Drug discovery against kinetoplastid diseases: the DND*i* perspective

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COST Action CM 1307 meeting
Belgrade, 27 October 2015

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OUTLINE

- DND*i*'s Model
- R&D landscape and portofolio
- DNDi's Discovery strategy
- Selected discovery approaches: lessons learnt
- Identifying and addressing the challenges
- Achievements

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DND*i*'s Model

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THE HISTORY OF DNDi

In the 1990s and after, MSF documented in the field that patients had no treatments for certain - neglected - diseases.

MSF used funding from the Nobel Prize and created the Drugs for Neglected Diseases working group, which then led to DNDi in 2003.

VISION & OBJECTIVES

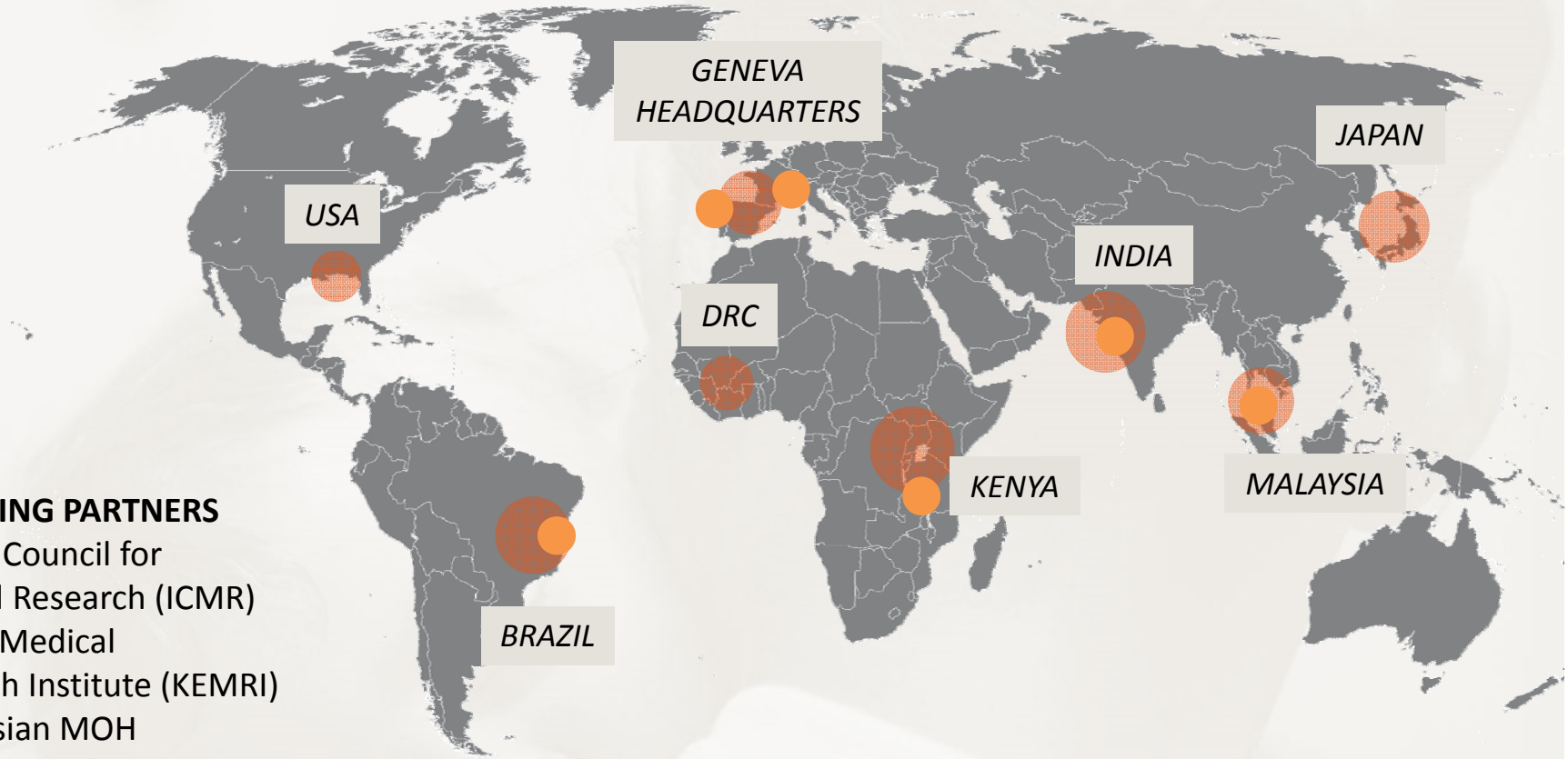
DNDi VISION

A collaborative, patients' needs-driven, virtual, non-profit drug R&D organisation to develop new treatments against the most neglected diseases.

DNDi OBJECTIVES

- Deliver 11 to 13 new treatments by 2018 for Sleeping sickness, Chagas disease, Leishmaniasis, Malaria, Paediatric HIV and specific Filarial infections
- Establish a robust pipeline for future needs
- Use and strengthen existing capacity in disease-endemic countries
- Raise awareness and advocate for increased public leadership

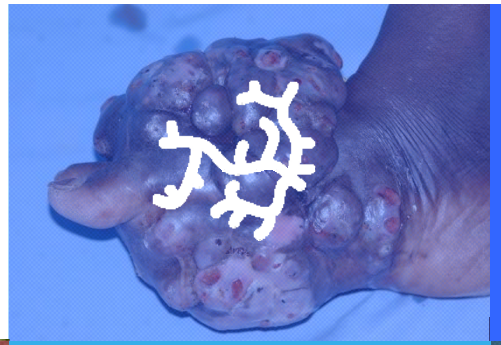
DNDi: PARTNERS & GLOBAL PRESENCE



FOUNDING PARTNERS

- Indian Council for Medical Research (ICMR)
- Kenya Medical Research Institute (KEMRI)
- Malaysian MOH
- Oswaldo Cruz Foundation, Brazil
- Médecins Sans Frontières (MSF)
- Institut Pasteur France
- TDR (permanent observer)

DNDi's PRIORITY: Neglected patients...



MYCETOMA

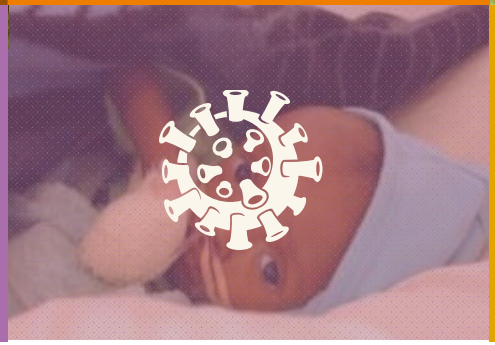
MALARIA

CHAGAS DISEASE

HAT

FILARIAL DISEASES

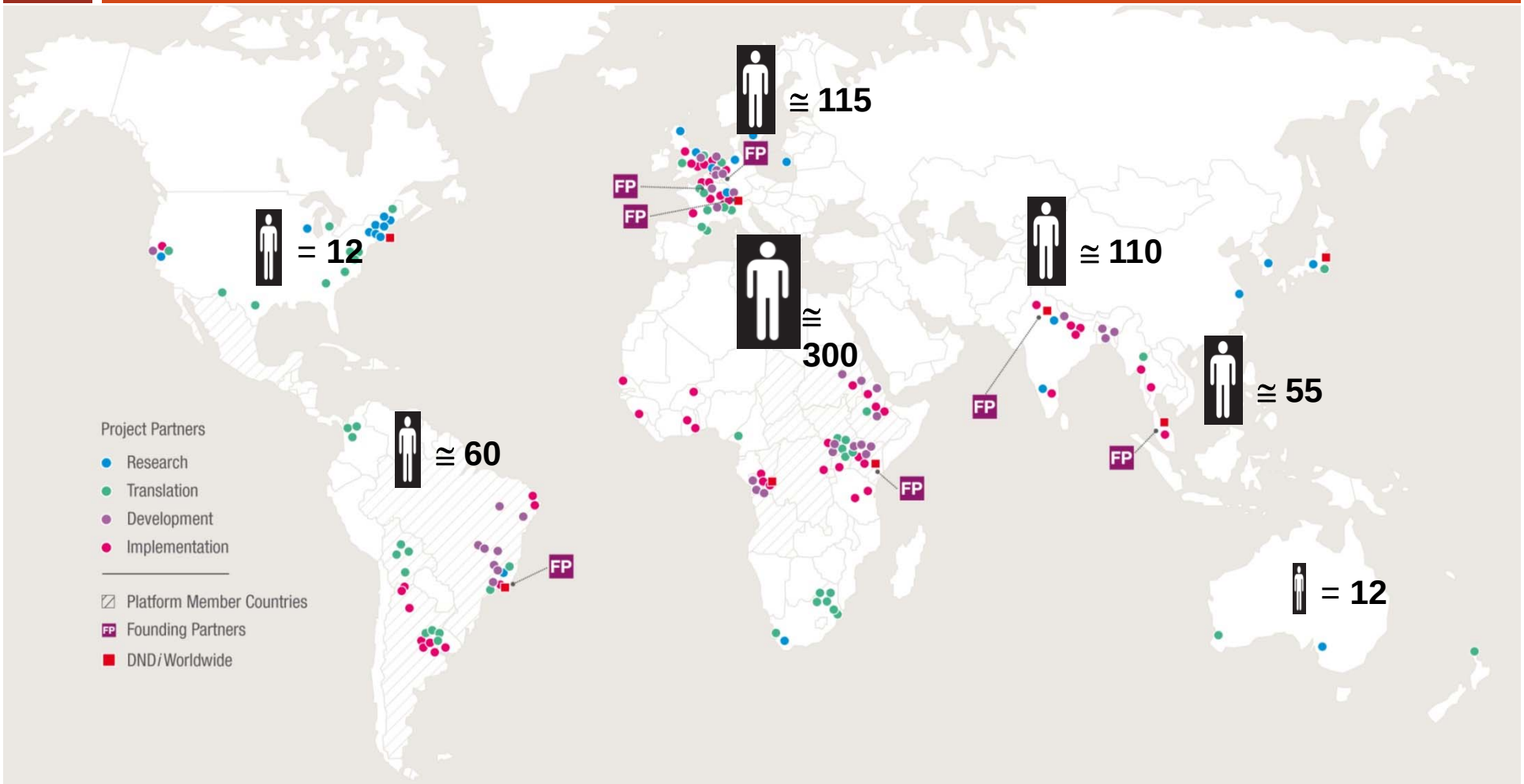
PAEDIATRIC HIV



LEISHMANIASIS

Dedicated Teams Worldwide

Over 660 People Committed to DND*i's* Vision



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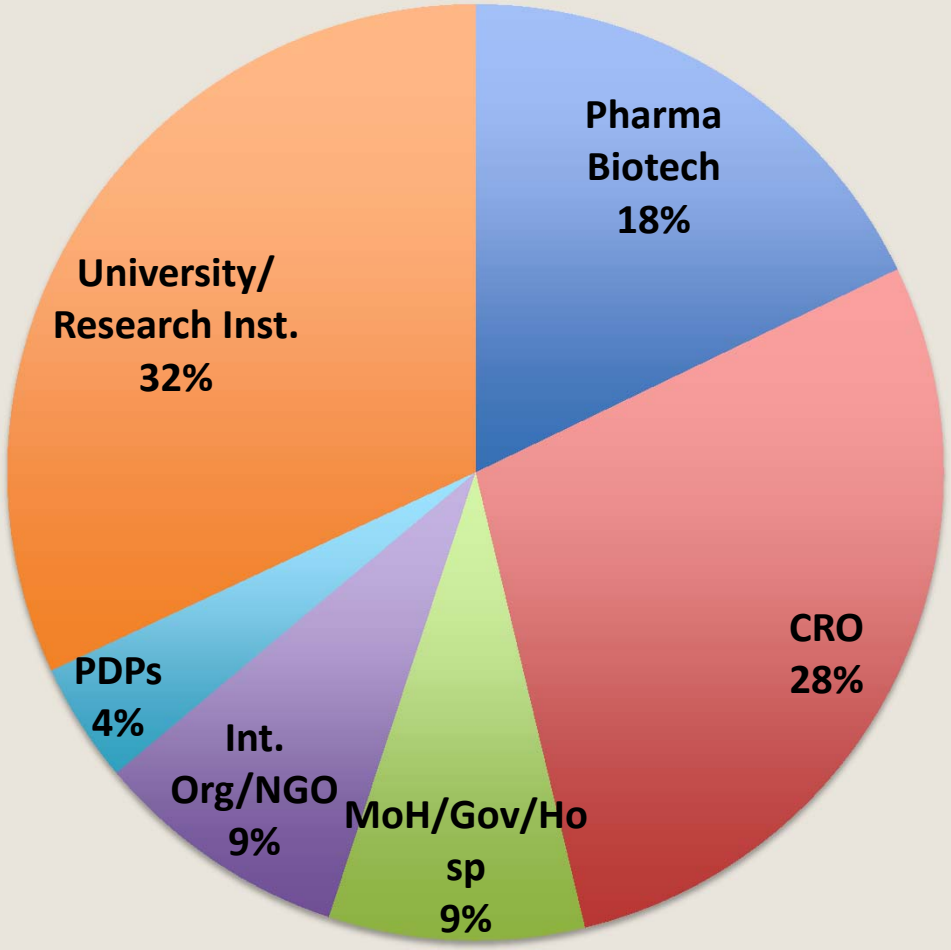
A Global Network to Leverage Resources

More Than 100 R&D Partners

- Balance of public and private partnerships worldwide



Oct. 2012

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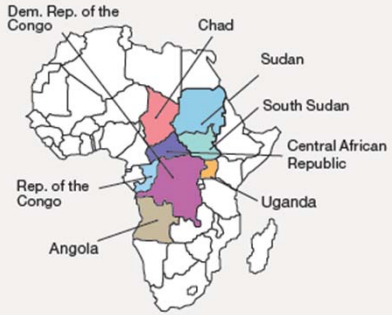
Utilizing and Strengthening Research Capacities in Disease-Endemic Countries

VL

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

HAT



PLATEFORME REGIONALE DE RECHERCHE CLINIQUE HAT
TRYPANOSOMIASE HUMAINE AFRICAINE
HUMAN AFRICAN TRYPANOSOMIASIS
REGIONAL PLATFORM FOR CLINICAL RESEARCH

CHAGAS

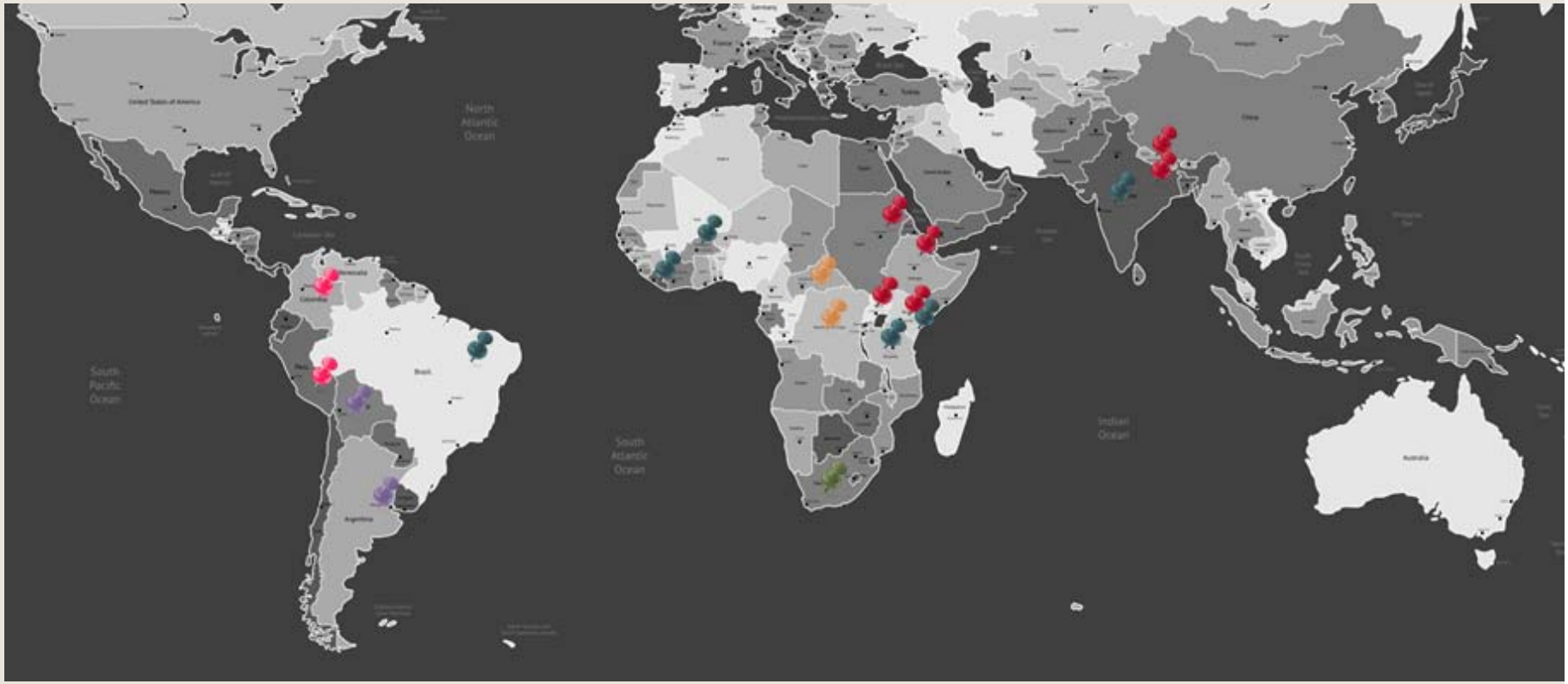
PLATAFORMA DE INVESTIGACIÓN CLÍNICA EN ENFERMEDAD DE CHAGAS
CHAGAS DISEASE CLINICAL RESEARCH PLATFORM

Major Role of Regional Disease Platforms:

- Defining patients' needs and target product profile (TPP)
- Strengthening local capacities
- Conducting clinical trials (Phase II/III studies)
- Facilitating registration
- Accelerating implementation of new treatments (Phase IV & pharmacovigilance studies)

Overcoming Challenges in the Field
Thanks to Our Partners in Endemic Countries

In 10 years: >33,000 patients enrolled in >20 clinical studies in five disease areas



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R&D landscape and portofolio

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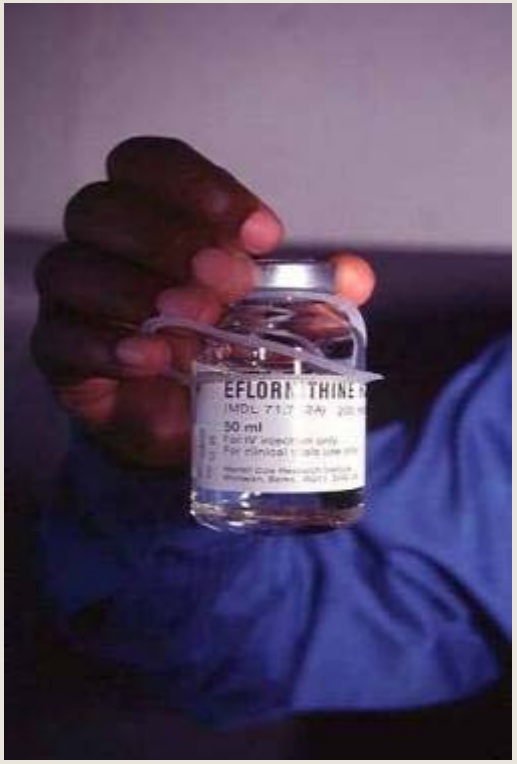
Neglected Diseases: Treatment Limitations 10 Years Ago

Melarsoprol



Eflornithine

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

We Need Safe, Effective, Easy-to-Use Drugs

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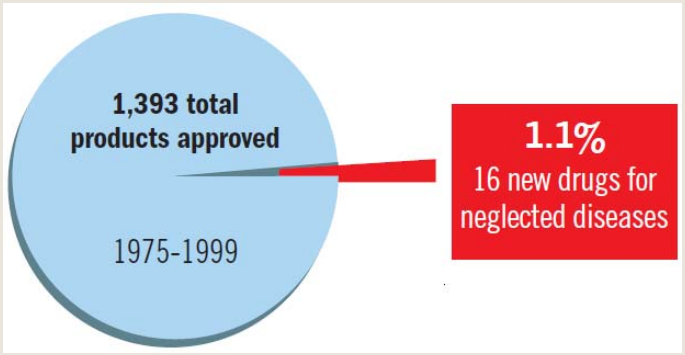
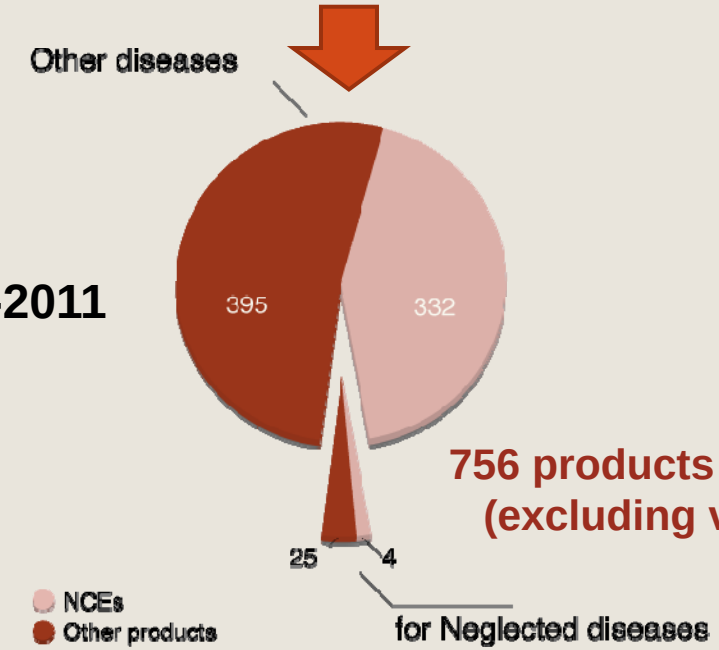
Fatal Imbalance Remains Despite Progress Over A Decade

1975-1999



2000-2011



756 products developed (excluding vaccines)

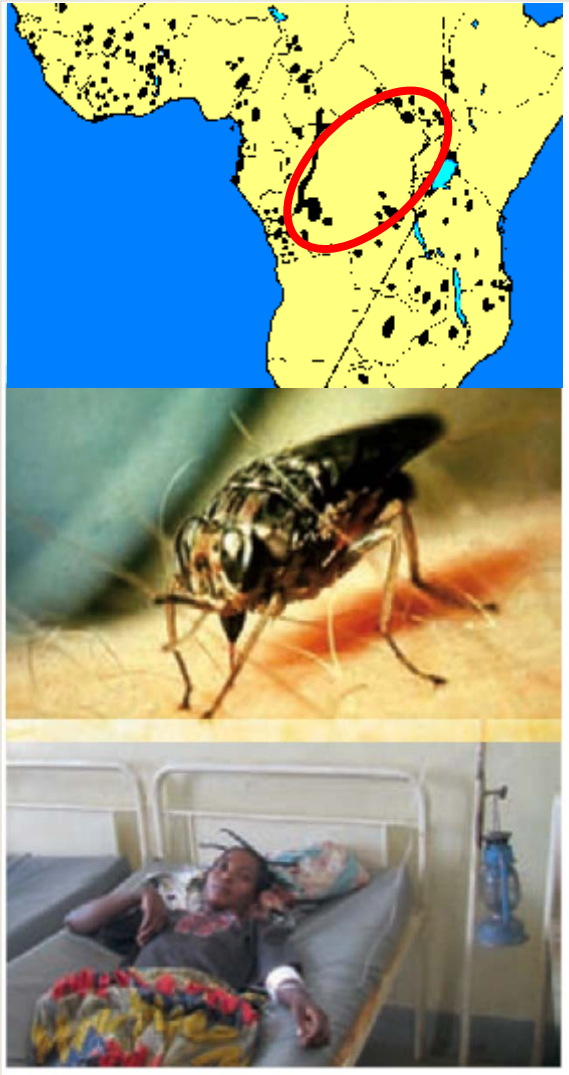
- **10% of R&D** dedicated to illnesses that affect **90% of global disease burden** (**'10/90 gap**')
- **3.8%** of new products for neglected diseases (reformulations, combinations)
- **1.2%** of NCEs for neglected diseases
- Only **1.4%** clinical trials
- Only **1%** of global health investment for neglected diseases*

Source
Fatal Imbalance: The Crisis in Research and Development for Neglected Diseases, MSF, 2001
'The drug and vaccine landscape for neglected diseases (2000-2011): a systematic assessment' Pedrique B et al. *Lancet*, Oct 2013

*Source '
Mapping of available health research and development data: what's there, what's missing, and what role is there for a global observatory?' Rottingen et al. *Lancet*, May 2013

Human African Trypanosomiasis (HAT) or Sleeping Sickness

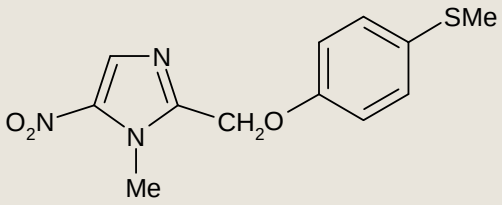
- 36 countries at risk in sub-Saharan Africa;
- *Trypanosoma b. gambiense and rhodesiense*
- Transmitted by the tsetse fly
- estimated current cases: 20,000
- Difficult to diagnose; many patients go undiagnosed until late stage of disease
- Fatal if untreated
- 7 countries bear 97% cases (RDC = 2/3)
- Current drugs: melarsoprol, NECT
- **Needs: a safe, effective, short-course and orally administered stage 2 treatment**



By 2018? New Oral Treatments and Rapid Diagnostic Tests at Village Level

Fexinidazole

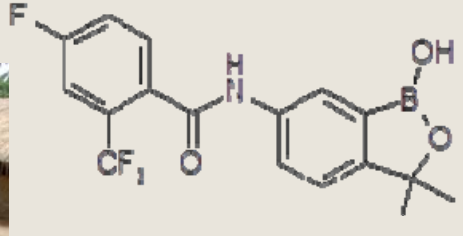
- A ‘rediscovered’ new chemical entity through compound mining
- Potential oral treatment
- Phase II/III in DRC and CAR

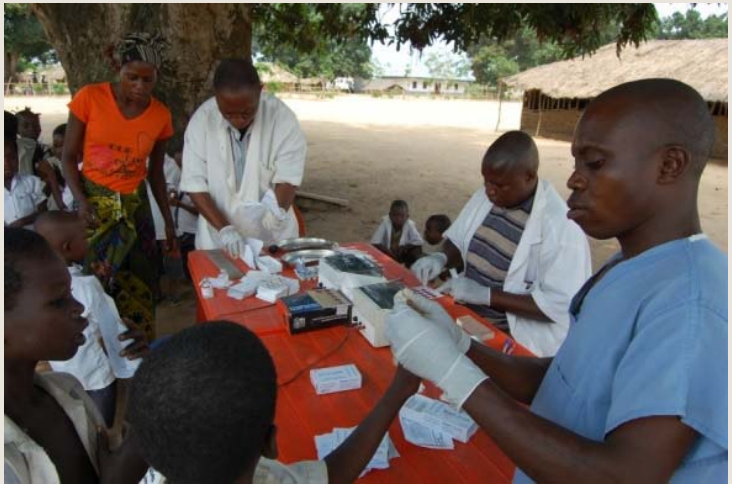


In partnership with Sanofi

Oxaborole SCYX-7158

- New chemical entity from the Lead Optimization programme
- Potential oral treatment with a single pill
- Phase I completed; Entering Phase II/III soon





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Sleeping Sickness: From Unacceptable To Better, Towards Tools for Elimination

15 years ago:

Eflornithine

Melarsoprol

Since 2009:

NECT

2018?

Oral treatment & rapid diagnostic test

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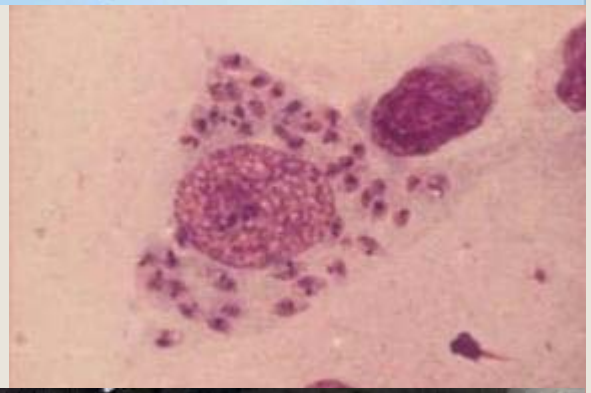
Leishmaniasis

- 200 million at risk worldwide (in 70 countries but 90% in 5 countries)
- 500,000 cases in total with 51,000 deaths/year
- *Leishmania donovani*
- Transmitted by the sandflies
- 2 types of leishmaniasis:
  - **Visceral (VL): fatal without treatment**
  - Cutaneous (CL): has a spectrum of presentations; typically with self-healing or chronic lesions on the skin
  - Current drugs: antimonials, Amphotericin B, AmBisome®, miltefosine, paromomycin
- **Needs: oral, safe, effective, low-cost and short-course treatment**

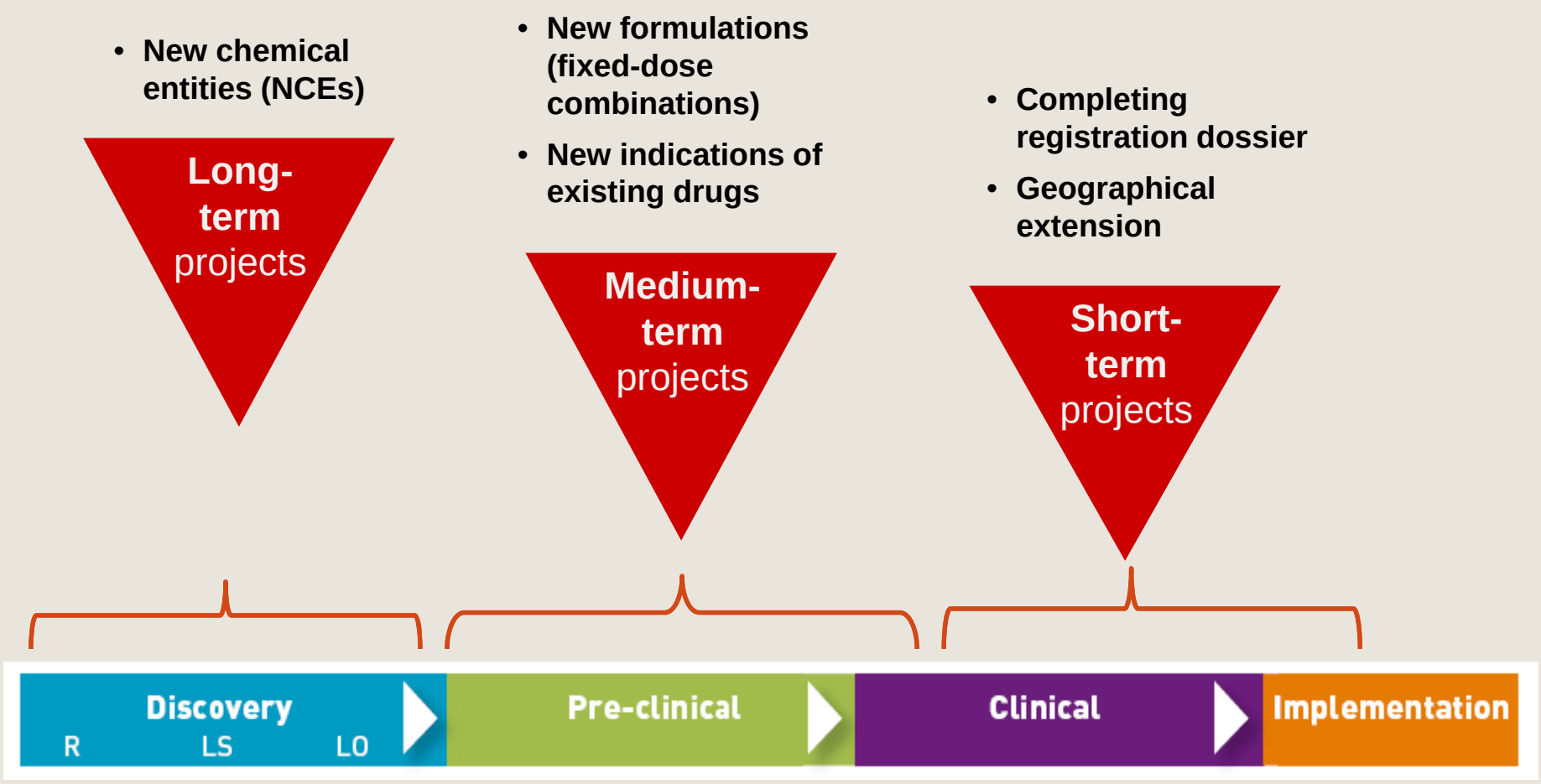


Chagas Disease

- 100 million at risk in Latin America
- 8 millions cases with 14’000 deaths/yea
- *Trypanosoma cruzi*
- Kills more people in region than malaria
- Patient number growing in non-endemic countries
- Transmitted by ‘kissing bug’, blood transfusion, organ transplantation, as congenitally or orally
- Majority of patients undiagnosed until late stage
- Current drugs: benznidazole, nifurtimox
- **Needs:**
  - **paediatric drug (benznidazole)**
  - **a new oral drug for early chronic stage**

DND*i* Portfolio-Building Model

Address Immediate Patient Needs & Deliver Innovative Medicines



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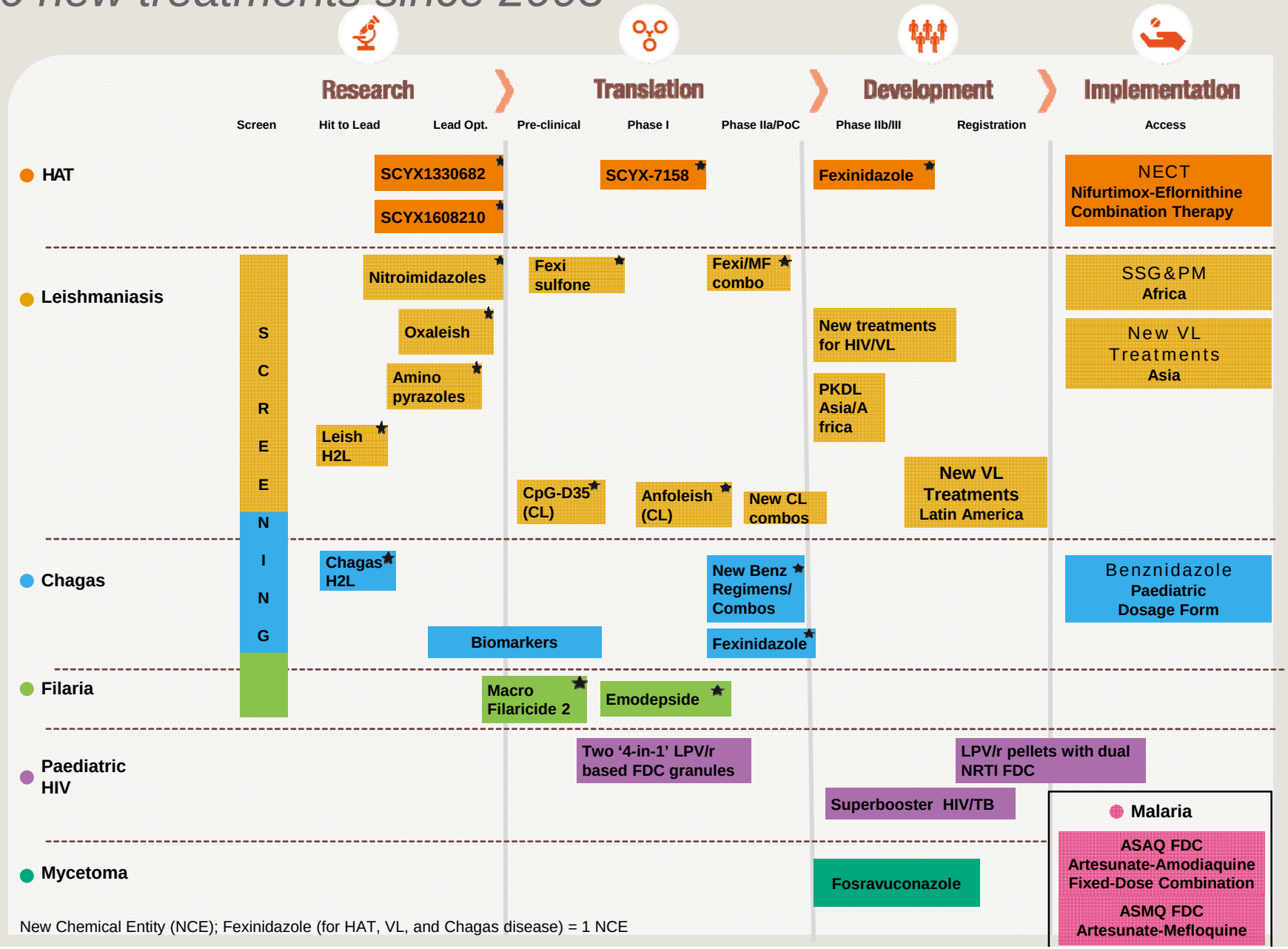
DND*i* Portfolio June 2015

6 new treatments since 2003



New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas disease) = 1 NCE

DND*i*'s Discovery strategy

An evolutive process

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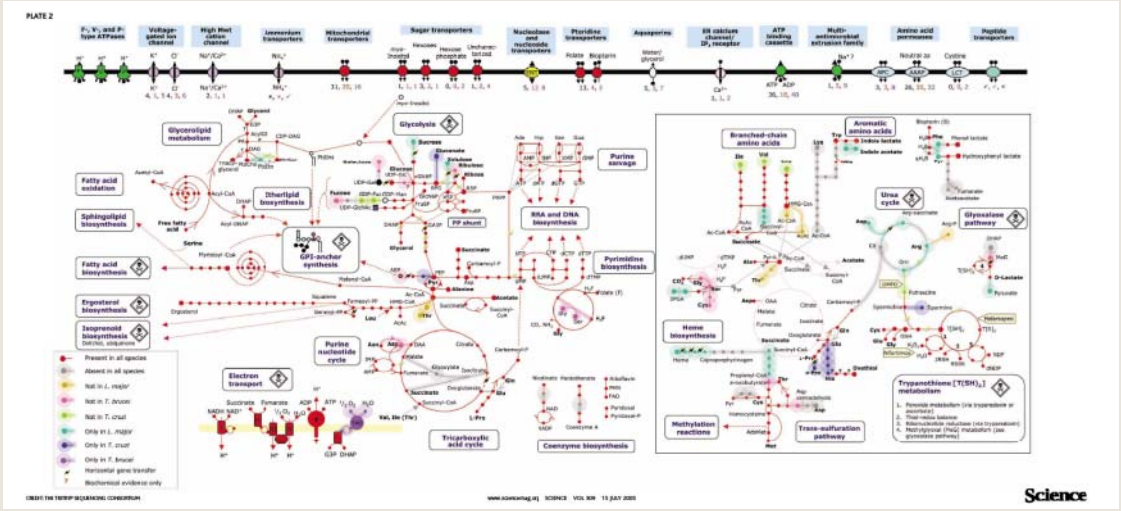
2003-2005: status of knowledge

Research

- genome sequenced by TriTryp consortium (2005)
- little know about target validation -> lack of translation
- Whole cell (phenotypic) assay in place at low throughput
- Little known about kinetoplastid biology relevant to disease
- few drugs used in the clinics (MoA unknown, empirical use)



CREDIT: THE TRITRYP SEQUENCING CONSORTIUM http://tritrypdb.org/tritrypdb/

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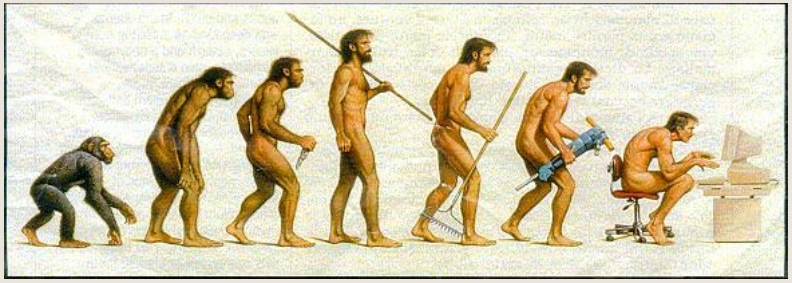
Discovery @ DND*i*: an evolution process

- Started with academia/parasitology partners (networking)
- From individual projects
- Selection on opportunistic, scientific-based criteria
- Little H2L/LO capactity and expertise (project based)
- small non-proprietary libraries (little related knowledge)
- Low screening capacity for all 3 protozoa



Adapt to changing R&D landscape

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Discovery at DND*i*: 2005-2008 lessons learnt

Research

- **success is the exception (fexinidazole)**

- **mostly library-based/chemistry-driven projects**
  - **individual projects**
  - **little known about developability of hits/hit series**
  - **little expertise and support (ADMET, PK, toxicity)**

- **in vitro to in vivo translation**

are we using pathology relevant models? Are we too stingent/too loose?
Has chemistry to be questioned ?

- **literature mining**

lack of reproducibility

- **chemical collections**

more opportunistic than rational selection

- **Screening**

limited screening capacity: few hundred cpd/month

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Discovery at DND*i*: since 2008

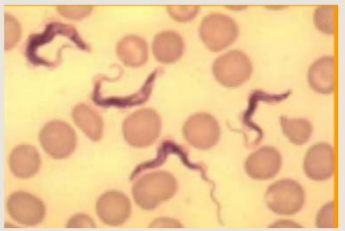
Research

- **increase phenotypic screening capacity**

strategic partnerships with **Eskitis** (HAT HTS assay development), **Institut Pasteur Korea** (VL and Chagas HCS development) and **University of Dundee** HCS assay development)

- **review strategy re selection of compounds**

selection of compound libraries and partnerships (focus on Pharmas)



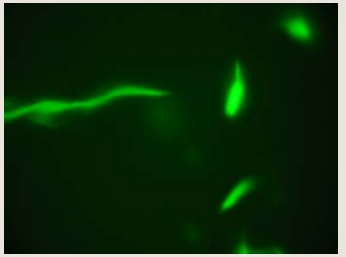
Picture STPH

- **invest in fully integrated Lead Optimization consortia supported by DMPK/parasitology**

delink funding from research teams and series

- **develop of guiding/decisional tools**

Target Product Profiles, discovery cascades



Picture CDRI

- **invest in better understanding of assay models**

understand biology (drugs/clinical candidates as benmarkers, in vitro and in vivo -> translation, PK/PD, integrate secondary assays (HAT, VL, Chagas) into screening cascade

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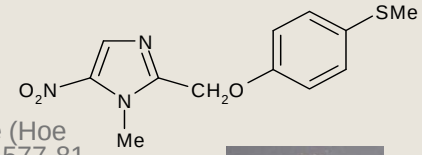
Selection of compounds for screening

1. Literature mining (1-100)

scientific litt and patent search (low hanging fruit)



Jennings, FW, Urquhart GM, The use of the 2 substituted 5-nitroimidazole, Fexinidazole (Hoe 239) in the treatment of chronic T. brucei infections in mice. Z Parasitenkd. 1983;69 (5): 577-81

2. Drug repurposing (100-1'000)

drug candidates and approved drugs (preclinical to registration)

3. ADME/PK biased sets (1-3K)

e.g. bioavailability, half-life, distribution, BBB…

4. Diversity screening core (10-150K) to larger decks (+500K)

lead-likeness/diversity algorithms (and other filters)

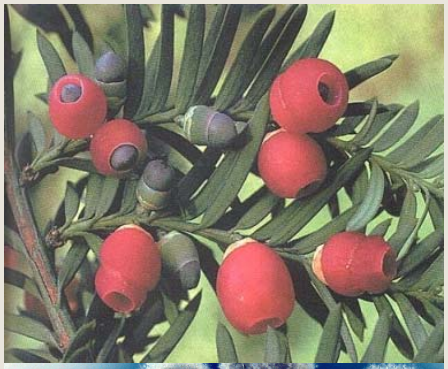
5. Specific sets: anti-infective classes, orthology (100-1000)

including target related and class related

6. Scaffold-hopping/analog mining (10-100)

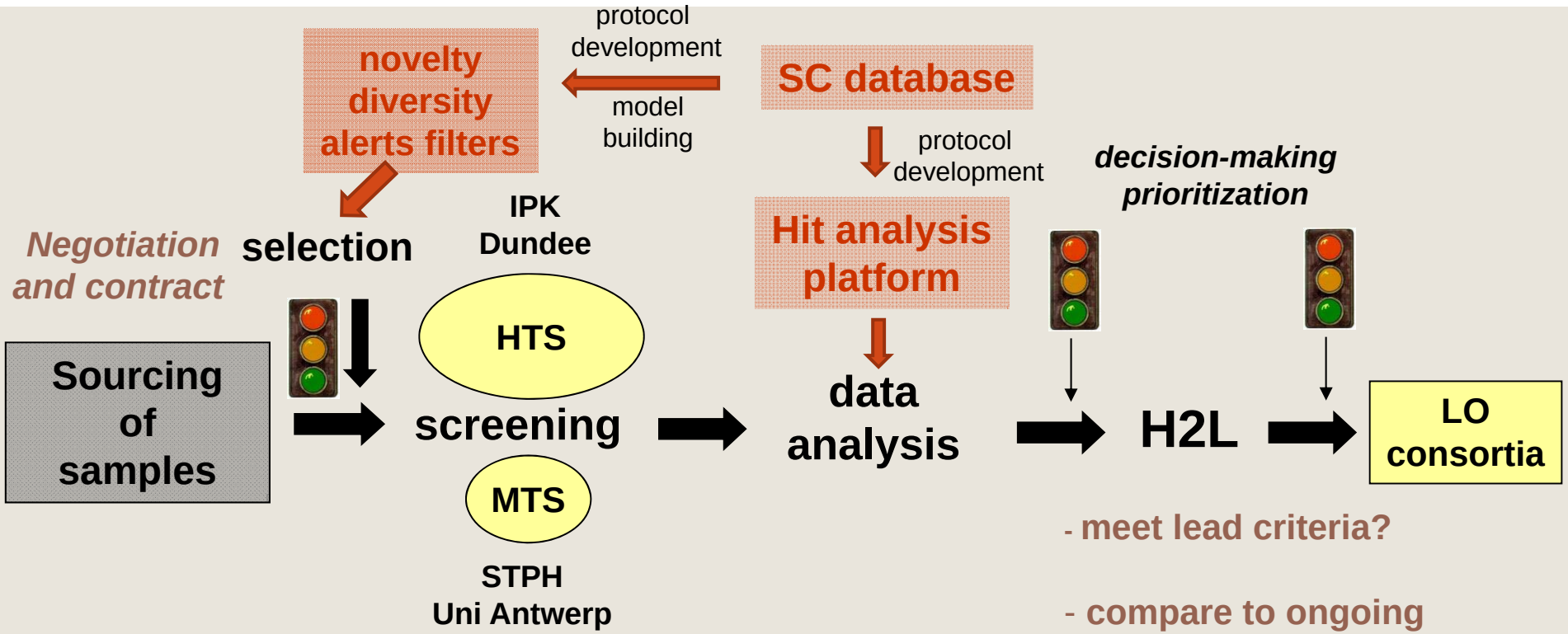
non-proprietary/published hits as templates

7. Others: NP, putative protozoan targets, activity predictive models, …



screening/early Discovery - Process

Research



- meet lead criteria?
- compare to ongoing candidates?
- way to work together (new partners)?

- **Challenges: keep track on data/information**
- **Ensure timely commmunication (internal/external)**
- **Deal with more data/ more partners**

coordination of partnerships and screening centers

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Discovery - Tools

Research

Target Product Profiles (TPPs)

• Defined in consultation with stakeholders:

- Patients, Physicians, Regulators, Public health agencies

Drug Discovery manuals and screening cascades

• Objective values for:

- Hits, Leads, Optimized leads, Drug candidates

• Surrogate markers to support the Discovery Manuals

Data Management

• Ensures rapid dissemination of data to partners (ScienceCloud)

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the TPP as a R&D guide
the example of Chagas Disease

Research

	Acceptable	Ideal
Target population	Chronic	Chronic and Acute (Reactivations)
Strains	TcI, TcII, TcV and TcVI (according to new 2009 classification)	All according to new classification (2009)*
Distribution	All areas	All areas
Adult/children	Adult	All
Clinical efficacy	Non inferior to benznidazole in all endemic regions (parasitological)	Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)
Safety	Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment	Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment
Activity against resistant strains	Not necessary	Active against nitrofuran- and nitroimidazole-resistant *T. cruzi* strains
Contraindications	Pregnancy/lactation	None
Precautions	No genotoxicity; No pro-arrythmic potential	No genotoxicity; No teratogenicity; No negative inotropic effect; ; No pro-arrythmic potential
Interactions	No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs	None
Presentation	Oral	Oral
Stability	3 years, climatic zone IV	5 years, climatic zone IV
Dosing regimen	Comparable to systemic antifungal treatments	Once daily/ 30days

Chagas' Disease 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%

Cytotoxicity on host cell 3T3

SI	> 10

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

Towards PoP

Research

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

PK in Balb/c mice
(PO 20 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)

Chagas' Disease Lead Optimisation screen sequence 2/3

Further profiling for a successful PoP

ADME

Plasma stability (mouse, rat & human)
Plasma protein binding (mouse, rat & human)
Permeability (Caco -2)

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 vitro ADME

In sillico

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

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

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

Scale up

In vivo ADME

PO exposure in Balb/c

In vivo efficacy

In vitro validation against *T. cruzi* CL Brener
Acute model
Chronic model
Dose –response in chronic model

Potential candidate

Research

Selected discovery approaches: lessons learnt

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Selection of compounds for screening

1. Literature mining (1-100)

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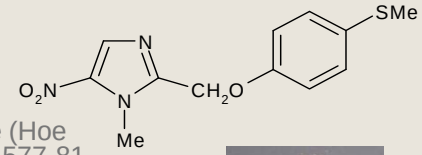

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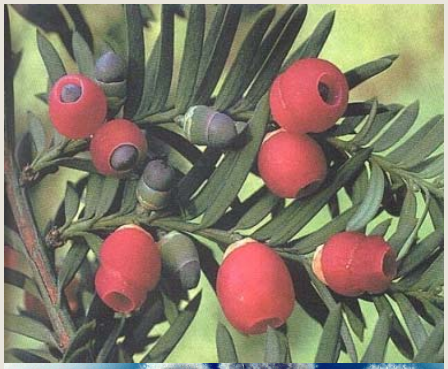
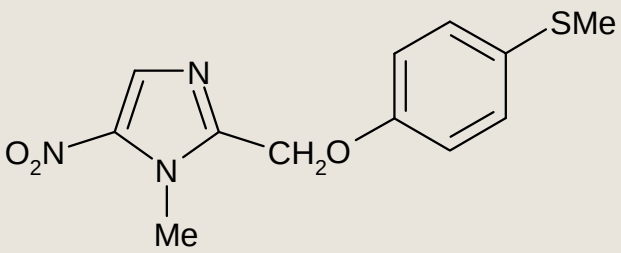


Fexinidazole: data mining for low-hanging fruit was worth the effort!

DNDi's First NCE to Reach Phase II/III Clinical Study (in DRC)

Research

Objective: Drug candidate to become an oral, short course treatment for stage 1+ 2 sleeping sickness treatment, caused by either *T.b. gambiense* or *T.b. rhodesiense*



- Literature review of nitroimidazoles as a class
- Sourcing and screening of > 500 nitroimidazoles from various sources
- Identification of fexinidazole as drug candidate
- Preclinical development including ADME-PK, GLP-toxicology and safety pharmacology
- Phase I clinical trials in Paris - completed
- Agreement to co-develop with Sanofi
- Phase II/III with Sanofi in DRC and CAR

DNDi
Drugs for Neglected Diseases *initiative*

Jennings, FW, Urquhart GM, The use of the 2 substituted 5-nitroimidazole, Fexinidazole (Hoe 239) In the treatment of chronic T. brucei infections in mice. Z Parasitenkd. 1983;69 (5): 577-81

Drug repurposing: attractive but …

Research

- Screening of marketed drugs from commercially available collections
- Screening of (terminated) drug candidates from Pharmaceutical companies

Outcome:

several candidates identified

- antidepressants for HAT
- antihistaminics/antiallergics (anti-H1 inh.) for Chagas
- clofazimine and disulfiram for VL
- auranofin for HAT/VL/Chagas
- disulfiram for VL…

Drug ID	[a]L.don. axen.	[b]L. don. intracell	[c]Cytotox. mac.inf.	[d]Cytotox. PMM	[e]SI	Indication	Chemical Class	Mode of Action
Auranofin	0.11	>1.47	4.42	N/A	40	Antirheumatic	Gold agent	kappaB kinase and thioredoxin reductase inhibitor
Amphotericin B	0.34	0.31	32.4	22.39	95	Antifungal/ Antiprotozoal	Polyenes	Membrane cell sterol binder
Ciclopirox olamine	1.64	9.09	20.3	20.27	12	Antifungal	Pyridinones	Polyvalent metal cation chelator
Tolnaftate	4.33	50.1	97.6	N/A	> 23	Antifungal	Thiocarbamates	Squalene epoxidase inhibitor
Artesunate	0.35	>7.8	7.8	N/A	> 22	Antimalarial	Endoperoxides	Unknown, acting via reactive oxygen radical species
Rifamycin SV	1.5	>13.87	41.62	N/A	28	Antibacterial/ Antituberculotic	Rifamycins	bacterial DNA-dependent RNA synthesis inhibitor
Rifampicin	1.53	>36.45	36.5	N/A	> 24	Antibacterial/ Antituberculotic	Rifamycins	Bacterial DNA-dependent RNA synthesis inhibitor
Nitrofurantoine	2.12	>41.81	125.44	N/A	59	Antibacterial	Nitroheterocycles	Oxygen-insensitive NADPH nitroreductase
Nifurtimox	2.76	20.68	34.8	15.7	13	Antibacterial/ Antiprotozoal	Nitroheterocycles	Induction of oxidative stress in target cells
Troglitazone	4.26	>67.94	68	N/A	> 16	Antidiabetic/ Antinflammatory	Thiazolidinediones	Nuclear receptor (PPAR) binder
Clofazimine	22.39	0.95	6.34	10.65	10	Antibacterial/ Antituberculotic	Riminophenazines	Mycobacterial DNA binder, Redox cycling, Cell membrane destabilizer, Acid sphingomyelinase inhibitor
Nifuroxazide	2.83	>10.86	36.2	N/A	13	Antibacterial	Nitroheterocycles	Lipoamide dehydrogenase inhibition
Tipranavir	1.64	>49.78	50	N/A	> 30	Antiviral/ Antiretroviral	Protease Inhibitors	HIV protease inhibitor
Lonidamine	8.66	>93.41	93.4	N/A	> 11	Anticancer	Indazoles	Glycolysis inhibition via hexokinase activation

Kaiser M, Mäser P, Tadoori LP, Ioset J-R, Brun R (2015) Antiprotozoal Activity Profiling of Approved Drugs: A Starting Point toward Drug Repositioning. PLoS ONE 10(8): e0135556. doi:10.1371/journal.pone.0135556

BUT

Key issues preventing further development

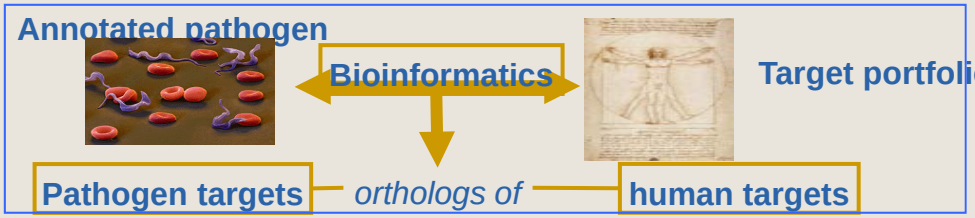
- unsuitable drug profile: lack of oral bioavailability, toxicity (safety marging)
- potency disconnect between primary (nM) and ND targeted (uM) indications

target drug classes: the added value of working with annotations

Research

- **Track record in R&D -> reduced attrition rate**
- **Access to analogs, data and expertise from Pharma**
- **Proceed quickly to PoC of in vivo efficacy**

- Oxaboroles (Anacor) **-> SCYX-7158 for HAT**
- Nitroimidazoles (TB Alliance) **-> VL-2098 and back-ups for VL**
- Other classes related to anti-infectives/oncology (macrolides, …)
- Orthologs to targets relevant to parasites (Sanofi)



- DMPK collections (Sanofi, GSK, Abbvie)
- Inhibitors of putative targets

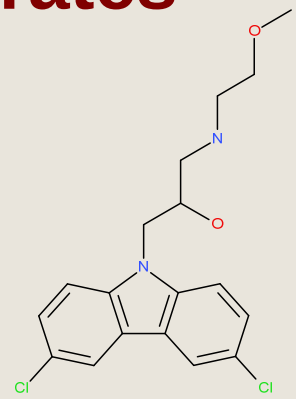
trypanothione reductase, PDE, HDAC, adenosine A2a antagonists, fatty acid synthase, methionine aminopeptidase 2, DHFR, squalene synthase, protein farnesyltransferase, cystein protease,…)

Compound collections biased for biological activities: enriched hit rates

Open Access Malaria Box

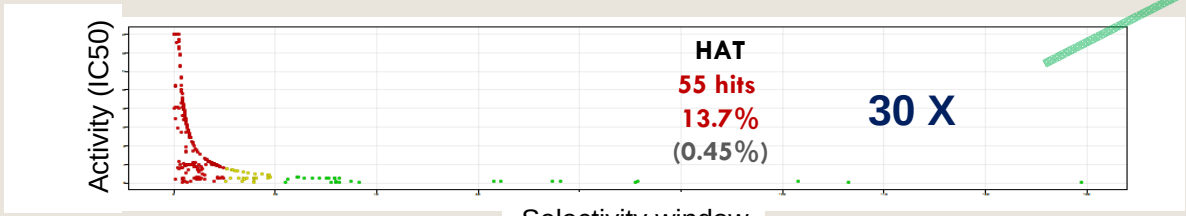
400 P. falciparum actives

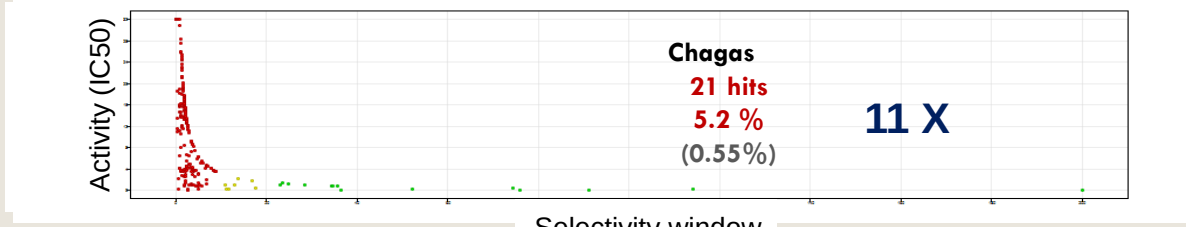
Research

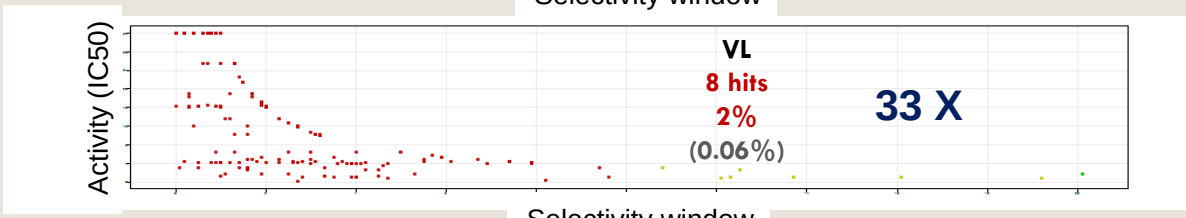


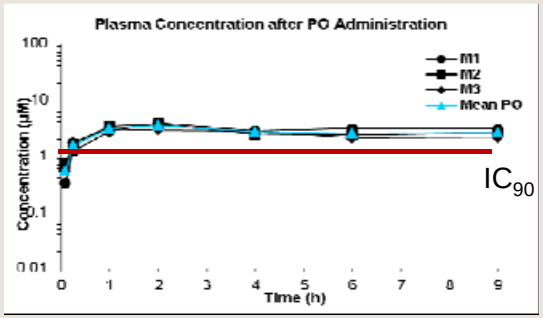
MMV019017

HAT in vitro
T. b. rhod. STIB 900
IC50 0.36 uM
IC90 1.41 uM



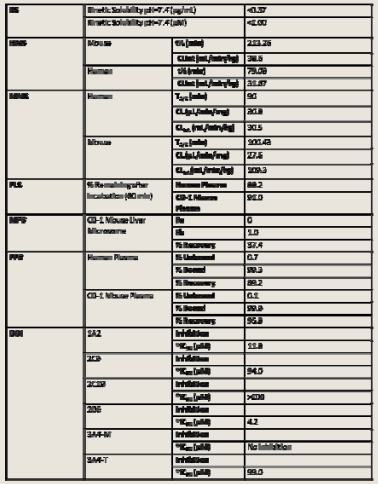






Administered dose (mg/kg) (PO)	59.13
Administered dose (µmol/kg) (PO)	161
Cmax (µmol/L)	3.57
Tmax (h)	1.66
T1/2 (h)	NR
Tlast (h)	9
AUC0-last (h*µmol/L)	24.13
AUC0-inf (h*µmol/L)	NR
MRT0-last (h)	4.44
MRT0-inf (h)	NR
AUC0-inf/AUC0-last (%)	NR

hERG % I (11uM)	82.69
hERG % I (1uM)	14.22



MMV Medicines for Malaria Venture

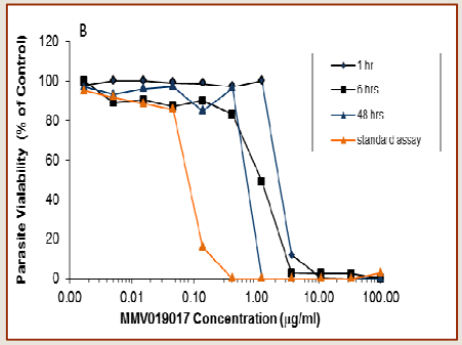
LMPH

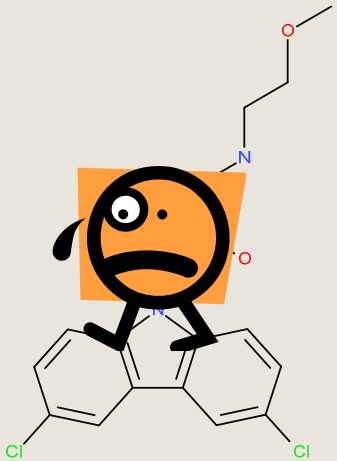
Swiss TPH Swiss Tropical and Public Health Institute Schweizerisches Tropen- und Public Health-Institut Institut Tropical et de Santé Publique Suisse

DNDi Drugs for Neglected Diseases *initiative*

Kaiser, M., Maes, L., Tadoori, L. P., Spangenberg, T, Ioset J.-R. Repurposing of the Open Access Malaria Box for kinetoplastid diseases identifies novel active scaffolds against trypanosomatids Journal of Biomolecular Screening 2015; 20(5): 634-45. doi:10.1177/1087057115569155.

… but in vitro potency and nice PK profile is not all!





MMV019017

HAT in vitro
T. b. rhod. STIB 900
IC50 0.36 uM
IC90 1.41 uM

		drug exposure time (h)			
	µM	1	6	24	72 standard assay
MMV665961	IC50	4.72±1.76	0.96±0.08	0.67±0.03	0.15±0.05
	IC90	9.05±1.22	2.16±0.60	1.72±0.94	0.29±0.05
MMV019017	IC50	2.36±0.28	1.18±0.47	0.71±0.05	0.08±0.03
	IC90	4.76±2.26	3.202±0.36	1.08±0.11	0.162±0.07

MMV19017 is a slow-killer

	T.b.rhodesiense STIB900					
in µg/ml	5%		15%		30%	
Compound	IC50	IC90	IC50	IC90	IC50	IC90
MMV000498			0.336	1.84	0.551	1.7
MMV665961	0.023	0.077	0.145	0.285	0.217	0.394
MMV019017	0.002	0.013	0.084	0.165	0.251	0.429
MMV019746			0.602	1.13	1.83	2.91

Activity of MMV19017 is affected by increase in serum concentration

	Treatment period (days)	Dose (mg/kg/day)	Route	Cured / infected
Control				0/4
MMV 019017	4	60	p.o.	0/4

MMV19017 is not active in vivo

DNDi
Drugs for Neglected Diseases *initiative*

Kaiser, M., Maes, L., Tadoori, L. P., Spangenberg, T, Ioset J.-R. Repurposing of the Open Access Malaria Box for kinetoplastid diseases identifies novel active scaffolds against trypanosomatids Journal of Biomolecular Screening, 2015; 20(5): 634-45, doi:10.1177/1087057115569155

Chemical Diversity : outcome

Research

Partner	Size	Nature of library	Pathogen	Outcome
Scynexis	100’008+	Scynexis Original Collection + few early collaboration (WEHI, Genzyme)	HAT	12 scaffolds, dropped
Eskitis	200’000	Natural Products (fractions)	HAT	2 scaffolds, dropped
WEHI	100’000	WEHI (commercial libraries)	HAT	10 scaffolds, H2L at WEHI
BioFocus	40’000	focused sets	HAT	3-4 scaffolds selected, not pursued
IPK	200’000	IPK (several commercial libraries)	VL	10 scaffolds, 1 selected for LO
GNF	700’000	GNF non-proprietary library	HAT, VL	10 scaffolds for VL, HAT (GNF and coll.), 2 Cha
Broad Institute	300’000	NIH library	Chagas	10 scaffolds in H2L/LO
Univ Dundee	100’000+	Various sets (commercial+HAT programme+VL programme)	VL	1 scaffold in H2L

low yield (especially for VL) and high attrition rate

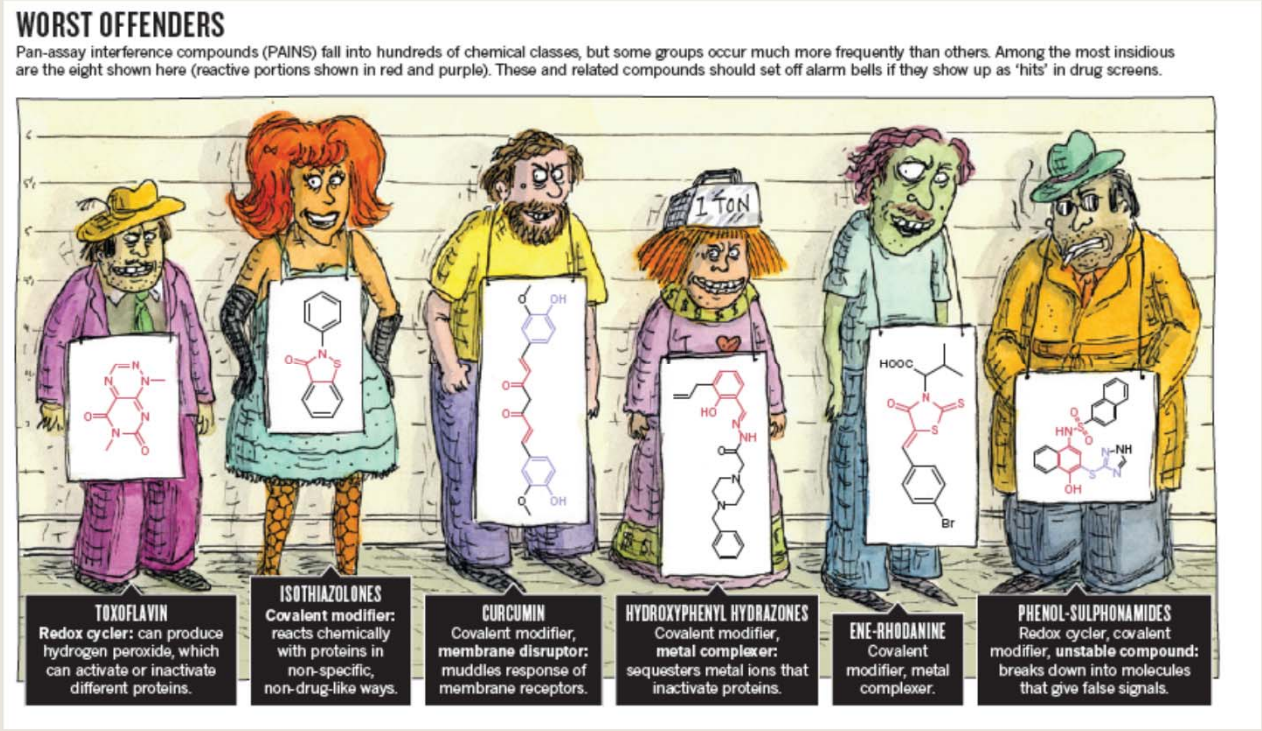
lack of related R&D knowledge -> focus on Pharma collections

Reducing the odds : getting rid of the garbage

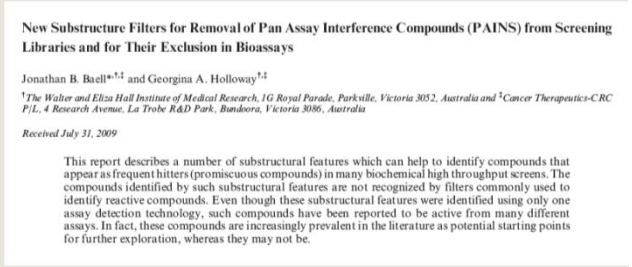
PAINS as Pan-Assay-INteference compoundS

Research

PAINS are sets of chemical motifs likely to be promiscuous inhibitors (= frequent hitters = false positives) in an assay



"Naivety about promiscuous, assay-duping molecules is polluting the literature and wasting resources" warn Jonathan Baell and Michael A. Walters



New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays

Jonathan B. Baell*,†,‡ and Georgina A. Holloway†,‡

†The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3052, Australia and ‡Cancer Therapeutics-CRC P/L, 4 Research Avenue, La Trobe R&D Park, Bundoora, Victoria 3086, Australia

Received July 31, 2009

This report describes a number of substructural features which can help to identify compounds that appear as frequent hitters (promiscuous compounds) in many biochemical high throughput screens. The compounds identified by such substructural features are not recognized by filters commonly used to identify reactive compounds. Even though these substructural features were identified using only one assay detection technology, such compounds have been reported to be active from many different assays. In fact, these compounds are increasingly prevalent in the literature as potential starting points for further exploration, whereas they may not be.

Baell JB, Holloway GA. New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. J Med Chem. 2010 Apr 8;53(7):2719-40. doi: 10.1021/jm901137j.

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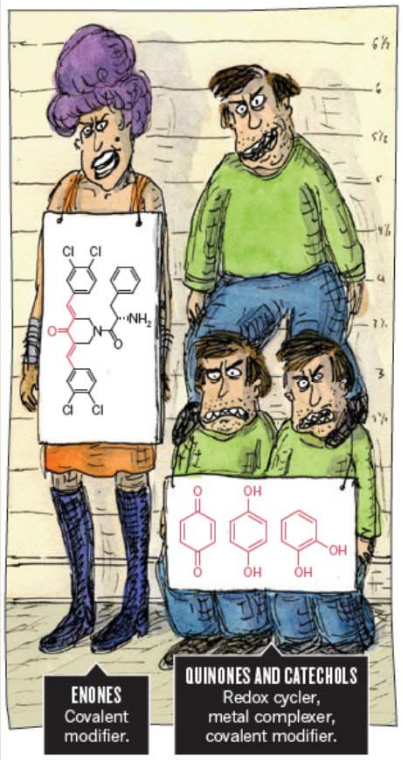
Reducing the odds : getting rid of the garbage

PAINS filters

Research



THREE TIPS

PAINS-proof drug discovery

Learn disreputable structures. Pan-assay interference compounds (PAINS) encompass some 400 structural classes, but more than half of PAINS in a typical library fall into just 16 easily recognizable categories[1,2]. Software tools can filter PAINS from screening libraries, but they are no match for sharp-eyed scientists.

Researchers should familiarize themselves with the most common structures and consult with PAINS-savvy medicinal chemists when these structures show up in hits. Scan compounds for functional groups that could have reactions with, rather than affinity for, proteins. These may not be flagged as PAINS, but can be similarly misleading.

Check the literature. Search by both chemical similarity and substructure to see if a hit interacts with unrelated proteins or has been implicated in non-drug-like mechanisms. Online services such as SciFinder, Reaxys, BadApple or PubChem can assist in the check for compounds (or classes of compound) that are notorious for interfering with assays.

Assess assays. For each hit, conduct at least one assay that detects activity with a different readout. Be wary of compounds that do not show activity in both assays. If possible, assess binding directly, with a technique such as surface plasmon resonance.

Drill into further details. Compounds that become more active over time are probably acting through non-drug-like mechanisms. When a compound is tested with a protein and then diluted away, its activity should decrease. If not, it might be a PAINS.

Verify the identity and purity of hits. Sometimes a positive readout is due to an unstable breakdown product of the chemical identified from the screening library[1,2]. Remake or repurify these molecules and test them again. J.B. & M.A.W.

- **480 substructures (filters)**
- **Most PAINS fall within 16 substructural motifs**
- **Publicly available as SMARTS**
  http://blog.rguha.net/?p=850
- **5-12% of academic libraries**
- **Several substructures are found in NP**

Saubern, S. et al. KNIME workflow to assess PAINS filters in SMARTS format. Comparison of RDKit and indigo cheminformatics libraries. Molecular Informatics, 2011, 30, 847 - 850

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Reducing the odds : getting rid of the garbage *toxicophores*

Research

List of reactive moieties related with toxicity effects (>100)

- **can be applied as filters to rule out unwanted compounds**
- **might not always be an issue: is the presence of the toxicophore essential to maintain activity? can it be replaced?**

Michael_acceptors	[#6]C(=O)C=C([H1])[#6]
beta_hetero_substituted_carbonyl	C(=O)CC(C)[N;R0,O;R0]
N_N	[#6]N-N[#6]
N_O	[#6]N-O[#6]
N_S_(not_sulfonamides)	[#6][S;O0][N;H0]
non_ring_S-O	[S;R0][O;R0]
triphenylphosphines	P(c1aaaaa1)(c1aaaaa1)(c1aaaaa1)
diazonium	cN=Nc
polyene_chain_between_aromatics	cC=CC=CC=Cc
pyrene_fragments	c1c2cccc3c2c4c(cc3)cccc4c1
reactive_carbonyls_and_sulfonyls	C=[O,S][S,CF,CBr,CCl]
non_ring_S=N	[S;R0]=[N;R0]
thiourea	NC(=S)N

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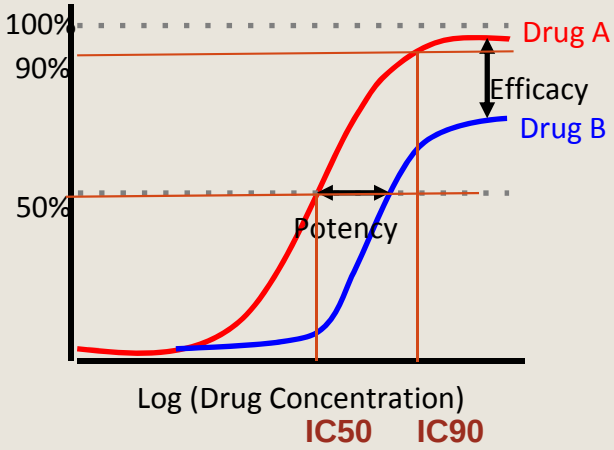
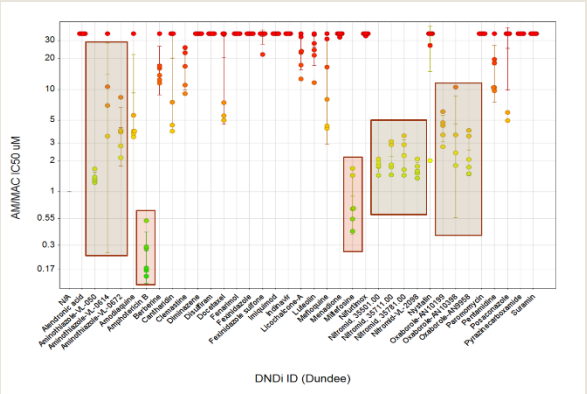
Drugs for Neglected Diseases *initiative*

Hit identification and prioritization

- **Activity**
- **Selectivity**
- **Quality**





Criteria of selection			
assay-related		**compound-related**	
relevance to the disease?	*promastigote* *epimastigote* trypomastigote axenic intracellular	chemical characterization	ID salt stereochemistry
relevance of end point?	IC50,IC90,Max %, hill slope,…		
performance	controls, Z', heat maps,…	purity	QC (>90/95%) resynthesis
criteria of selection	Ref below	drug-likeness	Ref below

standardization - *benchmarking*
continuous optimization of assay protocols
better undertstanding of assays

Don R, Ioset JR. Screening strategies to identify new chemical diversity for drug development to treat kinetoplastid infections.Parasitology. 2014 Jan;141(1):140-6. doi: 10.1017/S0031182013001420X

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Identifying and addressing the challenges : VL

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Global Hit rates of kinetoplastid screens

Research

Assay	Compounds screened	Average Hit Rate	Range
T. brucei	ca 1.3 M	0.45 %	0.1-1.2 %
Leishmania donovani (intracellular)	ca 500 K	**0.06 %**	**0.02 - 0.09 %**
T. cruzi (intracellular)	ca 500 K	0.55 %	0.03 - 0.85 %

hit is defined as non-cytotoxic (SI>10) and IC_{50} < 2μM (HAT), <10 μM (VL) and <5uM (Chagas)

VL: 6 hits out of 10'000 compounds !

before hit analysis (clustering, toxicity/reactivity, physchem properties)

Attrition stikes early on: hit confirmation rate

Challenge: Deliver novel quality starting points for VL

Don R, Ioset JR. (2013). Screening strategies to identify new chemical diversity for drug development to treat kinetoplastid infections. Parasitology, 28:1-7.

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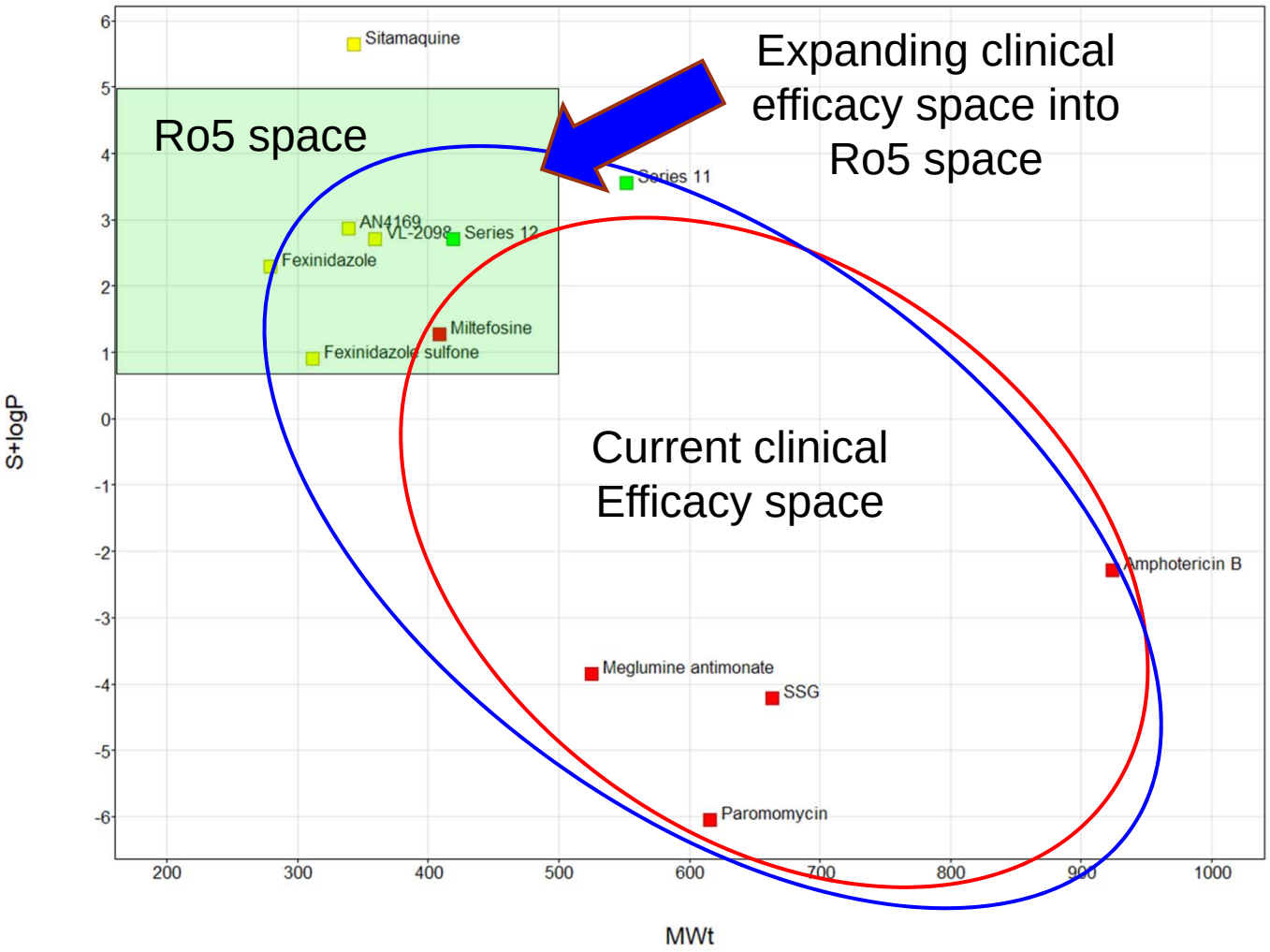
Evolution of drug chemical space for VL

Combining good drug-like properties and clinical efficacy

Research



S+logP model is based on artificial neural network ensembles (ANNE) constructed by our automatic model builder ADMET Modeler™ from almost 13,000 example compounds selected from the "StarList" of ion-corrected experimental logP values (Hansch, C. et al, 1995).

Adressing the challenges

Research

- **Develop and validated cost-effective higher throughput assays predictive of L. don. intracellular activity (cidal axenic assay)**
- **Screen more: highly diverse, novel and high quality collections**
- **Confirm activity in INMAC VL assay (Qced material)**
- **Move quickly to PoC of in vivo efficacy (build SAR, PK)**
- **Better understand drivers of in vivo efficacy: transition cidal axenic -> INMAC, INMAC to in vivo, PK/PD for novel series**
- **Obtain rights to develop (H2L/LO and beyond)**
- **Avoid duplication**

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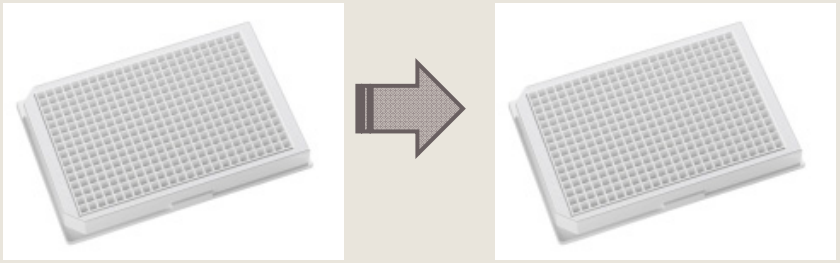
Leishmania cidal axenic assay

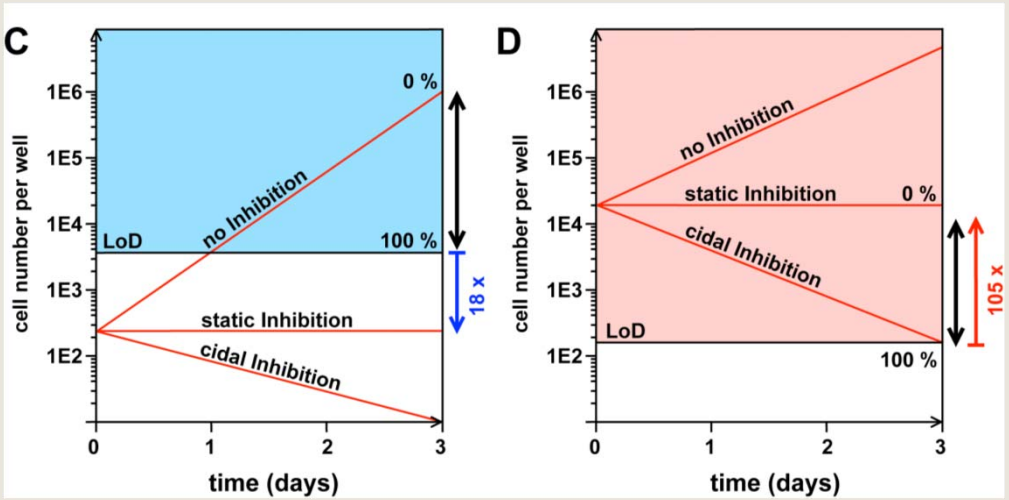
compounds

LdBOB
axenic amastigotes



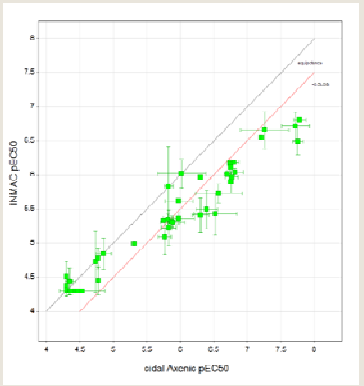
72 hours

in collaboration with University of Dundee and the Broad Institute

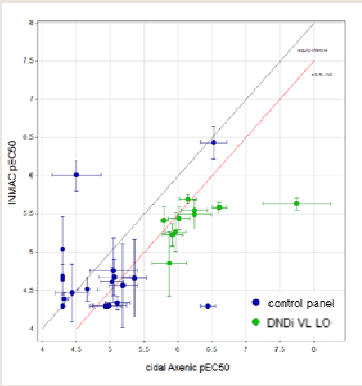


historical axenic assay

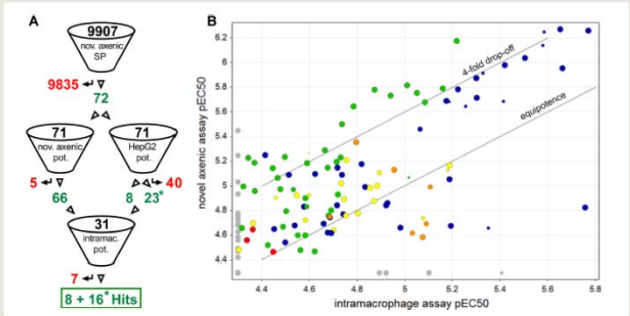
cidal axenic assay



Lead-Opt series



DNDi control panel



- **good correlation of potencies between cAxenic and INMAC assay -> predictivity**
- **screening of DOS collection (10K, Broad Institute): 2 novel series identified (INMAC activity confirmed)**

Nühs A, De Rycker M, Manthri S, Comer E, Scherer CA, Schreiber SL, Ioset JR, Gray DW. Development and Validation of a Novel Leishmania donovani Screening Cascade for High-Throughput Screening Using a Novel Axenic Assay with High Predictivity of Leishmanicidal Intracellular Activity. PLoS Neglected Tropical Diseases 2015 25;9 (9): e0004094. doi: 10.1371/journal.pntd.0004094

Expand on diversity screening: a reasonable approach to generate novel active starting points

- **Pfizer global diversity research set (GDRS) 150’000**

- **Core diversity collection from Pharmas**

typically 10-50K collections

- **GSK global 1.8 M collection screening** (DDW Tres Cantos)

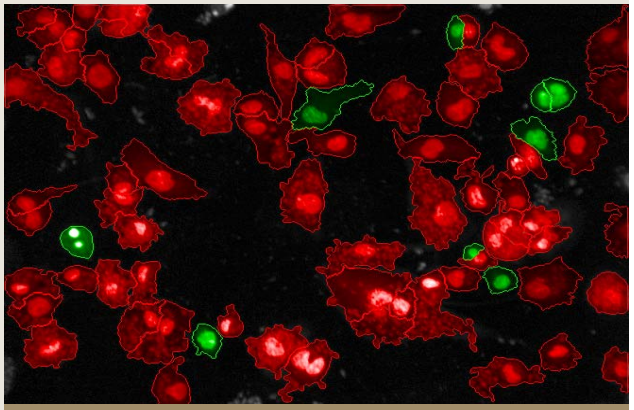
data and structures made public domain

- **Natural Product collections**

focus on pure compounds (Pharma and beyond)

- **Commercial collections**

novelty/diversity/quality and rights to develop/publish



THP1 cells infected with eGFP *L. donovani*
(DAPI staining, 20x objective)
in red: cells infected, in green: cells non infected
courtesy of GSK Tres Cantos

Peña L. et al. New compound sets identified from high throughput phenotypic screening against three kinetoplastid parasites: an open resource. Sci Rep. 2015 5;5:8771. doi: 10.1038/srep08771.

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Screening for more diversity

- **access commercial compound libraries within but also outside of Pharmaceutical partnerships**
  - complement on chemical diversity
  - de-risking IP restrictions/delays related hits identified from proprietary collections

access 0.5 Mio cpds to be screened against VL and secure screening capacity

- library only include structurally characterized chemicals
- access granted at no/low initial cost (apart from compound plating and material shipment)
- no IP restriction with regard access to chemical structures of entire file
- FTO related to hits (hits to be made public domain)

Status:

- 420K compound secured (Axxam, Biofocus and SPECS)
- contract in place at University of Dundee to screen 500K (started Q1 2015)
- Screening to be completed by end Q1 2016 (confirmation in INMAC assay)

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Identifying and addressing the challenges: Chagas

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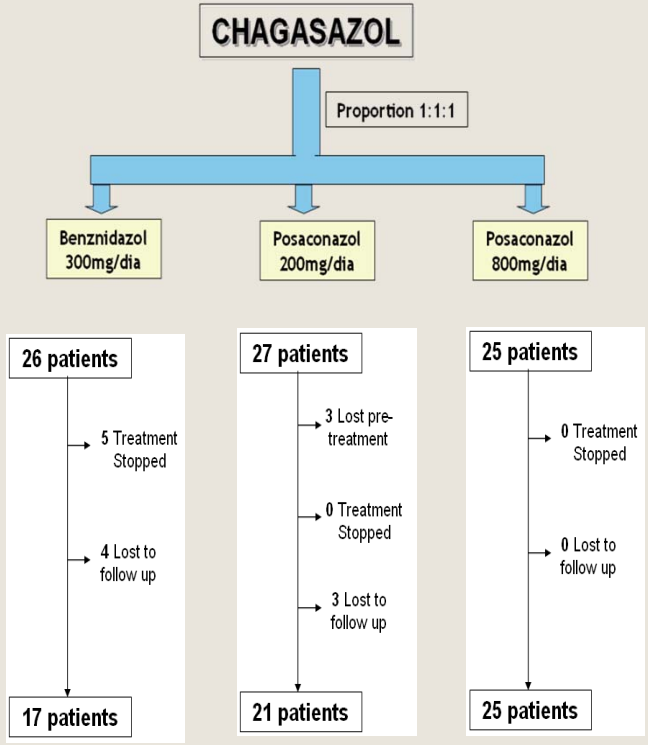
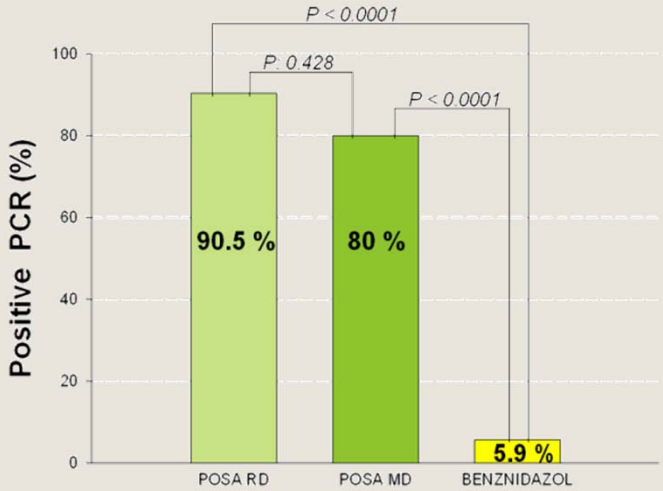
Better Understanding of assay models: Chagas learning from clinical trials

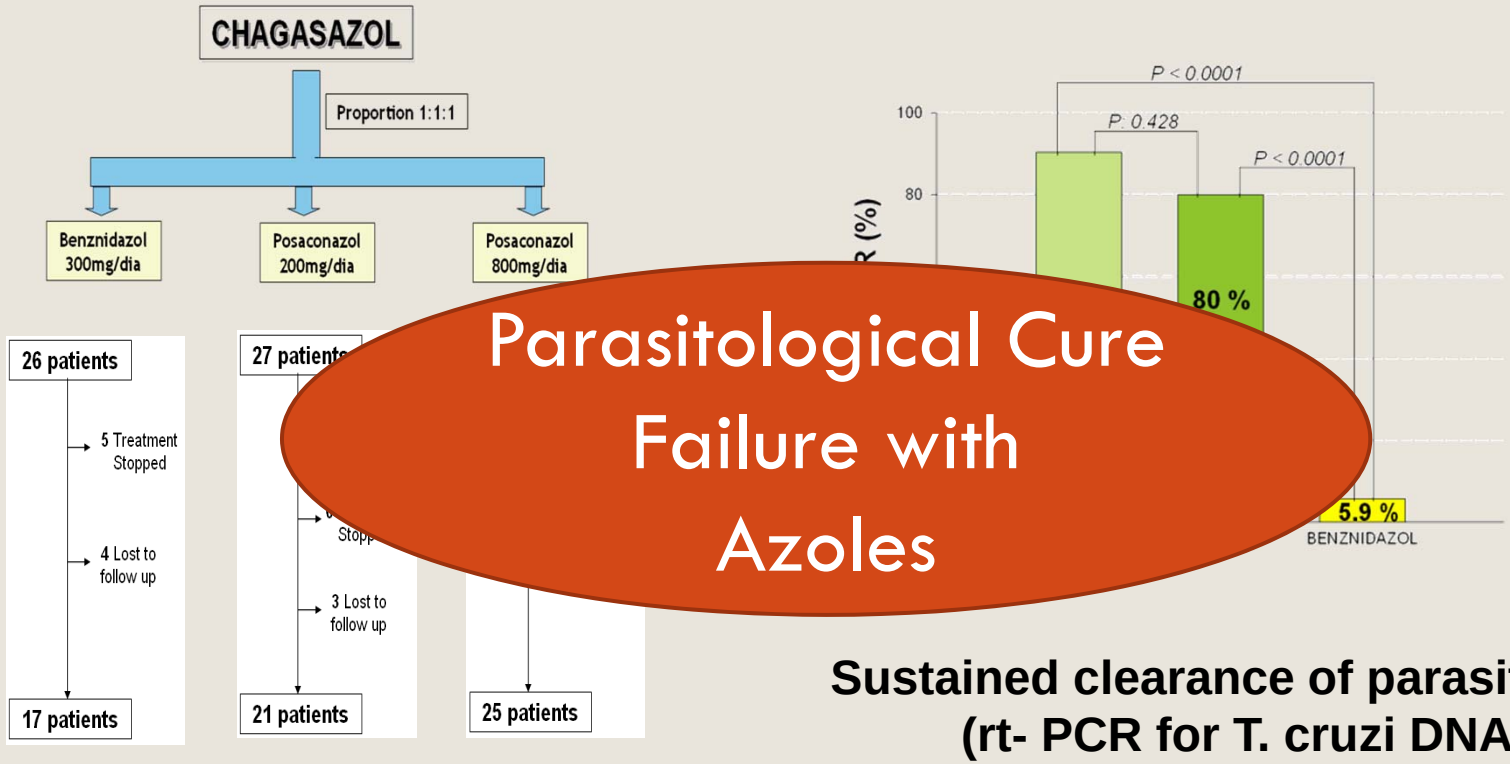




Sustained clearance of parasiteamia (rt- PCR for T. cruzi DNA) 10 months after treatment

Molina et al. N. Engl. J. Med. 2014 May 15;370(20):1899-908. doi: 10.1056/NEJMoa1313122.
Randomized trial of posaconazole and benznidazole for chronic Chagas' disease

Better Understanding of assay models: Chagas learning from clinical trials



Parasitological Cure Failure with Azoles

Sustained clearance of parasiteamia (rt- PCR for T. cruzi DNA) 10 months after treatment

Molina et al. N. Engl. J. Med. 2014 May 15;370(20):1899-908. doi: 10.1056/NEJMoa1313122.
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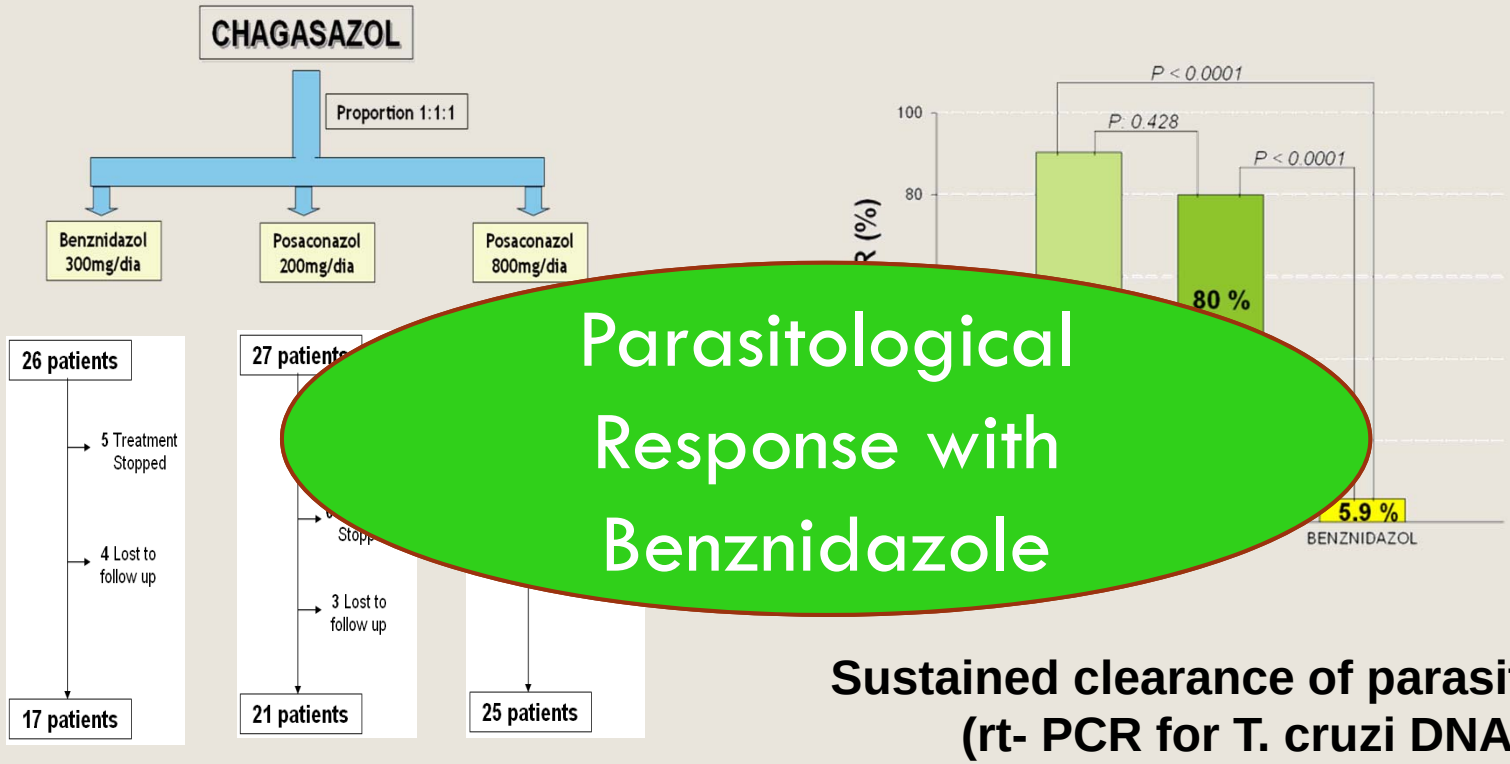


Parasitological Response with Benznidazole

Sustained clearance of parasiteamia (rt- PCR for T. cruzi DNA) 10 months after treatment

Molina et al. N. Engl. J. Med. 2014 May 15;370(20):1899-908. doi: 10.1056/NEJMoa1313122.
Randomized trial of posaconazole and benznidazole for chronic Chagas' disease

Impact on Chagas discovery screening cascade

Research

- **Deprioritze azoles as a class**
- **Deprioritize any alternative CYP51 inhibitors**

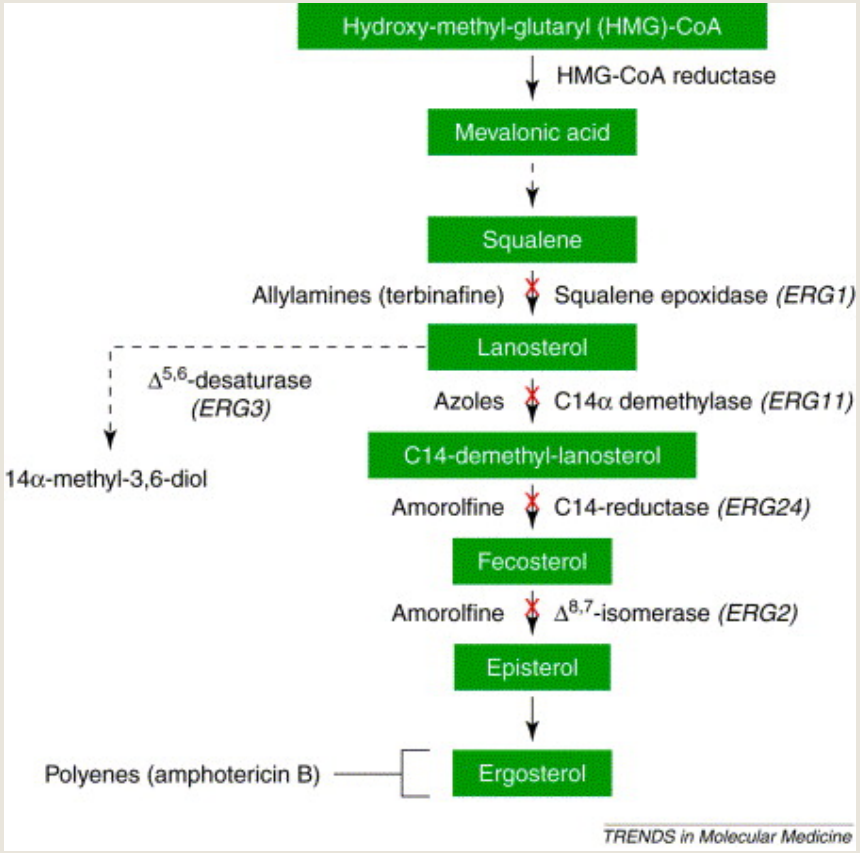
and likely

- **Deprioritize any inhibitor of the Sterol biosynthesis pathway**

Way forward:

- can we reproduce this observation at the preclinical level?

- can we develop suitable models to predict/rule out CYP51 inhibitors?



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Learning from clinical data in vivo Chagas murine chronic models

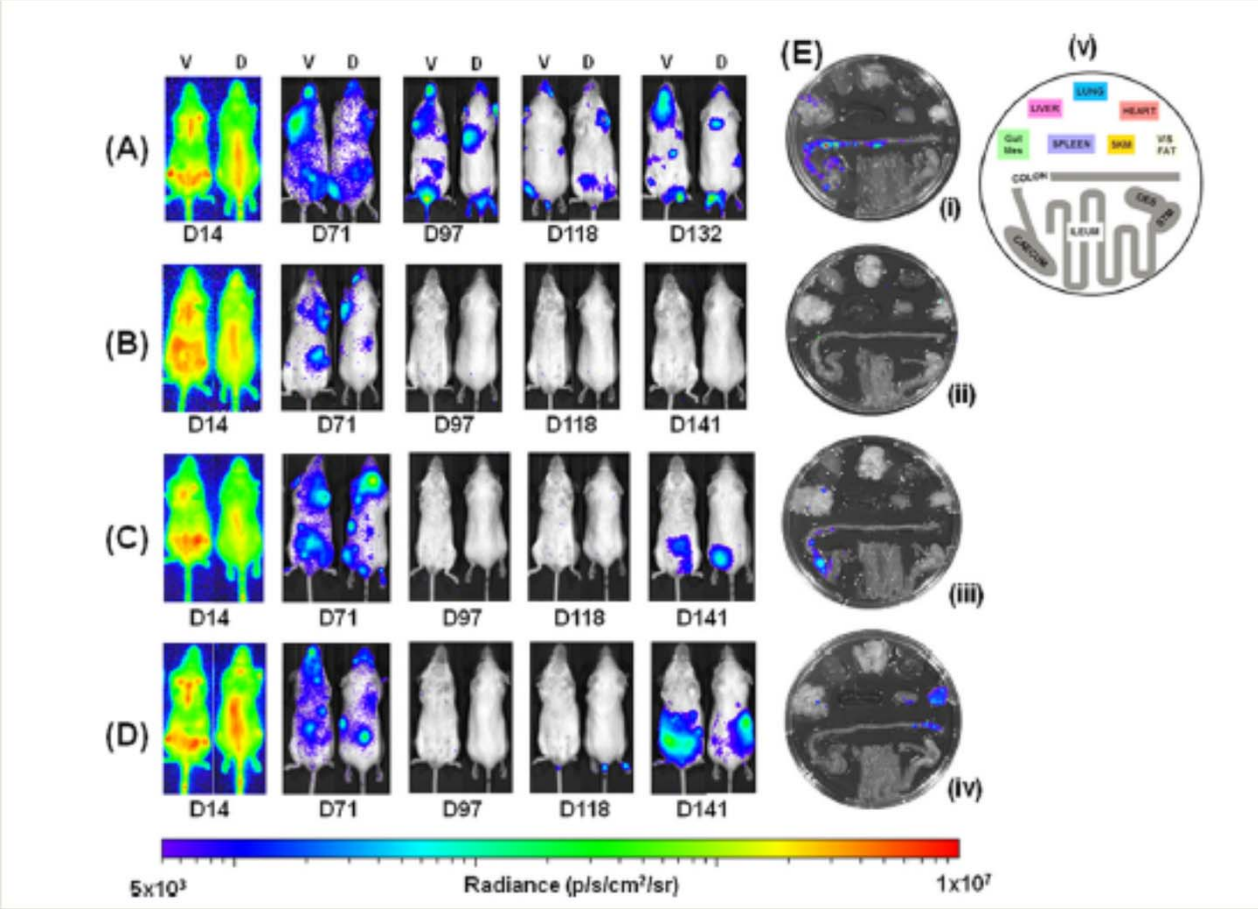
Research

untreated control

benznidazole

posaconazole (Noxafil)

posaconazole (HPMC-SV formulation)



AAC Journals.ASM.org

Limited Ability of Posaconazole To Cure both Acute and Chronic *Trypanosoma cruzi* Infections Revealed by Highly Sensitive *In Vivo* Imaging

Amanda Fortes Francisco,[a] Michael D. Lewis,[a*] Shiromani Jayawardhana,[a] Martin C. Taylor,[a] Eric Chatelain,[b] John M. Kelly[a]
Department of Pathogen Molecular Biology, London School of Hygiene and Tropical Medicine, London, United Kingdom[a]; Drugs for Neglected Diseases Initiative, Geneva, Switzerland[b]

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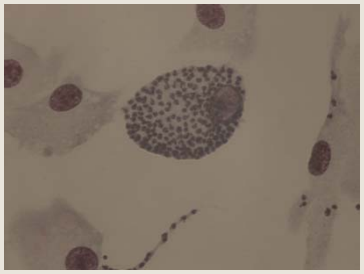
Better Understanding of assay models: Chagas

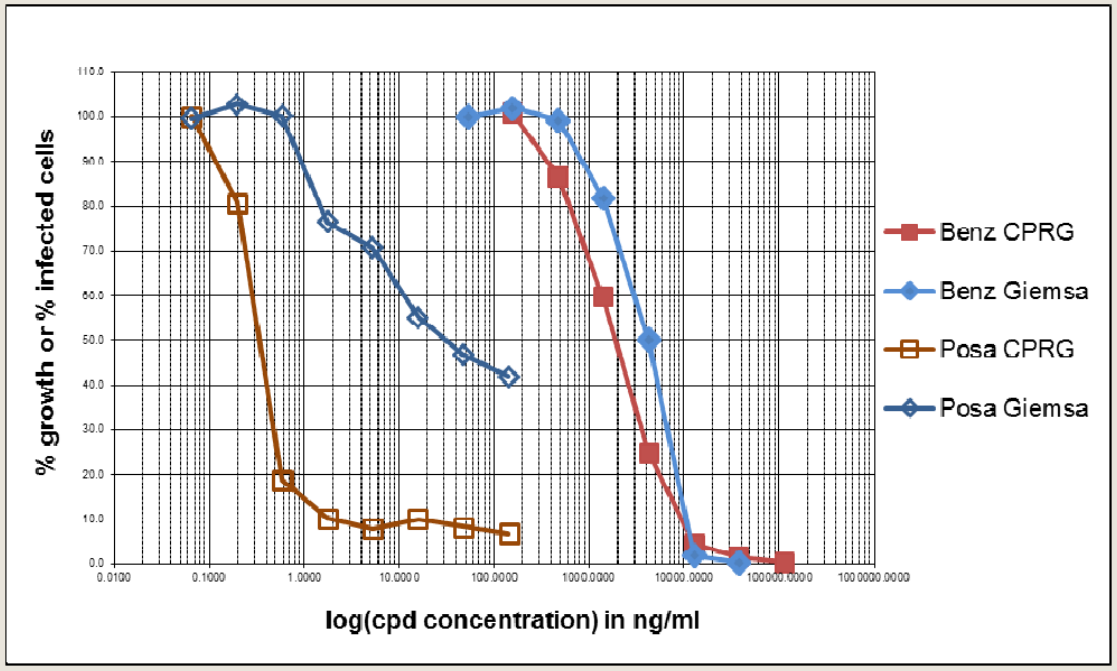
in vitro potency doesn't necessarily mean efficacy

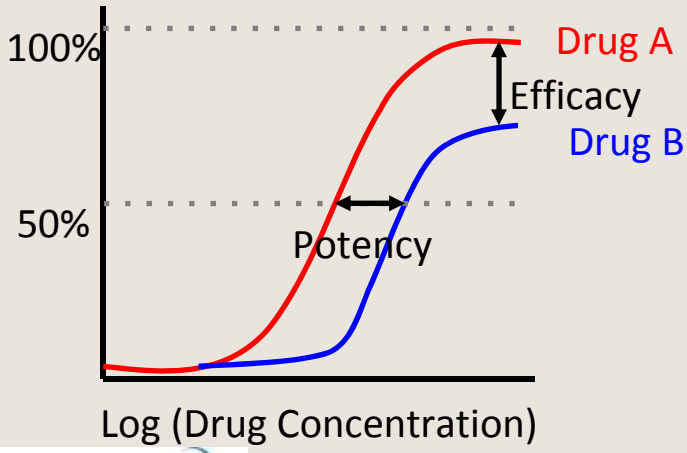
Research

Comparison of two T. cruzi assay read-outs CPRG (OD measurement) and microscopical counting of Giemsa stained cells.

	CPRG		Giemsa	
values in nM	**IC50**	**IC90**	**IC50**	**IC90**
Benznidazole (n=5)	984 ± 163	3237± 388	3011 ± 1206	9016 ± 3539
Posaconazole (n=2)	0.4	na	33.5	na







An in vitro assay to assess antichagasic candidates for sterile cure
Monica Cal, Jean-Robert Ioset, Matthias Fügi, Pascal Mäser, Marcel Kaiser, 9th ECTMIH meeting, Basel, 7-10 September, poster

Global Hit rates of kinetoplastid screens

Research

Assay	Compounds screened	Average Hit Rate	Range
T. brucei	ca 1.3 M	0.45 %	0.1-1.2 %
Leishmania donovani (intracellular)	ca 500 K	0.06 %	0.02 - 0.09 %
T. cruzi (intracellular)	**ca 500 K**	**0.55 %**	**0.03 - 0.85 %**

hit is defined as non-cytotoxic (SI>10) and IC_{50} < 2μM (HAT), <10 μM (VL) and <5uM (Chagas)

Chagas : 55 hits out of 10'000 compounds

before hit analysis (clustering, toxicity/reactivity, physchem properties)

Hit confirmation: higher than VL

So far so good but ...

Don R, Ioset JR. (2013). Screening strategies to identify new chemical diversity for drug development to treat kinetoplastid infections. Parasitology, 28:1-7.

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CYP51 inhibitors are prevalent…

Research

…and enriched in T. cruzi hit list

…in compound collections

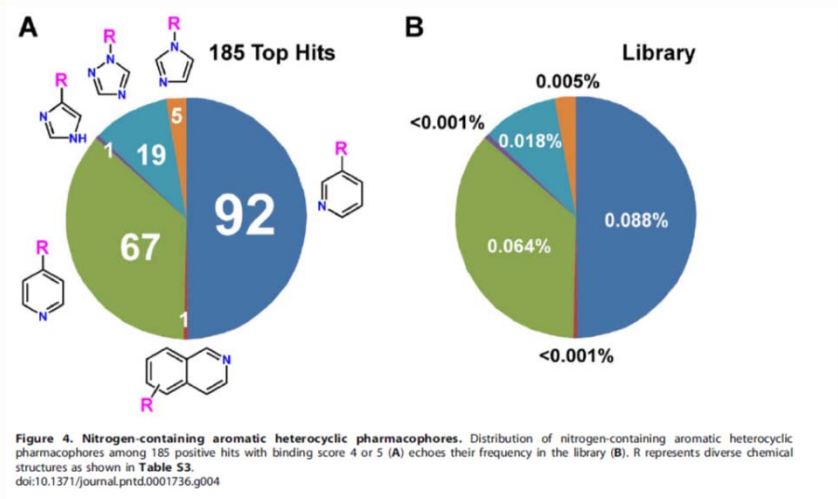


Figure 4. Nitrogen-containing aromatic heterocyclic pharmacophores. Distribution of nitrogen-containing aromatic heterocyclic pharmacophores among 185 positive hits with binding score 4 or 5 (**A**) echoes their frequency in the library (**B**). R represents diverse chemical structures as shown in **Table S3**.
doi:10.1371/journal.pntd.0001736.g004

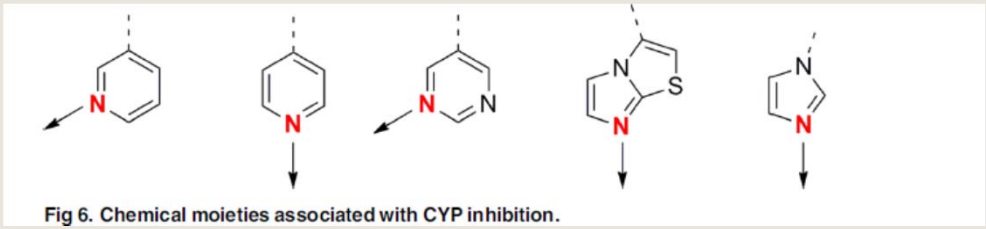
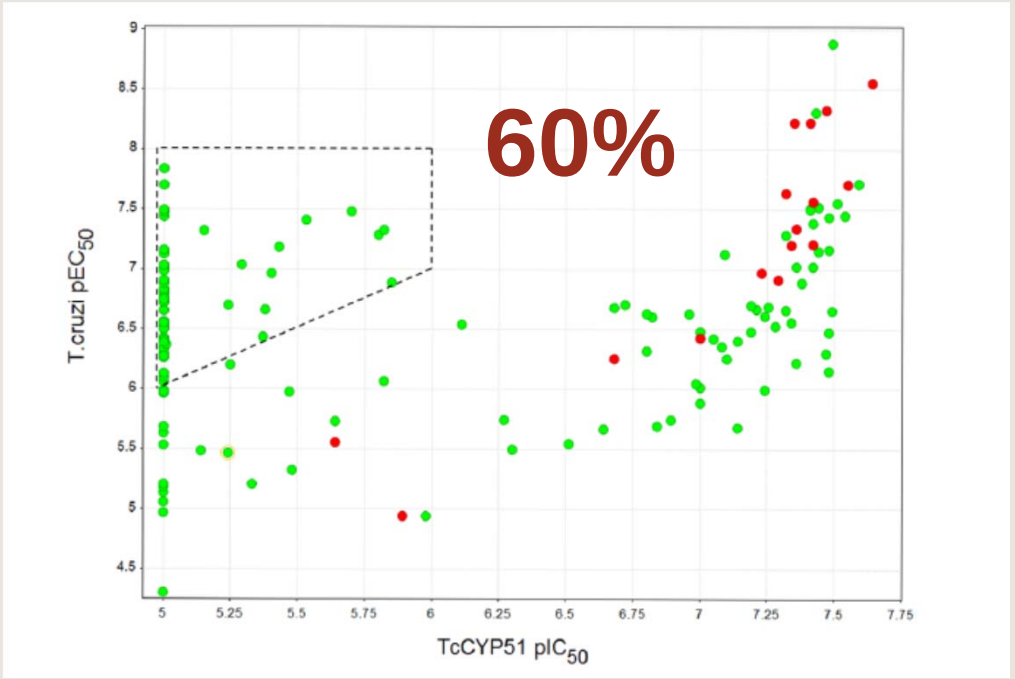


Fig 6. Chemical moieties associated with CYP inhibition.



Riley J, Brand S, Voice M, Caballero I, Calvo D, Read KD (2015) Development of a Fluorescence-based Trypanosoma cruzi CYP51 Inhibition Assay for Effective Compound Triaging in Drug Discovery Programmes for Chagas Disease. PLoS Negl Trop Dis 9(9): e0004014. doi:10.1371/ journal.pntd.0004014

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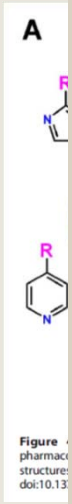
Citation: Gunatilleke SS, Calvet CM, Johnston JB, Chen C-K, Erenburg G, et al. (2012) Diverse Inhibitor Chemotypes Targeting *Trypanosoma cruzi* CYP51. PLoS Negl Trop Dis 6(7): e1736. doi:10.1371/journal.pntd.0001736

CYP51 inhibitors are prevalent…

Research

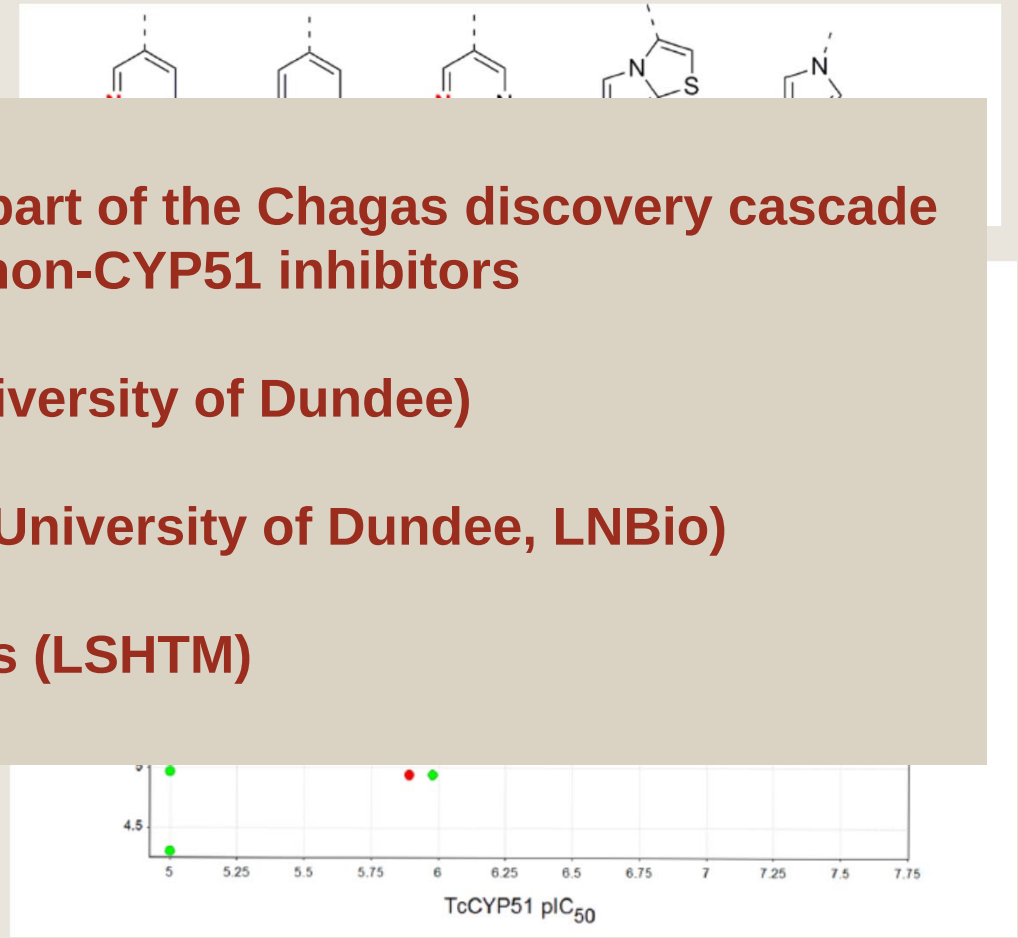
…and enriched in T. cruzi hit list

…in compound collections



Use of secondary assays as part of the Chagas discovery cascade to prioritize non-CYP51 inhibitors

- CYP51 functional assay (University of Dundee)
- in vitro MoA assays (STPH, University of Dundee, LNBio)
- In vivo acute/chronic models (LSHTM)



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Identifying and addressing the challenges: the NTD Booster

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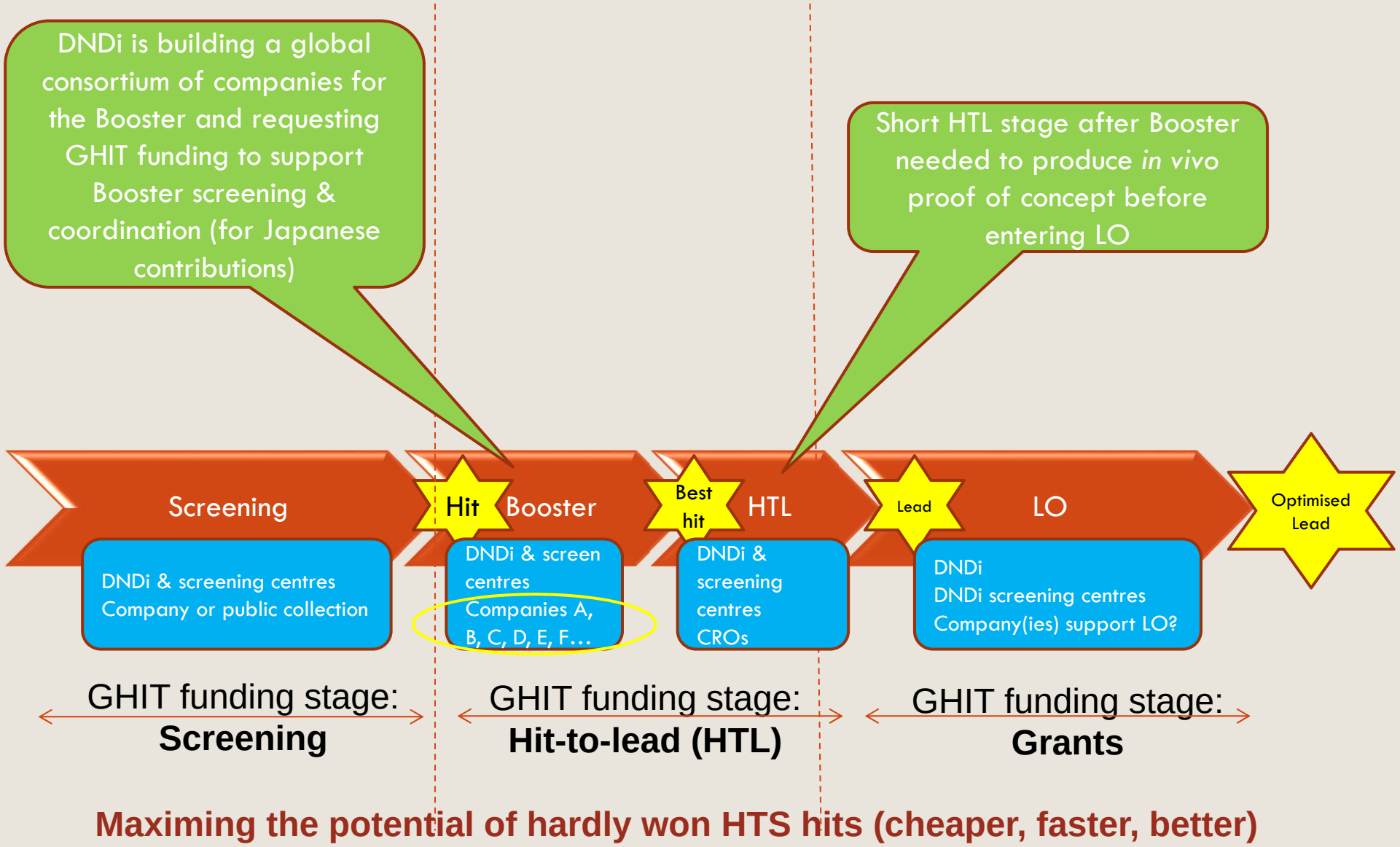
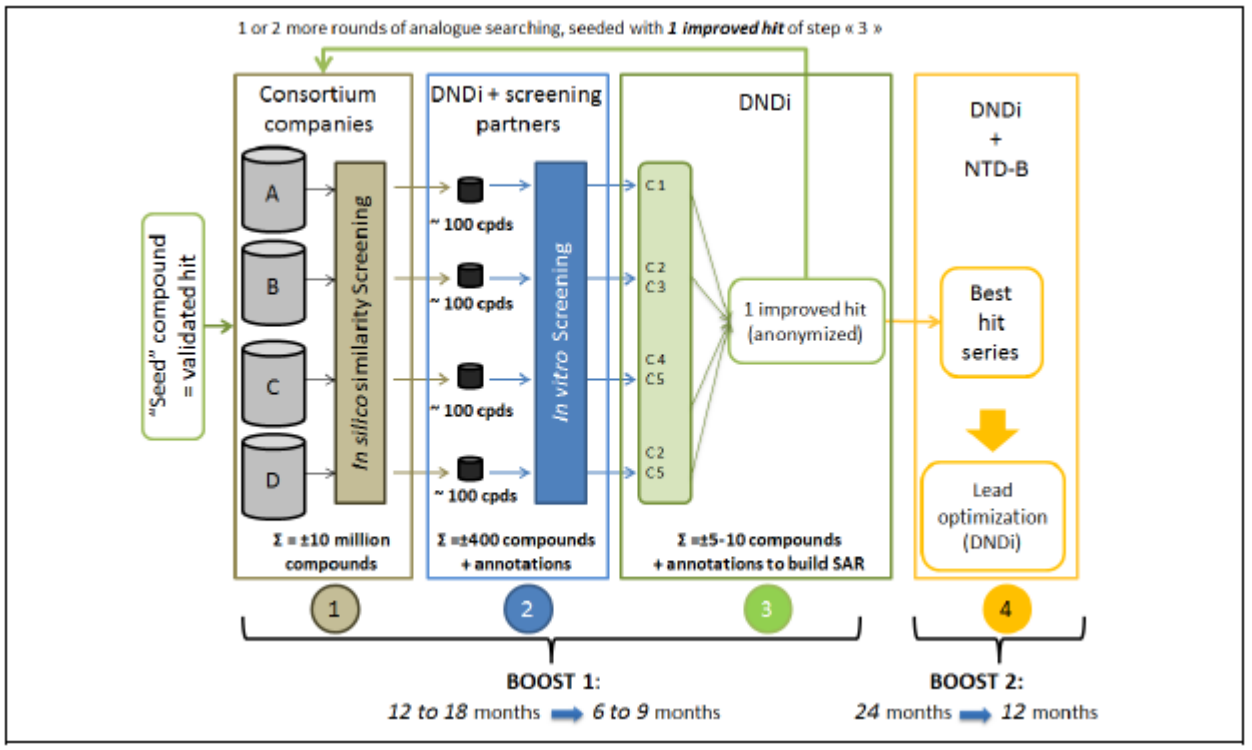
The NTD Drug Discovery Booster: an novel approach to address collaborative early drug discovery



Maximing the potential of hardly won HTS hits (cheaper, faster, better)

Overview of NTD Booster

Objective: Delivering Novel Chemical Series for Leishmaniasis & Chagas disease:
Overall during the first two years the Booster project will rapidly expand at least 4 promising hits/hit series each against *Leishmania donovani* and *Trypanosoma cruzi*, the causative agents of Leishmaniasis and Chagas disease, respectively. This will provide series with well-developed structure activity relationships (SAR) ready for immediate *in vivo* proof of concept studies or, where necessary, focused medicinal chemistry optimization to provide improved tools ready for *in vivo* studies. We aim that at least one novel chemical series will provide promising *in vivo* activity for each of the two parasites.



Takeda

Eisai

AstraZeneca

SHIONOGI

Institut Pasteur Korea

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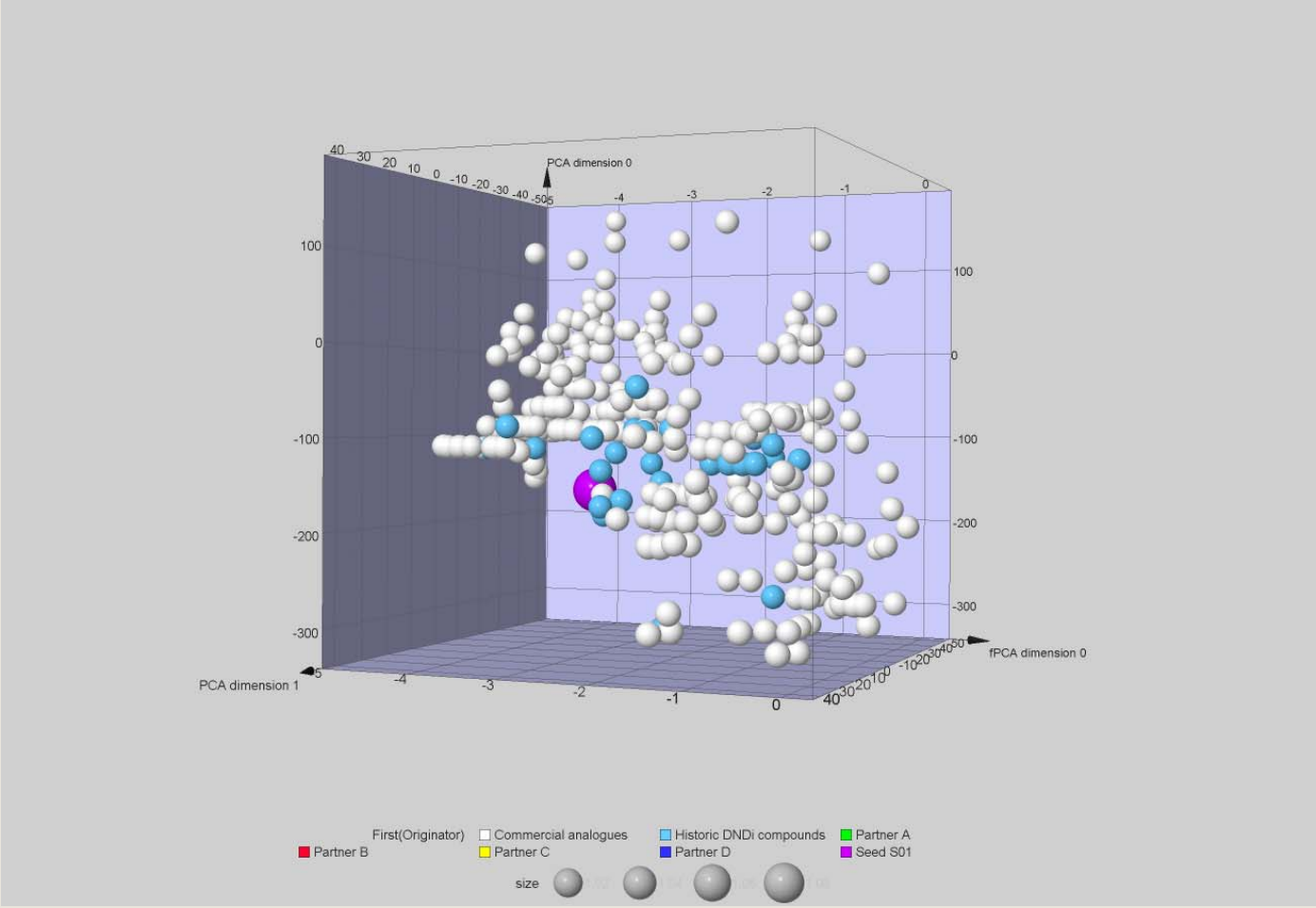
First Iteration: S01 - Results

Source	# hits
Seed S01	1
DNDi (Historic)	27
Commercial*	314
Partner A	~90
Partner B	~90
Partner C	~90
Partner D	~40

*(Scifinder 80% similarity search; used to represent possible chemical space)

Plot shows Coverage of «Chemical Space» around the starting seed.
Axes are Principal Component Analysis dimensions of Chemical fingerprint (X) and Molecular Properties (Y, Z)



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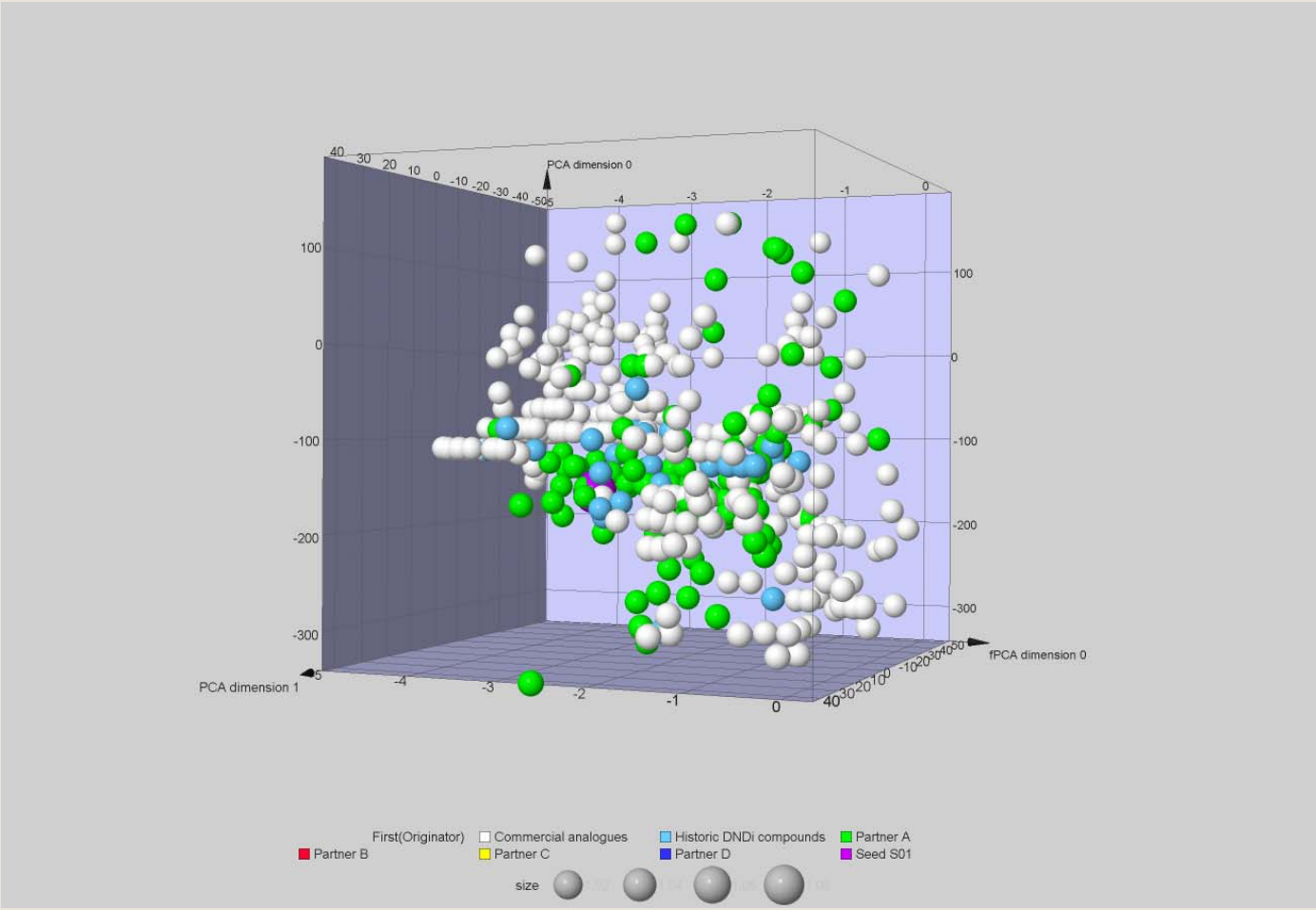

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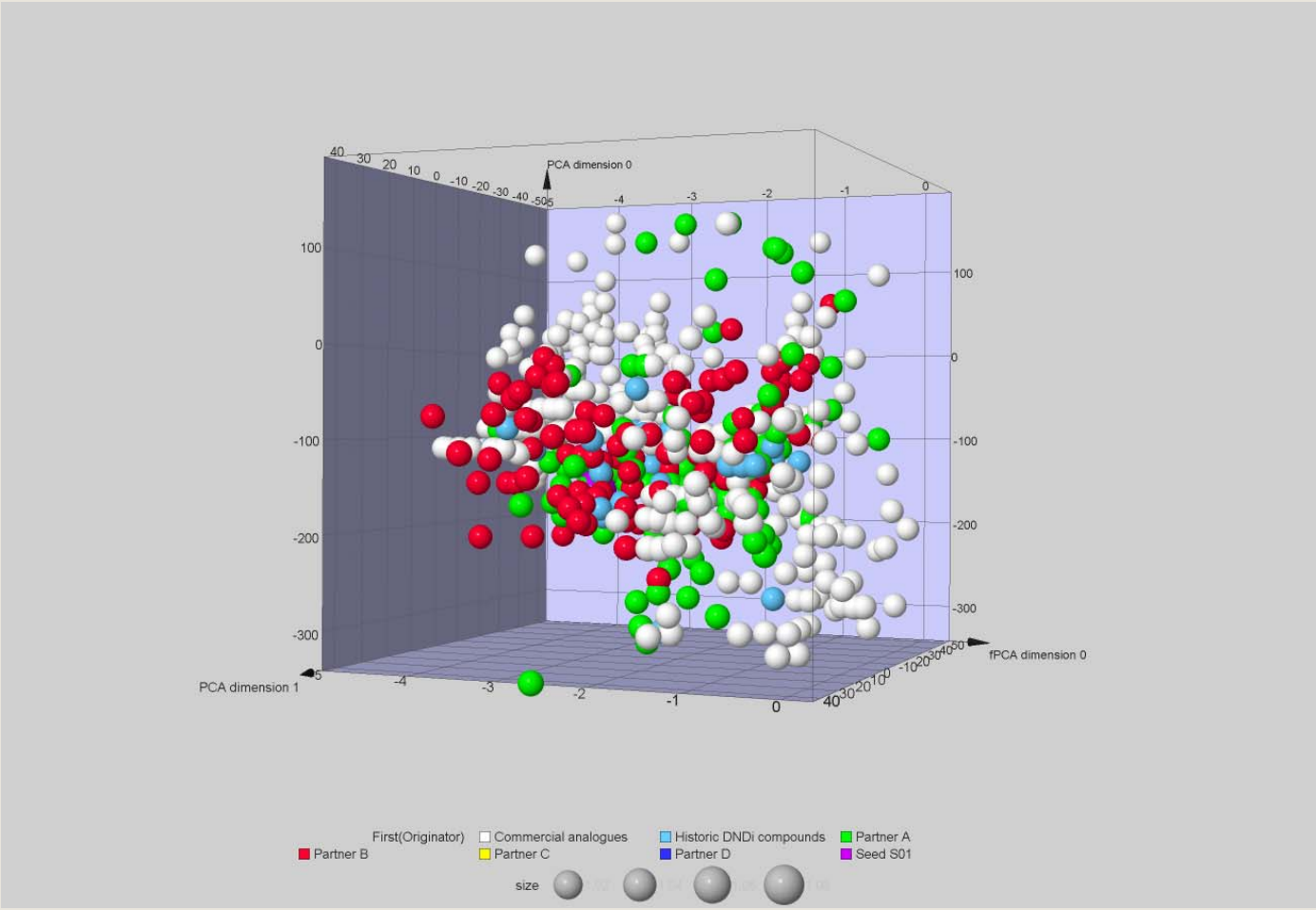

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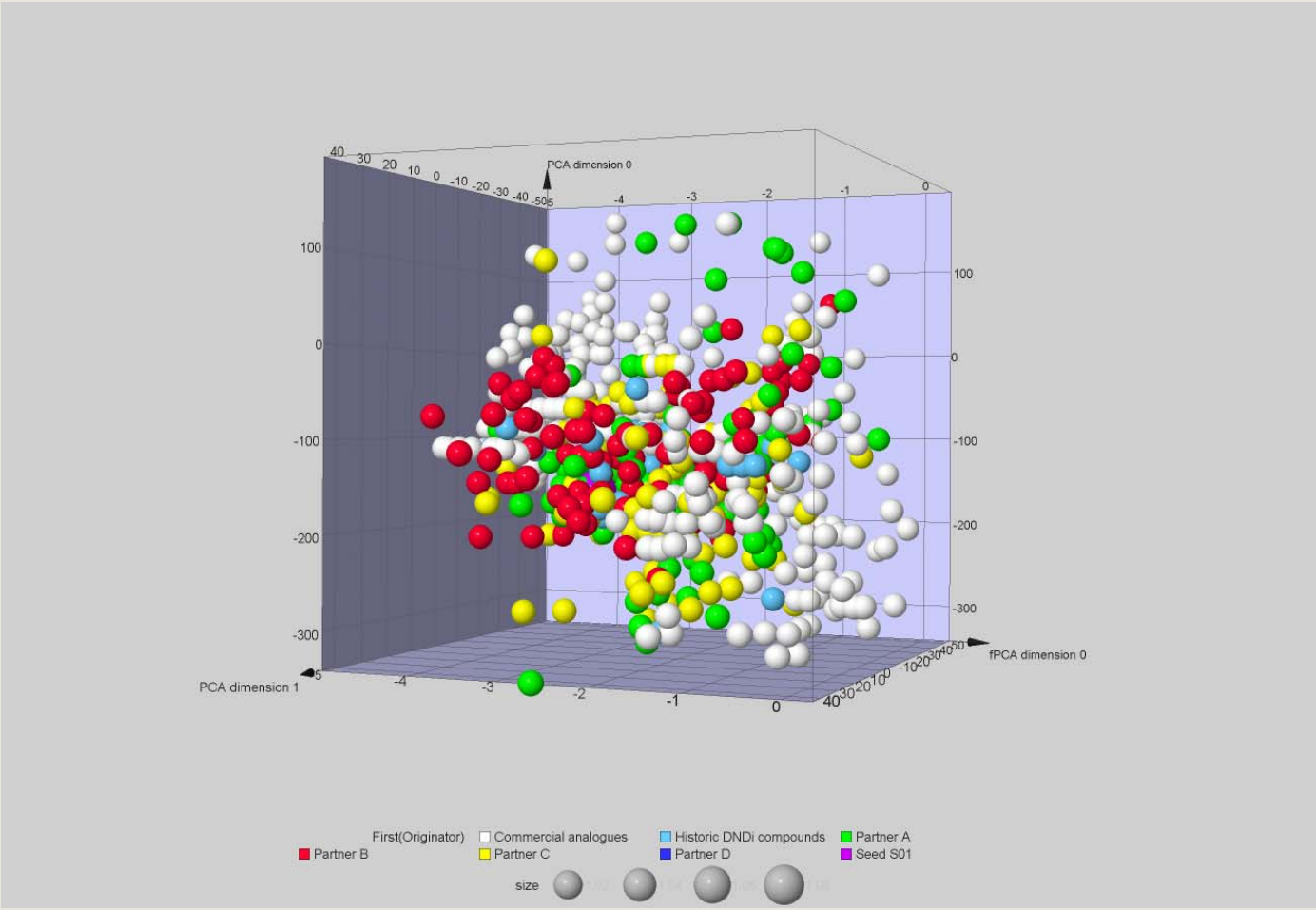

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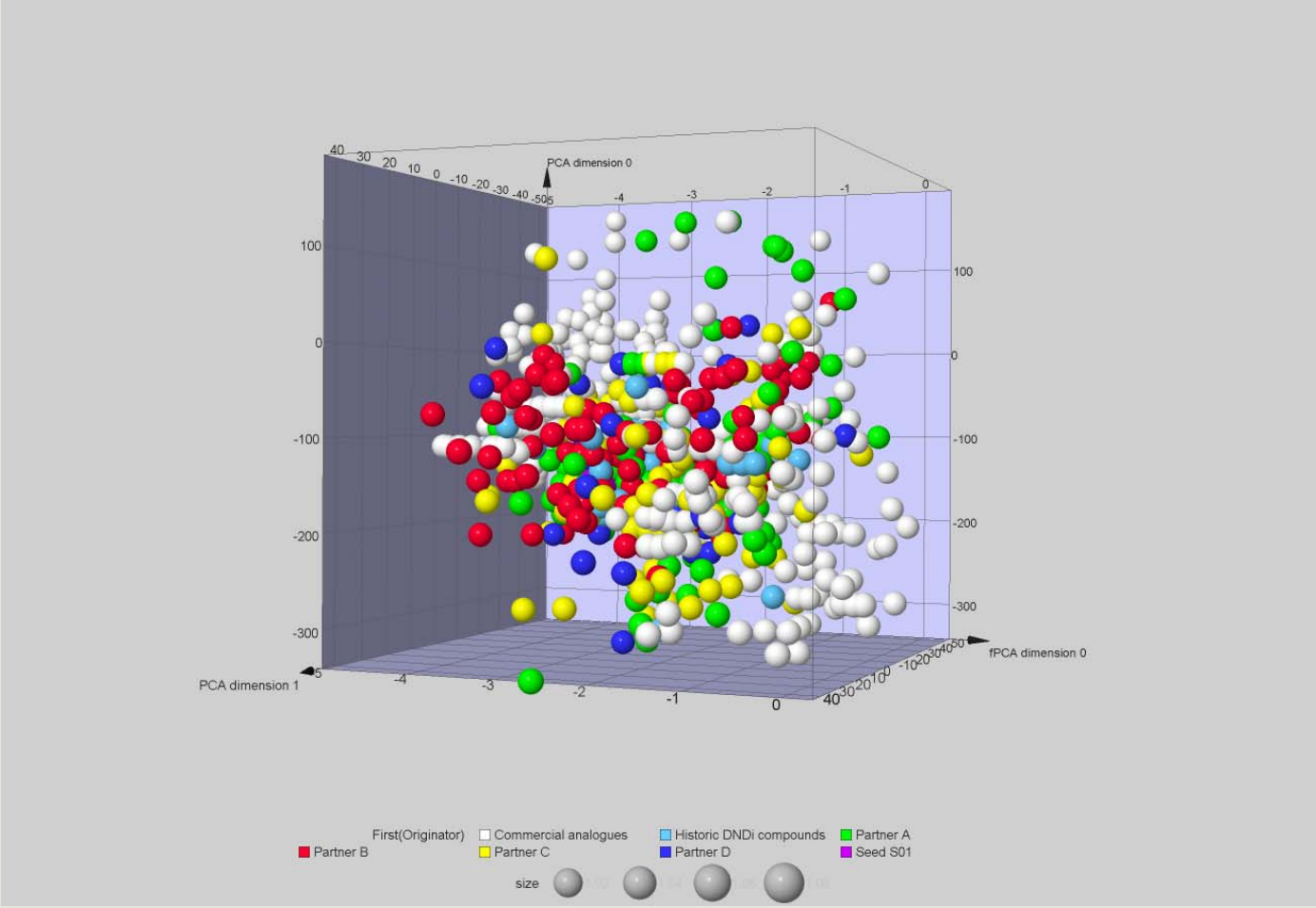

Conclusion: For Seed S01 the Booster contributions are highly complementary and explore the chemical space well

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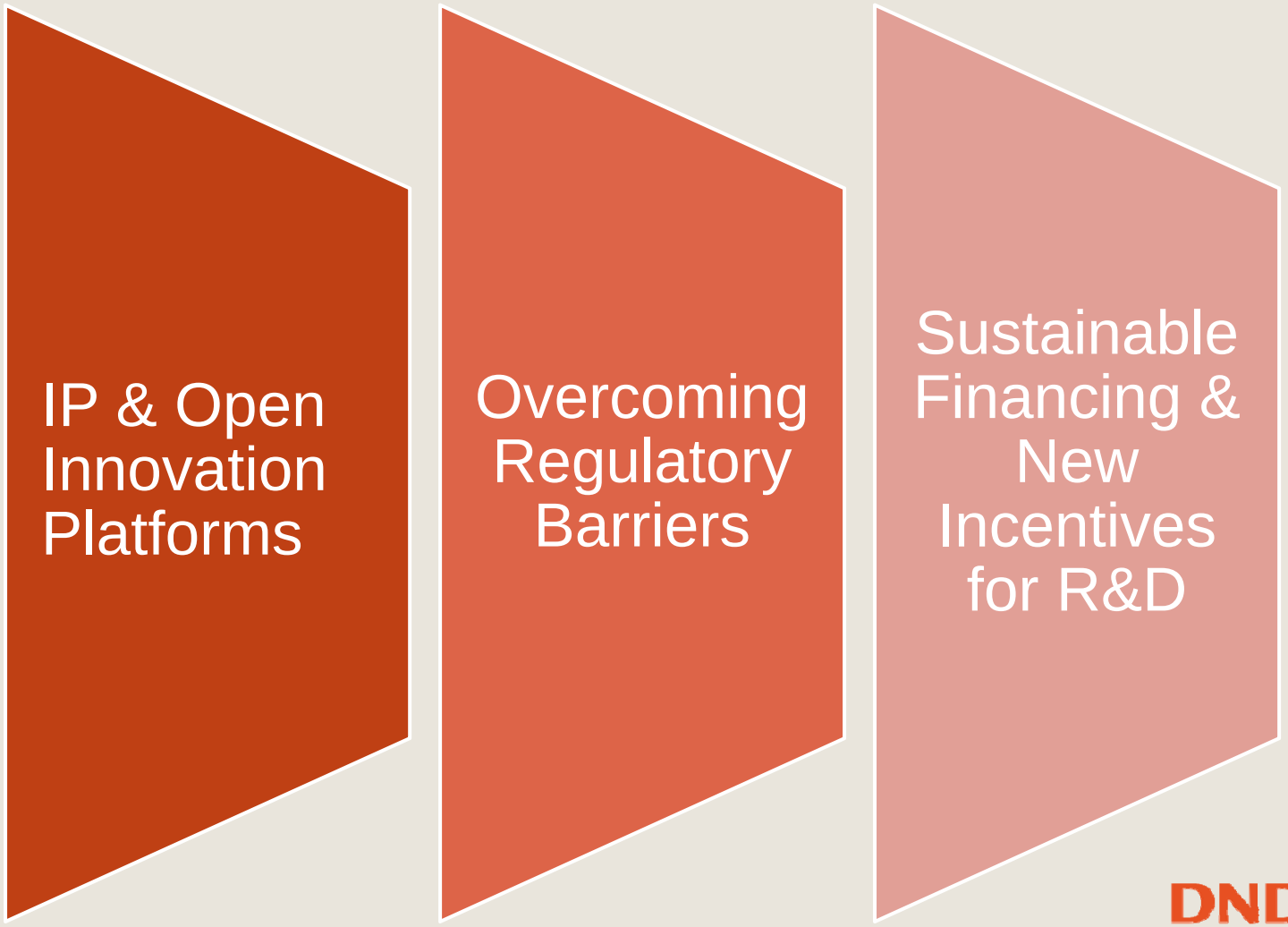
Main Challenges for Sustainable R&D for Neglected Patients



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IP & Open Innovation Practices

- Access to compounds, know-how and knowledge
- Increase access to innovation
- Ensure equitable access to all patients & affordable treatment

⇒ Medicines Patent Pool

⇒ WIPO Re:Search

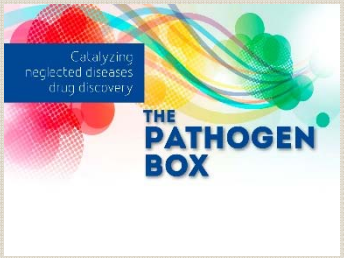
⇒ Open & equitable licensing

⇒ Open Innovation portal/CHEMBL

www.dndi.org/diseases-projects/open-innovation.html

- **Open Access Drug Discovery**

Malaria Box, Pathogen Box,…



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DNDi sharing discovery data via

The Pathogen Box

The **Pathogen Box** will contain ~400 diverse, drug-like molecules active against neglected diseases of interest and will be available free of charge at the end of 2015 (in collaboration with MMV)

Antiprotozoal activity profiling of approved drugs: a starting point toward drug repositioning

A set of 100 registered drugs with drug repositioning potential for neglected tropical diseases was assembled. The compound collection was systematically screened against protozoan parasites, *T. b. rhod.*, *L. donovani*, *T. cruzi* and *P. falciparum*

www.dndi.org/diseases-projects/open-innovation.html

Two series of fenarimols for the treatment of Chagas disease

This second release includes data on a **further 84 compounds from the two more advanced series of fenarimols** which include the preclinical candidates EPL-BS0967 and EPL-BS1246, both of which are *T.cruzi* CYP51 inhibitors

Source data from neglected disease R&D pipeline review

In late 2013, DNDi and colleagues published an **analysis in The Lancet Global Health looking at the R&D landscape over the last decade in terms** of new therapeutic products for 49 so-called neglected diseases.
In the hope of promoting further research we have created a public data-sharing page with full datasets from the study freely accessible to all.

Screening and lead optimization of new compounds for Chagas disease (>300,000 compounds)

We have evaluated multiple hits generated from a **high-throughput screen of over 300,000 compounds to identify inhibitors of *T. cruzi*** (Broad Institute Screening of NIH collection). These studies have resulted in the discovery of two novel series currently in lead optimisation.

iNTRODB - an Integrated system for searching drug-target proteins from parasitic protozoa genomes

iNTRODB is **an integrated system for searching drug-target proteins from parasitic protozoa genomes that cause neglected tropical diseases** including leishmaniasis, Chagas' disease and human African trypanosomiasis. Japanese academic organizations and a pharmaceutical companies, including Tokyo Institute of Technology, University of Tokyo and Astellas Pharma Inc. **www.bi.cs.titech.ac.jp/introdb**

Screening identifies new compounds for HAT

Identification of compounds against *Trypanosoma brucei brucei* BS427 by high-throughput screening of whole parasites (87,926 compounds, WEHI)

DNDi Screening of the MMV Open Access Malaria Box for HAT, VL, and Chagas disease

Screening of the MMV Open Access Malaria Box in the search for new drugs against Leishmaniasis, Chagas' disease and Human African trypanosomiasis

SCYNEXIS Inc. as part of the DNDi HAT Lead Optimization Consortium

Screening and optimization of specific chemical series against human African Trypanosomiasis (HAT): 4926 compounds

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Achievements

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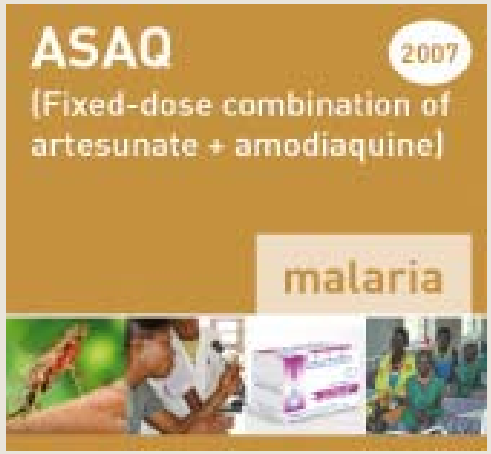
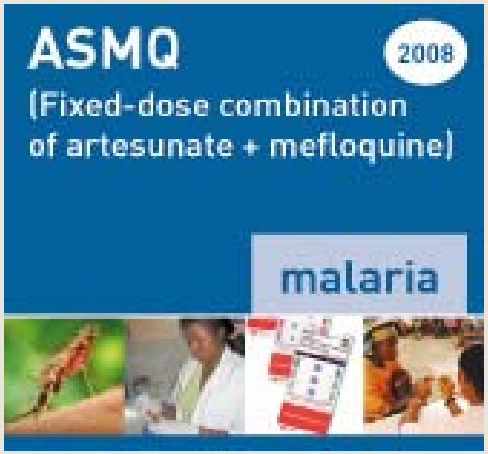
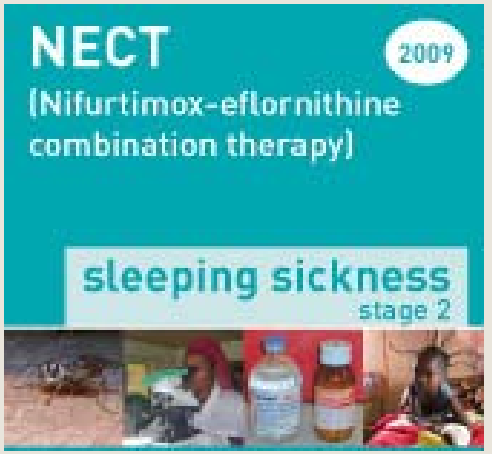
10-Year Results

- **2 new malaria treatments**
- **1 new sleeping sickness** combination
- **1 new visceral leishmaniasis** combination for Africa
- **1 set of VL treatment modalities** for Asia
- **1 Chagas paediatric dosage** form
- **Largest pipeline** ever for the kinetoplastid diseases
- Clinical research platforms in Africa
- Over 350€M raised equally from public and private sources
- On track to deliver new treatments per business plan

6 New Treatments Developed Since 2007







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