

What's been happening on the AEROPATH Project?

June 2010 Update



Bacterial infections are particularly problematic for people with cystic fibrosis, burns victims and patients whose immune systems are

compromised, for example by chemotherapy during cancer treatment. Some of these life-threatening, difficult to treat infections are caused by Gram-negative bacteria, often called "superbugs" because they are resistant to common antibiotics. The **AEROPATH** project is particularly focused on the pathogen *Pseudomonas aeruginosa*, which is notorious for its ability to exploit any weakness in its host. One in ten hospital-acquired infections are caused by *P. aeruginosa*. The bacterium can grow in water, tolerates a wide range of temperatures, doesn't mind high concentrations of salt or weak antiseptics and is impervious to most antibiotics.

The **AEROPATH** collaboration, launched in November 2008 under the EU's 7th Framework Programme (FP7), is led by the University of Dundee and involves partners in Scotland, Sweden and Germany. The aim is to characterise potential new drug targets and seek out and develop new compounds called "hits" that will bind to the target proteins and decrease or compromise the ability of the bacterium to cause infection. Our hits have the potential to underpin early stage drug discovery to develop antibiotic drugs that kill *P. aeruginosa* and other Gram-negative bacteria that are highly resistant to most current drugs.



The research exploits genome data to identify and characterise new therapeutic targets and ultimately seek out chemicals that kill the bacteria by using modern computational and high-throughput technologies. The researchers are employing the following multidisciplinary approach to investigate the new targets:

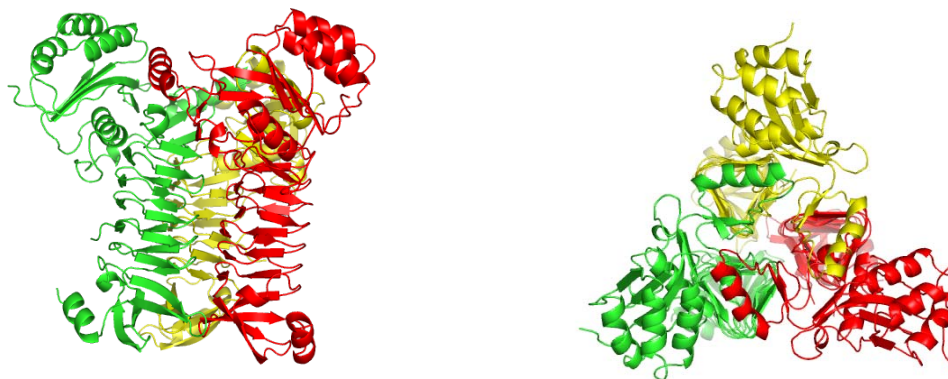
1. A prioritisation of potential drug targets has been carried out using an informatics analysis of a *P. aeruginosa* genome.
2. Researchers identify if these target proteins are essential to cause infection in an animal model.
3. An imaging method called single crystal diffraction is used to build accurate 3-D models of the key proteins.
4. Hit molecules are sought by high-throughput screening of compound libraries using enzyme and ligand binding assays together with computational methods.
5. The details of how the hits bind to the targets are clarified by diffraction methods or *in silico* modelling.

This data allows researchers to understand how essential proteins can be targeted; information that underpins future efforts to develop chemicals with the right properties to disrupt a biological reaction and kill the bacteria.

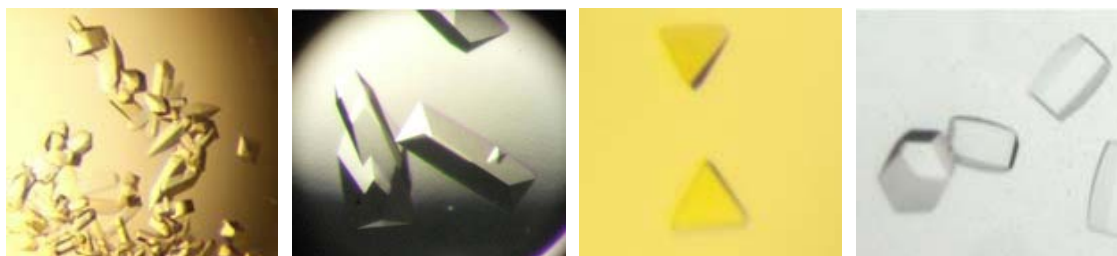
In the first 18 months **AEROPATH** has focussed on identifying and characterising target proteins and screening to identify hits. Achievements include:

- Computer-based druggability assessment of over 5000 targets
- 11 targets validated using gene knockout
- > 80 genes of prioritised targets cloned
- > 50 protein samples into crystallisation trials
- 21 crystal structures determined
- 14 targets in fragment screening, 3 in virtual screening and 1 in high-throughput screening

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First crystal structure, representing one of the selected targets from *Pseudomonas aeruginosa* at 2.6 Å resolution, determined by the **AEROPATH** consortium



AEROPATH crystals grown at the Karolinska Institute and the University of St Andrews

A particular highlight is the release of the **AEROPATH** Target Database. The *P. aeruginosa* proteome has been assessed and prioritized by a range of criteria and can be queried via the database. The database integrates information from various sources including the *Pseudomonas* genome database (DNA and protein sequences, synonyms, alternative identifiers, genomic co-ordinates), ChEMBL (information on inhibitors) and XtalPred (crystallisability predictions). The database can be accessed from the **AEROPATH** WEB site (www.aeropath.eu). It will be updated throughout the project to incorporate new information.

Looking ahead, the next stage of the research will be to perform more detailed analysis of the structure and binding properties of the most promising hits from the screening campaigns. See www.aeropath.eu for more details on **AEROPATH**.