NodThera
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Unlocking the potential of the NLRP3 inflammasome to treat chronic inflammatory diseases

NodThera is developing a portfolio of novel, potent and selective NLRP3 inflammasome inhibitors, with one clinical-stage candidate and several others in preclinical development. The company is seeking partners to advance its programs through clinical development in a range of indications.

Global biotechnology company NodThera is developing a new class of potent and selective small-molecule NLRP3 inhibitors for the treatment of diseases driven by chronic inflammation, such as osteoarthritis, Alzheimer's disease and heart disease. Chronic inflammation is now recognized as a primary driver of many chronic conditions and NodThera's platform of novel NLRP3 inhibitors paves the way for reducing the burden of chronic inflammation in a wide spectrum of these diseases.

"Chronic inflammation happens when the natural inflammatory mechanisms orchestrated by the innate immune system to fend off pathogens and other sterile triggers are never properly turned off or, worse yet, go into overdrive," said Adam Keeney, CEO of NodThera. "The current therapeutic targets for treating chronic inflammation have been only partially effective and novel and more selective options are needed to tackle chronic inflammation at its root. We believe NodThera's NLRP3 inhibitors address this need and could provide future options to patients suffering with diseases driven by chronic inflammation."

NodThera's pipeline includes three drug candidates and other compounds in discovery. The compounds target NLRP3 systemically in the periphery or directly in the brain. The company's lead compound is NT-0796, a small molecule with differentiated chemistry that is currently in a phase 1 clinical study.

Focusing on NLRP3

The etiology of many chronic diseases caused by chronic inflammation includes dysregulation of the pro-inflammatory cytokines IL-1β and IL-18. Therapeutic strategies developed to date have focused on targeting IL-1β directly with biologics. However, this approach has several shortcomings, including limited compound accessibility to specific organs and cell types due to the size of the biologics and the need for regular injections.

To address these issues, NodThera has focused its attention to an alternative upstream target, the cytosolic signaling receptor NLRP3 (NOD-, LRR- and pyrin domain-containing 3). NLRP3 is a central node of the innate immune system responsible for activating IL-1β and IL-18 (Fig. 1). Targeting NLRP3 affords the possibility to regulate chronic inflammation mechanisms caused not only by IL-1β but also by IL-18 and can provide protection from other inflammation-associated processes such as pyroptotic cell death[1].

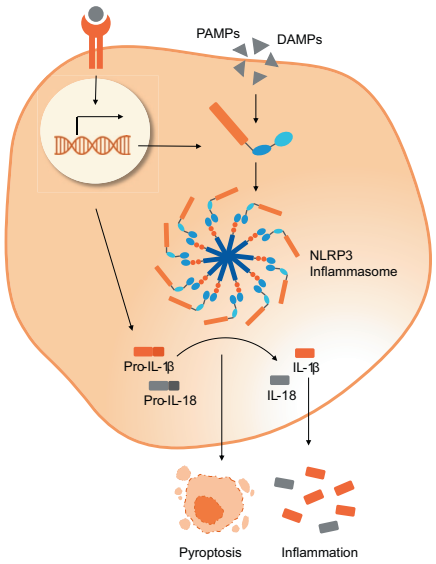

Fig. 1 | The NLRP3 inflammasome is an upstream activator of IL-1β and IL-18. NodThera is employing novel chemistry to create small molecules that inhibit the NLRP3 inflammasome that have now advanced into clinical trials. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns.

NLRP3 can be targeted with small molecules that can be administered orally, and NLRP3 inhibition can be fine-tuned so that the reduction in IL-1β is sufficient to dial down inflammatory processes with the potential to not affect the body's ability to fight infection.

NT-0796—leading the charge against inflammation

NodThera's lead small molecule is NT-0796, a novel chemotype that sets it apart from other small-molecule NLRP3 inhibitors. NT-0796 has unprecedented potency to inhibit NLRP3, with prolonged pharmacodynamic effect in animal models of inflammatory diseases. NT-0796 is orally available, exhibits good systemic distribution and can cross the blood–brain barrier in preclinical species, opening the possibility of treating a number of conditions associated with chronic inflammation of the periphery or central nervous system. An ongoing phase 1 clinical study incorporates an ex vivo IL-1β stimulation assay to evaluate how effectively NT-0796 lowers IL-1β and IL-18. NodThera is planning to initiate a phase 2 proof of concept study in patients in 2022.

Other NLRP3 inhibitors in development

A second NLRP3 inhibitor, NT-0249, is peripherally restricted and in development to treat chronic inflammatory diseases. NT-0249 is a novel molecule that exhibits sub-micromolar blood potency and optimized plasma protein binding to provide an optimal pharmacokinetic and pharmacodynamic profile. NT-0249 is slated to enter a phase 1 clinical study in early 2022.

NodThera is also advancing other development candidates from different chemotypes that are differentiated for use in peripheral indications and brain-penetrant molecules for central nervous system diseases.

"NLRP3 stands as one of the best biologically and genetically validated therapeutic targets, and we are working tirelessly on harnessing this knowledge to bring new solutions to treat chronic inflammatory disease and meet the needs of patients around the world," said Keeney. "The recent convergence of key insights into innate immunity, IL-1β and NLRP3 have revolutionized our understanding of chronic disease and at NodThera we now can envision a world in which chronic inflammatory disease can be treated at the source."

1. Mangan, M. et al. *Nat. Rev. Drug Discov.* **17**, 588–606 (2018).

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