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Fatty liver disease pandemic needs 'gold standard' human-relevant research

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A new study by scientists from the Vrije Universiteit Brussel calls for a new gold standard in research to treat non-alcoholic steatohepatitis (NASH), an obesity-linked chronic liver disease impacting millions of people of all ages worldwide, which can progress to liver cancer if untreated. The study, published today in *Pharmacological Research*, proposes a human-specific roadmap to better understand the biological mechanisms behind NASH, a crucial missing link in the effort to develop effective and urgently needed treatments for the disease.

Dr. Robim Rodrigues says, "In vitro models that reflect population diversity and specific mechanisms of the disease are already valuable tools today. Modern techniques, including transcriptomics, proteomics, and metabolomics, are rapidly becoming more reliable and may therefore provide insights into the mechanistic background of NASH."

Dr. Rodrigues explains that several drugs in development for NASH have been tested using in vitro models, clearly indicating the value of these systems in NASH R&D. He is optimistic that further development of predictive, human-based tools will provide a more cost-effective and reliable methodology for much-needed drug development for NASH.

Although the causes of NASH are well known, decades of animal research and different approaches to create animal models (dietary modification, chemical injury and gene manipulation) have largely failed to reveal the underlying disease mechanisms, and recapitulate at most a handful of features of the human condition. Difficulties translating data

from animal models to humans are well known; National Institutes of Health (NIH) Director Francis Collins stated that over 95 percent of new drugs that pass animal testing fail to achieve any clinical efficacy when trialled in people or worse, present with life-threatening side-effects. This was seen with Vioxx and other COX2-inhibitors (used as powerful anti-inflammatory drugs), fialuridine (used to treat hepatitis B), bitopertin (for treating patients with Schizophrenia), or darapladib (for atherosclerosis), to name a few among many.

Given the obesity pandemic, and the fact that NASH is caused by fat accumulation in the liver, the incidence of the disease is on the rise. Coupled with the absence of any effective treatments for NASH, there is a growing global recognition of this "silent epidemic," culminating in the first International NASH Day in June of this year. Clearly, it is time to dedicate more funding for human-relevant in vitro and systems biology tools described in this paper, in order to enable better understanding of the mechanism of NASH, identifying drug targets, and ultimately developing new drugs.

More information: Joost Boeckmans et al, Human-based systems: Mechanistic NASH modelling just around the corner?, *Pharmacological Research* (2018). DOI: 10.1016/j.phrs.2018.06.029

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