



Bio21 Molecular Science and
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Beyond the Genome

In this post-genomic age, genome sequence data underpins new approaches to understanding the molecular processes by which cells survive, communicate and proliferate, and how these functions are regulated. This information is fundamental to understanding how humans and other organisms adapt to stress and fight infections and why diseases occur as a result of inherited or somatic mutations.

The Institute's post genomics research in biomedical areas is focused on pathogenic microbes, cancer, neurological diseases and autoimmune diseases, and in environmental areas, on the products of candidate genes determining pesticide resistance and heavy metal detoxification and targets for new pesticides. These programs are underpinned by a combination of expertise and platform technologies in an array of disciplines, including cell biology, protein structure and their covalent modifications, functional proteomics, metabolomics, animal models, bio imaging, ultra structural analysis, and bioinformatics, that will ensure a rapid translation of research discoveries into community benefits.

Proteomics

An unexpected consequence of genomics was the discovery of appreciably fewer genes (ca 30,000) in the human genome than previously predicted. In fact, the number of proteins is at least 40 times the number of genes. This has led to massive investment in proteomics technology for defining the precise chemical structures of proteins.

The bringing together of the mass spectrometers, NMR and related proteomics facilities and expertise into the Institute from the University's disciplines of chemistry, biochemistry and molecular biology and dental science, as well as from the Howard Florey Institute, provide the Institute with a major proteomics capability.

The proteomics investment is important for understanding the bewildering complexity of chemical modification of proteins which drive many of the

regulatory processes in cells and abnormalities associated with diseased states.

The Institute's substantial proteomics resources are being harnessed to identify and functionally analyse a range of physiologically important covalent modifications of protein regulators and enzymes, as well as protein-protein interactions.

Metabolomics

The complexity of cell regulation at the protein level usually means that measurements of levels of individual messenger RNA and protein species do not provide the information needed for understanding the physiological condition of cells. A better indication is often the profile of individual end point metabolites, defined as the cell's "metabolome". The Institute has made substantial investment in metabolomics technology (NMR, mass spectrometry and small molecule separation systems) to support a number of research programs, for example, identification and quantification of:

- Levels of individual metabolites, which identify active enzyme pathways and often better reflect the net responsiveness of cells to individual regulators, particularly in *Leishmania* and other pathogenic protozoa
- Levels of metabolites in genetically diseased or genetically modified cells as a measure of the physiological consequences of the altered genetic state of the cells

- The capacity of individual proteins and isolated organelles to bind specific metabolites and other small molecule regulators,
- Small molecules functioning as enzyme regulators and second messengers
- Metabolites of candidate drugs and other test compounds which may have physiological actions, either beneficial or toxic.

Recombinant gene and protein expression technologies

Knowledge of gene sequences has enabled applications of recombinant DNA technology to alter gene expression in cells and whole animals and engineer bacteria and other cells to make mammalian proteins of interest. The latter capability underpins the Institute's NMR analyses of 3D protein structures and biochemical assessments of function. It also enables the preparation of protein and peptide analogue vaccines which, for low abundance proteins, would otherwise have not been attainable. A related technology of emerging importance is the use of interference RNA to functionally suppress expression of individual proteins of interest.

Specific examples of projects using the proteomics, metabolomics and/or recombinant DNA technologies, are investigations of:

- The 3D structures of a variety of proteins of biomedical and agricultural (eg novel legume gene regulators) importance
- Metabolic pathways that are critical for the infectivity of pathogenic micro-organisms, including tuberculosis and malaria.

- New inhibitors and vaccines that target essential processes in pathogenic microbes
- Animal models of autoimmune diseases and chronic inflammation for identifying factors responsible for the immune system attacking its own tissues and to develop strategies for the treatment of autoimmune disorders
- The neurotoxicity and pathogenesis of diseases linked with abnormal protein folding (e.g. prion diseases), including suppression of prion expression using interference RNA technology
- Mechanisms of cell regulation mediated by specific protein phosphorylation and methylation pathways, creating opportunities for the development of new drugs for the treatment of a variety of cancers.
- Novel interactions between plasma proteins and apolipoprotein E, which is a key lipid-binding protein genetically linked to age-related diseases affecting millions of people worldwide
- Molecular triggers of immunity towards viruses and cancers and the aberrant immune response in autoimmune diseases like diabetes mellitus and arthritis
- Insect proteins identified as candidate targets for new pesticides
- Plant-derived allergens for development of vaccines against human allergies
- Pain therapeutics discovered by molecular mining of the expressed genome of Australian predatory cone shells are providing lead compounds for the treatment of neurological diseases such as multiple sclerosis, shingles, diabetic neuropathy and other painful neurological conditions.

