London School of Hygiene & Tropical Medicine

"world's leading research-focused graduate school"

Faculty of Epidemiology and Population Health

Faculty of Infectious & Tropical Diseases

Faculty of Public Health and Policy

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LSHTM

Faculty of Infectious & Tropical Disease

- Malaria Centre
- International Diagnostics Centre
- Vaccine Centre
- International Centre for Eye Health

Partners include:

Wellcome Trust Sanger Centre

UCL (BRI)

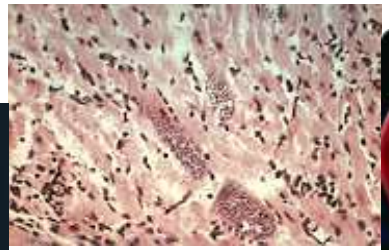
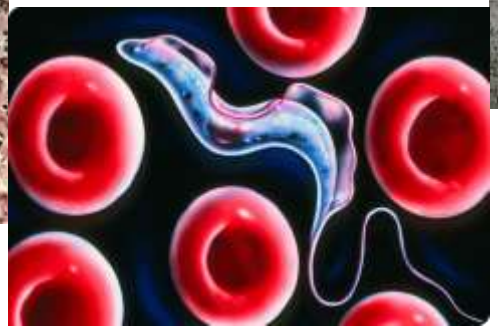
other LSHTM Centres

- Bloomsbury Centre for Genetic Epidemiology & Statistics
- Centre for Evaluation
- Centre for Global Mental Health
- Centre for Global Non-Communicable Diseases
- Centre for Maternal Adolescent Reproductive & Child Health
- Centre for Mathematical Modeling of Infectious Diseases
- TB Centre

Neglected Tropical Diseases @ LSHTM

R & D on drugs, vaccines and diagnostics for Leishmaniasis, South American Trypanosomiasis (Chagas Disease) and Human African Trypanosomiasis (Sleeping Sickness)

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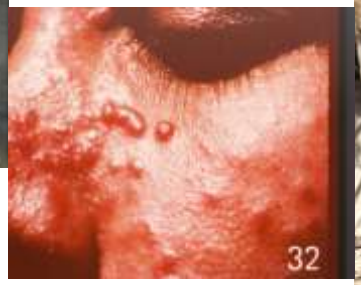
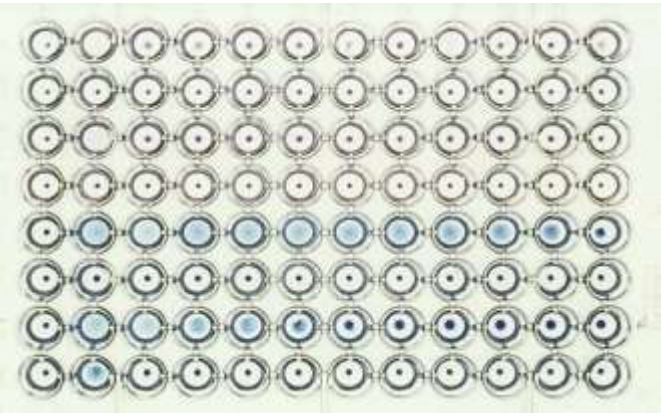
Order : *Kinetoplastida*

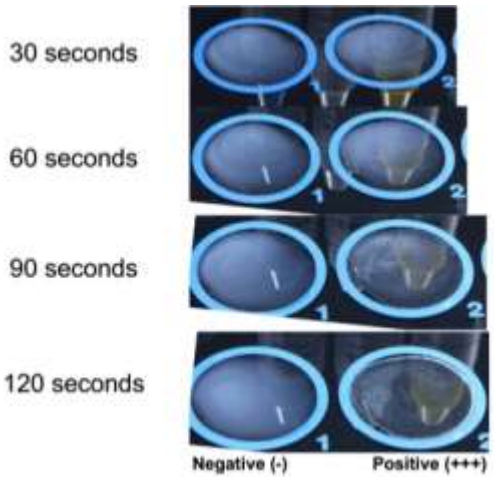
- Protozoan flagellates
- Cause 3 major (most) neglected diseases”
  - Human African trypanosomiasis (HAT) - *Trypanosoma brucei gambiense / rhodesiense*
    - Endemic in 36 countries, 60 million at risk
  - Chagas disease (South American trypanosomiasis) *Trypanosoma cruzi*
    - Endemic in 21 Latin American countries. malaria in the region.
  - Leishmaniasis (*Leishmania sp)*
    - Occurs in 98 countries. 350 million at risk

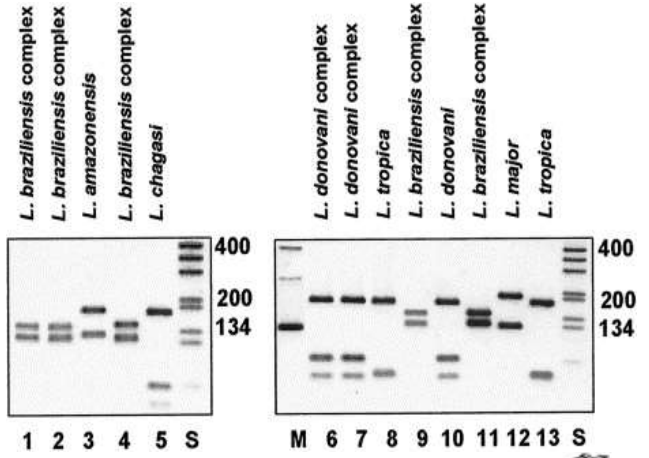


Order : *Kinetoplastida*

- Commonalities
  - Diagnosis often limited by available tests/technology
    - **PCR-based diagnostics available but not at POC in rural health facilities**
  - Treatment challenges
    - Few & dangerous drugs
    - emerging resistance
    - Test of cure
    - Infected asymptomatics……..







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Overview @ LSHTM

Drugs	
Leishmaniasis	to follow
Chagas disease	Mouse model for evaluation (J Kelly, M Taylor, M Lewis) *T cruzi* strain variation (M Miles, M Yeo)
HAT	CNS mouse model for evaluation and PK (S L Croft, H Burrell-Saward + Univ. of Glasgow Formulations with KCL
Vaccines	
Leishmaniasis	DNA vaccine (S Croft and K Seifert)
Diagnostics	
Leishmaniasis	EU project (NIDIAG) with ITN Antwerp (M Miles, R Peeling) MRC CiC with SGUL (pm session)
Chagas disease	Various (M Miles, T Battacharya)

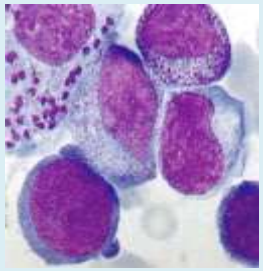
VL drug discovery and development opportunities

Simon Croft, Vanessa Yardley, Rose Diaz-Gonzalez, Karin Seifert, UCL (Steve Brocchini), Pharmidex (Mo Alavijeh), Paul Kaye (Univ York), Jeremy Mottram (Univ Glasgow)

Are new compounds/drugs (i) selective, (ii) active against strains/species, (iii) active in rodent models?

(i) Working with DNDi, GSK, Celgene and Advinus Therapeutics

(ii) *In vitro* macrophage models



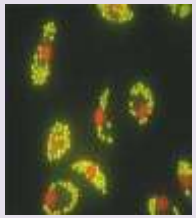
(ii)+ (iii) Recent clinical isolates from endemic countries (e.g. RMRI, Patna; Univ. of Khartoum, Sudan)

Can we develop more predictive models to determine drug efficacy?

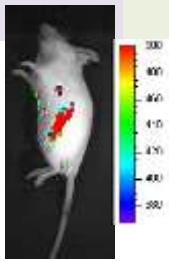
PK PD in rodent models (Pharmidex)

In silico liver model (University of York)

Intracellular rate of division. Rate of kill (GSK Open Labs)



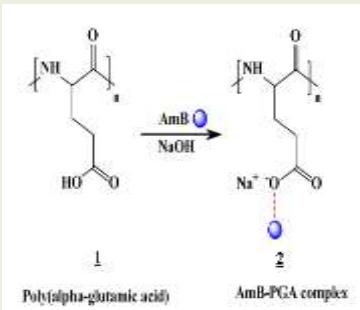
Intra-vital imaging to evaluate course of infection through treatment (Univ. of Glasgow)



Can we develop more effective targeting and drug delivery?

Nanoparticles *in vitro* and *in vivo* (KCL)

Macrophage targeting (UCL School of Pharmacy)



Funding: MRC, NC3Rs, Tres Cantos Open Lab Foundation, DNDi

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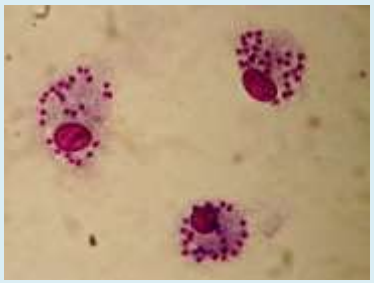
Current CL drug discovery and development opportunites

Simon Croft, Vanessa Yardley, Katrien van Bocxlaer, Alec O'Keeffe and UCL (Sudax Murdan) and Pharmidex (Mo Alavijeh)

Are new compounds/drugs active against all species

In vitro macrophage model

Panel of 6 – 8 species (reference strains & recent clinical isolates)



DNDi, Anacor, Provepharm

Can we develop more effective topical formulations?

Skin *in vitro* system (e.g. Franz cell)

Mouse models of infection

UCL School of Pharmacy, DNDi, Scynexis, Anacor

Can we develop more predictive models to determine drug activity?

2D *in vitro* flow culture

3D *in vitro* and *ex vivo* systems

New biomarkers

UCL School of Pharmacy, InVitroCue, Kirkstall

Funding: BBSRC, Bloomsbury Studentship, DNDi