BIOBUSINESS BRIEFS

DEAL WATCH

Abbott boosts investment in NRF2 activators for reducing oxidative stress

In one of the largest preclinical-stage deals ever, Abbott has agreed to pay US$400 million upfront to Reata Pharmaceuticals as part of an agreement to jointly develop and commercialize a series of second-generation oral antioxidant inflammation modulators (AIMs) with potential applications in cardiovascular disease, neurodegenerative disorders and immunology. Abbott and Reata, which signed a $450 million deal in September 2010 on Reata's first-generation AIM bardoxolone methyl (now in Phase III trials), will share costs and profits on the preclinical AIMs in all newly licensed indications, except for selected autoimmune diseases such as rheumatoid arthritis. The first clinical study of an agent covered by the latest deal is expected to begin later this year.

Oxidative stress and inflammation are intimately interrelated and are common manifestations and mediators of many chronic disorders. Although strategies aimed at reducing oxidative stress to alleviate or prevent various diseases have been widely investigated, success so far has been elusive. "The past 40 years have been frustrating, as supplementation with direct antioxidants has failed, as has administration of specific individual antioxidant enzymes, or their mimetics, as drugs," notes Professor Joe McCord, University of Colorado, USA.

Reata has pursued an alternative approach for reducing oxidative stress. Its AIMs act by potently activating NFE2-related factor 2 (NRF2), a ubiquitously expressed transcription factor that controls the expression of various genes involved in the oxidative stress response. "While NRF2 was originally thought to be primarily a regulator of the antioxidant enzymes, it is now known to participate in the regulation of many genes responsible for other stress-related processes such as inflammation and fibrosis, neurodegeneration and addictive behaviour, cancer chemoprevention, metastasis and drug resistance," explains McCord. So, the activation of NRF2 may be beneficial in numerous disorders. "Because NRF2 production appears to decline with ageing, while free radical production increases, the regulation of NRF2 may be key to the management of the so-called 'diseases of ageing', which include cardiovascular disease, neurodegenerative diseases, cancer, type 2 diabetes and chronic failure of the kidneys and heart," adds McCord.

Indeed, Reata's bardoxolone methyl is showing promise in the treatment of advanced chronic kidney disease (CKD), a common disorder that is caused by conditions including high blood pressure and diabetes and for which current treatment options are limited. "Despite full adherence to the current standards of care, patients with severe CKD still progress to end-stage renal disease (ESRD) and, especially in patients with diabetes, suffer increased risk for cardiovascular death and events," notes Professor David Warnock, University of Alabama at Birmingham, USA, and Senior Medical Advisor and Consultant to Reata.

Bardoxolone methyl has successfully completed Phase II trials, including a study known as BEAM in which 227 patients with moderate to severe CKD and type 2 diabetes who were treated for 52 weeks with the AIM experienced a sustained improvement in kidney function (*N. Engl. J. Med.* **365**, 327–336; 2011). Importantly, side effects were generally mild. However, "while the overall safety profile is encouraging at present, there is always the possibility that some unanticipated untoward effect may become evident when a large population of patients are exposed to this new class of agents", cautions Warnock. The Phase III BEACON trial of bardoxolone methyl in patients with stage 4 CKD and type 2 diabetes is currently underway. "We should know within the next 2 years whether or not this new treatment approach makes an important contribution to reducing the occurrence of ESRD or cardiovascular death in this high-risk group of patients," says Warnock.

The second-generation AIMs are anticipated to have several applications. However, as McCord notes: "It is unlikely that any NRF2-activating drug will achieve a 'one size fits all' status. A family of NRF2-activating drugs and dietary supplements will probably emerge to deal with the therapeutic and regulatory challenges of acute versus chronic versus preventative applications."

Sarah Crunkhorn