Computing Workflow Accelerates Antibiotic Booster Drug Discovery

CoSeC
Computational Science Centre for Research Communities

Dr. Natalie Tatum of the Cancer Research UK, Drug Discovery Centre, Newcastle University wrote the winning application for the 2020, Inaugural CoSeC Impact Award, for her work on antimicrobial drug resistance. Natalie and colleagues developed a tailored, adaptable, computing workflow that successfully saves clinical time and development costs by identifying the most likely booster drug candidates. This accelerates the treatment of diseases such as tuberculosis (TB), HIV, cancer and COVID-19, potentially benefitting tens of thousands of patients worldwide.

Background

Tuberculosis infections are the leading cause (1 in 3) of death for people living with HIV/AIDS, and an estimated 44% of people living with HIV and TB are unaware of their co-infection[1].TB incidence is high in regions where malaria is also prevalent; co-infection with malaria can mask symptoms of either disease, and reduce immune response to TB[2].

Estimates by the World Health Organisation (2019) indicate there are 10 million tuberculosis (TB) infections annually, causing 1.5 million fatalities, and drug-resistance is increasing. Rifampicin – the front-line drug – proved ineffective in half a million cases in 2018, 78% of which were multi-drug resistant.

Effective treatment of TB is crucial to tackling mortality especially where this is affected by many potentially life-limiting infections beyond TB alone.

Drug development typically takes 10-15 years and costs vary - being somewhere around $1bn[3]. An estimated 1 in 70 potential antibiotics develop to reach a patient[4] and far fewer progress through clinical trials to use, making it essential to explore multiple potential lines of enquiry to find suitable drug candidates. A key route of enquiry includes computational workflows that play a crucial role in accelerating the drug discovery process.

Challenge

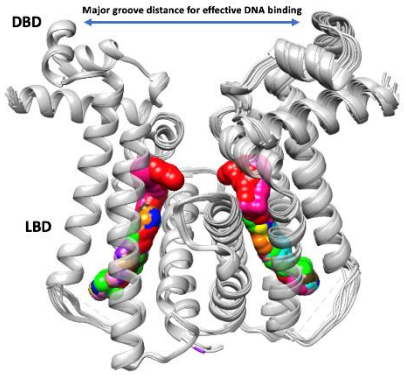
Since the 1980s, no new classes of antibiotics have been discovered, which is driving research into alternatives such as 'booster' drugs. The first drug used in treatment is sometimes ineffective because the disease becomes resistant to it, or the drug itself has toxic side effects. A second drug is then tried, which for TB is ethionamide, but it is often toxic and lacks effectiveness itself because it is vulnerable to inactivation by the 'gene changer' EthR. To prevent drug-inactivation requires the presence of a gene changer inhibitor also described as a 'drug booster'.

The drug booster increases the chances of successful treatment of TB especially benefitting those patients suffering from co-infections, who are better able to manage these diseases.

Therefore, it is essential to identify drug boosters quickly and efficiently.

Natalie's role in addressing the challenge

Dr. Tatum began constructing a computational research workflow or 'pipeline' by using existing knowledge of EthR and employing the software of Collaborative Computational Projects CCP4: Software for Macro-Molecular X-Ray crystallography, and CCP5: Computer Simulation of condensed Phases. By combining crystallographic and atomistic modelling computational techniques, Natalie developed methods to identify and assess quantitatively and qualitatively novel inhibitors of the gene-changer, EthR that show ethionamide-boosting capability in biological tests.
During her PhD, she developed a virtual screening approach that used the known crystal structures of EthR-inhibitor complexes to train and test the computational protocols, designing them to filter a database of potential molecules based on the structure and properties of the drug's active site. This lead to screening large volumes of structural data, filtering over 6 million compounds to just 85 that were selected for experimental, biophysical testing, thereby accelerating the discovery of booster drugs.



Structure of gene-changer EthR used to train protocol for computational pipeline[5]

Features of the booster drug discovery computational pipeline:

- Crystallographic software
- Atomistic modelling simulation software
- Open-source
- Free-to-academic software
- Provides an accessible blueprint for application to other types of drug candidates for treating other diseases
- See Reference 5. for a detailed description of the pipeline

CoSeC's Impact

> My crystallographic training was supported by CCP4 Study Weekends and the feedback I received after presenting at the CCP4 Northern Meetings. Attending the 2019, CCP5 Summer School I learnt how to run simulations that confirm my crystallographic findings.
>
> Dr. Natalie Tatum

CoSeC provides a community hub for exchanging knowledge and expertise through training and outreach. Both CCP4 and CCP5 belong to this hub and offer a variety of support for researchers, including CCP4's annual Study Weekends and CCP5's annual Summer School. These training events provide participants with the opportunity to engage with experienced developers and users of the CCP software, as well as to build on their own supportive network of peers and potential collaborators.

https://www.scd.stfc.ac.uk/Pages/CoSeC-Case-Studies.aspx

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References:

1. Global HIV & AIDS statistics:https://www.unaids.org/en/resources/fact-sheet
2. Chukwuanukwu, R. C. et al. *Clinical & Experimental Immunology* 187, 259–268, 2017
3. Årdal, C. et al. *Nature Reviews Microbiology* 18, 267–274 (2020)
4. Payne, D. J., et al. *Nature Reviews Drug Discovery* 6, 29–40 (2007)
5. Tatum N. J., et al. *Org. Biomol. Chem.* 15, 10245–10255 (2017)

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