

The NTD Drug Discovery Booster: a novel approach for hit to lead chemistry

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DNDi
Drugs for Neglected Diseases *initiative*

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Keystone Symposium on Drug Discovery for Parasitic Diseases

Responding to the Needs of Patients Suffering from Neglected Diseases...

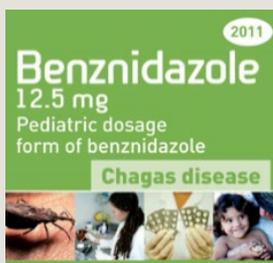
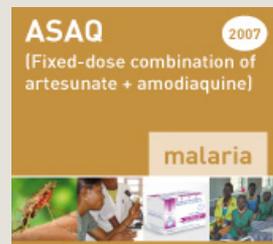


DNDi's PRIORITY:
Neglected
Patients



...from Bench to Bedside

In a decade of R&D, 6 new treatments delivered



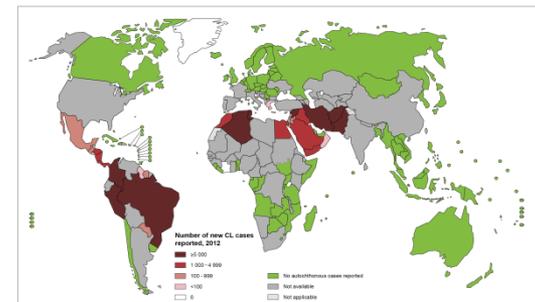
- ✓ Easy to use
- ✓ Affordable
- ✓ Field-adapted
- ✓ Non-patented

- 30 projects, 6 diseases areas
- 15 entirely new chemical entities (NCEs)
- Over 130 partnerships, most in endemic countries
- 150 staff, half in endemic countries & 600 people working on DNDi projects
- Over EUR 350 million raised equally from public and private sources
- 3 regional disease-specific clinical trial platforms and 2 technology transfers

Visceral Leishmaniasis (VL)

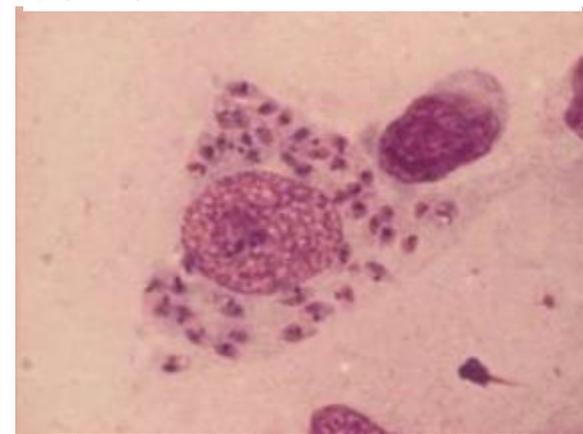
- ❑ 350 million at risk worldwide (in 98 countries)
- ❑ Transmitted by sandflies
- ❑ VL is most serious form of Leishmaniasis:
 - ❑ Prolonged fever, enlarged spleen & liver, substantial weight loss, progressive anaemia
 - ❑ **Fatal** without treatment
 - ❑ 150,000-300,000 new cases of VL every year
 - ❑ 20,000-40,000 deaths from VL
 - ❑ HIV/VL co-infection is a rising problem
 - ✓ 35% of new infections in Ethiopia
 - ❑ PKDL & asymptomatics contribute to transmission

Status of endemicity of cutaneous leishmaniasis, worldwide, 2012



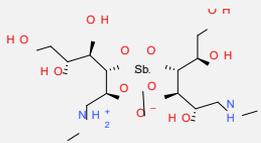
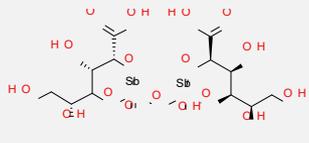
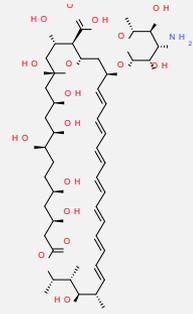
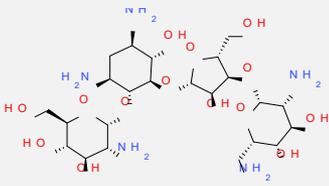
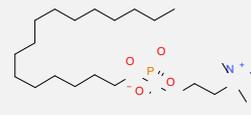
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Data Source: World Health Organization
Map Production: Center for Geographic Information Science
World Health Organization



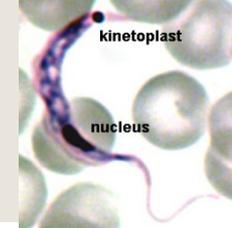
Drugs for Visceral Leishmaniasis

The good, the bad & the ugly

				
MW 525, clogP -3.8	MW 664, clogP -4.2	MW 924, clogP -2.3	MW 616, clogP -6.1	MW 409, clogP +1.3
Meglumine antimoniate	Sodium Stibogluconate (SSG)	Liposomal Amphotericin B	Paromomycin sulfate	Miltefosine
Slow iv or im infusion	Slow iv or im infusion	2h iv infusion	im	po
20mg/kg/day 30 days	20mg/kg/day 30 days	10-30mg/kg total dose over 1-10 days	15-20mg/kg/day 21 days	1.5-2.0mg/kg/day 28 days
35-95% depending on area, resistance in India	35-95% depending on area, resistance in India	>95% efficacy in India, variable response in Africa	93-95% India 64-85% Africa	94-97%
<ul style="list-style-type: none"> • painful injections • nephro- & cardiotoxicity • pancreatitis 	<ul style="list-style-type: none"> • painful injections • cardiotoxicity • pancreatitis 	<ul style="list-style-type: none"> • rigors & chills • nephrotoxicity • hypokalemia • anaphylaxis 	<ul style="list-style-type: none"> • painful injections • reversible nephro-, hepato- & ototoxicity 	<ul style="list-style-type: none"> • teratogenic • gastrointestinal, nephro- & hepatotoxicity

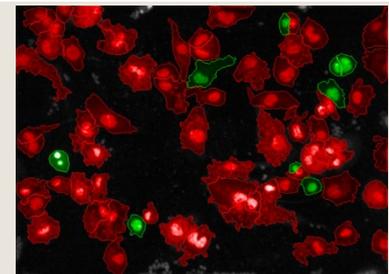
- Variable efficacy, serious toxicities, only one is oral & rest are painful iv/im
- Urgent need for new effective, safe, and convenient treatments

A **BIG** Experiment in Early Drug Discovery



- Drug discovery for tropical diseases is neglected
 - ▣ Little interest, limited investment, few researchers, *few tools*
- Parasites are very difficult to kill
 - ▣ HTS hit rate for *L. donovani* (intracellular) <0.1%

Hits are scarce and precious – need to fully exploit them



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

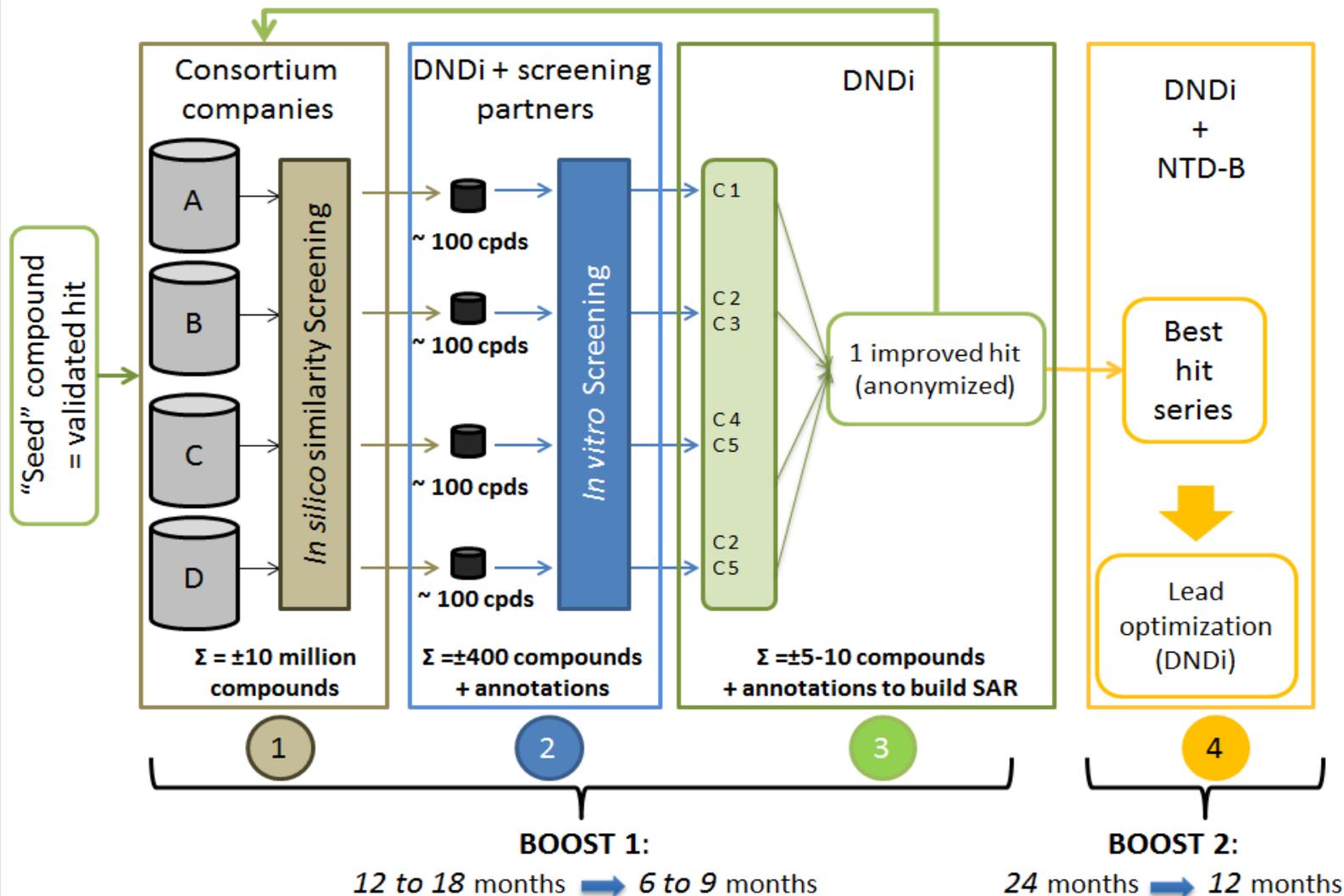
□ The NTD Drug Discovery Booster

- ▣ Expand HTS hits and enable scaffold-hopping
 - Extensive SAR accessible before starting new chemistry!
- ▣ Benefit from the pooling of structures and information
- ▣ Accelerate discovery and reduce costs
- ▣ Experiment with a new open innovation approach to drug discovery



The Booster Concept

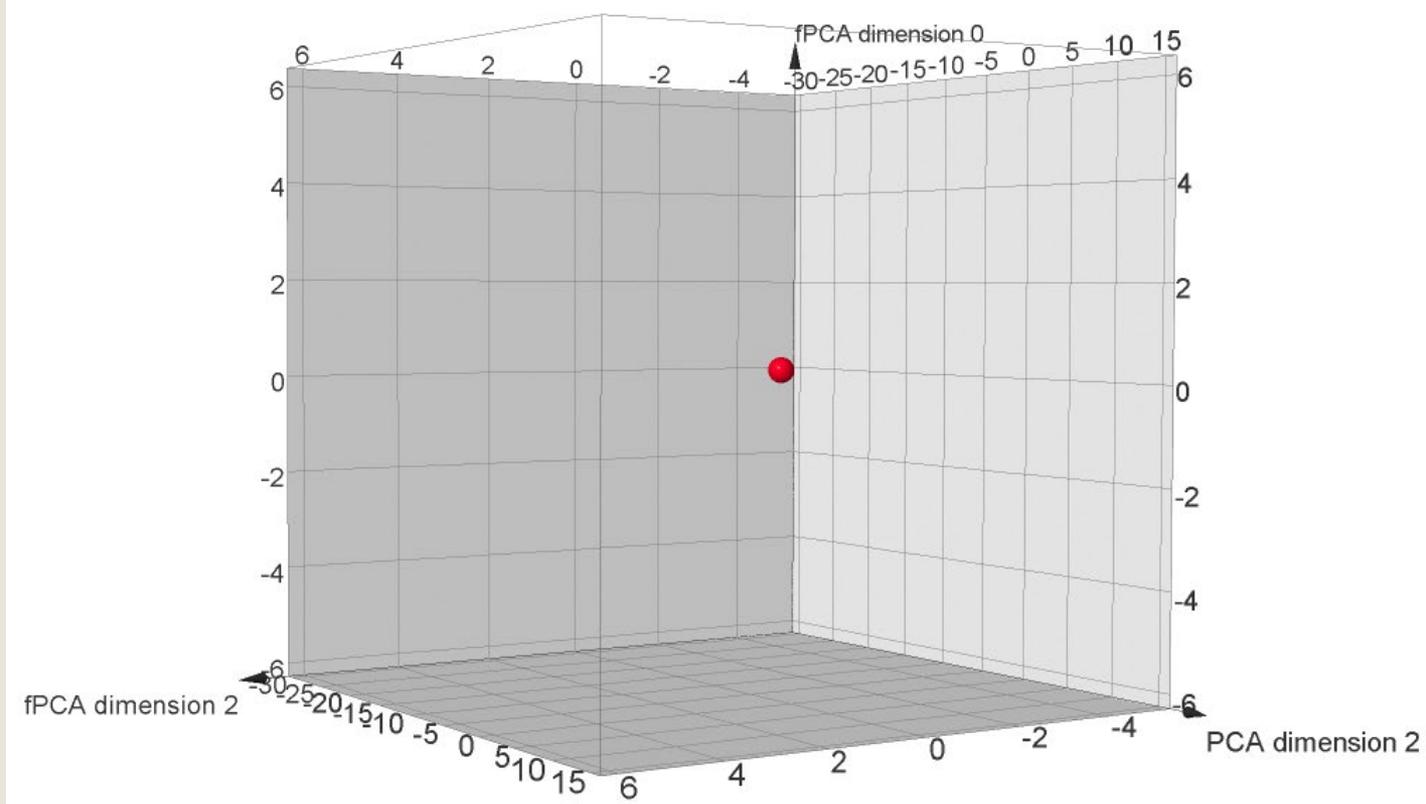
1 or 2 more rounds of analogue searching, seeded with **1 improved hit** of step « 3 »



Drug Booster Output

First Iteration: seeding with S01

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

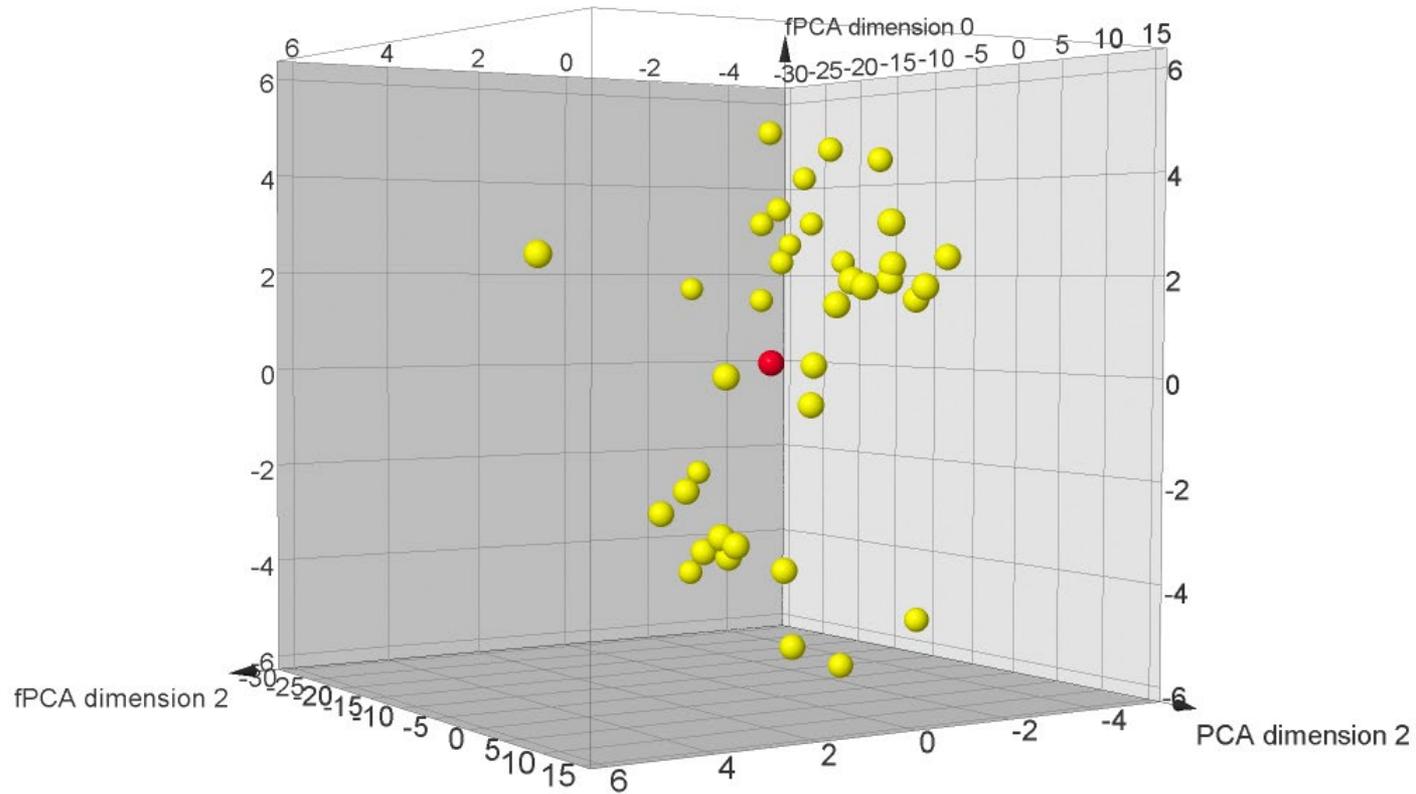


- Plot shows Coverage of «Chemical Space» around the starting seed.
- Chemical Space has been defined using the *in silico* screening hits along with known literature and commercial compounds.
- Axes are Principal Component Analysis dimensions of Chemical fingerprint (X) and Molecular Properties (Y, Z)

S01- First Iteration

Partner D similars

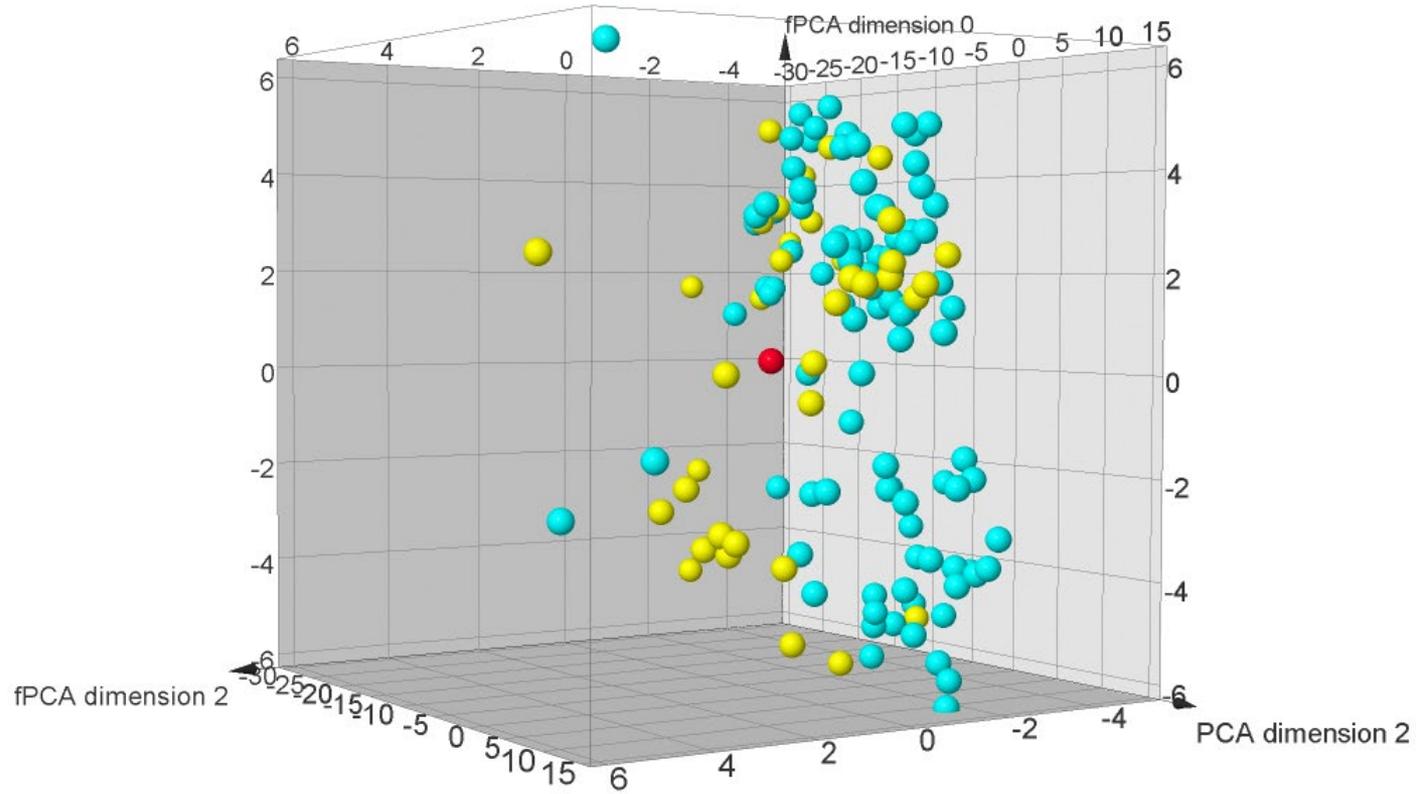
Source	# hits
Seed S01	1
Partner A	~90
Partner B	~90
Partner C	~90
Partner D	~40



S01- First Iteration

Partner C similars

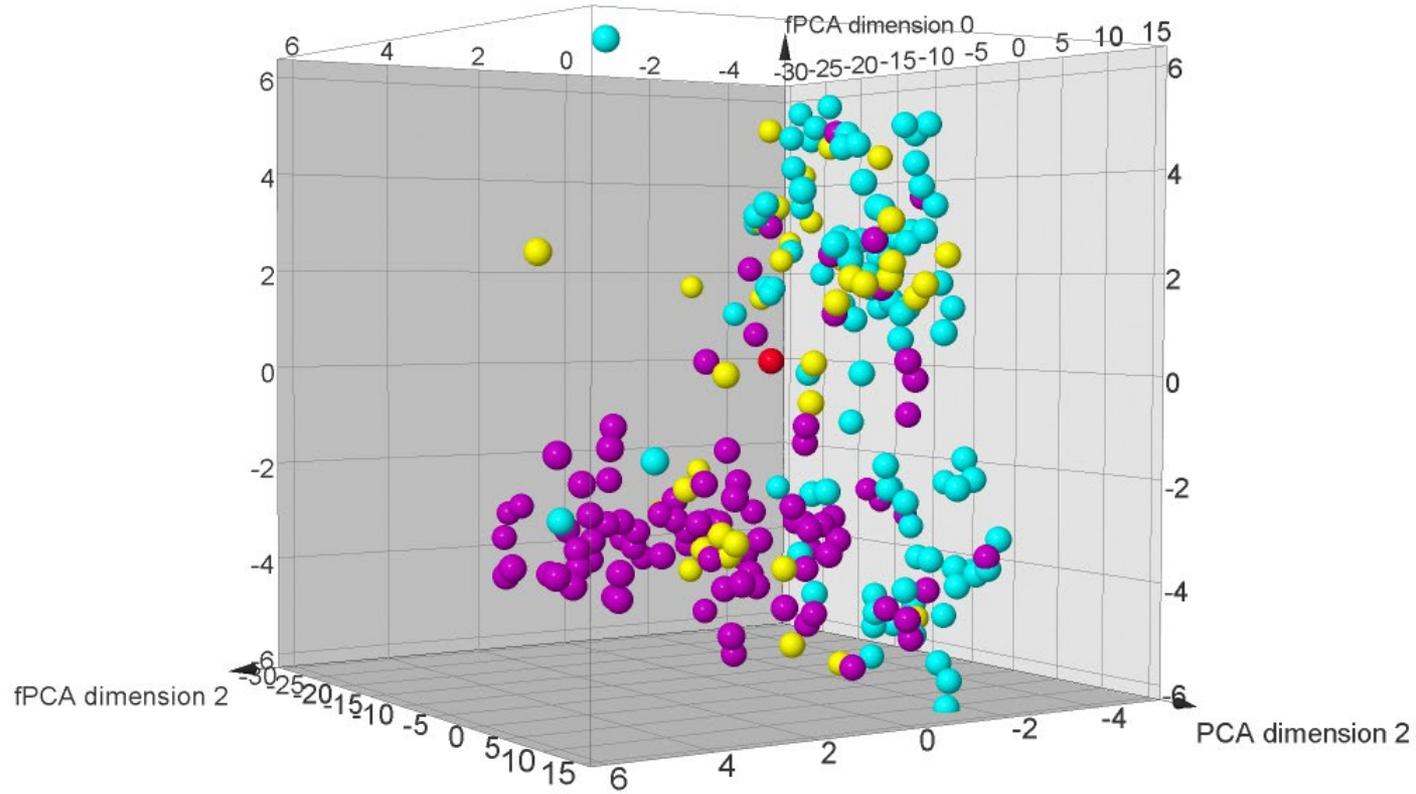
Source	# hits
Seed S01	1
Partner A	~90
Partner B	~90
Partner C	~90
Partner D	~40



S01- First Iteration

Partner B similars

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

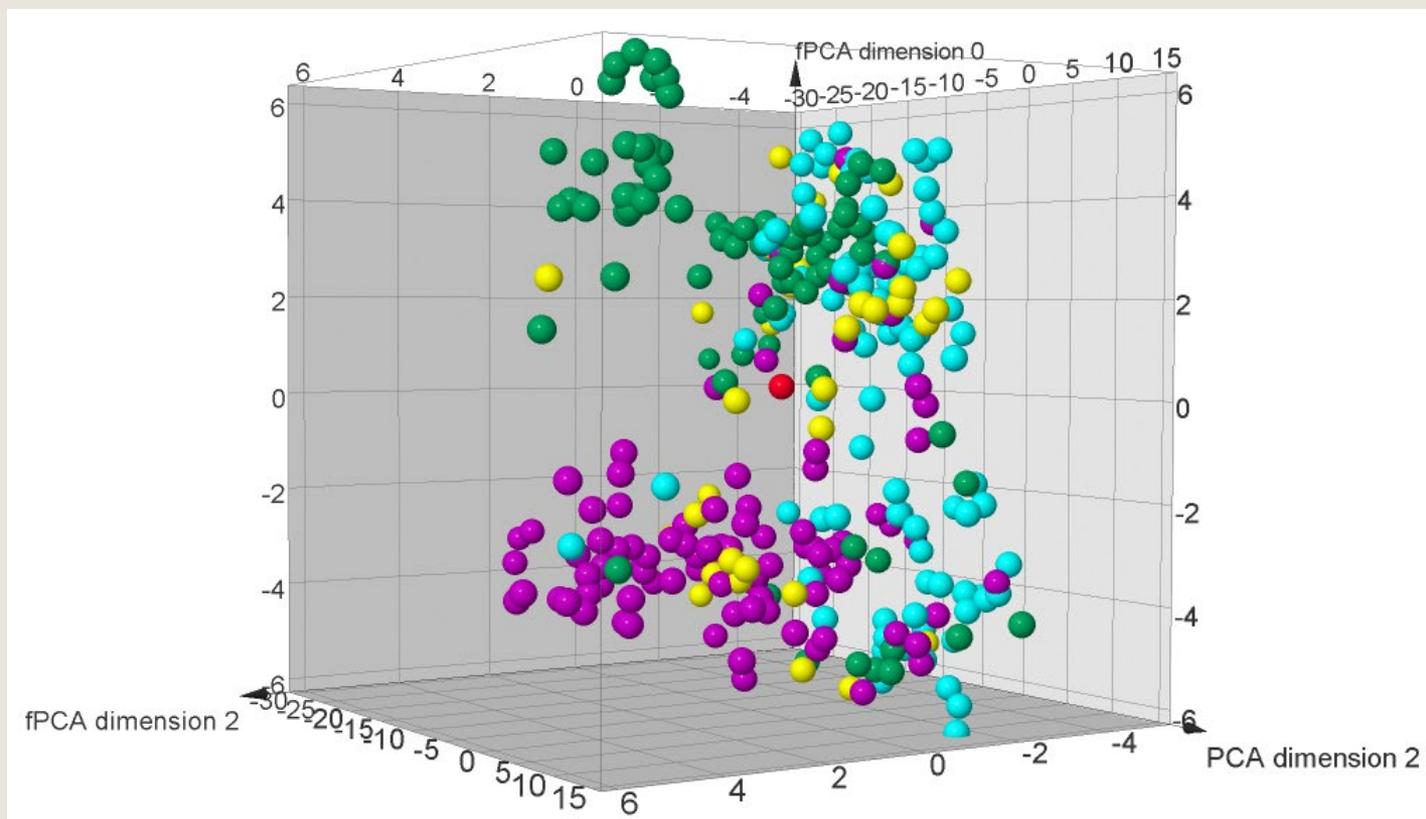


S01- First Iteration

Partner A similars

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

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

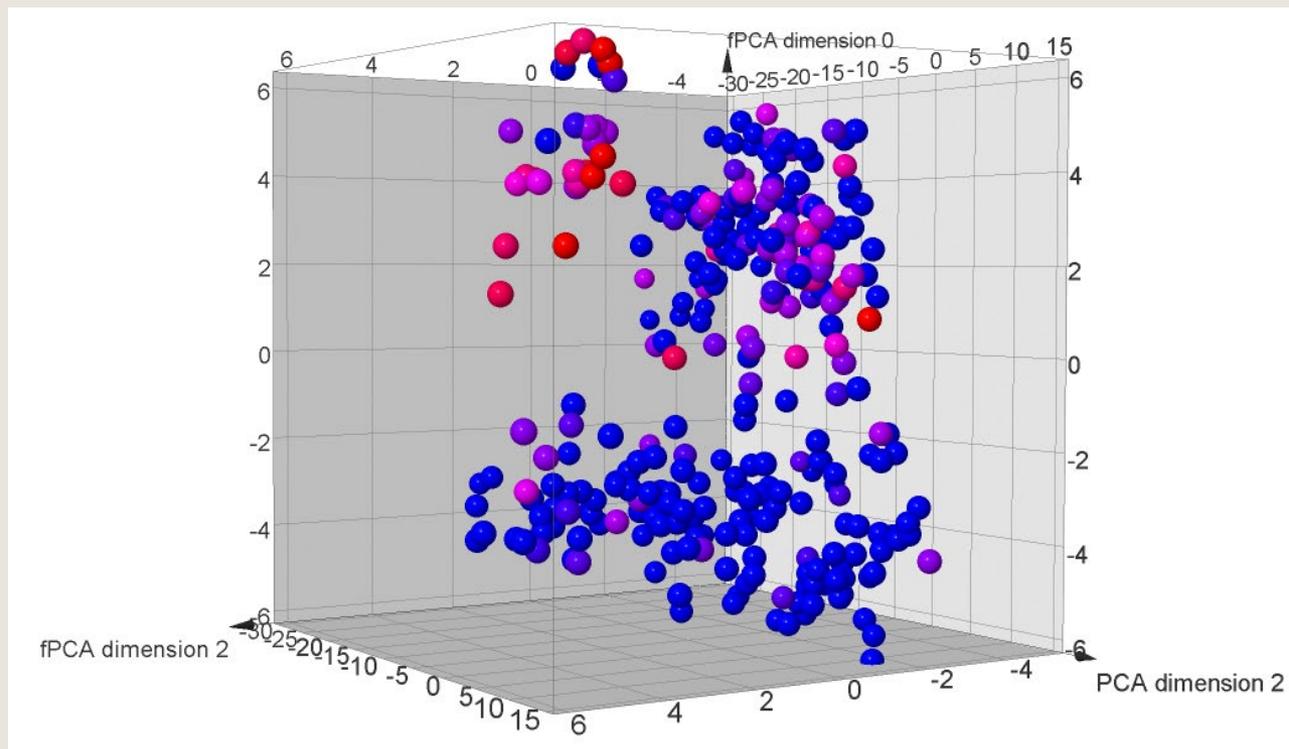


Screening results of S01 first iteration

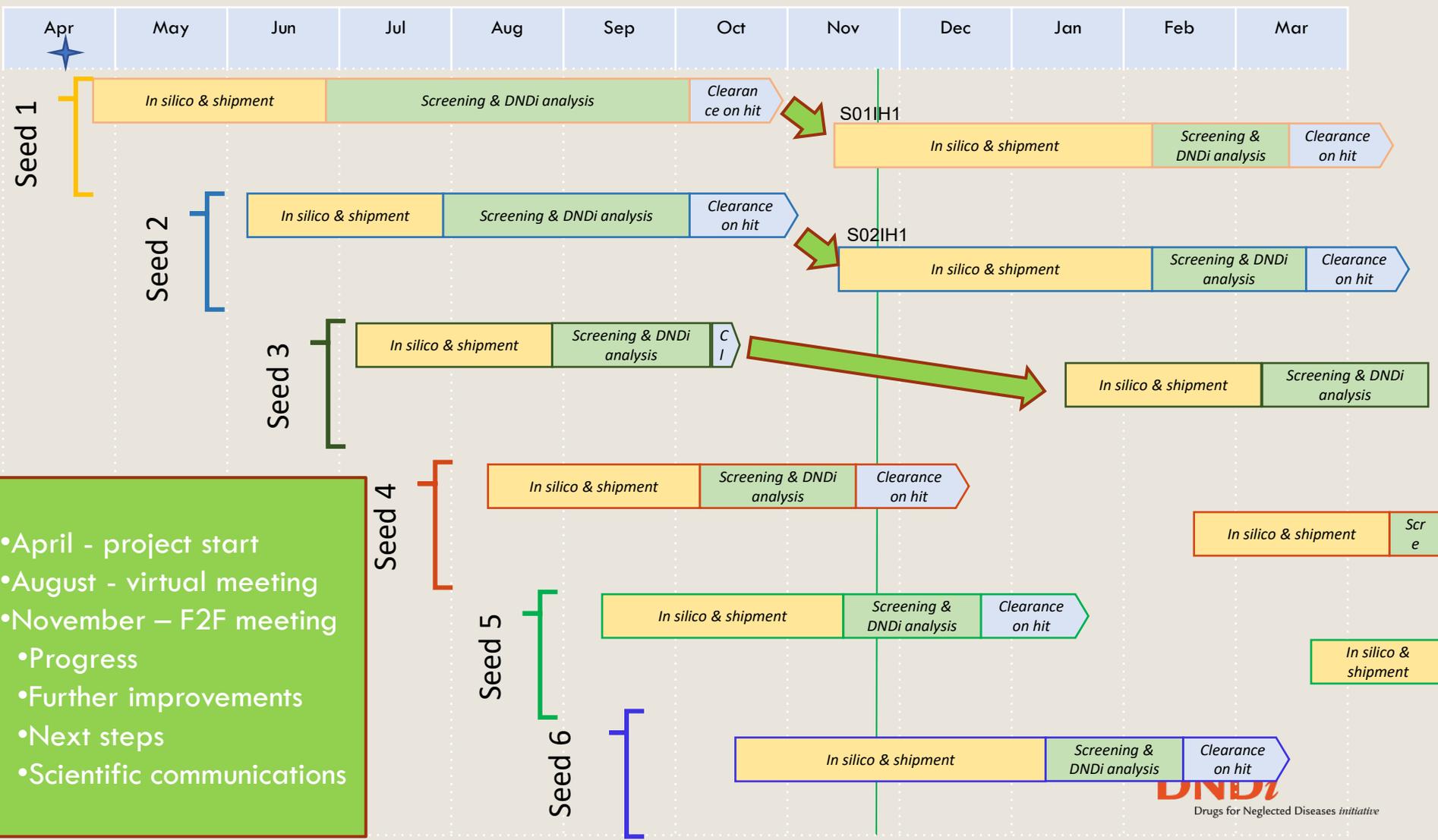
Clear hot spots of active compounds in different chemical space

- Actives (red) are clustered in a number of areas of chemical space
- Clear hot-spot regions exist away from the original seed

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



Booster Project Progress



- April - project start
- August - virtual meeting
- November – F2F meeting
 - Progress
 - Further improvements
 - Next steps
 - Scientific communications

Launching the Booster!

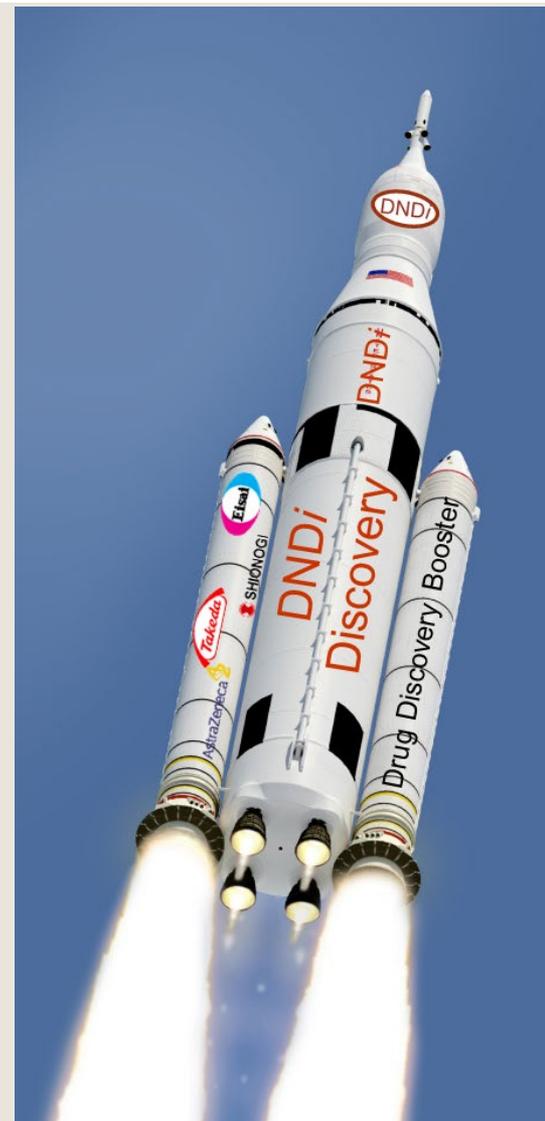
- A shift from bilateral to **multilateral collaboration**
- Companies working together on a **shared project**
- Ownership and IP rules agreed in advance
- Three year countdown to launch in April 2015
- Initial results very promising



Starr International Foundation
GHIT
WHO (TDR-DEMO project)
Core funding (DFID, MSF, SDC)



Starr International Foundation





Thank you for
your attention

DNDi

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