MONASH University

MONASH INNOVATION

AMINOPEPTIDASE INHIBITORS FOR HUMAN, ANIMAL AND MICROBIAL USE

Aminopeptidase enzymes are potential drug targets for diseases ranging from cardiovascular disorders to cancer, as well as infectious diseases caused by parasites and bacteria. Our aminopeptidase inhibitor compounds are efficacious in controlling human leukaemic cell lines, growth of bacterial pathogens and malaria parasites.

- **Novel class of aminopeptidase inhibitors - non-peptidic, orally active and stable.**
- **Novel 'best in class' compounds that are highly potent (low nM affinity) inhibitors of cancer target human aminopeptidase N.**
- **Potential to develop 'first-in-class' anti-microbial drugs to new enzymatic targets.**
- **Chemical scaffold that allows rapid development of potent inhibitors of different aminopeptidase subtypes.**

THE CHALLENGE

Aminopeptidases catalyse the removal of amino acids from proteins or peptide substrates, a key reaction essential to the finely regulated process of protein-turnover in a wide range of organisms. Inhibition of aminopeptidase activity disrupts this essential process, resulting in profound effects on cell survival and proliferation. The key role played by aminopeptidases in human, animal and microbial cells, make them attractive targets for devastating human diseases such as cancer, malaria and bacterial infections.

The peptide-based aminopeptidase inhibitor Bestatin is approved for treatment of acute myeloid leukaemia, lung cancer and nasopharyngeal cancer. Bestatin and other first-line aminopeptidase inhibitors have been shown to have anti-malarial and anti-bacterial activity. However, the effectiveness of these early compounds is limited by low potency for the enzyme target(s) or lack of tissue specificity and poor pharmacokinetic profiles.

There is an urgent need to identify new drug classes to combat drug-resistance in the microbial world as well as treat chronic human disease. Aminopeptidase inhibitors have the potential to address these needs.

To unlock the enormous therapeutic potential of aminopeptidase inhibitors, novel chemical series are required that are potent and selective inhibitors whilst retaining appropriate pharmacokinetic properties.

THE TECHNOLOGY

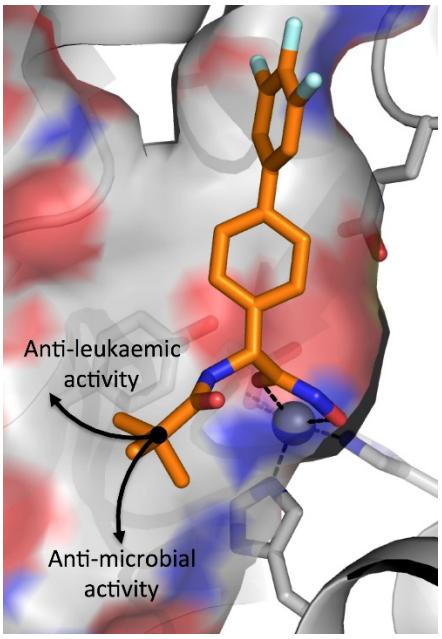
Monash researchers have developed a novel chemical scaffold based on a biaryl-linked hydroxamic-acid metal binding group, which tightly coordinates the catalytic metal of the target aminopeptidase. The scaffold is designed to anchor through interactions with the catalytic metal(s), and present tractable synthetic routes to rapidly build into selectivity pockets of the target aminopeptidase.

We have used the technology to rapidly develop multiple compound series that each demonstrate potent activity against different aminopeptidase targets. For example, we have developed inhibitors of the human Aminopeptidase N that mediate cancer cell death. The current series of Monash Aminopeptidase N inhibitors are 75-fold more efficacious against leukaemic cell lines than the marketed drug, Bestatin.

Another area of therapeutic potential includes defence against microbial pathogens such as parasites and bacteria. Our current lead series can control drug-resistant cross-species malaria parasites and is active in animals after oral administration. This series has also shown efficacy against the bacterial hospital pathogen, Clostridium difficile, with a minimum inhibitory concentration in the low micromolar range.

Further, preliminary studies show that selected compounds of the series possess good physiochemical properties and excellent plasma stability.

Intellectual Property: PCT/AU2016/000248 covering Novel Aminopeptidase Inhibitors and Methods of Use.



THE OPPORTUNITY

We seek commercial partners for further development of these inhibitors. The multidisciplinary team is led by structural biologist Sheena McGowan (Medicine, Nursing and Health Sciences) and medicinal chemist Peter Scammells (Pharmacy and Pharmaceutical Sciences) who have extensive experience in the structure, function and inhibition of aminopeptidases. The Faculty of Pharmacy and Pharmaceutical Sciences have extensive academic and industrial experience.

CONTACT US

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