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UCL PhD Project Proposal:
Meeting the challenge of drug resistant tuberculosis

Background

With 8 million new cases and 2 million deaths per year tuberculosis still represent one of the major health problems in the world. It is the most common cause of death among HIV-infected patients accounting 11% of AIDS deaths worldwide¹.

Since the introduction of effective tuberculosis chemotherapy in the 1950s, the prevalence of strains of *Mycobacterium tuberculosis* resistant to one or more anti-tuberculous drugs has steadily increased².

Currently there are only three novel compounds (TMC-207, OPC-67683 and PA-824) in Phase II clinical trials for the treatment of both drug-susceptible and drug-resistant diseases and new anti-tuberculous drugs with novel actions are urgently needed^{3, 4, 5}. In particular, it is necessary to expedite the development of more novel compound classes with mechanisms of action that are effective against both phenotypic drug persistence and genetic drug resistance.

Objectives

The main scope of this project is to address the challenge of multi-drug resistant tuberculosis with preclinical testing of anti-tuberculous drugs.

The introduction of a screening protocol will allow a better evaluation of new compounds at early preclinical testing and the selection of the most suitable for pharmaceutical development.

Further studies on mutation rates and genome sequencing (from laboratory and clinical strains) will allow us a better understanding of mechanisms of action/resistance.

Study design

Different microbiological criteria will be explored from traditional microbiological *in vitro* testing (spot/agar culture, microdilution method, resazurin test) to cell culture models of infected macrophages, synergism with established drugs and activity against dormant bacilli.

Three main categories of new compounds will be tested:

- ATC compounds: these are synthetic compounds from Geoff Coxon's group (Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, UK) designed by molecular modelling to target the Fatty Acid Synthase (FAS) II to inhibit mycolic acids biosynthesis⁶.
- PAS analogues: created by Andrew Boa (Department of Chemistry, University of Hull), they are derivatives of PAS (Para-Aminosalicylic acid). PAS is known to inhibit folic acid and mycobactin (cell wall component) synthesis. Due to its side effects, it is used only as third line in case of MDR TB.
- Natural compounds: the Department of Microbiology at RFH/UCL has some natural compounds with possible activity against *Mycobacterium*. Further studies are needed to better identify the active molecules and mechanism of action.

In addition, all new compounds will be tested against a library of resistant MTB samples obtained from clinical specimens. These represent all resistant strains collected from the microbiology service at RFH, from single antibiotic resistant to XDR MTB isolates.

At the same time, clinical samples from known outbreaks (i.e. Isoniazid resistant outbreak in North London) will be analyzed to try to understand if these particular strains have a specific selective advantage (and possible targets for new drugs) and potential to develop into MDR-TB^{7,8}.

On the basis of future findings, the project will focus on the mechanism of action of some of the new compounds and the discovery of new possible drug targets. Mutants will be created, mutation rate experiments and genome sequencing performed to try to better understand the mechanisms of action/resistance.

References

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