NTD Drug Discovery Booster

SHIONOGI Takeda Eisai DNDi Drugs for Neglected Diseases *initiative* AstraZeneca Celgene Institut Pasteur Korea

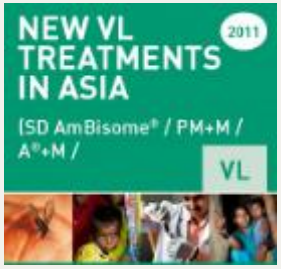
Charles E. Mowbray Ph.D.
Drugs for Neglected Diseases *initiative*
Geneva, Switzerland

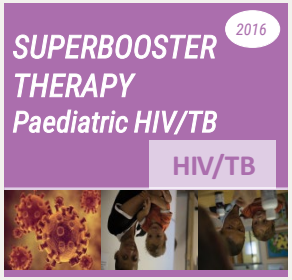
Responding to the Needs of Patients Suffering from Neglected Diseases…

DNDi's PRIORITY:
Neglected Patients

…from Bench to Bedside

7 new treatments delivered, recommended, implemented





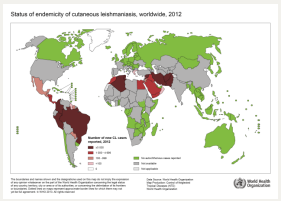
- ✓ Easy to use
- ✓ Affordable
- ✓ Field-adapted
- ✓ Non-patented

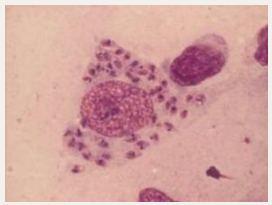
- **30 projects, 8 diseases areas**
- **13 entirely new chemical entities (NCEs)**
- **Over 160 partnerships,** most in endemic countries
- **160 staff**, half in endemic countries & 700 people working on DND*i* projects
- **EUR 400 million** raised equally from public and private sources
- **4 regional disease-specific clinical trial platforms/ networks** and several technology transfers

Drug Discovery Booster: Disease focus

Visceral Leishmaniasis

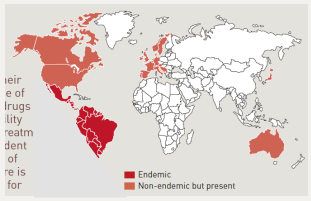
- The most severe form of leishmaniasis, caused by protozoan parasites of the *Leishmania* genus
- 350 million at risk worldwide in 98 countries
- Transmitted by sandflies
  - Prolonged fever, enlarged spleen & liver, substantial weight loss, progressive anaemia.Fatal without treatment
  - 150,000-300,000 new cases of VL every year
  - 20,000-40,000 deaths from VL
  - HIV/VL co-infection is a rising problem





Chagas Disease

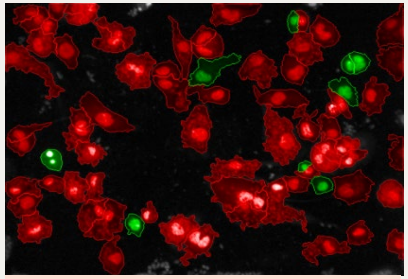
- A tropical parasitic disease caused by the protozoan *Trypanosoma cruzi* parasite
- 100 million at risk in Latin America
- 7.6 million people affected by CD
  - Largest parasitic cause of death in western hemisphere
  - Leading cause of cardiomyopathy
  - Kills more people in region than malaria
  - Patient number growing in non-endemic, developed countries
  - Majority of patients undiagnosed until late stage



A BIG Experiment in Early Drug Discovery

- Drug discovery for tropical diseases such as Visceral Leishmanisais and Chagas Disease is neglected
  - Little interest, limited investment, few researchers, *few tools*
- Parasites are very difficult to kill
  - High Throughput Screening hit rates:
    - L. donovani (intracellular) <0.05%
    - *T. cruzi* (intracellular) <0.15%

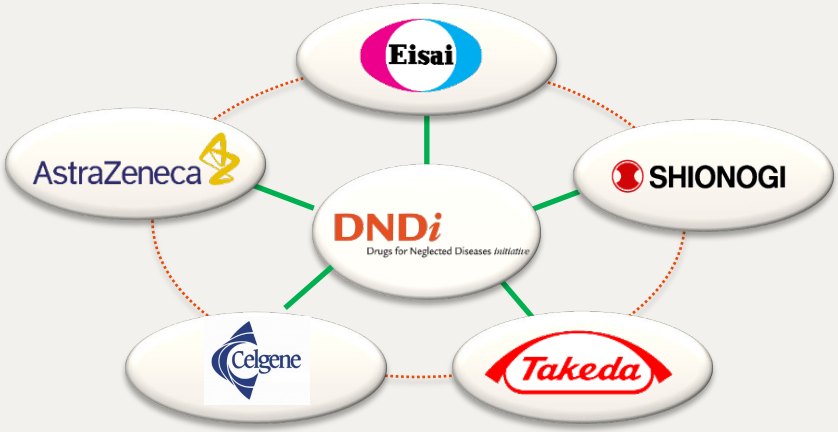
Hits are scarce and precious – need to fully exploit them



THP1 cells infected with eGFP-*L. donovani* *(courtesy of GSK Tres Cantos)*

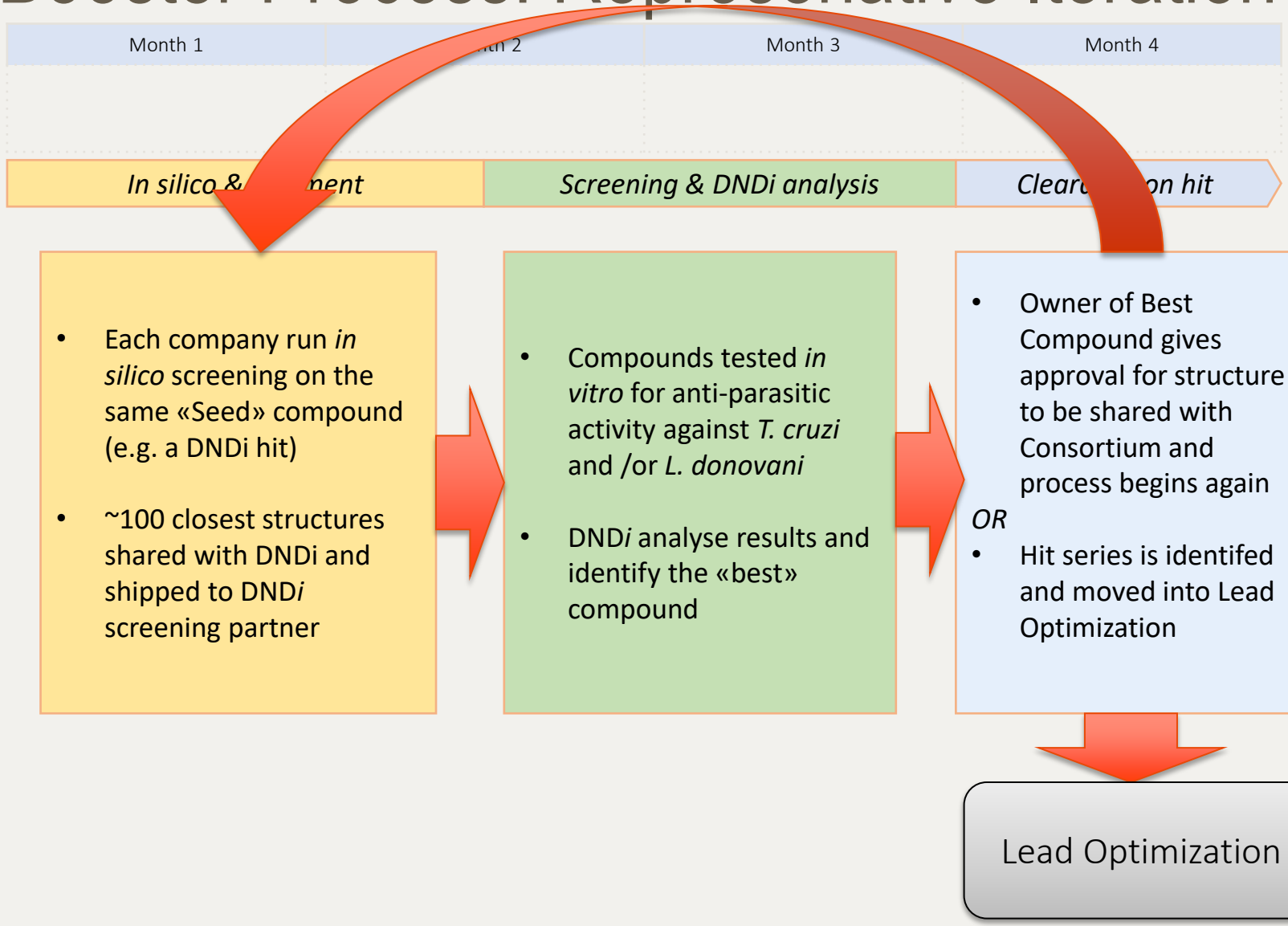
- **The NTD Drug Discovery Booster Goals:**
  - Expand precious HTS hits and enable scaffold-hopping to find new hits
  - Benefit from the pooling of structures and information
  - Accelerate discovery and reduce costs
  - Experiment with a new open innovation approach to drug discovery

Booster Process: The idea



- Ligand-based virtual screening around DNDi hit compounds
- Partner companies work on the same *in silico* virtual screen in parallel
  - Use whichever virtual screening methods they deem appropriate
- Resulting structures and samples are shared bilaterally with DNDi
- DNDi generate experimental data and share with parent companies
- *The most interesting compounds are shared with the consortium for use in repeat cycles of virtual screening*

Booster Process: Represenative Iteration



Booster Process

3 Key Questions:

1) Is there an advantage to screening multiple libraries?

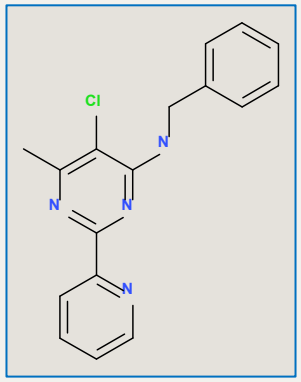
2) Does computational screening yield improved compounds?

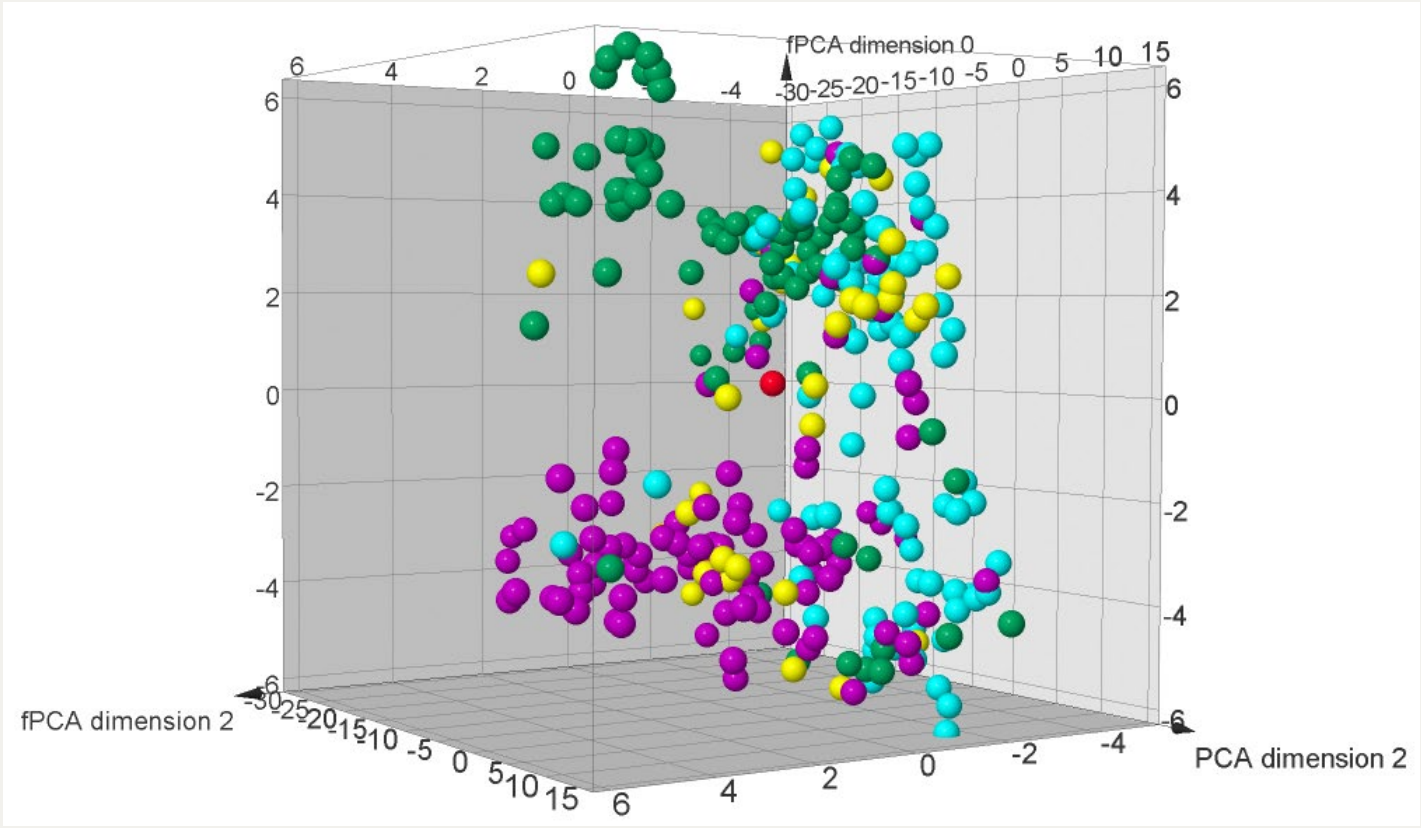
3) Does “repeat-cycle” yield improved results?

Representative example
S01

Booster Process - Representative Example

Source	# hits
Seed S01	1
Partner A	~90
Partner B	~90
Partner C	~90
Partner D	~40

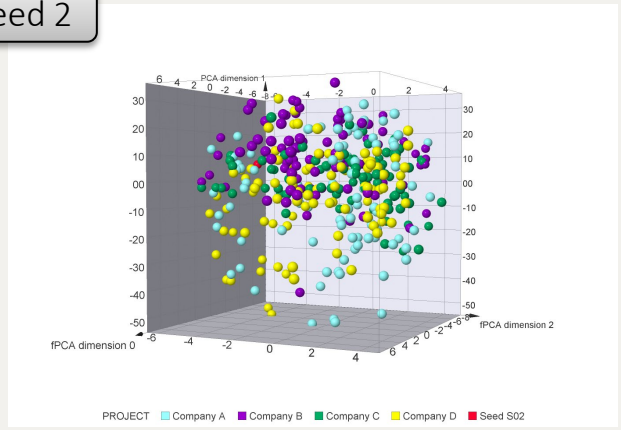




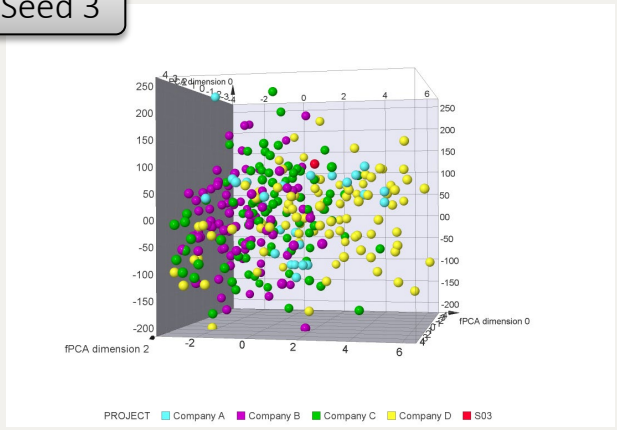
- Good coverage of chemical space by the Consortium screening process
- Clear distinct regions of coverage coming from individual consortium members

Booster Process - Representative Example

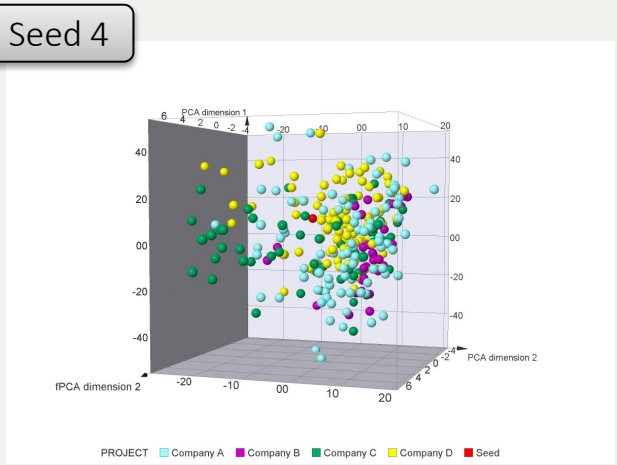
Seed 2



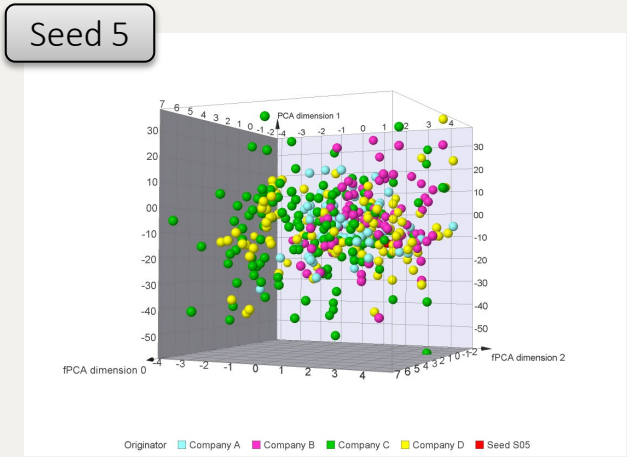
Seed 3



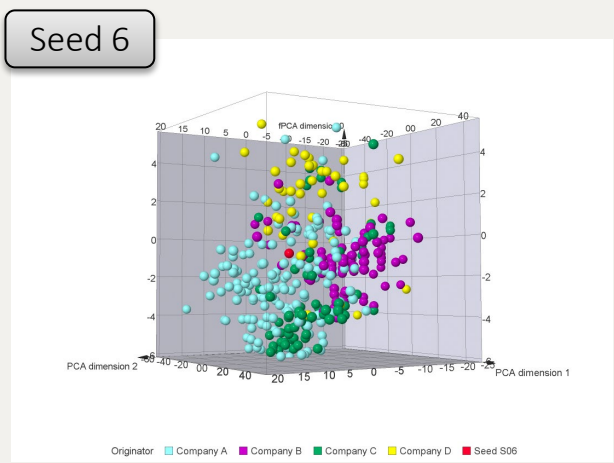
Seed 4



Seed 5



Seed 6



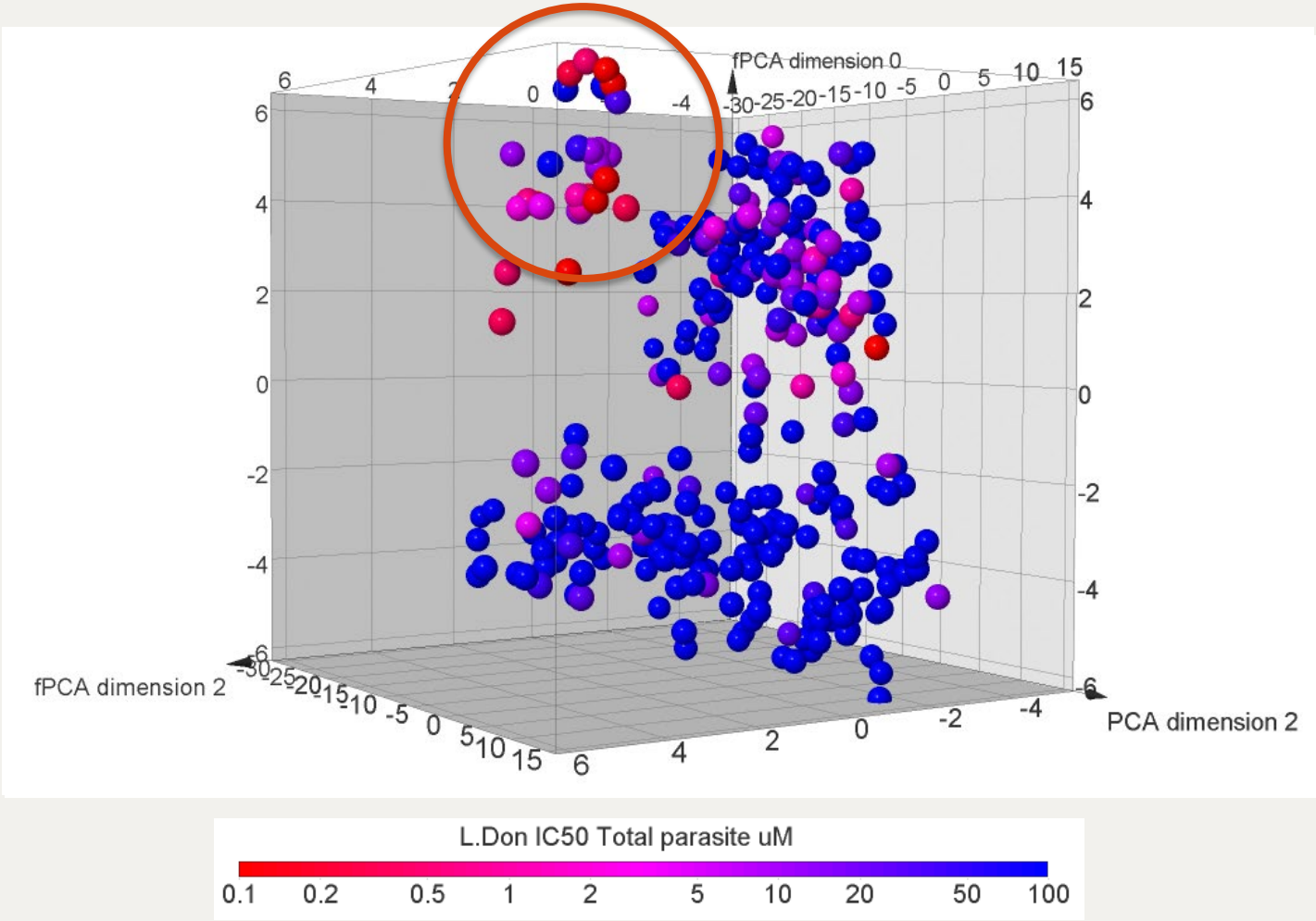
Key question 1: Is there an advantage to screening multiple libraries?

YES

Booster Process - Representative Example

Actives (red) are clustered in a number of areas of chemical space

Clear hot-spot regions exist away from the original seed

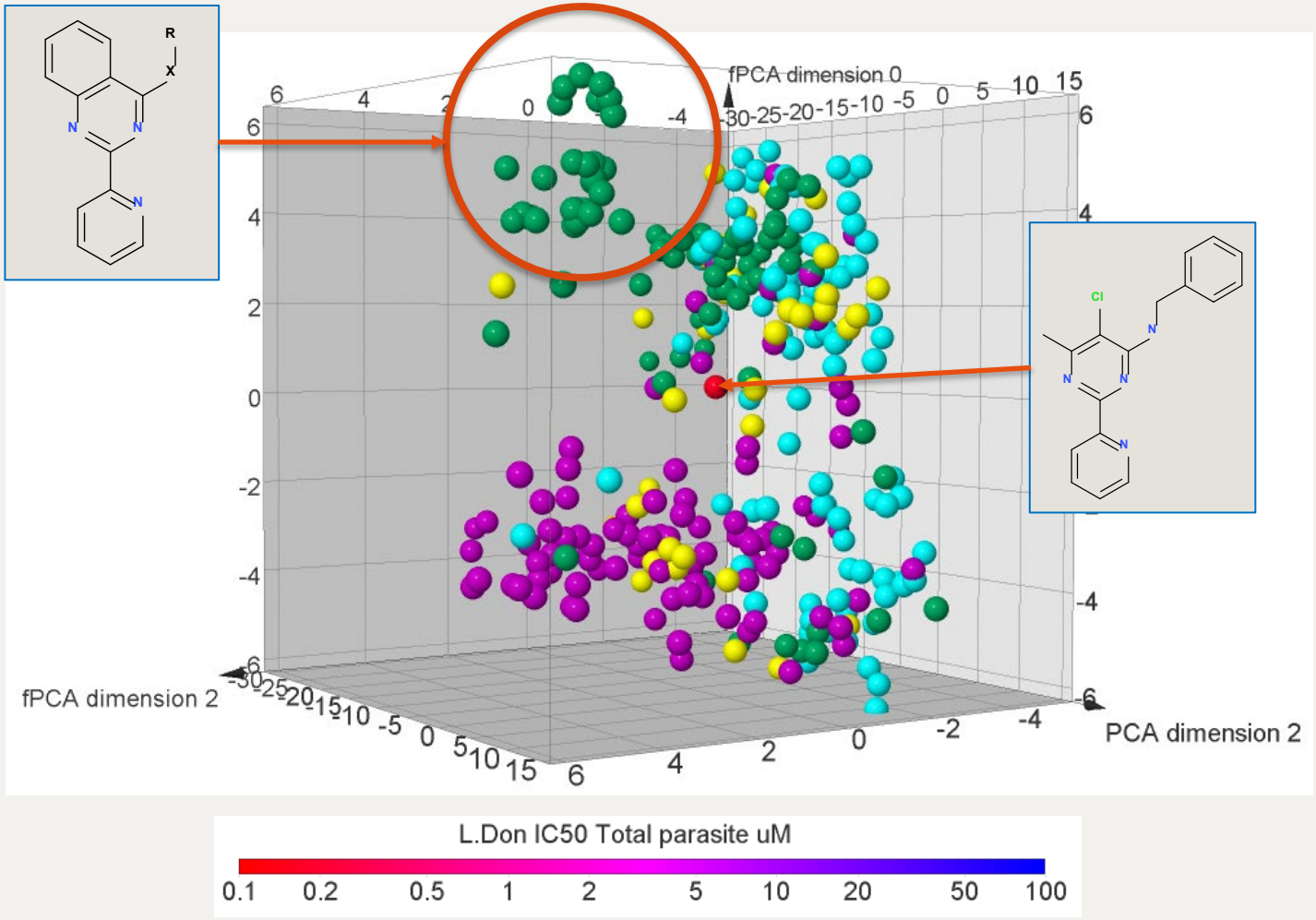


Key question 2: Does *in silico* screening yield improved compounds?

YES

Booster Process - Representative Example

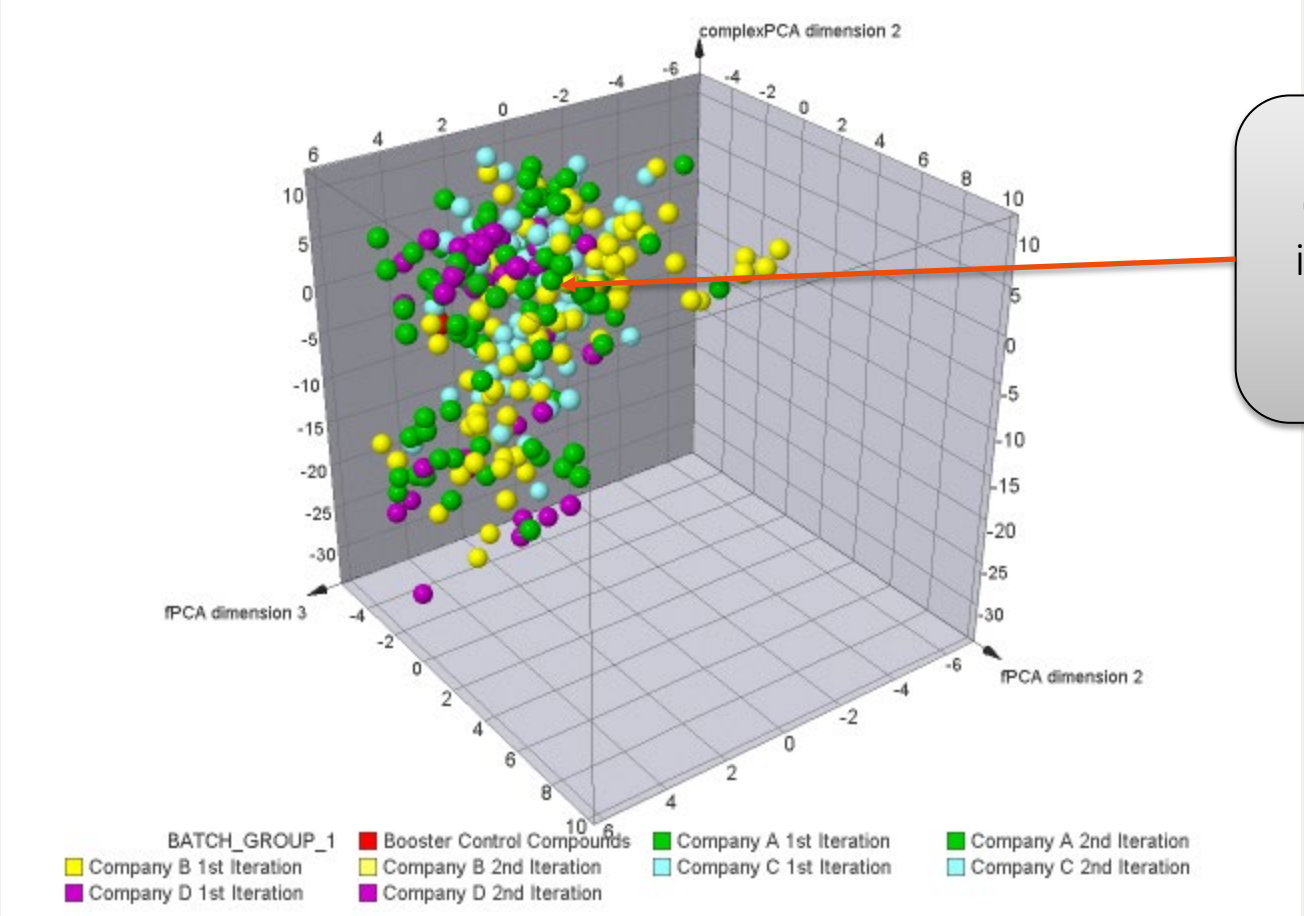
Most interesting compounds come from scaffold hop proposed by only one consortium partner



Key question 2: Does *in silico* screening yield improved compounds?

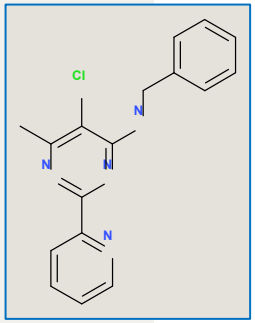
YES

Seed S01 - Representative Example



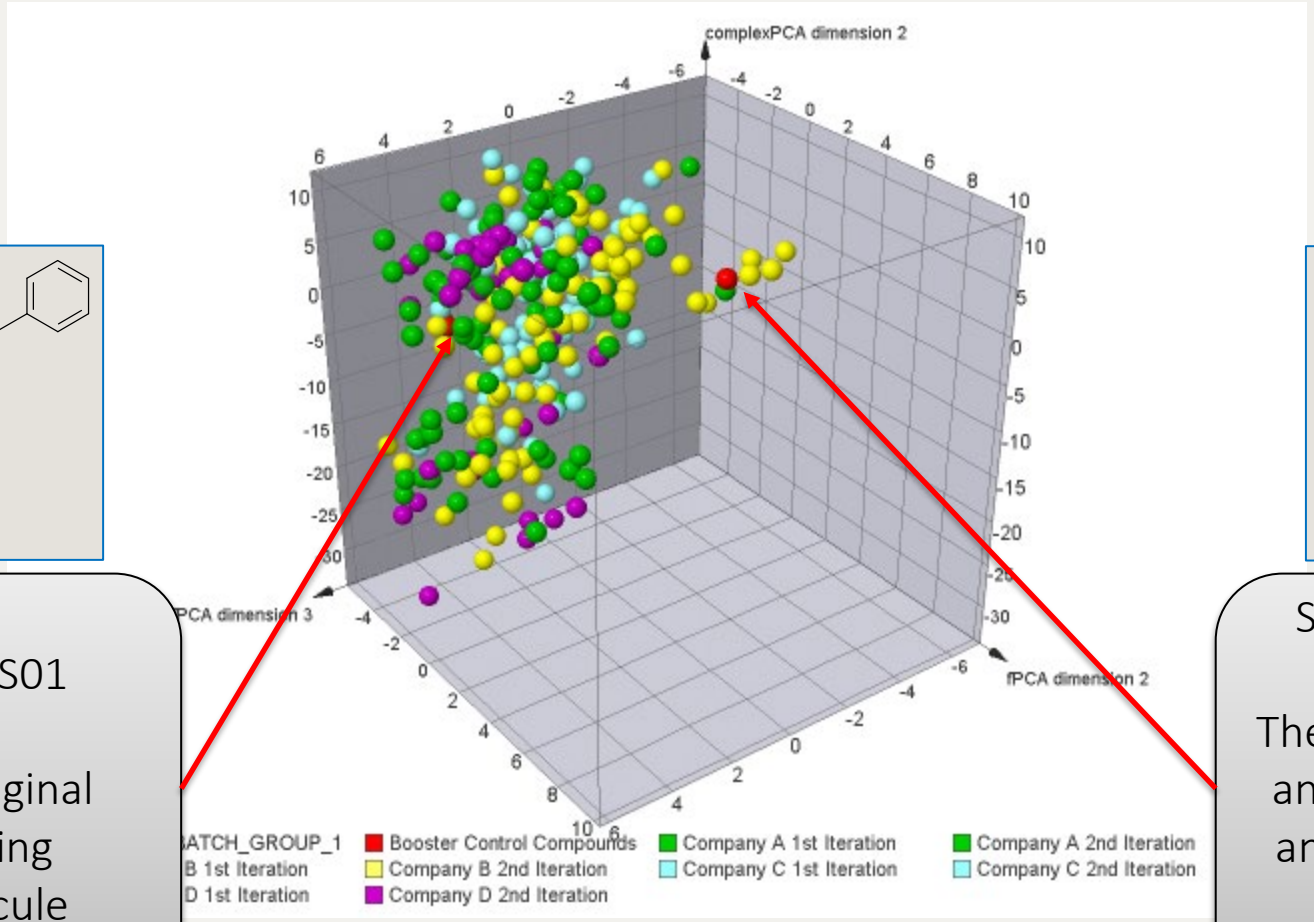
>350 compounds identified by consortium partners

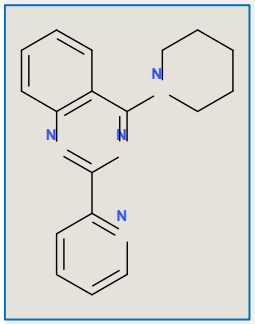
Seed S01 - Representative Example



Seed S01

The original starting molecule

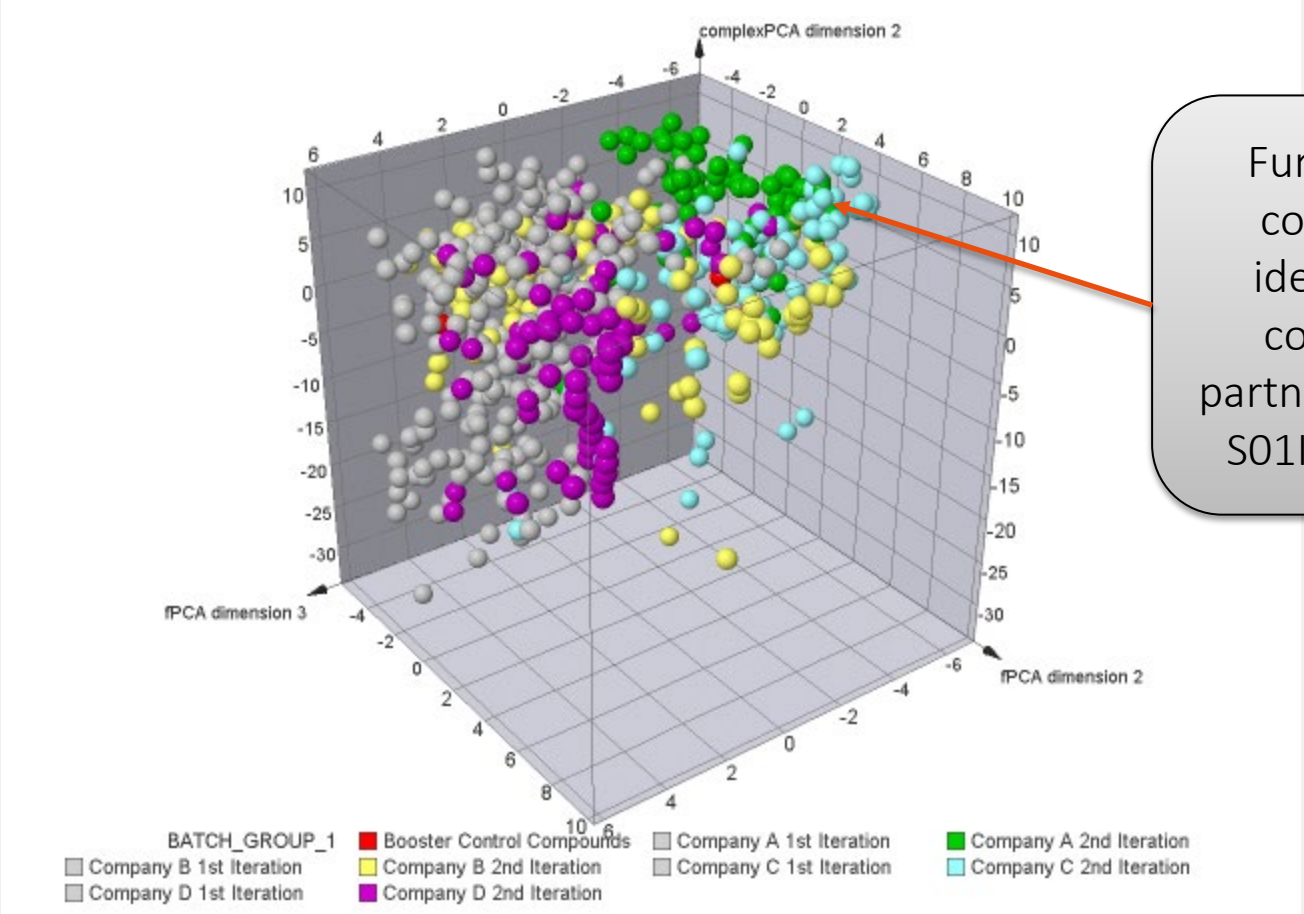




Seed S01IH1

The most potent and interesting analogue from the 350 compound set

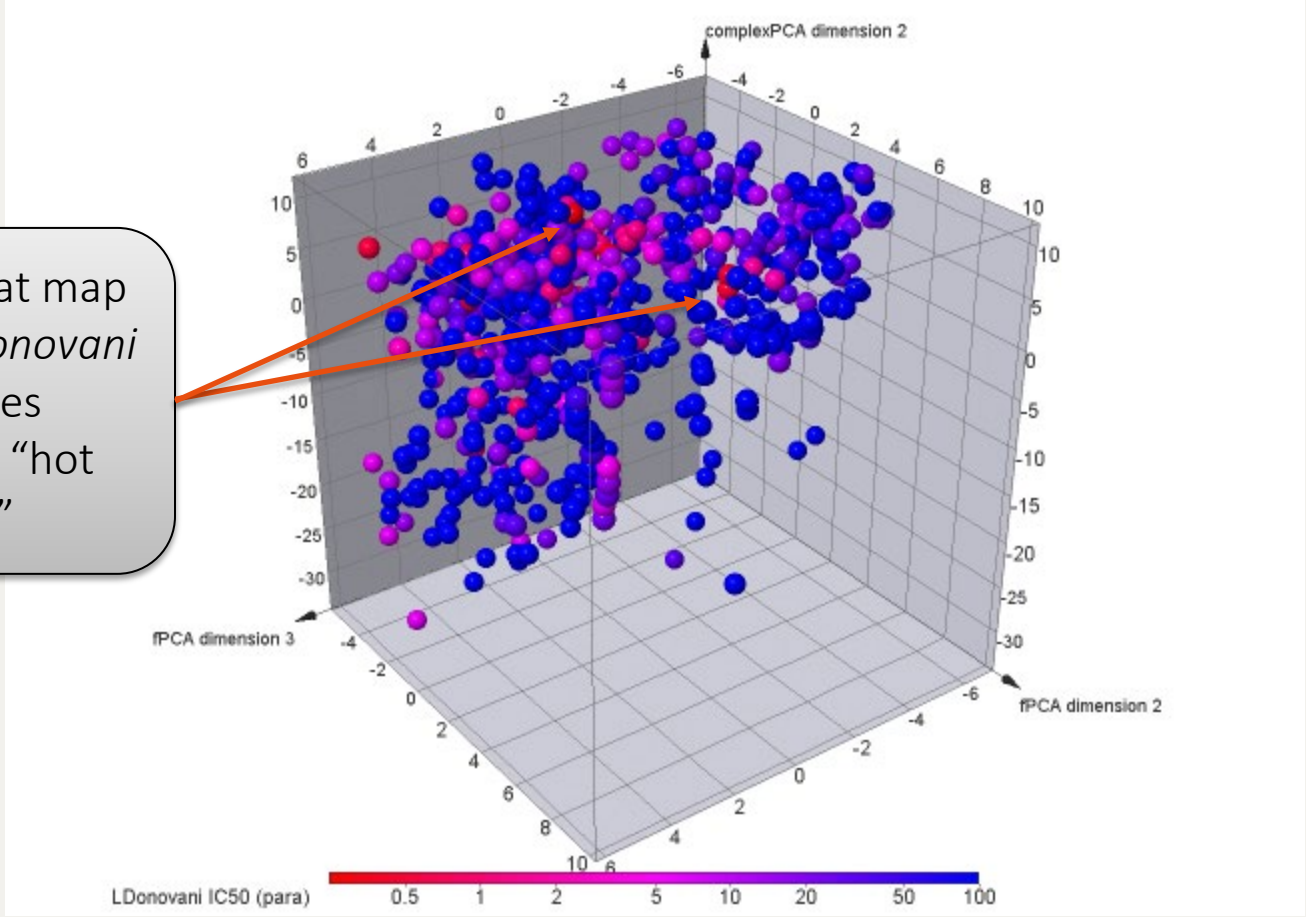
Seed S01 - Representative Example



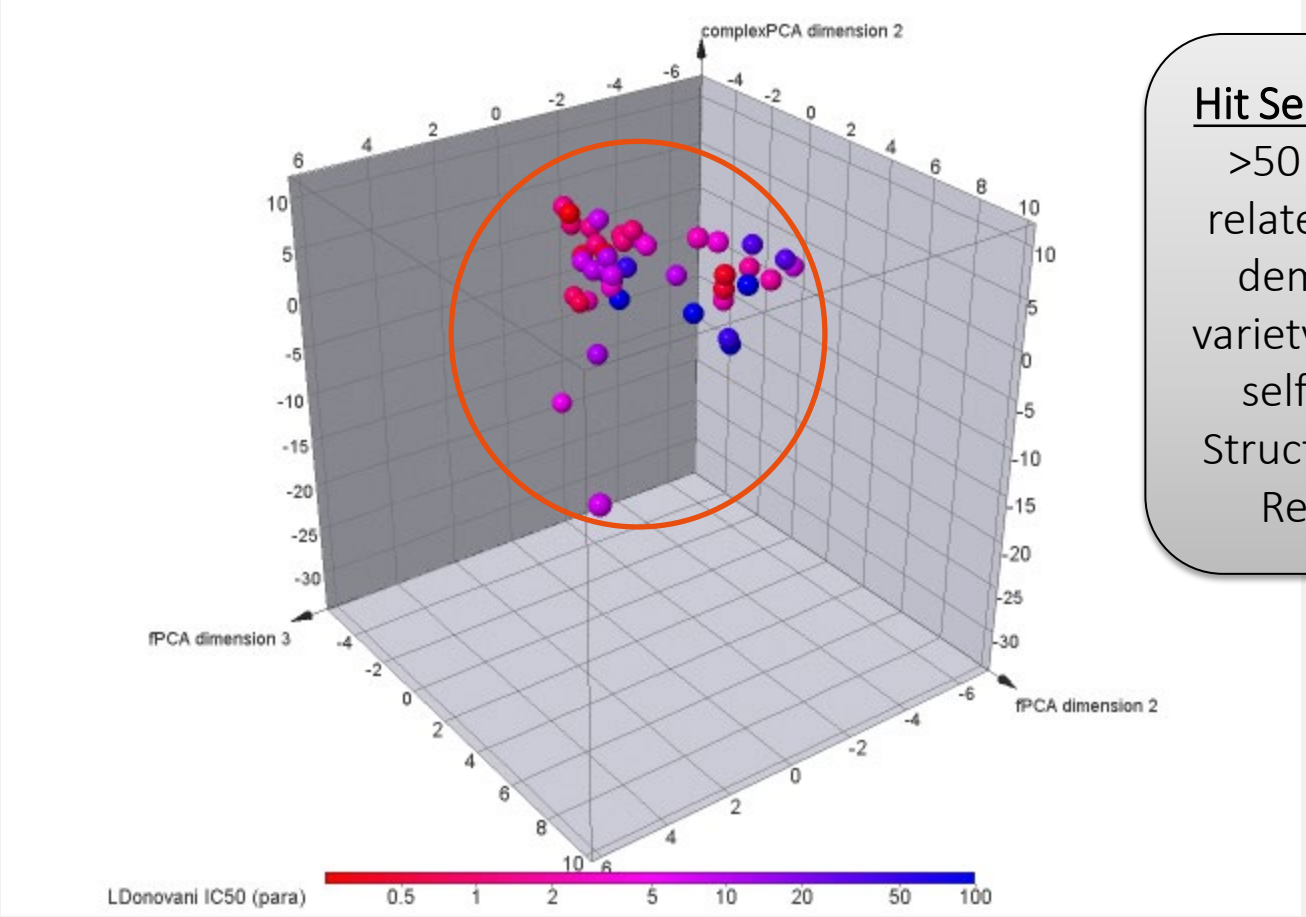
Further ~350 compounds identified by consortium partners based on S01IH1 identity

Seed S01 - Representative Example

Potency heat map against *L. donovani* identifies structural "hot spots"



Seed S01 - Representative Example



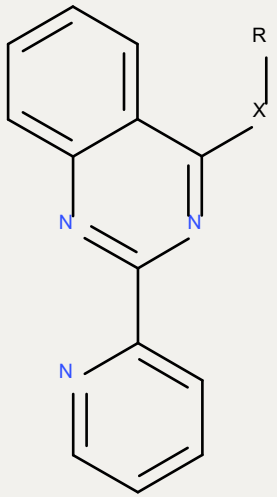
Hit Series identified

>50 structurally related analogues demonstrating variety of activity & self-contained Structure-Activity-Relationship

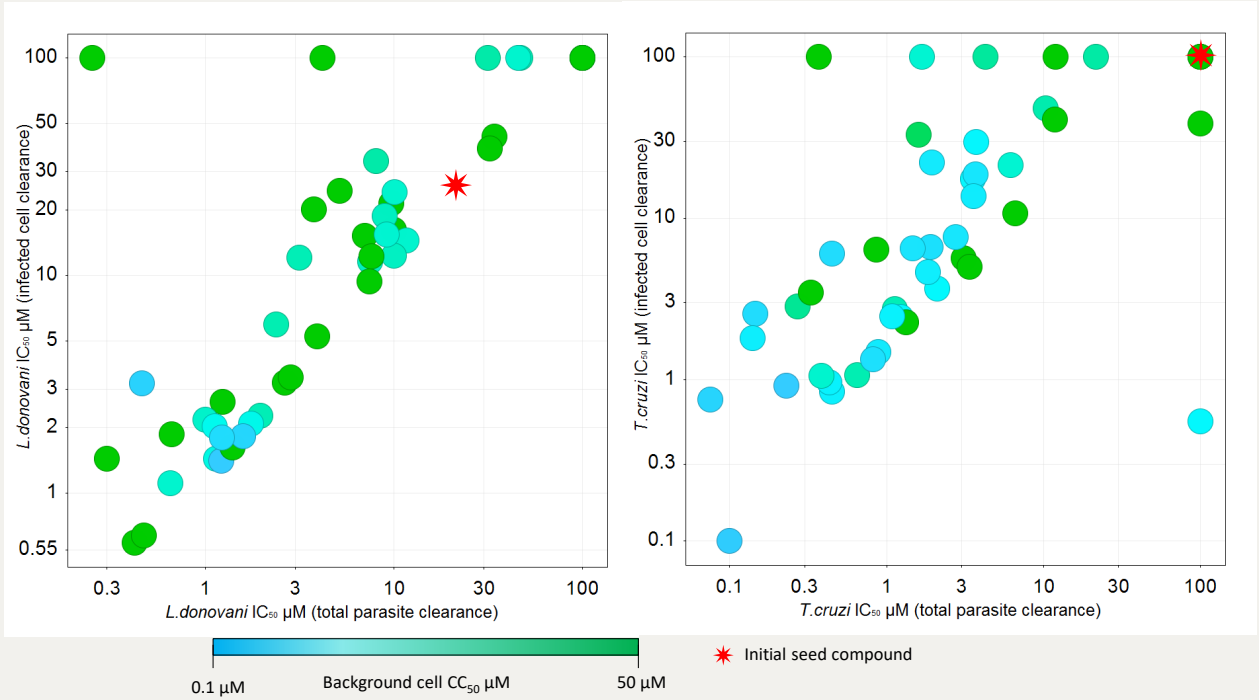
- Key Question 3: Does "repeat-cycle" yield improved results?

YES

Seed S01 - Representative Example



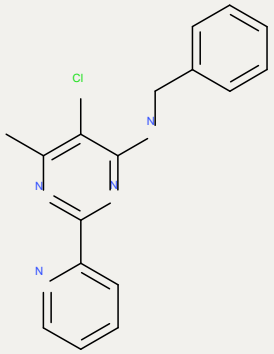
X = O,NR'
R= Alkyl, Aryl
R' = H, Alkyl



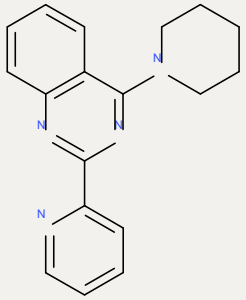
Hit Series identified

>50 structurally related analogues demonstrating variety of activity & self-contained Structure-Activity-Relationship against both parasites of interest

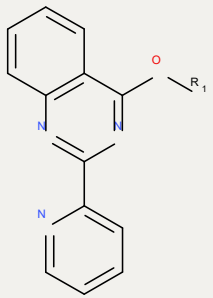
Seed S01 - Representative Example

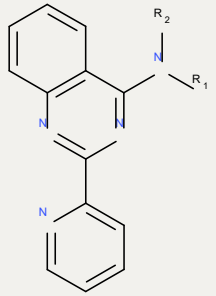


Booster 1



Booster 2





L.D. IC_{50} µM		T.C. IC_{50} µM	
Para	Inf	Para	inf
20.0	27.2	>50	>50

L.D. IC_{50} µM		T.C. IC_{50} µM	
Para	Inf	Para	inf
0.5	0.6	0.4	1.1

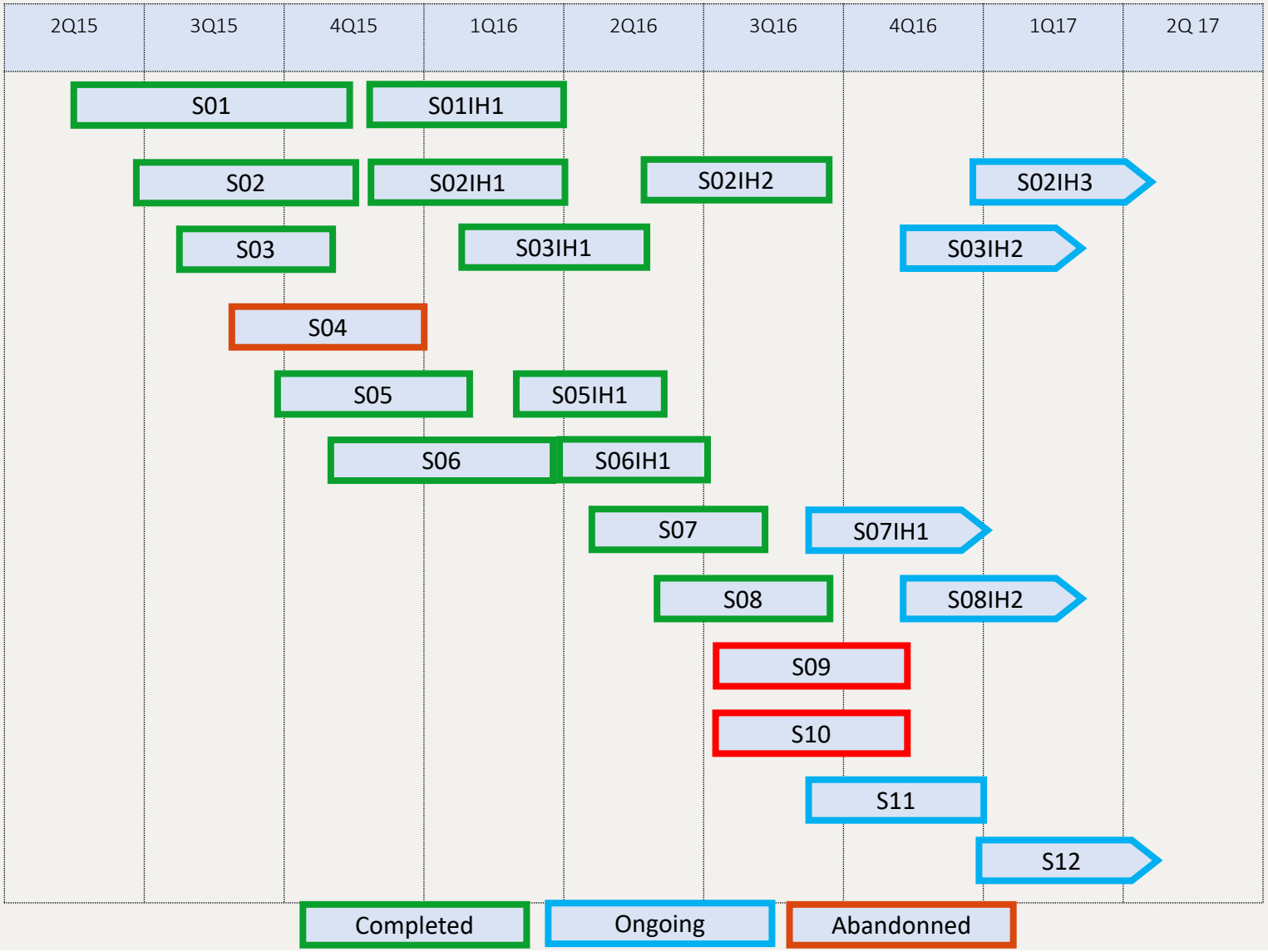
	L.D. IC_{50} µM		T.C. IC_{50} µM	
	Para	Inf	Para	inf
BIC*	0.4	0.5	<0.1	<0.1

* Most active representative compound

First iteration identified scaffold change to quinazolines and improvement in potency against both parasites

Second iteration annotated the SAR around the Quinazolines; Hit Series identified and annotated, 52 compounds in total

Booster Process to date



Status
Hit Series approved
Hit Series approved
3rd iteration ongoing
Abandonned – no improved hits identifed
Hit Series approved
Hit Series approved
2nd Iteration ongoing
2nd Iteration ongoing
Abandonned – no improved hits identifed
Abandonned – no improved hits identifed
2nd Iteration planned
1st iteration ongoing

NTD Booster – Summary

- 22 Booster iterations have been completed
  - 12 Booster seeds launched
  - 4 seeds completed and moving towards *in vivo* proof-of-concept model

- Screened >300 compounds in each iteration, building Structure-Activity-Relationships around each seed compound (SAR)
  - Effective savings of >$90,000 per booster iteration*
  - Broader range of compounds tested compared to traditional Hit to Lead

- Rapid improvement in potency (from tens of µM to submicromolar) of parasitocides for both *T. cruzi* and *L. donovani*

- Easy and quick scaffold hopping into new chemical space/matter
  - Identification of new chemical series and sub-series powering new avenues for compound optimization and research

*Assuming average cost per compound of $300 when purchased or synthesised / negligible cost when screened via booster

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Charles E. Mowbray
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UKaid
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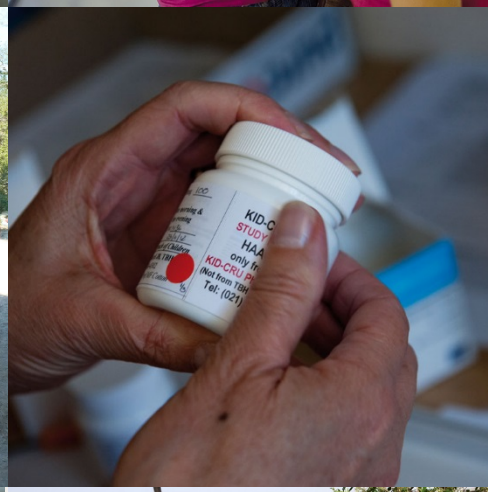
Swiss Agency for Development and Cooperation SDC









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