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Drug Discovery to Combat GNB Infections: current challenges and possible progress

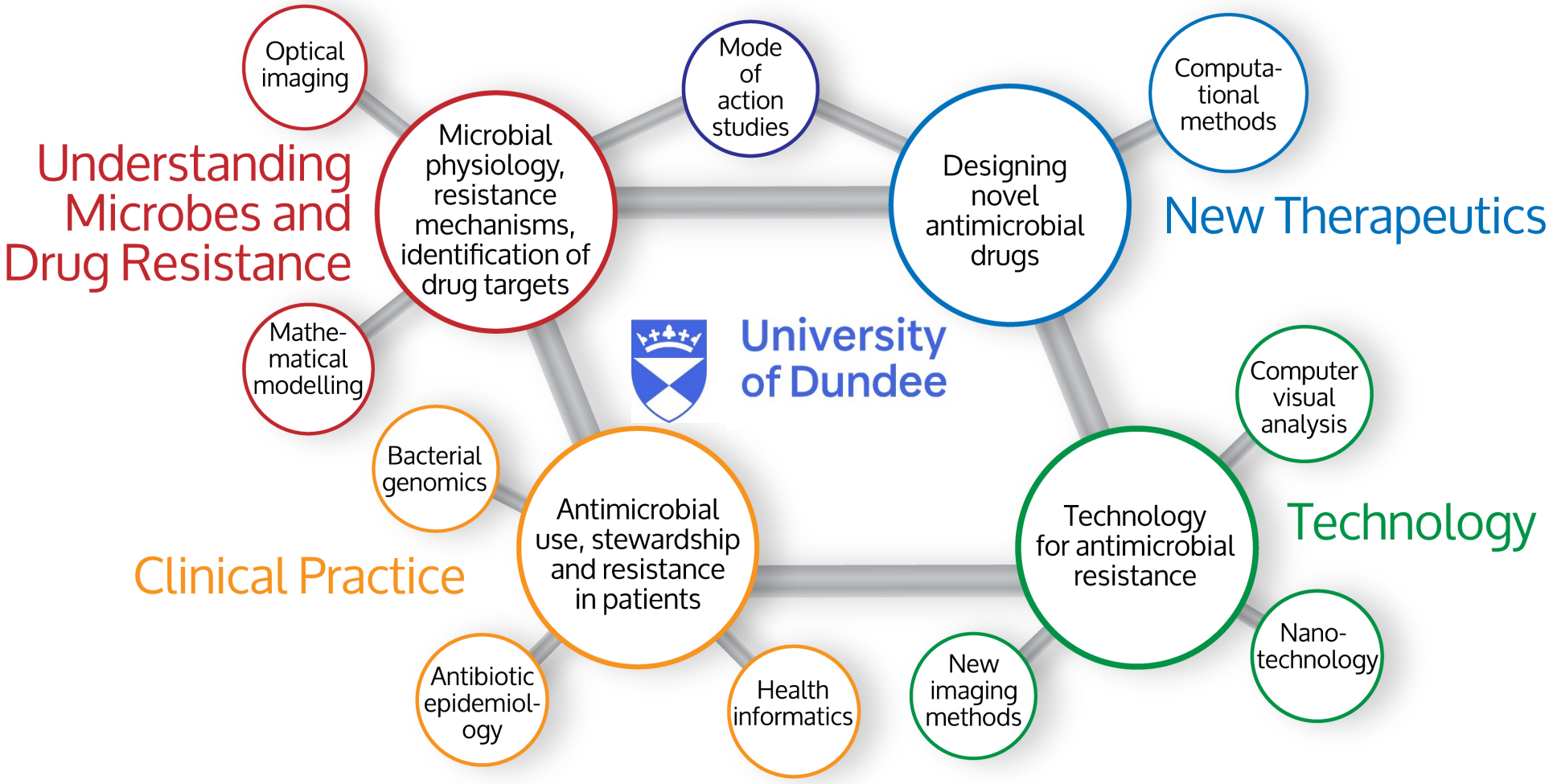
Ian Gilbert

Ian Gilbert & Mike Ferguson

Wellcome Centre for Anti-Infectives Research

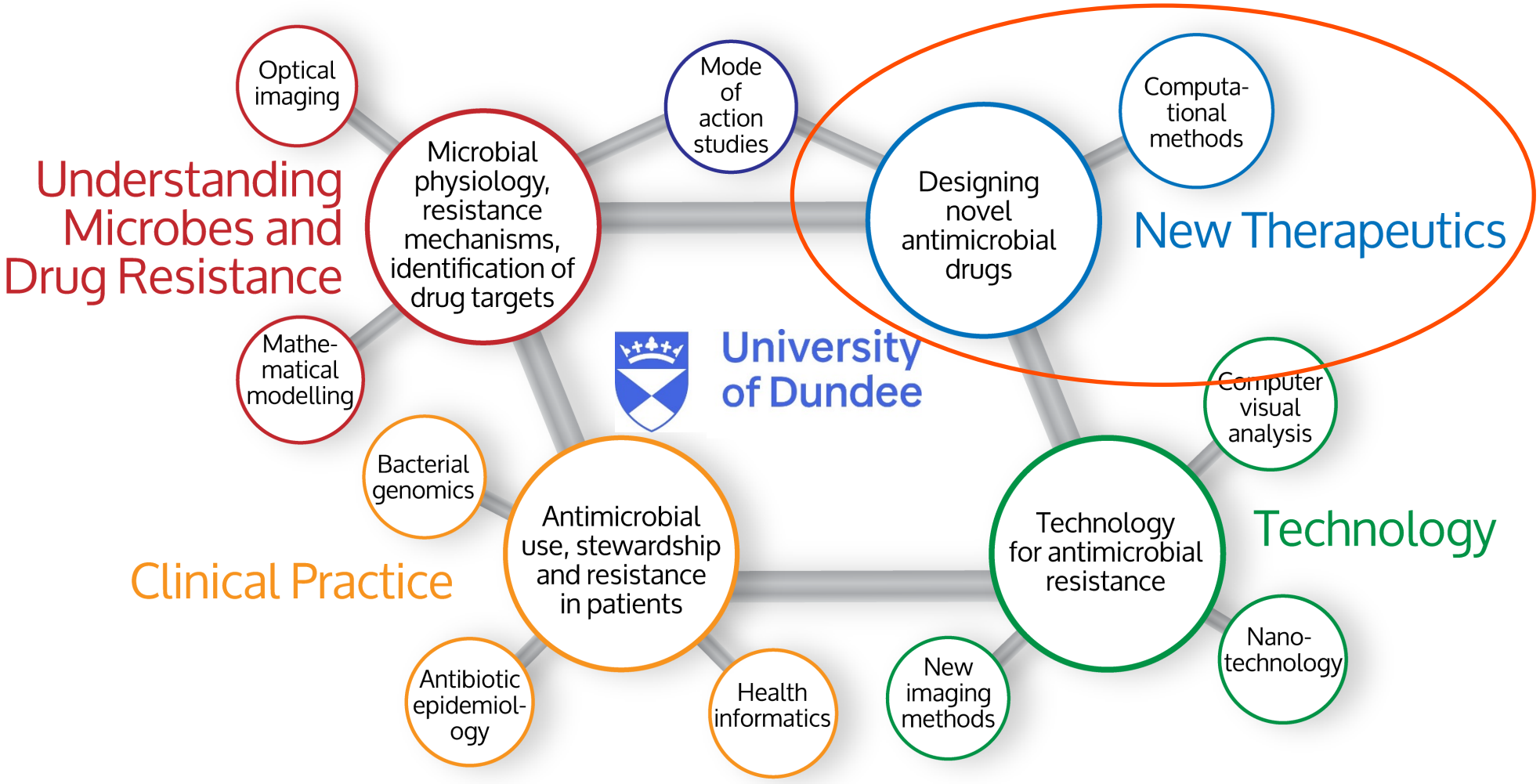
School of Life Sciences

University of Dundee:
Centre for Antimicrobial Resistance



http://amr.dundee.ac.uk

University of Dundee:
Centre for Antimicrobial Resistance



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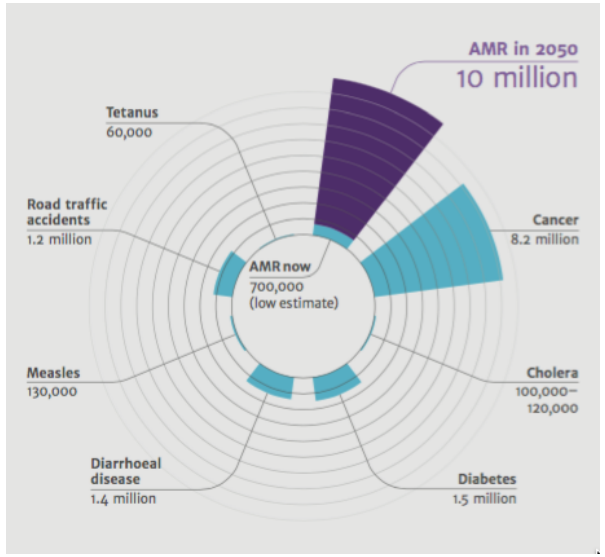
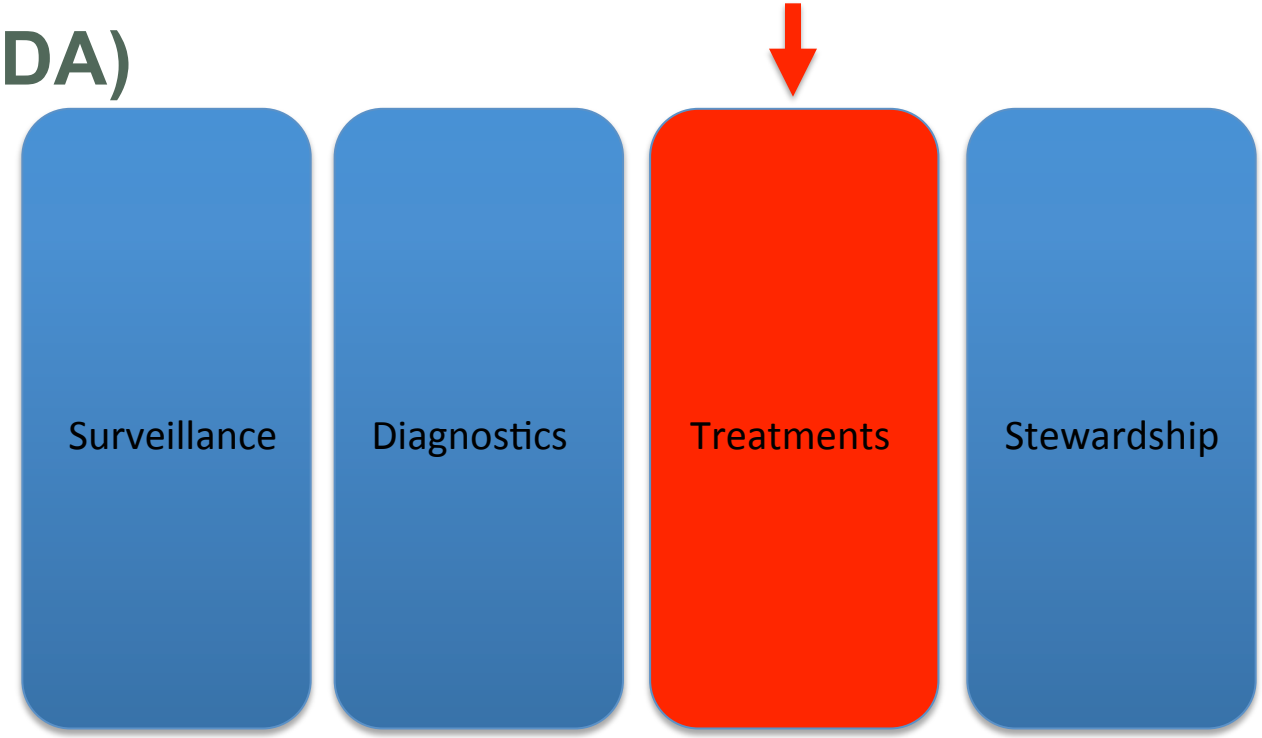
Creating an Antibacterial Drug Discovery Accelerator (ADDA)

Drug Discovery Unit



O'Neill Report, 2015



Four parallel, interacting, pillars of activity are necessary to tackle AMR

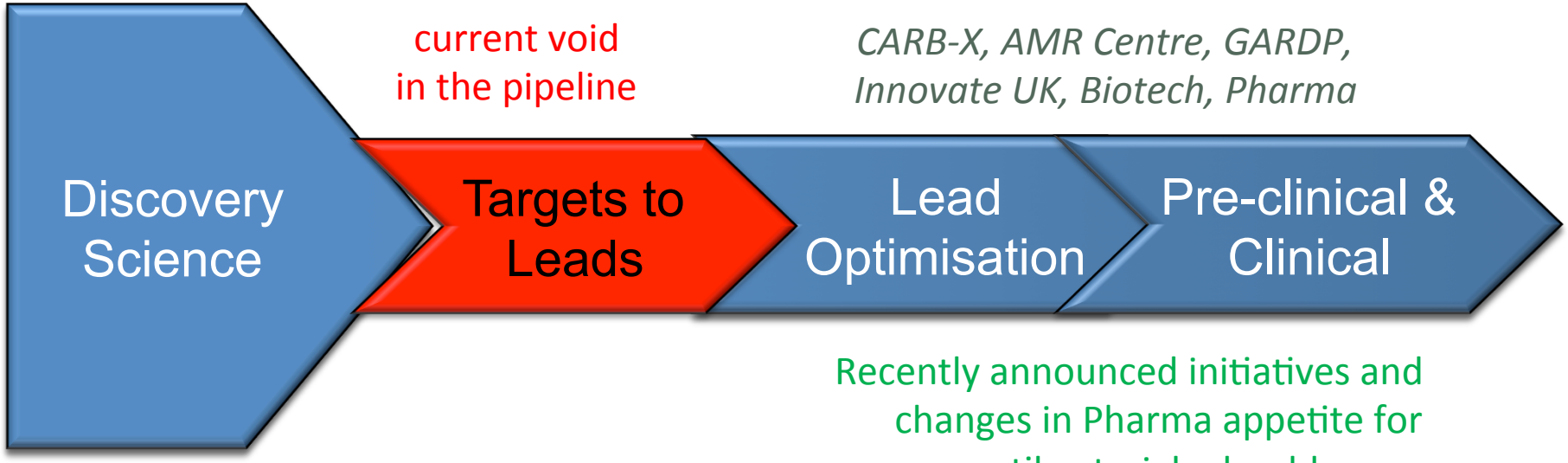
Timeline from target to drug, 10-15 years

ADDA concept in context:

Universities supported by funding agencies (MRC, BBSRC Wellcome, BSAC others)

current void in the pipeline

CARB-X, AMR Centre, GARDP, Innovate UK, Biotech, Pharma



Recently announced initiatives and changes in Pharma appetite for antibacterials should move forward stalled assets (mostly in Biotech)

Then what?

Innovation

ADDA

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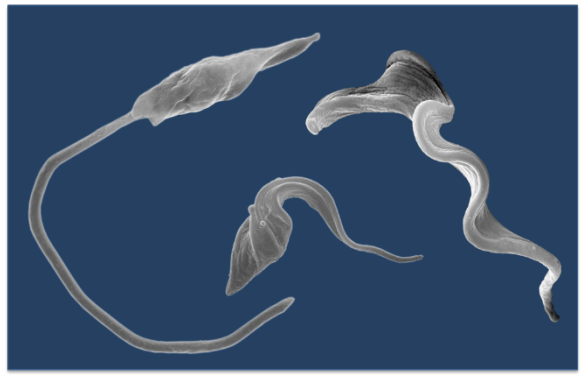
The Drug Discovery Unit

Drug Discovery Unit

- A “Biotech company” within a university
  - With better equipment and facilities
  - Current funding streams - ~£35 million (£ 7m pa)
  - Biopharma industry drug discovery experienced team, 95 people
  - From companies including – AstraZeneca, Merck (MSD), GSK, Pfizer, Novartis
- Combines excellence in basic science with biopharma industry expertise
- Complements the pharmaceutical industry
  - Diseases of the Developing World (tropical & orphan)
  - Innovative Targets Portfolio (new approaches for tackling major diseases)



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Management Team

Drug Discovery Unit

Paul Wyatt
Head Of DDU & Director CAIR
- 11 years in the DDU
- 23 years in BioPharma
- 7 pre-clinical and 3 clinical candidates

Ian Gilbert
Head of Med Chem
- 11 years in the DDU
- 1 year in BioPharma
- 13 years in academia
- Led team to develop malaria candidate

Susan Wyllie
Head of Mode of Action
- 2 years in the DDU
- 13 years in academia

David Gray
Head of Biology, Innovative Targets Portfolio Manager
- 7 years in the DDU
- 15 years in BioPharma
- 10 pre-clinical, 10 clinical candidates and 1 marketed drug

Kevin Read
Head of DMPK, Animal Models
- 10 years in the DDU
- 18 years in BioPharma
- 6 pre-clinical and 4 clinical candidates

Andrew Woodland
Portfolio Manager, Dermatology
- 9 years in the DDU
- 5 year in BioPharma

Julie Brady
Business Development Manager
- 4 years in DDU
- 14 years in commercialisation

Louise Burns
Finance Officer
- 4 years in DDU
- 6 years industry experience
- Chartered Accountant

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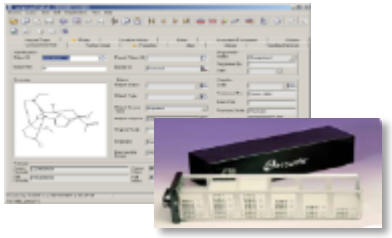
ADDA: will build on existing infrastructure

Drug Discovery Unit

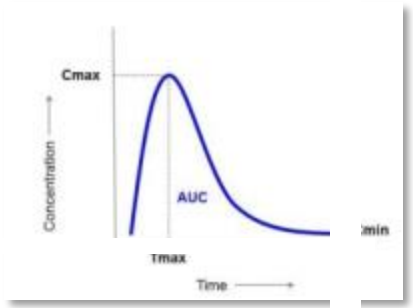
Target Selection

Validation
Druggability
Assay Feasibility
Toxicity
Resistance potential
Structural Information

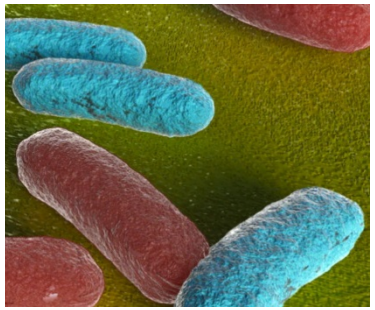
384 MTS/HTS Robotics



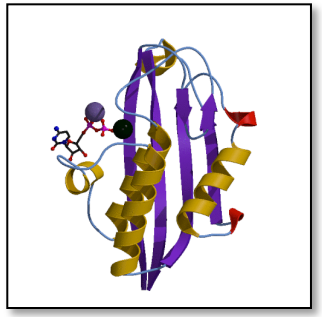
Compound Sets



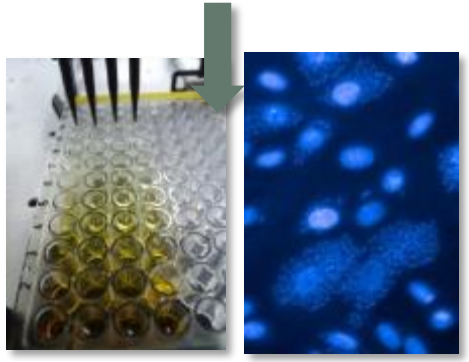
DMPK



in vitro models

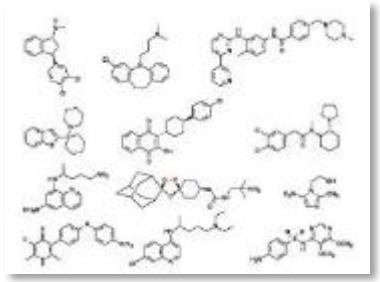


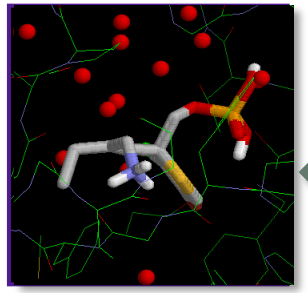
Structural Biology



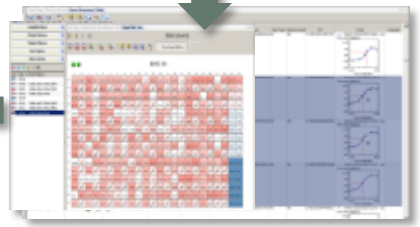
Target or cell screen

in vivo models





Medicinal & Computational Chemistry



Data Management

ADDA: will build on existing infrastructure

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Drug Discovery Unit

First ADDA-dedicated Funding:
Innovate UK AMR Competition 2016
£870k to extend labs for ADDA medicinal chemistry

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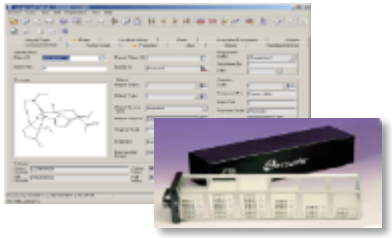
384 MTS/HTS Robotics



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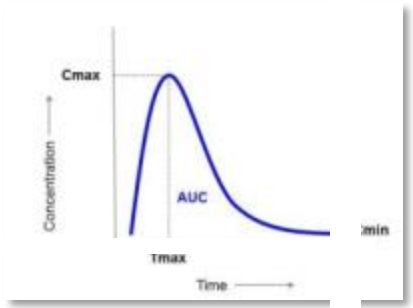

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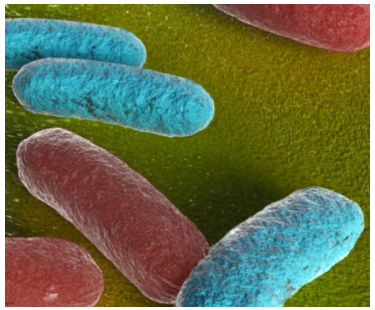

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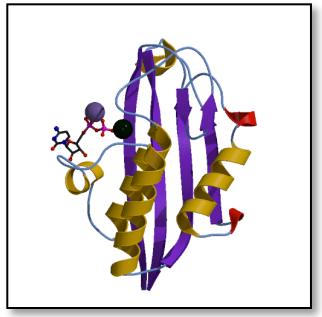

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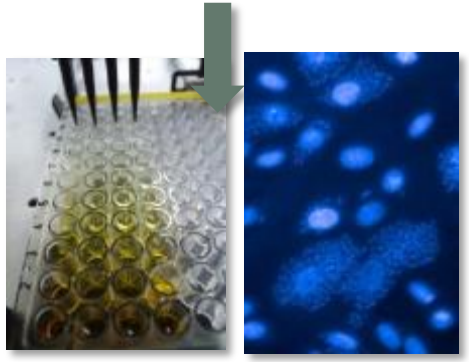

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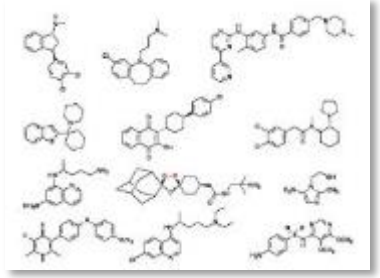

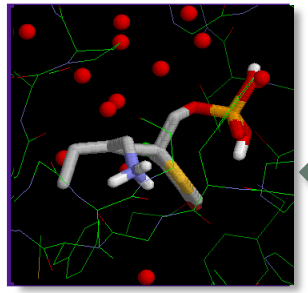

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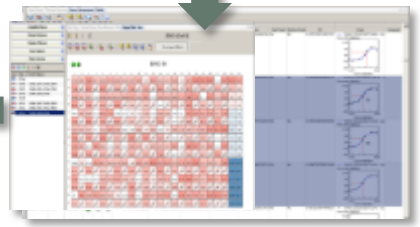

Data Management

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Track record as an infectious diseases drug accelerator

Disease	Lead Optimisation	Preclinical	Clinical
Malaria	1 series	SGC	DDD498
Leishmaniasis	1 series	2 candidates	*Fexinidazole*
Human African trypanosomiais		1 candidate	
Animal African trypanosomiais			1 drug candidate in vet trials
Chagas' Disease	3 series		
Cryptosporidiosis	1 series	SGC	
Tuberculosis	2 series		

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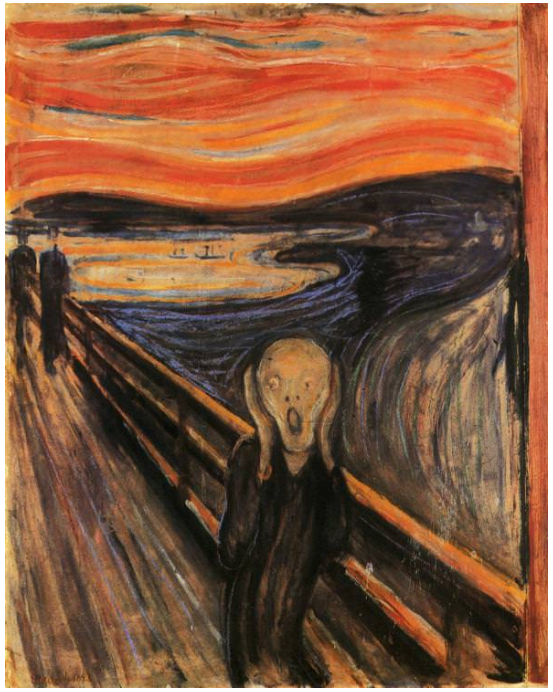
Multi-parametric optimisation problem

Increase drug *potency* – the desired effect of the drug
Increase drug *solubility & volume of distribution* – necessary to get the drug into the body
Reduce drug *toxicity* – the undesired effect(s) of the drug
Adjust drug *metabolism* – how quickly the body eliminates the drug



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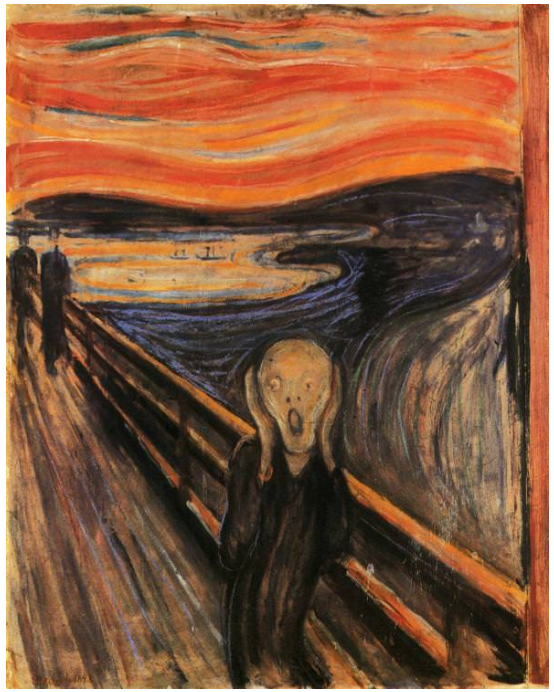
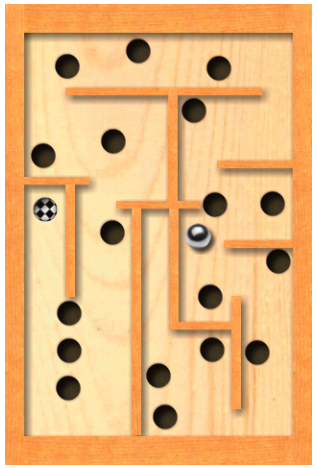
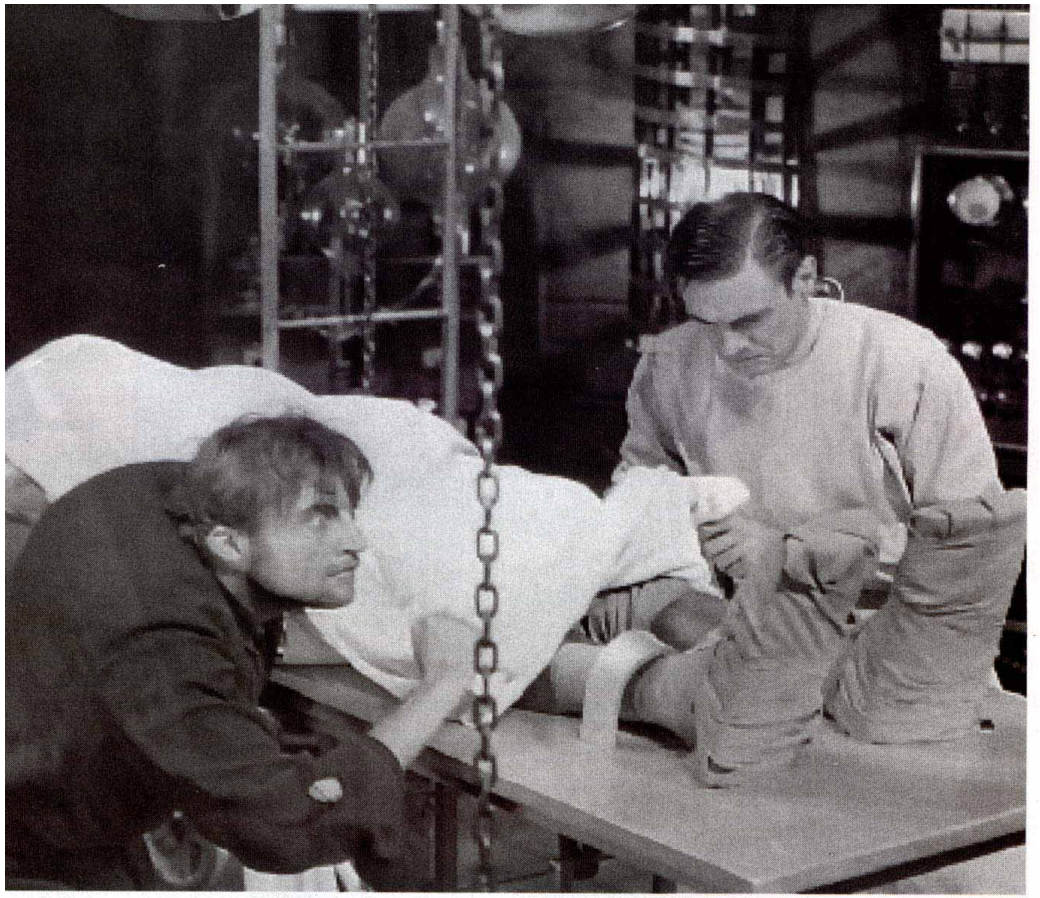




The *Hit to Lead* and *Lead Optimisation* processes involve **Chemists** "splicing together" new molecules that contain desirable features and eliminate undesirable features. **Biologists** then test them and, together, they design the next round of compounds.



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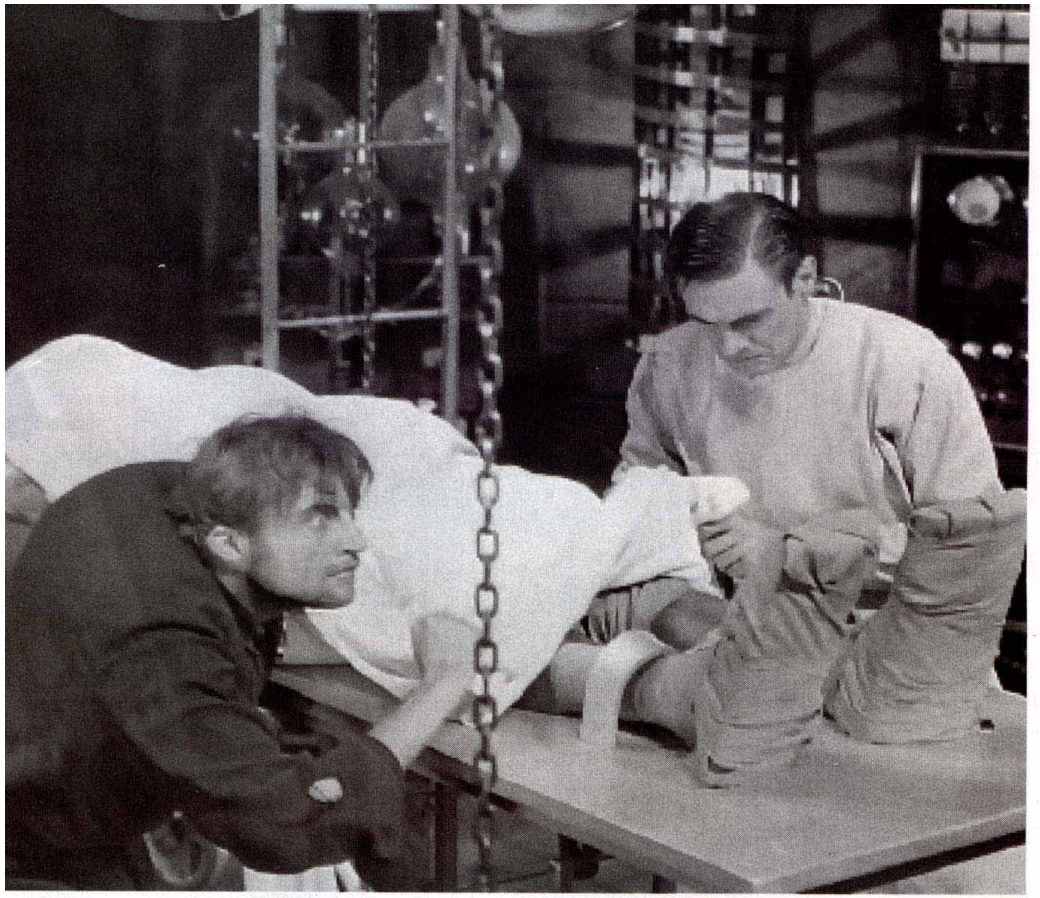

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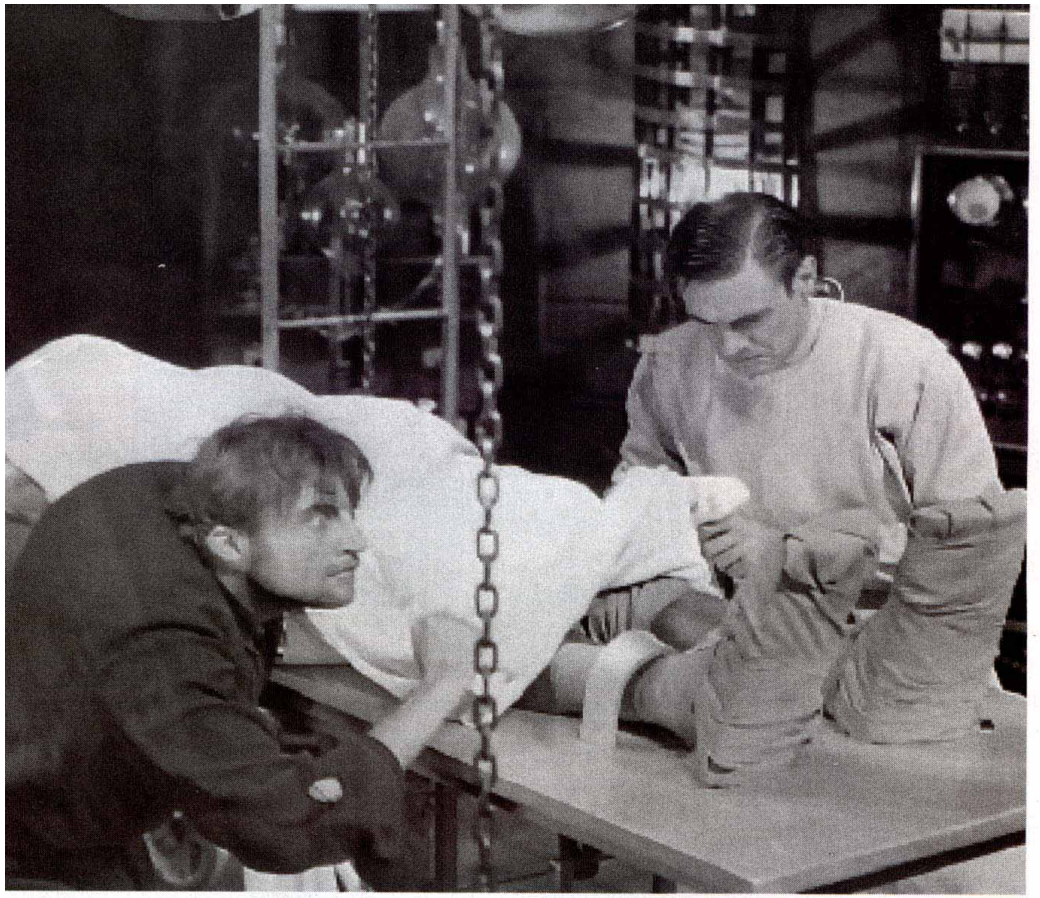
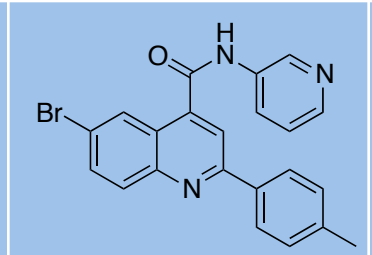
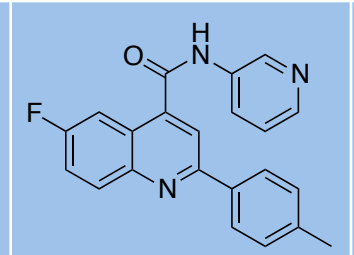
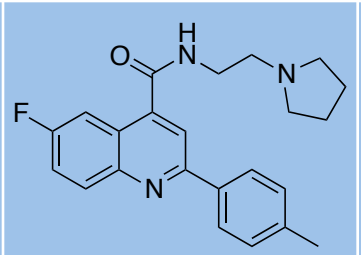
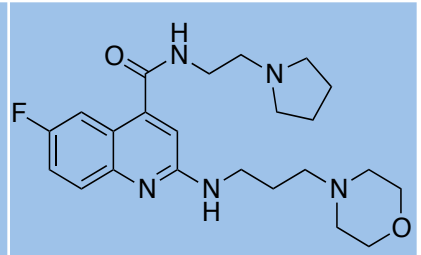
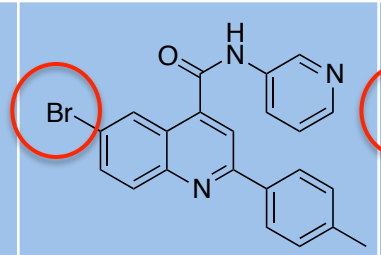
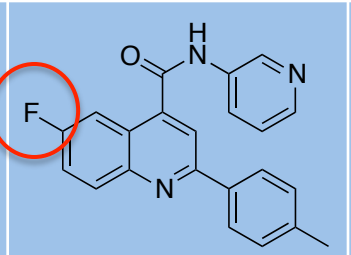
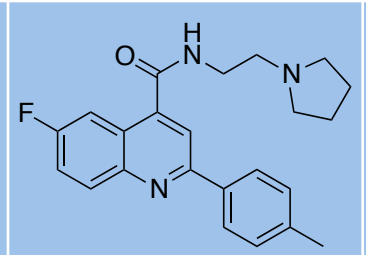
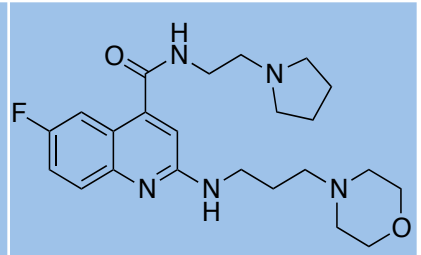


Biologist

MMV04 Series: Hits to Lead - focus on properties

				
Potency	0.12	0.35	0.70	0.05
	418	357	377	430
Solubility	4.3	3.7	3.7	2.1
		36	180	>230
Metabolism	5.3	8.6	3.4	0.8
		97.2		59

MMV04 Series: Hits to Lead - focus on properties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	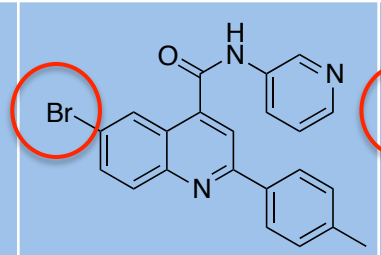	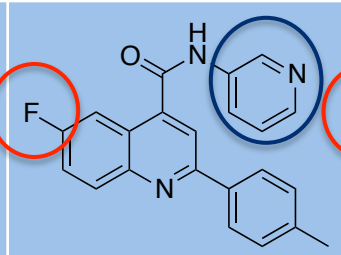	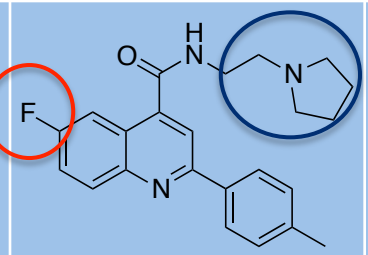	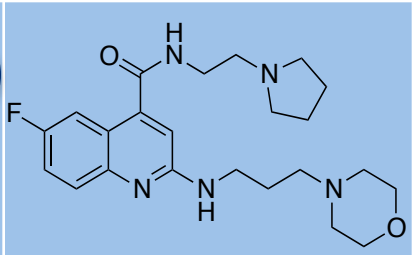
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	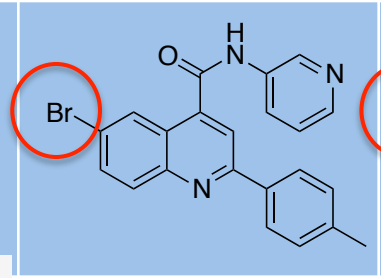	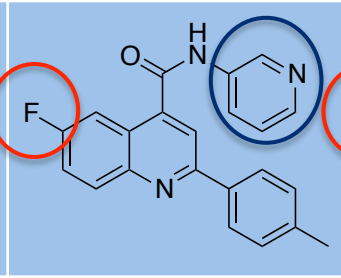	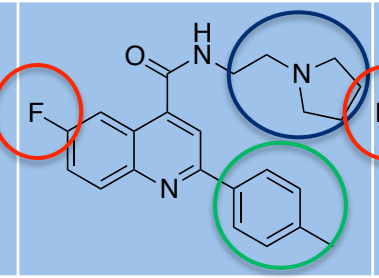	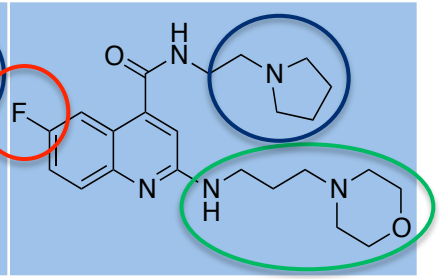
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MALARIA

Drug Discovery Unit

International collaborations with expert parasitologists

Partnership with the Medicines for Malaria Venture

Medicines for Malaria Venture

ARTICLE

doi:10.1038/nature14451

A novel multiple-stage antimalarial agent that inhibits protein synthesis

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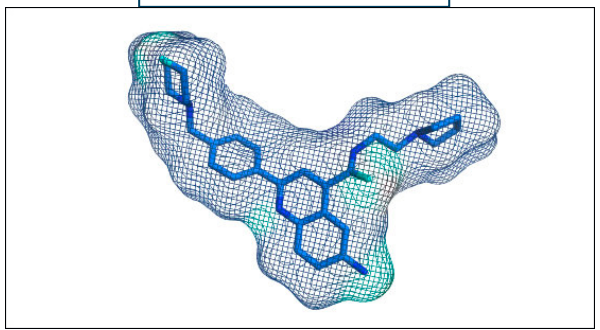
2009 — Initial screen for compounds that kill the malaria parasite

Medicines for Malaria Venture

2012 — Drug lead Declared for MMV

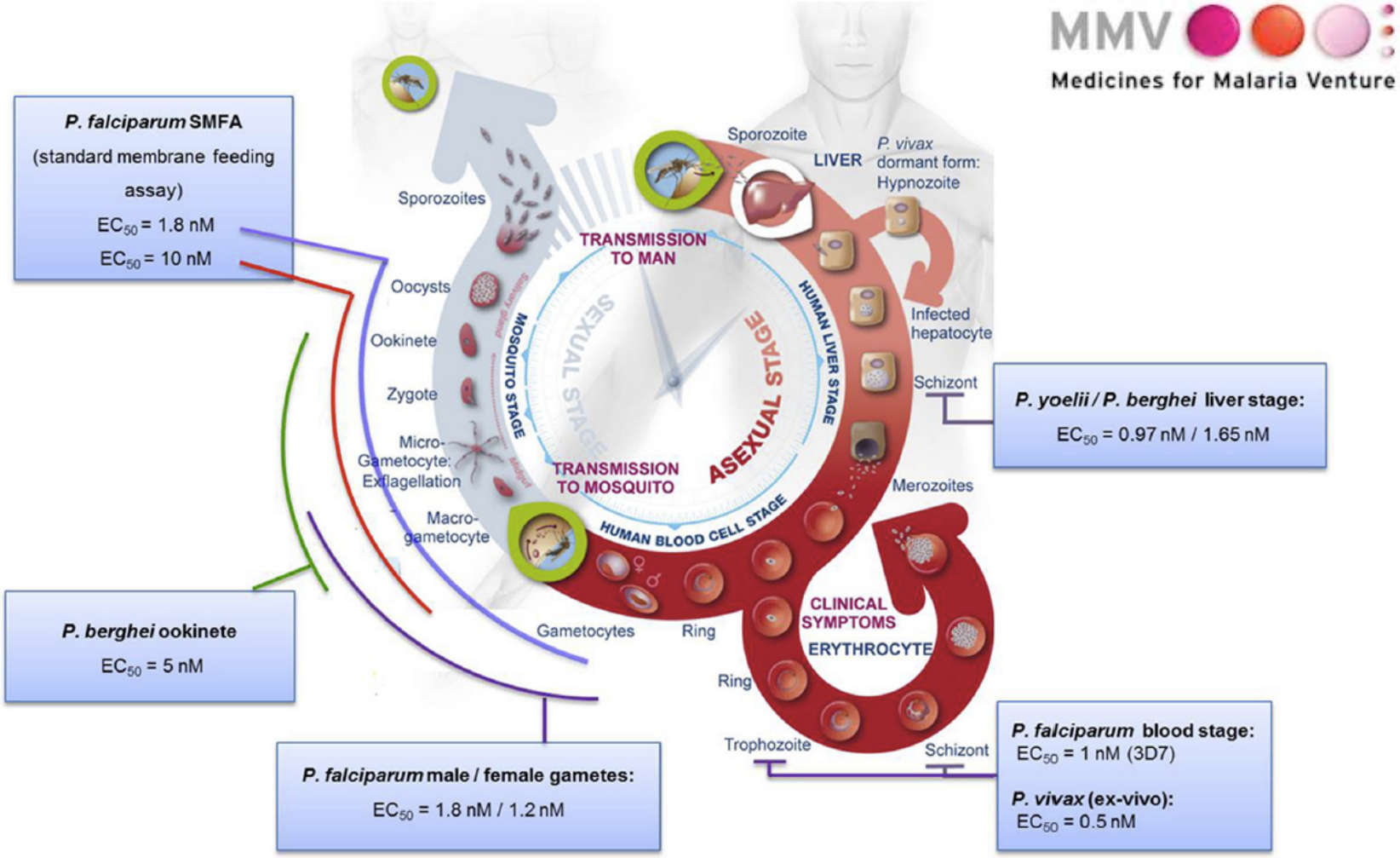
2014 — Drug candidate DDD498 delivered to MMV



2015 — DDD498 Declared MMV "Project of the Year" and partnered with Merck Kga for pre-clinical and clinical development

MERCK

MoA of DDD498 means that compound can cure, prevent and block transmission



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Track record as an infectious diseases drug accelerator

Disease	Lead Optimisation	Preclinical	Clinical
Malaria	1 series	SGC	DDD498
Leishmaniasis	1 series	2 candidates	*Fexinidazole*
Human African trypanosomiais		1 candidate	
Animal African trypanosomiais			1 drug candidate in vet trials
Chagas' Disease	3 series		
Cryptosporidiosis	1 series	SGC	
Tuberculosis	2 series		

Wellcome Centre for Anti-Infectives Research

INSTITUTIONAL SUPPORT & INTEGRATION

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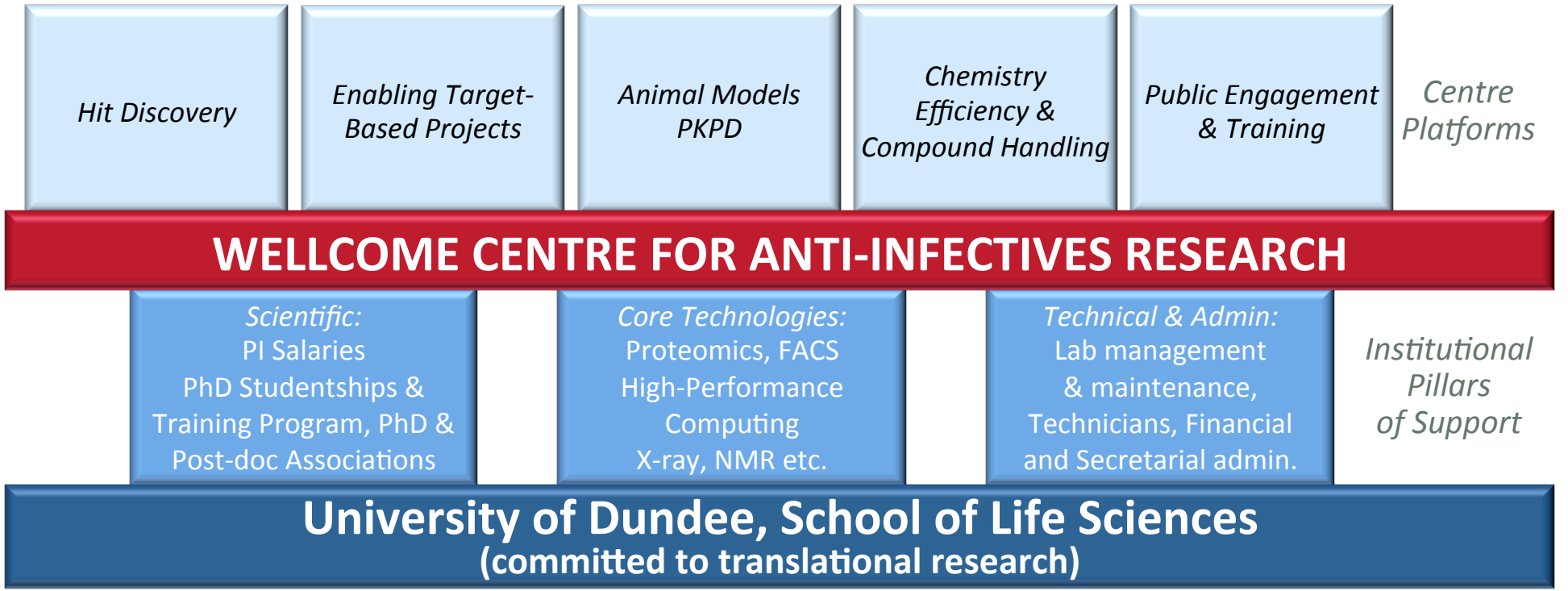

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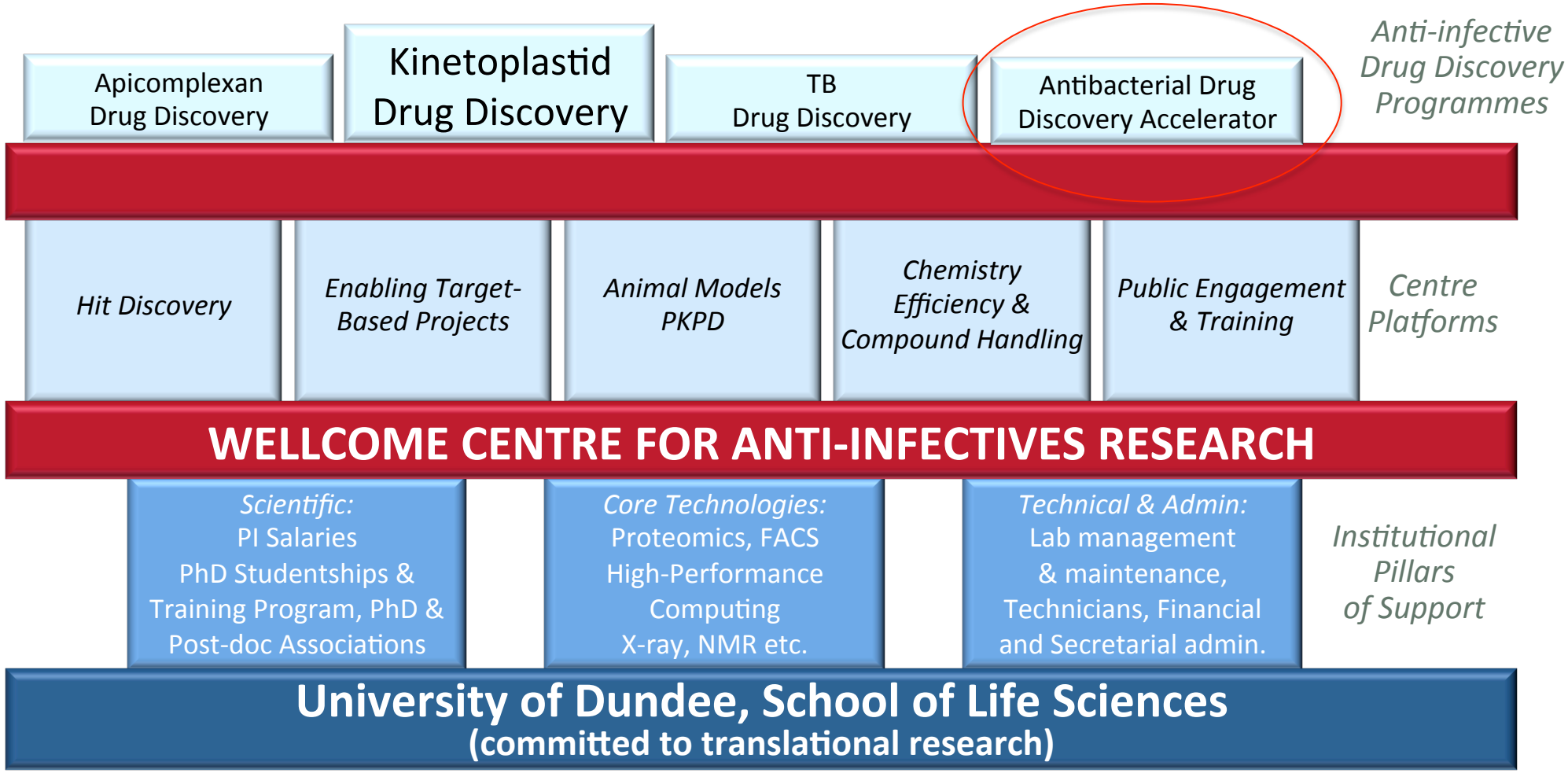

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The University of Dundee Drug Discovery Unit is a key member of international consortia to deliver new anti-TB drugs

Paul Wyatt

Drug Lead Discovery → **Drug Lead Optimisation** → **Clinical Development**

Shorten TB consortium

NIAID · University of Cape Town · University of Pretoria · University of Stellenbosch · University of KwaZulu-Natal · University of Dundee Drug Discovery Unit

TB Drug Accelerator consortium

NIAID · IDRI · gsk · abbvie · Lilly · MERCK · BAYER · Eisai · RUTGERS New Jersey Medical School · AstraZeneca · SANOFI · Cornell University · University of Dundee Drug Discovery Unit

→ TB ALLIANCE

FNIH Foundation for the National Institutes of Health

BILL & MELINDA GATES foundation

wellcome

University of Dundee

Current (and aspiration for future) capacity in antibacterials

Current	Future
Current Antibacterial Team (8) • 3 medicinal chemistry FTE • 5 other FTE • Part of larger portfolio team • Funding: MRC/ UoD • (Targets from Bristol, Exeter, Glasgow, Karolinska)	**ADDA: Final Team Size (22)** • 1 Team Leader • 12 medicinal chemistry FTE • 2 DMPK FTE • 4 assay developers • 2 computational chemist • 1 structural biologist • Funding: MRC/ Wellcome (£2 M /annum)
TB Team (projected to remain constant in size) (21) • 14 medicinal chemistry FTE • 7 other FTE • Funding: Gates Foundation/ Wellcome (£1.8M /annum)	**TB Team (projected to remain constant in size) (21)** • 14 medicinal chemistry FTE • 7 other FTE • Funding: Gates Foundation/ Wellcome (£1.8M /annum)
Grand Totals: 29 FTE	43 FTE

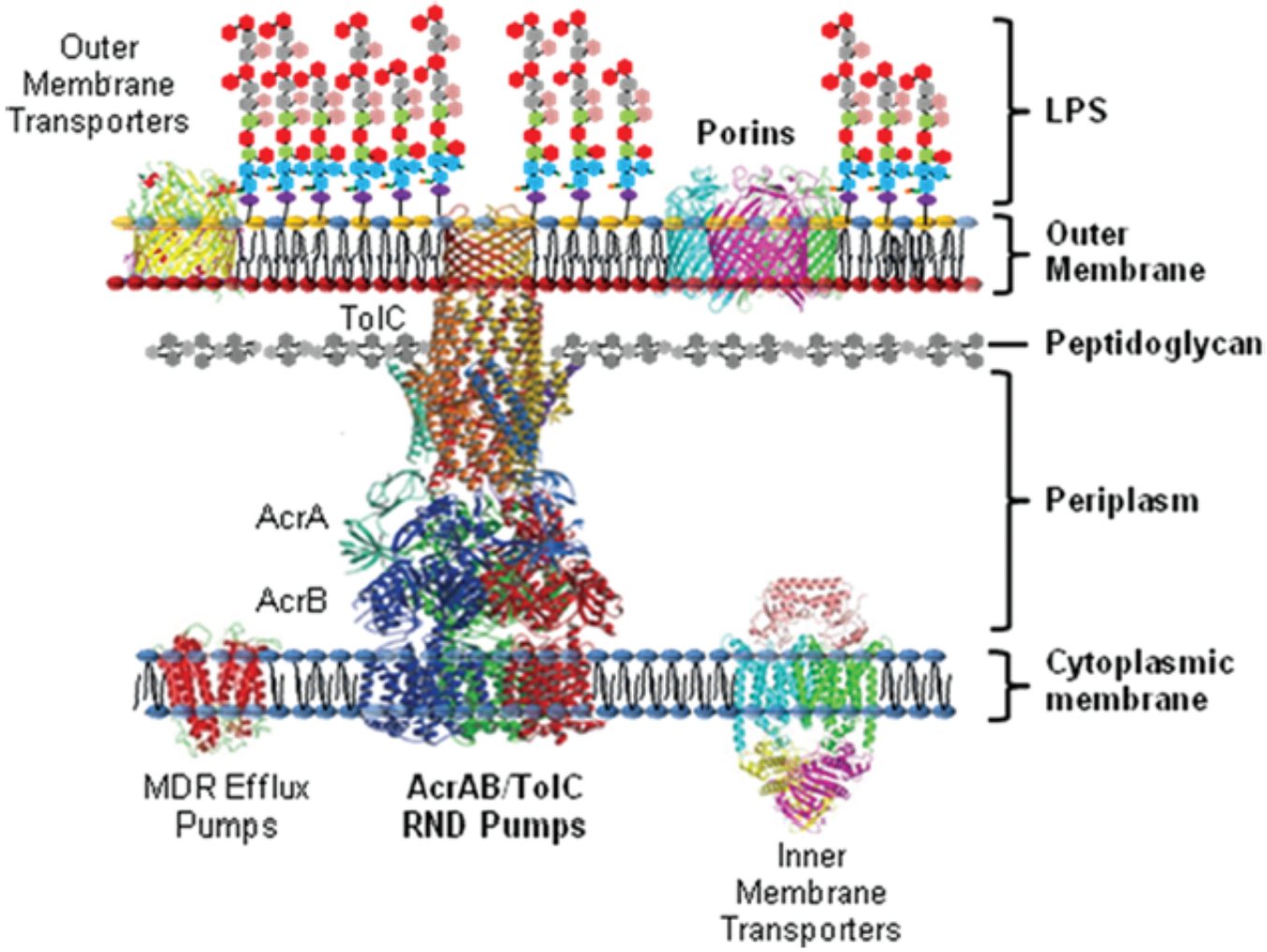
Why is it so hard to kill GNBs?

Drug uptake and efflux.
Drug uptake and efflux.

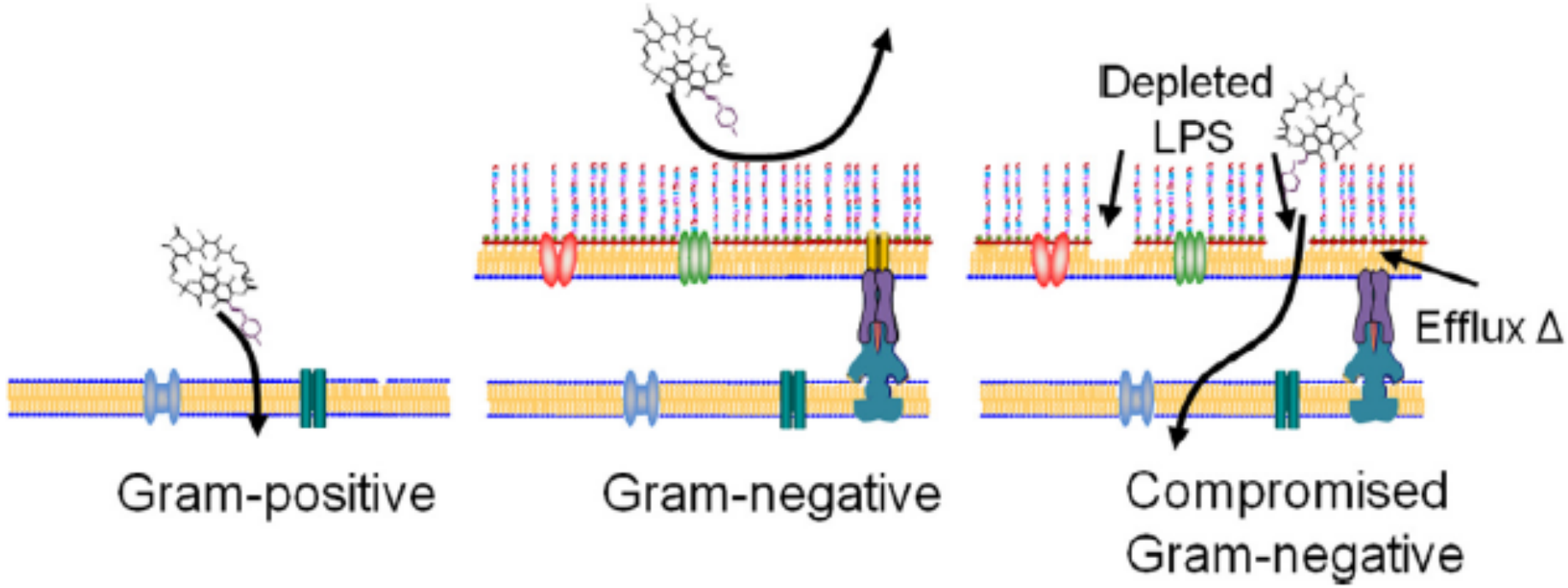
The four horsemen of the apocalypse!

Orthogonal selectivity of outer and inner membranes

Efflux systems across both



From Manchester at al


Depleted
LPS
Efflux Δ
Gram-positive
Gram-negative
Compromised
Gram-negative

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An Antibacterial Drug Discovery Accelerator for the community

Discovery Microbiology

- New Targets
- Phenotypic assays
- Reporter cell assays
- Active compounds

e.g. Bristol, Cambridge, Dundee, Exeter, Glasgow, Imperial, Karolinska, LSHTM, Oxford, Sanger, Sheffield, St Andrews, Warwick

CO-ADD
Community for Open Antibacterial Drug Discovery

CO-ADD

Target-based Screen → Cell Activity → Animal Efficacy → Drug Leads

Partnering or Licensing

- Pharma Partners
- PDPs (eg GARDP)
- AMR Centre
- CARB-X / IMI

Additional funding
(eg MRC DPFS / WT) with/ without industrial partners

Spinout companies

Roche

SANOFI

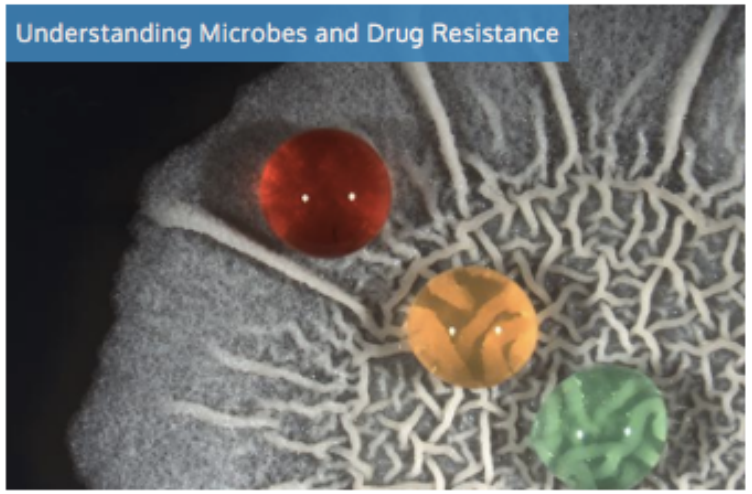
ENTASIS THERAPEUTICS

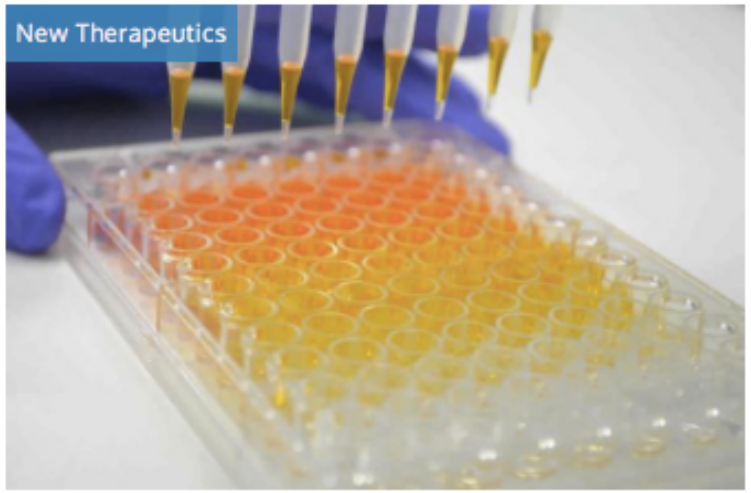
CENTRE OF ANTIMICROBIAL RESISTANCE

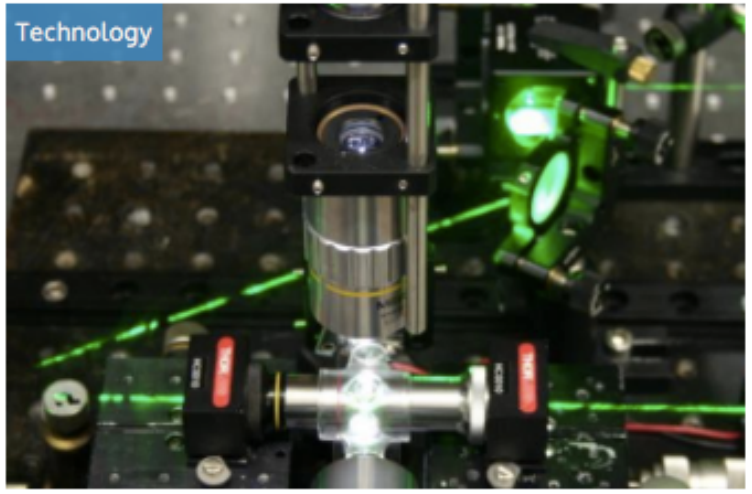
University of Dundee & NHS Tayside

University of Dundee

AHSP
Academic Health Science Partnership in Tayside







Prof Dilip Nathwani OBE,
Consultant in Infectious Diseases and Honorary Professor of Infection at the University of Dundee.

Antimicrobial stewardship

NHS Tayside

University of Dundee

Co-Director of:

AHSP
Academic Health Science Partnership in Tayside

President of:

BSAC
The British Society for Antimicrobial Chemotherapy

University of Dundee

Acknowledgements

Thanks to all my colleagues for allowing me to present their work

Thanks to all the funding agencies, and our PDP and Pharma partners that enable us to tackle infectious diseases

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Thank you for listening