Celgene Corp's deal with Nimbus Therapeutics LLC is another vote of confidence that Nimbus' computational drug design technology can solve druggability problems that trip up standard medicinal chemistry. The partnership gives Celgene access to two promising but problematic autoimmune disease targets: TYK2 and STING.

In the partnership announced Oct. 3, Celgene agreed to pay Nimbus an upfront undisclosed fee to help fund the two programs through clinical proof of concept, at which point Celgene has an option to acquire each program for an additional fee. Nimbus is also eligible for milestones. Financial details are not disclosed.

Rupert Vessey, Celgene's EVP and president of global research and early development, told BioCentury the Nimbus team will take the programs into the clinic to generate initial evidence of biological and clinical activity, and Celgene would be responsible for further development.

The partnership marks the fourth therapeutics deal for Nimbus, whose business model is to house its programs in separate subsidiaries for the express purpose of making them easier to sell off early in the development process.

Its earlier deals included a clinical stage program from its Nimbus Apollo Inc. subsidiary, sold to Gilead Sciences Inc. in 2016; a preclinical IRAK4 program from its Nimbus Iris Inc. subsidiary licensed to the Genentech Inc. unit of Roche in 2015, and a 2013 option deal with Shire plc to develop small molecules against an undisclosed target to treat lysosomal storage diseases.

The Gilead deal involved a portfolio of ACAC inhibitors for liver diseases, including GS-0976, an ACC inhibitor in Phase II testing for non-alcoholic steatohepatitis (NASH). Nimbus received $400 million up front and up to $800 million in development milestones, at least $200 million of which has been paid out. The Genentech deal gave the pharma an exclusive, worldwide license to develop and commercialize Nimbus' IRAK4 inhibitors. Genentech is responsible for all preclinical and clinical development, manufacturing and commercialization.

In this week's deal with Celgene, both targets are immune signaling molecules that have strong genetic links to autoimmune disorders: TYK2 has been implicated in rheumatoid arthritis, lupus, Crohn's disease, psoriasis and multiple sclerosis; STING is associated with lupus and other diseases driven by excess type I interferon signaling.

Robert Plenge, VP of translational development and research and early development at Celgene, told BioCentury the genetic underpinning was a key factor in the selection of those targets. “Genetics takes you to the target, it takes you to the mechanism, it takes you to the range of effect size that would be desirable, and it takes you to what potential adverse events could be,” said Plenge.

Plenge said having biological data on a range of human TYK2 loss-of-function mutations provides a road map for the clinical effects of antagonizing the target. “You know what complete loss of function looks like — immunodeficiency — and you know what partial loss of function looks like — protection from autoimmunity.”

In contrast, he said the link between STING and auto-inflammatory conditions is based on pathogenic gain-of-function mutations, which he said provides “very compelling,” but less direct, evidence to support inhibiting the target in autoimmune disease.

The deal taps into Plenge's work on TYK2 while at Brigham and Women's Hospital, where he was director of genetics and genomics in the institution's Division of Rheumatology, Immunology and Allergy until 2013. In 2015, Plenge published a study that showed loss-of-function TYK2 alleles were protective against RA, lupus and inflammatory bowel disease.

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Rosana Kapeller, Nimbus
how changes in a protein’s amino acid sequence influence its physical properties, such as its affinity for a small molecule. “That’s part of the reason why they’re in our portfolio,” he said. For TYK2, the challenge has been engineering selective inhibitors that don’t cross-react with other members of the JAK family. For STING, it’s been developing antagonists that can deal with the target’s dramatic changes in structure as it switches from active to inactive states, but that are not structurally based on endogenous STING ligands — cyclic dinucleotides — which are unstable in circulation.

“If a large pharma can throw 100 chemists on a program, and that’s the way that we’re going to have to pursue the chemistry, we don’t really believe that we can be competitive in that type of venue,” said Nicholson. “But if it’s something complex like both TYK2 and STING, where structural biology and computational chemistry can provide unique insights, then we really feel we have a leg up” (see “Structuring a Partnership”). The TYK2 antagonist program is housed in the subsidiary Nimbus Lakshmi Inc., and the STING antagonist program in Nimbus Saturn Inc.

TYKING OFF
Nimbus has developed a diverse set of TYK2 antagonists, which all fall under the deal’s umbrella. But the partners are prioritizing allosteric inhibitors over catalytic site antagonists due to their greater selectivity.
“The allosteric approach that we’re taking allows us to inhibit just TYK2, with about a 5,000-fold or greater functional separation versus all the other JAK family members, and that’s an important technical breakthrough,” Nicholson told BioCentury.

Nimbus CSO Rosana Kapeller told BioCentury that protein FEP turned out to be “the key technology to solve the selectivity challenges for TYK2.”

“These four kinases have 98% homology in their active sites. What was really key for us was to understand the differences in energy between the four molecules on that active site,” she said.

Protein FEP calculates the free energy difference between a protein in its ligand-bound and -unbound states, and compares it to the free energy difference for the same protein with an altered ligand, or the same ligand with an altered protein. The method was developed by researchers at Nimbus co-founder and equity stakeholder Schrödinger LLC (see “Energetic Approach”).

“If you use the same ligand in two proteins that differ by one amino acid, there’s going to be a difference in energy in how these proteins interact with the ligand,” said Kapeller. Those energy calculations can then be used to determine ligand affinity.

According to Kapeller, protein FEP analyses showed a TYK2 antagonist could be highly selective if it bound the ATP binding domain within the target’s allosteric site alone, without engaging the catalytic site. “Initially we thought we needed to bridge the catalytic domain and the allosteric site and keep them together. What we found out was that you didn’t need the bridge.”

By occupying the ATP binding pocket in the allosteric site, she said Nimbus’ compounds trigger formation of the protein’s natural auto-inhibitory conformation.

Nimbus has presented preclinical proof-of-concept data for TYK2 inhibition in multiple models of autoimmunity using the catalytic site antagonist NDI-031301, but has not yet presented data from its allosteric inhibitors. According to Nicholson, the NDI-031301 program is now inactive.

He said the company is part way through replicating the data with the allosteric inhibitors, and plans to take a lead compound into the clinic in 2018 or “shortly thereafter.”

Nimbus has also presented preclinical evidence that TYK2 inhibition with NDI-031301 could help treat T-cell acute lymphoblastic leukemia (ALL). Vessey said that while the partnership’s primary focus is autoimmune disorders, Celgene will be entitled to pursue other indications if it acquires Nimbus’ TYK2 program.

COMPETING FOR TYK

At least three other companies have TYK2 antagonists in development.

Pfizer Inc. and Sareum Holdings plc each have a dual inhibitor that binds TYK2 and JAK-1. Pfizer’s PF-06700841 is in Phase II testing for ulcerative colitis, plaque psoriasis and alopecia areata, and Sareum’s SAR-20347 is in preclinical testing for inflammatory bowel disease (IBD) and MS, and in discovery for lupus, psoriasis and RA. The Sareum program is partnered with SRI International, and the partners expect to select a lead candidate for further development in the 1H18.

Sareum CEO Tim Mitchell told BioCentury SAR-20347 and its newer TYK2/JAK-1 inhibitors are designed to inhibit TYK2 at the active site and have a “minimal effect at JAK-2 and JAK-
3, both of which are associated with unwanted side effects.” But he thinks dual specificity for TYK2 and JAK-1 is a feature, not a bug. “Many cytokines implicated in psoriasis and other autoimmune diseases signal via TYK2 or JAK-1,” said Mitchell.

Plenge countered that while dual inhibition might be beneficial in some contexts, human genetics points to the protective effects of inhibiting TYK2 alone. “The more that we can mimic what evolution has already done for us, the better off we’ll be.”

Bristol-Myers Squibb Co. has also disclosed an allosteric modulator of TYK2, BMS-986165, which is in Phase II testing for systemic lupus erythematosus (SLE) and psoriasis, and in Phase I for IBD. BMS spokesperson Christina Trank said BMS-986165 antagonizes TYK2 by stabilizing its regulatory pseudokinase domain. The compound was identified in a phenotypic screen.

According to Nicholson, Nimbus has “extensively characterized its own allosteric compounds versus others in the public domain” — including compounds from BMS — “in head-to-head enzymatic and cellular assays.”

Nicholson said Nimbus is “investing heavily in making sure our compounds have superior drug-like properties.” In addition, he said Nimbus’ compounds are distinguished by “the level of functional selectivity versus other JAK family members, which exceeds 5000x in primary human cellular assays for Nimbus compounds. We believe this will be an important advantage in the clinic.”

In a 2016 presentation at the American College of Rheumatology, BMS researchers showed BMS-986165 was about 200-fold more selective for TYK2 over JAK-1 and JAK-3 in primary human T cells, and more than 3,000-fold selective for TYK2 over JAK-2-dependent EPO signaling in a human bone marrow cell line. Pfizer declined to provide information on PF-06700841’s TYK2 binding site.

RELIEVE THE STING
Nicholson said Nimbus’ STING antagonist program sprung out of its search for STING agonists for immuno-oncology. Its agonist program is not included in the Celgene deal.

“As you’re building agonists, you by default stumble across antagonists,” he said. “It was pretty clear, emanating largely out of human genetics and autoimmune diseases where this pathway is perturbed, that the STING antagonists were going to offer other opportunities for us on the autoimmune front.”

Nicholson said Nimbus’ STING antagonist and agonist compounds are differentiated from others in the space because the company is not using the target’s natural ligands, cyclic dinucleotides, as a starting point for its chemical matter.

“In oncology, you have to administer them through intratumoral injection because they’re so unstable and their potency is so low,” he said. “If you’re trying to treat an autoimmune disease, that kind of chemical profile is just not going to be suitable.”

Kapeller said Nimbus is tapping structural information on STING-cyclic dinucleotide complexes for clues. “We’re developing small molecules that mimic what the cyclic dinucleotides are doing.”

The company is also conducting virtual screens to probe new chemical spaces, combing through compound libraries based on natural products, studying gain-of-function and loss-of-
function STING mutants, and modifying small molecules that bind the mouse STING protein to create compounds capable of binding the human equivalent. Nimbus is not disclosing a timeline to the clinic for its STING antagonists.

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Aduro Biotech Inc. and partner Novartis AG have the cyclic dinucleotide-based STING agonist ADU-S100 in Phase I testing for lymphoma and solid tumors. Aduro also has a discovery program for autoimmunity, dubbed “STING-Blok,” which CSO Andrea van Elsas said is exploring “other approaches beyond cyclic dinucleotides.”

“The STING-Blok program is looking at multiple entry points into this pathway,” said van Elsas.

COMPANIES AND INSTITUTIONS MENTIONED

Aduro Biotech Inc. (NASDAQ: ADRO), Berkeley, Calif.

REFERENCES

