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REVIEW ARTICLE

ET-traps: A Potential Therapeutic for Use in Human Complications of the Heart and Kidneys

Arjun Jain[1-4] and Ira Jain[1,5,6]*

[1]ET-traps Limited, Cambridge, UK
[2]Accelerate Cambridge, Judge Business School, University of Cambridge, UK
[3]Department of Physiology, Development and Neuroscience, University of Cambridge, UK
[4]Imperial College, London, UK
[5]Indian Institute of Management, Ahmedabad, India
[6]National University of Singapore, Singapore

ABSTRACT

Endothelin-1 (ET-1) is a potent bioactive mediator that induces vasoconstriction and promotes vascular remodeling. Previous studies indicate that ET-1 plays an important role in the pathophysiology of humans. This includes various cardiovascular and renal complications.

Some humans with chronic heart failure might also have chronic renal failure.

The organ damage in heart and kidneys increases with age. While symptoms of organ damage will vary according to the affected organ, the patient will likely need special management, including a restricted diet and/or a therapeutic.

The ET-traps, a patented technology, are a novel molecular construct, which has been shown to significantly sequester the increased levels of ET-1 found in different disease states. ET-traps have been found to be a potential therapeutic for ameliorating different pathologies related to elevate ET-1 levels, such as disruptions in the heart and kidney functions. Hence, the ET-traps could effectively tackle serious health conditions associated with disruptions in the endothelin system. This paper discusses the potential application of ET-traps as a therapeutic for use in human complications of the heart and kidneys.

***Corresponding author(s)**

Ira Jain, ET-traps Limited, UK 28 St. Stephens Place, Cambridge CB3 0JE, UK

Email: ira@et-traps.co.uk

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Introduction

Endothelin-1 (ET-1) is a vasoactive peptide that is considered critical for life. It is involved in various physiological functions, which includes maintaining the blood flow in the body, cell growth and protein synthesis, salt-water balance and embryonic development [1]. In fact, ET-1 is the most potent vasoactive peptide known to man. However, when there are increased levels of ET-1 in the body, it induces pathological processes, such as sustained vasoconstriction, oxidative stress, inflammation, endoplasmic reticulum stress, and fibrosis [2]. As such, elevated ET-1 levels are implicated in a host of different diseases, where they are a cause of the disease pathology [2]. In this paper, we discuss pathologies of the

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heart and kidneys, where ET-1 levels are elevated and could be potentially treated with ET-traps.

What are ET-traps

ET-traps are a novel therapeutic that sequester pathologically elevated ET-1 levels in the body. ET-traps are Fc-Based Fusion Proteins (FFP) that previous *in vitro* and *in vivo* research has shown potently and significantly bring down elevated ET-1 levels and in doing so, significantly prevent different pathologies associated with the increased ET-1, including the induction of Extracellular Matrix (ECM) proteins (collagen 4α1 and fibronectin) and other heart and kidney dysfunction markers [3,4].

Current therapies in the market that target ET-1 are ERAs (Endothelin Receptor Antagonists). Their mechanism of action is to bind to receptors and completely block the action of ET-1. Since this inhibits the normal physiological functions of the endothelin system, ERAs have serious side effects like fluid retention, teratogenicity and liver damage [5].

Thus, ERAs have so far been only approved for pulmonary arterial hypertension despite being around for over 20 years and showing their efficacy in a number of other diseases [6].

Since ET-traps bind to only the excess ET-1 in the body to bring it down to non-disease levels and do not completely block the action of ET-1, which is needed for normal physiological functions, there are no side effects. Furthermore, ET-traps are Fc fusion proteins, which can be modulated easily so as to not elicit a negative immune reaction.

Our binding assays confirmed the solubility of ET-trap construct and high specificity (exhibit binding to ET-1 over homologues ET-2 and ET-3 in the double digit picomolar range) [3]. This further reduces risk of side effects as we do not block important functions of these homologues unlike receptor antagonists.

ET-traps are small in size (46.837 kDa) and with an isolectric point of 7.67, similar to the pH of human blood, ET-traps would have efficacy in penetrating tissues.

The dissociation of ET-traps once bound to ET-1 is very slow. ET-traps have been found to have a longer serum half-life and a better binding affinity (1000 fold higher than ERAs) and so have much lower patient dosing which is important in chronic disease uses.

Coronary Artery Disease: Heart Failure

Coronary heart disease is the most common type of cardiovascular disease, killing 382,820 people in 2020 in the US alone. About 20.1 million adults which is 7.2% of the US population of age 20 and above have Coronary Artery Disease (CAD) [7].

In 2020, about 2 in 10 deaths from CAD happened in adults less than 65 years old. Over time, CAD can weaken the heart muscles. This may lead to heart failure, a serious condition where the heart can't pump blood the way it should [8].

The endothelium is an important regulator for vascular tone and is disrupted in heart failure. Chronic heart failure is characterized by increased ET-1 levels and studies with ERAs (endothelin receptor antagonists) have shown that antagonism of endothelin-1 has a beneficial effect on endothelial dysfunction, atherosclerosis, arterial stiffness and left ventricular failure/remodeling [1].

However, ERAs have not been approved for heart failure due to side effects like fluid retention, which lead to peripheral and pulmonary edema [2].

ET-traps could help prevent sustained vasoconstriction thus reducing arterial hypertension. The improvement in blood flow would reduce risk of myocardial ischemia and myocardial infarction. ET-traps could also reduce monocyte/macrophage infiltration, ECM protein deposition and oxidative stress and improve the lipid profile thus preventing inflammation, fibrosis and atherosclerosis.

In vivo studies demonstrated ET-traps treatment significantly returned different echocardiography markers, including measures of left ventricular systolic function in the Ejection Fraction (EF) and Fractional Shortening (FS) or diastolic dysfunction (E/A and E'/A') ratios and ECM protein deposition in the heart to non-disease levels [4].

Chronic Kidney Disease

Chronic Kidney Disease (CKD) is a major cause of morbidity and mortality. CKD is a progressive condition that affects more than 10% of the general population worldwide, amounting to more than 800 million individuals. It is more prevalent in older individuals, women, racial minorities, and in people suffering from diabetes mellitus and hypertension [9].

With limited access to treatments like dialysis and organ transplants in advanced kidney disease, CKD causes a million deaths annually [9].

There are limited therapeutic options in CKD with medications managing blood pressure, anaemia and fluids.

Current standard of care (ACE inhibitors) slow disease progression but do not stop progression to end stage renal disease and have limited use in advanced cases of CKD due to side effects like hyperkalaemia [10].

Studies have shown targeting the endothelin system even when added to maximum tolerated doses of ACE inhibitors provides significant benefit in reversing structural damage, reducing proteinuria and further slowing disease progression [11].

Endothelin-1 is an important regulator of kidney health and disease [12]. By targeting the ET-1 system, we can manage the structural damage to tissues and organs that is prevalent in CKD.

Our ET-traps are one such potential medicine that would alleviate heart and kidney dysfunction [4]. ET-traps could be used as an alternative or as an add-on treatment to ACE inhibitors to help reduce ACE inhibitor dosage, allowing better treatment options for advanced CKD patients.

SGLT2 inhibitors (SGLT2i) have recently emerged as a disease modifying therapy for CKD by inhibiting sodium absorption in the body and thus reducing blood pressure. This hemodynamic action helps reduce proteinuria and kidney decline. SGLT2i need careful patient selection and management as they can lead to side effects like genital mycotic infections, volume depletion, diabetic ketoacidosis and respiratory infections [13].

ET-traps could be used as a combination therapy with SGLT2i to address residual albuminuria and cardiovascular risk; help lower dosage of SGLT2i to reduce their side effects; and also ease fibrosis, inflammation, structural damage and stroke risk in CKD that is currently insufficiently addressed.

Our in vivo studies showed ET-traps significantly reduced the deposition of ECM proteins in the kidneys of diabetic mice, indicating improved kidney function [4]. Furthermore, there was a significant improvement in urinary albumin and creatinine levels excreted by diabetic mice treated with ET-traps. Targeting endothelin-1 in previous research has also shown efficacy in improving the lipid profile, glomerular filtration rate and reversing glomerulosclerosis and podocytes loss [2].

Potential Use of ET-traps

ET-1 levels have been studied as markers for various diseases in medicine; for example, in hypertension, chronic kidney disease, neurological diseases, tumour, heart failure and stroke [2].

We conducted in vitro (cellular) and in vivo (animal) studies (in the diabetes disease space) and found ET-traps to be efficacious and non-toxic i.e. it returned different markers of kidney and heart function to normal, control levels with no side effects.

ET-traps would be a valuable therapeutic for individuals with kidney disease, heart disease and other conditions like neurological diseases [1,14], cancers [15,16] and diabetes [17-19] where ET-1 levels are elevated and lead to endothelial dysfunction and other pathologies.

Conclusion

Perhaps, the ET-traps could be administrated to patients exhibiting increased levels of ET-1 in a simple blood test. This would help circumvent their progression to the described ailments. After all, prevention is better than cure.

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