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Can targeting one protein complex solve multiple diseases? NodThera is betting on it

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Alex Hogan/STAT

You bump your elbow, it swells and gets red, then it hurts. Your body dispatches white blood cells to release chemicals that promote wound healing and protect against infection. These are signs of inflammation, the body's defense against outside dangers.

Inflammation starts with inflammasomes, large protein complexes that assemble in response to pathogens or danger signals in a cell. These complexes activate additional signals that ultimately lead to an inflammatory response. When overactive, they can cause chronic inflammation, resulting in the tissue damage found in a number of diseases.

NodThera, a startup based in Cambridge, England, is targeting one type of inflammasome, called NLRP3, in hopes of treating diseases ranging from fibrosis — the overgrowth of connective tissue in response to injury or infection — to neurodegenerative disorders also marked by too much inflammation.

NLRP3 is a protein sensor found predominantly in macrophages, white blood cells that eat foreign particles such as microbes as well as dead cells. When NLRP3 detects a pathogen or danger signal, multiple NLRP3 proteins cluster in a ring to form the seed for the NLRP3 inflammasome. Adaptor proteins attach to the seed, which allows the inflammasome to activate downstream signals and promote an inflammatory response.

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The NLRP3 inflammasome is unique in being triggered by signals such as cholesterol crystals in atherosclerosis or urate crystals in gout, according to Dr. Joseph Duncan, an associate professor at the University of North Carolina School of Medicine with no ties to NodThera. These triggers can lead to chronic inflammation and cellular damage.

NodThera seeks to reduce that inflammation by blocking the NLRP3 inflammasome, developing molecules tuned specifically to different diseases. The company was formed in 2016 by Epidarex Capital, a life sciences venture capital firm, and received $40 million in Series A funding in 2018. Adam Keeney, previously the global head of business development at Sanofi (SNY[7]) Genzyme, leads the company.

"We are currently focused on fibrosis and NASH for our lead compound and neuro-indications for our second-generation" compounds, Keeney said.

NASH[8] is the most severe form of non-alcoholic fatty liver disease, characterized by liver inflammation. While its cause is unknown, the disease is linked to obesity and type 2 diabetes. The prevalence of NASH has increased with the growing obesity epidemic, and there are currently no FDA-approved therapies for NASH, although Intercept Pharmaceuticals (ICPT[9]) and Genfit (GNFT[10]) have drugs in Phase 3 clinical trials.

Currently, the most widely used treatment is weight loss and exercise.

Other diseases NodThera hopes to target include lung fibrosis, Alzheimer's disease, and Parkinson's disease, all of which are associated with increased inflammation.

Scott Friedman, chief of the Division of Liver Diseases at the Icahn School of Medicine at Mount Sinai who has no ties to NodThera, sounds a note of caution. While he thinks the scientific rationale for targeting NLRP3 is strong, he said that because inflammation has evolved to protect tissues and organisms, fundamentally antagonizing such a response to injury "could make the disease worse."

Any risks of inhibiting the pathway are unclear at this point because these drug candidates are just now making their way toward human trials. Experiments in animals have shown that lab mice lacking certain inflammasome components may be more susceptible to infection than their wild-type counterparts, UNC's Duncan said.

Besides NodThera, several other companies are also looking to target NLRP3, including pharma giants Novartis (NVS[12]), Genentech, and Bristol-Myers Squibb (BMY[13]) as well as biotechs Olatec Therapeutics, Inflazome, and TWi Pharmaceuticals.

NodThera is currently testing compounds in cells, animal models, and human tissue samples. Keeney said the company aims to file an investigational new drug application to the Food and Drug Administration for a fibrosis compound and bring that to clinical trials in the next few months.

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