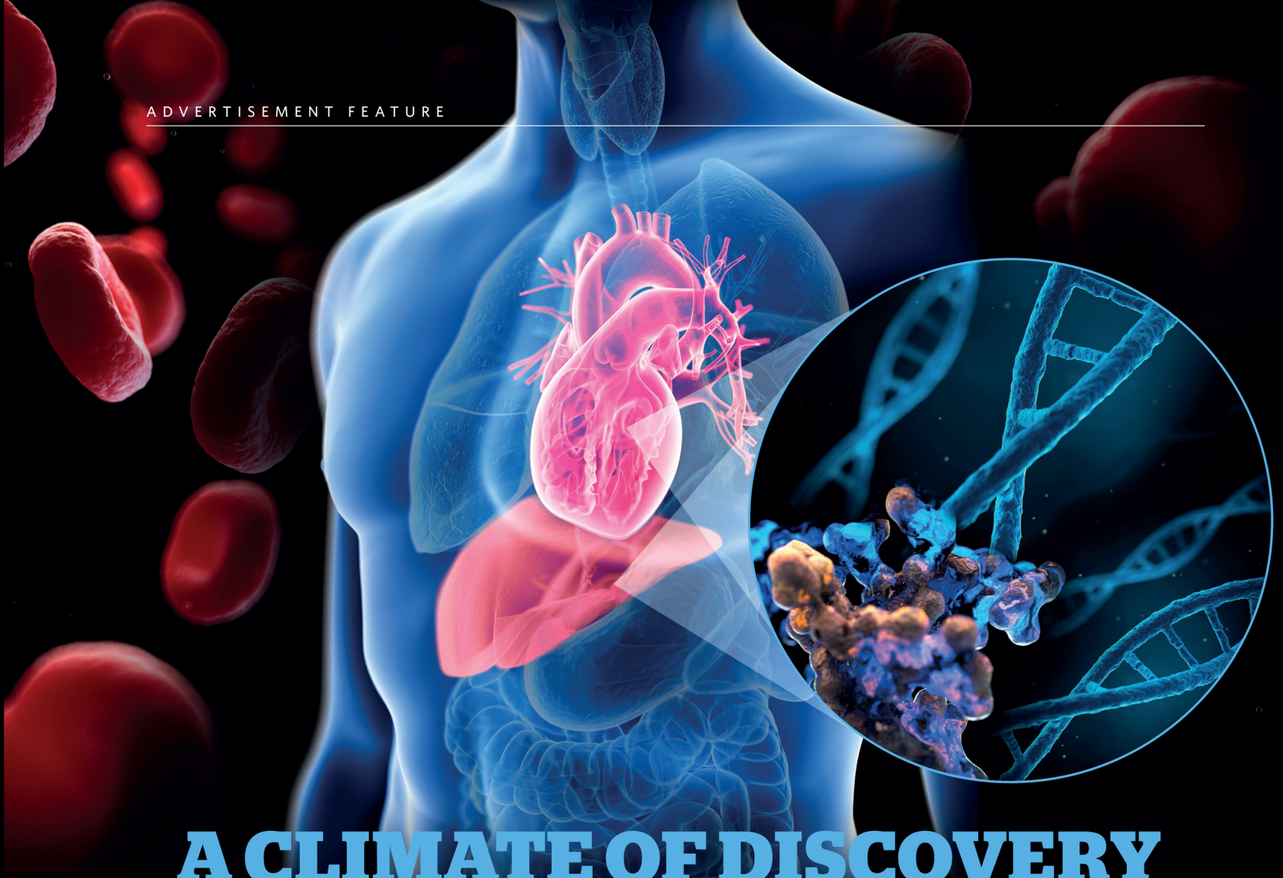


A CLIMATE OF DISCOVERY AT THE IMA

Affecting more than 25% of the global population, non-alcoholic fatty liver disease (NAFLD) is becoming a common chronic disorder. It may induce serious liver diseases like cirrhosis and cancer, as well as cardiovascular diseases and other types of tumours, creating significant clinical cost and social burden.

At IMA, researchers are unravelling mechanisms underlying NAFLD and its associated list of medical conditions, including cardiovascular diseases and reperfusion injury, shedding light on treatment strategies. Adoption of the latest technologies and novel animal models will break new ground for other human disease research.

Decoding the mystery of NAFLD

Despite the substantial volume of research on NAFLD in the last 20 years, some key questions remain, including the mechanisms underlying the pathogenesis of NAFLD, and its progression to non-alcoholic steatohepatitis (NASH), a more aggressive form of NAFLD, the strategies of disease modelling for NASH, and the fundamental mechanisms of liver fibrosis. No effective anti-NASH drugs are available for clinical use.

To tackle these key questions, IMA researchers have been working on deciphering NAFLD in the last decade. One IMA team identified genes (*TNFAIP3* and *CFLAR*) that can work directly on a key target for the treatment of NASH (*ASK1*), and suppress its progression. More encouragingly, they developed a peptide that inhibits *ASK1* activation, which has shown to be effective in blocking the onset and progression of NASH in mouse and monkey models.

Another team working on the role of protein degradation in NASH progression found CYLD, a kinase protein essential in inflammatory signalling pathways, which suppresses the excessive action of *TAK1*. In a study on the role in NASH of lysosome system, an intracellular waste disposal system, IMA researchers also identified a previously unknown regulator that inhibits NASH progression by promoting lysosomal degradation. All these results help deepen our understanding of the pathogenesis of NASH, and potentially provide new treatment strategies.

In the last five years, IMA has successfully transitioned from the traditional research model to one that integrates clinical big data, systems biology analyses, and multilevel animal models into the study of NASH and its drug discovery. Applying this comprehensive approach, an IMA team has developed a new compound for NASH therapy, which inhibits ACC1 activity without raising the lipid level, nor affecting physiological liver functions, as shown in monkey models.

It is promising for clinical use as a novel drug for NASH. Lead molecules that treat NASH by inhibiting over-activation of target molecules, such as *ASK1* and *TAK1*, were also developed, all showing successful results on monkeys.

To further clarify the cause and development of NAFLD, IMA launched a multi-omics project involving models and samples ranging from rodents and monkeys to humans. It is expected to lead to more discoveries about NAFLD pathogenesis, and new concepts for developing treatment targets and approaches for NASH.

Shedding light on the crucial link to NAFLD-induced cardiovascular diseases

Many clinical studies have demonstrated the link between NAFLD and the genesis and progression of cardiovascular diseases (CVDs), a major public health issue. With incidence rates of these diseases on the rise in China, IMA teams, based on their studies of NAFLD, have been focusing on heart failure and vascular injury, which are related to NAFLD, for a systematic and in-depth study to clarify how natural immune signalling networks function under CVDs.

The team has identified multiple key molecular targets regulating the pathogenesis of cardiovascular diseases. Importantly, they demonstrated that these traditional innate immune regulators generally regulate CVD progression via an immune-independent pathway.

Clarity on the relationship between innate immune and cardiovascular systems has been provided, expanding understanding in this field.

Reducing surgical injuries of the liver and other organs

When NASH has developed into liver cirrhosis or cancer, liver resection or transplantation becomes the only treatment option. Success in this operation may be hampered by ischemia-reperfusion (I/R) injury.

A common outcome in organ surgery is tissue damage caused by the re-establishment of blood supply after a period of ischemia, or oxygen depletio. This may lead to high incidences of organ failure or sudden death.

Reducing these outcomes has been a big challenge for clinicians, given the lack of understanding about its mechanisms.

Dedicated to solving multi-organ ischemia-reperfusion injury (I/R), an IMA team has revealed the mechanism of a series of innate immune regulatory network molecules. Based on multidisciplinary studies of animal models and clinical samples, they proposed a new concept, which, unlike the traditional theory that sees inflammation and cell death as the determinant of hepatic I/R injury, emphasizes early reprogramming of lipid metabolism as the primary contributor, paving a new way for hepatic I/R therapy.

Harnessing multi-omics technologies, particularly, single-cell omics, another IMA team revealed the rapid dynamic process of organ I/R injury. Their cutting-edge technology has been used to unravel the fundamental pathway and treatment targets for myocardial and cerebral I/R injuries. Studies on the innate immune network checkpoints have shed light on potential treatments of I/R injuries.

Led by IMA director, Hongliang Li, these studies have driven the development of five lead compounds for hepatic and myocardial I/R injuries. New drugs are under development for multi-organ I/R injuries, with strong prospects for solving this clinical challenge.

Innovation on disease modelling

Central to the success of studies on the causes of human diseases is the establishment of appropriate animal models that reflect the pathophysiology of these diseases.

Applying cutting-edge technologies, IMA has developed and preserved more than 3,000 strains of gene-edited mice and rats.

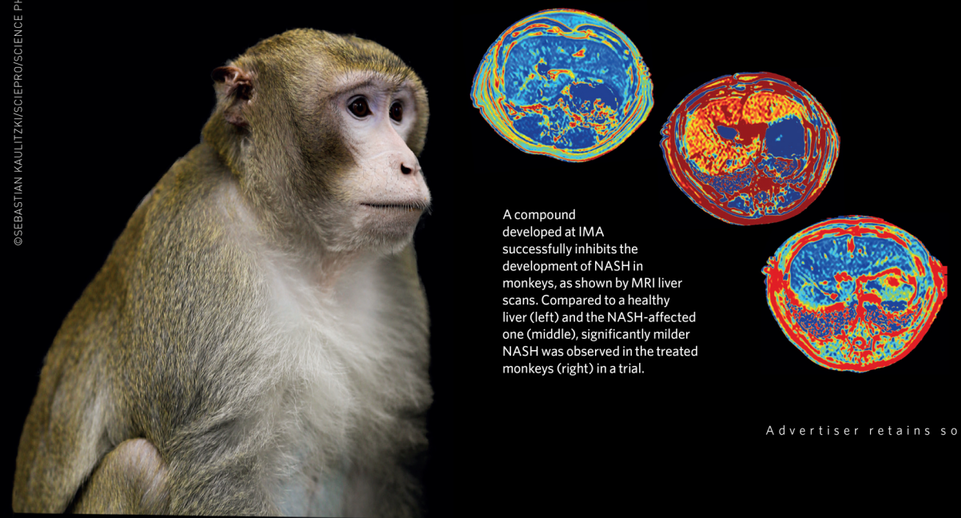
Seeing the need for large animal models to hasten the development of therapeutic strategies for cardiometabolic diseases, IMA has established a systematic platform for gene-editing projects on larger animals, such as monkeys and pigs. It has also established a complete evaluation system based on pathophysiological indices, ensuring that all their animal models closely mimic clinical characteristics of humans.

IMA can construct 40-plus human disease models, covering NASH, myocardial infarction, I/R injury, among others. Its work has contributed to basic and translational research from hundreds of laboratories at Wuhan University and other collaborating universities. It has trained nearly 10,000 professionals on model animals so far, while providing animal model resources and services to more than 1,000 domestic and international research labs.

The IMA also contributed to vaccine development for the SARS outbreak in 2003.

IMA's approach, which combines an advanced research system with the latest gene modification technologies, ensures its leading position in disease modelling.

As a provider of diverse animal model resources for the research community, IMA promotes a conducive environment for the development of animal models, and advancing studies on human diseases. ■



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A compound developed at IMA successfully inhibits the development of NASH in monkeys, as shown by MRI liver scans. Compared to a healthy liver (left) and the NASH-affected one (middle), significantly milder NASH was observed in the treated monkeys (right) in a trial.

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