Novartis trial validates inflammasome as chronic disease driver

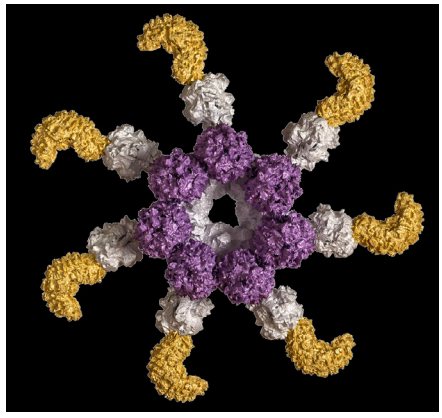
The dramatic finding that an antibody that inhibits interleukin-1β (IL-1β) can reduce the risk of heart attack and stroke is the first clinical evidence that tackling the inflammatory component of cardiovascular disease can benefit patients. Drug maker Novartis reported results from a mammoth trial testing Ilaris (canakinumab) in 10,061 patients with inflammatory atherosclerosis and a prior history of heart attack at the European Society of Cardiology Congress in Barcelona, Spain, on August 27. Whether the magnitude of the effect observed in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) is sufficient to influence clinical care is currently an open question. But the significance of these results extends beyond the immediate findings in cardiovascular disease. They provide the first concrete support for the general principle that tackling 'sterile'—or low-grade, persistent—inflammation may improve outcomes in a range of chronic diseases such as type 2 diabetes, gout, osteoarthritis, Parkinson's disease, Alzheimer's disease, liver fibrosis and cancer. Because IL-1β production depends on the inflammasome, a series of multi-protein complexes involved in an inflammatory form of programmed cell death known as pyroptosis, some drugmakers are looking to target it directly. In light of the CANTOS results, this area of biomedical research has taken on a new urgency.

Several biotech startups are already developing molecules that target the inflammasome, and they are focusing on the NOD-like receptor family pyrin-domain-containing protein 3 (NLRP3) inflammasome in particular. New York–based Bristol-Myers Squibb recently entered the field by acquiring one of these young companies, IFM Therapeutics (**Box 1**).

Interest in tackling chronic inflammation is booming, but Ilaris itself is not new. Novartis initially gained the go-ahead for the monoclonal antibody drug in 2009 for treating cryopyrin-associated periodic syndromes (CAPS), a group of rare inherited disorders characterized by high levels of auto-inflammation and excessive IL-1β production. Most CAPS cases arise from activating mutations in one of the genes encoding NLRP3 inflammasome components. Endogenous or environmental factors can also overactivate the inflammasome, with pathological consequences. "Fundamentally, the NLRP3 inflammasome is a crystallopathy detector. As we age, toxins build up in the body and form aggregates that cause chronic inflammation," says Matt Cooper, CEO and co-founder of Dublin-based Inflazome. Its triggers include uric acid crystals in the case of gout, cholesterol deposits in atherosclerosis, α-synuclein aggregation in Parkinson's disease and Lewy body dementia, β-amyloid deposition in Alzheimer's disease, and the accumulation of drusen (sub-retinal fatty deposits) in age-related macular degeneration.

But so far, most IL-1β inhibitors have gained approval only in niche indications (**Table 1**). In conditions that affect larger populations, drug developers have struggled to make headway. Six years ago, Novartis failed to convince a US Food and Drug Administration (FDA) advisory committee that the risk–benefit profile of canakinumab was favorable in gout. Around the same time, Berkeley, California–based Xoma and Suresnes, France–based Servier failed to achieve efficacy in a phase 2b trial of another IL-1β inhibitor, gevokizumab (Xoma 052), in type 2 diabetes. CANTOS succeeded by including only patients with clinically significant inflammation—defined as a minimum of 2 mg/L high-sensitivity C-reactive protein (hsCRP), an established biomarker for inflammation and cardiovascular disease risk. The trial established that canakinumab reduced the risk of a "major adverse cardiovascular event" (defined as a composite of non-fatal heart attack, non-fatal stroke and cardiovascular death) by 15%, compared with placebo, in patients who were already on cholesterol-lowering therapy, although it failed to provide a statistically significant survival benefit (*New Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1707914, 2017). The drug's cardiovascular effect was most pronounced in patients who also exhibited the sharpest drop in hsCRP. "The magnitude of effect of Ilaris is in proportion to my own expectation of the contribution of inflammation to atherosclerosis," says Jay Bradner, president of Novartis Institutes for Biomedical Research (NIBR). Basel, Switzerland–based Novartis plans to file for FDA approval in cardiovascular disease in the current quarter.

Intriguingly, canakinumab also had dose-dependent effects on lung cancer in the individuals treated in CANTOS. Compared with placebo, those on the highest dose had a 67% reduction in lung cancer incidence and a 77% reduction in death from lung cancer



IFM Therapeutics

Drugmakers are targeting the 'inflammasome' (pictured), a multi-protein complex involved in low-grade inflammation and programmed cell death.

Table 1 Approved drugs targeting IL-1

Company	Drug	Description	Approved indications	Sales 2016
Novartis	Ilaris	Human IgG1 antibody targeting IL-1β	CAPS; active systemic juvenile idiopathic arthritis; tumor-necrosis-factor-receptor-associated periodic syndrome; hyperimmunoglobulin; familial Mediterranean fever	$283 million
Regeneron Pharmaceuticals (Tarrytown, New York)	Arcalyst (rilonacept)	Fusion protein comprising ligand-binding domains of IL-1 receptor and IL-1 receptor accessory protein, linked to human IgG1 Fc fragment	CAPS	$15.3 million
Swedish Orphan Biovitrum (Stockholm)	Kineret (anakinra)	Recombinant version of the human IL-1 receptor antagonist	Rheumatoid arthritis; CAPS; neonatal onset multisystem inflammatory disease	SEK 1 billion ($125.9 million)

Sources: FDA, company websites, SEC filings

Box 1 BMS targets innate immune pathways through IFM acquisition

Bristol-Myers Squibb's acquisition of Boston-based IFM Therapeutics for $300 million upfront, plus about $2 billion more in potential milestones, represents a highly profitable and rapid exit for the company's investors. IFM, which was formed in 2015, had raised $27 million in first-round funding in June 2016. The scale of the deal, which followed a highly competitive bidding process, is evidence of the intense level of interest that is now being brought to bear on precision modulation of innate immune pathways. New York–based Bristol-Myers Squibb (BMS) is picking up two preclinical programs at IFM, based on the development of STING (stimulator of interferon genes) agonists and NLRP3 agonists. The goal of each is to improve the response rates of immuno-oncology drug regimens by marrying an innate response to the adaptive responses that are already activated by checkpoint inhibitors, such as BMS's CTLA4 inhibitor Yervoy (ipilimumab) or its PD-1 inhibitor Opdivo (nivolumab).

"Up until now we've only been working on the adaptive arm of the immune response with checkpoint inhibitors," says IFM co-founder and CEO Gary Glick. Their success, although spectacular in some cases, is still limited. "Checkpoint inhibitors only work for a small number of cancers, and even within those tumors, for a small number of patients," he says.

Glick envisages using an NLRP3 agonist as an acute or episodic therapy—its administration would not lead to the chronic inflammation associated with ongoing inflammasome activation. "No one else has an NLRP3 agonist program we're aware of," he says. BMS has also gained options on earlier-stage NRLP3 inflammasome antagonist programs in liver fibrosis, inflammatory bowel disease and gout—the IFM team will continue to develop these for now. IFM's agonists and antagonists are chemically distinct and interact with the NLRP3 inflammasome in different ways. The company's ability to drug the complex in both directions was helped by its expertise in inflammasome biology and structural biology, as well as by some luck, Glick says. Both approaches are useful for further probing its function. "Being able to turn something on and being able to turn something off is remarkably helpful."

(*The Lancet* http://dx.doi.org/10.1016/S0140-6736(17)32247-X, 2017). The effect "is very compelling and is the opposite of a chance finding," Bradner says. Novartis will need to confirm the result in a prospective trial before it can seek approval in that indication as well. Until it does so, some will remain skeptical. "I don't think this drug prevents lung cancer," says Charles Rudin, chief of the thoracic oncology service at Memorial Sloan Kettering Cancer Center in New York. "It may impact the rate of progression, from undetectable lung cancer to detectable lung cancer." Bradner counters that the "biology of IL-1β in cancer is decades old and is quite robust." Blocking the cytokine could have a direct impact on tumorigenesis, as well as on metastasis. "We just don't know—both are possible," he says.

The most important safety issue observed in CANTOS was an increased incidence of fatal infection or sepsis across all drug treatment groups (78 cases in 6,717 patients) compared with the control group (23 cases in 3,344 patients). That will form part of the risk–benefit calculation that will accompany the Novartis effort to widen the approval for the IL-1β-blocking drug beyond the rare conditions for which it is currently approved. The infection risk also supports the rationale for targeting the NLRP3 inflammasome directly instead of IL-1β. "Selective NLRP3 inhibition will leave other inflammasomes—there are 14 in the family—able to respond to infection, but if you block IL-1β with an antibody, you block everything," Cooper says.

The late Jürg Tschopp, of the University of Lausanne, in Switzerland, described the structure and function of the NLRP3 inflammasome 15 years ago (*Mol. Cell* **10**, 417–426, 2002). It has proven a difficult target for drug developers, but Cooper, who also holds an academic post at the University of Queensland, in Brisbane, Australia, and Inflazome co-founder and CSO Luke O'Neill, of Trinity College, Dublin, galvanized the field by reporting that MCC950, a compound originally described by New York–based Pfizer as an inhibitor of IL-1β processing, exerts its effects by acting directly on the NLRP3 inflammasome (*Nat. Med.* **21**, 248–255, 2015). "No one had really drugged the inflammasome before—and many had tried, including the big guys," Cooper says. The finding has spurred a medicinal chemistry effort at Inflazome to capture the high selectivity and nanomolar potency of MCC950 in a new series of compounds. "MCC950 has liabilities," O'Neill says. "The dose needs to be quite high." The company, whose backers include the Novartis Venture Fund, expects to be in the clinic in less than a year, he says, although it is keeping details of its development plans under wraps for now.

Olatec Therapeutics of New York is already testing dapansutrile (OLT1177) in a phase 2 trial in acute gout flare. The company's co-CSO, Charles Dinarello, of the University of Colorado, Denver, who pioneered IL-1 research in the 1970s, demonstrated last year that the drug works by preventing the assembly of the NLRP3 inflammasome. Jecure Therapeutics, of San Diego, aims to be in the clinic in 2019. The company, whose scientific founder is Ariel Fieldstein, of the University of California, San Diego, is developing small-molecule inhibitors of the NLRP3 inflammasome for treating non-alcoholic steatohepatitis (NASH) and liver fibrosis. Nodthera, an Edinburgh-based joint venture between the Edinburgh-based venture capital firm Epidarex Capital and Selvita, a Krakow, Poland–based drug discovery services company, has yet to reveal its lead indications. The CANTOS findings will inevitably swell the number of contenders in this emerging field. "It wakes up big pharma to the area again," O'Neill says. "They'll begin to dust off their molecules."

As well as targeting chronic inflammation by inhibiting IL-1β, Novartis is also targeting the NLRP3 inflammasome directly and has, Bradner says, reached lead optimization. It also in-licensed gevokizumab from Xoma. "Novartis wants to own the space—that's what that means," says O'Neill. For now, it has a commanding position, thanks to the big bet it made by funding CANTOS. O'Neill notes that Paul Ridker of Brigham and Women's Hospital in Boston, who chairs the CANTOS steering committee, is now investigating whether methotrexate, a commonly used immunosuppressant and anti-inflammatory, could have effects similar to those of canakinumab. The Cardiovascular Inflammation Reduction Trial (CIRT) has recruited 7,000 patients with coronary artery disease or a prior history of heart attack, and the results could be ready late next year. A positive result there, too, would really shake up the field.

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