

## **PROGRAM 3: ANTIMICROBIAL RESISTANCE AND NOVEL ANTIMICROBIAL TARGETS OF CF PATHOGENS: MECHANISMS OF BIOCIDES RESISTANCE AND ACTION**

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### **Summary of research**

Biocides, or disinfectants as they are more commonly known, form the major first line anti-infective agent used both in the home and in hospital to reduce the risk of infection. However, in comparison to antibiotics we know very little about how they kill bacteria or how bacteria resist them. The bacteria that cause infection in individuals with CF, *Burkholderia cepacia* complex and *Pseudomonas aeruginosa* bacteria are well known for their lack of susceptibility to biocides. The major aim of this component of the consortium was to examine biocide susceptibility of these bacteria, especially in the *Burkholderia cepacia* complex group where a number of new species have been identified.

The work resulted in two significant scientific outcomes:

- (i) **Completion of a detailed survey of biocide susceptibility in the *Burkholderia cepacia* complex.** Using a large collection of genetically characterised strains we were able to show that certain species such as *B. vietnamiensis*, *B. cenocepacia*, *B. cepacia*, *B. lata* and *B. contaminans* were less susceptible to disinfectants such as chlorhexidine (widely used in hospitals) and cetylpyridinium chloride (used in many commercial cleaning and disinfection agents). Strains which had spread between individuals with CF (so called “epidemic strains”) also appeared to have elevated resistance to these antimicrobials. We also demonstrated that certain *B. cepacia* complex strains could survive short term exposure to commercial biocide formulations sold as hand washes or skin disinfectants. The data suggest that these agents could be improved to ensure they kill *B. cepacia* complex. To facilitate testing of future disinfectants we proposed that three reference *B. cepacia* complex strains with the highest levels of biocide resistance be included as standards for disinfectant testing.
- (ii) **The identification of *Burkholderia cenocepacia* genes involved in the resistance to chlorhexidine.** Using a DNA microarray, we were able to see which genes are switched on and off when *B. cenocepacia* is exposed to low concentrations of the disinfectant chlorhexidine. A total of 32 genes were switched on to a significant degree and included genes that coded for efflux pumps which are capable of eliminating antimicrobials from bacteria. These upregulated genes are worthy of examination as potential drug targets, since if the proteins they encode can be blocked, then the resistance of *B. cenocepacia* to antimicrobials should be reduced. We also identified that all the 41 genes that were switched for after exposure to chlorhexidine were linked to motility. The microarray data is now being prepared for publication. The biocide sensing response is also being examined in detail as it appears to be a mechanism by which *B. cenocepacia* can sense low concentrations of antimicrobials and adopt a growth state which it allows survive. By understanding the genetic mechanisms of this process we could develop strategies to interfere with antimicrobial sensing and improve the ability of antibiotics to kill these problematic CF bacteria.

### **Publications arising from research**

Rose H, Baldwin A, Dowson C & Mahenthiralingam E. (2009) Biocide susceptibility of the *Burkholderia cepacia* complex. *Journal of Antimicrobial Chemotherapy* 63(3), 502-510.

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