Engineering a safer MR antagonist for heart failure

Mineralocorticoid receptor antagonists have been used clinically to treat chronic heart failure for decades. Yet, due to their side effect profile, the full potential of these drugs to benefit patients has not been realised.

Summary

Cardiovascular disease is the single largest cause of death and disability globally, responsible for nearly one third of all deaths worldwide.

The prevalence of heart failure is predicted to rise across the globe, as the population ages and life expectancy increases. The number of deaths from chronic heart failure has markedly increased in the past decade, such that its prognosis is now worse than for many common cancers.

The use of mineralocorticoid receptor (MR) antagonists has been a part of chronic heart failure treatment for decades. Current MR antagonists have proven clinical benefit in >30% patients with heart failure and cardiovascular disease. However, their clinical use has been severely limited by negative safety profiles – in particular, the risk of hyperkalemia (increased serum potassium) and renal dysfunction.

> Our team are developing cardiac-selective MR antagonists, designed to retain primary activity in the heart but that avoid the side effect of hyperkalemia.

Safe, cardiac-selective drugs will have substantial benefits for chronic treatment regimens in high risk patients with co-morbidities such as renal disease or diabetes. There is also potential for use in patients at earlier stages of disease to limit disease progression, and potential to expand into other fibrotic indications.

Market

The market for heart failure therapeutics is expected to rise from $3.7B in 2016 to $16.1B by 2026, representing a CAGR of 15.7% (Global Data). In 2015, the majority (95.5%) of the heart failure therapeutics market was comprised of treatments for chronic heart failure (Global Data). Drivers of expected growth are the ageing population and the launch of novel first-in-class medications in late stage development.

Team

The research team is led by Dr Morag Young, head of the Cardiovascular Endocrinology research group at Hudson Institute and world expert in MR signalling, joined by Prof Jonathan Baell, co-director of the Australian Translational Medicinal Chemistry Facility, Monash Institute of Pharmaceutical Sciences at Monash University. The team also includes experts in steroid hormone receptor molecular biology and biochemistry, and interventional cardiologists as clinical partners to ensure patient need is met.

Development pathway

Our team has developed a set of tool compounds which demonstrate *in vitro* proof of concept, and are working towards a series of lead compounds for preclinical assessment.

Key biological assays and preclinical models are established in house at Hudson Institute for drug optimization.

Opportunities for co-investment, licensing, or collaboration are sought to further develop these compounds for treatment of heart disease.

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- Reproductive, women's and children's health
- Regenerative medicine
- Inflammation and immunology
- Diagnostics and biomarkers

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