New approaches for therapeutic targeting of the protective arm of the renin-angiotensin system

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The renin–angiotensin system (RAS) is one of the most frequently targeted pathways in pharmacological treatment of hypertension, heart failure, and chronic kidney disease. Approved drugs for these indications—ACE inhibitors, AT_1 receptor antagonists (alone or in combination with neprilysin inhibitors), and renin inhibitors—all aim to attenuate AT_1 receptor activation by angiotensin II, i.e., activation of the classical axis of the RAS.

In addition to the classical axis, the RAS comprises a protective axis, with the AT_2 receptor and the receptor MAS as its main components. These receptors mediate tissue-protective effects (anti-inflammatory, anti-fibrotic, anti-apoptotic, etc.) and—at least under certain conditions—can lower blood pressure.

Several attempts have been made to pharmacologically target the protective RAS and harness its tissue-protective actions. The most advanced drug development program in this area is the development of the AT_2 receptor agonist buloxibutid (also known as Compound 21, or C21) for the treatment of idiopathic pulmonary fibrosis (IPF), with a phase 2b clinical trial currently ongoing.

This lecture will describe the development of C21/buloxibutid from its initial in vitro characterisation to advanced clinical stages. It will also highlight other drug development programs targeting the protective RAS and conclude by discussing the possibility that AT_2 receptor agonists may bind to and activate the receptor in different ways resulting in biased agonism. This concept could open new avenues for designing future AT_2 receptor agonists with improved efficacy and pharmacokinetic properties.