The Epigenomic Medicine Laboratory uses advanced materials to construct protein targeting conjugates for therapeutic and imaging applications. Combinatorial approaches with receptor targeting conjugates and natural or synthetic chromatin modifying compounds in models of disease are investigated. Mechanisms of action of novel compounds are explored using next generation sequencing technologies.

Research Brief
Overall, work in the laboratory is focussed on two complementary research directions. The first objective, an extension of work from Professor Roger Martin’s Molecular Radiation Biology Laboratory at the Peter MacCallum Cancer Centre, is the development of DNA-targeted therapeutics and diagnostics using receptor-targeted nanoparticle carriers. The nanoparticle preparations undergo preclinical evaluation in relevant models of disease for targeted Auger radiotherapy, UVA phototherapy and diagnostic imaging (both oncological and non-oncological applications). The research strategy involves the incorporation of an iodinated DNA minor groove binding bibenzimidazole into peptide- or antibody-coated biodegradable nanoparticles. The aim is to accumulate the DNA ligand in the nucleus of target cells following successive cycles of receptor-mediated endocytosis and intracellular degradation. Use of radioactive iodine enables radiotherapy and imaging, whereas the photopotency of the UVA Sens ligand (analogue substituted with non-radioactive iodine) provides the basis for phototherapy.

The other major research direction involves evaluation of natural and synthetic chromatin modifying compounds in models of disease. This direction is focussed on the evaluation of histone deacetylase inhibitors (HDACis); the mechanism of action of novel compounds is explored using genome-wide next generation sequencing (NGS) technologies. Of particular importance is that we can combine HDACis with the DNA targeting strategy described above to 1) improve the therapeutic efficacy of targeted radiotherapy and phototherapy and similarly, to 2) improve the window for safe imaging by ameliorating the effects of radiation in normal tissue.

Methodologies
- Synthetic and conjugation chemistry; DNA ligand and protein radiolabelling
- Confocal microscopy and quantitative immunofluorescence
- Next generation gene sequencing and detailed pathway analysis

Selected Publications
Development of Protein-Coated Nanoparticles Incorporating DNA-Ligands for Targeting Specific Receptors

Schematic representation of DNA targeting nanoparticles (A). 3D photomicrographs of microparticles encapsulating DNA binding ligand (blue) (B). Merged image of nanoparticle depicting the DNA ligand (blue) encapsulated in the PLGA polymer (red). Lipid coating is depicted in green (C). SEM images of nanoparticles (D). Uptake of DNA ligand in A431 cells following incubation with nanoparticles (E).

Evaluation of DNA Damage & Quantitative Immunofluorescence

Immunofluorescence assay for evaluation of DNA damage using γH2AX, a sensitive marker of DNA double-strand breaks. Evaluation of the effect of chromatin-modifying compounds using a model of doxorubicin-induced cardiac hypertrophy and cardiotoxicity (A). Colocalisation of γH2AX foci (green) in euchromatic (red; H3K4me3) and DAPI-dull regions (nucleus=blue) (B). Quantitative immunofluorescence is used to investigate epigenetic phenomena. In this example, the relative expression cellular expression of selected histone deacetylase enzymes is shown (C).

Investigation of the Genetic & Epigenetic Effects of Dietary Antioxidants & Chromatin-Modifying Compounds in Models of Disease

Schematic diagram depicting various post-translational modifications (A). We investigate the biological effects of chromatin modifying compounds using various methodologies and in multiple models of disease. For example, Dr Simon Royce’s (Monash University) murine model of chronic allergic airways disease has been used to investigate. Trichostatin A, suberoylanilide hydroxamic acid, valproic acid, resveratrol and LSF, in the example shown (B). Chromatin remodelling is investigated using various methodologies. In this example, the effect of the dietary compound, CPF, on the cellular uptake of doxorubicin is shown (C).