



Bio21 Molecular Science and  
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# Making Molecules

***Institute chemists, in collaboration with cell biologists, molecular geneticists, biochemists, pharmacologists and engineers, are pursuing a range of applications of chemical synthesis of both small and polymeric molecules with applications in medical and environmental biology***

**General Chemical Synthesis:** The research groups of Federation Fellows Andrew Holmes and Paul Mulvaney, consisting of both University of Melbourne and CSIRO researchers, are pursuing applications of chemical synthesis of small and polymeric molecules and quantum dot composites at the interface of biology and materials science. Examples of chemical synthesis of biologically important molecules and other chemistry applications include:

- Frog venom inhibitors of neuromuscular communications mediated by acetylcholine nicotinic receptors
- Covalently-immobilized analogues of the naturally occurring acidic phospholipids, cardiolipin, phosphatidic acid inositol phosphate, for use as specific affinity ligands in the isolation and structural characterisation of cell signaling and other membrane-targeting proteins from mammalian cells and human pathogens, particularly leishmania and malaria
- Quantum dots covalently linked to protein and nucleic acid reporter molecules
- Analogues of substrates or ligands for particular candidate pesticide targets will be investigated for their potential as new pesticides
- Light-emitting polymers of the type previously developed for electronic flat screen and solar cell applications, will be investigated for potential use in biosensors
- Artificial enzymes engineered to be less accessible and, therefore, more resistant to degradation by naturally occurring proteolytic enzymes
- Supercritical carbon dioxide fluid is being evaluated for various applications ranging from the preparation

of decaffeinated green coffee beans to the preparation of functional biocompatible polymers for use in tissue engineering.

**Free Radical Chemistry Applications:** The Institute-based ARC Centre for Free Radical Research led by Carl Schiesser, Uta Wille and Richard O'Hair, is engaged in a number of collaborative research programs, including:

- The development of inhibitors of reactive oxygen species (ROS)- and other free radical-induced tissue damage, with potential as drugs for the treatment of damage associated with age-related cardiovascular disease, ischemia, trauma and inflammation. In collaboration with other Bio21 Institute scientists, the aim is to develop new candidate antioxidant-based therapeutic agents that possess cardiovascular- or neuro-protective properties, for example, the inhibitors of the formation of amyloid associated with disease
- Investigations of free radical damage of amino acid, peptide and proteins and its relevance to various age-related protein disorders, including Alzheimer's disease, as well as the deterioration during storage of protein pharmaceuticals and other commercially valuable proteins during storage.

**Medical Applications of Metal-protein Interactions:** Tony Wedd, Kevin Barnham, Paul Donnelly and Denis Scanlon lead investigations of:

- Proteins involved in copper metabolism, intracellular storage and transport
- Design and synthesis of metal complexes with potential diagnostics applications in medicine, for example diagnostic imaging and therapeutic applications of radioisotopes of copper and rhenium

- Design, synthesis and testing of compounds which suppress the effects of metal ions on proteins leading to amyloid formation
- Design and synthesis of metal-based drugs, capable of crossing the blood brain barrier for the treatment and imaging of Alzheimer's disease.

**Protein inhibitors, natural products and their analogues with potential as new antibiotics and disease prevention drugs:** Mark Rizzacasa, Spencer Williams, Frances Separovic and Craig Hutton, in collaboration with biochemists, Malcom McConville, Matt Perugini, David Stapleton and Darren Kelly, lead investigations of bioactives and natural product chemistry directed towards the development of inhibitors with potential as antibiotics, antidiabetes drugs, anticancer drugs or probiotics for the prevention of cardiovascular disease, in collaboration with other researchers in the Bio21 Institute and the Departments of Medicine (St Vincent's Hospital), Pharmacology, Microbiology and Immunology, the Peter MacCallum Cancer Research Institute and the Walter and Eliza Hall Institute.

- Synthesis of complex biologically active natural products and analogues with potential as therapeutic agents for the treatment of various diseases.
- Novel inhibitors of diabetes-associated tissue pathogenesis (eg kidney disease) and the use of these inhibitors as affinity ligands to identify drug targets

- Sulfatase substrates and their analogues with potential as inhibitors of glycosamoglycan metabolism for the control of cancer and insect pests
- Substrate analogue inhibitors of enzymes involved in mannose metabolism and cell wall biosynthesis with potential as antibiotics in the treatment of the pathogenic microorganisms, Leishmania and mycobacterium
- Flavonoid analogues with potential as drugs against cardiovascular disease are being synthesised and tested for biological effects in rat and sheep models
- Conformational analysis of the antibiotic virginiamycin and its analogues, which function as specific inhibitors of bacterial protein synthesis
- Anti-tumour cyclic peptides, with high potency against human breast and lung cancer and as antifungal agents effective in the treatment of HIV-related fungal infections
- Design and synthesis of new antibiotics which target protein-interactions involving an enzyme essential in lysine biosynthesis
- Design and synthesis of novel protein kinase inhibitors.

