Defusing the ticking bomb of aortic aneurysm

An aortic aneurysm is a permanent dilation of the main blood vessel leaving the heart, creating a bulge which has the potential to rupture suddenly with deadly consequences. These aneurysms can occur at different locations, either above or below the diaphragm, and are thus termed either thoracic aortic aneurysms (TAA) or abdominal aortic aneurysms (AAA), respectively.

WHEN A BULGE BECOMES A BOMB
Although it is unclear why aneurysms develop, there are several risk factors associated with this condition, including smoking and advanced age. They are also more prevalent in men than women. Since the disease has no medical therapy, a diagnosis can be devastating.

Early research led by Dr Daugherty and Dr Cassis investigated the role of angiotensin II, a signalling molecule, in the development of arterial plaques. Dr Daugherty’s interest in aneurysms however, was sparked by the serendipitous discovery that AAAs were formed in a mouse model developed by his team to determine the effects of increased blood pressure on atherosclerosis. The model was developed to exhibit excessive blood lipid content (fat in the form of cholesterol). Early experiments showed that angiotensin II promoted plaque formation without increases in other measures, such as blood pressure. More interestingly, it significantly increased the occurrence of aortic aneurysms.

BLOWING THE FIELD WIDE OPEN
This discovery was further strengthened by the absence of any such effects in the control mice that do not express hyperlipidaemia (high levels of lipids in the blood). This led Dr Daugherty to conclude that high angiotensin II levels combined with hyperlipidaemia have “profound and rapid effects on vascular pathology”.

TAAs are the life-threatening manifestation of Marfan’s disease
This model has now been used by many labs to investigate the underlying causes of aortic aneurysm generally, leading to substantial progress in this area. The upper aorta, where TAA’s are located, is the subject of intense research interest due to the implications of hyperlipidaemia on Marfan syndrome—a genetic disorder of the connective tissue which leads to a collection of symptoms including elongated body shape, flexible joints and increased risk of aortic aneurysm, among others. One of Dr Daugherty’s colleagues and collaborators, Dr Mary Sheppard, has first-hand experience of this condition, so this research is all the more poignant for this connection.

IDENTIFYING THE DETONATOR
Progress was made on this aspect of aneurysm development whilst examining the effects of chemokine receptors on atherosclerosis and AAA. In the same hyperlipidaemic mouse model, with CCR2 (a chemokine receptor) knocked out, instances of AAA and atherosclerosis were diminished. The research team observed that mice with active CCR2 also developed TAA’s with markedly different pathological profiles when compared to AAA. Despite these differences, they also were diminished in CCR2-depleted mice thereby demonstrating a distinct role for chemokines in this vascular pathology. Dr Daugherty describes TAA’s as “the life-threatening manifestation of Marfan’s disease”, so progress on understanding the mechanisms underlying their formation is vital for the development of protective...
Above: Short term angiotensin II infusion promotes the presence of blood in the outer layers of the ascending aorta.

Left: Localization of aortic pathology in the ascending aorta during prolonged angiotensin II infusion

The highly contrasting pathologies between [these areas] are indicative of different mechanisms by which angiotensin II generates these diseases.

A primary motivation for my research is the hope that it will directly alleviate Marfan syndrome.

One class of drugs, currently used to treat hypertension (high blood pressure), shows promise as a treatment due to its blocking of the angiotensin II type 1 receptor. There is considerable debate among scientists in this field as to whether this is preferential to the alternative treatment which inhibits the formation of angiotensin II by blocking the angiotensin converting enzyme (ACE).

This effect is seen because there is also an inhibitory effect of angiotensin II via the type 2 receptor, which appears to be beneficial in reducing many of the type 1 receptor’s effects. Dr Daugherty and Dr Sheppard are actively pursuing this concept.

The identification of similar signalling pathways in the aortic wall of patients with other syndromes where aortic aneurysm is a major risk factor, suggests that any treatment which is successful in one area may have broad action across these conditions. It is also true that there are potential risks with such treatments that disrupt the normal signalling pathways in a non-tissue-specific manner, but for Drs Daugherty and Sheppard defusing this ticking bomb for those with Marfan syndrome and other conditions is of prime importance.

Many differences such as flow patterns, extracellular matrix fibres, oxygen and nutrient delivery, and cell types that form the outside scaffold of the aorta. Presumably the location specificity is a consequence of one or a conglomeration of these factors.

What are the implications for this in research and treatment?

Elucidation of the basis for the regional specificity of aneurysms may provide insight into a mechanism that is effective and well-tolerated. Many of the currently proposed mechanisms have the potential to lack specificity. For example, drugs that inhibit the proteolysis of extracellular matrix have been proposed to benefit aneurysms, but this class of drugs is known to have side effects. However, if a unique mechanism could be determined in the aneurysmal region, it may provide the opportunity to inhibit a unique mechanism of action or develop a focal delivery mechanism to reduce effects outside of the aneurysm.

What are next steps in tackling TAA in Marfan syndrome?

There are several ongoing clinical trials testing whether it is beneficial to administer drugs that inhibit the ability of angiotensin II to stimulate one of its major receptors. The currently completed trials have provided a mixed message. However, they have all used a drug that is suboptimal to inhibit the action of angiotensin II. Some of the ongoing trials are using more effective drugs, and the outcome of these trials will be a major driver of the adoption of angiotensin receptor inhibition therapy, or illustrate the need to take another direction. At the moment, there is little consensus of an alternative mechanism.