Drug Discovery Workshop

Eric Chatelain, PhD

Chagas Plataforma / Rede Leish
Rio de Janeiro, 6th June 2016

DNDi
Drugs for Neglected Diseases *initiative*

Agenda

8:30-8:40 Greetings – Introduction (Fabiana Barreira/Mady Barbeitas, DNDi)

8:40-9:10

- The Path to a Candidate: A multidisciplinary Effort and a lot of Hurdles (Eric Chatelain, DNDi)

9:10-9:50

- Chemical Matter: the Good, the Bad and the Ugly (Luiz Carlos Dias, UNICAMP)

9:50-10:30

- *In vitro* screening assays: HTS/HCS and secondary assays (Carolina Borsoi-Moraes, LNBio)

10:30- 10:50 COFFEE BREAK

10:50-11:30

- Drugs for Chagas and Leishmaniasis from a translational medicine perspective (Facundo Garcia Bournissen, Hospital de Ninos, Argentina)

11:30-12:10

- Exploring drug efficacy in experimental Chagas disease using highly sensitive bioluminescence imaging (John Kelly, LSHTM)

12:10-12:50

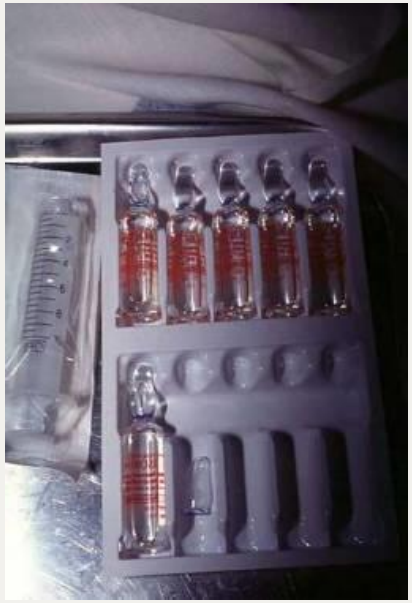
- Discovery of biomarkers for diagnostics and treatment efficacy assessment: from the “eye” to the –omics (Momar Ndao, McGill University)

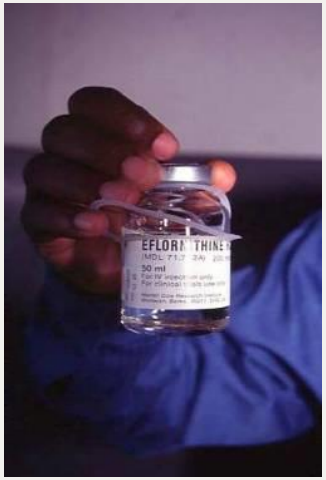
12:50-13:00 Wrap-up/ Conclusions

The Path to a Candidate
A Multidisciplinary Effort
and a Lot of Hurdles

The Context

Neglected Diseases
Why New Chemical Entities (NCEs)?
Why Discovery?



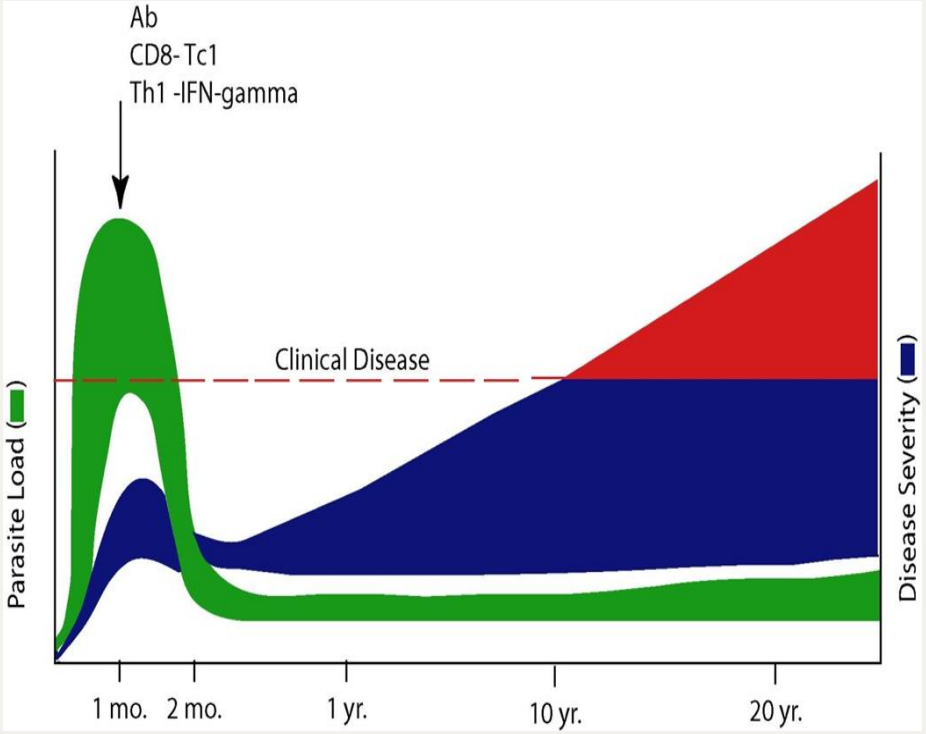


- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to use and not adapted to the field
- Not registered in endemic regions
- Restricted by patents

To respond to specific needs in endemic countries

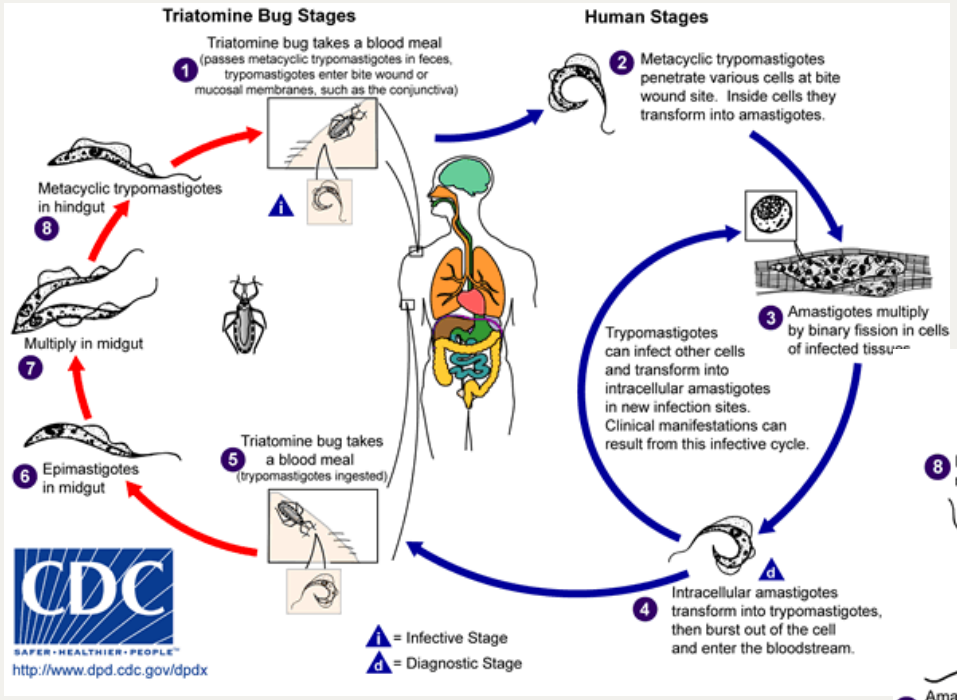
Diseases with Complex Pathologies

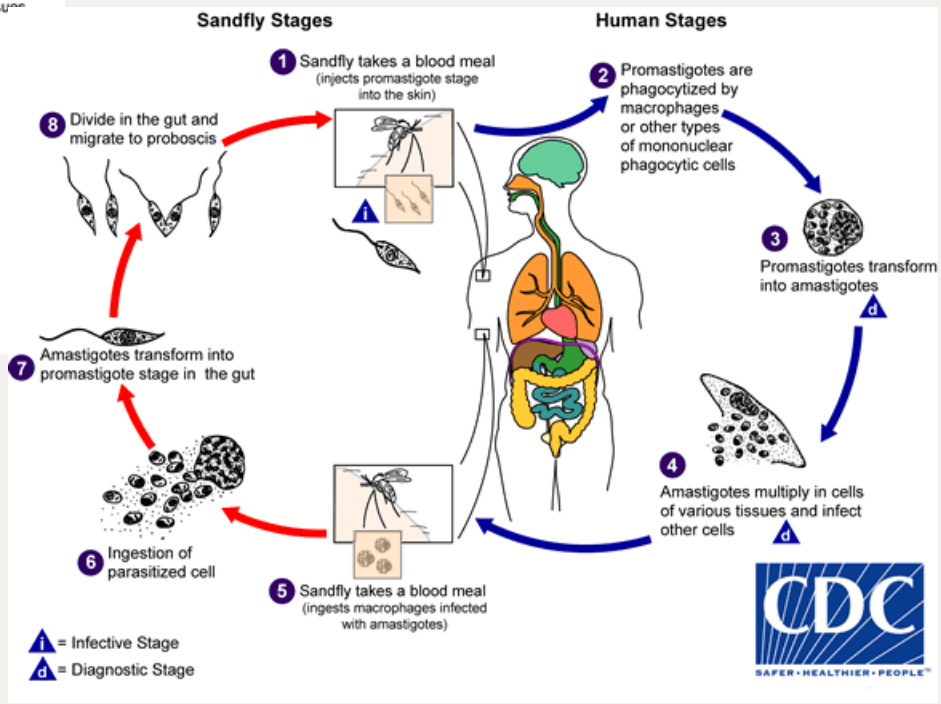
- Chagas disease
  - Understanding the disease, its pathology, factors related to progression of the disease
- Leishmaniasis
  - Wide clinical spectrum
  - VL, CL, MCL, PKDL
- Host/Parasite interactions



(Tarleton, 2003)

Complex Parasite Life Cycle





Complexity of Drug Development Process

- Long
- Complicated and dependent upon the expertise of a wide variety of scientific, technical and managerial groups
- Costly
- Risky (attrition rate)

In Short……

→ Lots of Hurdles

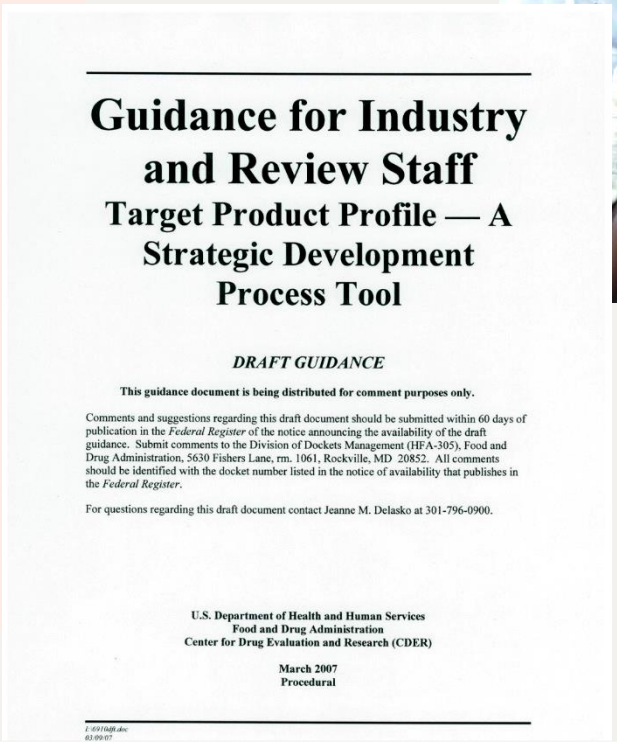
Where do we start?
Driver's Documents

Beginning With The End In Mind
The Target Product Profile (TPP)

Patient Needs-Driven: Definition of the Target Product Profiles with experts of endemic countries, researchers, clinicians, control programmes, patients associations, WHO, etc.

TPP Criteria

- Indications
- Population
- Clinical Efficacy
- Safety and Tolerability
- Stability
- Route of Administration
- Dosing Frequency
- Cost



Guidance for Industry and Review Staff
Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Jeanne M. Delasko at 301-796-0900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural

Target Product Profile* for VL NCEs

	Optimal Target Profile	Minimal Target Profile
Target Label	VL and PKDL	VL
Spp	All species	*L. donovani*
Distribution	All areas	Either India or Africa
Target Population	Immunocompetent and immunosuppressed	Immunocompetent
Clinical Efficacy	> 95%	> 90%
Resistance	Active against resistant strains	
Safety and Tolerability	No AEs requiring monitoring	1 monitoring visit in mid/end - point
Contraindications	None	Pregnancy/lactation
Interactions	None - Compatible for combination therapy	None for malaria, TB, and HIV concomitant therapies
Formulation	Oral / im depot	Oral / im depot
Treatment Regimen	1/day for 10 days po/ 3 shots over 10 days*	bid for <10 days po; or >3 shots over 10 days
Stability	3 yrs in zone 4	Stable under conditions that can be reasonably achieved in the target region (> 2 yr)
Cost	< $10 / course	< $80 / course

DNDi

* This is for primary VL only - PKDL, HIV co-infection and relapse case treatments may require longer treatment durations

VL Draft Target Candidate Profile (TCP)

to select optimised leads with the potential to meet the TPP for VL

	Acceptable (Functional Cure)	Ideal (Sterile Cure)
Efficacy		
In vivo:	>95% reduction in parasitemia in liver & spleen in mouse or hamster model with *L. donovani*	100% reduction in parasitemia in liver & spleen in mouse or hamster model with *L. donovani & L. infantum*
In vitro:	Consistent activity within 10x *vs.* a panel of drug sensitive and drug resistant strains and isolates from India and E. Africa	Consistent activity within 10x *vs.* a panel of drug sensitive and drug resistant strains and isolates from India and E. Africa
	In vitro: E_{max} >99%[1]	*In vitro:* E_{max} >99% Cidal mechanism of action
Safety		
In vitro:	No *in vitro* signals preventing development[2]	No *in vitro* signals preventing development
In vivo TI:	(AUC at NOAEL[3])/(AUC at MED_{95}[4]) > 3[5]	(AUC at NOAEL)/(AUC at MED_{100}[6]) > 3
CMC	Synthesis and formulation acceptable to enable PO or IV dosing for 1-10 days in human	Synthesis and formulation acceptable to enable PO or IV dosing for 1-10 days in human
DMPK	Human dose prediction < 60mg/kg/day given QD or BID	Human dose prediction < 60mg/kg/day given QD or BID

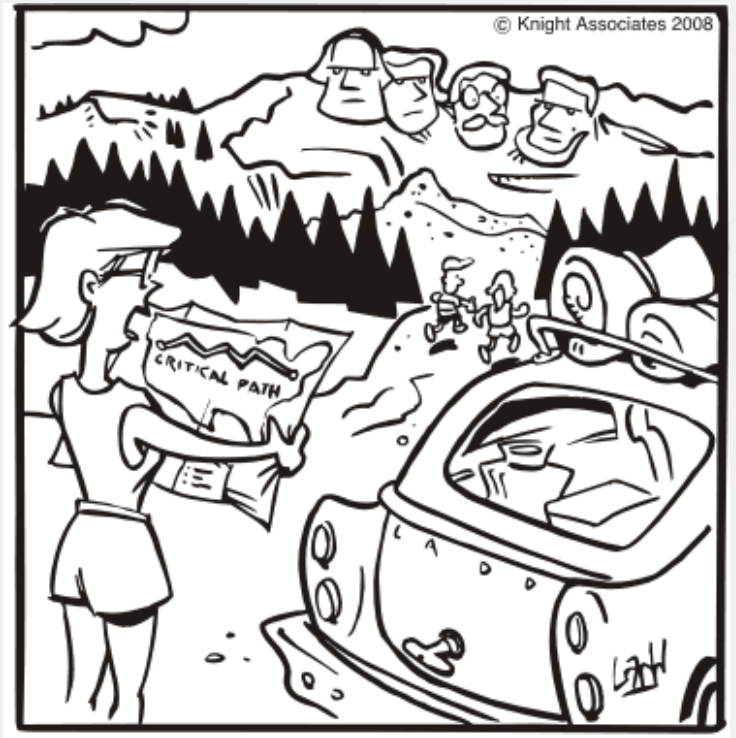
Explanatory notes:

1 Compound able to give *in vitro* >99% reduction of intracellular amastigotes relative to untreated control
2 Includes: mammalian cytotoxcity, HERG, Ames, micronucleus, broad profiling
3 Determined in rat repeat dose toxicology for duration ≥ length of treatment in efficacy model
4 Minimum dose required to achieve >95% reduction in parasitemia *in vivo*
5 Applies equally to **both** total AUC and free AUC comparisons.
6 Minimum dose required to achieve 100% reduction in parasitemia *in vivo*

Consider the Critical Path

- Define which experiments are on the Critical Path

(Ex: if you have a good mouse model, do you need NHP data to move forward?)



"KIDS! This stop is on the CRITICAL PATH and is scheduled to take exactly 43 minutes! ~ So no slack time!"

Longest sequence of activities in a project plan which must be completed on time for the project to complete on due date.

CD Lead Optimisation Screen Sequence (1/3)

Acceptance criteria for a new chemical series

Screening on *T. cruzi* Tulahuen strain (TcVI)

IC_{50}	< 5 µM
Max. activity	> 90-95%

Cytotoxicity on host cell 3T3

SI	> 10

Towards PoP

Primary ADME characterisation

In sillico predictions of Phys/Chem properties
→ no predicted absorption liabilities

Kinetic solubility (pH 2 & 6.5)	> 50 µg/mL
gLog D	< 4
CYP 3A4 inhibition (1 & 10 µM)	(> 10 µM)
In vitro metabolism (mouse LMs)	EH < 0.5

Scale up

New series profiling

Pannel of *cruzi* strains → potency against all genotypes (priority to TcI, TcII, TcV and TcVI) or NO GO

CYP51> 10 µM, or DE-PRIORITISATION

Trypomastigotes→potency or DE-PRIORITISATION

Time to kill Fast-acting preferred

Intelectual Property assessment → FTO

PK in Balb/c mice
(PO at dose used in PoP –max 100 mg/kg- and IV 1 mg/kg)

Pre- formulation (if needed)
Tolerability in Balb/c

In vitro validation against *T. Cruzi* CL Brener

PoP efficacy *in vivo* – 5 days
(Balb/c mice infected with CL Brener -at the highest dose

CD Lead Optimisation Screen Sequence (2/3)

Potential candidate

Further profiling for a successful PoP

ADME

Plasma stability (mouse, rat & human) – see below

Plasma protein binding (mouse, rat & human) – initially only do mouse; generally similar between species; other species added if PoP successful; same for mouse plasma stability (probably do blood rather than plasma)

Permeability (Caco -2) – low priority if we have oral exposure; ;primarily useful to determine basis for low exposure

Safety & Toxicology

Panel of mammalian cells for cytotoxicity > 10 µM

CYP screening	> 10 µM
hERG	> 30 µM
Mini AMES	negative
In vitro Micronucleus	negative
CEREP profiling	
Preliminary CV test in rat	negative

Potency

Reversibility in *T. cruzi* Tulahuen assay

Entrance in LO

LO

In vivo efficacy

In vitro validation against *T. cruzi* CL Brener

Acute model

Chronic model

Dose –response in chronic model

In vivo ADME

PO exposure in Balb/c

Scale up

In vitro ADME

In sillico

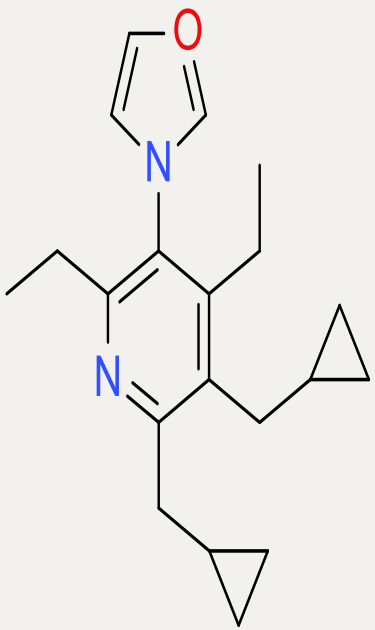
KS	> 100 µg/mL
gLog D	< 3
In vitro met. (mouse LMs)	EH < 0.3
CYP 3A4 inhibition	< 50% (10 µM)
PPB (mouse)	

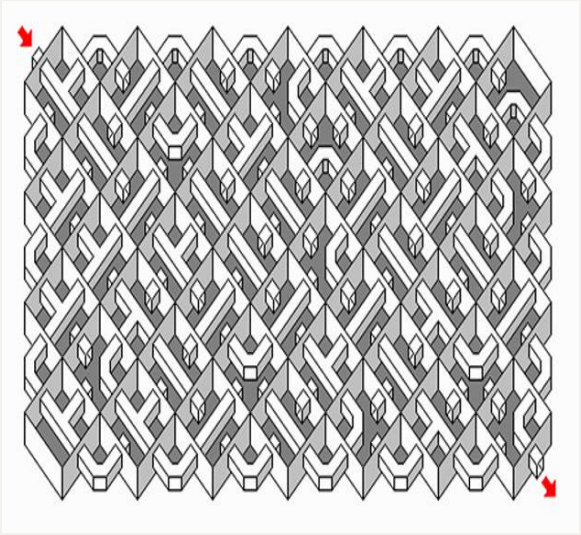
In vitro efficacy – *T. cruzi* Tulahuen strain in 3T3

IC_{50}	< 1 µM
Max. activity	> 95%
SI	> 100

The Process

The Journey from ‘Hit’ to Drug





The Journey from ‘Hit’ to Drug

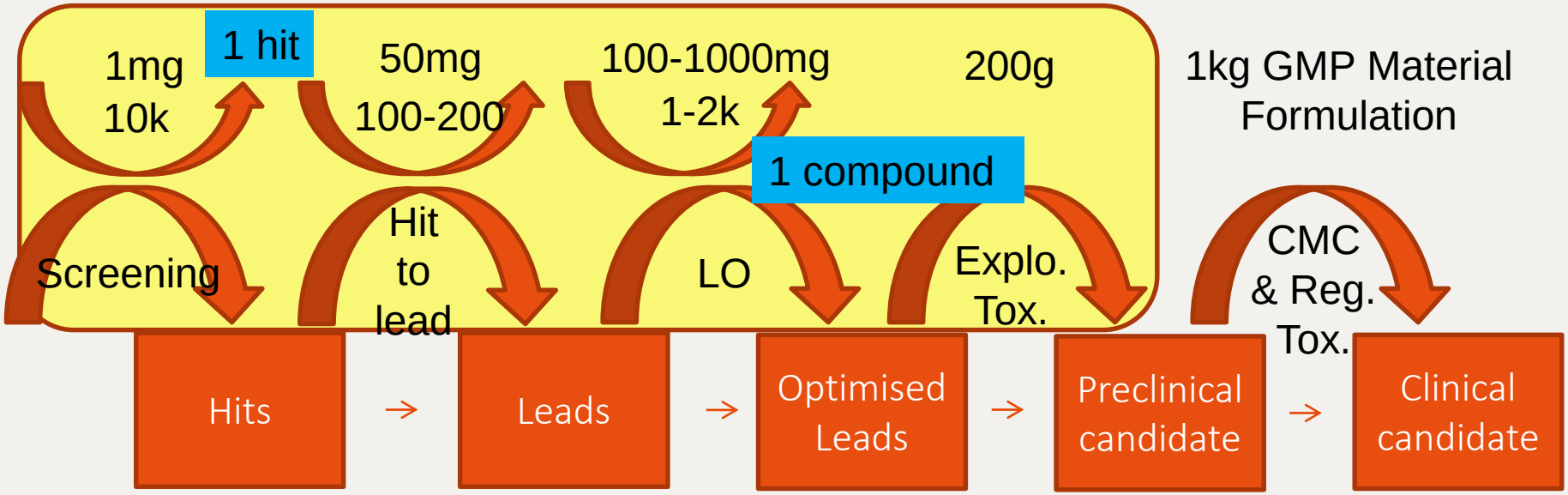
To move from a hit to a possible drug we move through several stages:

- Screening → Hit to lead → Lead Optimisation → Preclinical → Phase I

What happens in each stage?

- Characterise the attributes of the individual compounds
- If consistent with the TCP move ahead
- If not go back and design a better molecule – Iterative Process
  - ‘snakes and ladders’
- As confidence grows that we may complete the journey from hit to drug we study compounds in more detail
  - Invest more time, money and effort

Stages of Discovery
Building confidence - Growing investments



Kill parasites *in vitro*

Kill parasites *in vivo*

Kills parasites *in vivo* & could meet TCP….
…no more chance to alter the chemical structure!

Kills parasites *in vivo* & is safe in rats

Kills parasites *in vivo* & is safe in rats & dogs

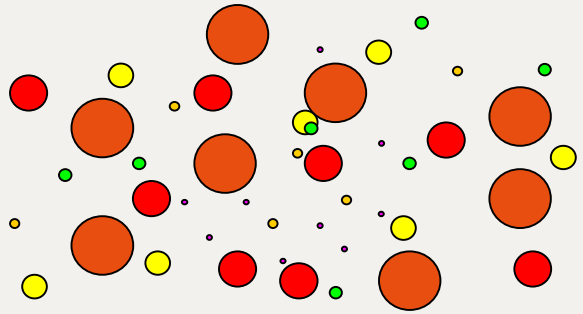
- Time?
- Cost?
- FTEs?
- Agreements?
- Chance of success?

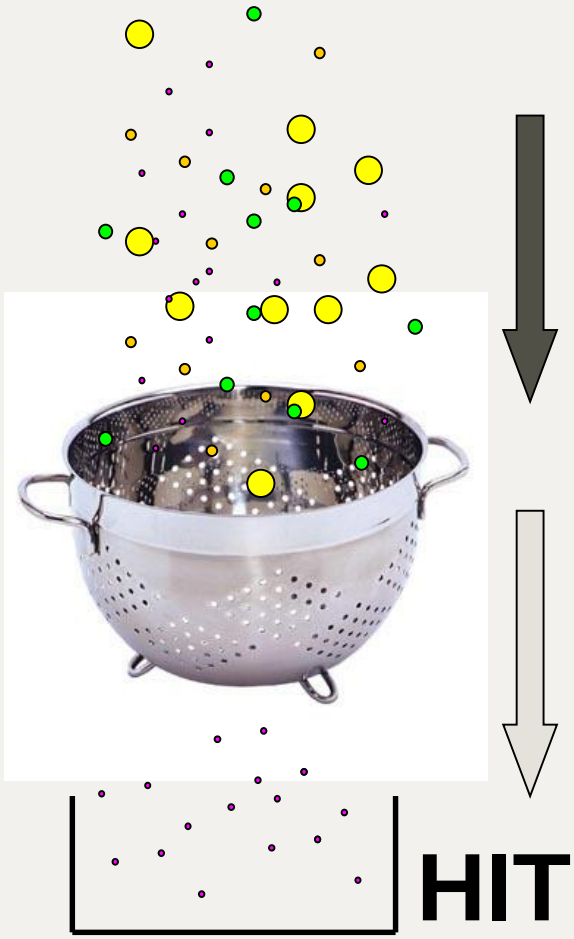
First, we need Hits!

Screening is:

- Time
- Money
- Resources

Screening: Remove the Odds





- Remove «junk» chemicals (Garbage In, Garbage Out)
- Rational selection of libraries
- Synthetic chemicals/Natural Products
- Adequate screening techniques

But ….. A ‘Hit’ is NOT a Drug

- A screening ‘hit’ can kill parasites…and not mammalian cells
- A drug will require many more “decorations”
- When designing a molecule need to consider
  - Synthesis, physical properties, solubility, permeability, stability to metabolism, distribution to the site of action, residence for long enough to kill parasites… without harming the patient or tasting awful!

From a Hit to a Lead: Still a long way to go…

Activity against parasite is not enough

Also need for:

- Safety (selectivity)
- Solubility
- Stability
- PoC *in vivo* (oral)
- Cost, IP, …

110 meter hurdle race …
with few reaching the line, with potential for optimization (SAR building)

A Focus on Lead Optimization

- *With the exception of re-purposing/indications discovery
  - Where one of the few hundred approved drugs or clinical development candidates is tested against a new disease, Small chance of success but high value if lucky! Few options remain…
    - Miltefosine – Drug candidate in clinical trials for cancer
    - Eflornithine – Drug candidate in clinical trials for cancer
    - Paromomycin – Drug for treatment of amoebiasis
    - Amphotericin B – Drug for treatment of fungal infections

If we identify compounds that kill the parasite which are **not** already drugs or clinical candidates

we will probably need to optimize them

Lead Optimization

A drug has to:

Get into the blood

Survive in the body

Get to the site of infection

Kill the parasite

Be safe

Absorption

Distribution

Metabolism / Excretion (ADME)

Potency

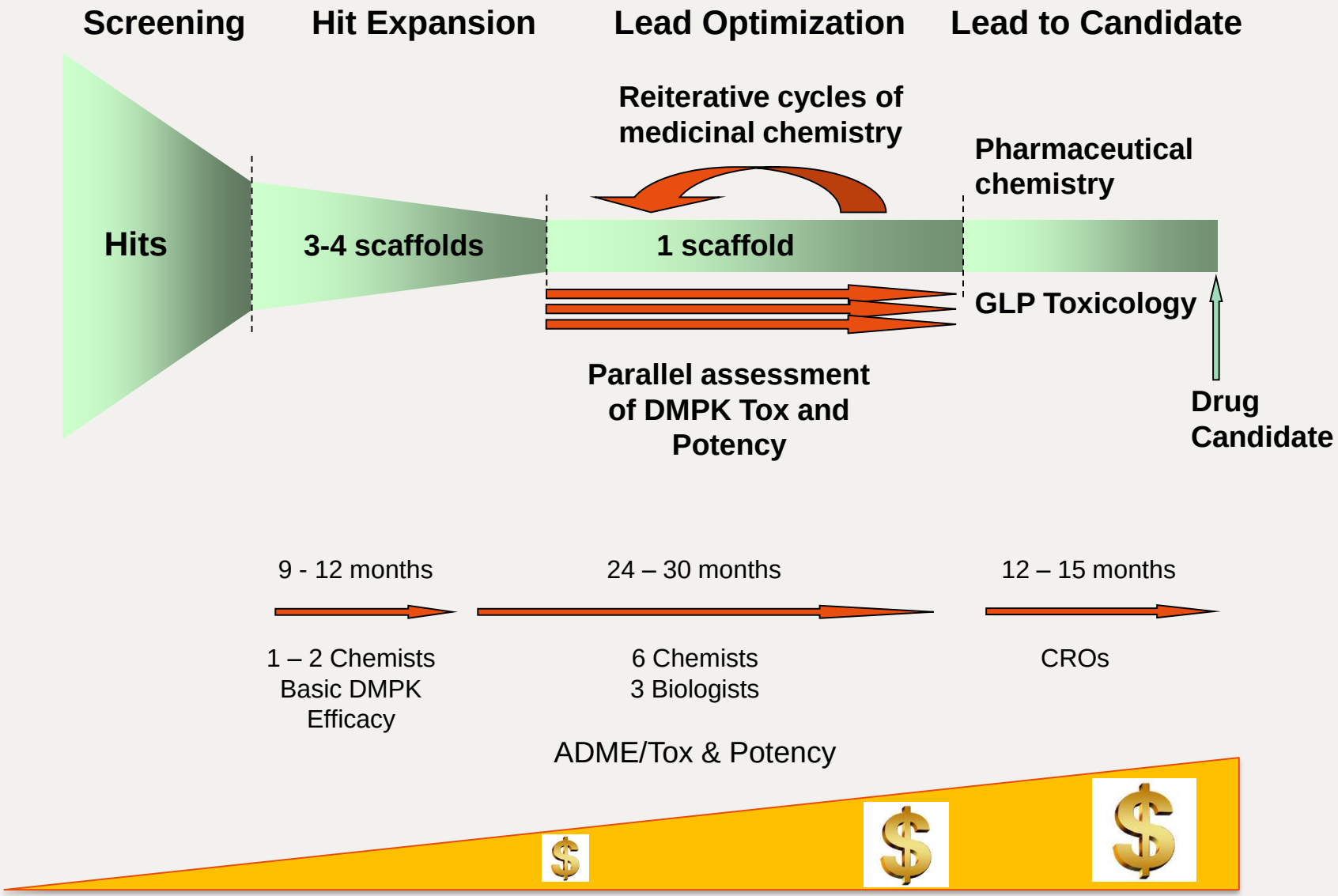
Toxicity

Pharmacokinetic studies → *What does the body do to the drug?*

Pharmacodynamic studies → *What does the drug do to the body?*

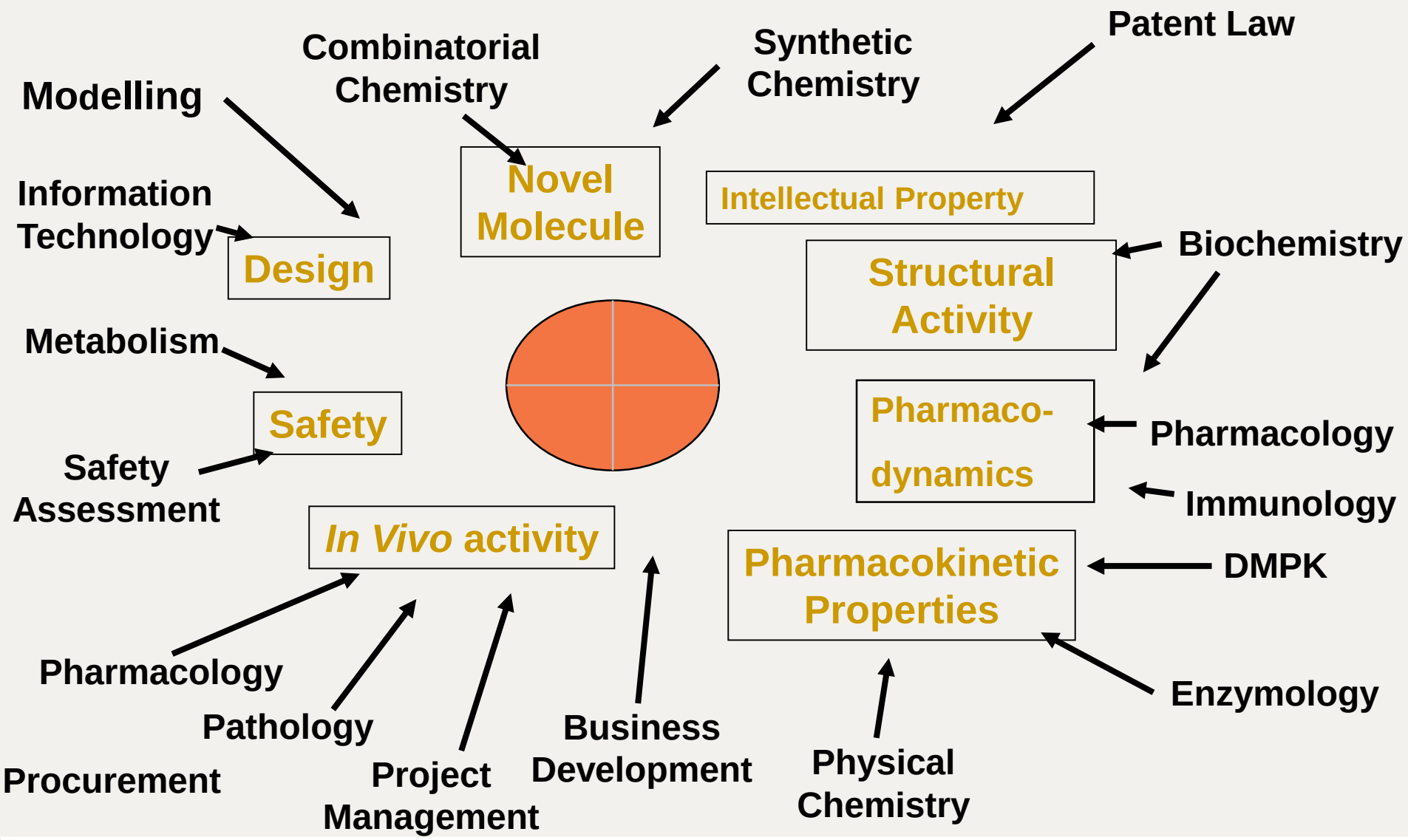
PK/PD Relationship

The Science(s) of Lead Optimization



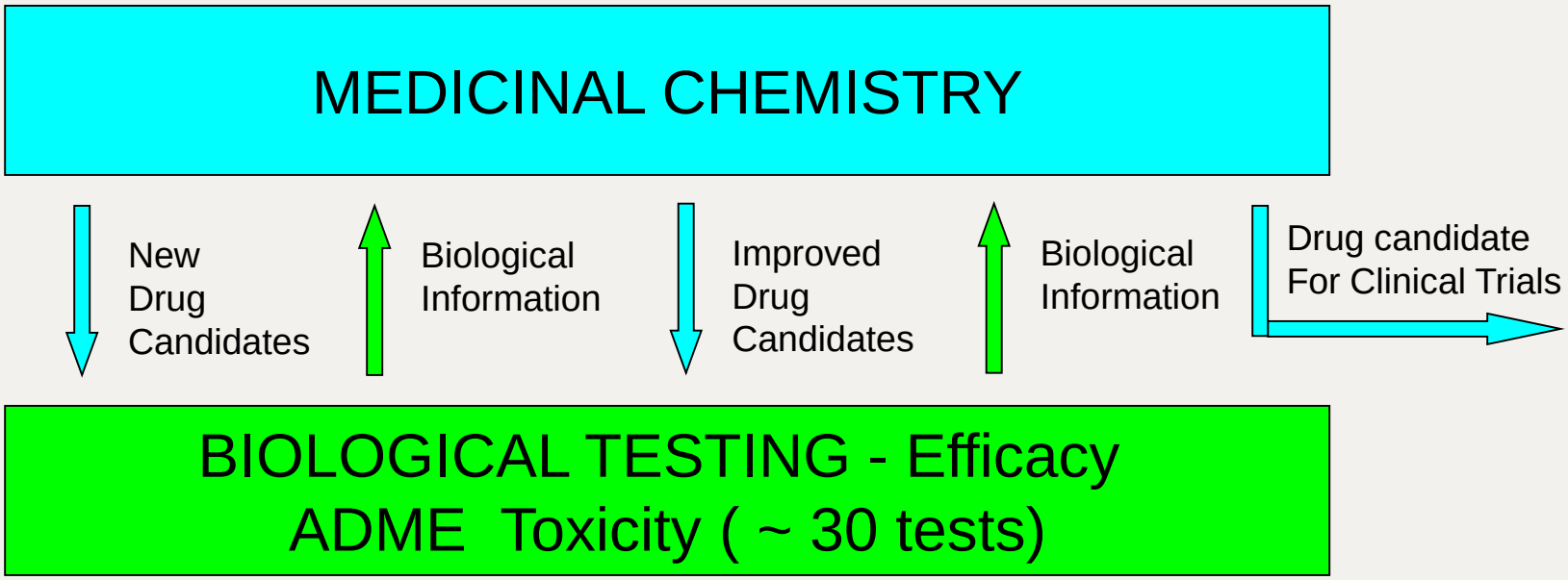
Partners / Disciplines

Drug Discovery - Multidisciplines



It Has All to be Managed….

Information Flow



Rapid Turnaround of testing

Effective communication & data management

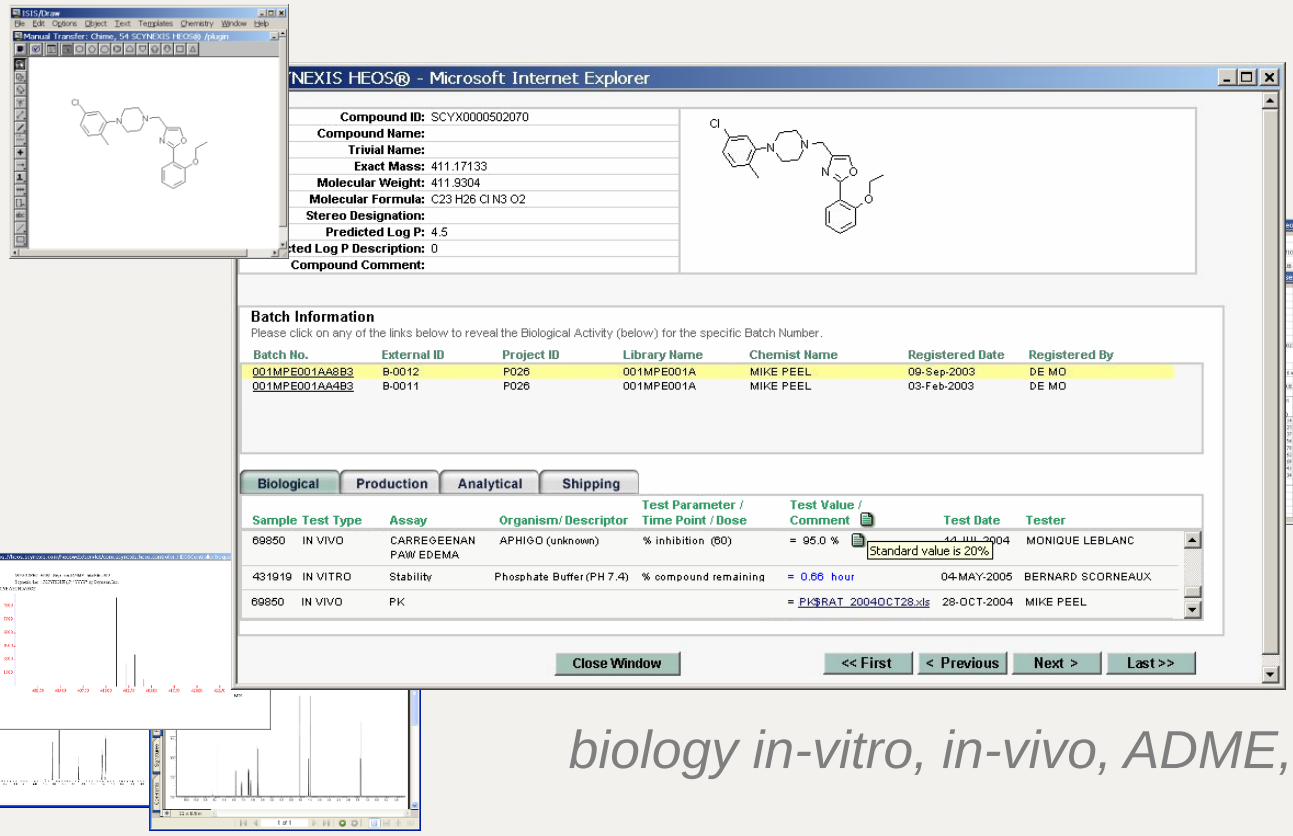
Effective decision making

Dedicated teams adequately staffed

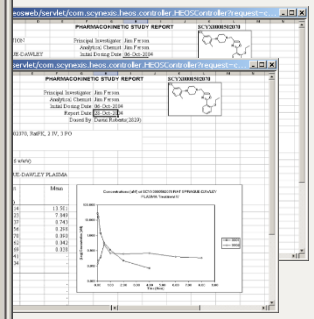
Secure web-based database

Data Management

Chemistry



PK, PD…



biology in-vitro, in-vivo, ADME, Toxicology

Analytical

Documents

Pharmaceutical Project Management

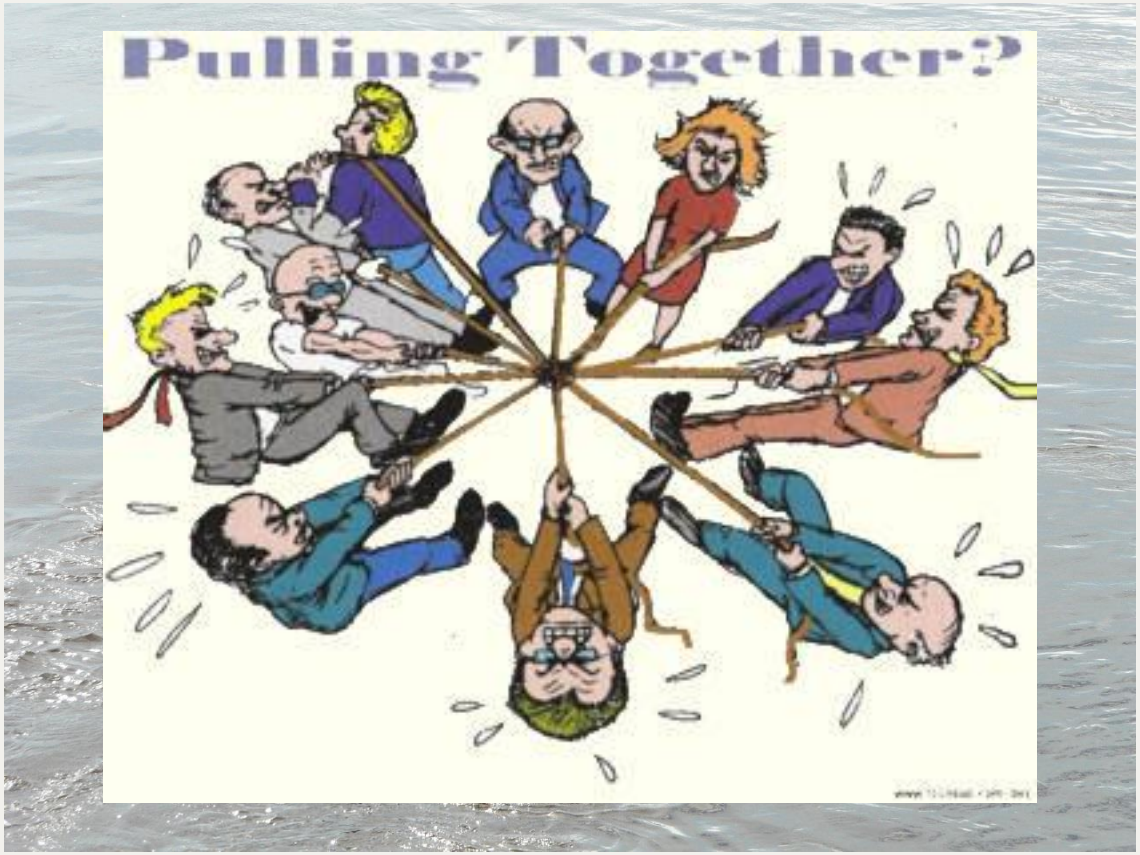
Minutes
TCP, TPP
GO, NoGO decisions
Resources Allocation
Prioritization

Poor Management Has a Cost

Patients are Still Waiting

Drug Discovery: A Team Effort

Pulling Together to Overcome Hurdles



Conclusions

Drug Discovery

- Lots of hurdles along the journey
- Tools that are helpful to overcome these issues
  - Guidance documents (TPP, TCP, decision matrices, screening cascades,…)
  - Technical tools: Access to chemical diversity and quality compounds, robust assays, ….
  - Partners and associated commitment and expertise/knowledge
  - Data management tools
- Look around (what has been done, what is ongoing), synergy and sharing between initiatives to avoid duplication


BEST
SCIENCE
FOR THE MOST
NEGLECTED
Thank you
DNDi
Drugs for Neglected Diseases initia