



Michael Parker

Professor

Room 402

Bio21 Molecular Science and Biotechnology Institute

30 Flemington Road

Tel +61 3 8344 2500 / +61 3 9288 2499

mwp@unimelb.edu.au

<http://www.bio21.unimelb.edu.au/group-leaders/affiliates-honorary/michael-parker>

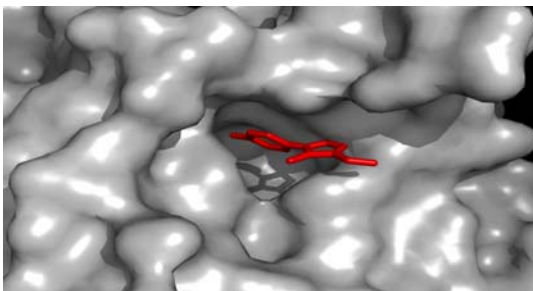
Structure-based drug discovery

The focus of our research is to visualise the three-dimensional structures of medically important proteins using X-ray crystallography. A particular focus is proteins that play a role in infection (bacterial, parasitic or viral), cancer and neurobiology (e.g. Alzheimer's disease, epilepsy). The structures provide a detailed understanding of how each protein works and how it contributes to disease. Most importantly, the structures can be used to discover drugs using computational approaches. Our work is supported by labs that specialise in protein expression, purification and electrophysiology. Example projects in each of the disease areas follow.

Projects:

A new target in breast cancer

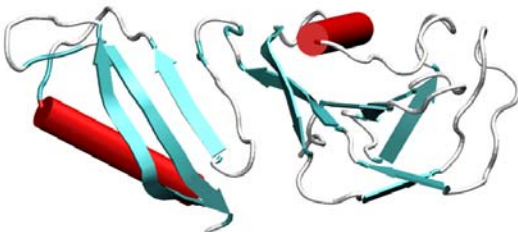
Liver Receptor Homologue-1 (LRH-1) is a member of the nuclear receptor family of transcription factors. Our collaborators and others have shown an unambiguous role for LRH-1 in breast cancer progression. In postmenopausal breast cancer patients (by far the most common age group), breast adipose fibroblasts are the principle source of estrogen for breast cancer cell proliferation, since the ovaries no longer produce this



hormone. Current hormone therapies produce significant adverse effects by inhibiting estrogen action throughout the body, whereas inhibition of LRH-1 activity would result in breast-specific anti-estrogen therapy, offering a clear therapeutic advantage. We have used virtual screening to identify small molecules that inhibit LRH-1 activity and these initial hits are being developed into drug-like molecules with the help of crystallography.

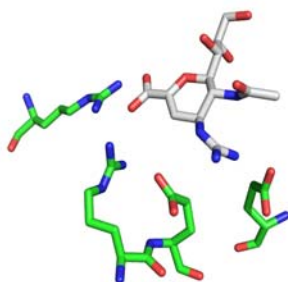
New approaches to Alzheimer's disease

Alzheimer's disease (AD) is the fourth biggest killer in developed countries. Amyloid precursor protein (APP) plays a central role in the development of AD, through generation of the Abeta peptide by proteolytic



breakdown of APP. Very recently, a new AD therapeutic protein target was discovered that greatly enhances Abeta production. Here we will determine the 3D atomic structures of APP and regulatory proteins using X-ray crystallography at the Australian Synchrotron and by nuclear magnetic resonance spectroscopy in order to understand how APP extracellular domains and associated proteins regulate Abeta production. All this work will provide the framework for developing therapeutics to treat AD.

Understanding how influenza virus resists anti-flu drugs



The ability of influenza viruses to mutate rapidly has the potential to render vaccines and antiviral drugs useless. Indeed, the seasonal H1N1 virus is already resistant to the drug Tamiflu™. This observation demonstrates the ease with which the recent swine H1N1 virus could rapidly become resistant to current and future treatments, whether they are vaccines or drugs. The availability of a precise three-dimensional atomic structure of swine N1 bound to current drugs in the clinic will allow mapping of resistance mutants as they are reported and also the prediction of likely escape mutants. In turn this knowledge will guide the structure-based development of new vaccines and antiviral drugs. Crystals of swine flu N1 are already available.

Recent publications:

1. Polekhina, G., Giddings, K.S., Tweten, R.K. & Parker, M.W. (2005) Insights into the action of the superfamily of cholesterol-dependent cytolysins from studies of intermedilysin. *Proc. Natl. Acad. Sci. USA* **102**, 600-605.
2. Brown, R.J., Adams, J.J., Pelekanos, R.A., Wan Y., McKinstry, W.J., Palethorpe, K., Seeber, R.M., Monks, T.A., Eidne, K.A., Parker, M.W. & Waters, M.J. (2005) Model for growth hormone receptor activation based on subunit rotation within a receptor dimer. *Nature Struct. Mol. Biol.* **12**, 814-821.
3. Iacovache, I., Paumard, P., Scheib, H., Lesieur, C., Sakai, N., Matile, S., Parker, M.W. & van der Goot, F.G. (2006) The rivet model for channel formation by aerolysin-like pore-forming toxins. *EMBO J.* **25**, 457-466.
4. Kong, G. K-W., Adams, J.J., Harris, H.H., Boas, J.F., Curtain, C.C., Galatis, D., Masters, C.L., Barnham, K.J., McKinstry, W.J., Cappai, R. & Parker, M.W. (2007) Structural studies of the Alzheimer's amyloid precursor protein copper-binding domain reveals how it binds copper ions. *J. Mol. Biol.* **367**, 148-161.
5. Hansen, G., Hercus, T.R., McClure, B.J., Stomski, F.C., Dottore, M., Powell, J., Ramshaw, H., Woodcock, J.M., Xu, Y., Guthridge, M., McKinstry, W.J., Lopez, A.F. & Parker, M.W. (2008) The structure of the GM-CSF receptor complex reveals a distinct mode of cytokine receptor activation. *Cell* **134**, 496-507.
6. Albiston, A.L., Morton, C.J., Ng, H.L., Pham, V., Yeatman, H.R., Ye, S., Fernando, R.N., De Bundel, D., Ascher, D.B., Mendelsohn, F.A.O., Parker, M.W. & Chai, S.Y. (2008) Identification and characterization of a new cognitive enhancer based on inhibition of insulin-regulated aminopeptidase. *FASEB J.* **12**, 4209-4217.
7. Ang, W.H., Parker, L.J., De Luca, A., Juillerat-Jeanneret, L., Morton, C.J., Lo Bello, M., Parker, M.W. & Dyson, P.J. (2009) Rational design of an organometallic glutathione S-transferase inhibitor and its interactions with GST P1-1. *Angew Chem.* **48**, 3854-3857.
8. Wielens, J., Headey, S., Deadman, J.J., Rhodes, D.I., Parker, M.W., Chalmers, D.K. & Scanlon, M.J. (2011) Fragment-based design of ligands targeting a novel site on the integrase enzyme of human immunodeficiency virus. *ChemMedChem* **6**, 258-261.
9. Jurczyk, J., Nouwens, A.S., Holien, J.K., Adams, T.E., Lovrecz, G.O., Parker, M.W., Cohen, S.B. & Bryan, T.M. (2011) Direct involvement of the TEN domain at the active site of human telomerase. *Nucleic Acids Res.* **39**, 1774-1788.
10. Parker, L.J., Italiano, L.C., Morton, C.J., Hancock, N.C., Ascher, D.B., Aitken, J.B., Harris, H.H., Campomanes, P., Rothlisberger, U., De Luca, A., Lo Bello, M., Ang, W.H., Dyson, P.J. & Parker, M.W. (2011) Studies of glutathione transferase P1-1 bound to a platinum(IV)-based anticancer compound reveal the molecular basis of its activation. *Chem.-Eur. J.*, in press.