Diseases of the Developing World.
The Open lab experience in Spain

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Diseases of the Developing World

- Group of diseases that are predominant in the poorest parts of the world.

- **Malaria, Tuberculosis** and Neglected Tropical Diseases (NTDs).
- NTDs. Dengue, rabies, blinding trachoma, Buruli ulcer, endemic treponematoses (yaws), leprosy (Hansen disease), **Chagas disease**, human African tripanosomiasis (sleeping sickness), **leishmaniasis**, cysticercosis, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematode infections, lymphatic filariasis, onchocerciasis (river blindness), schistosomiasis (bilharziasis), soiltransmitted helminthiases (intestinal worms).
- chromoblastomycosis and other deep mycoses, scabies and other ectoparasites and snakebite envenoming

- NTDs are prevalente in 149 countries, affecting > 1.4 billion people (WHO).

World Health organization.Neglected tropical diseases. Geneva, 2014.Availableat: http://www.who.int/neglected_diseases/diseases/en/. cited2015Sep17.

Diseases of the Developing World.

New chemical entities approved 1975-1999

Therapeutic areas	Approved NCEs 1975–99*	Disability-adjusted life-years (DALYs)†			
		Number (×10⁶)	World-wide (%)	High-income countries (%)	Low- and middle-income countries (%)
Central nervous system	211 (15·1%)	159·46	11·5	23·5	10·5
Cardiovascular	179 (12·8%)	143·02	10·3	18·0	9·7
Cytostatics (neoplasms)	111 (8·0%)	84·87	6·1	15·8	5·2
Respiratory (non-infectious)	89 (6·4%)	61·60	4·5	7·4	4·2
Anti-infectives and antiparasitics§	224 (16·1%)	409·08	29·6	4·2	31·8
HIV/AIDS¶	26 (1·9%)	70·93	5·1	0·9	5·5
Tuberculosis‖	3 (0·2%)	28·19	2·0	0·1	2·2
Tropical diseases (total)**	13 (0·9%)	130·35	9·4	0·3	10·2
Malaria	4 (0·3%)	39·27	2·8	0·0	3·1
Other therapeutic categories	579 (41·6%)	524·54	37·94	31·08	38·59
Total	1393 (100%)	1382·56	100	100	100

1.4%

15%

Table 1. New chemical entities (NCEs) approved between 1975 and 1999 by drug class and relative to disease burden

Pyrazinamide, rifabutin, rifapentine. **Benznidazole, nifurtimox (Chagas' disease); albendazole (helminthic infection); eflornithine (human African trypanosomiasis); artemether, atovaquone+proguanil, halofantrine, mefloquine (malaria); ivermectin (onchocerciasis); oxamniquine, praziquantel (schistosomiasis) and two reformulations of already approved drugs: liposomal amphotericin B (leishmaniasis) and pentamidine (African trypanosomiasis).

Trouiller P et al, Lancet. 2002;359:2188–2194.

Diseases of the Developing World.

New chemical entities approved 2000-2011

	All new products*	NCEs only	DALYs (in thousands)
Neuropsychiatric disorders	134 (16%)	49 (15%)	199 280 (13%)
Cancer	103 (12%)	81 (24%)	79 765 (5%)
Cardiovascular diseases	70 (8%)	29 (9%)	151 377 (10%)
Genitourinary system and sex hormones	55 (7%)	18 (5%)	14 754 (1%)
Digestive diseases	46 (5%)	23 (7%)	42 498 (3%)
Sense organ disorders	37 (4%)	13 (4%)	86 883 (6%)
Neglected diseases	37 (4%)	4 (1%)	159 976 (11%)
Malaria	12 (1%)	3 (1%)	33 976 (2%)
Tuberculosis	7 (1%)	0	34 217 (2%)
Diarrhoeal diseases	7 (1%)	1 (<0·5%)	72 777 (5%)
Neglected tropical diseases	5 (1%)	0	18 325 (1%)
Other neglected diseases	6 (1%)	0	681 (<0·5%)
HIV/AIDS	36 (4%)	12 (4%)	58 513 (4%)
Respiratory diseases (non-infectious)	31 (4%)	7 (2%)	59 039 (4%)
Diabetes mellitus	28 (3%)	9 (3%)	19 705 (1%)
Musculoskeletal diseases	26 (3%)	13 (4%)	30 869 (2%)
Other infectious and parasitic diseases	113 (13%)	23 (7%)	181 441 (12%)
All other diseases†	134 (16%)	55 (16%)	439 159 (29%)
Total	850 (100%)	336 (100%)	1 523 259 (100%)

1.5%

11%

Data are n (%). *Includes NCEs, new formulations, fixed-dose combinations, new indications, and vaccines or biologicals. †Maternal and perinatal disorders, nutritional deficiencies, congenital abnormalities, skin diseases, endocrine disorders, oral diseases, and injuries.

***Table 2:* Disease indications of all new products and of new chemical entities (NCEs) compared with worldwide disability-adjusted life-years (2004 DALYs; 2000–11)**

Pedrique B et al, Lancet Global Health. 2013(6):e371-9.

Diseases of the Developing World.

New chemical entities approved 2000-2011

- Lack of NCE approved reflects not only lack of investment……
  - 2010. US$2.4 billion (1% overall healthcare expenditure).
  - 2011. US$3.04 billion.

- ...but also lack of knowledge, tools and platforms and innovation, etc
  - Increase attrition rate

- Multifactorial issue requires a "**Collaborative effort**" in drug discovery

GSK announced 'Open Innovation' strategy for DDW in 2010

Trouiller P et al, Lancet. 2002;359:2188–2194.

GSK DDW Open Innovation approach

Collaboration and flexibility as key principles

"TRES CANTOS DDW"

DRUG DISCOVERY UNIT FULLY DEDICATED TO DDW

"PATENT POOL"

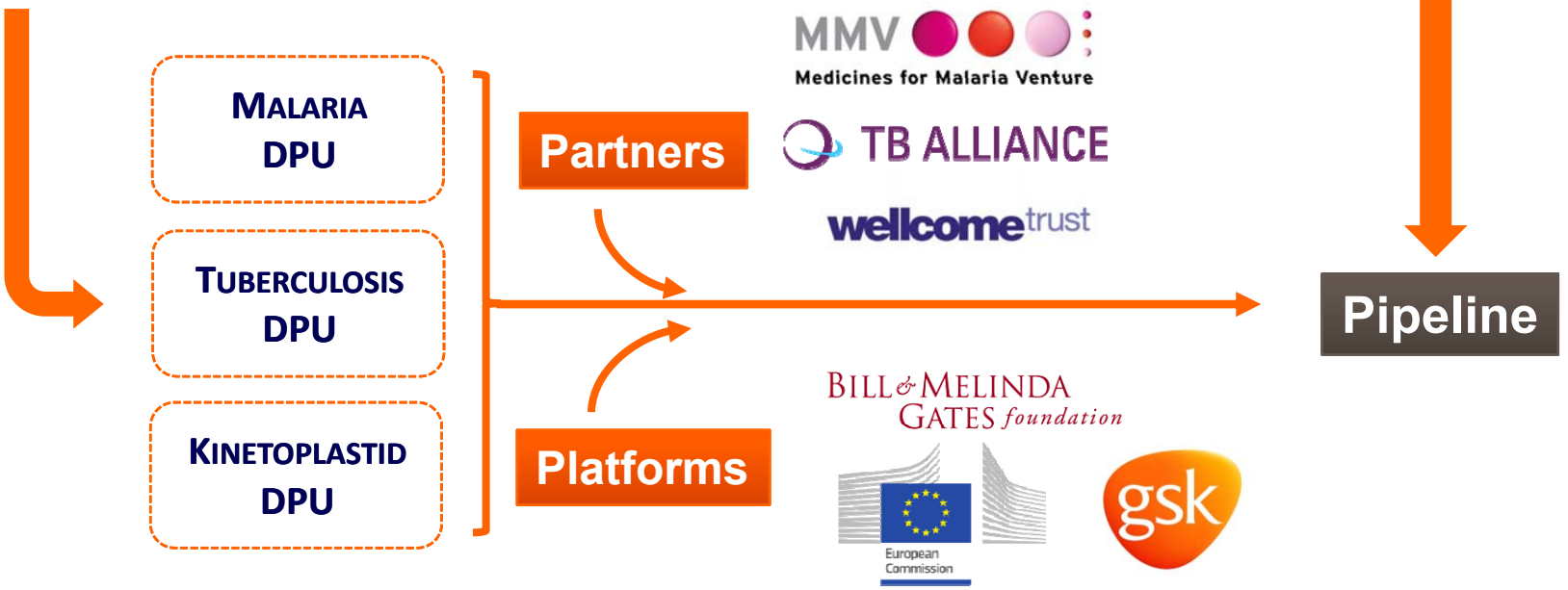
BEING MORE FLEXIBLE WITH OUR INTELLECTUAL PROPERTY

"OPEN SOURCE"

SHARING OUR DATA AND ASSETS WITH THE RESEARCH COMMUNITY

"OPEN LAB"

PROVIDING ACCESS TO OUR KNOW-HOW AND RESOURCES



The Open Lab: What it is and how it works

Merging academic and pharma R&D in a discovery environment

Academic Research

Pharma R&D

tres cantos OPEN LAB FOUNDATION

- Independent foundation focused on TB, Malaria and Kinetoplastids DD
- Established in 2010 (£10M by GSK + €1.2M from EU FP7)

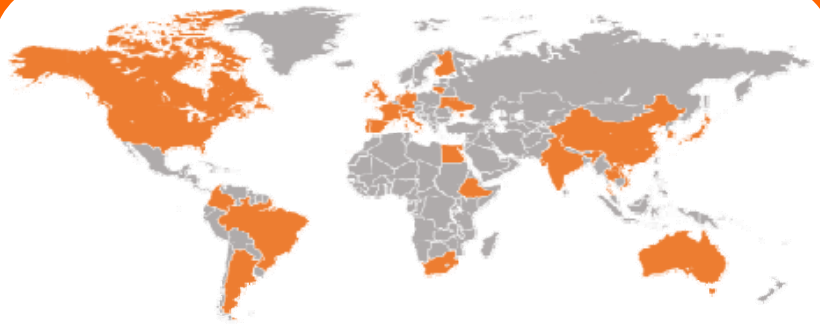
GOVERNING BOARD FORMED BY KEY OPINION LEADERS IN DDW

Alan Fairlamb | Tim Wells | Peter Piot | Carl Nathan | Elisabeth Winzeler | Mel Spiegelman | Nick Cammack | Jose Maria Romero | Graeme Bilbe | Kip Guy

The Open Lab: What it is and how it works

Merging academic and pharma R&D in a discovery environment

PHARMA R&D



ACADEMIC RESEARCH

256 PROPOSALS EVALUATED, **72** PROJECTS FUNDED

85 VISITING SCIENTISTS

22 ACTIVE PROJECTS

48 COMPLETED PROJECTS

Open Lab Project: Phenotypic screening.
Kinetoplastid paraites

- Lack of translational assays

in vitro → *in vivo*. Many false positive

  - Reaching the biophase
  - Relevant form of the parasite

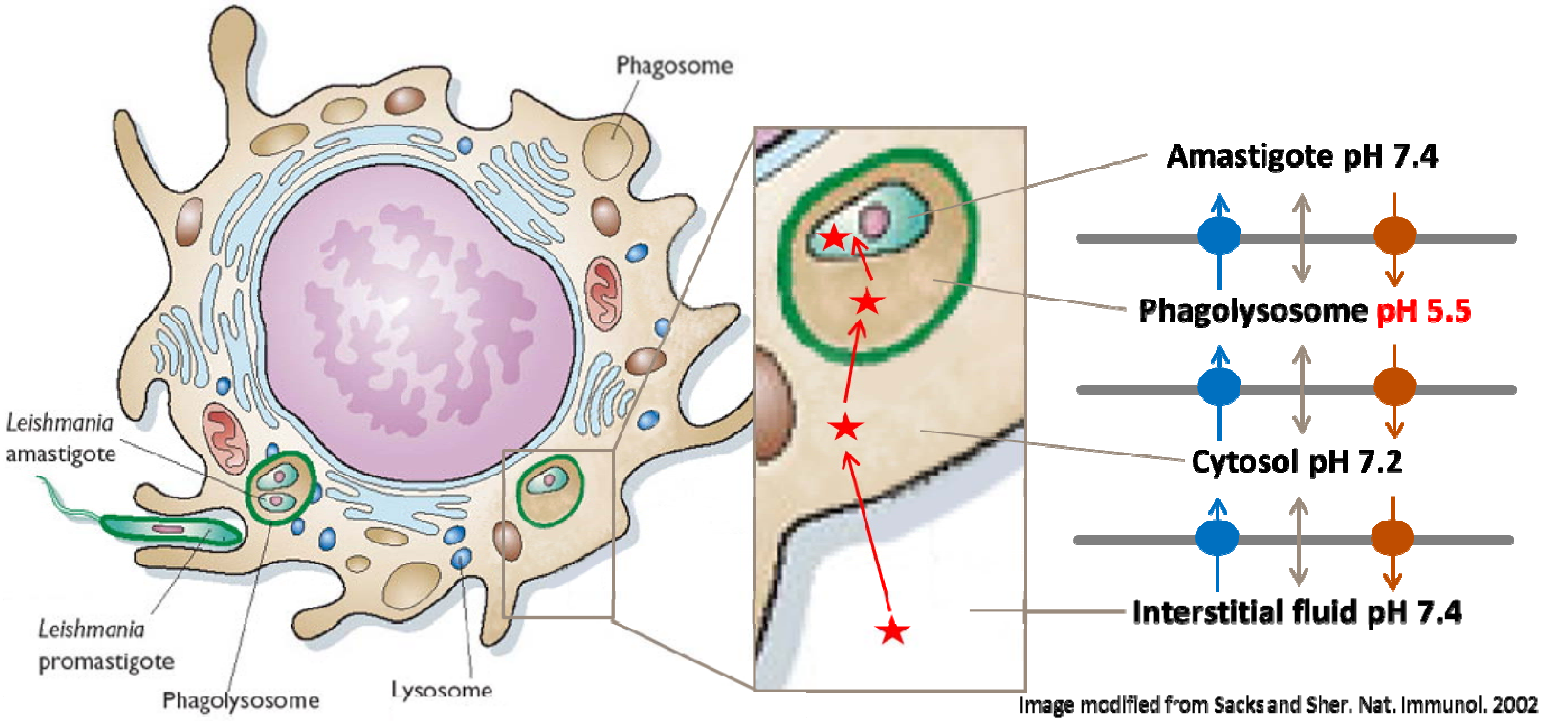
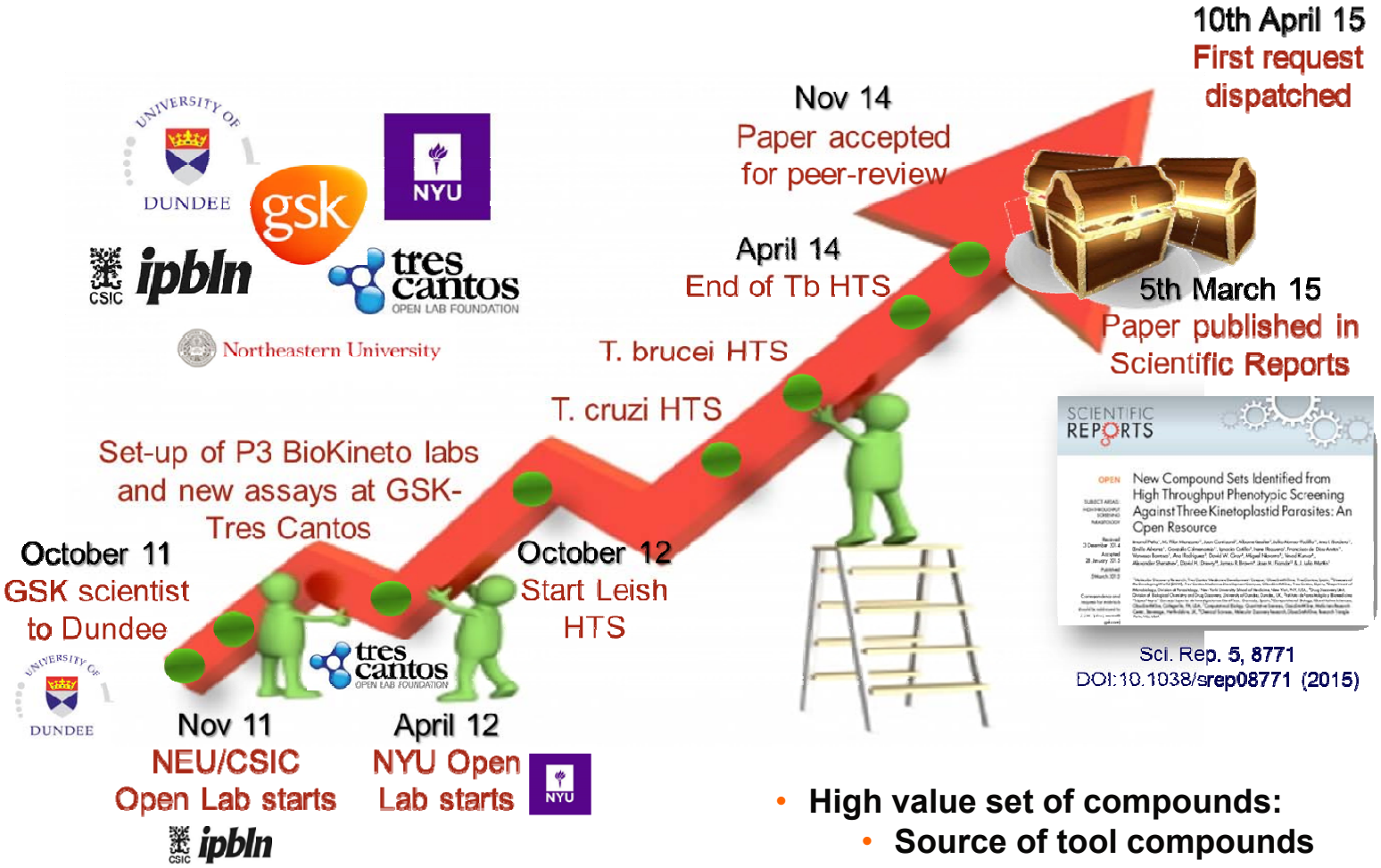


Image modified from Sacks and Sher. Nat. Immunol. 2002

Long and Eventful Travel to Kineto Boxes

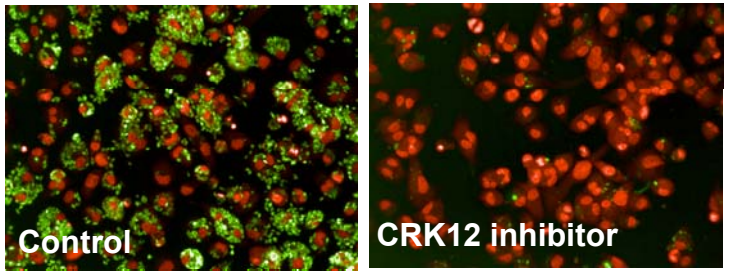


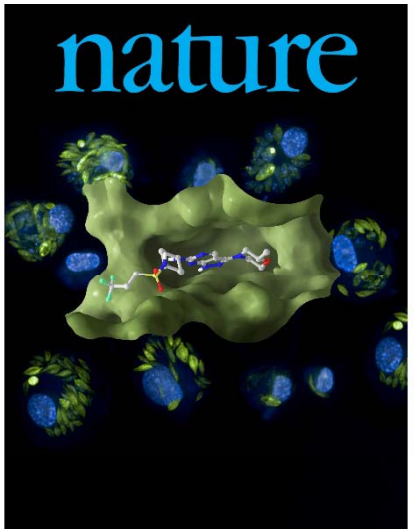
- **High value set of compounds:**
  - **Source of tool compounds**
  - **Source of Lead Optimization Projects**

Preclinical candidate for VL

GSK3186899A

- Collaboration with Dundee University
- Identified by phenotypic screening.
- Deconvoluted their primary targets. CRK12.
- Novel, cidal and highly selective mode of action.
- Similar oral *in vivo mouse* efficacy to miltefosine (unique oral treatment but teratogenic).
- The assets fits our Target Medicine Profile.
- World-leading science





Nature (2018), 560(7717), 192-197

"The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol."


gsk
do more
feel better
live longer
BIG
THANK TO ALL….