

## Opportunities for Research Projects in Structural Biology & Drug Design

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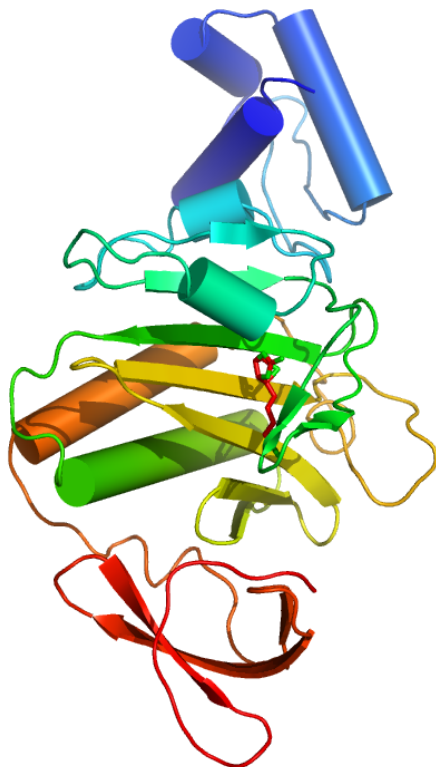
### The Biotin Biocycle

Co-supervised by Dr Steven Polyak ([steven.polyak@adelaide.edu.au](mailto:steven.polyak@adelaide.edu.au))

Biotin (Vitamin H or B7) is an important micronutrient that is utilised throughout the living world. All organisms possess biotin-dependent enzymes to perform a variety of carboxylation, decarboxylation and transcarboxylation reactions. Here, biotin functions as an enzyme cofactor to facilitate the transfer of carbon dioxide between metabolites. These biotin-dependent enzymes often catalyse key steps in important metabolic pathways, such as fatty acid biosynthesis, gluconeogenesis and amino acid synthesis.

Bacteria can obtain biotin either by *de novo* synthesis or scavenged from exogenous sources through a high affinity biotin transporter. Biotin is then either covalently attached to the biotin-dependent enzymes, where it functions as a coenzyme, or functions as a co-regulator of gene expression.

Both activities are controlled by the multifunctional protein biotin protein ligase (BPL).



### Drug Discovery

Due to the rise of drug-resistant pathogenic micro-organisms, there is a desperate need to discover novel anti-infective agents that are safer, cheaper and have improved efficacy. There is also a great challenge to produce novel drug classes that are immune to pre-existing resistance mechanisms. The goal of our group is to explore the biotin biocycle as a source of new drug targets. This collaboration employs biochemistry, microbiology and medicinal chemistry together with structural biology to exploit this pathway for the discovery of new anti-infective agents.

Figure 1. X-ray crystal structure of BPL from *Staphylococcus aureus*

## Antagonists of cell cycle control proteins

Co-supervised by Dr Kate Wegener ([kate.wegener@adelaide.edu.au](mailto:kate.wegener@adelaide.edu.au))

Gankyrin is overexpressed in a large proportion of primary liver cancers. It is composed of 7 ankyrin repeats and acts as a scaffolding protein to modulate the activities of important cell cycle regulators including cdk4, Rb, MDM2 and p53. It also plays a role as a component of the 26S proteasome via interactions with the S6 protein, an AAA type ATPase.

We aim to identify or design novel antagonist molecules that bind to gankyrin and suppress gankyrin's role in cell proliferation. Such molecules could be useful in treating primary liver cancer and potentially other cancers.

This is a multi-disciplinary project that is a collaboration with Professor Andrew Abell in the School of Chemistry and Physics.

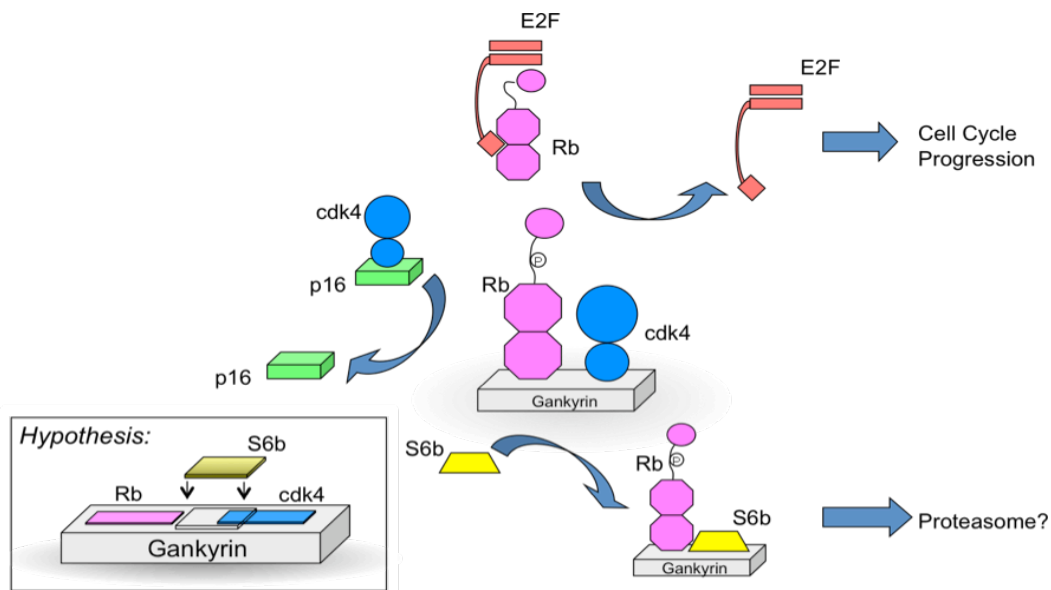


Figure 2. A schematic showing the proposed role of gankyrin in cell cycle progression.