The keynote address for the FRAME symposium was eloquently delivered by Professor Shervanthi Homer-Vanniasinkam. Professor Homer-Vanniasinkam, a consultant vascular surgeon and tissue engineer, reminded the audience that the major challenge faced by clinicians every single day is to find solutions to complex healthcare issues to suit a given patient. Often, the clinician has dwindling confidence in whether products which are deemed safe and effective according to animal studies, are, in fact, safe and effective for the patient at hand.

Many clinicians and scientists regard animal data with increasing scepticism, in the face of a growing body of evidence that even subtle differences between species can have profound clinical consequences. Many others continue to justify the need for animal models, on the basis that they are the best models of in vivo physiology that we currently have at our disposal and that they yield invaluable information during medicinal product development and beyond. In between these two diametrically opposed positions, Professor Homer-Vanniasinkam — like a growing number of clinicians and researchers — champions the search for models that can more-reliably capture the level of complexity of the human body.

Professor Homer-Vanniasinkam drew upon her own extensive expertise in the area of vascular medicine to illustrate why medical research must be revolutionised in this way. A summary of her lecture is presented below.

Human diseases don't develop overnight

Many human diseases have chronic timelines. Professor Homer-Vanniasinkam described a classic example of this — atherosclerosis, one of the most prevalent clinical problems in vascular medicine. Atherosclerosis is a chronic inflammatory condition that causes narrowing of the blood vessels. Fatty streaks, the earliest forms of atherosclerotic lesions, are visible at birth, even though the clinical manifestations of vascular diseases depend on a variety of lifestyle, environmental, physiological and pathophysiological factors that can vary widely between individuals and generally arise in the fifth to sixth decades of life. Here lies the first of many limitations of animal models, since, on the whole, the most commonly-used models of atherosclerosis are rodent models. These animals are obviously much shorter-lived species than humans are, and therefore are ill-suited to capturing the chronic onset of the human disease. Indeed, despite years of development effort, these rodent models have not been able to capture the chronic pathophysiology of atherosclerosis. In humans, atherosclerosis can progress to a point where plaques deposit on vessel walls, which reduces their elasticity. If the plaques destabilise, fragments can break off and occlude the vessel lumen, thrombotic material is exposed, and this can go on to clot the blood, resulting in ischaemia. Clinically, this can culminate in myocardial infarction, brain ischaemia, stroke, cerebral vascular accident, or limb amputation. Most species simply do not have the propensity to develop atherosclerosis in the same organs and tissues as humans, often because key inflammatory mechanisms are absent. Forcing animals to eat high-cholesterol diets, or mechanically disrupting plaques, only gives rise to poor and unrepresentative models.

Other species differences, such as the fact that there are 3000-times fewer cells in a cross-sectional area of a mouse artery than in an equivalent human artery, or the fact that cholesterol and fats are distributed differently around the bodies of different species, appear to be wholly irreconcilable, regardless of the ingenuity of the development and use of the animal model. This means that therapies which are wholly effective in animal models are often, at best, only partially effective in patients. This is certainly the case for therapies directed against CD40, and this appears to relate to the lack of receptor redundancy in the test species, but not in humans. Ironically, the presence of receptor redundancy in mice, but not humans, explains why sulphonylurea reagents were not effective in mice, but can, and are, effective for the treatment of human diabetes.

The end result is that animal models often give rise to as many questions as they answer. This has resulted in the waste of a great deal of time and effort, not to mention animals, in the development of new treatments that have ultimately failed in the clinic.

Little and often helps the medicine go down

Another factor that might play a pivotal role in determining the activity of a drug in patients, is