

## Dr Dominic Campopiano Senior Lecturer in Organic Chemistry

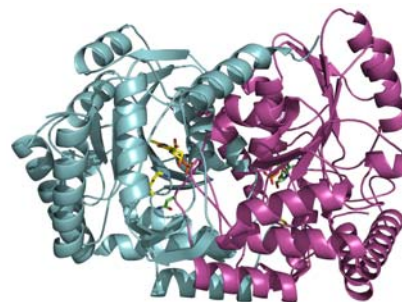
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Research Interests: natural product biosynthesis, enzymology, protein structure, antibiotics, innate immunity enzyme inhibitors



### Sphingolipid biosynthesis

We have been studying how bacteria, mammals and yeast produce sphingolipids – these are essential components of the cell membrane and play important roles in regulation and metabolism ([www.lipidmaps.org](http://www.lipidmaps.org)). In collaboration with Prof. Jim Naismith (St. Andrews), we have determined the structure of Serine palmitoyltransferase (SPT), the first enzyme in the sphingolipid biosynthetic pathway which catalyses a decarboxylative, Claisen-like condensation. This work has allowed us to explore the molecular basis of human disease and the mechanism of this complex enzyme (1). We have also studied how SPT interacts with a range of natural and synthetic inhibitors such as cycloserine (2).



### Protein drug targets

We are interested in a range of protein targets which are involved in essential metabolic reactions such as drug detoxification, metal uptake and vitamin-dependent, post-translational modifications e.g. Glutathione S-Transferases (GSTs), Ferric binding proteins (FBPs), Biotin Protein Ligases (BPLs). We have used GST as a target for Dynamic Combinatorial Library (DCL) selection in collaboration with Dr. Mike Greaney. We have developed a reversible chemical reversible acylhydrazone library and found that two different GST isoforms amplified a specific library member (3). We think an excellent platform to probe generate new inhibitors and aim to expand this approach to other interesting protein targets.

### Defensins

Mammals have a range of self-defense mechanisms as part of their innate immunity. Defensins are a small family of antimicrobial peptides (AMPs) characterized by their +ve charge, conserved cysteine residues, disulfide bonds and 3D fold. In collaboration with various colleagues within “Team Defensin” we have characterised various peptides including Defr1, a novel mouse defensin. Defr1 kills a broad range of pathogenic bacteria and is a dimeric peptide held together by an unusual intermolecular S-S bond (4).

### Antibiotic resistance

We are part of a team “The UK Cystic Fibrosis Microbiology Consortium” which brings together scientists and clinicians with complementary expertise funded by grants from the Big Lottery Fund and the Cystic Fibrosis Trust, ([www.cfmicrobiology.org.uk/](http://www.cfmicrobiology.org.uk/)). Together we are characterising the mechanisms of resistance to antimicrobial agents in bacterial pathogens, with a view to develop novel antimicrobial agents (5).

I am chair of the organising committee of the RSC conference “Antibiotics – where now?” ([www.rsc.org/antibiotics11](http://www.rsc.org/antibiotics11)).

### SELECTED RECENT PUBLICATIONS

1. Raman, M. C., Johnson, K. A., Yard, B. A., Lowther, J., Carter, L. G., Naismith, J. H. & Campopiano, D. J. (2009) The external-aldimine form of serine palmitoyltransferase; structural, kinetic and spectroscopic analysis of the wild-type enzyme and HSAN1 mutant mimics. *J. Biol. Chem.*, 284, 17328-17339.
2. Lowther, J., McMahon, S., Johnson, K. A., Yard, B. A., Carter, L. G., Raman, M. C., Naismith, J. H. & Campopiano, D. J. (2010) Serine palmitoyltransferase displays a novel mechanism of cycloserine inhibition. *Molecular Biosystems*, 6, 1682-1693.
3. Bhat, V. T., Caniard, A. M., Luksch, T., Brenk, R., Campopiano, D. J.,\* & Greaney, M. F.\* (2010) Nucleophilic catalysis of acylhydrazone equilibration for protein-directed dynamic covalent chemistry. *Nature Chemistry*, 2, 490-497.
4. Campopiano, D. J., Clarke, D. J., Polfer, N. C., Barran, P. E., Langley, R. J., Govan, J. R. W., Maxwell, A., & Dorin, J. R. (2004) Structure-activity relationships in defensin dimers. *J. Biol. Chem.*, 279 (47), 48671-48679.
5. Ortega, X. P., Cardona, S. T., Brown, A. R., Loutet, S. A., Flannagan, R. S., Campopiano, D. J., Govan, J. R. W., & Valvano, M. A. (2007) A putative gene cluster for aminoarabinose biosynthesis is essential for *Burkholderia cenocepacia* viability. *J. Bacteriol.*, 189, 3639-3644.