An Exclusive Interview With...

Mike Crackower
Head, Research & Development
Ventus Therapeutics

Dr. Crackower, Head of Research and Development at Ventus Therapeutics, has been leader in drug discovery for over 18 years, with deep expertise in the fields of respiratory, immunology and fibrotic disease drug discovery.

Prior to Ventus, Michael was an entrepreneur-in-residence at Versant Ventures where he played an instrumental role in the formation of Ventus. Michael has also held leadership positions at Celgene, Biogen and Merck & Co.

Michael holds a PhD in molecular and medical genetics from the University of Toronto.

Inflammasome Therapeutics Summit

Challenges & Opportunities of Inflammasome Targeted Drug Discovery

As Ventus is one of the most recent companies to enter the innate immune space, what drove you to enter this space?

Until recently, our understanding of the innate immune system far lagged our knowledge of the adaptive immune system. As such, much of the drug discovery efforts for inflammatory disease has focused on modulating the adaptive immune system. We now know that far from being a non-discriminative first defense that aims to neutralize pathogens and present antigens to the cells involved in acquired immunity, the innate immune system is discriminative, evolved and self-regulated, therefore offers many opportunities to develop drugs that target innate immune pathways .

Navigating the innate immune system's complexity and harnessing its power to fight disease has presented difficulty for conventional drug development approaches. Supported by our founding team of leading scientists who have made major contributions to the fields of structural biology and immunology. Ventus is uniquely enabled to solve the historical challenges by using our platform capabilities to develop first-in-class and best-in-class therapeutics that target innate immunity.

What do you see as the most compelling opportunities to create innovative medicines targeting the innate immune system?

The innate immune system is the body's first line of defense against invading pathogens. However, it also plays a critical role in responding to cell stress and cellular damage to maintain cell and tissue homeostasis. Because of these critical roles, innate immune pathways are tightly regulated. Dysregulation of these pathways have been implicated in numerous diseases.

- Mutations in numerous innate immune proteins the cause of many **genetic auto-inflammatory diseases**, highlighting the importance for tight regulation of these pathways and providing key clinical validation of these targets in human disease.
- In several **autoimmune diseases**, the importance of inflammasome and nucleic acid sensing pathways as key drivers of disease is supported by clinical validation of anti-IL-1b and the type I interferon therapies.
- Innate immunity plays a crucial role in many **neurodegenerative disease**, where accumulation of cellular stressors (e.g. amyloid or tau proteins) and tissue damage activate, often improperly, the innate immune pathways which orchestrates the downstream inflammatory sequalae and are drivers of disease progression.
- Also, in **cancer**, clinical results continue to establish the importance of the innate immune system and new data points to additional compelling targets.

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What have been some of the challenges for innate immune drug discovery?

The innate immune system's inflammasome and nucleic acid sensing pathways are comprised of many proteins that make compelling drug targets. However, many of these pathways have complex mechanisms of activation that require oligomerization of multimeric protein complexes. The mechanism of activation is often driven by large conformational changes in protein structure that are usually not governed by enzymatic functions that would be readily inhibited. Therefore, successful targeting of these activation mechanisms requires a deep knowledge of the complex structural changes that occur to rationally design targeting approaches.

Gaining the requisite understanding of protein structure and dynamics has been very challenging for this field. This challenge has, in large part, been driven by the inherent difficulty to express monomeric forms of these proteins as a necessary starting point for high resolution structural determination as well as target directed drug discovery efforts. Without this underlying molecular understanding of the targets, drug discovery efforts would be operating 'in the dark' without the ability to use all the tools for small molecule drug discovery.

How is Ventus overcoming these challenges of targeting the innate immune system?

Ventus has created a disruptive technology approach to overcome many of the barriers for drug discovery in the innate immune system. Our structural immunology platform is based on protein engineering capabilities with the necessary know-how to uniquely generate and express stable monomers of known targets, including the inflammasomes and nucleic acid sensing targets. With these proteins in hand we can implement direct biochemical and biophysical assays, that previously did not exist, to screen for target specific and diverse chemical matter

A second component of our immunology platform is the ability to employ diverse structural biology approaches to solve high resolution protein structures. Adding to our biological platform, we have also developed unique cutting-edge computational chemistry approaches that allow us to gain an exquisite understating of protein molecular dynamics and enable us to pursue structure-based drug design to optimize compounds with best in class and distinct pharmacological profiles. Therefore, conducting drug discovery with "the lights on."

Can you describe any exciting development that has emerged as a result of your unique approaches and capabilities?

Since the launch of Ventus in 2019, we have fully operationalized drug discovery efforts for three distinct pipeline programs. We recently declared that one of our pipeline programs is NLRP3. This program epitomizes the challenges associated with pursuing innate immune targets, as NLRP3 readily forms large oligomeric structures in vitro and this has prevented target-directed drug discovery approaches. To date, the small molecule inhibitors identified for this pathway have resulted from drug discovery efforts based on the limitations of phenotypic screening approaches. As a result, the diversity of chemical matter has been very limited and developing best-in-class molecules will likely be hampered by the inability to pursue novel molecules with structurally-enabled, rational drug development approaches.

At Ventus, we have used the disruptive technology in our unique platform to stably express monomeric forms of NLRP3. This has enabled us to pursue target directed drug discovery approaches and we have successfully identified many new series of small molecule inhibitors of NLRP3, that are, for the first time, completely distinct from known chemical matter. Importantly, through our structural biology capabilities and our advanced computational chemistry tools, we have been able to define the precise binding mode of the small molecules at an atomic resolution. This significant advancement has now enabled us to pursue best in class NLRP3 inhibitors using structurally-enabled drug discovery approaches.

Join Ventus Therapeutics at the **2nd Annual Inflammasome Therapeutics Summit** taking place virtually November 4-6, 2020. For more information, visit: **www.inflammasome-therapeutics.com**

VENTUS THERAPEUTICS

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Ventus Therapeutics is a biopharmaceutical company discovering and developing novel small molecule medicines that target the innate immune system to treat autoimmune diseases, inflammatory diseases and cancer. Our structural immunology platform offers unprecedented drug development insights in the innate immune system: proprietary protein engineering capabilities that elucidate innate immune mechanisms, and leading-edge rational and structure-based drug design tools. Ventus has an emerging pipeline of multiple drug programs addressing key targets in the innate immune system.

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