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

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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) (Figure 1). 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.

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 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 Thrombocytopenia, and Primary Myelofibrosis.

• Other JAK-STAT driven disorders. For example, multiple cancers.

Figure 1: The structure of SOCS3 bound to JAK2

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.

Figure 2. SOCS3 inhibition of JAK2 is independent of ATP
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


Walter and Eliza Hall Institute of Medical Research

The Walter and Eliza Hall Institute is Australia’s longest-serving medical research institute, celebrating its centenary in 2015. Our multidisciplinary research teams are focused on solving complex biological questions, and effectively linking laboratory research to the clinic. With a strong collaborative focus, the institute is a founding member of Biomedical Research Victoria, Cancer Trials Australia, BioGrid Australia and the Victorian Comprehensive Cancer Centre.

Research

- 750 research staff trained nationally and internationally
- 81 research laboratories

The institute’s scientists are driving innovative programs aimed at understanding, preventing and treating:

- Cancer: especially leukaemia, lymphoma, breast cancer, bowel cancer, ovarian cancer, lung cancer, pancreatic cancer and stomach cancer
- Immune disorders: including diabetes, rheumatoid arthritis, coeliac disease, rheumatic fever and other inflammatory conditions
- Infectious diseases: focusing on malaria, HIV, tuberculosis and hepatitis viruses

Research outcomes

- More than 300 publications annually
- 74% of publications in biomedical journals with an impact factor >15
- 34% of publications in the top 10% of their field

Strong translational focus

- Discovery pipeline fed by more than 300 projects
- Institute research is the basis of more than 100 clinical trials, and has resulted in 4 start-up companies and 5 spin-out companies
- Institute research has benefited more than 20 million people worldwide
- More than 470 collaborative partners across 120 cities in 43 countries

Opportunities for partnership

- Therapeutics
- Biomarkers and diagnostics
- Unique pre-clinical models
- Access to platform technologies including
  - bioinformatics
  - clinical translation centre
  - drug discovery including high-throughput screening and medicinal chemistry
  - systems biology including proteomics

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