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TARGETS & MECHANISMS

Biotechs explore the next generation of inflammasome targets, with caution

BY LAUREN MARTZ, ASSOCIATE EDITOR

As the NLRP3 field gains momentum, drawing VC and pharma interest for the role the target plays in diseases ranging from NASH to neurodegeneration, biotechs are beginning to eye the next crop of inflammasome targets.

At least two companies — IFM Therapeutics LLC and ZyVersa Therapeutics Inc. — are diving in with preclinical programs against novel inflammasome targets, while others are waiting to see the first clinical data from NLRP3 programs before committing to their choice of target.

Inflammasome complexes have come to the fore as attractive targets because they sit upstream of cytokines, meaning interfering with them can cut off inflammation at the source. Because there are several types of inflammasomes that are dysregulated in different diseases, their modulation could lead to fewer side effects than general immunosuppressants.

Each type of inflammasome complex is made up of a distinct sensor molecule, which detects pathogenic molecules, and the conserved adaptor molecule ASC which work together to activate caspase-1 and trigger inflammatory signaling cascades.

NLRP3 was the first inflammasome sensor discovered and has the largest body of preclinical research behind it (see "NLRP3 Early and Often").

In the last four years, at least four biotechs have launched to develop therapies that target NLRP3, and at least three pharmas have acquired biotechs with NLRP3 programs (see Sidebar: "NLRP3 Pharma Deals").

"The thing that makes this target, and this class of targets, so unusual at the moment is the broad association with so many diseases. This isn't just autoimmune conditions. It is linked to everything from gout to Alzheimer's disease, and it's a pretty unusual target in that sense. That's what makes this stand out," said Alexander Pasteur, partner at F-Prime Capital, which has invested in inflammasome company NodThera Ltd.

Beyond NLRP3, there are at least 23 other NLR family members, many of which form inflammasomes and represent opportunities

for target discovery, while some inflammasomes contain non-NLR sensor molecules. Each of these sensors detects different pathogenic molecules and triggers a distinct inflammatory cascade, and the number of academic studies linking newly identified sensor molecules to various disease states is growing.

In addition, some groups are beginning to target ASC or other proteins that get recruited to the complex.

It isn't clear which the nascent targets can be selectively modulated, or which are involved in the most commercially viable indications, but several companies and academic groups are beginning to sort out those details.

Sensing selectivity

Given the high interest in NLRP3, studying other inflammasome sensor molecules is a logical next step.

"When we say 'inflammasome,' most people think NLRP3, the canonical IL-1-inducing inflammasome. But, there are other NLRPs, NLRCs, NLRBs and As, and others, and what's interesting about a number of them is that there are gain and loss of function mutations that tie them to different diseases," said Gary Glick, co-founder and CEO of of IFM.

For example, the literature suggests NLRP1 and NLRP2 are tied to autoimmunity and fibrosis; NLRP12 is involved in arthritis; NOD2 may play a role in Crohn's disease; NLRC4 is elevated in infantile enterococcus and may be involved in non-alcoholic steatohepatitis (NASH), inflammatory bowel disease (IBD) and multiple sclerosis (MS); and NLRP7 and other family members are linked to rare diseases.

IFM has discovery programs against inflammasome sensor molecules NLRP1 and AIM2; development timelines are not disclosed.

"NLRP1 is the second most studied inflammasome target, but there are some differences between the human and mouse protein, so it's not as straightforward to study as NLRP3, and that has thrown some folks off," said Glick.

He said that IFM has generated genetically modified animals expressing the human version of the target to get around the problem. The company is going after inflammation, fibrosis and neuroinflammation through its NLRP1 program.

IFM is taking a different approach with AIM2. Instead of inhibiting the protein to suppress inflammation, it is developing AIM2 activators to boost the inflammatory cascade.

IFM plans to launch a new subsidiary early in the fourth quarter that will focus on inflammasome targets including NLRP1, AIM2 and others that aren't yet disclosed.

Glick is aware of other undisclosed "quiet" companies working on some of the alternative sensor molecules.

Adapting to new targets

At least one other company, ZyVersa, is going after the adaptor molecule ASC.

NLRP3 pharma deals

At least three pharmas have acquired or partnered with NLRP3 companies in the last two years.

Most recently, in April, Novartis AG acquired the IFM Tre subsidiary of IFM Therapeutics LLC for $130 million upfront and up to $1.3 billion in milestones, gaining IFM's trio of NLRP3 antagonists in the deal. The most advanced candidate, IFM-2427, is in Phase I testing for an undisclosed inflammatory indication. Novartis said in a press release the compound is in development to treat conditions including gout, atherosclerosis and non-alcoholic steatohepatitis (NASH). The deal also included two preclinical NLRP3 antagonists: a gut-directed compound to treat IBD and a CNS-penetrant molecule to treat neurodegenerative diseases.

IFM Therapeutics LLC itself was created in 2017 as a spinout triggered by another acquisition involving NLRP3. Bristol-Myers Squibb Co. acquired IFM Therapeutics Inc. for $300 million up front and up to $1 billion in milestones for the first program, plus additional undisclosed milestones for subsequent products. BMS gained IFM's NLRP3 and STING agonists, and the remaining assets were spun out into the new LLC. The NLRP3 agonist, BMS-986299, is in Phase I testing for solid tumors.

The third acquisition happened last year, when Roche's Genentech Inc. unit bought Jecure Therapeutics Inc. for undisclosed terms, gaining preclinical small molecule NLRP3 inhibitors for inflammatory diseases including NASH.

— Lauren Martz

ZyVersa licensed an anti-ASC mAb, IC 100, from InflamaCORE LLC earlier this year. Financial terms were not disclosed.

Karen Cashmere, Zyversa's chief commercial officer, thinks targeting ASC will have a much more potent anti-inflammatory effect in a broader range of diseases than blocking individual sensor molecules.

"ASC polymerization is pivotal for activation and perpetuation of inflammation, which is responsible for prolonged damaging inflammation," whereas inflammasome sensor molecules "have a more limited role in stimulating the formation of the inflammasome," said Cashmere.

That's an important distinction, she said, because anti-inflammatory drugs are administered when there's already active inflammation. ASC may be a better bet for both stopping existing inflammation and preventing more from occurring.

She also argued that many inflammatory diseases are triggered by more than one inflammasome, so targeting ASC may be more effective than targeting any one sensor molecule.

The company has seen reduced T cells and other inflammatory cells in animal models of MS. It is considering several diseases involving

dysregulated ASC for its initial indication, including MS, NASH and diabetic kidney disease. ZyVersa CEO Stephen Glover expects the first ASC blocker to be in the clinic in 18-24 months.

However, other biotech CEOs think going after ASC means losing the key advantage of inflammasome targeting — the selectivity.

"If you block all of the inflammasomes, you do have the potential for a safety issue and there's a risk of not responding to infections," said Inflazome Ltd. CEO Matt Cooper.

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>
> ALEXANDER PASTEUR, F-PRIME CAPITAL

NodThera CSO Alan Watt agreed. "It's a double edged sword. The more anti-inflammatory you go, the more infection risk you get. A big advantage of NLRP3 is the selectivity you get because you're really only taking out the aberrant NLRP3 response, and maintaining the rest of the IL-1 response to fight infection."

Cashmere said that based on ZyVersa's current body of preclinical data, it isn't seeing complete immune suppression.

Other companies have attempted to drug caspase-1, but have struggled with efficacy. Most notably, Vertex Pharmaceuticals Inc. discontinued development of its caspase-1 inhibitor VX-765 in 2014 after disappointing Phase IIa efficacy results in epilepsy patients.

TWi Biotechnology Inc. is still developing a caspase-1 inhibitor for inflammatory diseases. The company's Caspase-1, IL-1β and SLC22A12 inhibitor AC-201 is in Phase II testing for several inflammatory conditions.

Hanging in the balance

Other companies are waiting to see how the NLRP3 story plays out in early clinical trials before pursuing new inflammasome targets.

Cooper and Watt both said NLRP3's clinical success will impact interest in other inflammasome targets, and neither of their companies has disclosed programs in alternative targets. NodThera is "watching the space," and Inflazome expects to disclose details on its programs and development plans next quarter.

"NLRP3's success will absolutely affect other inflammasome targets," said Cooper. "I expect other targets to get a lot more interest if there's good Phase II data."

The field will be watching for Phase I data from Novartis on IFM-2427, which is slated to read out next quarter, as well as early clinical data from NodThera, which plans to begin clinical testing of its lead NLRP3 inhibitor NT-0164 early next year. The company is interested in diseases ranging from NASH to neurodegeneration.

A Phase I trial of NLRP3 agonist BMS-986299 from Bristol-Myers Squibb Co. in cancer patients is expected to readout in 2021.

Glick also believes NLRP3 success will stimulate interest in other inflammasome targets, but thinks a failure won't necessarily kill interest because NLRP3 companies are going after notoriously difficult indications.

Novartis hasn't disclosed the inflammatory indication for its Phase I compound. However, NodThera and Jecure Therapeutics Inc. are both eyeing NASH for their lead indications, and Inflazome is developing its small molecule for Parkinson's disease (PD). Both indications are driven by highly complex, incompletely understood mechanisms and may not be the best proving grounds for the target class.

"If IFM-2427, which is in Phase I now, does spectacularly well in Phase IIa, it should catalyze more interest broadly in the inflammasome. If it fails, the impact will depend on why it failed," Glick said.

COMPANIES AND INSTITUTIONS MENTIONED

Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
IFM Therapeutics LLC, Boston, Mass.
Inflazome Ltd., Dublin, Ireland
Jecure Therapeutics Inc., San Diego, Calif.
NodThera Ltd., Little Chesterford, U.K.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
TWi Biotechnology Inc. (TPEx-E:6610), Taipei, Taiwan
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Boston, Mass.
Zyversa Therapeutics Inc., Weston, Fla.

TARGETS

AIM2 - Absent in melanoma 2
ASC (PYCARD) - PYD and CARD domain containing
CARD16 - Caspase recruitment domain family member 16
CARD18 - Caspase recruitment domain family member 18
Caspase-1 (CASP1)
IL-1β - Interleukin-1β
NLRC4 - NLR family CARD domain containing 4
NLRP1 (NALP1) - NLR family pyrin domain containing 1
NLRP2 (NALP2) - NLR family pyrin domain containing 2
NLRP3 (NALP3; CIAS1) - NLR family pyrin domain containing 3
NLRP7 (NALP7) - NLR family pyrin domain containing 7
NLRP12 (NALP12) - NLR family pyrin domain containing 12
NOD2 (CARD15) - Caspase recruitment domain family member 15
SLC22A12 (URAT1) - Solute carrier family 22 organic anion urate transporter member 12
STING (TMEM173) - Transmembrane protein 173

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