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April 22-25, 2019 | Boston, MA, USA

3rd Annual NASH Summit 2019

An Interview with NASH Summit Speaker:

Resat Cinar
Co-Chair NIH Fibrosis Scientific Interest Group
National Institutes of Health

Q. What is the biggest challenge currently faced to develop effective therapies in NASH?

Resat: "NASH is a complex and multi-factorial disease. For multifactorial chronic diseases, such as NASH, the conventional pharmacological approach based on the **"one-disease/one-target/one-drug" paradigm limits therapeutic efficacy.** This is an important challenge. Therapeutic efficacy could be improved by simultaneously hitting multiple therapeutic targets. There are ongoing efforts in both preclinical and clinical research for implementing multi-targeted therapies for NASH."

Q. Why is polypharmacology a viable drug development strategy in NASH?

Resat: "For multi-targeted therapies, you could have two options, either combination therapy or poly-pharmacology, the latter involving a single drug that engages two or more therapeutic targets. Combination therapy is a commonly used and straightforward approach, as long as there are approved drugs with proven safety. However, there are some drawbacks for combination therapy.
First, liver function is compromised in NASH. Considering the role of the liver in drug metabolism, one will likely face issues of drug-drug interactions and differences in pharmacokinetics when using different chemical entities. Second, experimental and systems biology approaches could uncover promising targets controlling distinct signalling pathways, which could be simultaneously engaged by rationally designed chemical compounds. However, dealing with multiple new chemical entities for combination therapy may complicate the design of clinical trials due to the need to meet regulatory requirements for efficacy and safety.
These issues related to combination therapy could be mitigated by a polypharmacology approach, that is the development of a single drug that has more than one therapeutic target. Therefore, polypharmacology is a viable and emerging strategy for developing effective NASH therapies. I think I would use "**killing many birds with one stone**' idiom for describing Polypharmacology."

Q. Why does targeting peripheral cannabinoid 1 receptors hold potential?

Resat: "NASH is a fibrotic disease that can develop on diverse backgrounds. So, an ideal therapeutic target for NASH should not only engage the fibrotic process itself, but also mitigate the underlying predisposing condition. There is both preclinical and clinical evidence to indicate that increased CB1R activity contributes to the conditions that predispose to NASH and, conversely, CB1R antagonism mitigates these conditions. Unfortunately, the first generation CB1R antagonist, rimonabant, had to be withdrawn from the market due to unwanted neuropsychiatric side-effects. In recent years, second generation CB1R antagonists with limited brain penetrance showed promising preclinical efficacy for NASH-related pathologies without eliciting neurobehavioral side-effects. Furthermore, dual-target peripheral CB1R antagonists as third generation compounds provided superior efficacy in preclinical models of fibrotic disorders, which will be the subject of my talk at the NASH Summit."

Q. What are you most looking forward to at the 3rd Annual NASH Summit?

Resat: "This will be my first attendance of the NASH summit. Looking at the program line-up, there is an abundance of exciting topics for discussion that cover a broad landscape of preclinical, translational and clinical challenges and opportunities, and offer learning opportunities during exchanges with industrial peers. I think that will be quite interesting: an intellectual exchange involving parties with different perspectives. I'm looking forward to it."

Q. Your talk at the NASH summit in areas we've not addressed in the meeting before. What other exciting news can we expect to come out of your research in the near future?

Resat: "We are investigating the pathogenic role of the endocannabinoids/CB1R system in fibrotic disorders and exploring the therapeutic potential of dual-targeted therapies using hybrid compounds in multiple organ fibrosis. Recently, we showed anti-fibrotic efficacy in mouse models of lung fibrosis in addition to liver fibrosis. Our patented compound used in these studies has been licensed by two start-up companies for clinical development. Hopefully, in the not too distant future, we will be able to share other examples of dual-targeted therapies in multiple fibrotic disorders and we may also hear about first in human studies."

Thank you to Resat for taking the time to share this thoughts and perspectives with us.

Join him and 72 other NASH experts as they discuss how to accelerate NASH drug development pipelines at the 3rd NASH Summit Boston (April 22-25, 2019).
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