BIOCENTURY
5:24 PM, APR 11, 2019

BC INNOVATIONS | PRODUCT DEVELOPMENT

NLRP3 EARLY AND OFTEN

BY ALLISON JOHNSON, STAFF WRITER

Inflammasome inhibitors could offer a step change for a slew of inflammatory diseases and pharma is taking notice. Two acquisitions in six months show the first inflammasome target -- NLRP3 -- is gaining momentum, but the question is how fast drug developers can discern the best set of indications from the sea of possibilities.

As the myriad contributions of innate immunity to disease become increasingly apparent, the attraction of the inflammasome, and in particular NLPR3, its most well-characterized component, is its therapeutic versatility.

Inhibitors of NLRP3 offer one of the most compelling alternatives to antibodies against IL-1β and other cytokines, which until now have been the mainstay of anti-inflammatory drug development.

The inflammasome drives innate immunity in a variety of cell types, sitting atop a inflammatory cascade that triggers cytokine release and immune cell recruitment. Preclinical studies have tied it to indications that cytokine mAbs can't address, spanning metabolic disease, autoimmunity, neurology and oncology. NLRP3 inhibition is also expected to have safety advantages over targeting cytokines.

At least four biotechs with NLRP3 inhibitors have been founded in the last four years, and in 2018, they raised a collective $117 million in venture capital.

Pharmas have been quick to join in.

Within one year of launching with a $31 million series A round, IFM Tre Inc. was acquired by Novartis AG, based on preclinical data. In the deal, announced April 1, the IFM Therapeutics LLC subsidiary received $310 million up front and up to $1.3 billion in milestones, and the pharma inherited one program, IFM-2427, that started Phase I trials in March, and two others in preclinical development.

Jecure Therapeutics Inc. was acquired by Roche's Genentech Inc. unit, for its preclinical NLRP3 program in non-alcoholic steatohepatitis (NASH), less than two years after raising $20 million in a series A round. The start-up received an undisclosed, all-cash sum, though sole investor Versant Ventures told BioCentury at the time it received "venture-like returns."

The two other NLRP3 inhibitor companies, NodThera Ltd. and Inflazome Ltd., also have preclinical programs.

Despite being preclinical, IFM Tre had multiple suitors, said Novartis.

Prakash Raman, VP and global head of BD&L at Novartis Institutes for BioMedical Research, told BioCentury the "breadth of applicability for this mechanism" was a key driver of the dollar amount of the acquisition.

A major part of the strategy for all four players will be gaining evidence that can narrow the funnel and help prioritize indications where NLRP3 can have the biggest impact.

"The issue is going to be teasing apart if the inflammasome is a driver of disease or a consequence of something else."

Adam Keeney, NodThera

"The issue is going to be teasing apart if the inflammasome is a driver of disease or a consequence of something else," said NodThera President and CEO Adam Keeney.

Novartis has not disclosed a lead indication. The Phase I trial of IFM-2427 is in healthy volunteers and a readout is expected in 4Q19.

Inflazome may be next to enter the clinic, with trials in undisclosed indications slated to start this year. NodThera and Genentech have not disclosed clinical timelines.

THE INFLAMMASOME ADVANTAGE

Innate immune and other cells use NLRP3 and its family of NLR (nod-like receptors) proteins to respond to cell damage or infection. When activated, these sensors form an inflammasome, a multi-protein complex that induces an inflammatory cascade by triggering release of IL-1β or IL-18 (see Figure: “Inflammasome Activation”; Sidebar: “All in the Family”).

SIDEBAR: ALL IN THE FAMILY

So far, companies exploring the inflammasome as a therapeutic target have focused on one version of the signaling complex, the type containing NLRP3, but other NLR family members may begin to come out of the woodwork in coming years.

At least 20 other NLR proteins form unique inflammasome complexes in innate immune cells, leaving a lot of territory yet to explore.

"The inflammasome continues to be of interest to us," said Versant Ventures's Graham Walmsley. Versant was a founding investor Jecure Therapeutics Inc., which Roche's Genentech Inc. unit acquired in November, giving the pharma access to a preclinical pipeline of NLRP3 inhibitors.

IFM Therapeutics LLC, whose inflammasome subsidiary IFM Tre was acquired this month by Novartis AG, is exploring NLRP1, NLRP3, NLRP6, NLRP10 and NLRC4 for inflammatory diseases.

Like NLRP3, activating polymorphisms or mutations in NLRP1 and NLRC4 have been shown to drive multiple inflammatory conditions in humans, providing a rationale for targeting them and a place to start. For example, polymorphisms of NLRP1 are linked to with vitiligo-associated autoimmune diseases and NLRC4 mutations drive autoinflammation with infantile enterocolitis and familial cold autoinflammatory syndrome 4.

“In some ways NLRP1 may be more or equally as validated as NLRP3,” said IFM Therapeutics Co-founder and CEO Gary Glick. But he said a challenge from a drug development standpoint is that the translatability of preclinical mouse studies is limited, because the mouse version of NLRP1 is missing a crucial domain found in the human protein.

Atlas Venture’s Michael Gladstone told BioCentury, “My hope is that NLRP3 inhibition will have value in multiple diseases, but I think there could be different footprints for other family members and innate immune signaling molecules.” Atlas was a founding investor in IFM Therapeutics Inc. and IFM Tre. Gladstone is a board observer for IFM Therapeutics LLC and was a board observer for IFM Tre.

He said inflammasome proteins are just one family of sensors in innate immune cells. Other major classes include the toll-like receptors (TLRs) and the STING/cGAS pathway.

Therapies targeting TLR and STING have a headstart on NLR family members in drug development, but all three of the families could be manipulated in opposite directions for cancer or inflammatory disease. What's ultimately needed is a roadmap of the indications and cellular contexts in which manipulating one class, or a particular member of the class, is preferential over another, said Gladstone.

Gladstone thinks ongoing academic research will help paint this picture.

IFM’s latest spinout, IFM Due, houses STING antagonist programs. The STING programs in the clinic to date are agonists intended to treat cancer.

-- *Allison Johnson*

FIGURE: INFLAMMASOME ACTIVATION

NLRP3 is an intracellular innate immune sensor that is activated by signals containing damage-associated and pathogen-associated molecular patterns (DAMPs and PAMPs), as well as a variety of other internal stressors and environmental insults.

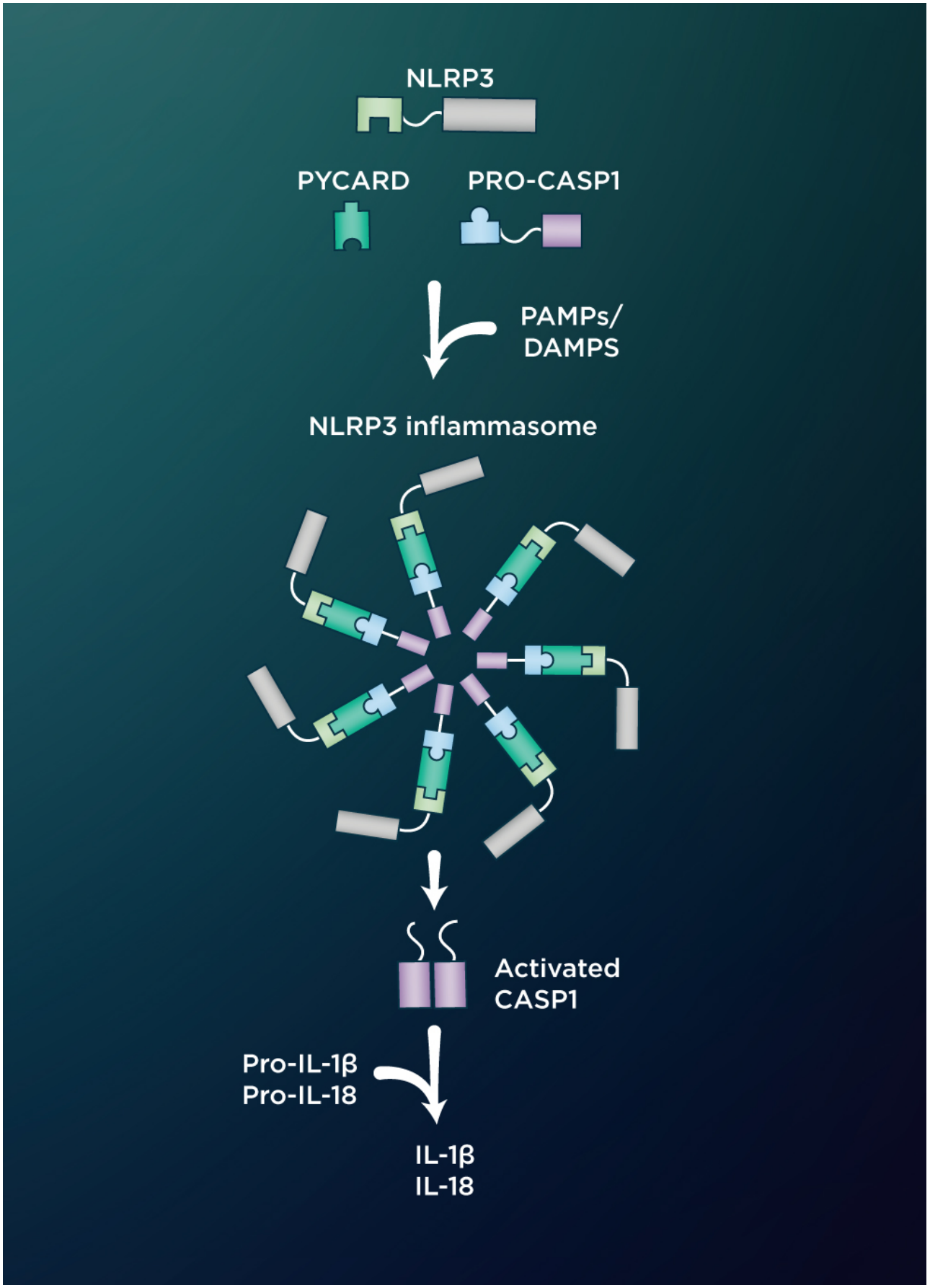
Activated NLRP3 recruits adaptor protein PYCARD and pro-CASP1, an inactive form of a caspase, to create an inflammasome complex.

Inflammasome formation triggers cleavage of pro-CASP1 into activated CASP1, which then leaves the complex and cleaves pro-IL-1β and pro-IL-18 into their active forms.

The cytokines induce an inflammatory cascade that recruits other immune cells to the site.

In the case of chronic, non-infectious inflammatory diseases such as non-alcoholic steatohepatitis (NASH) or Alzheimer's disease, the NLRP3 inflammasome is thought to be chronically activated by the presence of persistent triggers, such as pathological protein aggregates. This chronic activation could exacerbate symptoms and accelerate disease progression.

Targets: CASP1 - Caspase-1; IL-1β - Interleukin-1β; IL-18 - Interleukin-18; NLRP3 (NALP3; CIAS1) - NLR family pyrin domain containing 3; PYCARD (ASC) - PYD and CARD domain containing



A breakthrough for drug developers came with the creation of the tool compound MCC950 by Inflazome Co-founder and CSO Luke O'Neill. Inflazome and other groups showed the NLRP3 inhibitor to be effective in over 50 models of disease, according to Co-founder and CEO Matthew Cooper (see **"Specificity in the Inflammasome"**).

The results, described in a 2015 *Nature Medicine* **publication**, established the target as druggable.

"That paper showed there was a medicinal chemistry angle that could be taken as a lead and optimized," said NodThera President and CEO Adam Keeney.

Jecure, Inflazome and NodThera were founded the following year.

NLRP3 inhibitors have garnered the most attention in NASH and neurodegenerative diseases.

In NASH, an NLRP3 inhibitor may be able to address the inflammation that triggers fibrosis.

It could also be combined with other MOAs to attack the disease from multiple angles, a strategy many companies, including Novartis, think will be key (see **"New Partners for NASH"**).

In neurodegeneration, NLRP3 is a good fit for drug developers looking to move beyond the historical focus on protein aggregation to attacking the neuroinflammatory component of these diseases. A handful of studies have implicated NLRP3 in Alzheimer's Disease and Parkinson's Disease (see **"Baby Steps Beyond Beta Amyloid"**).

The even-broader pastures are in taking over from cytokine mAbs.

"They could open up additional indications where IL-1β mAbs may not provide strong efficacy signals, particularly those with activated NLRP3," said Versant's Graham Walmsley.

"There's 14 inflammasomes, and we're only blocking one so that if you get an infection the body can still respond."

Matthew Cooper, Inflazome

This is because inflammasomes do more than just induce IL-1β, so inhibiting NLRP3 may have a broader therapeutic impact than IL-1β blocking antibodies, he said.

NLRP3 inhibition could also score a safety win over IL-1β therapies. The idea is that blocking NLRP3-containing inflammasomes will reduce IL-1β activity and inflammation in diseased tissue, but will leave non-NLRP3 inflammasomes intact to produce IL-1β in response to infection.

"There's 14 inflammasomes, and we're only blocking one so that if you get an infection the body can still respond," Cooper said.

For example, Novartis's IL-1β mAb Ilaris canakinumab has been associated with increased risk of serious infection, according to its label.

PIPELINE IN A TARGET

Companies are banking on having the option to build an entire pipeline from a single target, given the breadth of possibilities.

"An opportunity here is to tailor make the chemistry for a particular disease," said Keeney.

IFM Therapeutics Co-founder and CEO Gary Glick told BioCentury, "Rather than taking one molecule and trying a formulation play for different routes of administration, we made three different molecules with very different product profiles, that were meant for different markets, with different price points, to address different commercial aspects."

In addition to IFM-2427, which is a peripherally restricted compound, Novartis gained an unnamed CNS-penetrant inhibitor, and a gut-targeted therapy.

"I think that was a really important strategic decision that [IFM] made in pursuing all of those simultaneously," Glick said.

NodThera and Inflazome are also developing peripheral and brain-penetrant NLRP3 inhibitors, and are looking to finely-tune PK/PD properties for different peripheral tissues.

Versant's Walmsley said Jecure was developing distinct NLRP3 inhibitors with differentiated pharmacologic properties prior to its acquisition.

NOVARTIS' MOVE BEYOND ILARIS

Novartis thinks it can springboard off its experience with Ilaris to develop its newly acquired NLRP3 inhibitors. And with Ilaris coming off patent in 2024, the NLRP3 programs could give the pharma a new growth driver in innate inflammation, including in areas where Ilaris has shown promise but is not approved.

"We wanted to identify opportunities in this space on the external front to see how we could take advantage of the results that we had in hand and also learn a new area of science," said Raman.

Novartis markets Ilaris to treat periodic fever syndromes including cryopyrin-associated periodic syndrome (CAPS), caused by NLRP3-activating mutations; systemic juvenile idiopathic arthritis; Still's disease; and gouty arthritis.

Raman said the 2017 readout of Novartis's Phase III CANTOS cardiovascular outcomes trial suggested a new use for an innate immune therapy.

The mid-dose level of Ilaris met the trial's primary endpoint of a reduced composite rate of nonfatal myocardial infarction (MI), nonfatal stroke and CV death vs. placebo (3.86 vs. 4.5 events per 100 person-years for placebo; HR=0.85, p=0.02075) using a threshold p-value of 0.02115.

"The real learning from CANTOS was that this was the first time that targeting the root cause of inflammation seemed to alleviate the cardiovascular events," said Raman.

In October, Novartis received a complete response letter from FDA for an sBLA for Ilaris for CV risk reduction.

Novartis had shown interest in NLRP3 before the IFM Tre acquisition. Novartis contributed to IFM Therapeutics Inc.'s $27 million series A round in 2016 and Novartis Venture Fund co-led Inflazome's $17 million series A in 2016 and participated in its €40 million ($46 million) series B round in November.

The first-in-class position of IFM Tre's lead candidate was an important factor in Novartis' decision, said Raman.

"Our goal is first to map out where we could first see a signal, and that could be based on our experience with Ilaris."

Prakash Raman, Novartis AG

He declined to specify which indications Novartis will explore first, but hinted the NLPR3 inhibitors might initially follow a similar path as Ilaris.

"Our goal is first to map out where we could first see a signal, and that could be based on our experience with Ilaris itself," said Raman.

"Once we've established that link and we start seeing data, the goal is to broadly develop it across multiple conditions," he added.

COMPANIES AND INSTITUTIONS MENTIONED

IFM Therapeutics LLC, Boston, Mass.
Inflazome Ltd., Dublin, Ireland
NodThera Ltd., Little Chesterford, U.K.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

TARGETS

NLRC4 - NLR family CARD domain containing 4
NLRP1 (NALP1) - NLR family pyrin domain containing 1
NLRP3 (NALP3; CIAS1) - NLR family pyrin domain containing 3
NLRP6 (NALP6) - NLR family pyrin domain containing 6
NLRP10 (NALP10) - NLR family pyrin domain containing 10
PD-1 (PDCD1; CD279)- Programmed cell death 1
STING (TMEM173) - Transmembrane protein 173