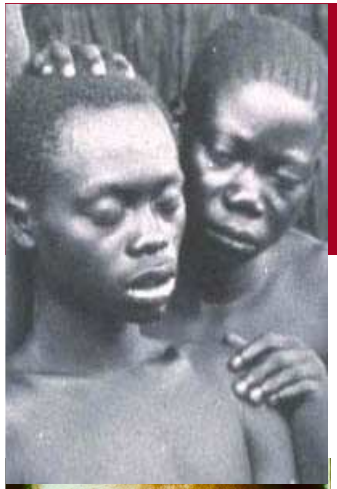
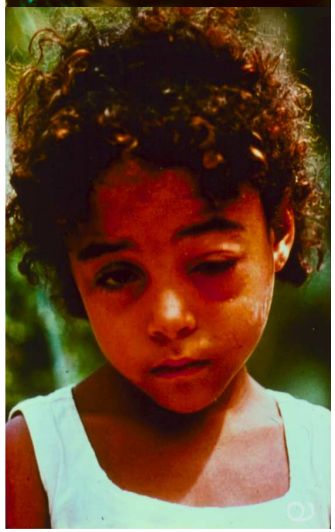
Drug Discovery for Neglected Diseases in an Academic Setting

UNIVERSITY OF DUNDEE

Ruth Brenk





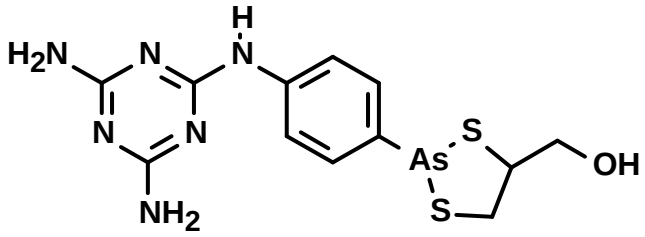
Major tropical parasitic diseases

Disease	Population at risk (thousands)	Deaths in 2002 (thousands)
Malaria	> 2,100	1,272
Leishmaniasis	350	51
African trypanosomiasis	> 60	48
Chagas' disease	120	14
Schistosomiasis	600	15

Pink R, Hudson A, Mouriès MA, Bednig M, Nat Rev Drug Discov 2005

Issues with current treatments

- Many drugs were introduced in the colonial times => do not comply with current standards
- Severe adverse effects
- Resistance
- Cost
- Difficult to administer
- Not effective against all stages of the disease



Melarsoprol (1946)

Need for new drugs

Pink R, Hudson A, Mouriès MA, Bednig M, Nat Rev Drug Discov 2005

The need for new drugs

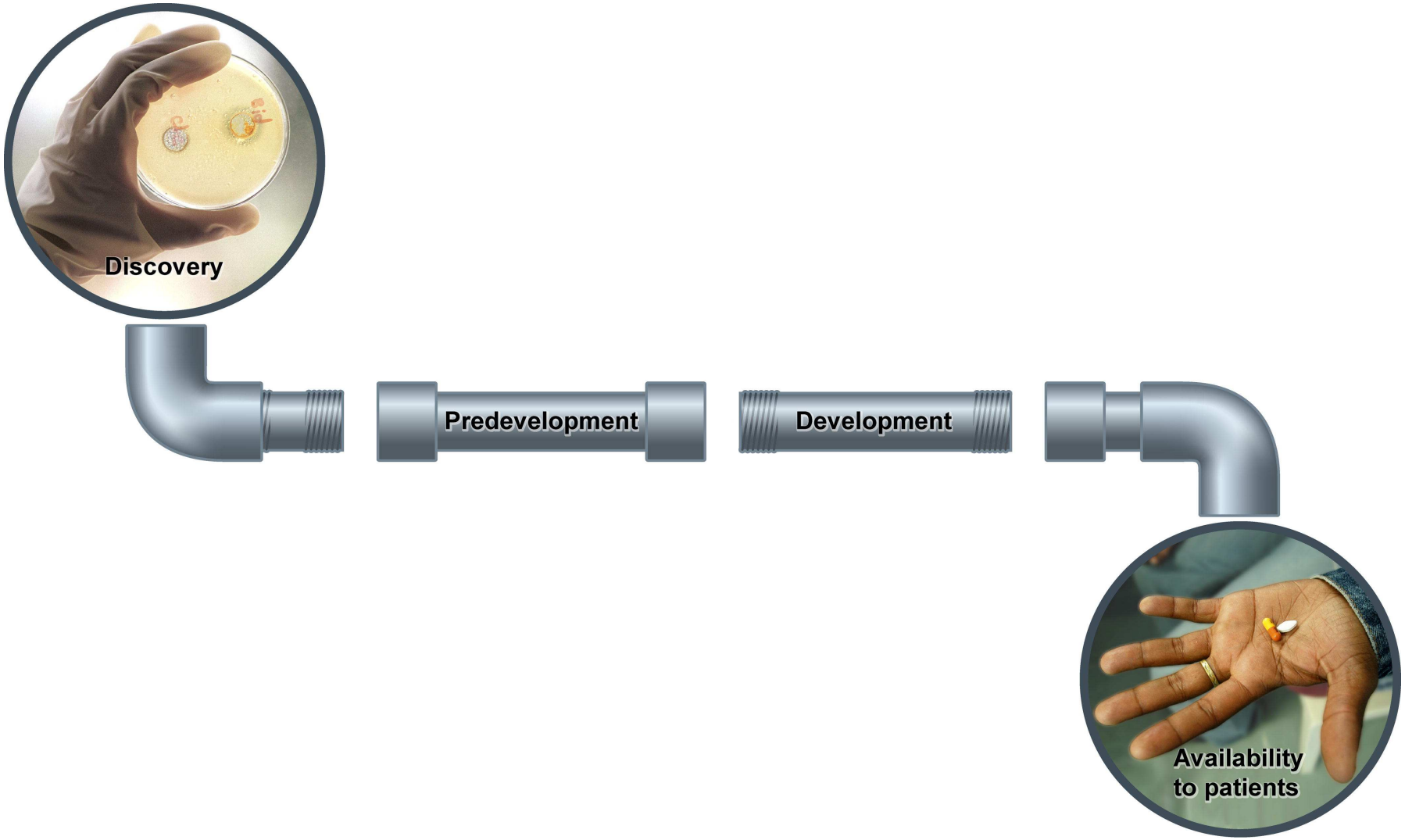
- > 1,300 new drugs introduced between 1975 and 1999
- Only 13 for tropical diseases
- An important problem is market forces:

U.S.A. healthcare budget:
$4,180 per capita per year

Sub-Saharan Africa:
$13 per capita per year

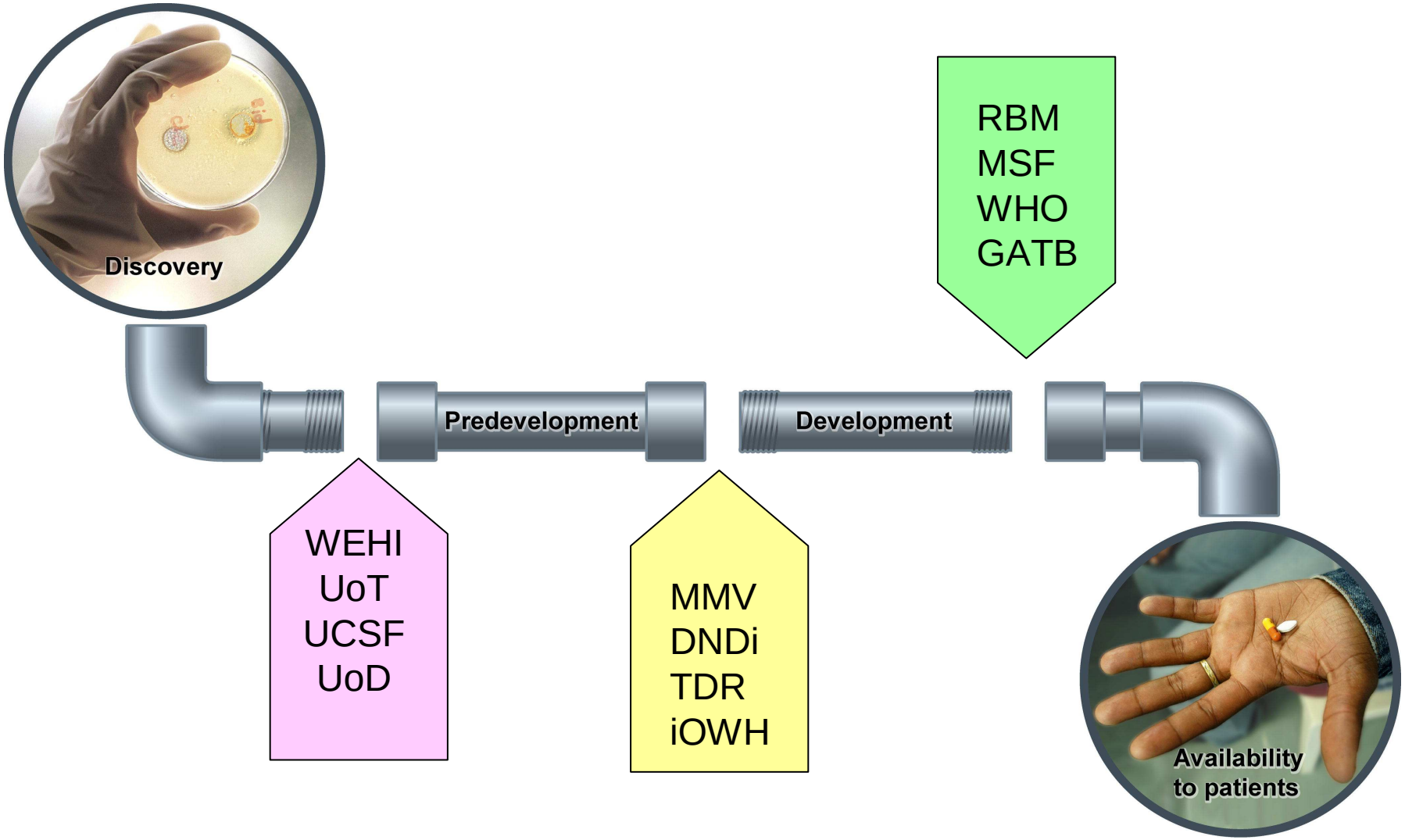
The solution does not lie solely with the commercial sector

The gaps in the pipeline



Pécoul B, PLoS Medicine 2004; Nwaka S, Ridely RG, Nat Rev Drug Discov 2003

The gaps in the pipeline



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Drug Discovery at the University of Dundee

PRE-EXISTING EXPERTISE:

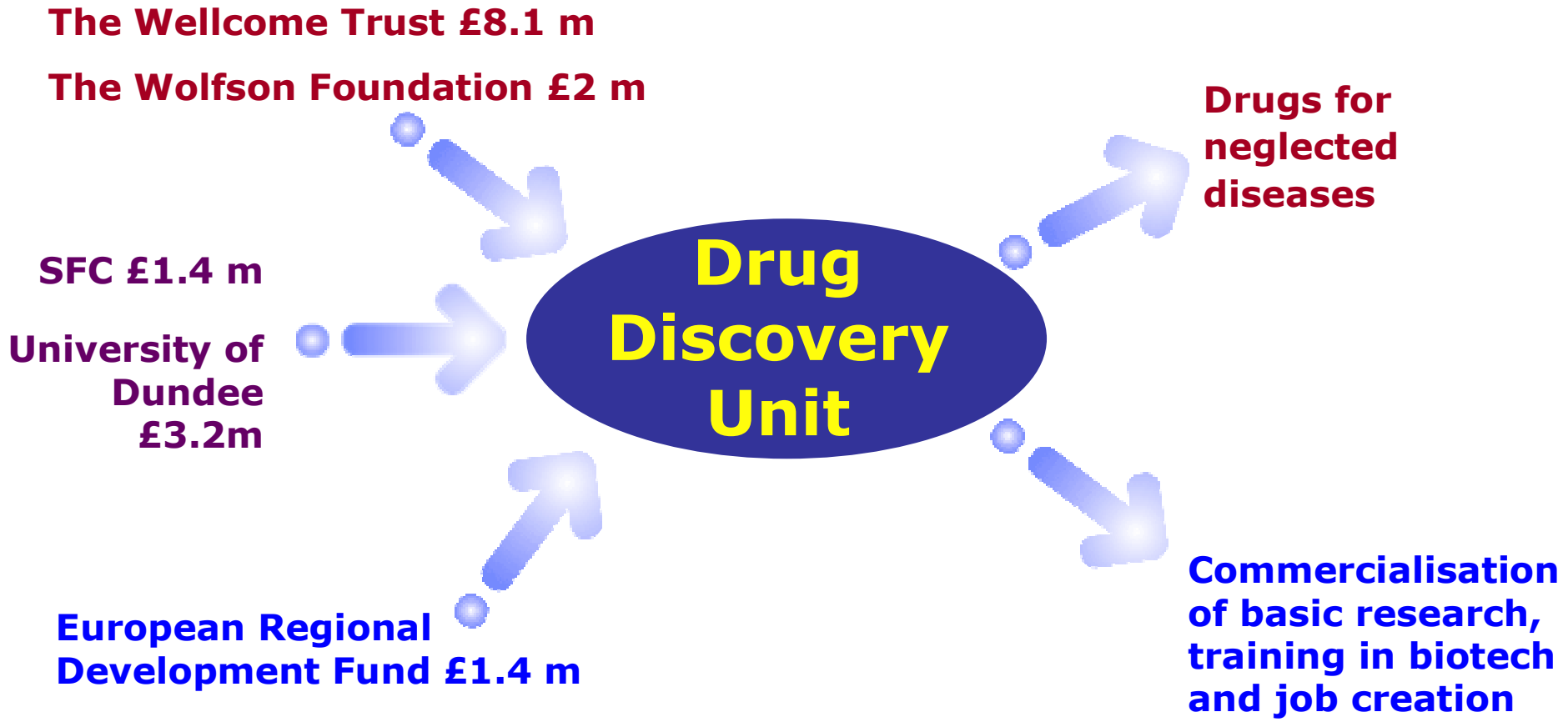
- Parasitology
- Bioinformatics
- Biochemistry
- Molecular Biology
- Structural Biology
- Synthetic Organic Chemistry

WHAT WAS MISSING?

Resources, space and Staff for:

- Computational Chemistry
- Medicinal Chemistry
- Compound Screening
- ADME-Tox

Resources



(Total funding over 5 yrs for translational research: £16.1 m)

Space

Our Drug Discovery Team @ Dundee

Alan Fairlamb

Mike Ferguson

Bill Hunter

Daan van Aalten

Julie Frearson
ex-BioFocus plc

Ian Gilbert
Ex-Cardiff Univ.

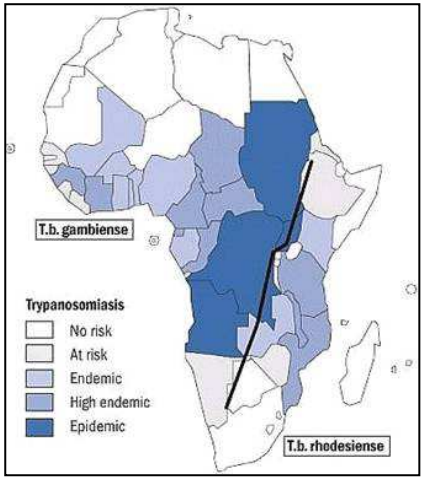
Ruth Brenk
ex-UCSF

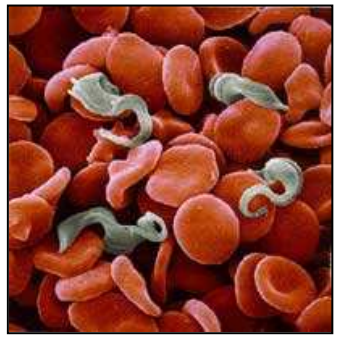
Paul Wyatt
ex-Astex Therapeutics

Our goal

To deliver at least ONE drug candidate for a neglected disease for entry into formal pre-clinical development by March 2011

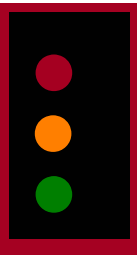
African trypanosomiasis / Sleeping sickness





- Distribution: sub-Saharan Africa
- Causative agent: Trypanosoma
- Transmission: Tsetse fly
- Symptoms:
  - Beginning: malaise, tiredness, joint pain, swollen tissue, fever, headache, …
  - Late: neurological and endocrine disorders, mental deterioration, coma, death
- Treatment:
  - Pentamidine : not effective against late stage, resistance
  - Suramin: only iv, severe side effects
  - Melarsoprol: late stage, sever side effects (including death)

Traffic Light Priority System

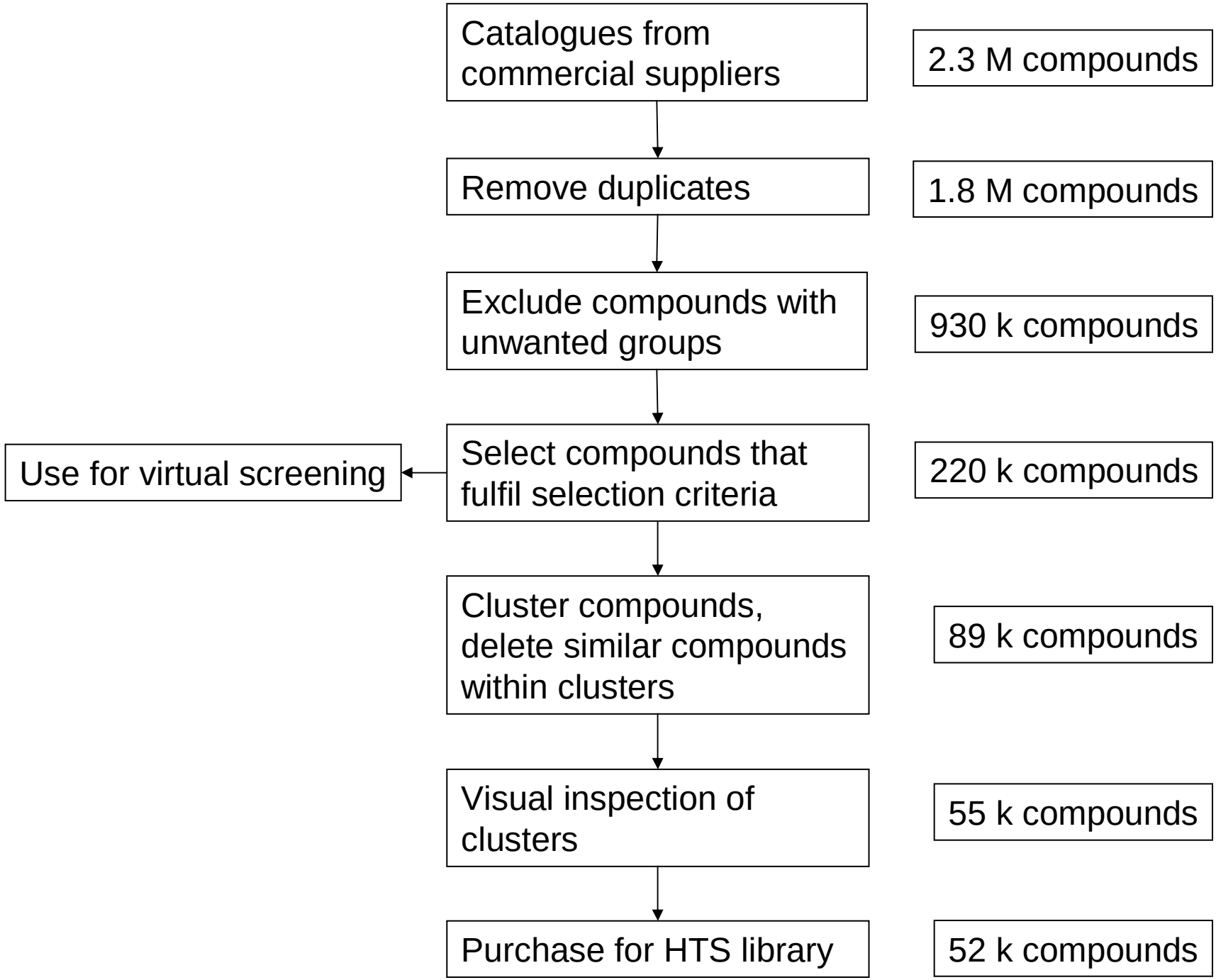


Target	Target 1	Target 2	Target 3
Target validation	●	●	●
Assay feasibility	●	●	●
Druggability	●	●	●
Chemical tractability	●	●	●
Toxicity issues	●	●	●
Resistance potential	●	●	●
Structural information	●	●	●

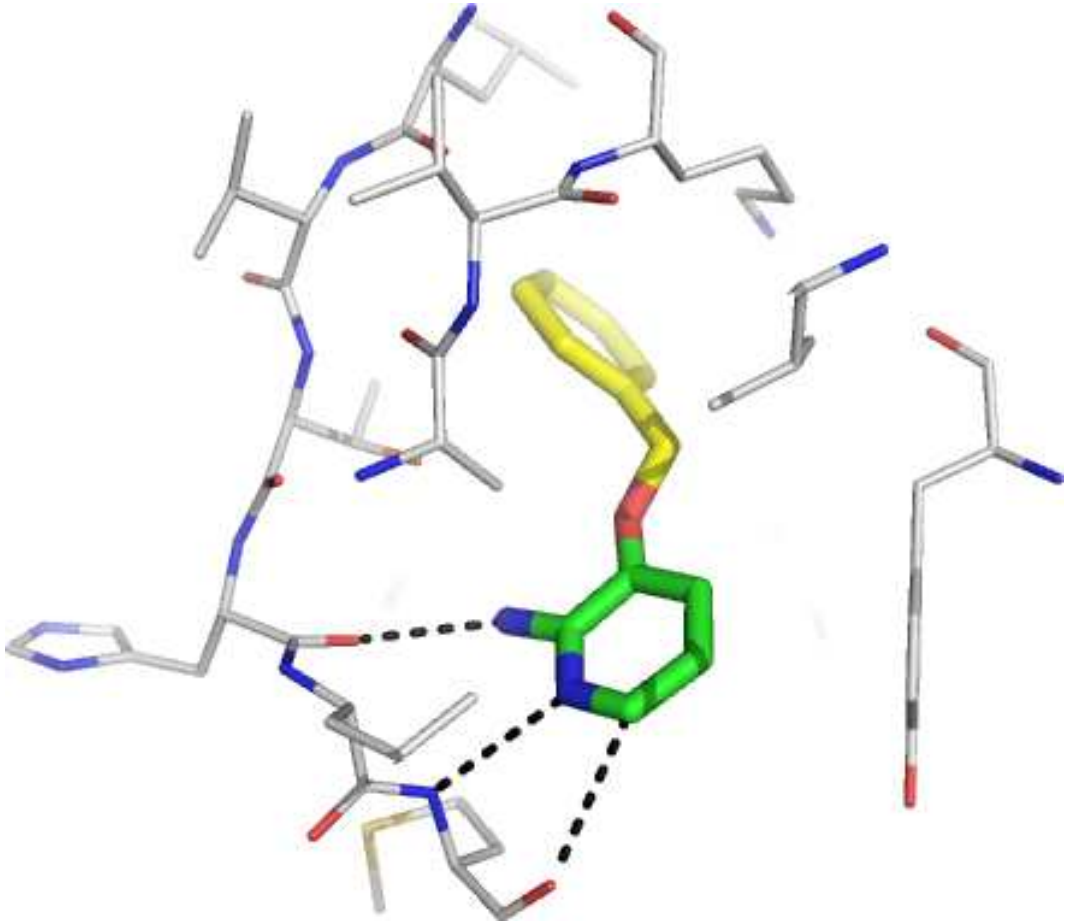
Target-tailored approach

- Random compound screening
- Screening of focused libraries
- Structure-based design

Brenk et al, ChemMedChem, in press

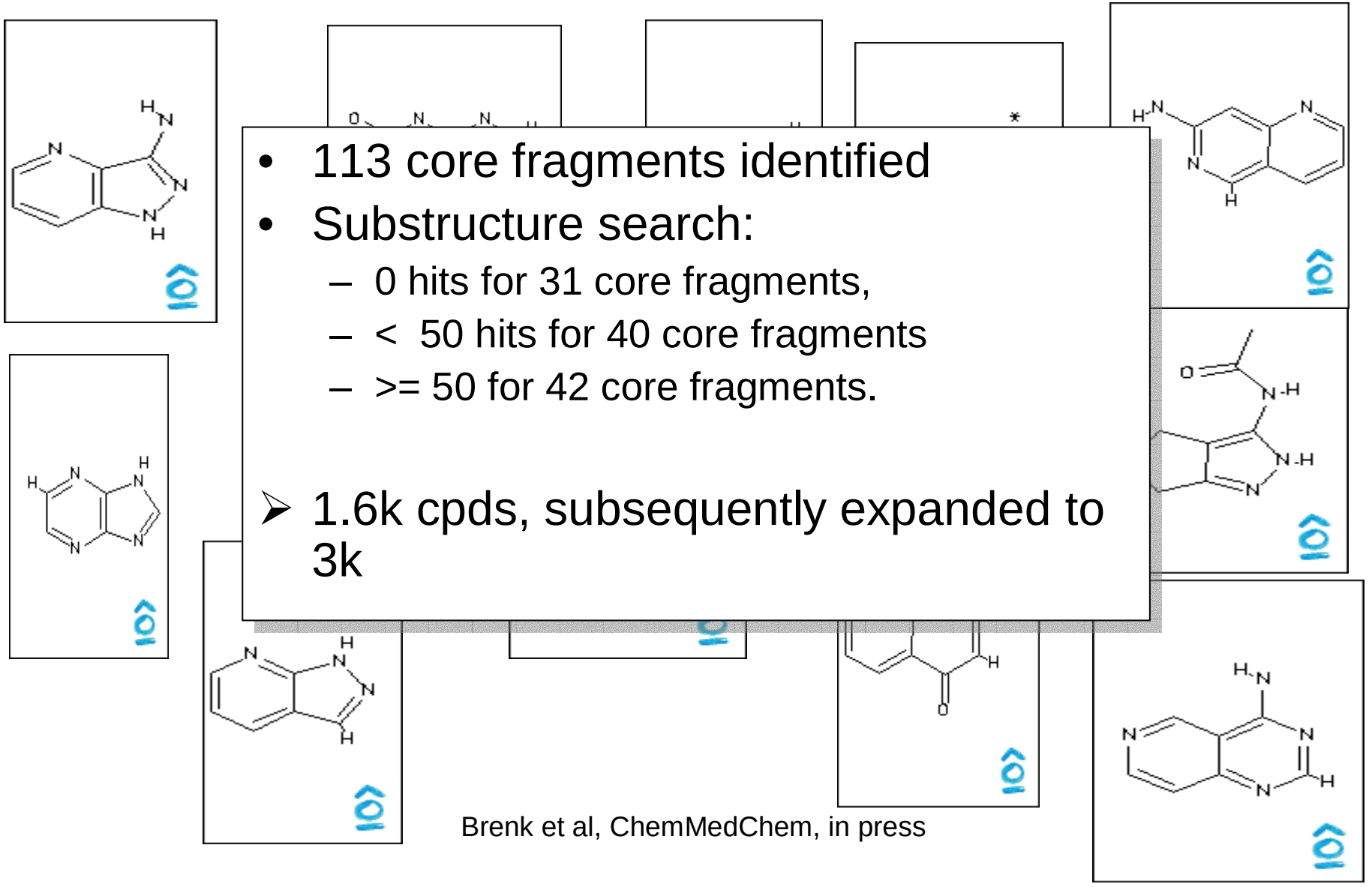

Catalogues from commercial suppliers
2.3 M compounds
Remove duplicates
1.8 M compounds
Exclude compounds with unwanted groups
930 k compounds
Select compounds that fulfil selection criteria
220 k compounds
Use for virtual screening
Cluster compounds, delete similar compounds within clusters
89 k compounds
Visual inspection of clusters
55 k compounds
Purchase for HTS library
52 k compounds

Kinase library



Brenk et al, ChemMedChem, in press

Kinase library



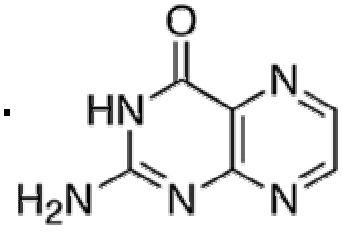
- 113 core fragments identified
- Substructure search:
  - 0 hits for 31 core fragments,
  - < 50 hits for 40 core fragments
  - >= 50 for 42 core fragments.

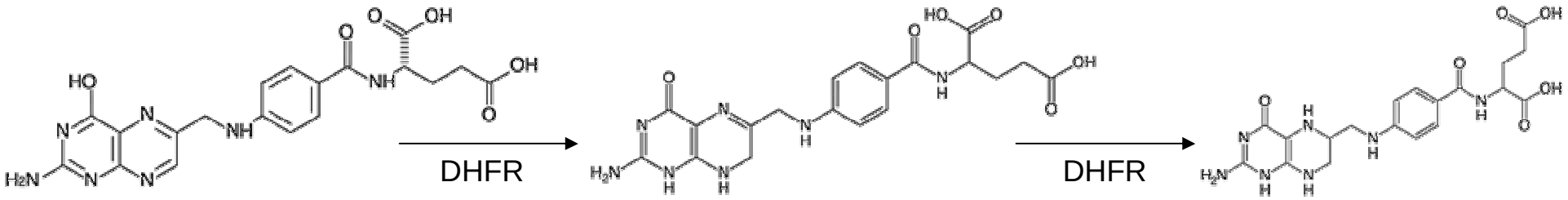
➢ 1.6k cpds, subsequently expanded to 3k

Brenk et al, ChemMedChem, in press

Pterin metabolism

- Pterins are import co-factors, e. g. for the synthesis of thymidylate which is necessary for DNA synthesis.
- Trypanosomes are auxotrophic for pterins such as biopterin and folate
- Take-up of oxidised pterins via specific transporters, subsequently reduction to active tetrahydro-form
- Dihydrofolate reductase (DHFR) reduces folic acid to tetrahydrofolic acid

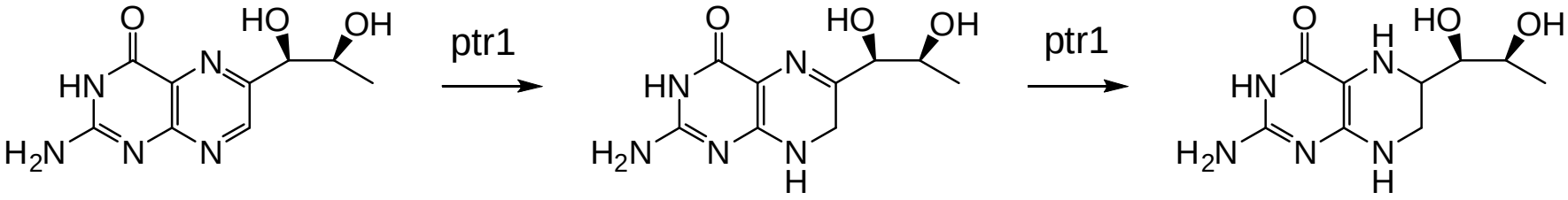




But: DHFR inhibitors are not effective against trypanosomes

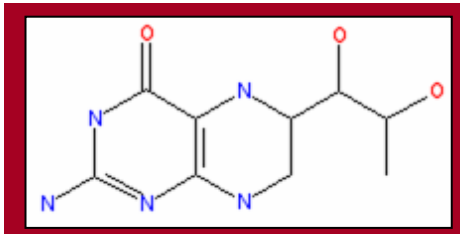
Pteridine Reductase 1 (PTR1)

- Short chain dehydrogenase
- Role not fully understood
- Broad-spectrum activity with pterins and folates

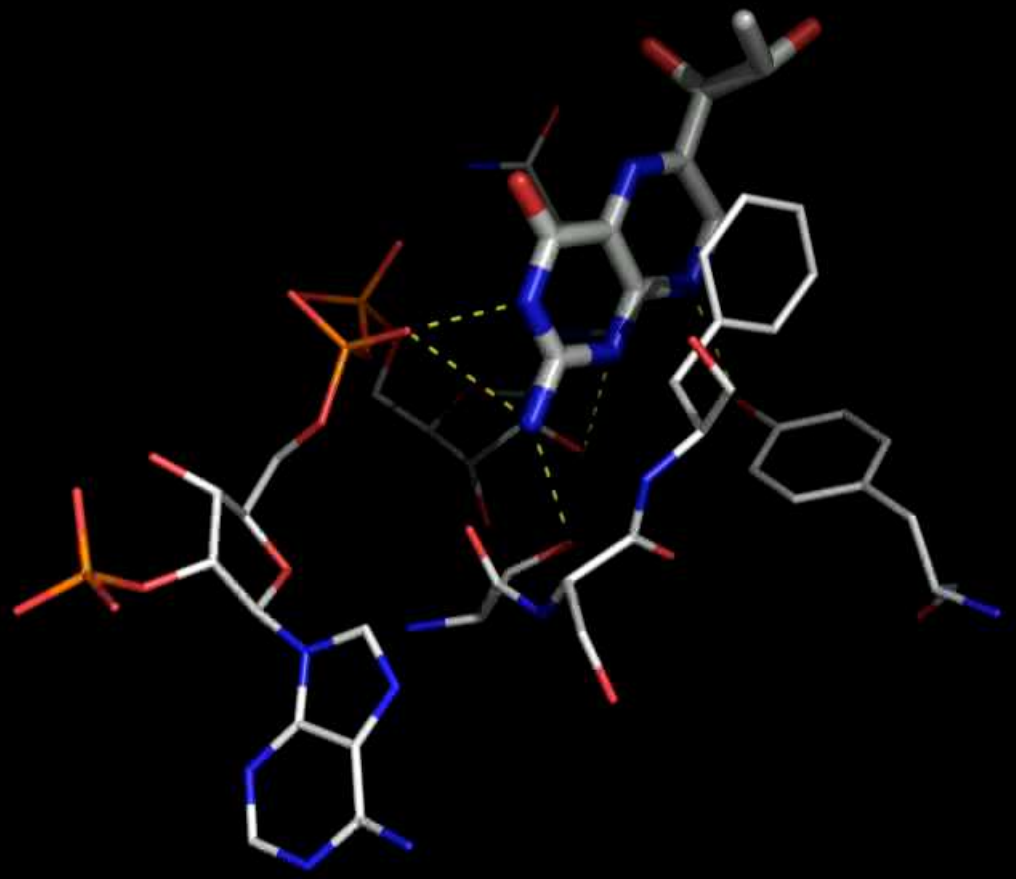


biopterin dihydrobiopterin tetrahydrobiopterin

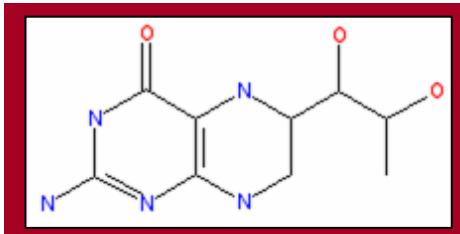
- Can act as by-pass for DHFR
- Up to now all attempts to obtain a PTR1 double knock out strain have failed -> might be essential on its own



PTR1 / DHFR



Hunter et al, Nat Struct Biol 2001, J Mol Biol 2005, Mol Microbiol 2006



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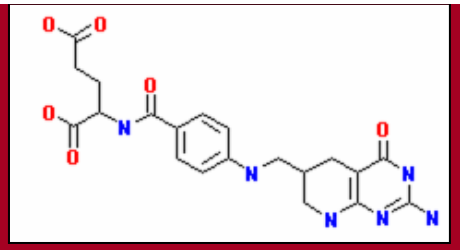

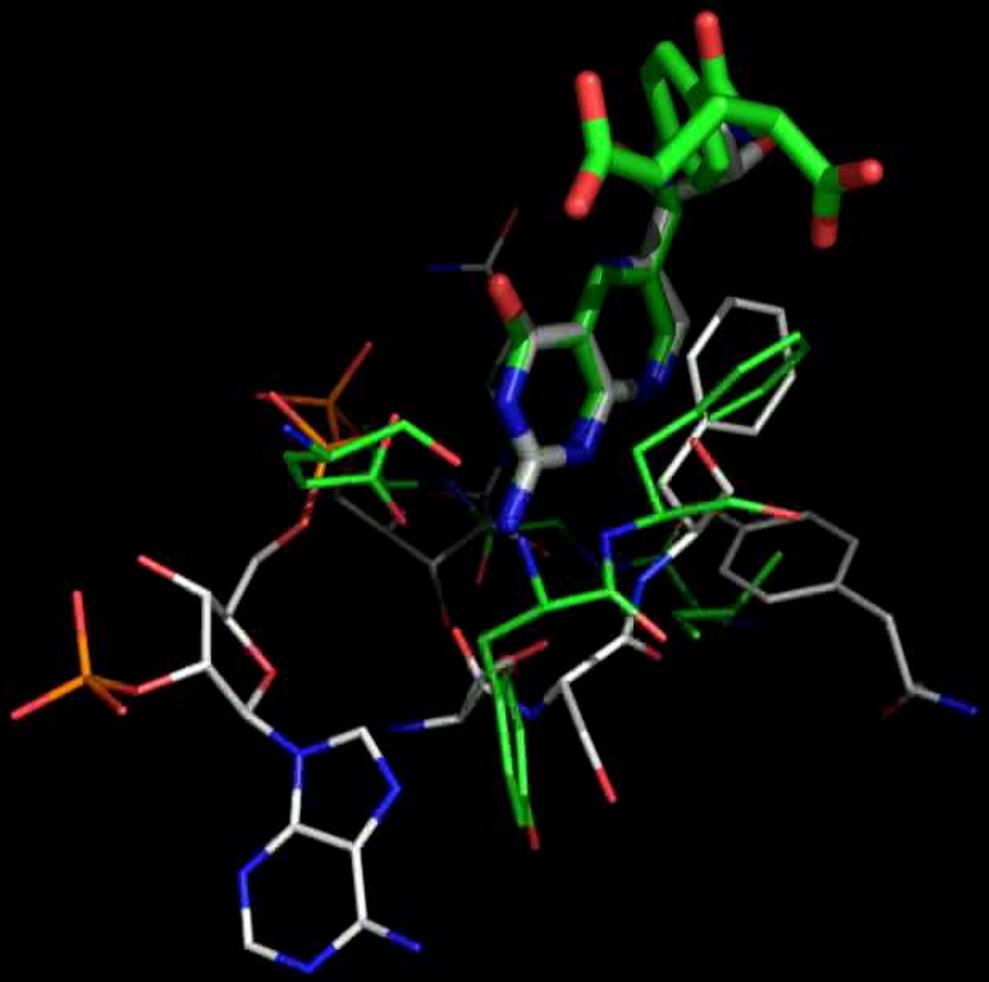

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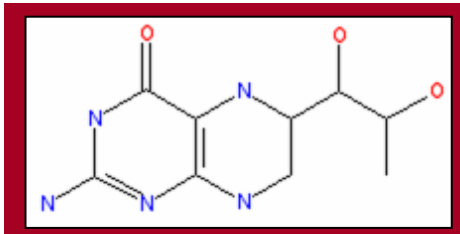
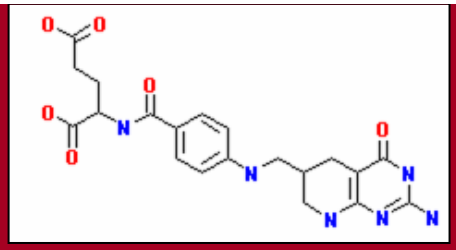
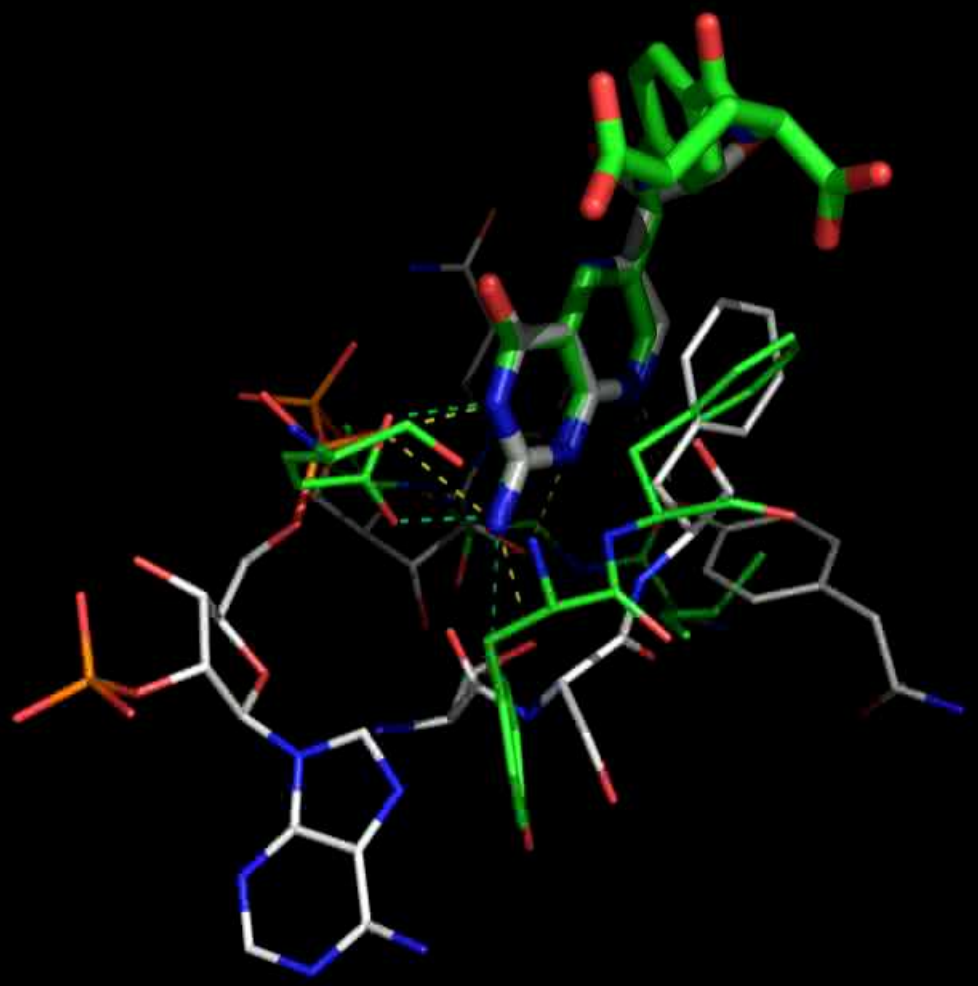
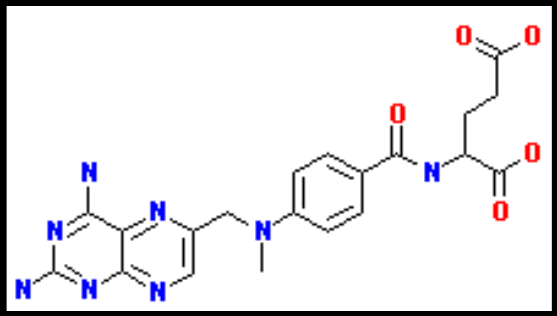


PTR1 / DHFR







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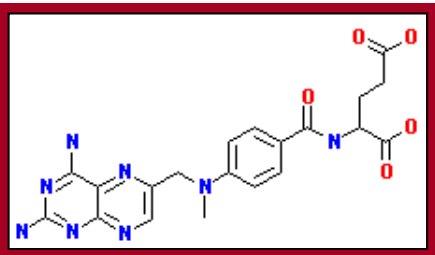

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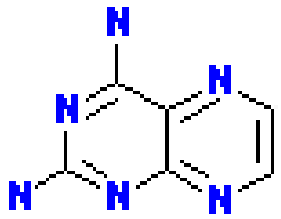
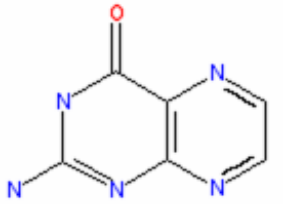
PTR1

- Derivatives of typical DHFR inhibitors inhibit PTR1, but
  - Low solubility
  - Large polar surface area





Summary

- Set up a functional drug discovery unit in an academic setting
- Virtual screening for PTR1 inhibitors resulted in two novel hit series
- Core fragment of hit series 2 can adopt three different binding modes
- Derivatives of series 2 are highly potent in the enzyme assay and selective over hDFR
- No activity against Tryps

Thank you!

Paul Wyatt

Ian Gilbert

Chido Mpamhanga, Agata Krasowski

David Robinson, Lindsay Tulloch, Bill Hunter

Emma Shanks, Julie Frearson