A novel class of JAK inhibitors

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

Scientific team

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The opportunity

The Janus Kinase (JAK) family of kinases is central to communicating cytokine signals from liganded extracellular tyrosine kinase receptors to intracellular effector proteins. Under normal physiological conditions, JAK activity is tightly regulated by a family of proteins called suppressors of cytokine signalling (SOCS). Mutations can render JAK constitutively active, resulting in the aberrant activation of normal cytokine signalling pathways that can no longer be held in check by SOCS proteins. Ultimately, these JAK mutations are implicit to the development of a number of human malignancies, including leukaemia and myeloproliferative disorders.

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

1. Non-competitive mechanism of JAK antagonism: non-competitive kinase inhibitors are highly desirable as they are not outcompeted 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, off-target effects can be encountered)

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

The technology

The family of four JAKs share a common architecture of an N-terminal FERM domain that binds receptor tyrosine kinases and C-terminal kinase domain. Within the kinase region of JAK1, 2 and Tyk2 is an evolutionarily conserved GQM motif (Figure 1), 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 or substrate binding (Figure 2). 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.
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.
- **Other JAK-STAT driven disorders.** For example, cancers.

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.

Intellectual property

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

Key publications


Figure legend

**Figure 1:** The SOCS3 binding site - GQM. The GQM motif (yellow) on JAK2 is solvent exposed and serves as the binding site for SOCS3.

**Figure 2:** SOCS3 inhibition of JAK2 is independent of ATP. Lineweaver-Burk plot that intersect on the abscissa indicated non-competitive inhibition in the presence of varying concentration of substrate (left hand plot) and ATP (right hand plot).

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Opportunities for partnership

- Therapeutics
- Biomarkers and diagnostics
- Unique pre-clinical models

Research

Scientists are driving innovative programs aimed at understanding, preventing and treating:

- Cancer
- Chronic inflammatory and autoimmune diseases
- Infectious diseases

Mastery of disease through discovery

- Australia’s oldest independent medical research institute - founded in 1915
- Multidisciplinary research teams focused on solving complex biological questions
- Fostering effective links between the laboratory and the clinic
- Thriving on collaboration - 300 projects, 470 collaborations, 120 cities, 43 countries
- Highest scientific publication citation rate of any Australian research organisation

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