Il processo di drug discovery

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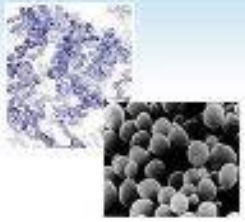
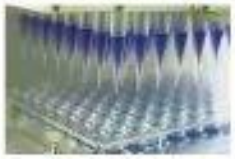
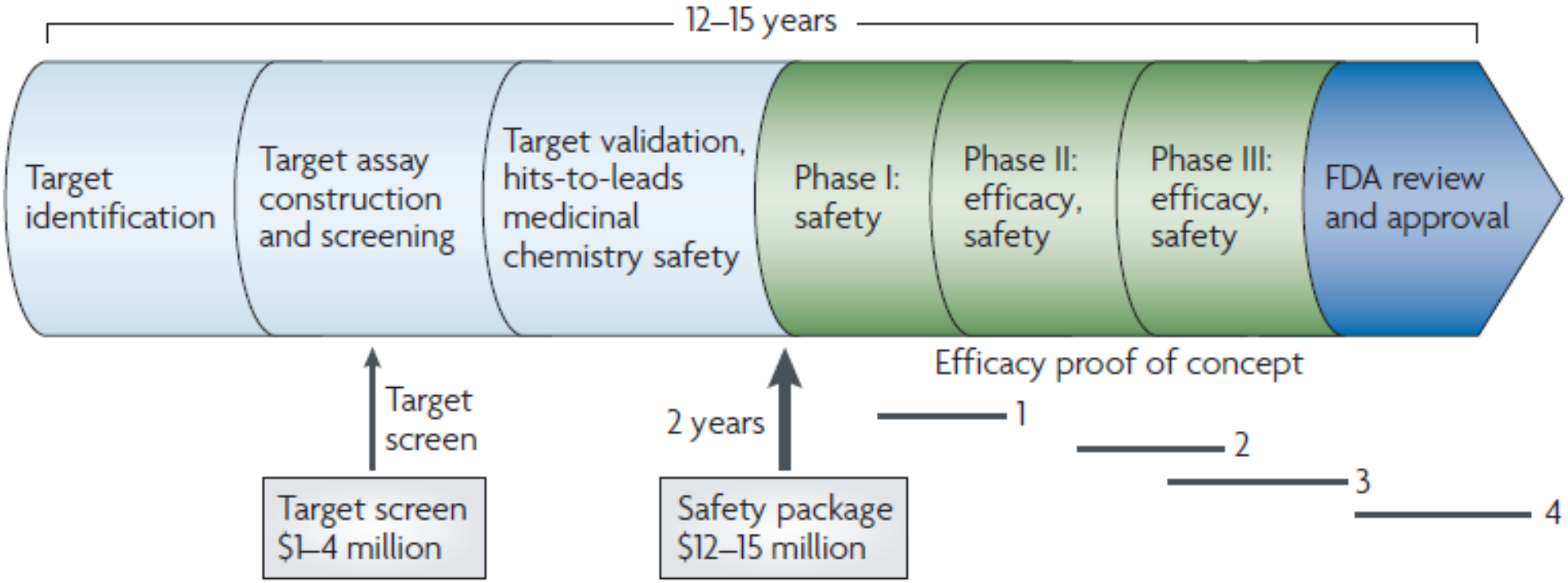
Drug discovery and development: overview

Drug research	Preclinical	Clinical trials	Evaluation/ Approval	Phase IV studies
 	Lab and animal experiments 	**Phase I:** 20-100 healthy volunteers **Phase II:** 100-500 patients → safety, dosing **Phase III:** 1,000-10,000 patients → efficacy, adverse events 	(up to 2 years)	(more than 2 years)

Source: based on PhRMA Profile Pharmaceutical Industry 2010

Drug discovery and development: phases



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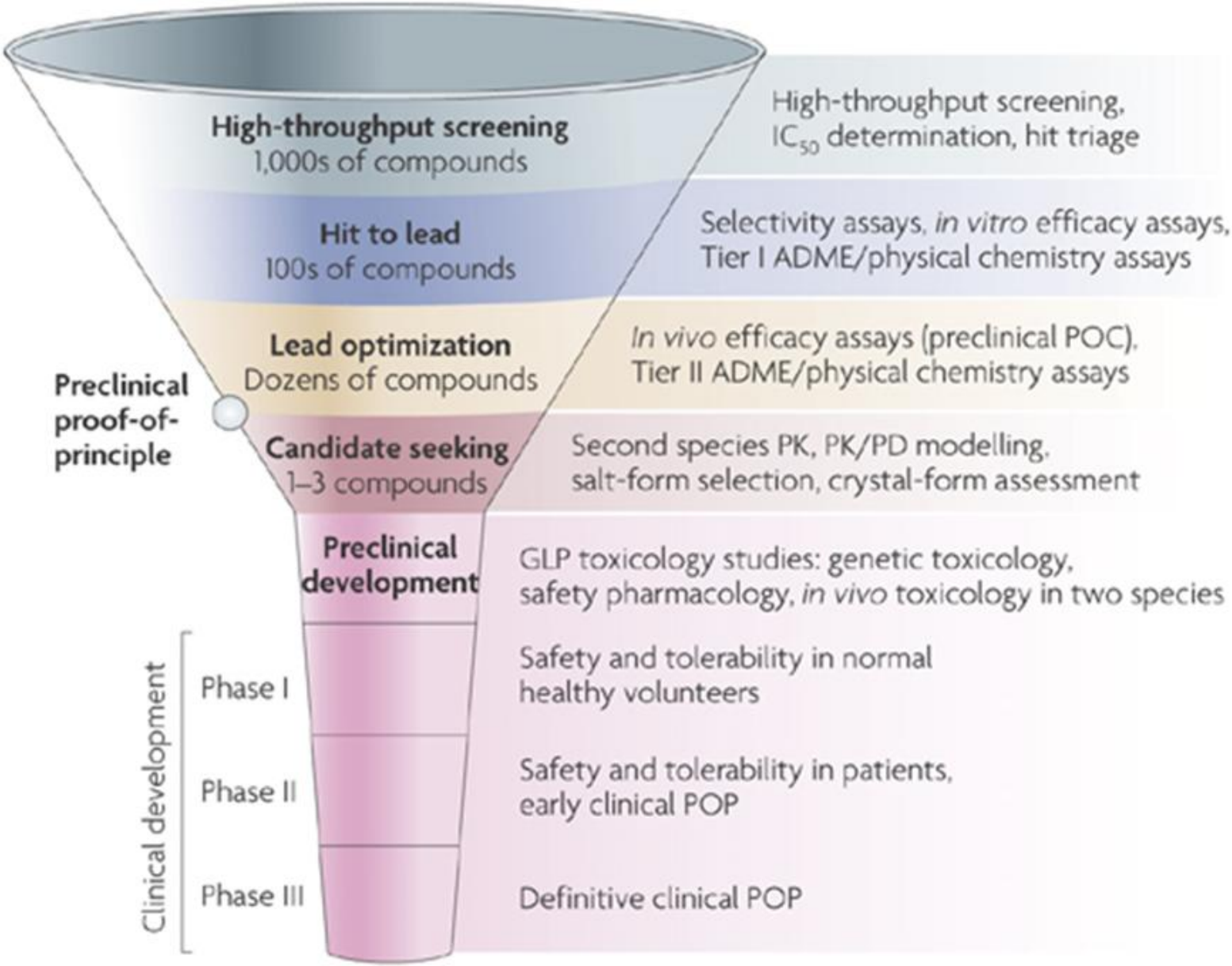
Roses AD, Nature Rev Drug Disc. 7:808, 2008

A typical testing scheme for a small-molecule drug



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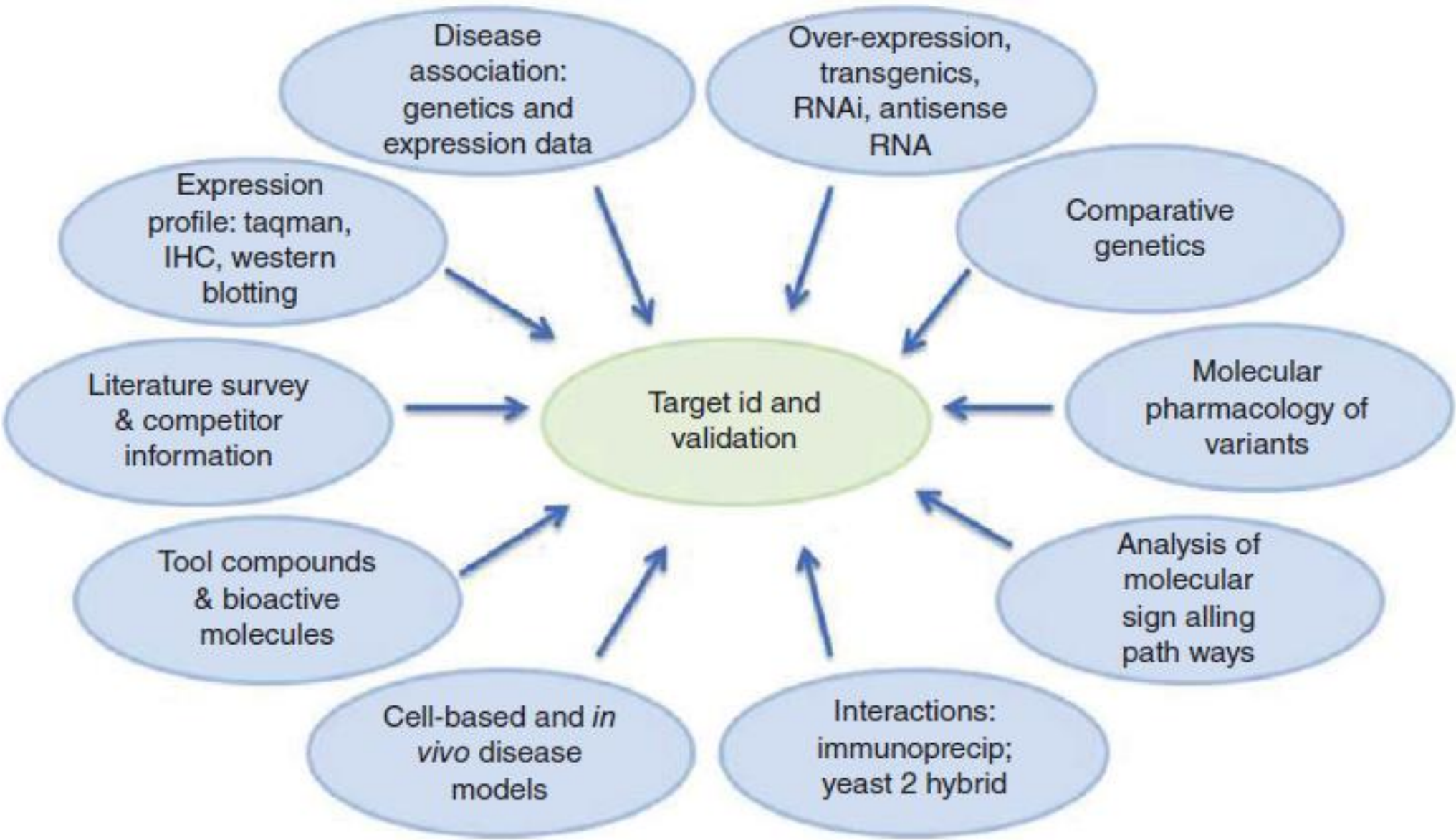
Kramer JA, Nature Rev Drug Disc. 6:636, 2007

Target identification and validation is a multifunctional process



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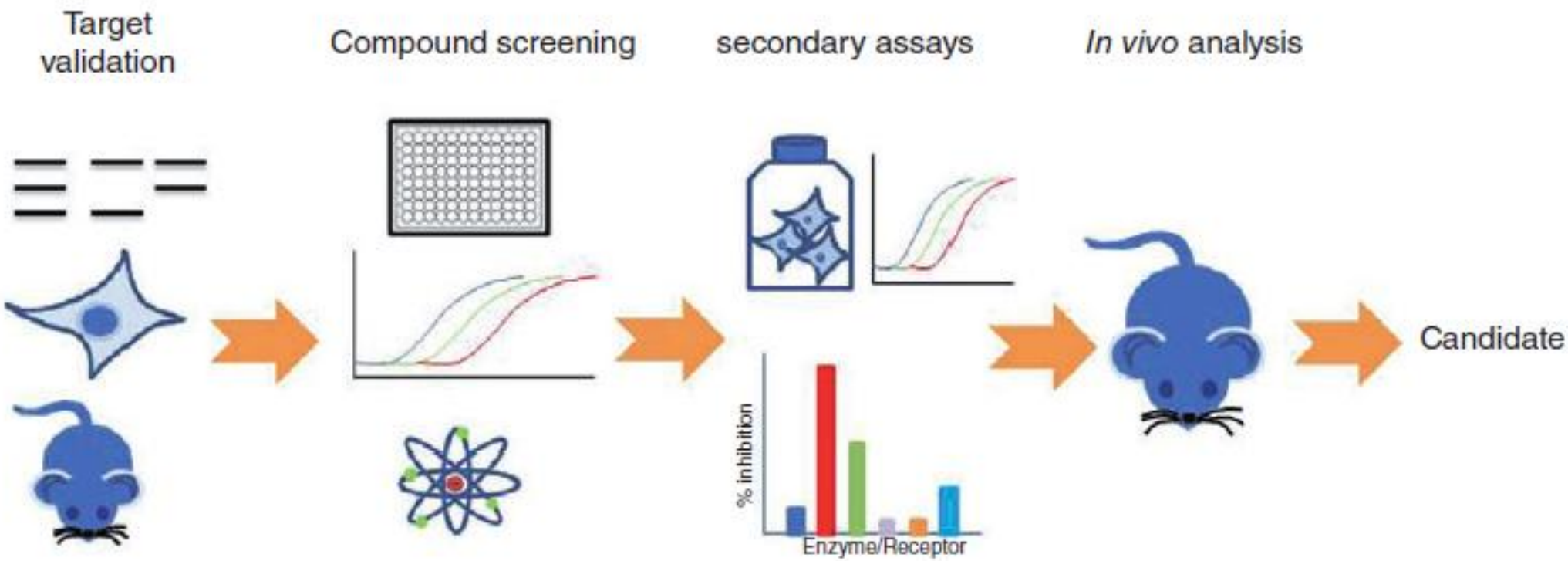
Hughes S, Br J Pharmacol. 162:1239, 2011

Overview of drug discovery screening assays: from hit to lead to clinical candidate



- Genetic, cellular and *in vivo* experimental models to identify and validate target
- HTS & selective library screens; structure based design
- Reiterative directed compound synthesis to improve compound properties
- *in vitro* & *ex vivo* secondary assays (mechanistic)
- Selectivity & liability assays
- Compound pharmacology
- Disease efficacy models
- Early safety & toxicity studies
- Preclinical safety & toxicity package

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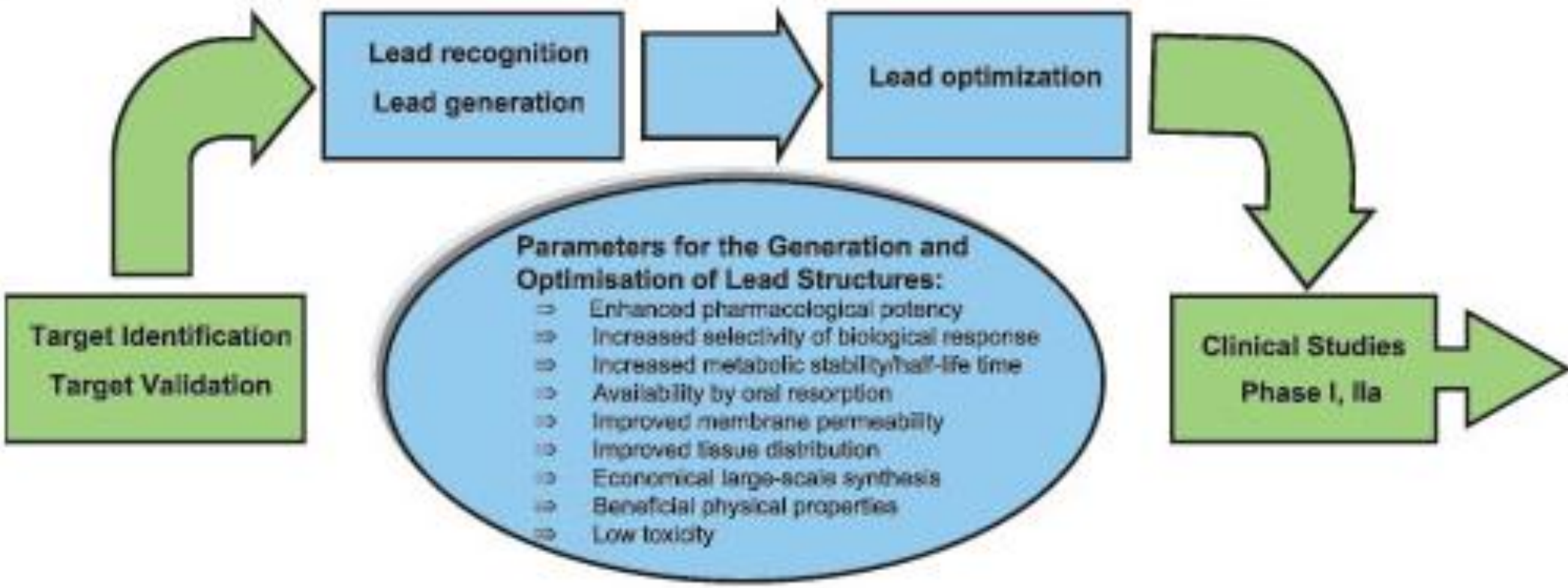
Hughes S, Br J Pharmacol. 162:1239, 2011

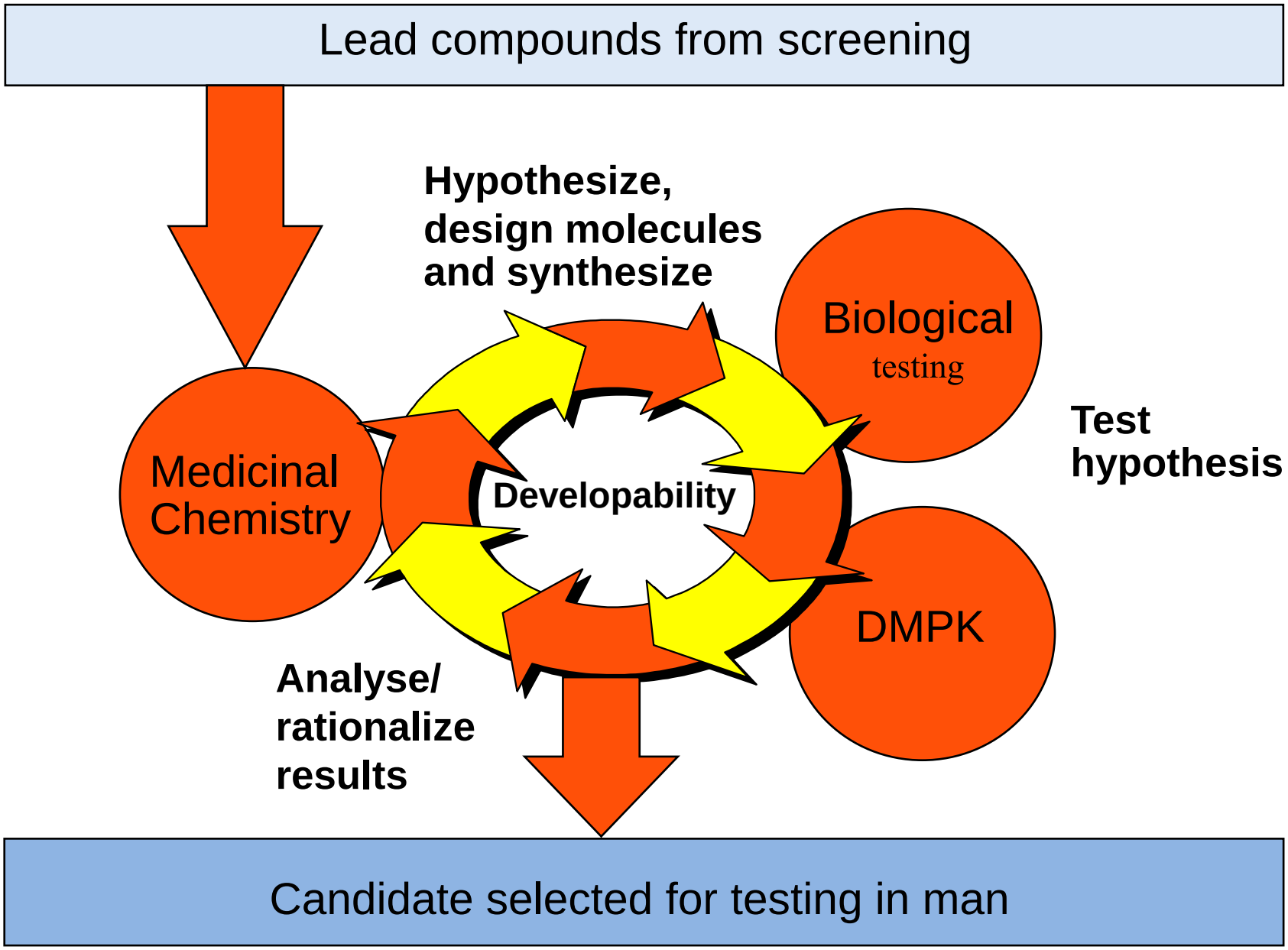
Lead optimization: key parameters



Also to consider:

- Cost of goods
- Scalability
- Structural alerts
- Freedom to operate
- Ability to create and protect intellectual property.

Optimizing lead compounds is an iterative process

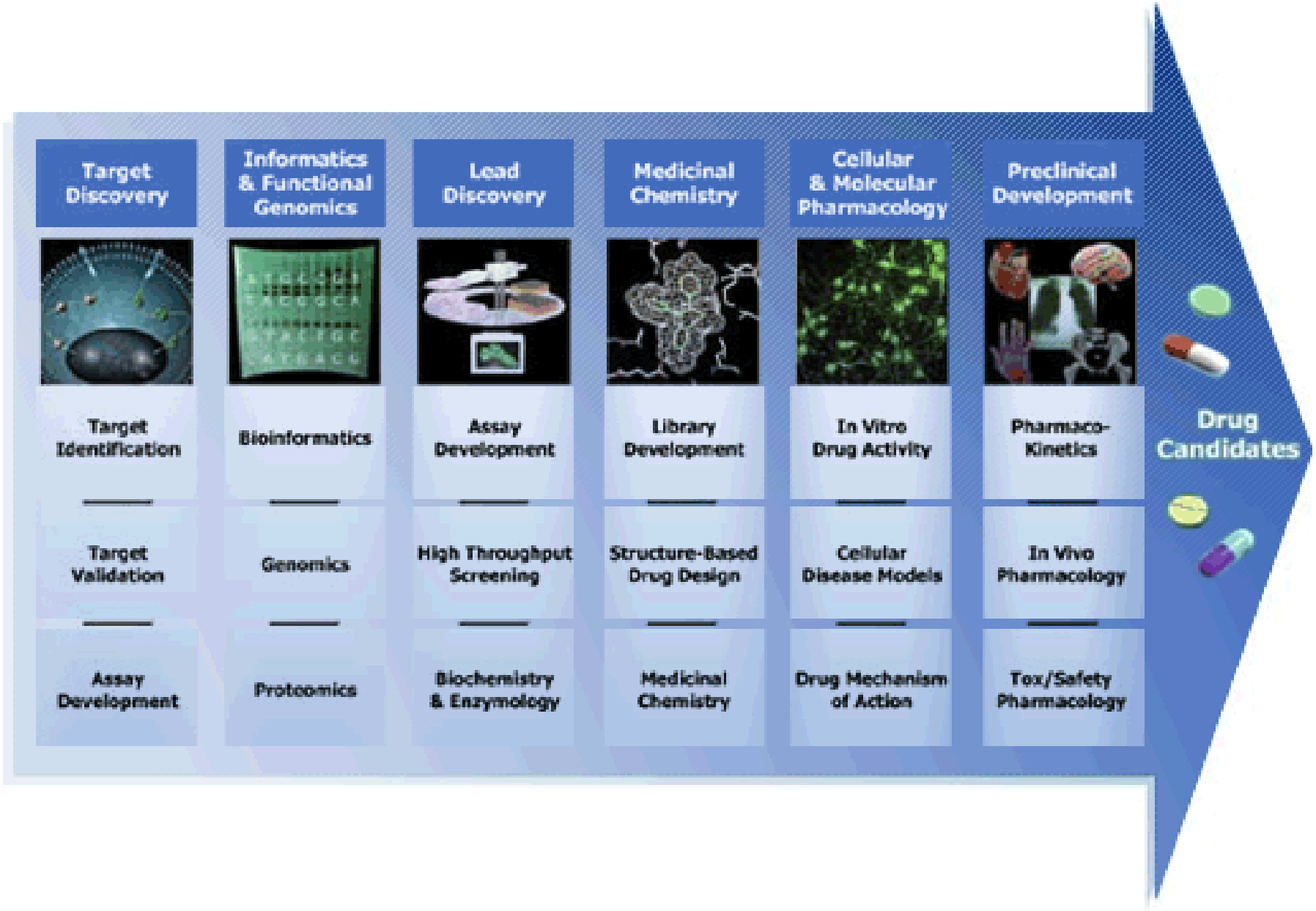


Key in vitro assays in early drug discovery

Assays	Target value	Comments
Aqueous solubility	>100 µM	Important for running *in vitro* assays and for *in vivo* delivery of drug
Log $D_{7.4}$	0–3 (for BBB penetration ca 2)	A measure of lipophilicity hence movement across membranes
Microsomal stability Cl_{int}	<30 $\mu L \cdot min^{-1} \cdot mg^{-1}$ protein	Liver microsomes contain membrane bound drug metabolizing enzymes. This assay measures compound clearance and can give an idea of how fast it will be cleared out *in vivo*
CYP450 inhibition	>10 µM	Main enzymes in body which metabolize drugs and their inhibition can cause toxicity
Caco-2 permeability P_{app}	$>1 \times 10^{-6}$ cm^{-1} (asymmetry <2)	Caco-2 colon carcinoma cell line used to estimate permeability across intestinal epithelium, important for drug absorption from gut
MDR1-MDCK permeability P_{app}	$>10 \times 10^{-6}$ cm^{-1} (asymmetry <2)	MDCK cells transfected with the MDR1 gene, which encodes the efflux protein P glycoprotein (P-gp). An important efflux transporter in many tissues including intestine, kidney and brain, P-gp can be used to predict intestinal and brain permeability
Hep G2 hepatotoxicity	No effect at 50 × IC_{50} or EC_{50}	Human HepG2 cells can act as a surrogate for effects of toxicity on human liver, an important cause of drug failure in the clinic
Cytotoxicity in suitable cell line	No effect at 50 × IC_{50} or EC_{50}	Reduce the likelyhood of cellular toxicity *in vivo*

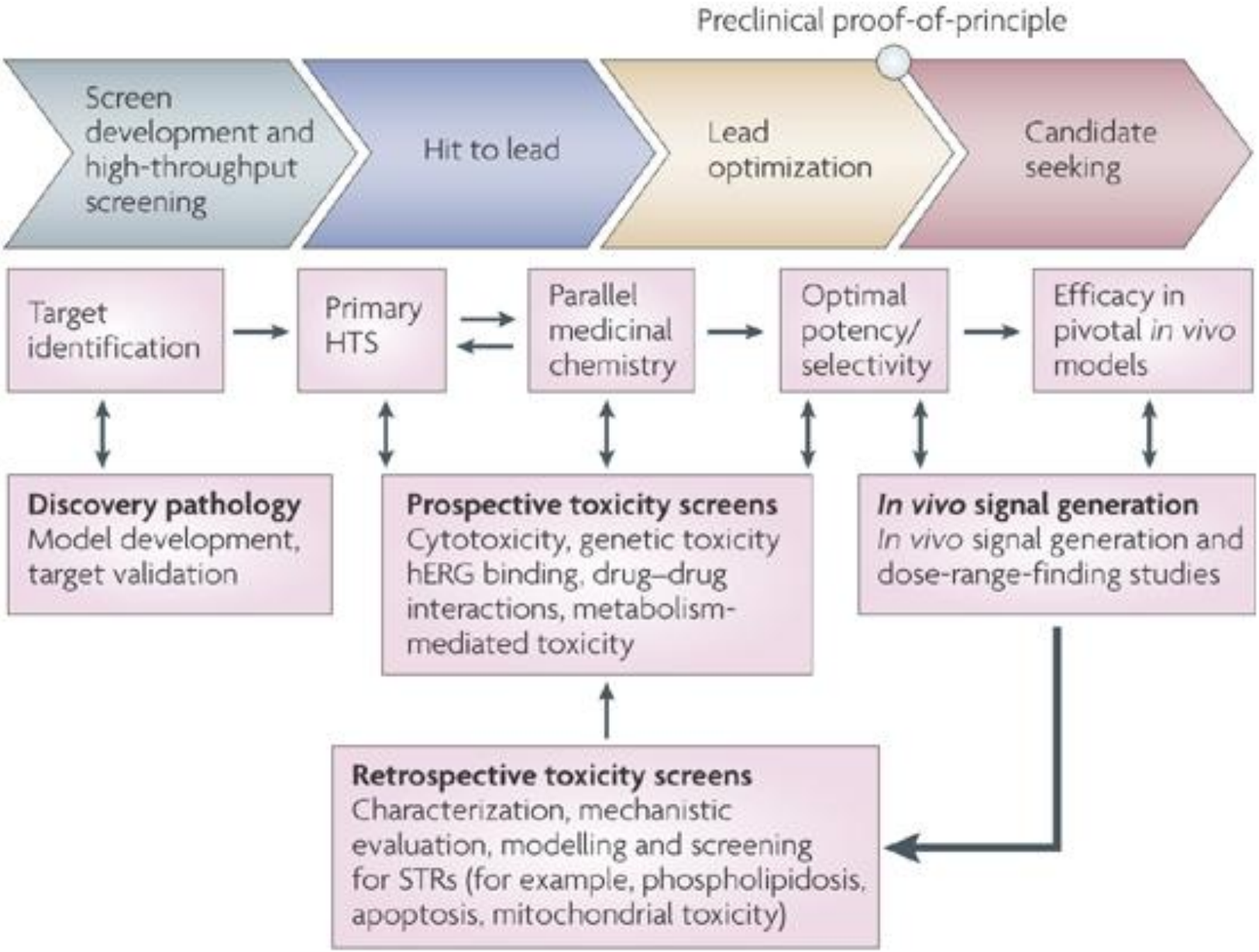
Hughes S, Br J Pharmacol. 162:1239, 2011

Selecting a clinical candidate drug: key elements



Adapted from FDA website, 2014

Toxicology profiling in drug discovery



Kramer JA, Nature Rev Drug Disc. 6:636, 2007

Five key questions for toxicity management

What is the safety margin?

An acceptable safety margin depends on the nature of the dose-limiting adverse event, the therapeutic indication being sought and the intended patient population, the competitive environment and present standard of care, etc.

Is the toxicity reversible?

Toxicity that is irreversible is typically unacceptable.

Is there a biomarker?

Toxicity that can not be monitored may develop into an irreversible toxicity before it is diagnosed.

What is the mechanism?

Understanding the mechanism is always important. Some mechanisms of preclinical toxicity may be species specific and not relevant to human health.

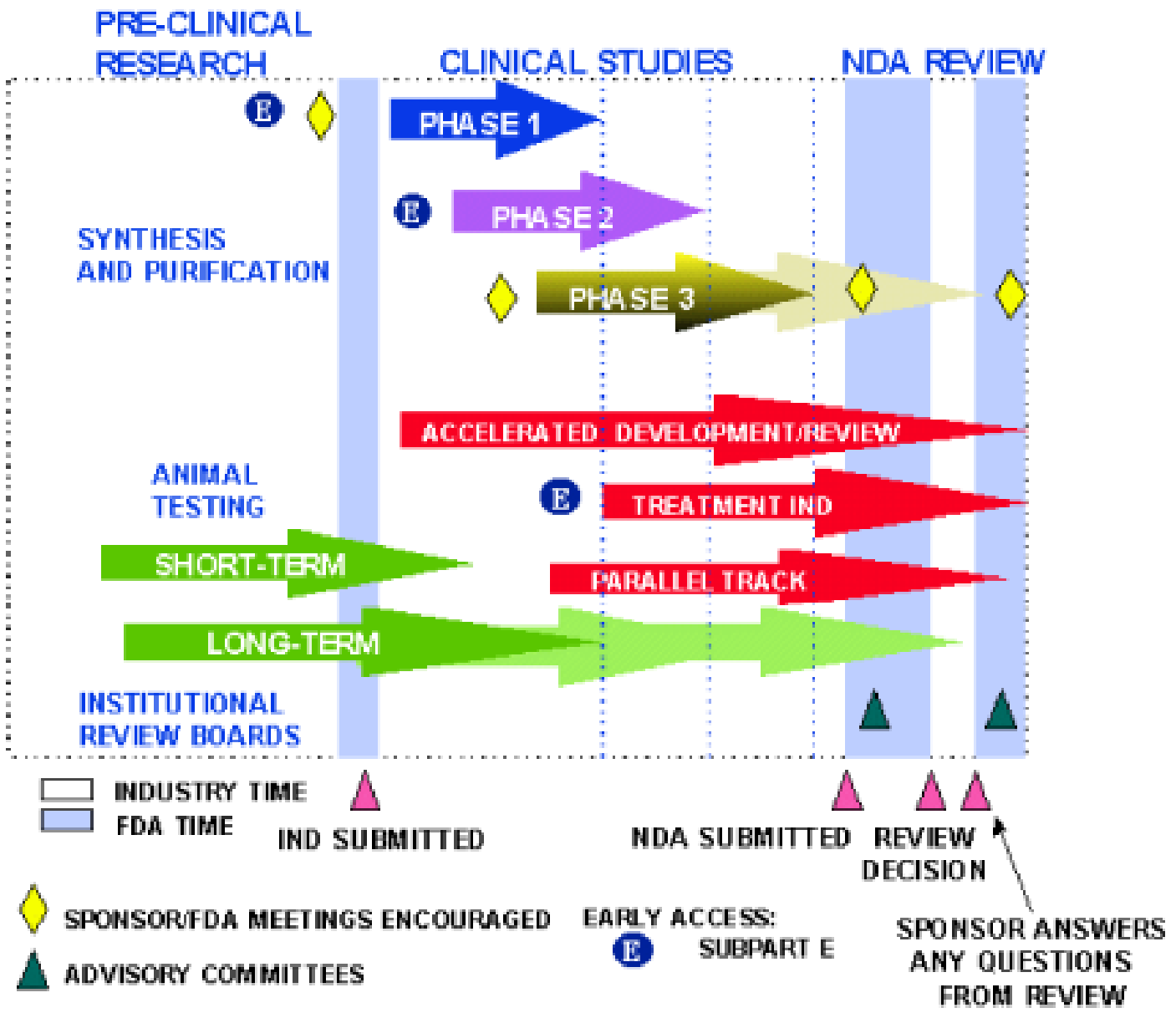
What is the relevance of the finding to humans?

The answers to the above questions will allow for an assessment of the risks of continuing to advance a particular compound into first-in-human trials.

Toxicology assessments

EXPERIMENTS	ENDPOINTS
Safety Pharmacology (in vitro, rodent, non-rodent)	Behaviour, function, physiology
General Toxicology (rodent & non-rodent)	Behaviour, function, physiology, clinical biochemistry, pathology
Genetic Toxicology (in vitro, in vivo)	Mutation, chromosomal changes
Carcinogenicity (rodents)	Non-genotoxic carcinogens
Reproductive & Developmental Toxicology (rodent & non-rodent)	Fertility, pregnancy, Fetal and peri/post-natal development

Steps from discovery to New Drug Application review: the role of FDA



Adapted from FDA website, 2014

Clinical development process: standard vs. orphan drugs

Clinical Study Phases	Standard Drug Development*	Orphan Drug Development† (For diseases that affect fewer than 200,00 patients in the United States)
Phase 1	• Generally 20-100 healthy volunteers • Safety • No efficacy studied • May include multiple doses	• Generally fewer than 10 patients • Safety • Initial efficacy • May include multiple doses
Phase 2	• Generally several hundred patients • Safety—short-term • Initial efficacy	• Generally 10-40 patients • Safety—short-term • Efficacy—how well the drug treats the disease; sometimes includes a placebo or other control (well controlled) • Could form the basis of FDA approval
Phase 3	• Generally 300-3,000 patients • Safety—longer-term • Efficacy—usually 2 well-controlled studies	• Generally up to 100 patients • Safety—longer-term • Efficacy—sometimes fewer than 2 well-controlled studies

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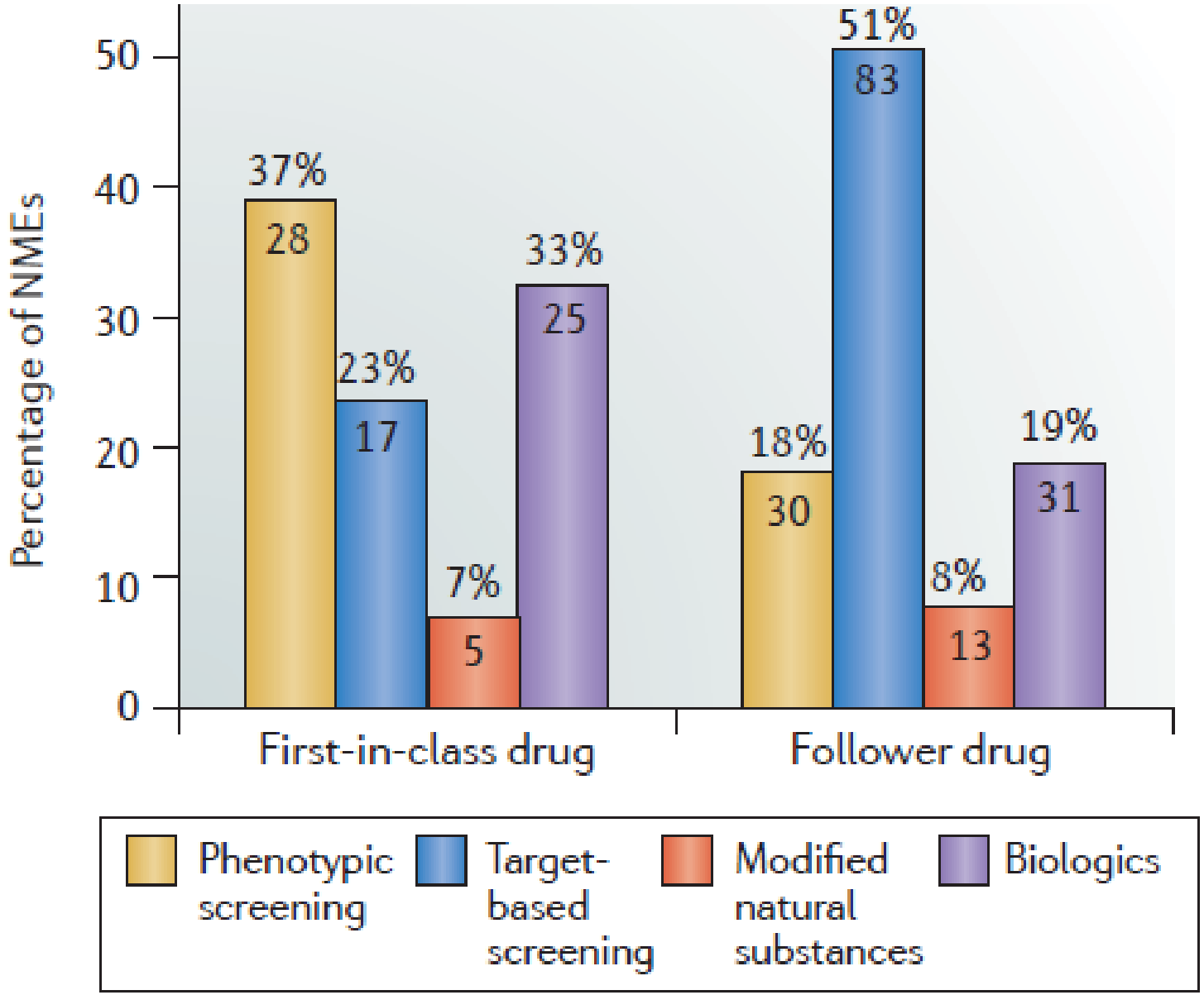
Adapted from FDA website, 2014

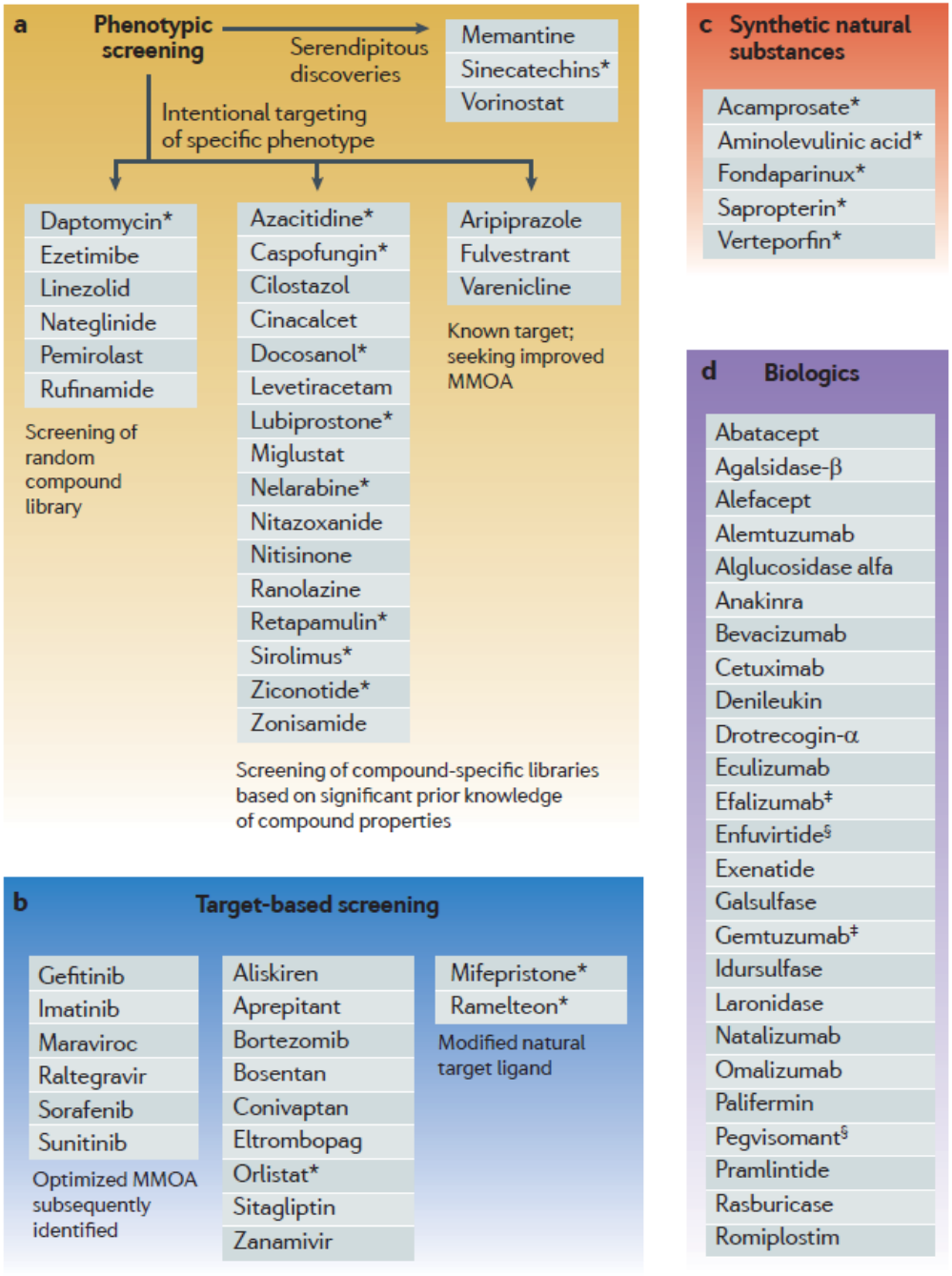
Protecting intellectual property

Discovery strategy for new drugs (1999-2008)



Swinney DC, Nature Rev Drug Disc. 10:507, 2011

Discovery strategies used to identify first-in-class medicines (1999-2008)



Swinney DC, Nature Rev Drug Disc. 10:507, 2011

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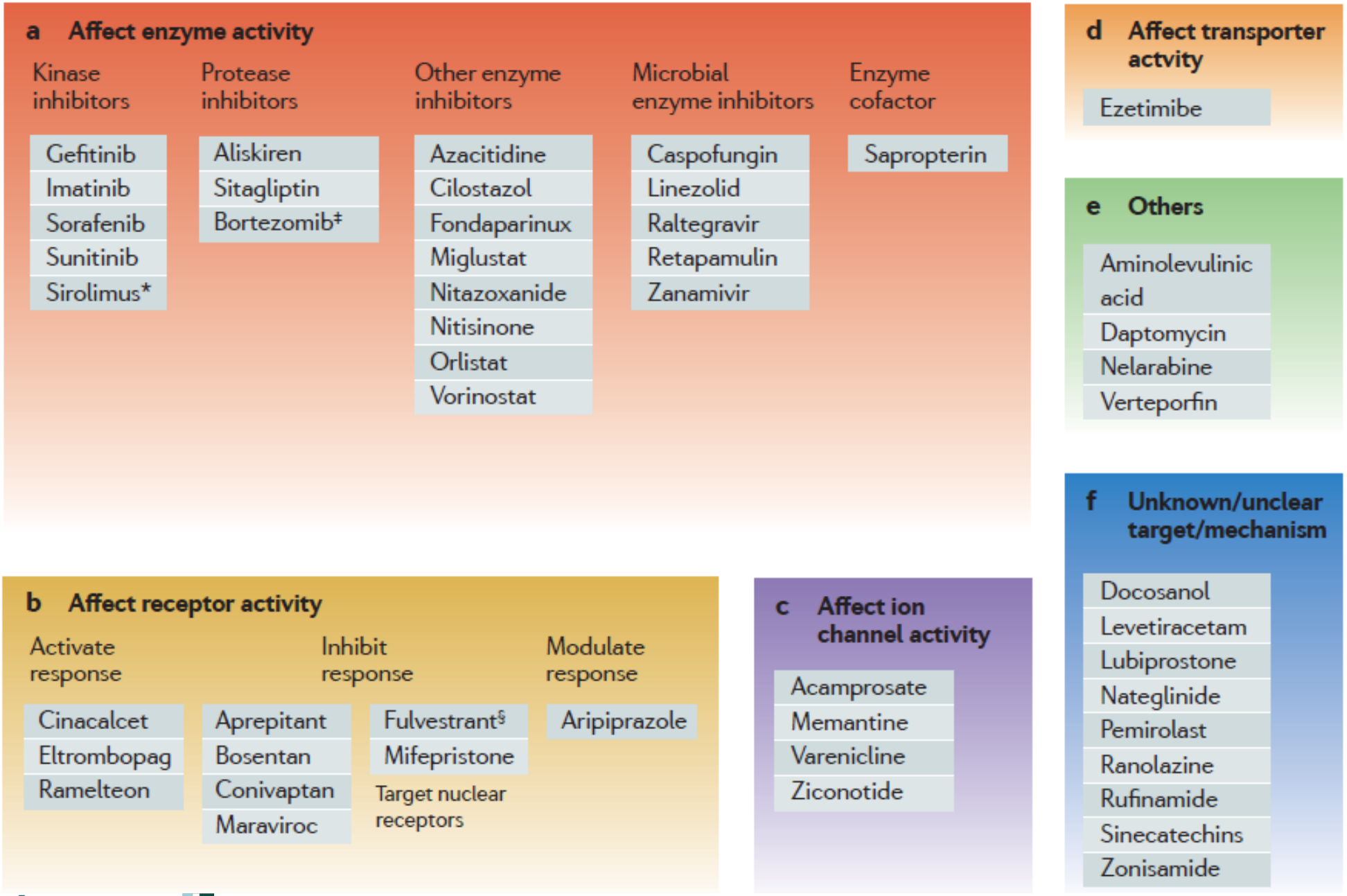
Discovery of first-in-class new molecular entities by therapeutic area (1999-2008)

Disease area	Target-based screening	Phenotypic screening	Biologics
Infectious diseases	3	7	1
Immune	1	0	6
Cancer	5	3	8
Central nervous system	1	7	1
Metabolic	3	2	2
Cardiovascular	2	3	0
Gastrointestinal	1	1	1
Others	1	3	1
Rare diseases	0	2	5

Swinney DC, Nature Rev Drug Disc. 10:507, 2011

Activities of first-in-class small-molecule new molecular entities approved in 1999-2008



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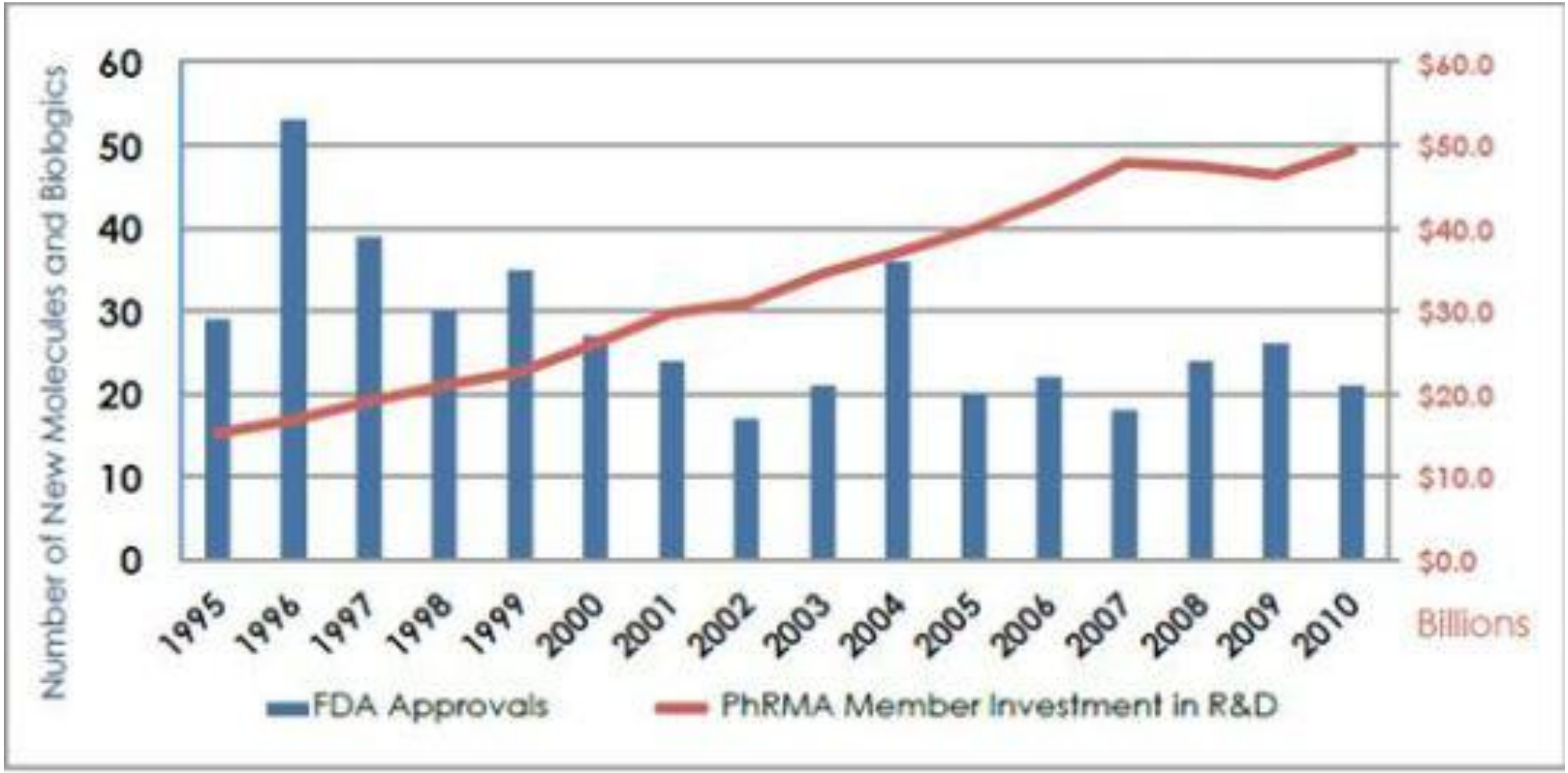
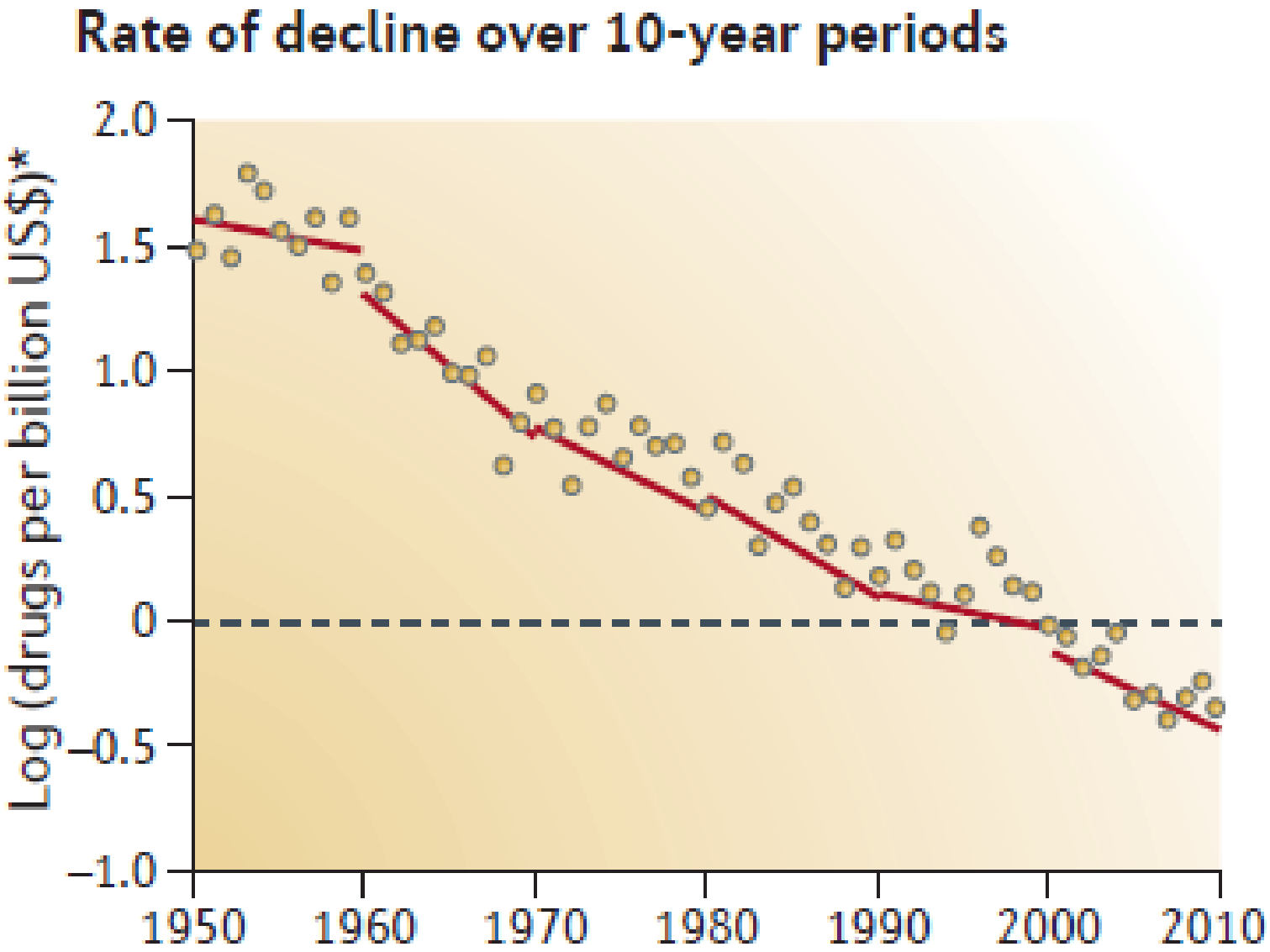
Swinney DC, Nature Rev Drug Disc. 10:507, 2011

FDA approvals vs. PhRMA R&D spending



Source: Data on FDA approvals obtained from FDA.gov 2011; Data on Pharma Investment from the Pharmaceutical Research Manufacturers of America, Profile 2011

Rate of decline in the approval of new drugs per billion US dollars spent in R&D



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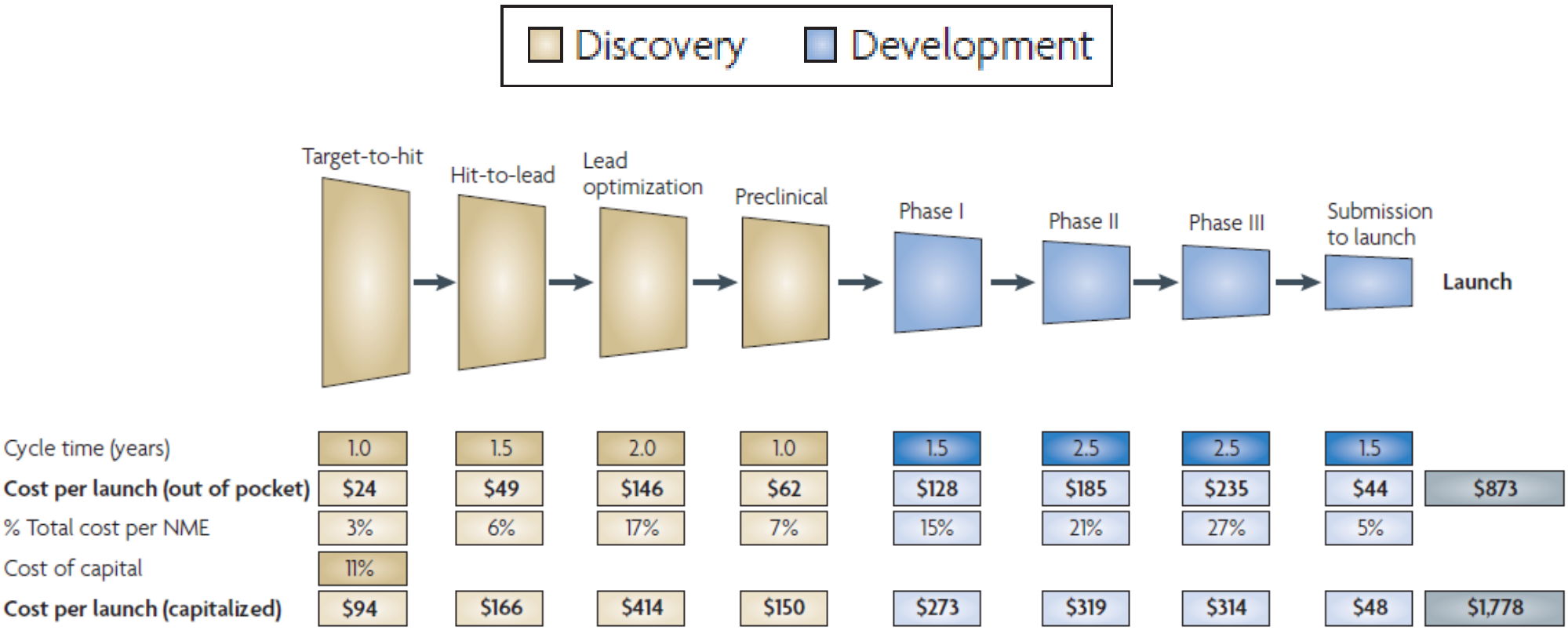
Scannell JW, Nature Rev Drug Disc. 11:191, 2012

R&D costs to successfully discover and develop a single new molecular entity



	Target-to-hit	Hit-to-lead	Lead optimization	Preclinical	Phase I	Phase II	Phase III	Submission to launch	
Cycle time (years)	1.0	1.5	2.0	1.0	1.5	2.5	2.5	1.5	
Cost per launch (out of pocket)	$24	$49	$146	$62	$128	$185	$235	$44	$873
% Total cost per NME	3%	6%	17%	7%	15%	21%	27%	5%	
Cost of capital	11%								
Cost per launch (capitalized)	$94	$166	$414	$150	$273	$319	$314	$48	$1,778

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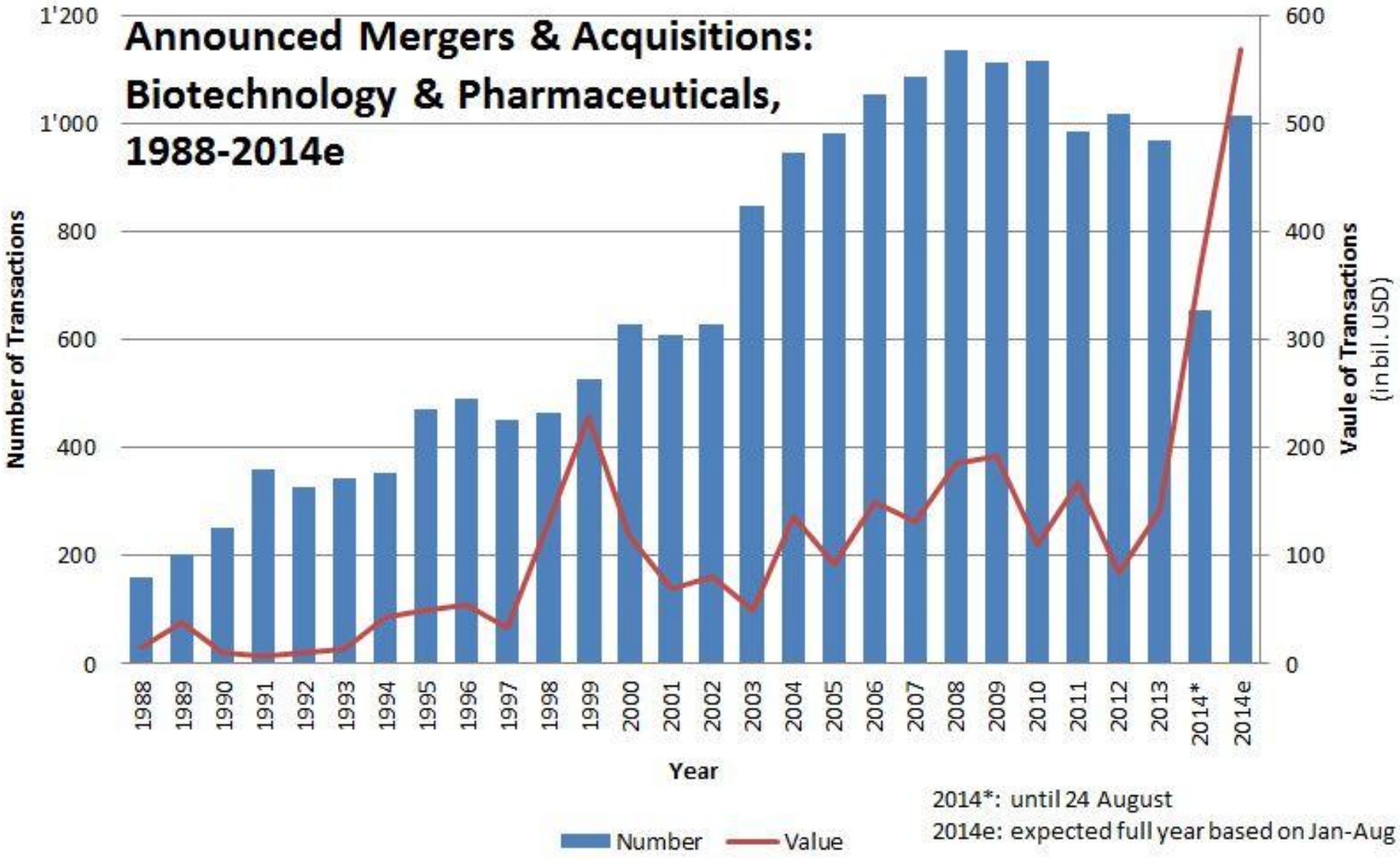
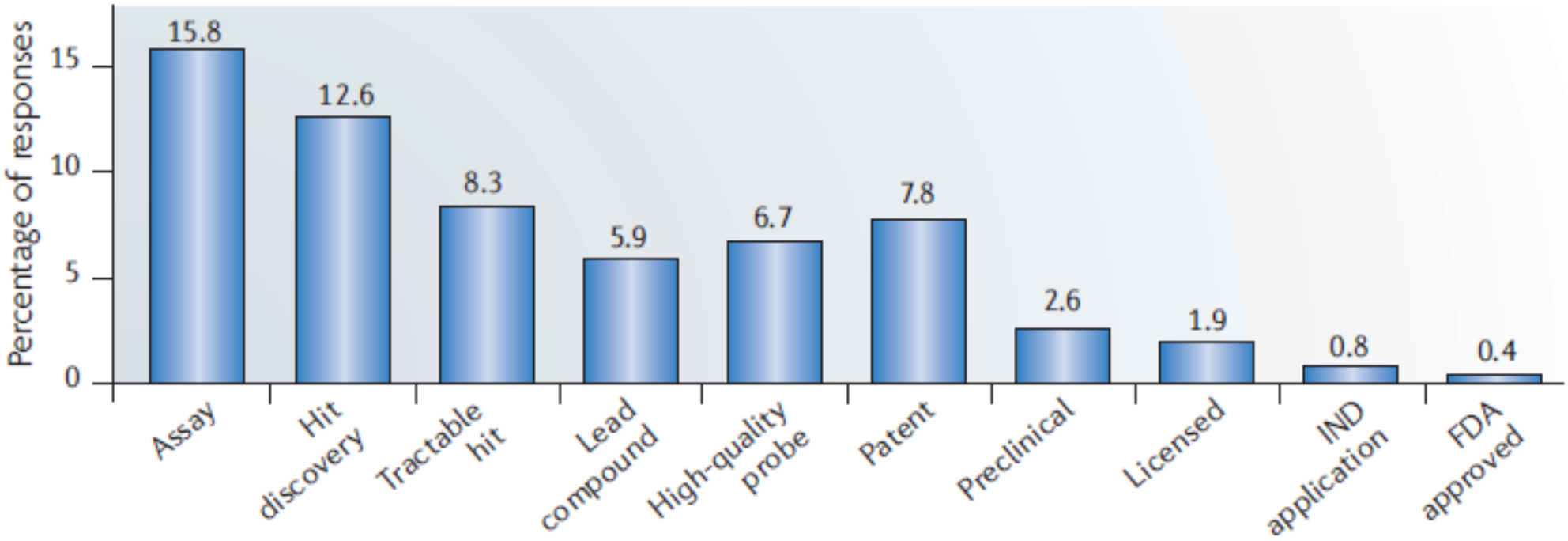
Paul SM, Nature Rev Drug Disc. 9:203, 2010

M&A activity: number and value of announced transactions in Biotechnology & Pharmaceuticals



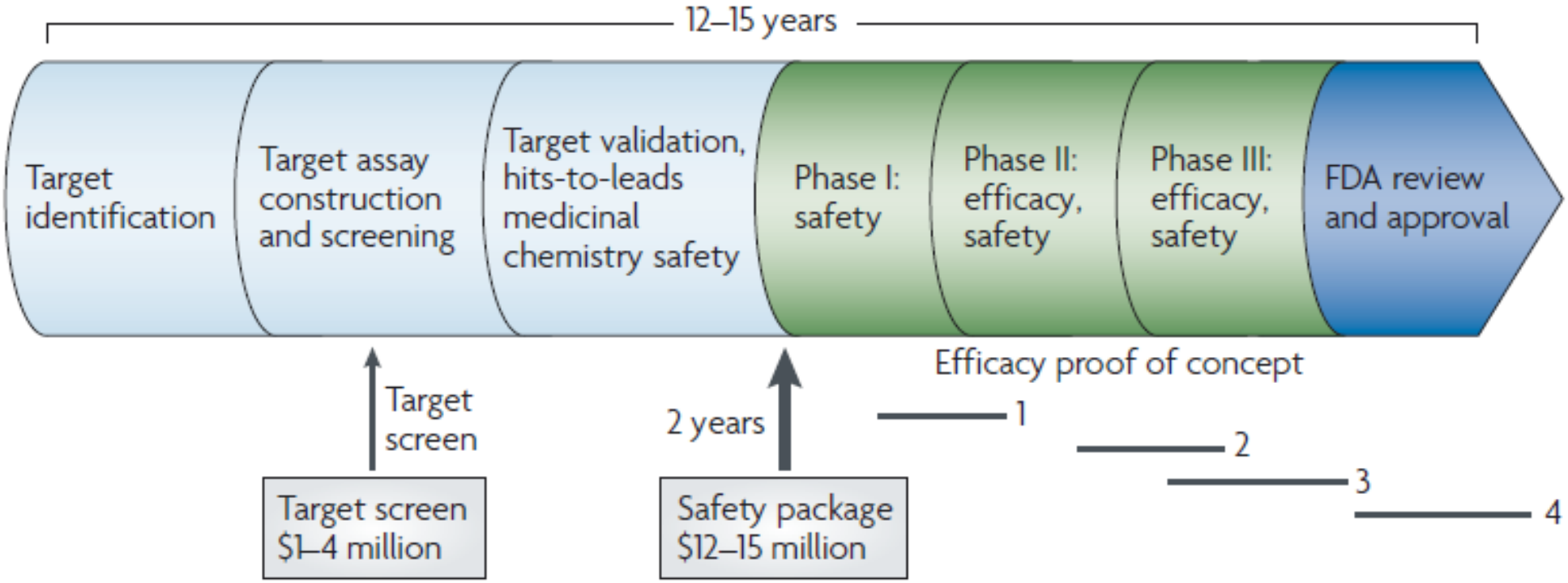
US academic drug discovery



Drug development pipeline by stage at 56 US academic centers

Frye S, Nature Rev Drug Disc. 10:409, 2011

Drug discovery and development: phases



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Roses AD, Nature Rev Drug Disc. 7:808, 2008

Intercept Highlights: OCA

- **OCA (obeticholic acid) is a first-in-class farnesoid X receptor (FXR) agonist**
  - OCA has successfully completed Phase 3 for orphan indication primary biliary cirrhosis, NDA submission in preparation (4Q 2014)
  - Two Phase 2 randomized trials met all primary ($p<0.0001$) and secondary endpoints
  - Patent terms projected through 2033
- **OCA Phase 2b trial for NASH stopped early for efficacy; met primary histologic endpoint**
  - Final results to be presented in 4Q 2014

OCA for PBC:
Attractive opportunity as second line therapy

Chronic Orphan Disease	■ PBC is an autoimmune cholestatic liver disease ■ Orphan drug designation in US and EU
Presentation & Diagnosis	■ Disease of women (10:1): 1 in 1,000 women >40 years old ■ Pruritus (itching) and fatigue are signature symptoms ■ Non-invasive diagnosis: elevated alkaline phosphatase & AMA
Significant Unmet Need	■ Up to 50% of PBC patients fail to respond adequately to SOC ursodiol therapy ■ Limited options for end-stage PBC patients: long liver transplant waiting list
Favorable Market Dynamics	■ Significant costs of treating complications of liver failure and liver transplant ■ Specialty care market with limited number of treating physicians
OCA Product Profile	■ Efficacy demonstrated in two Phase 2 and one Phase 3 trials ■ Well tolerated for >4 years ■ Ease of use with low single daily oral dose of 10 mg

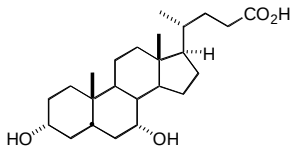
FXR: the Endogenous Bile Acid Sensor

1999: FXR – Orphan Adoption

Makishima, M. *Science* 1999, *284*, 1362
Parks, D. *Science* 1999, *284*, 1365
Wang, H. *Mol. Cell* 1999, *3*, 543–553

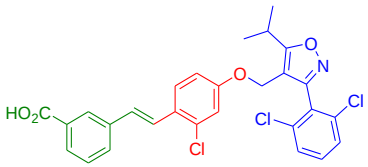
Farnesoid X Receptor (FXR)

Nuclear receptor expressed in liver, intestine, kidney, adrenal glands



CDCA (primary bile acid)

Discovery: FXR - bile acid receptor: CDCA natural ligand (1999)



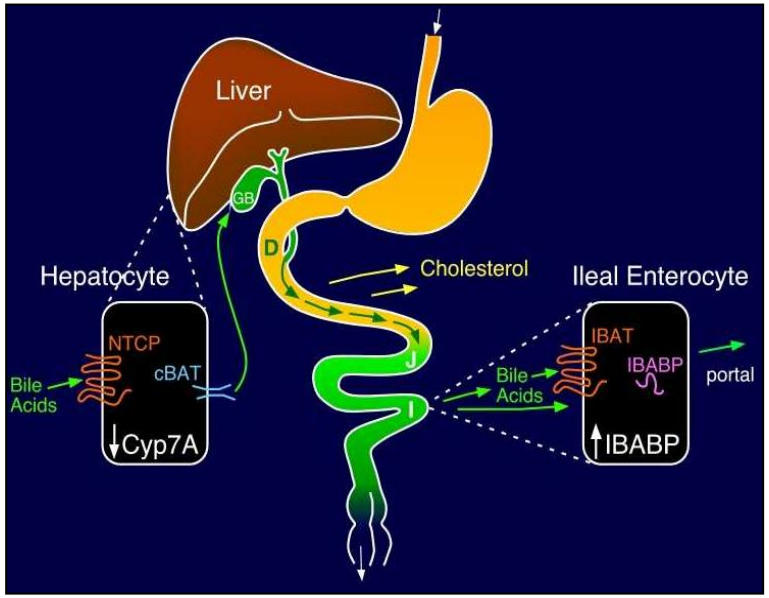
GW4064

Potent FXR agonist as a chemical tool compound developed (2000)

CYP7A1, SHP, BSEP, MRP2, MDR3, I-BABP

FXR target genes identified (2000)

- **FXR role in bile flow and biosynthesis regulation (2001)**



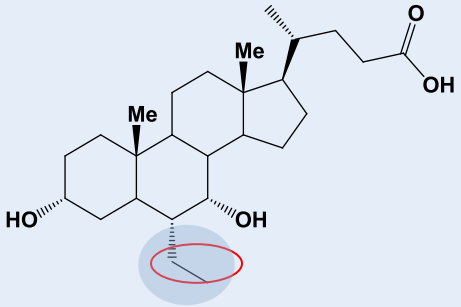
- **Concluded FXR agonist is a rational therapeutic approach to cholestatic diseases (2002)**

FXR - a new understanding of bile acids as hormones with potential for multiple therapeutic clinical indications

OCA: Potent first-in-class FXR agonist and bile acid analog

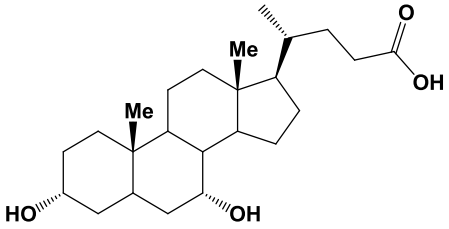
- Proprietary capability to rationally modify bile acids to efficiently generate potent NCEs

OCA (6E-CDCA)
obeticholic acid

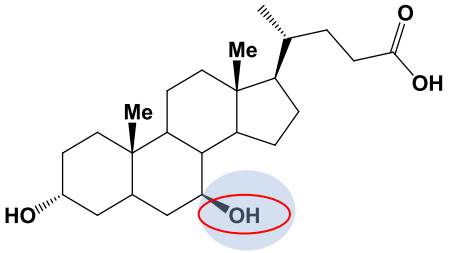


6-α ethyl substitution

CDCA
chenodeoxycholic acid



UDCA
ursodeoxycholic acid



Epimer of CDCA

FXR EC_{50}	**0.09 µM**	**8.6 µM**	**No activity**

~100x increased potency

OCA

- Close analog to bile acid CDCA but **100x more potent on FXR**
- Metabolic stability
- First-in-class with novel mechanism of action

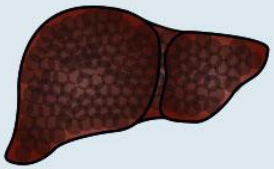
CDCA

- Endogenous FXR agonist

UDCA (Ursodiol)

- Only product approved for PBC
- Displaces more detergent bile acids in pool
- **No FXR activity**

OCA modulates key FXR-dependent pathways in multiple animal models

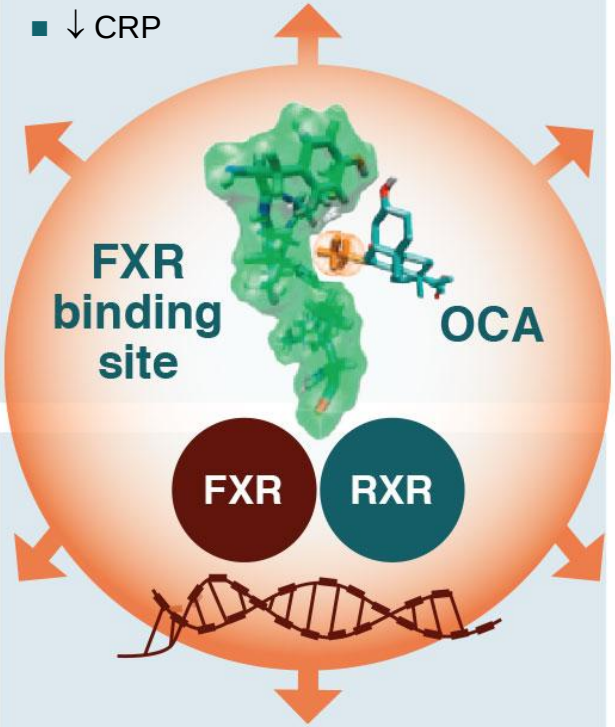


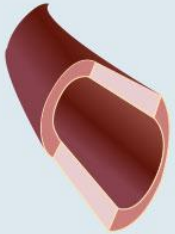
FIBROSIS

- ↓Stellate cell activation (PDGF)
- ↑Stellate cell apoptosis (TIMP-1)
- ↓Fibrogenesis (TGF-β1)
- ↑Matrix degradation (MMP-2)

INFLAMMATION

- ↓ NF-κB
- ↓ TNFα, IL-1β, IL-17, IFN-γ, etc.
- ↓ IgM
- ↓ CRP





ATHEROSCLEROSIS

- ↑Vasodilation (eNOS)
- ↓Inflammation (COX-2, IL-1β, etc.)
- ↓Calcification (JNK)
- ↓Smooth muscle cell migration (PDGF)

LIPID METABOLISM

- ↓Triglyceride synthesis (SREBP-1c)
- ↑Triglyceride clearance (apoC-III)
- ↓VLDL formation (MTP)
- ↓HDL-C (SR-B1, CETP)
- ↑LDL-C (CETP)

GLUCOSE METABOLISM

- ↑ Insulin signaling (FGF19)
- ↑ Insulin sensitivity (IRS-1, IRS-2)
- ↑ Insulin production (KLF11, GLUT-2)
- ↓ Hepatic gluconeogenesis (PEPCK)

BILE ACID HOMEOSTASIS

- ↓ Bile acid synthesis (CYP7A1)
- ↓ Bile acid uptake (NTCP)
- ↑ Bile acid secretion (BSEP)
- ↓Bile acid absorption (ASBT)

OCA clinical development in PBC

All trials randomized, double-blind, placebo-controlled with long-term safety extension (LTSE) phases

	Trial	Description	Duration	N=	Dose	Status
Phase 3	POISE	Combination therapy in non-responders on ursodiol	1 year	217	5 mg or 10 mg	Double-blind phase completed: met primary and secondary endpoints: >95% in LTSE
Phase 2	202	Combination therapy in non-responders on ursodiol	12 weeks	165	10 mg, 25 mg or 50 mg	Completed: met primary and secondary endpoints
	201	Monotherapy in treatment naïve or ursodiol-intolerant patients	12 weeks	59	10 mg or 50 mg	Completed: met primary and secondary endpoints

OCA in PBC: regulatory path to approval

EU Regulatory Status

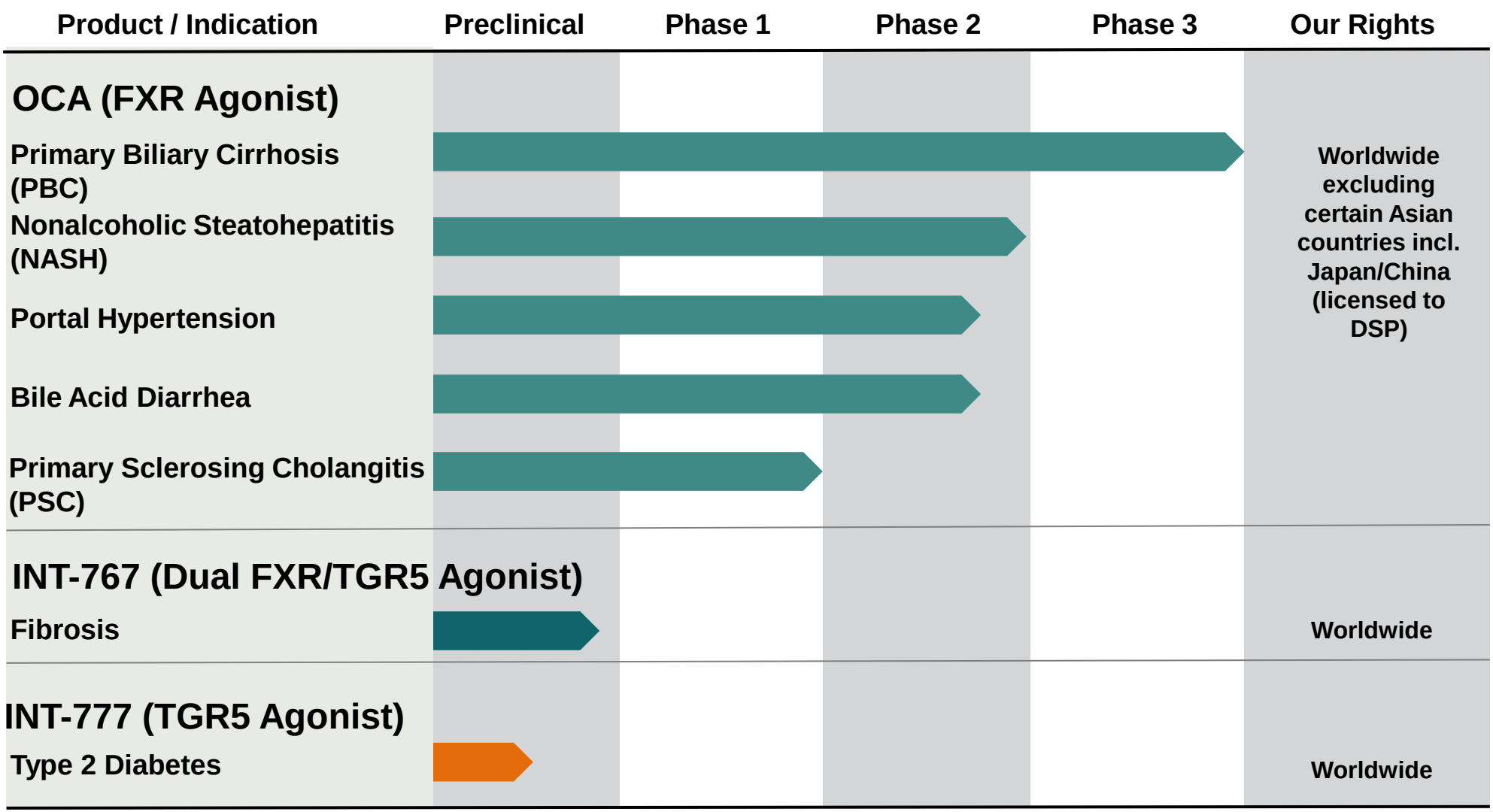
- **POISE trial designed in accordance with EMA scientific advice concerning requirements for approval of OCA for PBC**

US Regulatory Status

- **Company intends to file with FDA for accelerated approval (under Subpart H), conditional on conducting an additional Phase 3 confirmatory clinical outcomes trial for full approval**
  - **Confirmatory trial design being finalized with FDA**

Leader in bile acid-derived therapeutics: Intercept's pipeline

- Current clinical focus primarily on chronic liver diseases with high unmet medical needs



PBC: medical management

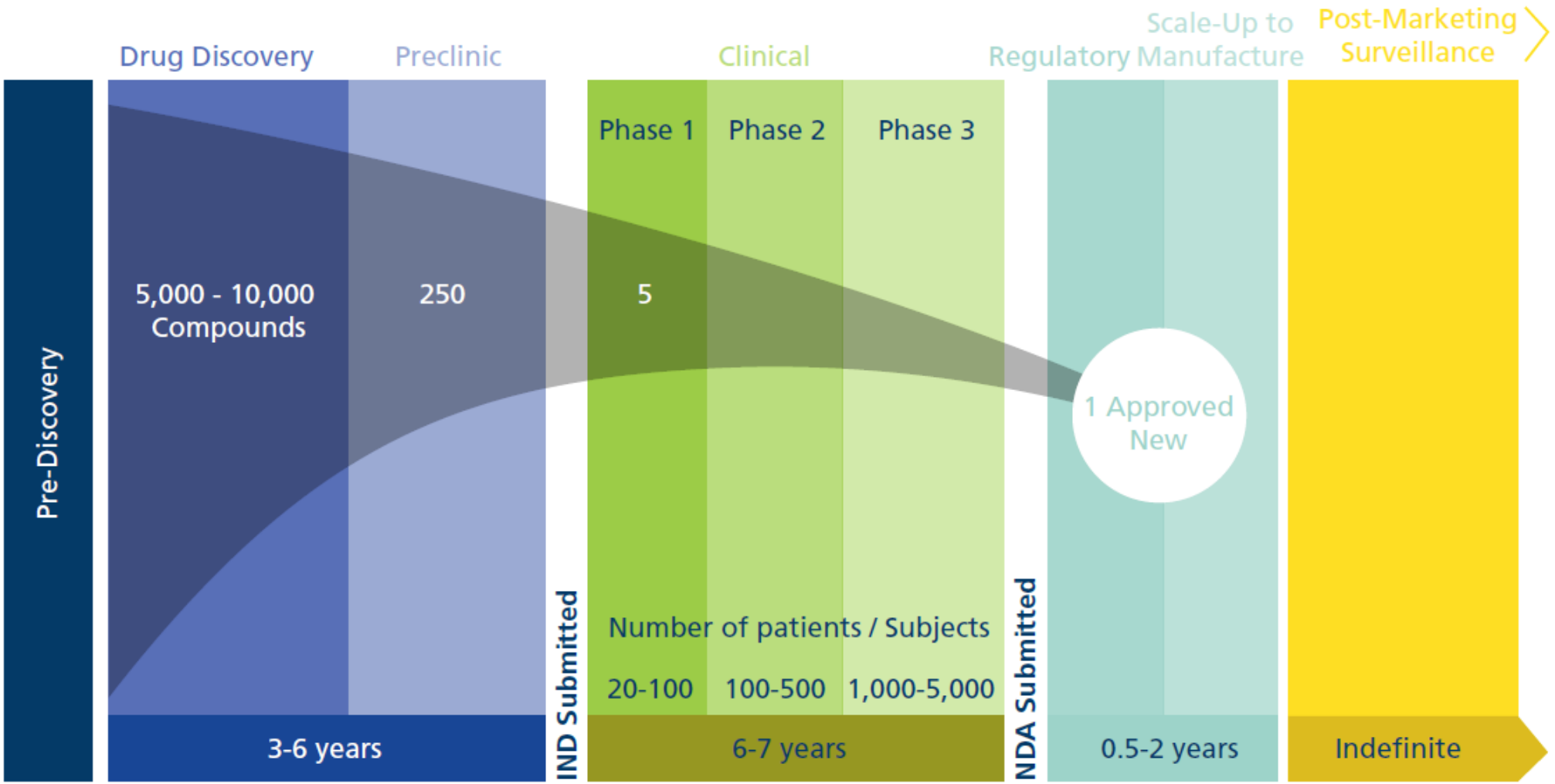
Ineffective

- Penicillamine
- Colchicine
- Chlorambucil
- Corticosteroids
- Azathioprine
- Cyclosporine
- Methotrexate
- Mycophenolate mofetil
- Rituximab (anti-CD20)
- Ustekinumab (anti-IL-12/IL-23)

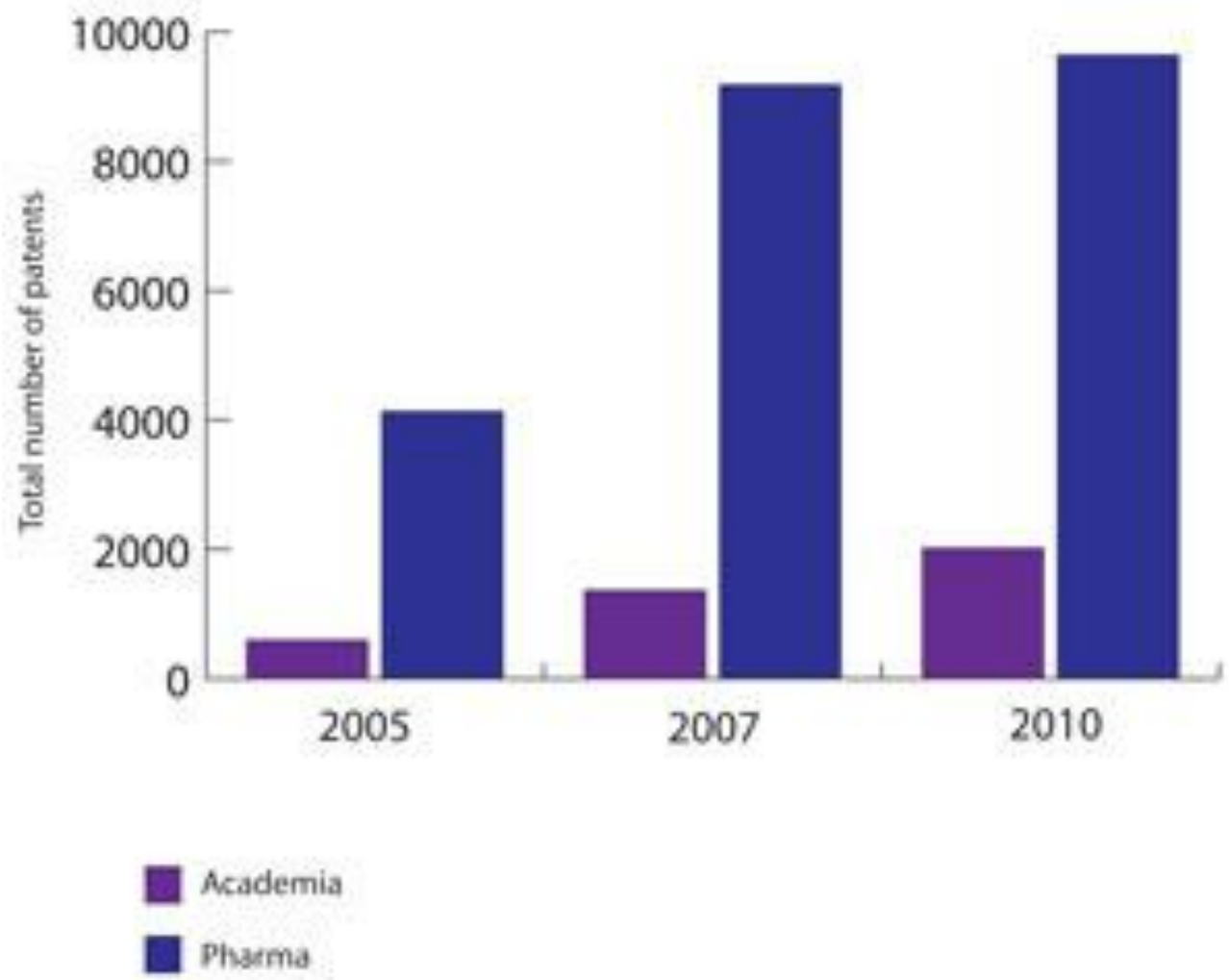
Effective

- Ursodeoxycholic acid (UDCA)
- Obeticholic acid (OCA)

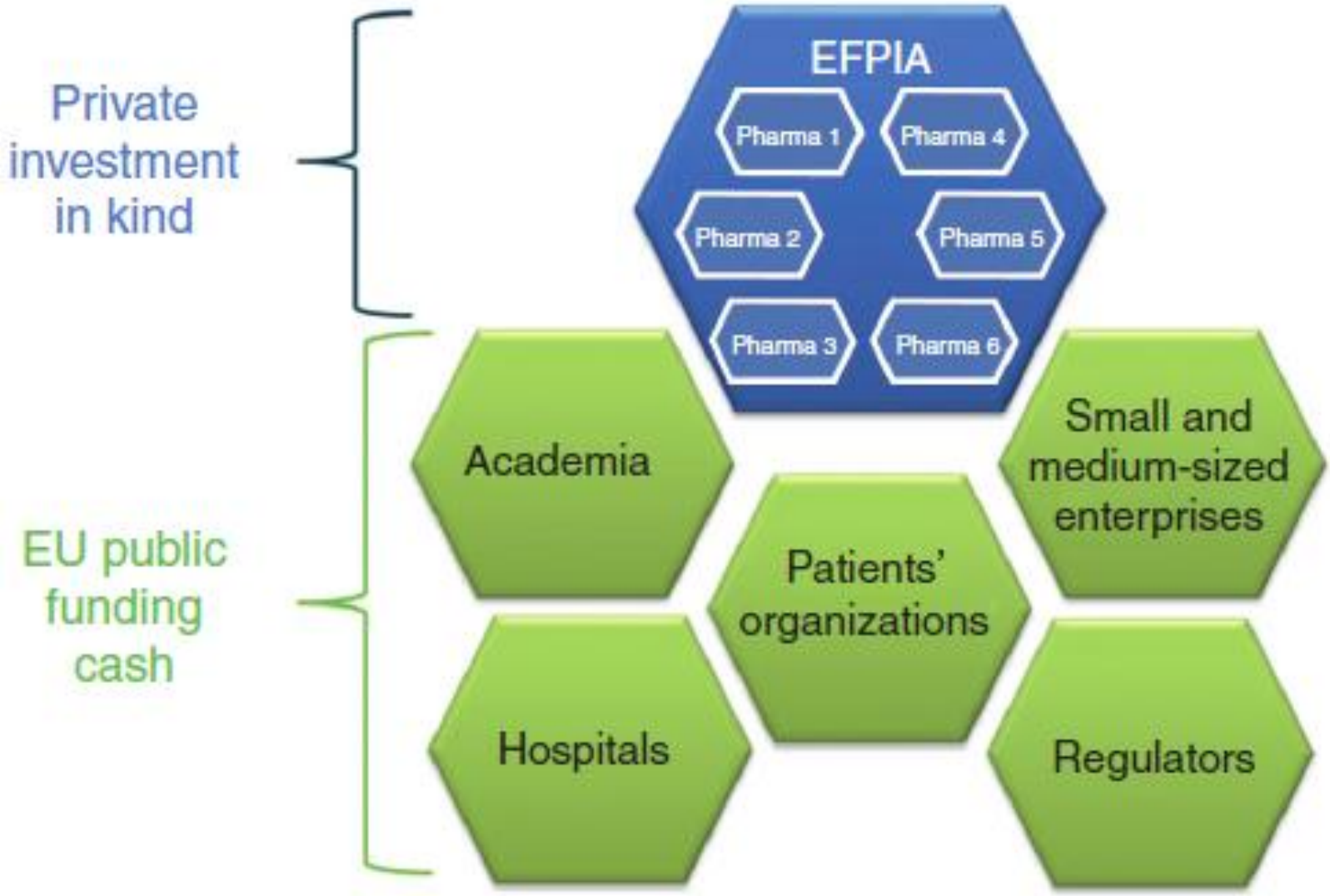
Pharmaceutical R&D Process



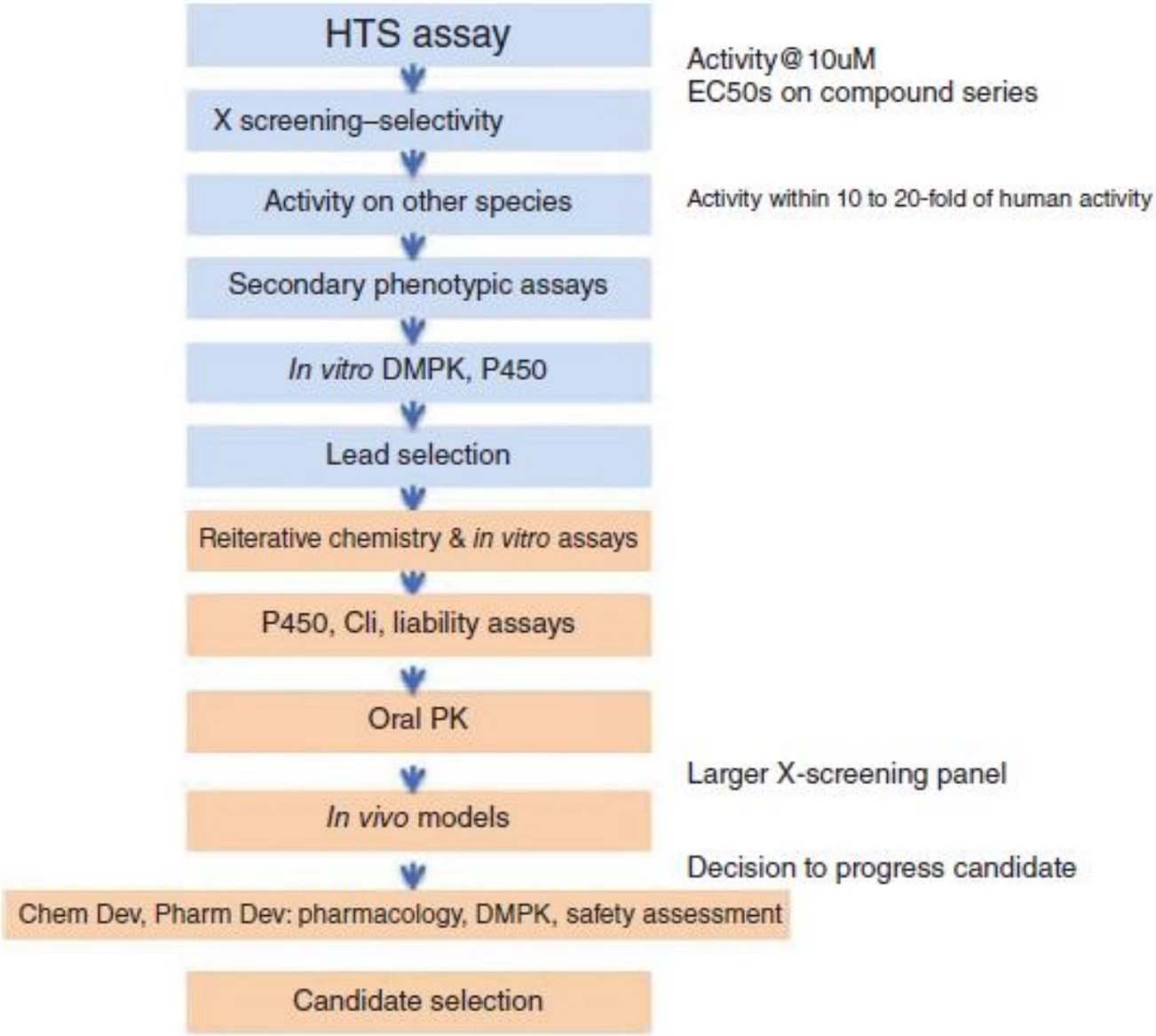
The Patent Output by Academia is Increasing



Public-Private Partnership: the Innovative Medicines Initiative



Hypothetical screening cascade



Hughes S, Br J Pharmacol. 162:1239, 2011

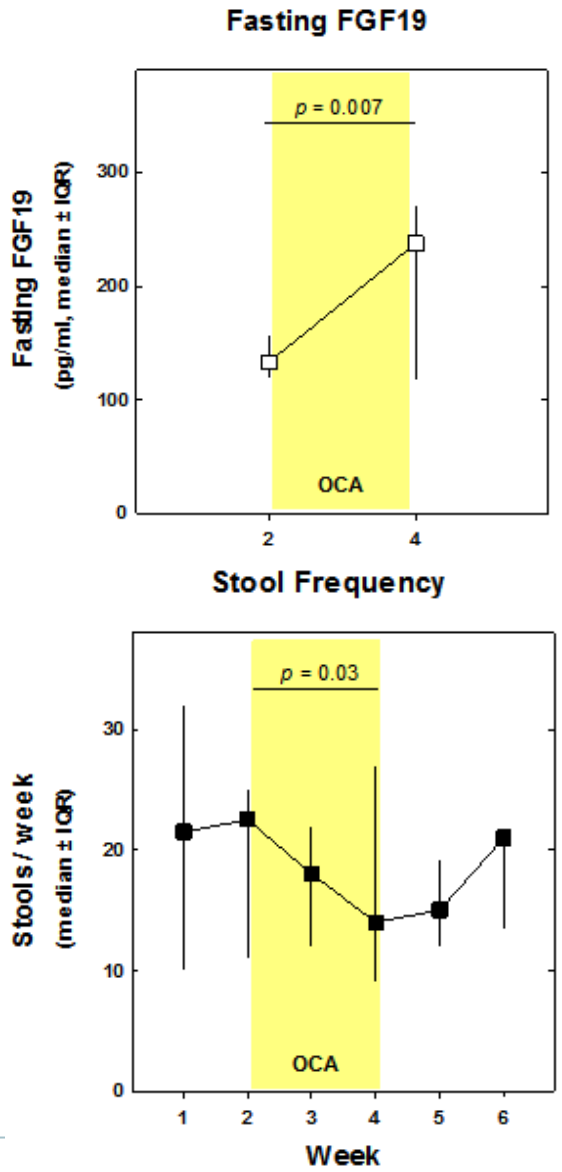
OCA for Bile Acid Diarrhea : Background

- Primary bile acid diarrhea (BAD) accounts for up to an estimated 1/3 of all IBS-D patients (i.e., up to 1% of the general population)
  - FGF19 production defect: no ‘shut off’ signal for bile acid production
  - Patients have high bile acid production and resulting chronic diarrhea
- Secondary bile acid diarrhea occurs in Crohn’s patients (potential orphan indication)
  - Deficient FGF19 due to insufficient ileal surface area
- Current treatment is with bile acid sequestrants (e.g., cholestyramine)
  - However, ~20% of primary BAD patients do not respond
  - Non-response in Crohn’s ~60% with surgical resection
- Rational therapeutic approach with OCA: FGF19 is directly regulated by FXR
  - Dose dependent induction by OCA seen in 3 completed Phase 2 trials

OCA for Bile Acid Diarrhea: Phase 2a OBADIAH Trial

- OBADIAH: Phase 2a trial in 30 patients (3 cohorts)
  - Primary BAD
  - Secondary BAD (Crohn's / ileal resection)
  - IBS-D (normal FGF19 –control group)
- Final results:
  - OCA increased FGF19 in pBAD & sBAD
  - No response in control group, as expected
  - Concomitant clinical improvements, including stool frequency, Bristol Stool Form Scale
  - **Results to be presented at DDW (May 2014)**
- Phase 2b to be initiated in 2H14 in sBAD

Interim Data (pBAD cohort)



Primary Sclerosing Cholangitis (PSC): Overview

- PSC is an autoimmune cholestatic liver disease: highly synergistic with PBC
  - Prevalence is ~1/3 of PBC: occurs in men 3:2 to women
  - Typically more complicated and aggressive course than PBC
    - Often see biliary obstruction & infections of biliary tract
    - Majority of patients have co-morbid ulcerative colitis
    - Increased incidence of cholangiocarcinoma & liver cancer
- Orphan indication with high unmet need: no approved treatment
  - Urso often used, although high dose is contraindicated
- ALP could potentially be used for approval based on evidence that <1.5x ULN correlates with good outcomes
  - Plan to initiate a multi-center, double-blind, placebo-controlled, randomized Phase 2 trial in 2H 2014

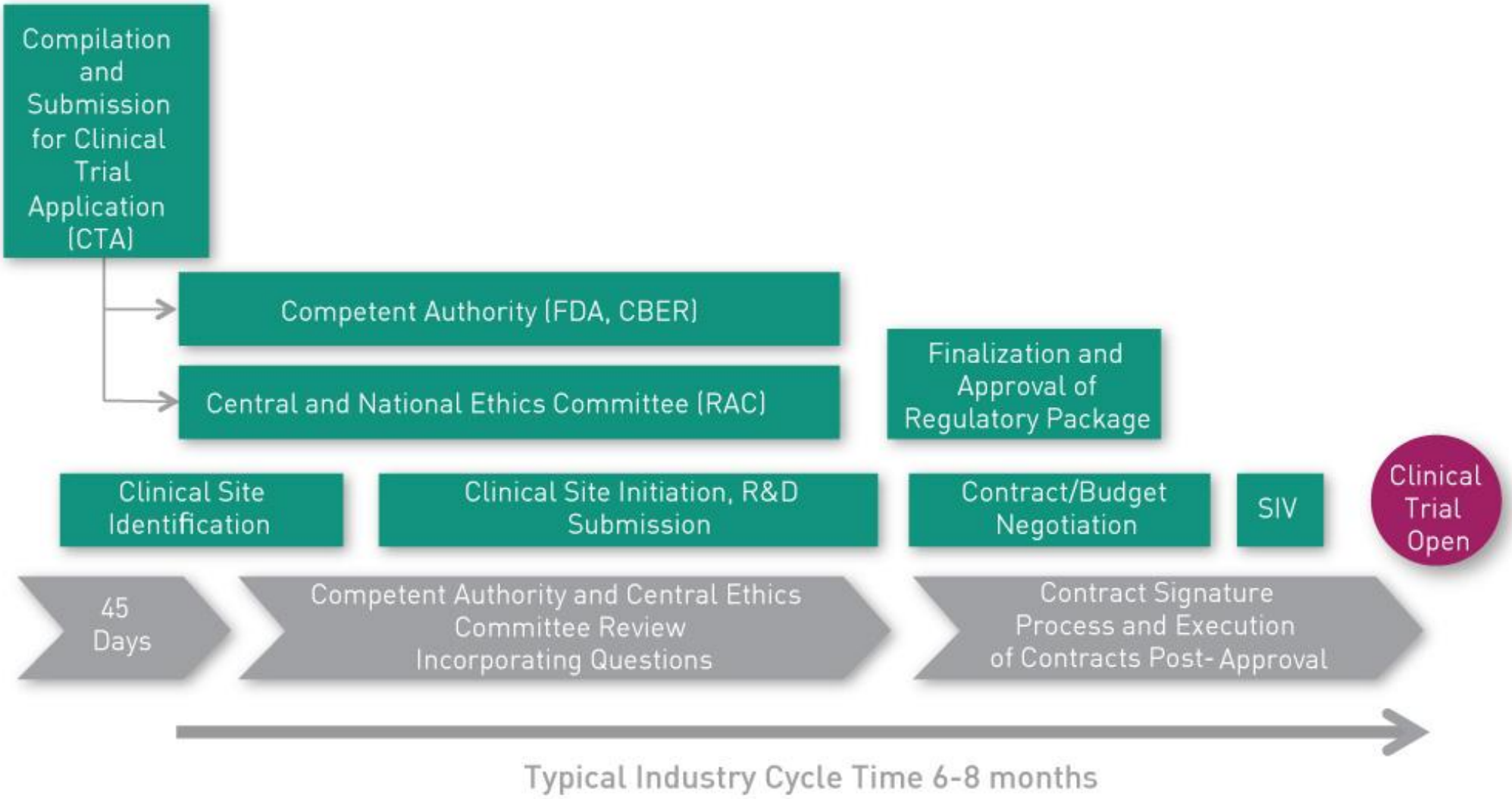
Alcoholic Hepatitis: Overview

- Alcoholic hepatitis (AH) typically presents as an acute episode in alcoholic liver disease
  - Associated with acute liver damage and significant mortality risk in severe cases
- Potential orphan indication synergistic with portal hypertension
  - Large proportion of AH patients have portal hypertension
  - Treated in hospital but envision many patients would stay on OCA chronically
- NIH's NIAAA is funding an AH consortium to conduct POC studies
  - Mayo Clinic, U. Indiana, Virginia Commonwealth
  - Selected OCA for hepatoprotective properties and sponsoring a 60-patient study in moderate alcoholic hepatitis (i.e., optimal population for therapy)
- Potentially challenging indication
  - Difficult population to treat and approval likely based on 30 day mortality

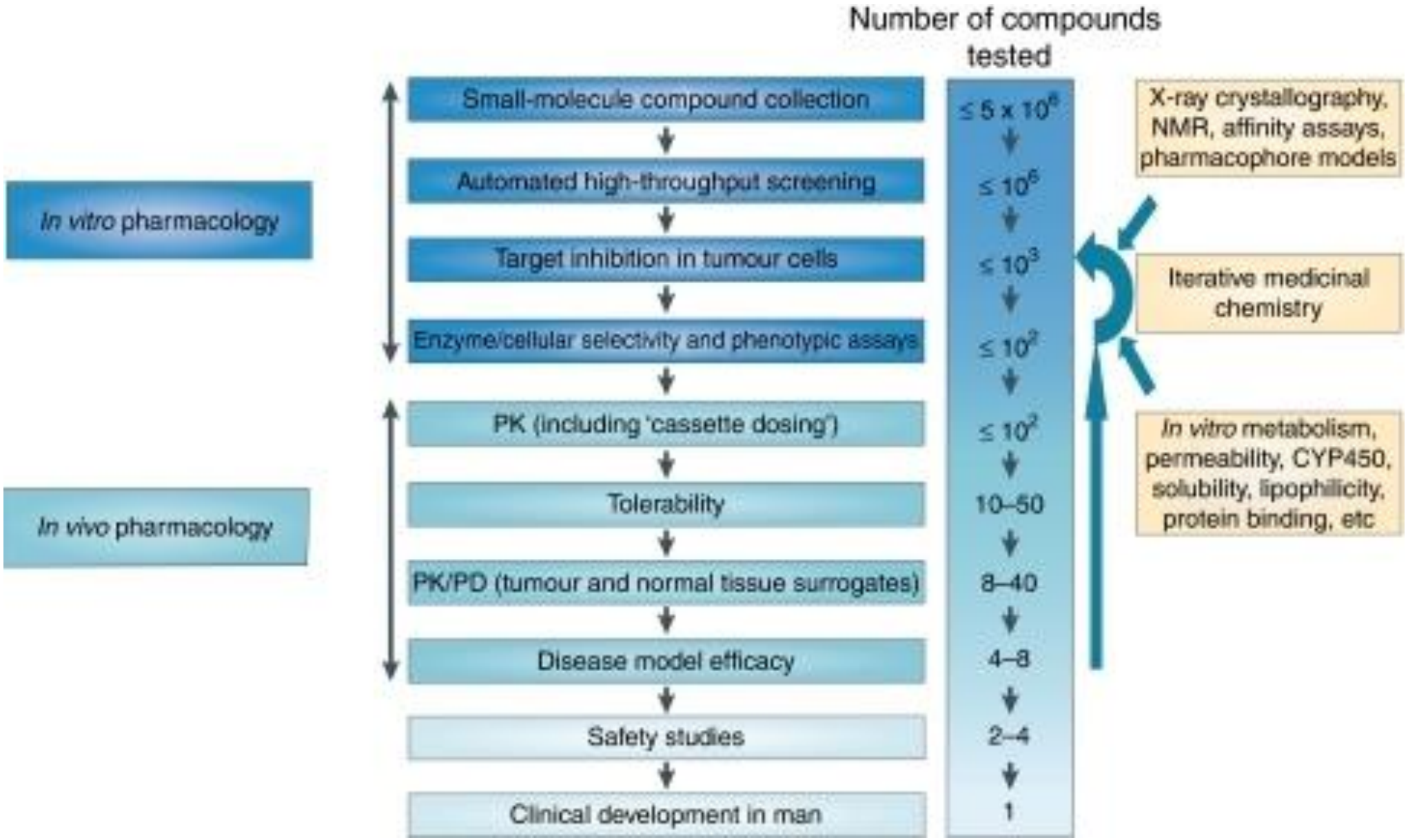
Biliary Atresia: Overview

- Biliary atresia is a congenital cholestatic liver disease
  - Ultra orphan indication: ~1/10,000 live births
  - Marked by blockage or absence of common bile duct with resulting need for liver transplant
  - Kasai surgical bypass procedure can facilitate bile flow: not curative but buys time prior to liver transplant
- OCA therapy in post-Kasai patients has strong scientific rationale
  - Stimulate bile flow and reduce cholestatic liver damage
- Synergistic with PBC and fulfills pediatric regulatory requirements

Regulatory Strategy to Clinical Trial Initiation



Hypothetical screening cascade



Workman P, Br J Cancer. 102:1555, 2010

Regulatory Strategy to Clinical Trial Initiation