

C&EN's 2020 10 Start-Ups to Watch

Nothing stops these chemistry entrepreneurs from working toward a better future

by Melody M. Bomgardner

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Every year, C&EN highlights 10 start-ups developing potentially world-changing chemistry innovations. And while 2020 has felt unlike any other year, the drive of science-based entrepreneurs to bring technologies that benefit people, the environment, and the economy to market hasn't changed.

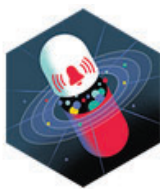
The start-ups profiled in this package illustrate the breadth of solutions that chemistry-based innovators can deliver. They've found new ways to discover drugs, produce sustainable food and materials, harness quantum computing, and even mimic the human nose.

Readers from around the world helped us find this year's crop of notable start-ups by sending in nominations via our website. We also keep track of all the great new companies we hear about in our day-to-day reporting. After much discussion and debate about more than 200 companies, we selected 10 on the basis of their revolutionary science and the importance of the problems they are working to solve.

It has not been easy for leaders of start-ups to navigate a world turned upside down by the novel coronavirus. The early days of a chemistry or biotech company are spent mainly in the lab, where space is often tight. Will Patrick, CEO of California-based Culture Biosciences, says his firm shuttered operations at the end of March and slowly reopened, with staggered shifts, in May.

Firms trying to grow quickly faced pauses in hiring staff and **difficulties** rounding up early-stage funding from investors. Culture Biosciences works with a number of biotech companies whose founders have told Patrick they worry about hitting their scientific milestones. "They're definitely stressed because they feel like they need to hit those goals in order to get additional funding, but they have to balance that with creating a safe working environment for employees," he says.

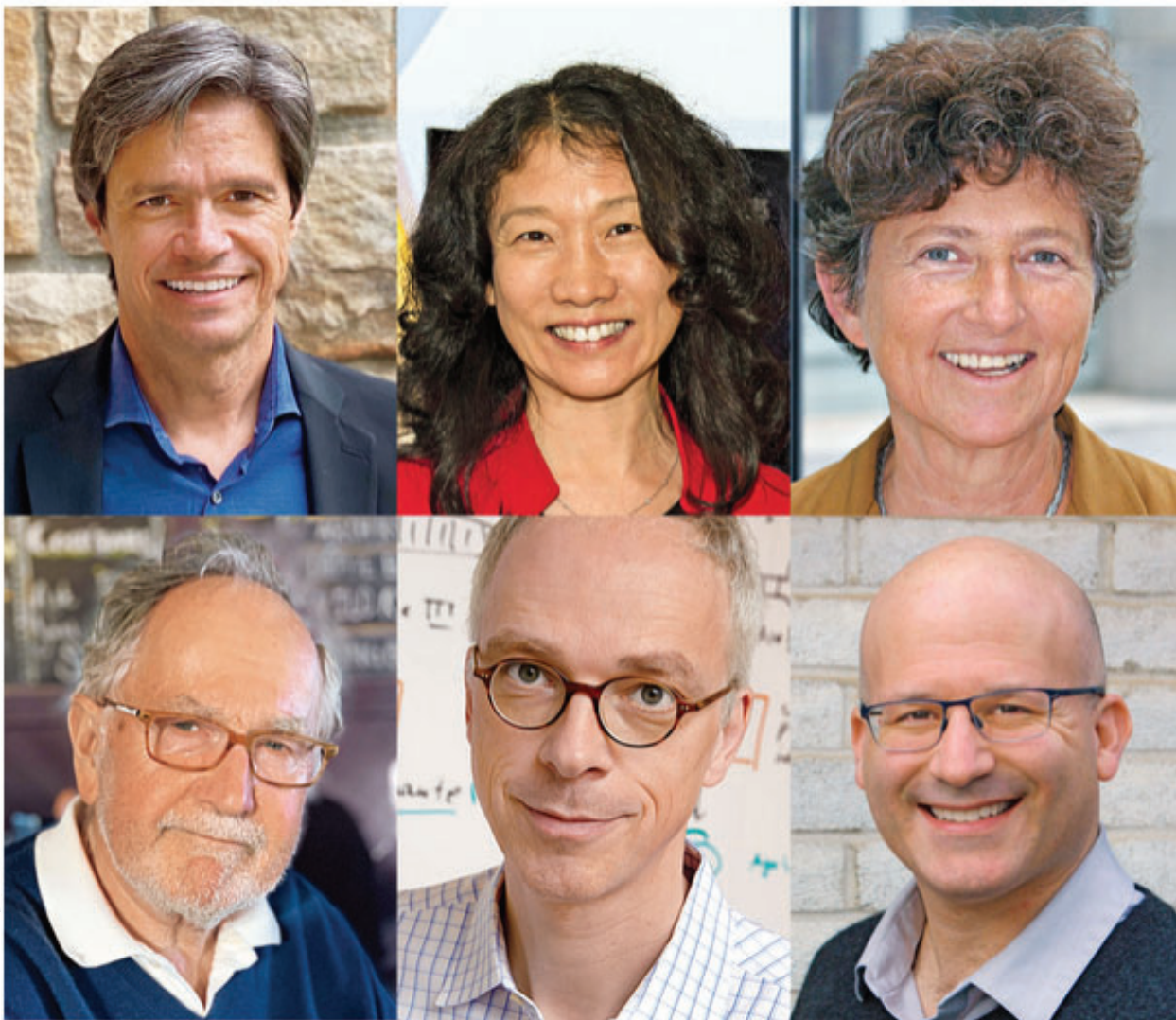
The year hasn't been only about stress and strife. Several companies in the group recently raised significant funding from investors, and all have made progress to market. If you know about a chemistry start-up with great news to share, nominate it for our 2021 feature at cenm.ag/startupnom.



VENTUS THERAPEUTICS

Structure-based drug discovery of inflammasomes and innate immune system proteins

by **Ryan Cross**



Credit: Ventus Therapeutics

Top row, from left: Ventus Therapeutics CEO Marcelo Bigal, cofounder Hao Wu, and cofounder Judy Lieberman.
Bottom row, from left: cofounder Richard Flavell, cofounder Thomas Tuschl, and Ventus head of R&D Michael Crackower

The innate immune system is our first line of defense against microbial invaders, and a protein called NLRP3 is one of its loudest alarms. When triggered by an intruder, NLRP3 proteins change shape and begin forming **a large structure called the inflammasome**, which in turn activates a flurry of molecules that beckon the immune system to send backup.

But it doesn't stop there. The inflammasome also initiates a cellular self-destruct sequence in which proteins called **gasdermins** kill the cell by poking holes in its membrane from the inside out.

Our bodies go to great lengths to protect us from infections. Maybe too great.

Such sensitive alarm systems can be a liability. Over the past decade, scientists have linked hyperactive NLRP3 inflammasomes to a dizzying list of diseases, including Alzheimer's disease, atherosclerosis, inflammatory bowel disease, nonalcoholic steatohepatitis (NASH), and Parkinson's disease.

AT A GLANCE

Launched: 2019

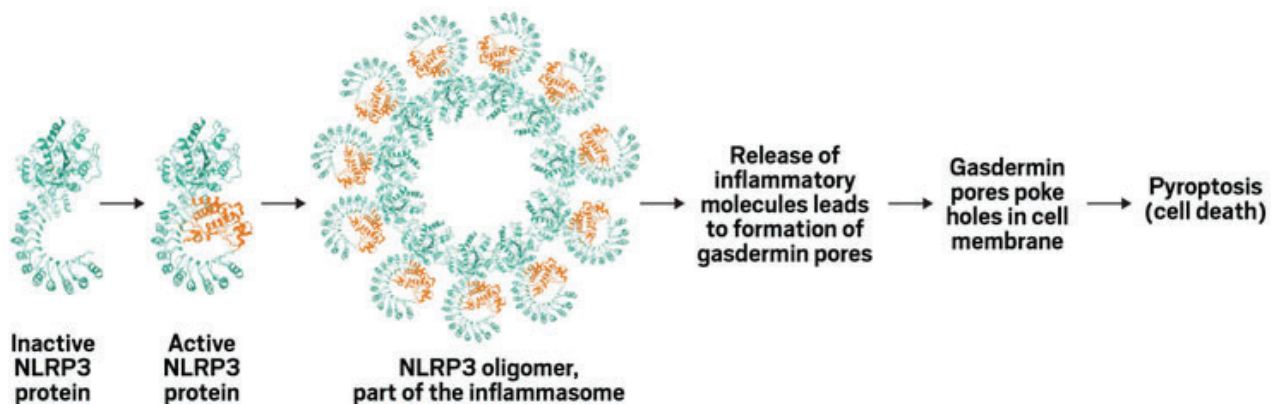
Headquarters: Montreal and Waltham, Massachusetts

Focus: Innate immune system drug discovery

Technology: Structural immunology

Founders: Richard Flavell, Judy Lieberman, Thomas Tuschl, Hao Wu, and Versant Ventures

Funding or notable partners: \$60 million in series A financing from Versant Ventures and GV



Credit: Adapted from Hao Wu/RCSB Protein Data Bank ID 6NPY/Yang H. Ku/C&EN

Ventus Therapeutics is designing small-molecule drug candidates that target proteins of the innate immune system, including NLRP3. When individual NLRP3 proteins are activated, they aggregate to form a wheel-like oligomer, which is part of the NLRP3 inflammasome. That inflammasome helps activate and release inflammatory molecules. It also causes the formation of other protein structures, called gasdermins, which poke holes in a cell and kill it. This self-destruction system is a last-ditch effort to rid a cell of microbial invaders. But improperly activated NLRP3 inflammasomes can also lead to a bevy of diseases. Ventus is designing compounds to stop inflammasome activation.

With a record like that, it's no surprise that NLRP3 is moving up on pharma's most wanted list. In the past 2 years, **Bristol Myers Squibb**, **Genentech**, **Novartis**, and **Roche** have all acquired start-ups developing small molecules that take aim at NLRP3. And in May, a new start-up called **Ventus Therapeutics** formally debuted with **\$60 million** and a fresh strategy for targeting NLRP3.

It's actually the second start-up backed by Versant Ventures to target NLRP3. In 2018, Genentech acquired the Versant-funded Jecure Therapeutics, which was developing small-molecule NLRP3 inhibitors to treat NASH. Jerel Davis, a managing director at Versant, thought there was plenty of room for another inflammasome company, and Michael Crackower, who is now head of R&D at Ventus, was charged with figuring out how to make the sequel even better than the original.

The new firm would take a broader look at innate immunity by investigating NLRP3, other inflammasome proteins, and different innate immune system alarm bells, such as **the cGAS-STING pathway**, which detects viral and cancer DNA. But Crackower wanted to set Ventus apart not just in its breadth of targets and potential disease areas but also in how it discovered its drug candidates in the first place.

“**V**entus is doing 'drug discovery with the lights on.'”

— **Marcelo Bigal**, CEO, Ventus Therapeutics

Jecure had relied on phenotypic screens in which researchers added different compounds to cells in hopes of finding one that quieted NLRP3's blaring alarms. But that strategy left scientists wondering what the molecules were doing to NLRP3 or if they were even targeting the protein directly. “They were really limited in how they could tackle these targets,” Crackower says.

Crackower wanted to take a more direct approach. The problem is NLRP3's natural propensity to shift its shape and clump together. That feature is key for quickly forming active inflammasomes in sick cells, but it causes headaches for researchers trying to study the proteins in a test tube. Those clumps make it impossible for scientists to screen drugs on the protein itself or capture a clean picture of its molecular structure.

Hao Wu's lab at Harvard Medical School found a solution through protein engineering. By changing amino acids at key interfaces, forming chimeric proteins, and purifying proteins in just the right way, her group developed methods to effectively paralyze the shape of NLRP3, gasdermin proteins, and other key players in the innate immune system and solve their structures.

Wu realized that her lab's techniques could help drug companies design compounds that specifically target the structure of NLRP3, as well as related proteins. She founded a small company called Smoc Therapeutics to explore the idea. Last year, Ventus acquired Smoc's assets and recruited Wu and several other innate immune system experts to be the scientific cofounders of Ventus.

Ventus CEO Marcelo Bigal thinks the firm's structure-based drug discovery approach to NLRP3 and other innate immune system targets will give it an advantage over more advanced and well-funded competitors. Other companies discovered NLRP3 inhibitors by “trial and error,” he says. Ventus is doing “drug discovery with the lights on.”

10 START-UPS TO WATCH CONTRIBUTORS

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