Cancéropôle Grand Sud-Ouest

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Développement d'un médicament : de la biologie à la recherche clinique

Anti-cancer drug discovery: from bench to bedside

Christian BAILLY, Ph.D.
christian.bailly@pierre-fabre.com

Pierre Fabre CDMO

"The whole process from ideas to drugs"

October 2nd, 2015

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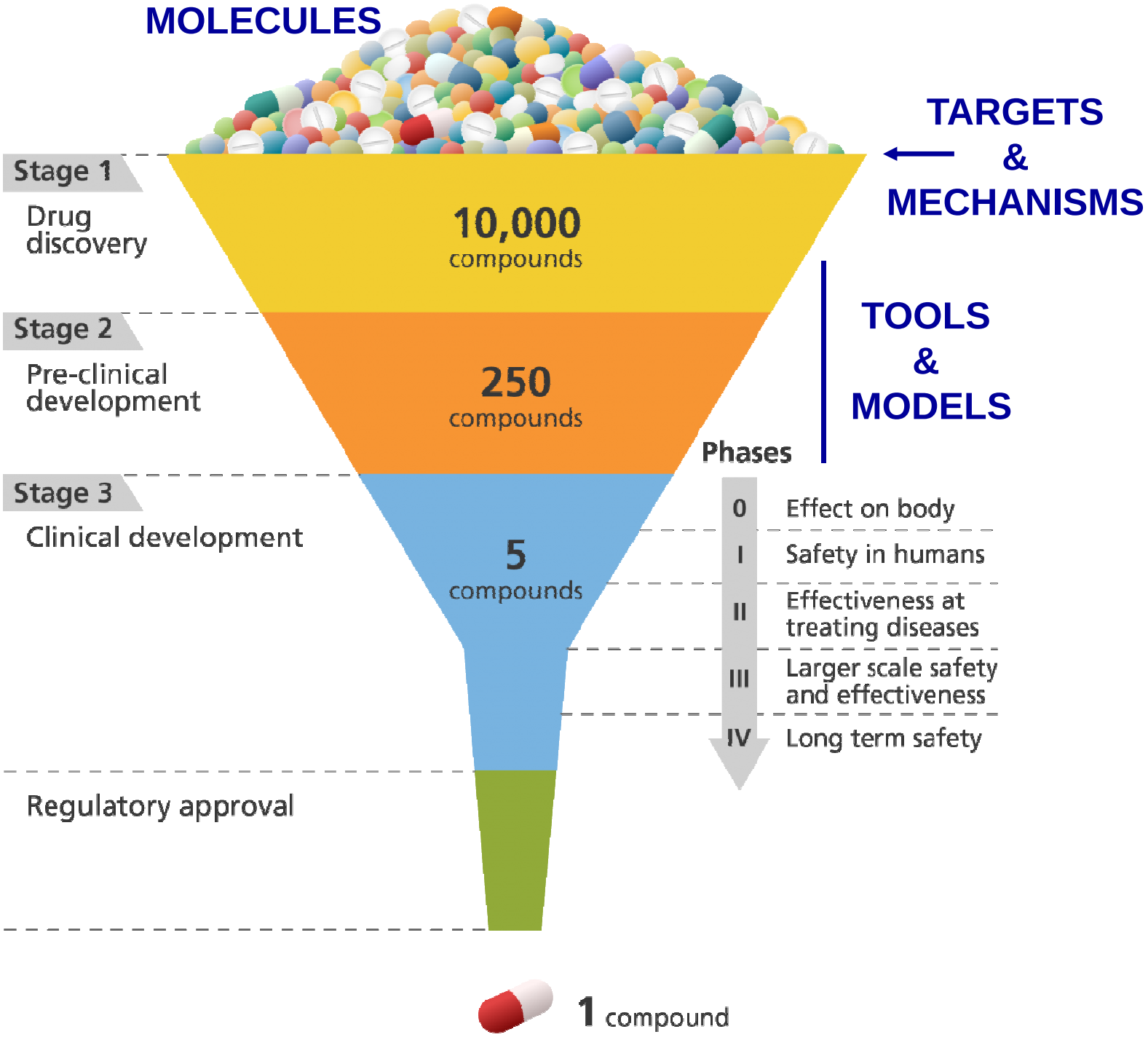

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Drug Discovery & Development

Pharmaceutical R&D
High risk, high costs

Drug Discovery → Early Development

Biology | **Target selection** | **Screening Hits** | **Lead optimisation** | **Extensive Pharmacol.** | **Preclinical Dev. Tox.** ▶

Process Dev. Synth. | **F.i.M.** | **Phase I trials** | **Phase II trials** | **Phase III trials** | **Registration** | **Post-launch Activities** ▶

Clinical Development → Commercial Act.

9-16 years
cost $~1 billion per successful product

A long, difficult, multidisciplinary and expensive process

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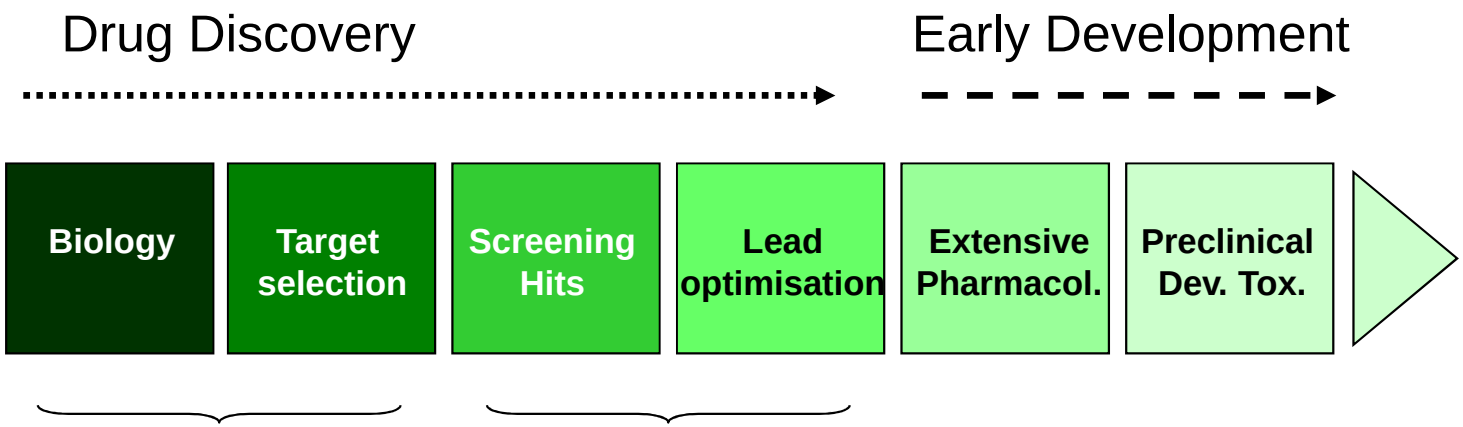

Target selection and validation

- large panel of biochemical, biological assays
- establish the role of a target in the disease
- adressing the cellular pathway
- and the physiopathology

Screening, hit & Lead compounds

- target-based assays and HTS
- compounds management & selection
- extensive chemistry, SAR
- use of in silico approaches
- ADMET properties
- drug design, back up series

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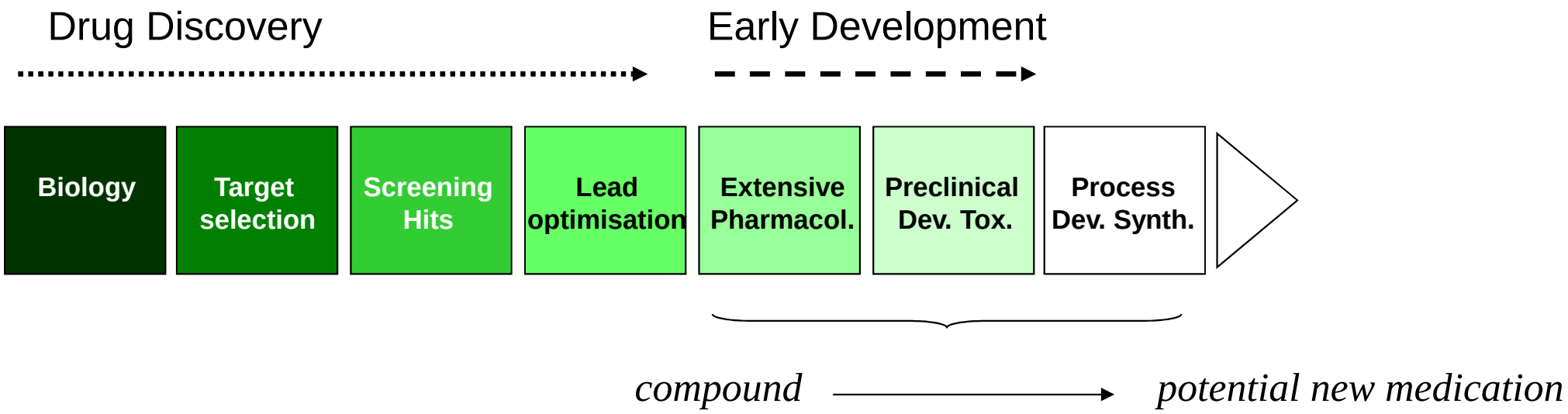

Pharmacology

- Mode of action, target modulation
- in vitro, in vivo activities
- ADMET profile
- Proof of Concept in animal
- Efficacy studies
- drug combinations
- PK/PD, metabolism

Preclinical Development

- Batch synthesis, (salts)
- Formulation, stability
- Toxicology studies: safety profile
- g/kg GMP synthesis, scale up
- complete chemical profile

+ dossiers

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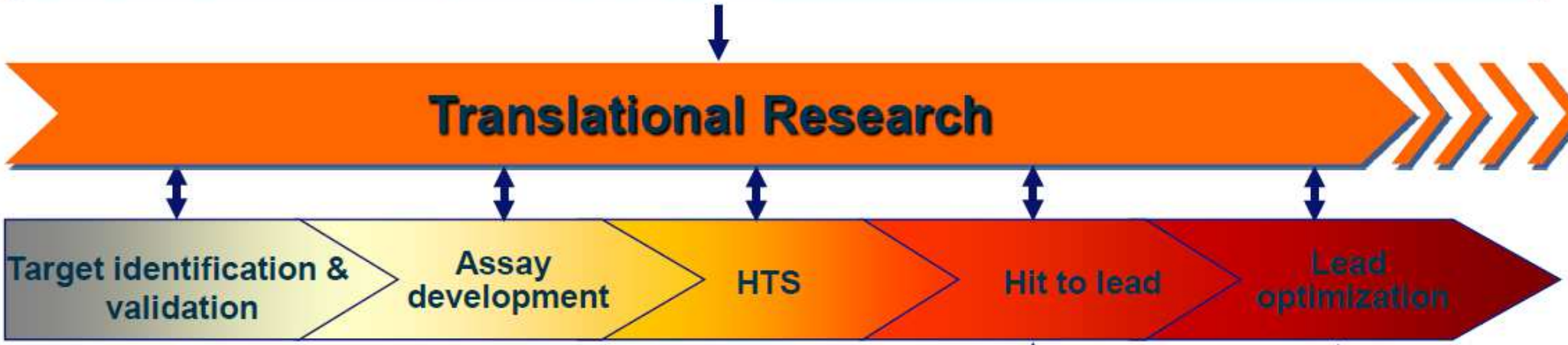
- Large panels of patient-derived tumor models (*in vitro* and *in vivo*) representing the heterogeneity of the disease
- Extensive data on the characteristics of these tumor models
- Orthotopic models, metastasizing models, imaging models



- Large panels of tumor models (*in vitro* and *in vivo*) representing the heterogeneity of the disease
- Corresponding tumor tissue bank
- Genetically engineered models (inducible knock out and knock in models, isogenic models)

- Homogeneous, standardized *in vitro* tumor models, naturally or genetically engineered with target over or under expression for screening (isogenic models)
- Corresponding homogeneous, standardized *in vivo* tumor models, natural or genetically engineered, with target over or under expression for pharmacodynamic optimization
- Models for pharmakokinetic/pharmacodynamic correlation studies in different species (mouse, rat and/or non-rodent species)
- Models for evaluation of side effects (toxicology) in correspondence to pharmacodynamic effects

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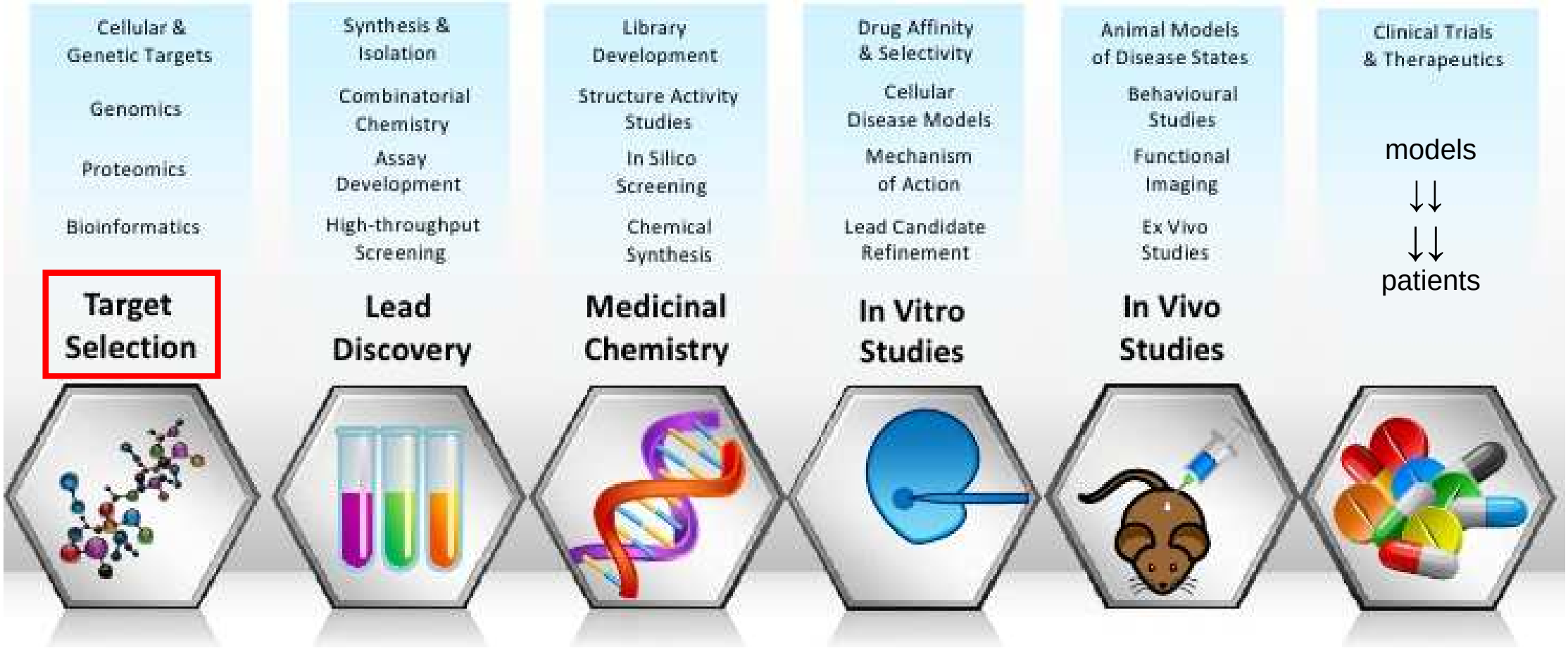

Target validation

Functions, efficacy safety

drugs, tools

TARGET SELECTION:
Scientific, Medical, Economical, & Strategic Considerations

Picking the right target is key… but confirmed only 10 years later

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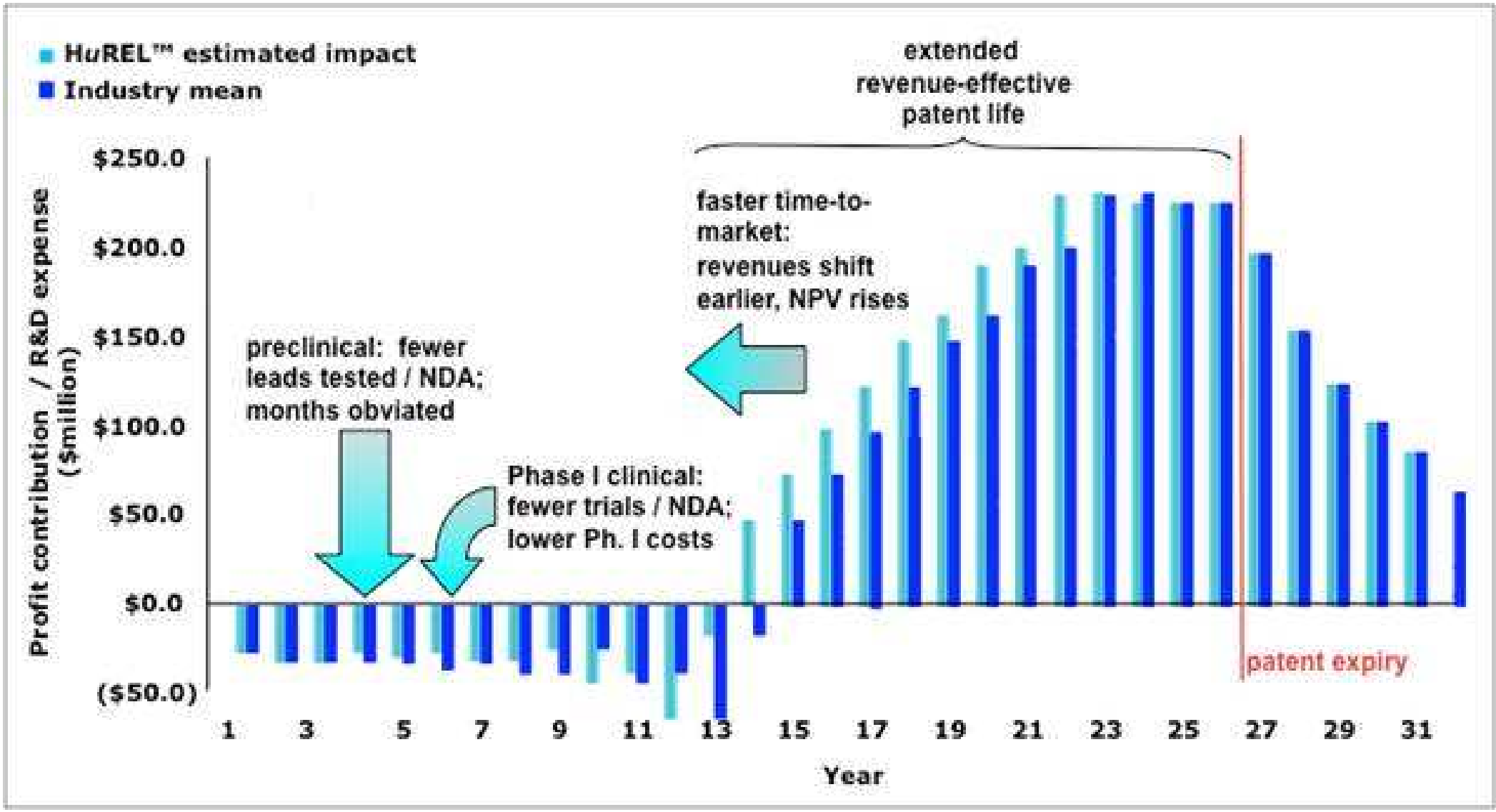

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Drug Discovery

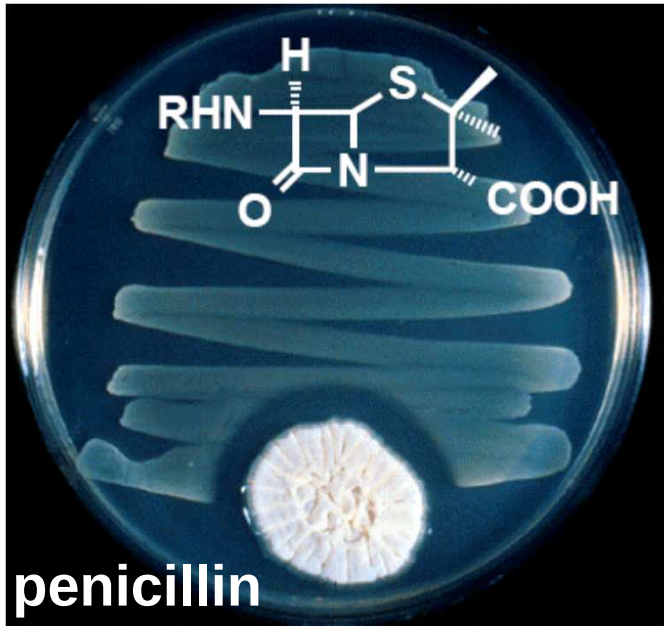
- by isolating active ingredients from traditional remedies

- by **random screening** of chemical libraries, including Nat. Prod.

- by **rational design** : based on understanding the metabolic pathways related to a disease state or pathogen, and manipulating these pathways using chemistry, mol./cell. biology and biochemistry

- by **repositioning**

- by **serendipity**…



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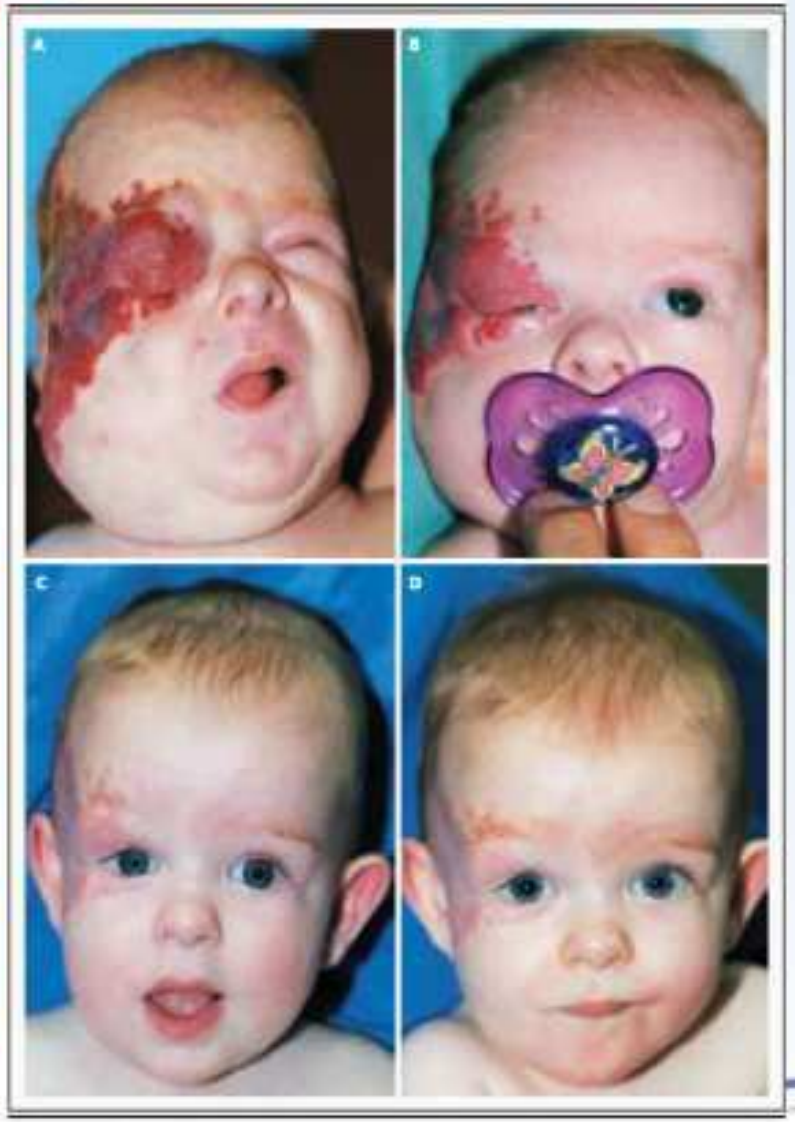
Serendipitous Drug Discoveries

Acetanilide, Acetylsalicylic acid, Aminoglutethimide, Amphetamine, Chloral hydrate, Chlordiazepoxide, Chlorpromazine, Cinnarizine, Cisplatin, Clonidine, Cromoglycate, Cyclosporin, Dichloroisoprotere-nol, Dicoumarol, Diethylstilbestrol, Diphenhydramine, Diphenoxylate, Disulfiram, Ether, Etomidate, Griseofulvin, Guanethidine, Haloperidol, Heparin, Imipramine, Iproniazid, Isoniazid, Levamisole, Lithium car-bonate, Lysergide (LSD), Meprobamate, Merbaphen, Methaqualone, Mifepristone, Naftifine, Nalorphine, Nitrogen mustard, Nitroglycerine, Nitrous oxide, Norethynodrel/Mestranol, Penicillin, Pethidine (Meperi-dine), Phenylbutazone, Phenolphthalein, Praziquantel, Prednisone, Propafenone, Sulfamidochrysoidine, Sulfonamides, Tamoxifen, Urethane, Valproic acid, Warfarin.

The NEW ENGLAND JOURNAL of MEDICINE

Propranolol for Severe Hemangiomas of Infancy



Christine Léauté-Labrèze, M.D.
Eric Dumas de la Roque, M.D.
Thomas Hubiche, M.D.
Franck Boralevi, M.D., Ph.D.
Bordeaux Children's Hospital
33 076 Bordeaux, France
christine.labreze@chu-bordeaux.fr

Jean-Benoît Thambo, M.D.
Haut-Lévêque Heart Hospital
33 600 Pessac, France

Alain Taïeb, M.D.
Bordeaux Children's Hospital
33 076 Bordeaux, France

N ENGL J MED 358;24 WWW.NEJM.ORG

How an accidental discovery paved the way for the treatment of complicated infantile haemangiomas
A revolution in the management of infantile haemangiomas.

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Drug screening & design

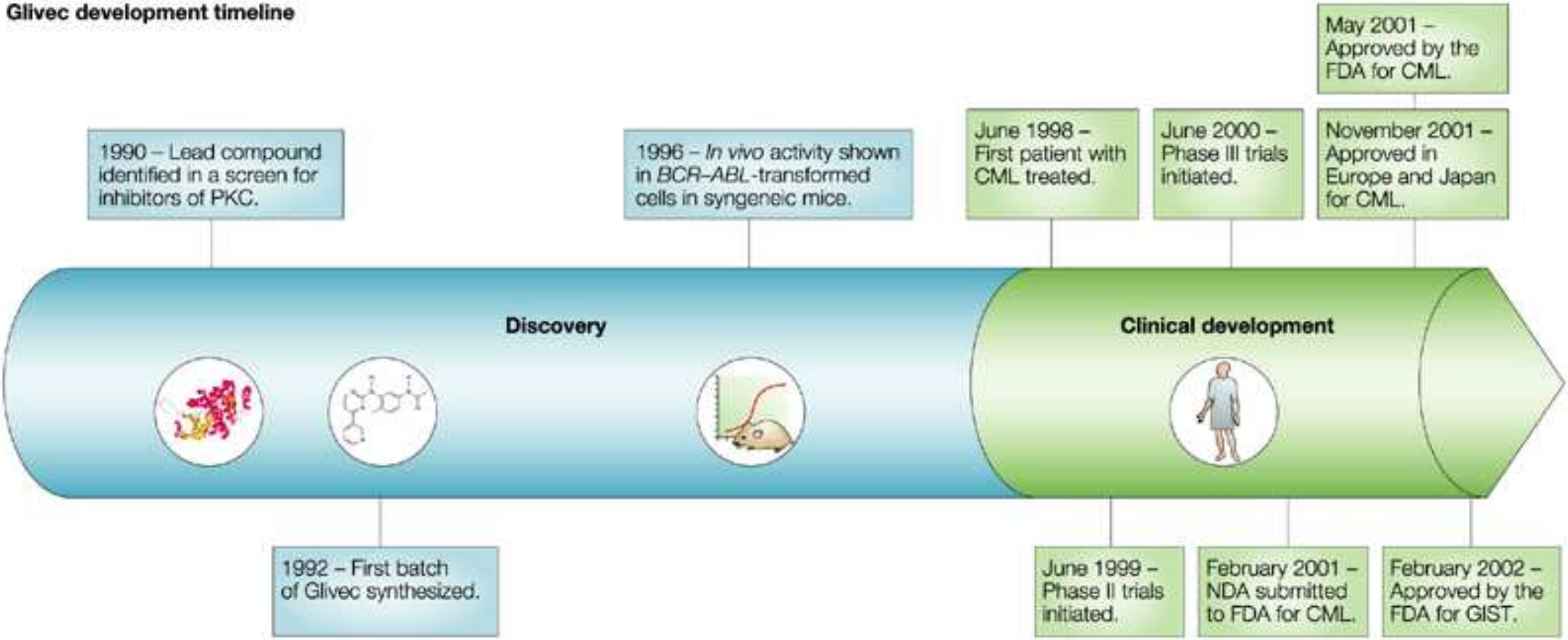
- **High throughput screening**: compound libraries, multi-well plates (96, 384,1536), robotics

- **Knowledge-based rational design**: computer modeling, structural analysis (NMR, X-ray crystal, etc), chemoinformatics…

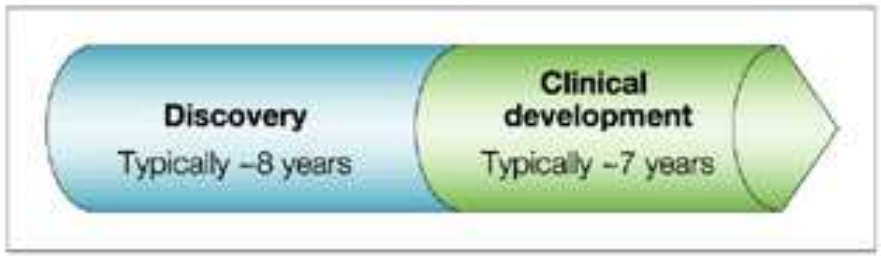
- Hit optimisation, lead selection, drug candidate
  - iterative cycles of chemistry and biology (cpd MoA, potency, SAR, selectivity, stability…)
  - Physicochemical properties (solubility, purity, complexity…)
  - ADME, DMPK, imaging, in vivo profiling…
  - initial safety assesment (preliminary Tox, predictive Tox)
  - innovation (I.P., patents): breakthroughs target/NCE, 2nd generation, formulation, etc…
  - potential market, time to market (RoI)

  - *Molecular attrition: From « >100,000 » cpds to « 3-5 » pre-candidate*
  - *A major challenge to combine all desired properties into one molecule*
  - *… back-up and fllow up programs*

Glivec development timeline



Typical development timeline



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Rational Design: ALK inhibitors

- Search for "oncogenic drivers" and development of targeted therapies.

- Discovery of the EML4-ALK fusion gene in a subgroup (<5%) of patients with NSCLC (2007)

- Accelerated approval of breakthrough therapy-designated drugs
  - Crizotinib in 2011, 2013 (Xalkori, Pfizer)

    [4 years from the discovery of ALK rearrangement in NSCLC to the FDA approval]
  - Ceritinib in 2014 (Zykadia, Novartis)

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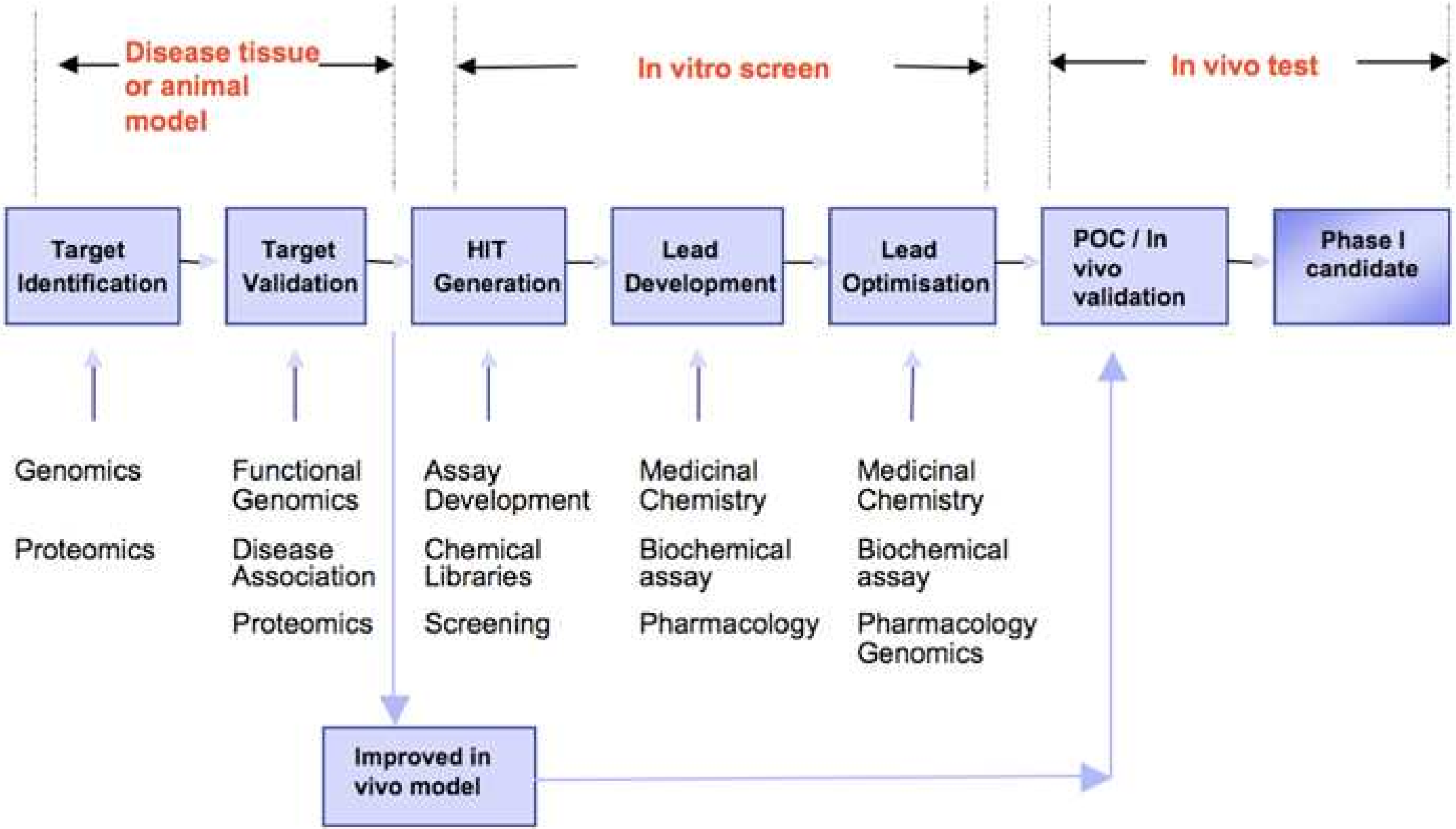

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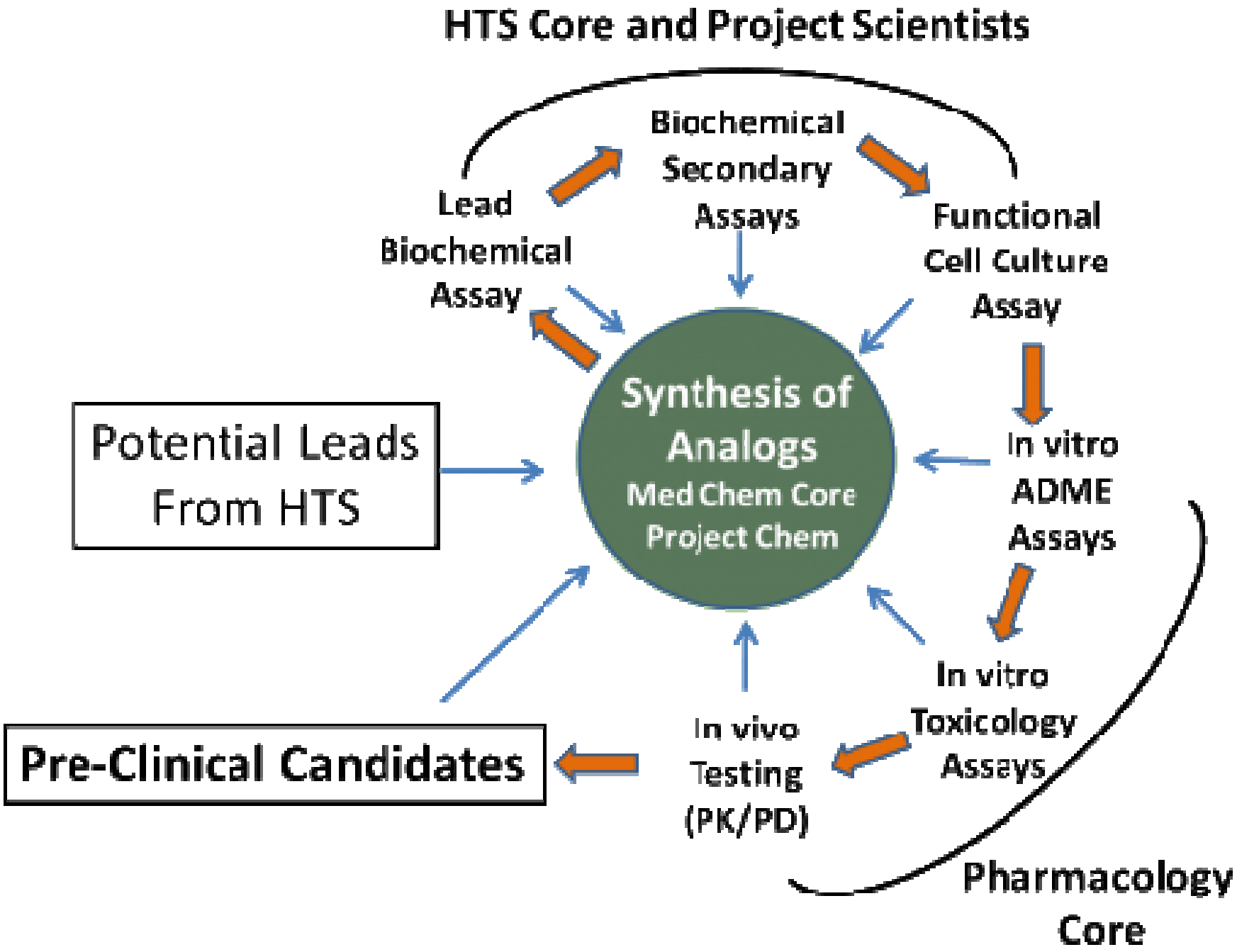

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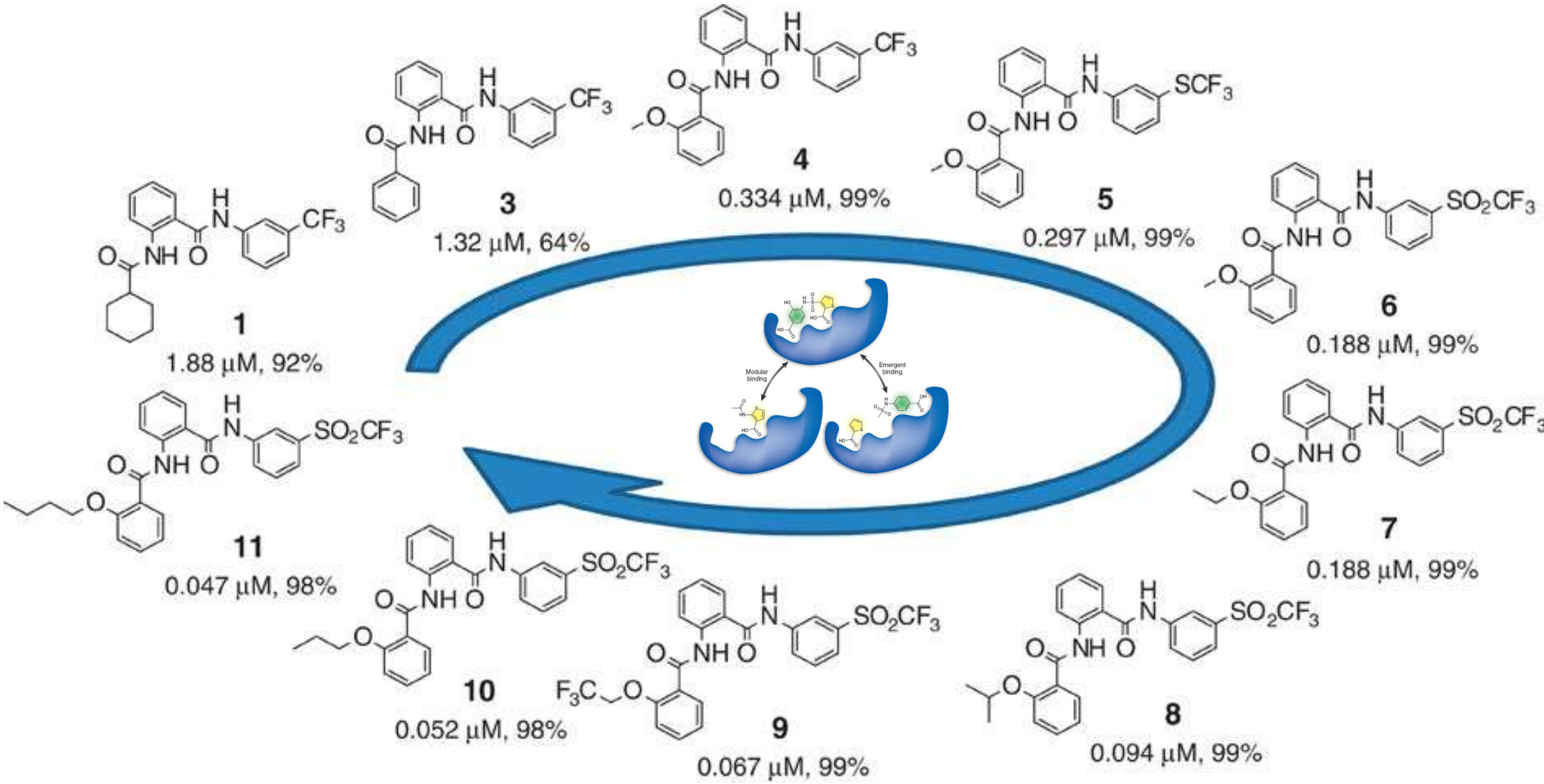

Structure activity relationship optimization campaign

1 HTS hit → 50-300 derivatives → 1 optimized Lead

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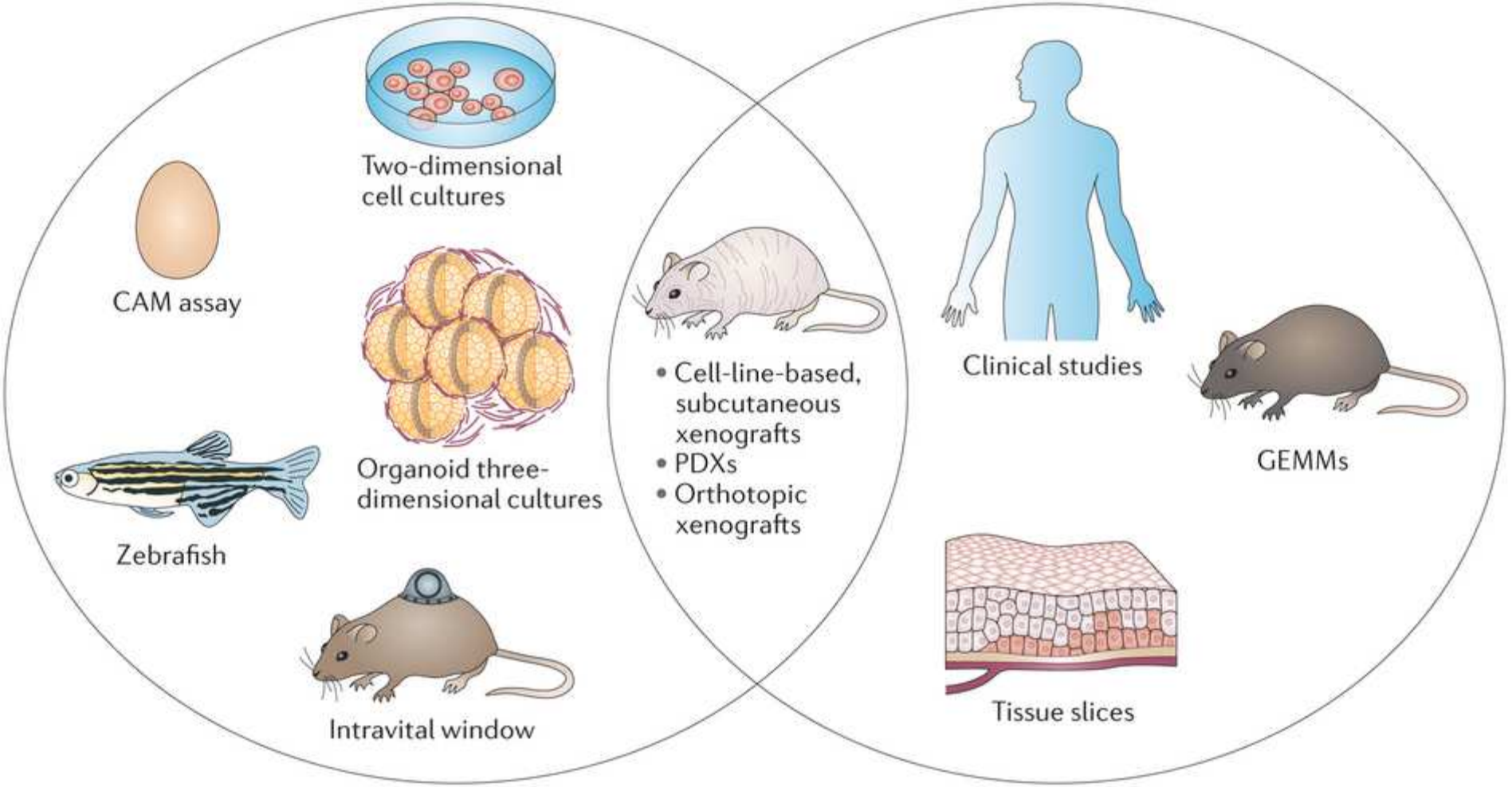
Models to evaluate mechanism of action & antitumor activity



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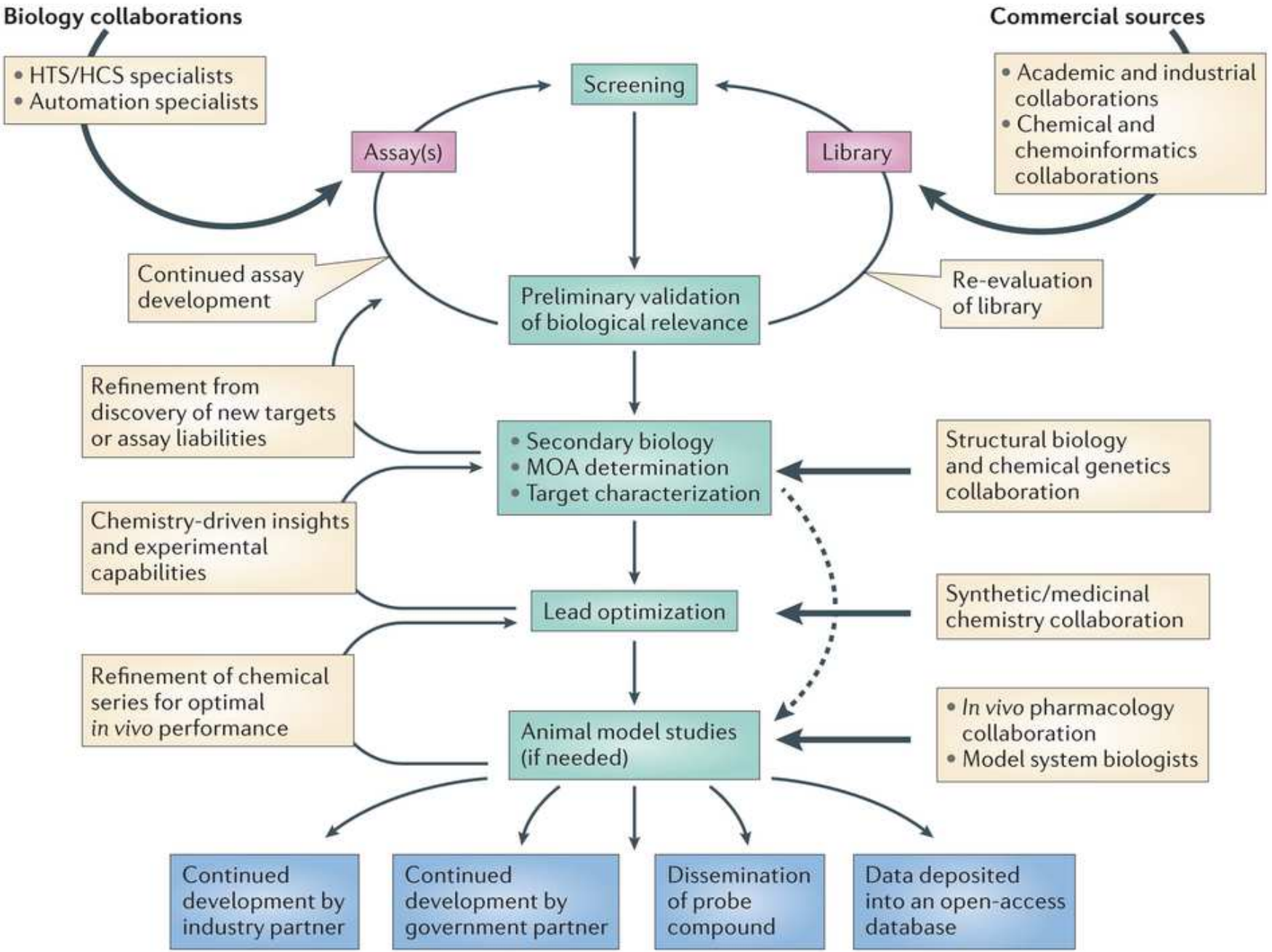

Mitigating risk in academic preclinical drug discovery. Dahlin et al., Nature Rev. Drug Discov. 14, 279-294 (2015)

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Failure: The Reality of Drug Discovery

Historically, the majority of Hit-to-Lead and Lead Optimization programs fail to deliver a pre-clinical candidate due to:

- Lack of efficacy (in animal models)
- Unexpected toxicity
- Poor pharmacokinetics

If you must fail…

"Fail early, fail cheap"

Preclinical safety studies

- To explore the response at up to maximum achievable doses
- To detect potential hazards and assess risks (general toxicology, geno-tox, carcinogenicity, repro-tox, etc…)
- To assist in dose-selection for initial clinical studies
- To suggest markers to monitor safety in humans
- To guide target-based investigations

- But not
  - to guarantee safety in humans
  - to predict human response
  - to define a mechanism

From molecules to medicines

- **Drug Substance (API)**
  - Cost to produce
  - Scalability
  - Analytical methods
  - Stability

➢ **Chemical Development**

- **Drug Product (Formulated API)**
  - Cost to produce
  - Scalability
  - Analytical methods
  - Stability
  - Packaging and storage

➢ **Pharmaceutical Development**

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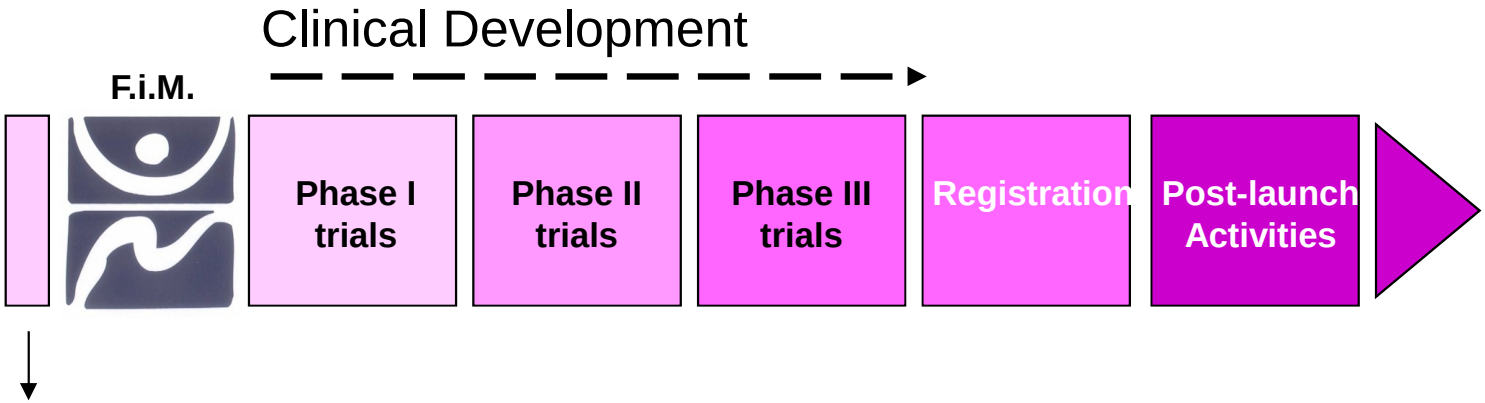
CMC: Chemistry, Manufacturing and Controls

- Preformulation / API stress studies
- Formulation : selection of prototype for early clinical studies.
- Process development to select sterilizing method
- Formulation optimization (final strength) for commercial product.
- Scaling-up and process validation
- Long term stability studies

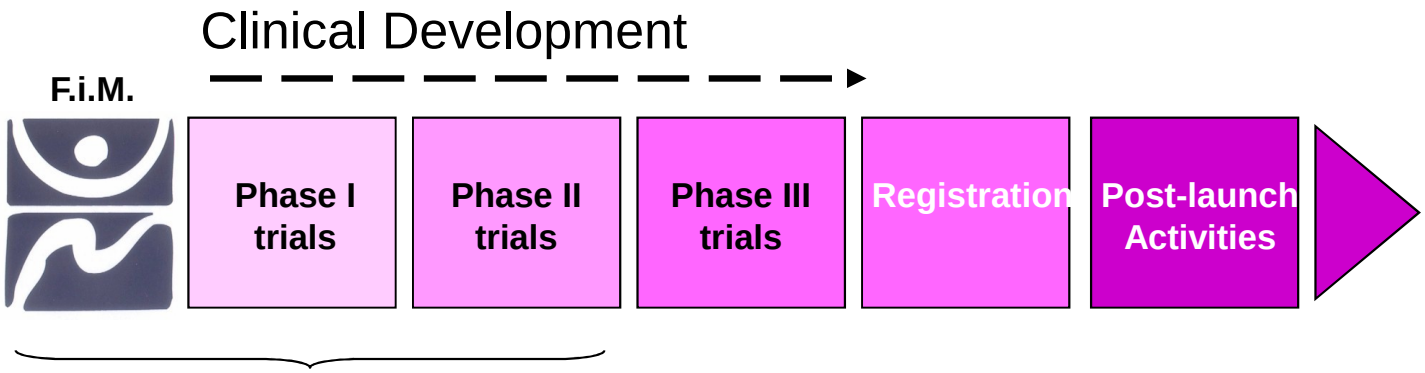
- ***Formulation development***
  - *pH solubility and stability profiles*
  - *Additional preformulation studies : sensitivity to light,oxygen, temperature…*
  - *Prototype formulation studies to select the best formulation based on stability studies (minimizing degradation products)*
  - *Choice of the final strength for clinical and manufacturing*
- ***Process development***
  - *Selection of the sterilisation method.*
  - *Scale-up and process validation*
  - *Manufacturing clinical batches for clinical studies*



USA: Investigational New Drug (IND) application:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.

Europe: Investigational Medicinal Product Dossier (IMPD), for approval of clinical trials by the competent authorities



Phase I: First in Man

- Small group of healthy volonteers or patients
- determine the active dose or MTD
- Verify the mechanism of action: target modulation
- Determine a safe dose range and identify side effects
- Test potential biomarkers

+ prelimenary information on efficacy

In general, heterogeneous tumor indications (s.t.)

Specific tumor indications
- BC, NSCLC, PC, etc…

Phase II: Efficacy studies

- Larger group of patients (50-300)
- Evaluate activity, efficacy: POC
- Determine effective dose range
- Route and scheme of treatment
- Further evaluate the safety
- Biomarkers
- (combinations)

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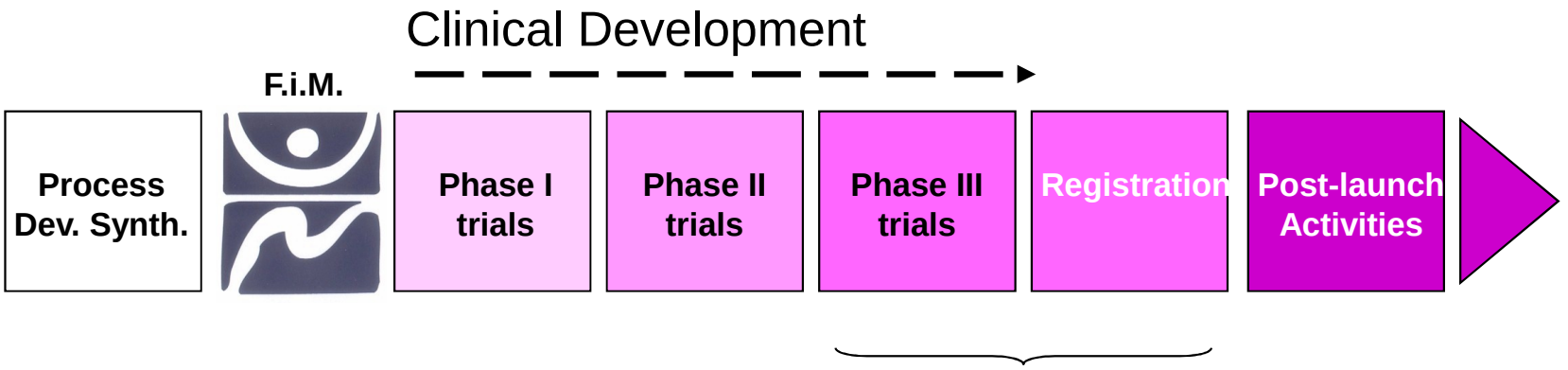


Phase III: Comparative studies

- Large group of patients (>500, >>)
- Comparative efficacy vs. used treatments
- Monitor side effects
- Dose range
- Safety
- Biomarker validation

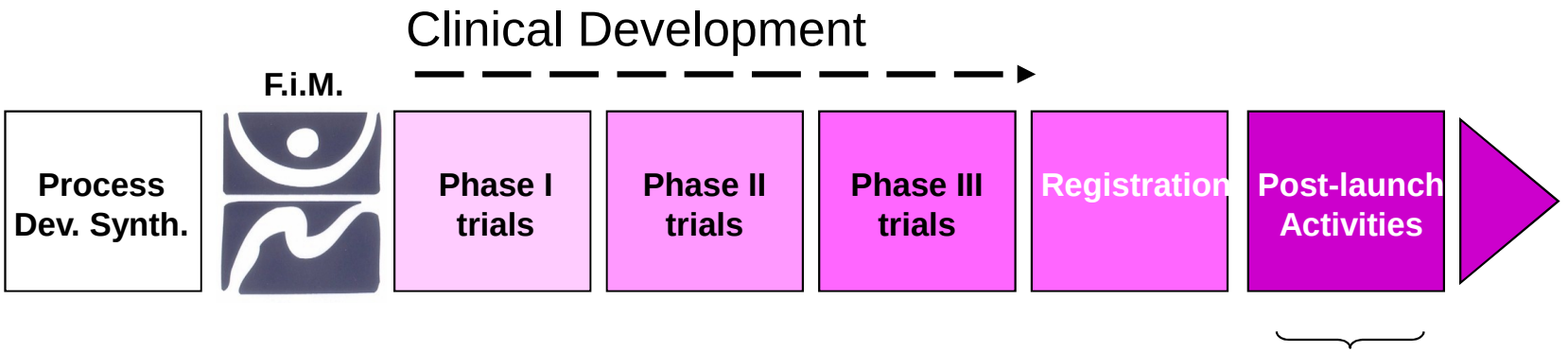
Specific tumor indications
- BC, NSCLC, PC, etc…

- pharmaco-economic impact
- market value

Registration of a new drug

- Compile preclinical and clinical data
- Quality of data (biometry, statistics)
- manufacturing process
- submit NDA to regulatory authorities:
  - quality + efficacy + safety
- NDA, from submission to approval:

→ ~2 years (2 months-7 years)
→ marketing authorization granted
→ Launching, commercialization

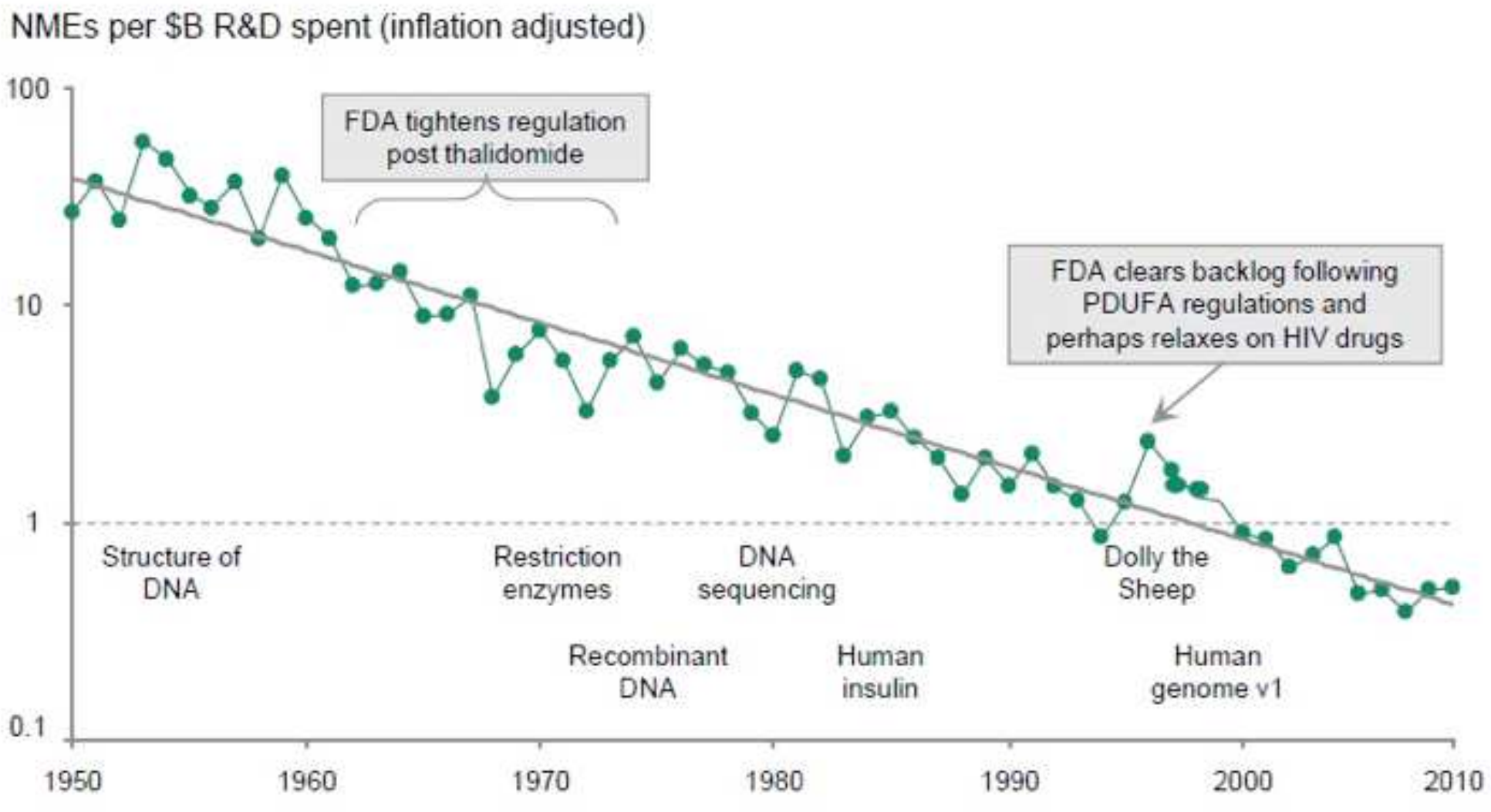


Phase IV & post-lauch activities

- Drug on the market
- post-market surveillance
- Continue to monitor and report adverse effects
- Life-cycle mamagement: new indications and/or formulations

several years after the use in wide population, the risk remains
Ex: rofecoxib (Vioxx), unacceptable cardiac side-effects → removed

R&D productivity over the past 60 years: on decline



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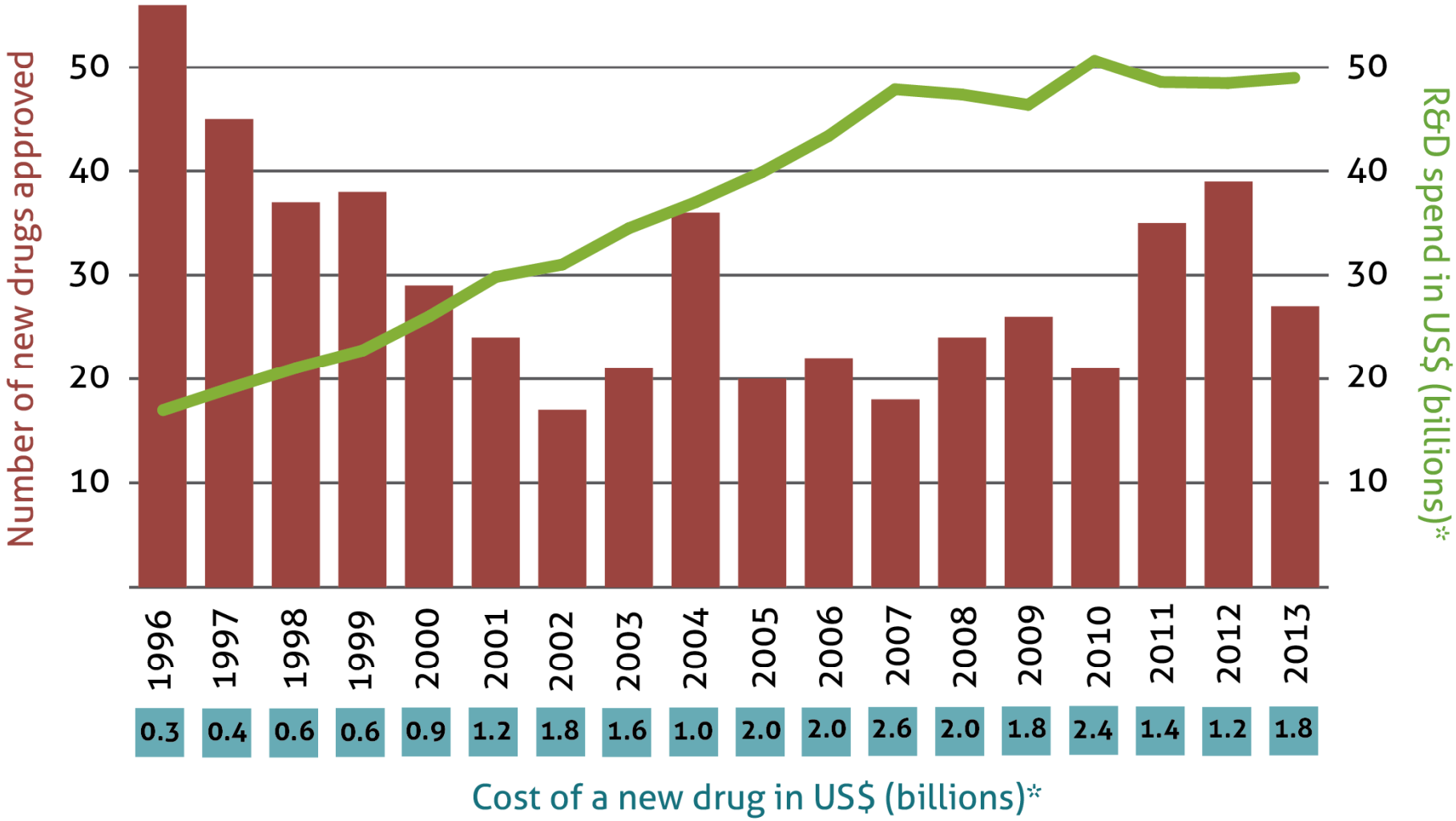
Productivity of the pharma industry

Finding the true cost of a new drug is complex and controversial...



Data: USFDA, PhRMA

Akshat Rathi | theconversation.com

** New drug cost and R&D spend could be 30% higher if non-PhRMA members are included*

The case of Oncology

CANCER is an attractive therapeutic field for pharmaceutical companies

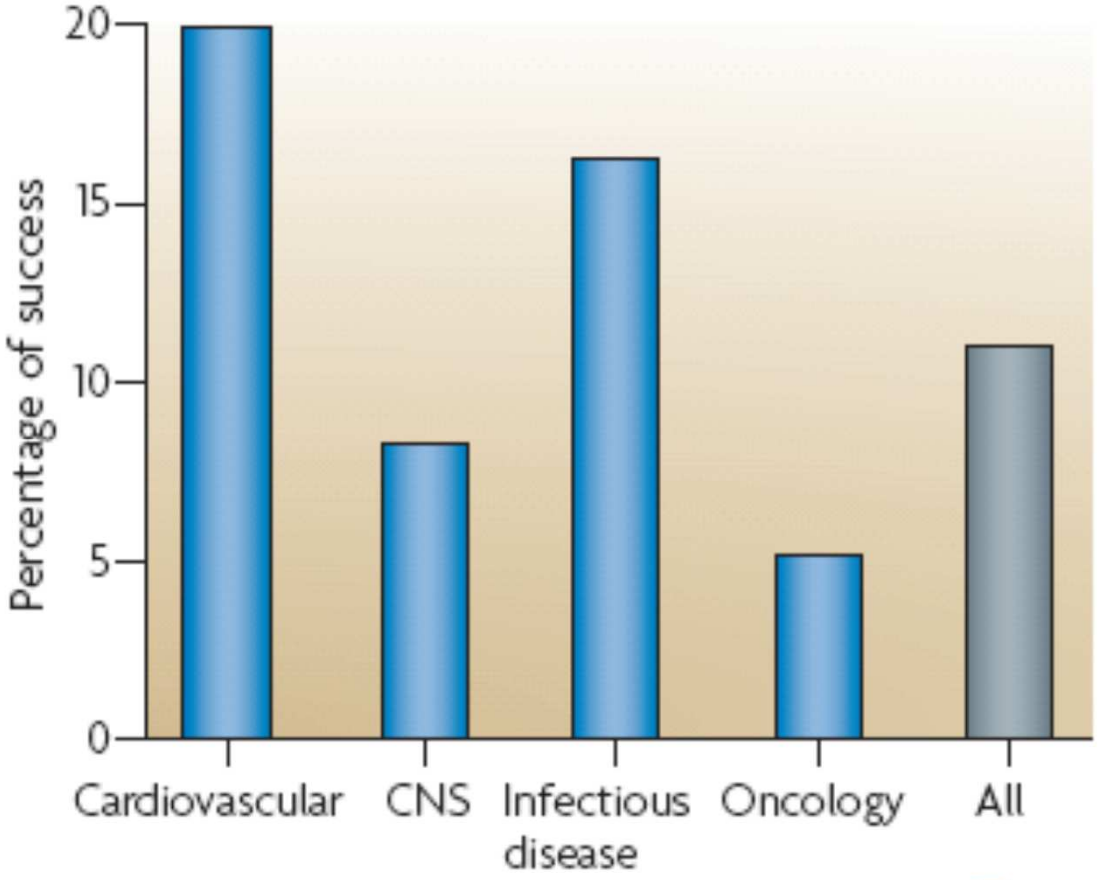
- new targets, multiple indications
- high price of drugs « tolerated » (thus far)

But a field with a limited success: *from F.i.M. to registration 90-95% attrition*

Why is cancer drug discovery so difficult?

Alexander Kamb, Susan Wee and Christoph Lengauer

NATURE REVIEWS | DRUG DISCOVERY
VOLUME 6 | FEBRUARY 2007 | 115



Drug repositioning

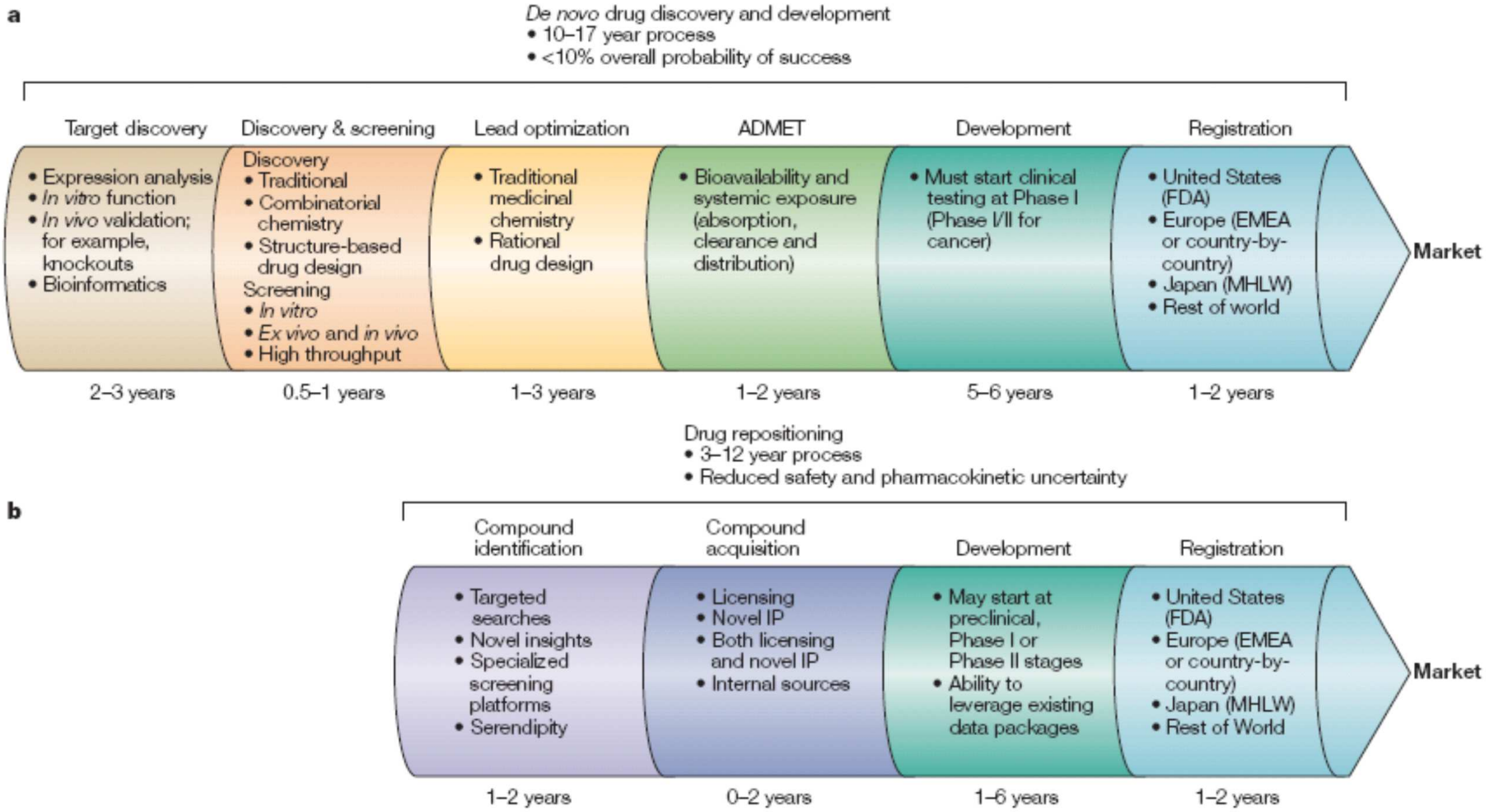


Figure 2 | **A comparison of traditional *de novo* drug discovery and development versus drug repositioning. a** | It is well

(Nat. Rev. Drug Discov. 2004, 3, 675)

Ex: repositioning of anti-depressant drugs

Table 1 | **Repositioned antidepressant drugs**

Generic (MOA)	Original indication (trade name; originator)	New indication (trade name; repositioner)	Comments
Bupropion (enhancement of noradrenaline function)	Depression (Wellbutrin; GlaxoSmithKline)	Smoking cessation (Zyban; GlaxoSmithKline)	Approved as Wellbutrin for depression in 1996 (REF. 39) and as Zyban for smoking cessation in 1997 (REF. 39). Worldwide sales in 2003 for Wellbutrin were US $1.56 billion and US $125 million for Zyban[41].
Dapoxetine (SSRI)	Analgesia and depression (N/A; Eli Lilly)	Premature ejaculation (N/A; Johnson & Johnson)	Currently in Phase III. If approved, it would be the first approved agent for premature ejaculation. Peak sales are projected to reach US $750 million[42].
Duloxetine (NSRI)	Depression (Cymbalta; Eli Lilly)	Stress urinary incontinence (Duloxetine SUI; Eli Lilly)	Simultaneously in development for depression and SUI. Projected worldwide peak sales are US $800 million in SUI and US $1.2 billion in depression[43].
Fluoxetine (SSRI)	Depression (Prozac; Eli Lilly)	Premenstrual dysphoria (Sarafem; Eli Lilly)	Approved 6 July 2000 in the United States for use in premenstrual dysphoric disorder[44]. Sold in January 2003 to Galen, US $60 million of revenue reported by September 2003.
Milnacipran (NSRI)	Depression (Ixel; Pierre Fabre Médicament)	Fibromyalgia syndrome (N/A; Cypress Biosciences)	Marketed as Ixel for depression in Europe and Japan*; currently in Phase III trials‡.
Sibutramine (NSRI)	Depression (Sibut; Boots Company)	Obesity (Meridia; Abbott)	Bought in acquisition of Knoll Pharmaceuticals in 2001. Approved 24 November 1997 in the United States for the management of obesity.

depression

fibromyalgia

NEW Savella milnacipran HCl tablets

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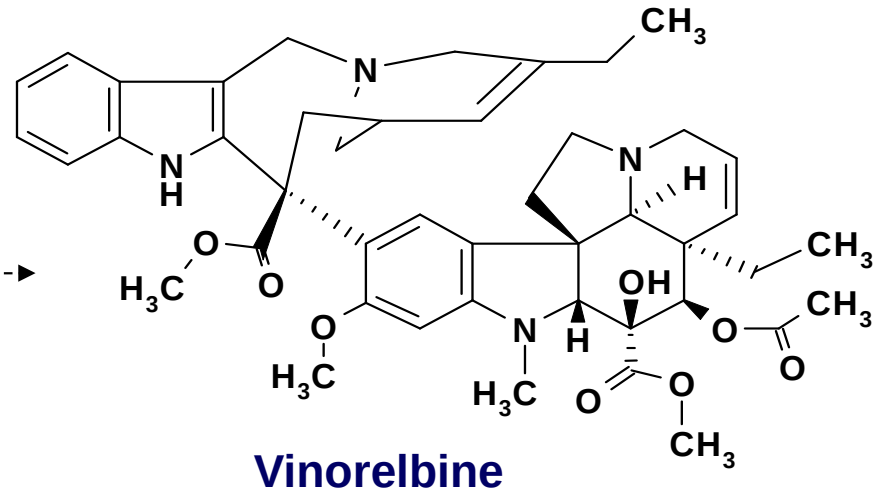
vinorelbine (Navelbine®)

Catharanthine+Vindoline

Anhydrovinblastine



Vinorelbine

injectable Navelbine

(1989)

oral Navelbine

(2001)

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Vinflunine (JAVLOR®)

- **1988: HF & vinca-alcaloïdes**
- **1991: 50 mg of PM391**
- **1994: *in vivo* activity**
- **1996: vinflunine**
- **1998: Phase I**
- **2000: Phase II**
- **2003: Phase III**
- **2009: EMEA Approval, bladder cancer**

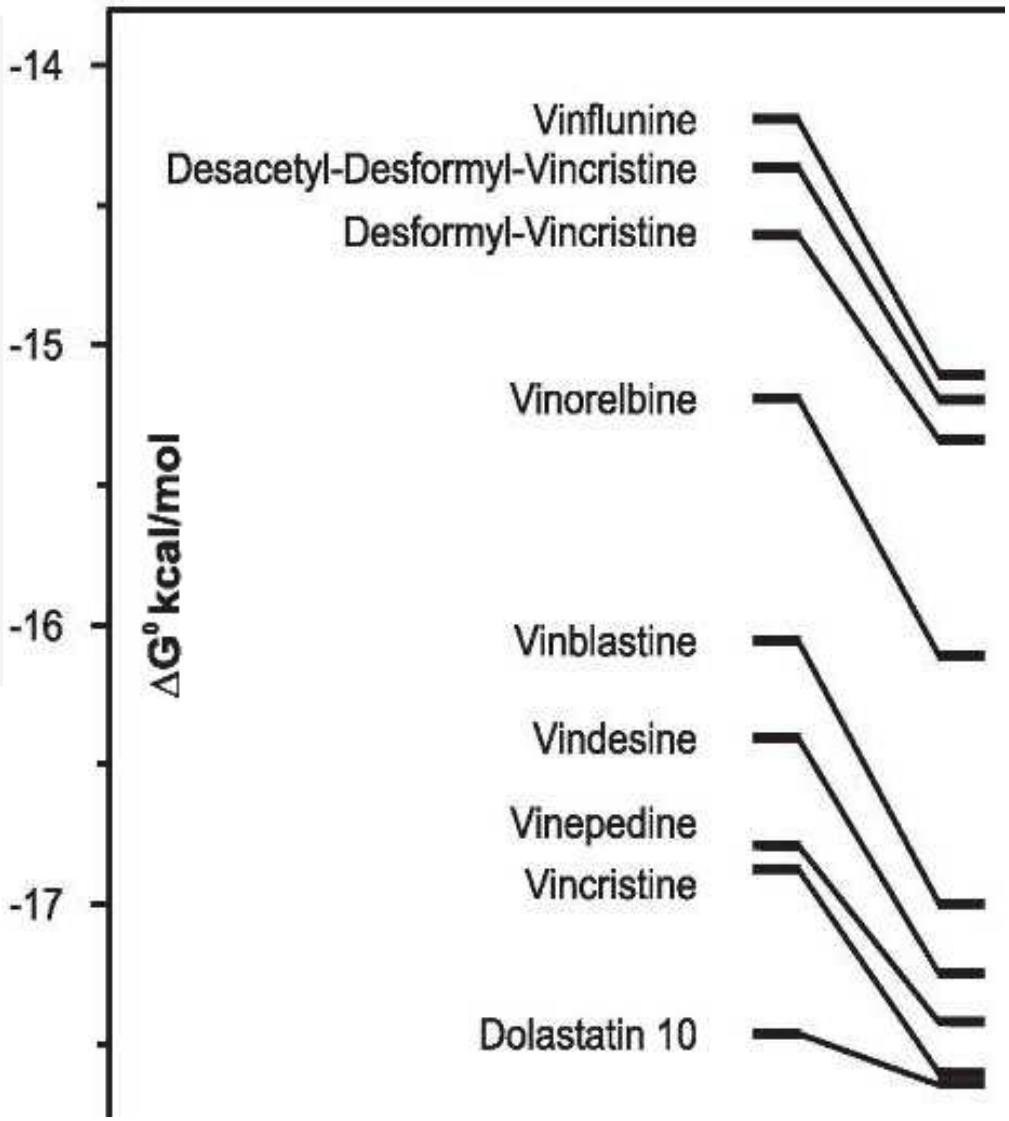
VFL: reduced affinity for tubulin dimers

Table 1. Equilibrium Constants for Vinca-Tubulin Interaction

Drug	$K_1(M^{-1})$	$K_2(M^{-1})$	$K_1K_2(M^{-2})$*
Vincristine	1.4×10^5	1.7×10^7	2.3×10^{12}
Vinblastine	1.2×10^5	5.1×10^6	6.1×10^{11}
Vinorelbine	1.3×10^5	1.1×10^6	1.4×10^{11}
Vinflunine	8.8×10^4	3.0×10^5	2.6×10^{10}

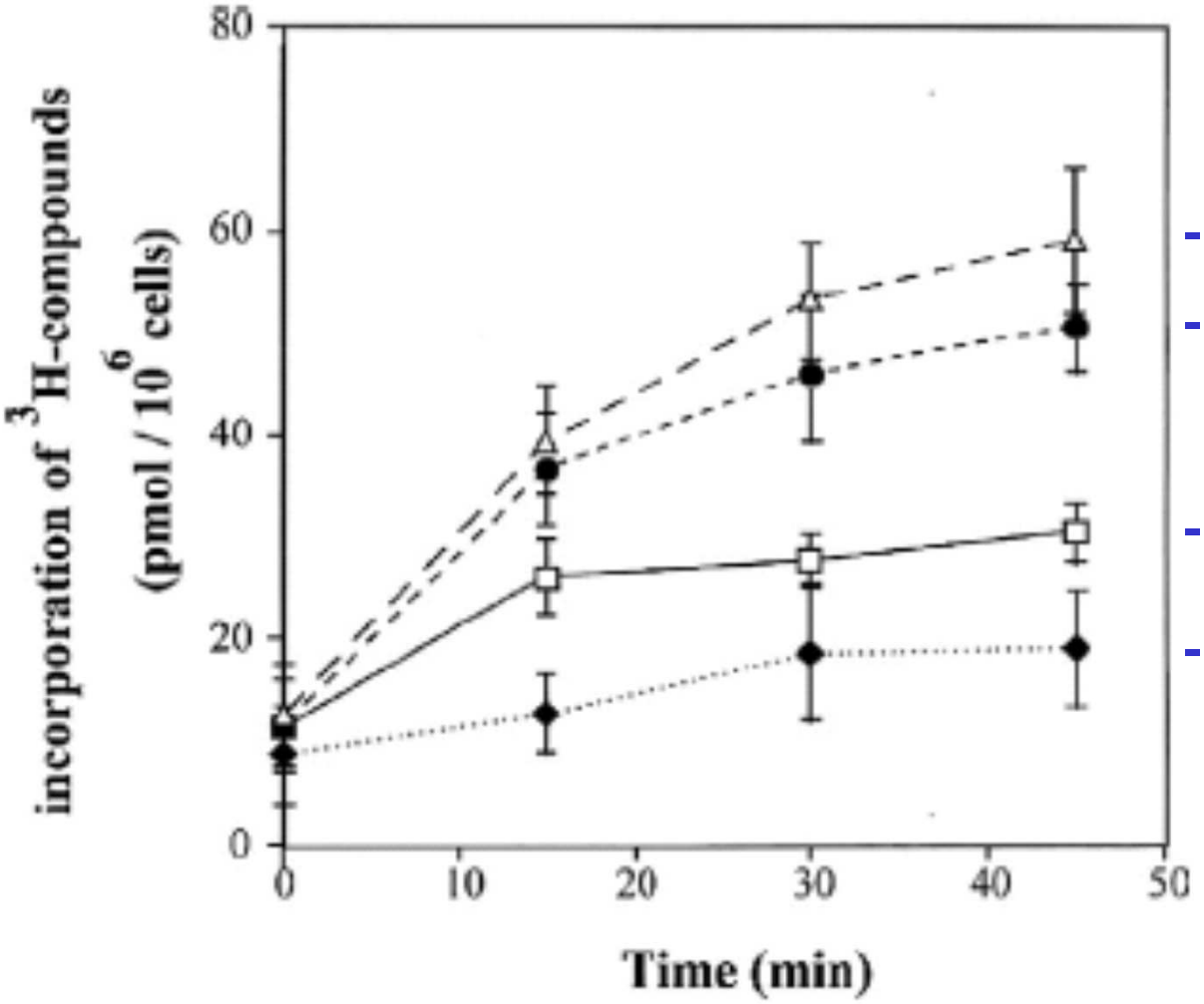
Abbreviations: K_1, affinity of drug for tubulin heterodimers; K_2, affinity of liganded heterodimers for spiral polymers; K_1K_2, overall affinity for tubulin.
*In the presence of guanosine triphosphate at 25°C.

(Lobert & Puozzo, Sem. Oncol. 2008, 35, S28)
(Lobert & Correia, Methods Enzymol. 2000, 323, 77)



« weak » affinity for tubulin → fewer and smaller spiral filaments → reduced neurotoxicity

VFL: high intra-cellular accumulation



- vinflunine
- vinorelbine
- vinblastine
- vincristine

Figure 3. Differential uptake of ^{3}H-vinca alkaloids.[13] Uptake of ^{3}H-vinflunine (Δ); ^{3}H-vinorelbine (○); ^{3}H-vinblastine (□); ^{3}H-vincristine (♦) in P388 murine leukemia cells.

(Lobert & Puozzo, Sem. Oncol. 2008, 35, S28)

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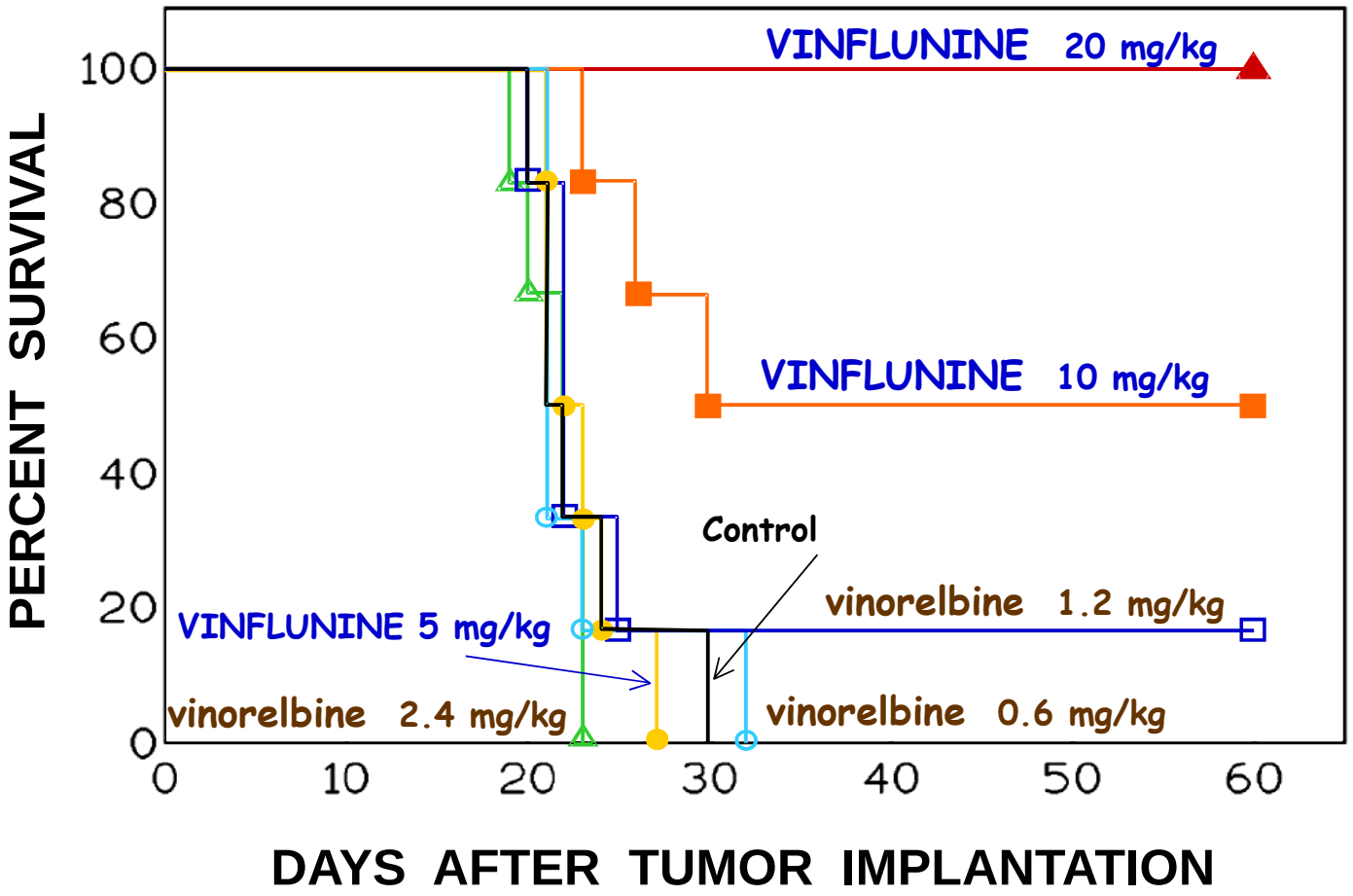
Vinflunine activity in bladder cancer

VFL increases lifespan of mice with bladder cancer



Intravesically-implanted murine MB-49 bladder cancer

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Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

from Bellmunt et al.,
J. Clin. Oncol. 2009, August

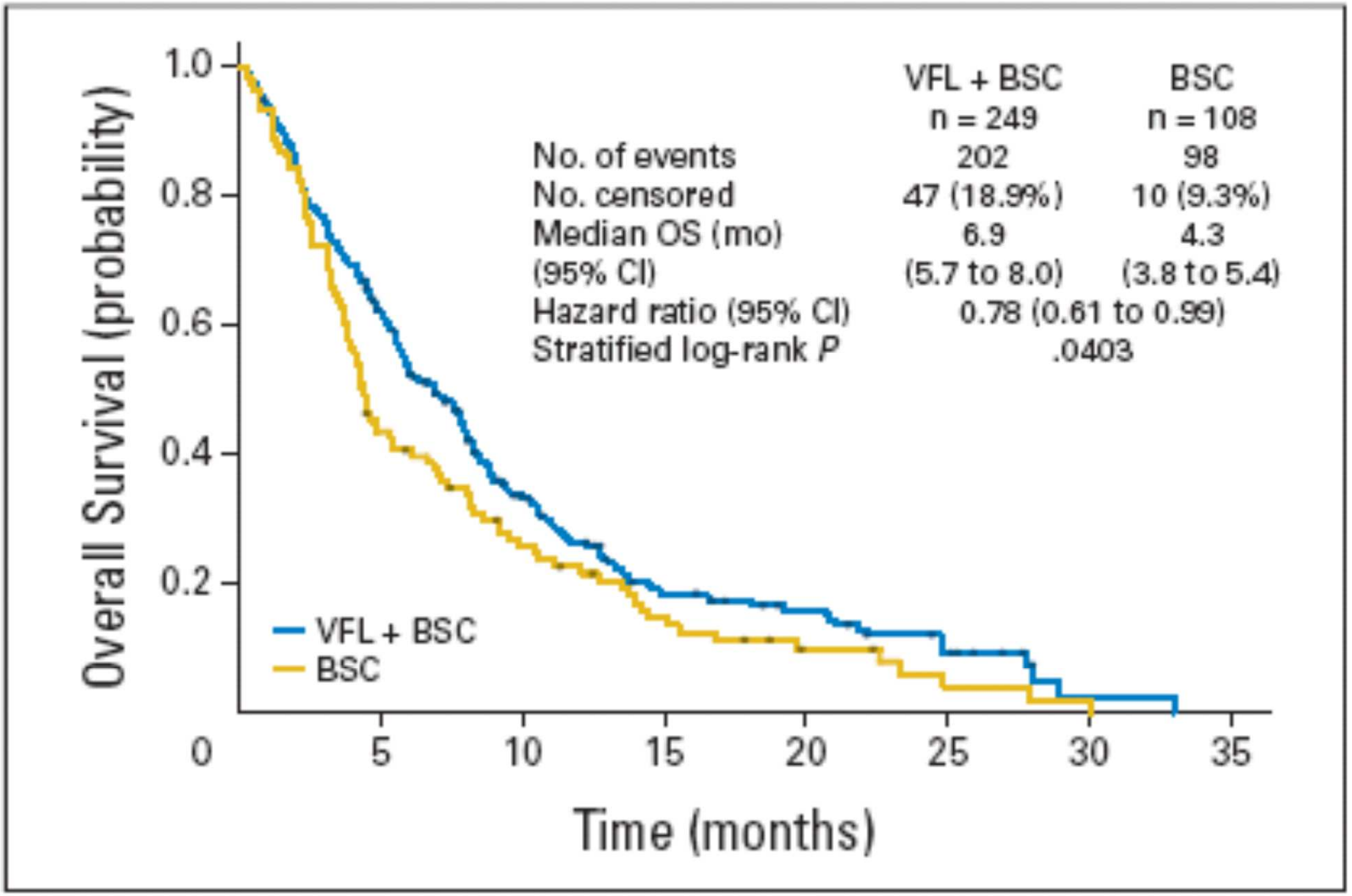

Fig 3. Overall survival (OS) in the eligible population (n = 357; 96.5% of intent-to-treat population). VFL, vinflunine; BSC, best supportive care.

Pierre Fabre

Vinflunine (JAVLOR®)

Pierre Fabre

- **1988: HF & vinca alk.**
- **1991: PM391**
- **1994: *in vivo* activity**
- **1996: vinflunine**
- **1998: Phase I**
- **2000: Phase II**
- **2003: Phase III**
- **2009: EMEA Approval, 1st indication**