A novel class of JAK inhibitors

- Novel druggable site identified on JAK
- Potential to develop non-competitive small-molecule JAK inhibitors
- Offers distinct advantages over current strategies

Scientific team

Jeff Babon, PhD
Structural Biology division

Professor Nick Nicola, PhD
Cancer & Haematology division

Background

Inhibitors of JAK kinases have been shown to be beneficial in the treatment of certain haematological neoplasms and inflammatory diseases. Two compounds, tofacitinib and ruxolitinib, are currently FDA approved and many others are in preclinical and clinical studies. All compounds being developed are ATP competitive and therefore there exists the challenge of kinase selectivity and potentially emergence of resistance.

Researchers at the Walter and Eliza Hall Institute offer a novel therapeutic mechanism: to target JAK activity in a non-ATP-competitive manner. This strategy holds two key advantages over the competitive ATP-mimetics that are currently used to inhibit JAK activity:

1. Non-competitive mechanism of JAK antagonism: non-competitive kinase inhibitors are highly desirable as they are not out-competed by endogenous ATP;

2. Greater specificity of JAK inhibition: the novel site is not an ATP binding site (Note. All kinase ATP binding pockets are relatively similar, thus, reduced selectivity leads to undesired off-target effects).

As such, development of this technology will lead to the emergence of a new class of highly specific JAK inhibitors.

The technology

The family of four JAKs share a common architecture of a N-terminal FERM domain that binds receptor tyrosine kinases and a C-terminal kinase domain. Within the kinase region of JAK1, 2 and Tyk2 is an evolutionarily conserved GQM motif, the mutation of which renders SOCS3 incapable of inhibiting JAK activity.

This exciting discovery led to the identification of a novel mechanism by which SOCS3 inhibits JAK catalytic activity in a manner that is unaffected by ATP (Figure 1). This is distinct from the conventional paradigm of SOCS3-mediated inhibition of JAK activity and paves the way for the development of a novel class of non-competitive small molecule JAK inhibitors.

We have begun a drug discovery program focused on targeting this new site.

Applications

Novel JAK inhibitors may be applicable to many indications, including:

- **Leukaemias.** For example, in childhood T-cell acute lymphoblastic leukaemia, the TEL-JAK2 chimeric protein results in constitutive JAK2 tyrosine kinase activity.
- **Myeloproliferative disorders.** An activating mutation in JAK2 causes Polycythemia Vera, Essential Thrombocythemia, and Primary Myelofibrosis.
- **Inflammatory diseases.** For example, rheumatoid arthritis.

Intellectual property

Compound structures have not been publicly disclosed. An opportunity exists to generate novel composition of matter intellectual property.

Opportunity for partnership

The Walter and Eliza Hall Institute is seeking a partner to co-invest in the development of novel small molecule compounds that target the SOCS3 binding site on JAK kinases. The ultimate goal is to develop a small molecule clinical candidate and back up compounds with the appropriate potency, safety and pharmacokinetic profile.
The institute is extensively experienced and has a successful track record in medicinal chemistry programs focused on high-throughput chemical screening, hit-to-lead and lead optimisation.

**Key publications**


**Figure legend**

**Figure 1:** SOCS3 inhibition of JAK2 is independent of ATP.