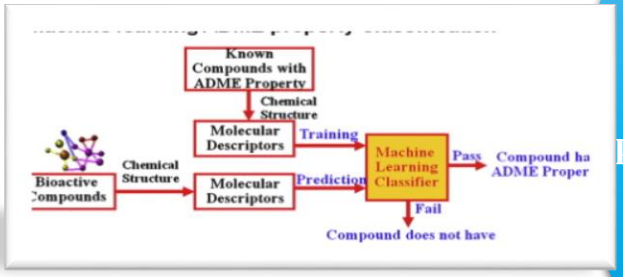
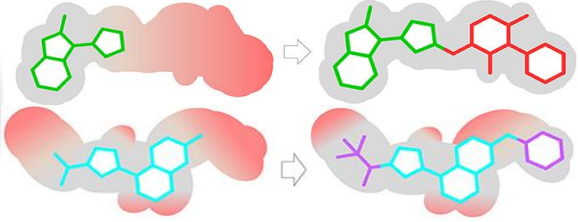
Areas of services

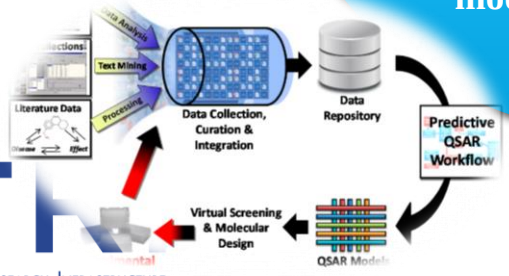
In Silico models

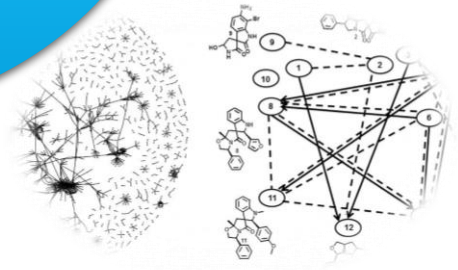












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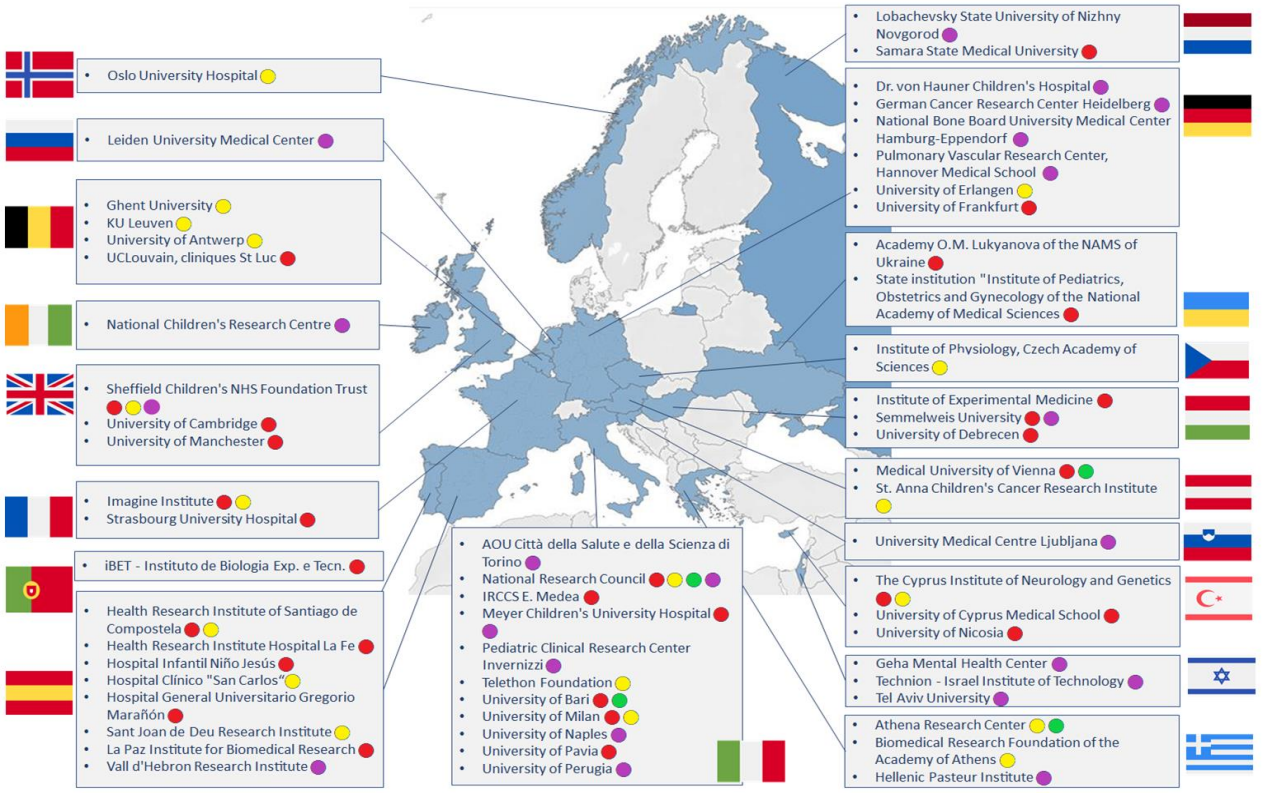
EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

PART OF EUROPEAN BIOTECH WEEK
INNOVATION IS IN OUR GENES

Resource description

Paediatric Medicines Discovery TRP



Countries	N° 19
Institutions	N° 58
Research Units	N° 82

Research Activities

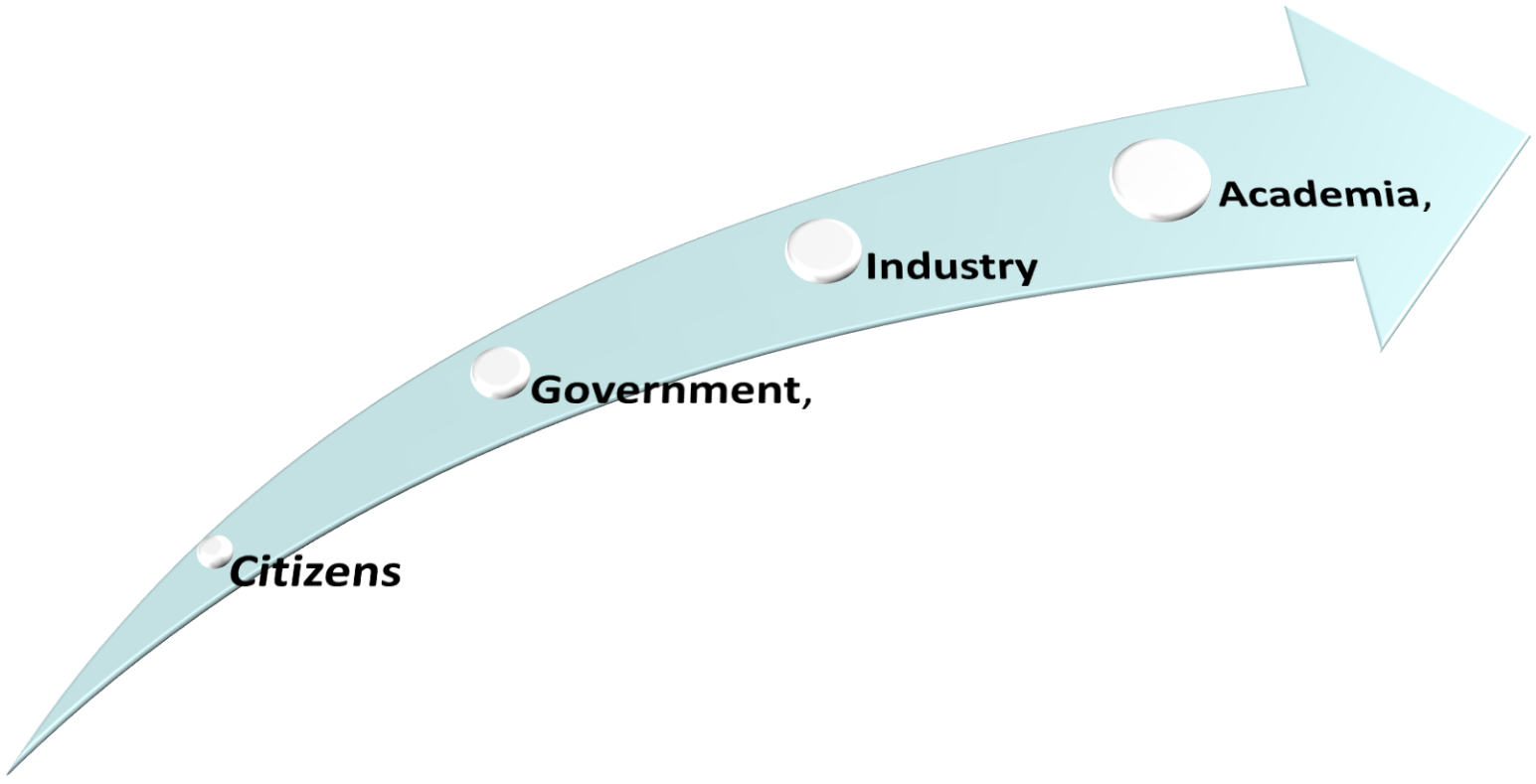
New Target identification:

- cell and tissue studies
- animal studies
- other

In silico drug screening and preclinical studies

EPT
EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH

PAEDIATRIC MEDICINES DISCOVERY



PRECISION THERAPIES FOR CHILDREN

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