Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

NLRP3 Inhibitors

Evidence Summary

NLRP3 inhibitors may protect against various age-related diseases by dampening chronic inflammation. Many inhibitors are in clinical development and show good short-term safety.

Neuroprotective Benefit: NLRP3 activation is an inflammatory component of several neurodegenerative diseases, and inhibitors are effective in preclinical models. Clinical studies are needed to determine if there is an optimal therapeutic window.

Aging and related health concerns: NLRP3-mediated inflammation underlies a variety of age-related conditions. Inhibitors may mitigate inflammaging and may be best suited to cardiovascular and metabolic conditions.

Safety: Clinically tested NLRP3 inhibitors show a good safety profile to date, with no clear evidence of class related toxicities or increased infection risk, however, the trials have been short, so long-term safety remains to be established.

Availability: In clinical trials	**Dose**: Varies. With the exception of RRx-001, which is typically administered intravenously for cancer, other clinically tested NRLP3 inhibitors are oral formulations.
Half-life: Dapansutrile: ~24 hours DFV890: ~9.6-16.2 hours (in Phase 1 study) RRx-001: ~30 mins in plasma, but biological T1/2 is related to covalent adduct formation on proteins, for hemoglobin ~3-4 days (allows for weekly i.v. dosing). Selnoflast: ~7 hours (in Phase 1 study) VTX3232 ~17 hours ZYIL1: ~6-8 hours (in Phase 1 study)	**BBB**: Varies (Dapansutrile, RRx-001, NT-0796, NT-0249, VENT-02, VTX3232, ZYIL1 are penetrant)
Clinical trials: RRx-001 has been tested in >300 patients for various cancers in Phase 1, 2, and 3 trials. Dapansutrile has been tested in Phase 1 trials in healthy volunteers, and heart failure (n=30) and 3 Phase 2 trials in osteoarthritis (range n=29 to n=202). Selnoflast has been tested in Phase 1 trials in healthy volunteers and ulcerative colitis. NT-0796 has been tested in Phase 1 trials in healthy volunteers, obesity (n=67), and Parkinson's disease. DFV890 has been tested in Phase 1 trials in healthy volunteers, and Phase 2 trials in covid-19 (n=143) and CAPS (n=4). VTX2735 and ZYIL1 have been tested in Phase 1 trials in healthy volunteers and Phase 2a trials in CAPS (n=7 and 3, respectively). NT-0249, VENT-02, and VTX3232 have been tested in Phase 1 trials in healthy volunteers.	**Observational studies**: NLRP3 has been found to be elevated in several neurodegenerative diseases, cardiovascular disease, and associated with disease prognosis in some cancers.

What is it?

The NLRP3 inflammasome is a central figure in the innate immune system – the non-specific immune response that occurs in the presence of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [1]. PAMPs are small conserved molecular motifs on classes of infectious pathogens while DAMPs are molecular patterns from the host itself (e.g. DNA, HMGB1, etc.).

NLRP3 is a supramolecular complex made up of a sensor molecular, the adaptor apoptosis-associated speck-like protein containing a CARD (ASC), and an effector protease, caspase-1. NLRP3 is usually present in low concentrations but can be primed by molecules such as PAMPs or DAMPs that bind to immune receptors and activate transcription factors that increase the expression of NLRP3. In addition, NLRP3 is typically held in an inactive state by post-translational modifications.

There are several mechanisms by which NLRP3 can be activated. Once activated, NLRP3 cleaves caspase-1 which can then lead to the release of pro-inflammatory mediators such as IL-1β, IL-18, high-mobility group protein B1 (HMGB1), leukotrienes, and prostaglandins [1]. On the other hand, TNFα and IL-6 are released through other pathways and usually not expected to change with NLRP3 inhibition.

NLRP3 can be activated through multiple mechanisms:

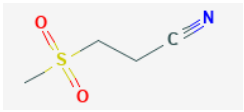
- *Pore formation and redistribution of ions*: opening of pores in the plasma membrane leading to potassium efflux with concomitant calcium influx or the opening of chloride channels (e.g. opening of the volume-regulated anion channel (VRAC)) can activate NLRP3.
- *Lysosomal disruption*: phagocytosis of crystalline structures can cause lysosomal disruption and ATP release leading to extracellular ATP-dependent NLRP3 activation.
- *Metabolic dysfunction*: inhibition of glycolysis and mitochondrial NADH oxidase (complex I) with depolarization of lysosomes can activate NLRP3.
- *Mitochondrial dysfunction*: increased mtROS or externalization of mitochondrial cardiolipin can activate NLRP3.

NLRP3 inhibitors have shown effectiveness in preclinical studies in a variety of diseases. Evidence for the growing interest in the target can be seen from the increasing number of patents for drugs targeting inflammasomes over the last several years [2]. There are several inflammasomes with overlapping functions, which is why targeting NLRP3 does not necessarily increase the risk of infections (as opposed

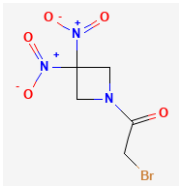
to drugs such as IL-1β inhibitors). In addition, NLRP3 seems to be especially involved with sterile inflammation.

There are numerous NLRP3 inhibitors in clinical development.

Dapansutrile (OLT1177) is considered the most advanced selective, oral NLRP3 inhibitor clinical candidate to date. It is a direct NLRP3 inhibitor that acts as an ATPase inhibitor by blocking the NLRP3-ASC interaction [3]. It is in clinical development by Olatec Therapeutics, and has been tested in clinical trials for osteoarthritis, gout, and heart failure. It will be discussed minimally in this report since details regarding dapansutrile can be found in a separate report focusing solely on dapansutrile. (Image source: PubChem; formula $C_4H_7NO_2S$ molecular weight 133.17 g/mol).



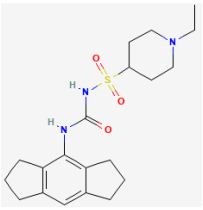
RRx-001 (nibrozetone) is an electrophilic compound that acts as a direct inhibitor of NLRP3. It forms covalent adducts with thiol sulfurs, and thus modifies amino nitrogens in proteins, largely on cysteine residues [4]. RRx-001 reacts with cysteine 409 of NLRP3, though the mechanism by which this inhibits the inflammasome is not fully clear [5]. RRx-001 exerts a variety of other actions through its interaction with cysteines on other proteins, including hemoglobin, and Keap1, which can lead to the induction of the Nrf2 endogenous antioxidant pathway [5]. Through these activities, RRx-001 also inhibits Myc, a difficult to target cancer-associated protein, and modulates immune function. Due to these pleiotropic properties, RRx-001 is in clinical development for cancer by EpicentRx, and has been tested in over 300 patients in Phase 1, 2, and 3 trials, with a promising safety and efficacy profile to date. RRx-001 appears to be best suited as a re-sensitizing and cytoprotective agent to be used in combination with chemotherapy, radiotherapy, and/or immunotherapy. RRx-001 is BBB penetrant and has also been tested and shown benefit in preclinical models for a variety of indications, including neurodegenerative diseases and cardiovascular disease. (Image source: PubChem, formula $C_5H_6BrN_3O_5$, molecular weight 268.02 g/mol).



DFV890 is an oral NLRP3 inhibitor developed by IFM Therapeutics. The subsidiary, IMF Tre, was acquired by Novartis in 2019, which received the rights to their portfolio of NLRP3 inhibitors (Press release). DFV890 binds directly to NLRP3 to prevent its activation [6]. In *in vitro* assays, it inhibits LPS-induced IL-1β release in peripheral blood cells with an IC_{50} range of 1.0–2.9 nM [6]. In *ex vivo* assays, the plasma concentrations corresponding to the IC_{50} and IC_{90} were 61 ng/mL (90% Confidence Interval [CI] 50 to 70

ng/mL) and 1,340 ng/mL (90% CI 1190 to 1,490 ng/mL), respectively [6]. It has been clinically tested in a Phase 1 trial assessing multiple formulations of DFV890, as well as in Phase 2a trials in covid-19 pneumonia and familial cold auto-inflammatory syndrome (FCAS). DFV890 is currently being tested in trials for myeloid diseases (NCT05552469), knee osteoarthritis (NCT04886258), and coronary heart disease (NCT06031844; NCT06097663). (formula $C_{19}H_{24}N_4O_3S_2$; molecular weight 420.6 g/mol).

Selnoflast is a peripheral, oral, selective, and reversible NLRP3 inhibitor developed by Inflazome, where it was called Somalix (IZD-334) and underwent successful Phase 1 testing. Inflazome was acquired by Roche in late 2020. Since the acquisition, selnoflast (RO7486967) has been tested in a Phase 1b trial in ulcerative colitis but did not show significant benefit. A Phase 1b trial in patients with chronic obstructive pulmonary disorder (COPD) was terminated due a re-evaluation of the development plan for selnoflast by the study sponsor, with only one participant completing the study (NHS). The status of a 2022 registered Phase 1c trial in coronary artery disease is unclear. Selnoflast is currently being tested in a Phase 1b trial in patients with early Parkinson's disease (NCT05924243). (Image source: PubChem; formula $C_{20}H_{29}N_3O_3S$ molecular weight 391.5 g/mol).



NT-0796 is a CNS-penetrant, oral NLRP3 inhibitor with a novel chemotype developed by NodThera. NT-0796 is an isopropyl ester that undergoes intracellular conversion to NDT-19795, the active carboxylic acid species. NDT-19795 interacts with NLRP3 at the NACHT domain [7]. In whole blood, it inhibits LPS-induced IL-1β release with an IC_{50} of 6.8 nM [7]. NT-0796 has been tested in a Phase 1 trial in healthy volunteers, and Phase 1b/2a trials in patients with Parkinson's disease and participants with obesity and cardiovascular risk factors. The company has stated that it plans to test NT-0796 in larger Phase 2 trials for these indications (press release). (formula $C_{23}H_{27}N_3O_4$; molecular weight 409.48 g/mol).

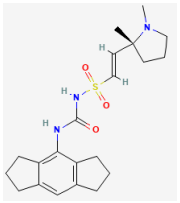
NT-0249 is a CNS-penetrant, oral NLRP3 inhibitor developed by NodThera. It was shown to inhibit LPS-induced IL-1β release in human PBMCs with an IC_{50} of 0.012 mM [8]. It has been tested in Phase 1 studies in healthy volunteers. ($C_{22}H_{28}N_5NaO_4S$; molecular weight 481.54 g/mol).

VTX2735 is a peripheral, selective, oral NLRP3 inhibitor developed by Ventyx Biosciences It inhibits LPS-induced IL-1β release in human whole blood with an IC_{50} of 75 nM (Corporate Presentation). It has been tested in a Phase 1 trial in healthy volunteers, and a pilot trial in patients with FCAS. The company states that it has plans to test VTX2735 in patients with pericarditis (press release).

VTX3232 is a rationally designed, selective, CNS-penetrant, oral NLRP3 inhibitor developed by Ventyx Biosciences . In human whole blood it inhibits IL-1β release with an IC_{50} of 15 nM (Corporate presentation). It has been tested in a Phase 1 trial in healthy volunteers, and is currently being tested in a Phase 2a trial in Parkinson's disease (NCT06556173). The company states that it has plans to test VTX3232 in a Phase 2 trial in patients with obesity and cardiovascular risk factors (press release).

VENT-02 is a CNS-penetrant NLRP3 inhibitor developed by Ventus Therapeutics. It has been tested in a Phase 1 trial in healthy volunteers, and is expected to be tested in a Phase 1b trial in Parkinson's disease (press release).

VENT-01 (NNC6022-0001) is a peripheral NLRP3 inhibitor developed by Ventus Therapeutics that was licensed to Novo Nordisk in 2022, and is now referred to as **NNC6022-0001**. A Phase 1 trial testing NNC6022-0001 in healthy volunteers was initiated in 2024 (press release) (NCT06336005).



ZYIL1, also called **usnoflast**, is a CNS-penetrant, oral NLRP3 inhibitor developed by Zydus Lifesciences. It inhibited LPS-induced IL-1β release in *in vitro* assays with an IC_{50} of 11 nM in a human monocyte cell line (THP-1) and 4.5 nM in human PBMCs [9]. It has successfully been tested in Phase 1 trials in healthy volunteers and a pilot trial in patients with FCAS. It is currently being tested in Phase 2 trials in patients with ALS (NCT05981040), and ulcerative colitis (NCT06398808), and has approval for a planned trial in Parkinson's disease (press release). (Image source: PubChem; formula $C_{21}H_{29}N_3O_3S$ molecular weight 403.5 g/mol).

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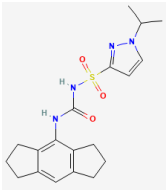
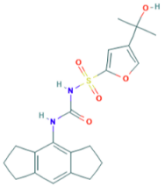


Emlenoflast is a CNS-penetrant, oral NLPR3 inhibitor developed by Inflazome, where it was called Inzomelid (IZD-174) and underwent successful Phase 1 testing. Trials were planned for Alzheimer's disease and Parkinson's disease, but after acquisition by Roche, clinical development of emlenoflast was suspended in favor of selnoflast. (Image source: PubChem; formula $C_{19}H_{24}N_4O_3S$; molecular weight 388.5 g/mol).

GDC-2394 is an oral NLRP3 inhibitor developed by Genentech. Clinical development was terminated due to safety concerns based on the development of drug-induced liver injury in multiple participants in a phase 1 drug interaction study [10]. (formula $C_{20}H_{25}N_5O_4S$; molecular weight 431.51 g/mol).

MCC950, also known as CRID3 and CP-456773, is the first clinically tested specific NLRP3 inhibitor. It is a direct NLRP3 inhibitor that binds to the NLRP3 Walker B motif to inhibit NLRP3-dependent ASC oligomerization [3]. It has been extensively tested in preclinical studies, and remains the most widely used NLRP3 inhibitor to date in animal models. It has also been used as the scaffold for a variety of other NLRP3 inhibitor candidates. MCC950 was in clinical development by Pfizer, but following the emergence of liver toxicity in a Phase 1b trial in rheumatoid arthritis, clinical development was terminated. (Image source PubChem; formula: $C_{20}H_{24}N_2O_5S$; molecular weight: 404.5 g/mol).



Neuroprotective Benefit for: NLRP3 activation is an inflammatory component of several neurodegenerative diseases, and inhibitors are effective in preclinical models. Clinical studies are needed to determine if there is an optimal therapeutic window.

Types of evidence:

- 1 open-label clinical trial of NT-0796 in early Parkinson's disease
- Several studies of NLRP3 expression in postmortem brain tissue or biofluids
- Numerous preclinical studies in other neurodegenerative diseases

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia

NLRP3 inhibitors have not yet been clinically tested in patients with Alzheimer's disease, however, there is evidence from studies in postmortem brain tissue and cerebrospinal fluid (CSF), that NLRP3 and its associated proinflammatory signaling pathways are elevated in the context of dementia, including caspase-1, cleaved GSDMD, ASC, IL-1β, and IL-8 [11].
For example, increased expression of cleaved caspase-1 in the hippocampus and frontal cortex has been observed in patients with Alzheimer's disease [12], while elevated levels of cleaved caspase-1, ASC, and IL-1β were reported in the cortex of patients with Frontotemporal dementia (FTD) [13].

Mechanisms of action for neuroprotection identified from laboratory and clinical research

To date, most of the evidence supporting a therapeutic role for NLRP3 inhibition in the context of neurodegenerative disease comes from animal models. The translatability of these findings may be impacted by species specific differences in NLRP3-mediated and immune responses in general [14]. Additionally, the majority of studies have utilized NLRP3 knockout animals, which may have compensatory responses, or the NLRP3 inhibitor MCC950, which is not suitable for clinical use. While the body of evidence supporting a role for NLRP3-mediated inflammation in driving neuropathology is compelling, more studies are needed using clinically viable inhibitors to determine whether there is a particular window of therapeutic benefit depending on the stage of the disease, as inflammatory processes are known to shift with disease progression. In addition to stage, it is unclear whether there are certain subpopulations of patients, or disease subtypes that are more likely to benefit. To date, the majority of clinical development of NLRP3 inhibitors for neurological disease has been focused on Parkinson's disease, though the mechanistic rationale for this indication relative to other neurodegenerative diseases is not fully clear.

Alzheimer's disease: POTENTIAL BENEFIT (Preclinical)
The NLRP3 inflammasome and its associated components have been found to be upregulated in a variety of Alzheimer's disease models [11; 14]. This upregulation is generally associated with a pathological, proinflammatory microglial profile. Amyloid and tau may serve as DAMPs, as they have been shown to trigger the activation of the NLRP3 inflammasome. The chronic activation of NLRP3 in the presence of amyloid and tau pathology may promote an inflammatory profile that further exacerbates pathology and neuronal damage.

Increased expression of cleaved caspase-1 and IL-1β was observed in the brain of an Alzheimer's animal model [12]. The expression was reduced to control levels when the animals were crossed with NLRP3 knockout animals. Similarly, NLRP3 or Caspase-1 knockout animals crossed with Alzheimer's animals were protected from memory deficits and long-term potentiation (LTP) impairment. The reduction in spine density in Alzheimer's animals (which was protected in NLRP3 or Caspase-1 knockout animals) was small, but significant, suggesting that deficits may be due to functional, rather than structural, changes in synapses. NLRP3 knockout was also associated with reductions in amyloid levels, amyloid plaque size, and an increase in phagocytic capacity of microglia *in vivo*. Finally, NLRP3 knockout animals also had increased levels of an amyloid degrading enzyme, insulin degrading enzyme (IDE).

The upregulation of multiple components of the NLRP3 inflammasome (NLRP3, ASC, cleaved caspase-1) were also observed in another Alzheimer's animal model, while caspase-1 was reduced after one-month

treatment with the NLRP3 inhibitor, JC-124 [15]. JC-124 also reduced levels of soluble amyloid-beta, amyloid oligomers, plaques, and plaque size. In addition, JC-124 also reduced levels of microgliosis (but increased astrogliosis), oxidative stress, and increased synaptic markers.

The CNS-penetrant NLRP3 inhibitor ***RRx-001*** has been tested in the 3xTg-AD mouse model. Aged 3xTg-AD mice, 21-24 months of age, were treated sub-chronically with RRx-001 (2mg/kg i.p. once per week for 3 months). Full details have not been published, but an overview from a conference abstract indicates that Rx-001 treatment was associated with an improvement on performance on learning and spatial memory tasks and greater risk assessment behavior based on the elevated plus maze test [16]. An antioxidant effect was also observed, including a significant increase in reduced glutathione and a decrease in lipid peroxidation as well as a reduction in amyloid plaque density in the brains of treated 3xTg-AD mice.

In vitro, MCC950, an NLRP3 inhibitor, reduced IL-1β release, caspase-1 expression, and increased phagocytosis of Aβ from LPS- and Aβ-challenged microglia but had no effect on TNFα or IL-6 (suggesting it was specific for NLRP3). In aged Alzheimer's mice, treatment with MCC950 improved cognition, reduced Aβ, IL-1β, and microglial activation [17].

Other neurological diseases

Parkinson's disease: POTENTIAL BENEFIT (primarily preclinical)
Elevated NLRP3 activation has been observed in disease affected regions in the brains of patients with Parkinson's disease, as well as in animal models [18]. In contrast to Alzheimer's disease, where the elevation in NLRP3 primarily occurs in microglia, NLPR3 has been found to be increased in dopaminergic neurons in Parkinson's patients. NLRP3 in dopaminergic neurons has been found to be a substrate for Parkin, a ubiquitin E3 ligase, such that Parkin inhibits NLRP3 activation [18]. Mutations in Parkin are a common genetic cause of Parkinson's disease. Alpha-synuclein has also been shown to trigger the activation of NLRP3 [18].
Genetic variations in NLRP3 have also been associated with Parkinson's disease. The single nucleotide polymorphism (SNP) rs7525979 (T allele), which impacts the stability of NLRP3, resulting in the accumulation of an inactive, insoluble ubiquitinated form, was found to be associated with decreased risk for Parkinson's disease (Odds Ratio [OR]: 0.55, 95% CI 0.34 to 0.89) [19]. However, an analysis of a large Parkinson's disease GWAS (including 49,053 cases and 1,411,006 controls) did not find any

significant associations between Parkinson's disease with NLRP3 genes or cytokines [20]. Similarly, no causal links were observed in a Mendelian randomization study by the same group.

Evidence from preclinical models supports a role for NLRP3 activation in the progression of Parkinson's disease [18]. Cleaved caspase-1 and ASC were found to be upregulated in the substantia nigra in Parkinson's patients and in mouse models of Parkinson's disease. *In vitro* exposure of microglia to alpha synuclein increased expression of IL-1β and ASC. Oral administration of MCC950 crossed the blood brain barrier and in multiple Parkinson's models was neuroprotective, reduced the expression of IL-1β and ASC, improved behavioral symptoms, and reduced the aggregation of alpha synuclein [21].

Several companies are developing NLPR3 inhibitors for Parkinson's disease.

NT-0796: The CNS-penetrant NLRP3 inhibitor from NodThera, NT-0796, is the only NLRP3 inhibitor with clinical results in a neurodegenerative disease to date. NT-0796, at a dose of 150 mg BID was tested in an open-label Phase 1b/2a trial in a cohort of healthy elderly adults as well as a cohort of patients with Parkinson's disease (stage ≤2.5 on the Hoehn and Yahr Scale) taking levodopa (symptomatic agents). Plasma and CSF samples were collected after seven days of treatment in both cohorts, and the Parkinson's cohort continued the study out to 28 days. Topline results presented in March 2024 indicate treatment with NT-0796 normalized levels of NLRP3-related inflammatory cytokines in the CSF of Parkinson's patients, including IL-1β, IL-6, IL-8, CCL2, and CXCL1, relative to the level of the elderly controls. NT-0796 also reduced CSF levels of the axon degeneration marker NFL, and the inflammatory marker, soluble TREM2, by approximately 10% in Parkinson's patients, relative to baseline levels. Additionally, NT-0796 treatment reduced levels of the plasma inflammation markers, C-relative protein (CRP) by approximately 50% and fibrinogen by around 15% in Parkinson's patients, relative to baseline. Though, it is not clear that any of these effects are statistically significant in this small study. Notably, CSF levels of NT-0796 were two to three times higher in Parkinson's patients relative to elderly controls, which may stem from a compromised BBB in Parkinson's patients.

Selnoflast: The peripheral NLPR3 inhibitor selnoflast (RO7486967) in clinical development by Roche, is currently being tested in a randomized, double blind, adaptive, parallel-group, placebo-controlled Phase 1b trial in patients with idiopathic early Parkinson's disease (modified Hoehn and Yahr stage ≤2.5). The study is primarily designed to assess safety, pharmacokinetics, and pharmacodynamics, with an estimated completion date in 2025 (NCT05924243).

VTX3232: An open-label Phase 2a trial testing the CNS-penetrant NLRP3 inhibitor VTX3232 from Ventyx Biosciences in patients with early-stage idiopathic Parkinson's disease (score ≤2 on the MDS-UPDRS Part IV) was recently initiated. The study is designed to test safety, pharmacokinetics, and pharmacodynamics and has an estimated completion date in 2025 (NCT06556173).

Dapansutrile: Olatec Therapeutics announced that it will conduct a Phase 2 trial testing the ability of their NLRP3 inhibitor, dapansutrile (OLT1177®), to slow disease progression in patients with early Parkinson's disease. Based on the press release, they plan to enroll 36 patients for a six-month placebo-controlled study, followed by a six-month open label phase. The study is being funded by a grant from Cure Parkinson's. To date, the trial has not yet been initiated.

VENT-02: Ventus Therapeutics plans to conduct a Phase 1b trial testing their CNS-penetrant NLRP3 inhibitor VENT-02 in patients with Parkinson's disease, according to a press release, but to date, the trial has not yet been initiated.

ZYIL1: Zydus Lifescience has conducted preclinical studies testing their NLRP3 inhibitor ZYIL1 in models of Parkinson's disease [9]. ZYIL1 was found to cross the BBB in mice, rats, and non-human primates, and reach CNS concentrations above the IC_{50} for IL-1β inhibition observed in cell culture studies [9]. It showed dose dependent decreases in LPS-induced IL-1β in the brain, starting at doses of 5 mg/kg. In the MPTP mouse model, treatment with ZYIL1 (60 mg/kg) improved falling time on the wire hanging test, but had no significant impact on the falling latency on the rotarod test. ZYIL1 inhibited the NLRP3 inflammasome and impacted gene expression in the brain in a manner consistent with less neuronal cell death. ZYIL1 treatment also led to dose-dependent improvements in motor performance on the rotarod and horizontal bar tests in the 6-OHDA mouse model. A dose-dependent reduction in phosphorylated alpha-synuclein accumulation, and the preservation of brain dopamine levels were also observed in these models. Zydus has received FDA approval to conduct a Phase 2 trial in Parkinson's disease (press release), though, to date, it has not yet been initiated.

RRx-001, the CNS-penetrant NLRP3 inhibitor from EpicentRx, has been tested in preclinical models of Parkinson's disease, in work funded by the Michael J. Fox Foundation (MJFF), in preparation for a planned clinical trial in this population. RRx-001 was found to dose-dependently reduce microglial activation and dopaminergic cell loss when administered prior to LPS injection into the substantia nigra pars compacta in male mice [22]. Additional studies have been presented at scientific conferences, but have not been published.

Frontotemporal Dementia (FTD): POTENTIAL BENEFIT (Preclinical)
Increased levels of cleaved caspase-1 and ASC in were found in cortical samples of old FTD mice compared to younger mice [13]. There were also increased levels of extracellular ASC specks in old FTD mice compared to controls. FTD mice crossed with ASC or NLRP3 knockout mice had reduced levels of ASC speck formation, cleaved caspase-1, p-tau, and misfolded tau. Knockout mice also displayed improved spatial memory.

NLRP3 knockout mice had reduced expression of several kinases and a phosphatase that regulate tau phosphorylation, reductions of some genes involved in inflammation, and increases in genes involved in synapse formation. Injection of brain homogenates from amyloid Alzheimer's mice can induce tau phosphorylation in FTD mice, and the investigators found that phosphorylation of tau was reduced when amyloid brain homogenates were injected into FTD/NLRP3-/- mice.

In a tau seeding model (intracerebral injection of aggregated tau in a tau transgenic model), both ASC knockout and treatment with MCC950 reduced the spreading of tau and reduced microgliosis [23].

MCC950 also had beneficial metabolic effects in the tau knock-in $PLB2_{TAU}$ mouse model of FTD [24]. The inhibition of NLRP3 was associated with a normalization of peripheral insulin signaling, as well as a reduction in levels of proinflammatory signaling molecules, such as IL-18 and NF-kB, both centrally and peripherally.

Traumatic Brain Injury (TBI): POTENTIAL BENEFIT (Preclinical)
In a mouse model of TBI, NLRP3 expression was increased after injury. Treatment with MCC950 improved neurological outcomes, reduced the infiltration of macrophages into the brain, reduced lesion size, reduced cell death, improved blood brain barrier integrity and the expression of tight junction proteins, and reduced cerebral edema [25].
Levels of NLRP3 genes were found to be increased in the brain tissue, blood, and CSF following severe TBI, and that elevated NLRP3 (> 6.63 ng/mL) in the CSF was associated with worse neurological outcome [26]. One study found that NLRP3 levels were not affected following mild TBI, while another study found that the impact of NLRP3 in mild TBI was mediated by metabolic status, such that levels of the NLRP3 associated cytokine IL-18 were elevated following mild TBI only in obese individuals [27]. High levels of IL-18 and IL-1β were also associated with worse cognitive outcomes following mild TBI in these individuals.

Multiple Sclerosis*:* POTENTIAL BENEFIT (Preclinical)
In a mouse model of multiple sclerosis, pretreatment with MCC950 before LPS injection reduced the serum levels of IL-1β and IL-6, but not TNFα. It also improved clinical symptoms in the model [28]. RRx-001 (i.p. administration) is reported to have mitigated inflammatory infiltration and demyelination in the spinal cord in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, in C57Bl/6J mice [5]. This was associated with decreased CNS expression of the proinflammatory cytokines IL-6, IL-18, and TNF-α. The anti-inflammatory effect was driven by the inhibition of NLRP3, as RRx-001 had no effect on EAE progression in NLRP3 knockout mice.

Amyotrophic lateral sclerosis (ALS): POTENTIAL STAGE-DEPENDENT MIXED BENEFIT (Preclinical)
Cleaved caspase-1 and IL-1β were upregulated in microglia from ALS mouse models. Expression of both was reduced after *in vitro* administration of MCC950 [29]. NLRP3 levels were found to be elevated in the peripheral blood from ALS patients. The gene expression of NLRP3 components was found to be elevated in the skeletal muscle during early (asymptomatic) stages of the disease in the $SOD1^{G93A}$ mouse model, while protein levels showed the opposite pattern, with high levels later in the disease [30]. This study suggests that NLPR3 may play a dual role in disease progression at different times, with a potentially protective effect early, and more detrimental effect later. Mice with lower NLRP3 expression levels had shorter lifespans, as did those treated with the NLRP3 inhibitor MCC950 starting during early asymptomatic stages.
The CNS-penetrant NLRP3 inhibitor RRx-001 will undergo preclinical testing for ALS as part of a study funded by FightMND (press release).

ZYIL1: Zydus Lifesciences is currently conducting a Phase 2 proof-of concept placebo controlled, randomized, multi-center, double blind clinical trial in patients with ALS (n=24). The trial is testing efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics, and has an estimated completion date in late 2024 (NCT05981040).

Stroke: POTENTIAL MIXED (Preclinical)
The expression of NLRP3 along with downstream components, such as caspase-1, IL-1, and IL-18 have been found to be elevated in the brain following stroke in postmortem brain tissue analysis in patients and animal models [31]. Numerous events take place during the course of a stroke that trigger the activation of the NLRP3 inflammasome, including disturbances in calcium homeostasis, disruption of mitochondrial function and oxidative stress, lysosomal dysfunction, and altered patterns of kinase activity [31].

In a model of ischemic stroke, NLRP3 (but not other inflammasomes) was increased 24 hours after stroke. However, treatment with MCC950 and NLRP3 genetic knockout had no effect on the extent of lesion volume [32]. On the other hand, other studies have suggested that treatment with MCC950 reduced the extent of lesion volume and improved neurological outcomes in stroke models [33] [34; 35; 36]. Further studies are needed testing the novel CNS-penetrant NLRP3 inhibitors currently in development, to determine the potential for benefit, and whether there is a particular therapeutic window for benefit, for this indication.

APOE4 interactions: Not established

Aging and related health concerns: NLRP3-mediated inflammation underlies a variety of age-related conditions. Inhibitors may mitigate inflammaging, and may be best suited to cardiovascular and metabolic conditions.

Types of evidence:

- 3 pilot clinical trials of NLRP3 inhibitors (DFV890, VTX2735, and ZYIL1) in CAPS
- Several clinical trials (Phase 1, 2, 3) of RRx-001 in various cancers
- 1 Phase 1b clinical trial of senoflast for ulcerative colitis
- 1 Phase 1b clinical trial of dapansutrile for heart failure
- 1 Phase 1b/2a clinical trial of NT-0796 in obesity with cardiovascular risk
- 1 Phase 2a clinical trial of DFV890 for covid-19
- 1 case series of RRx-001 for covid-19
- Numerous preclinical studies

Lifespan: MIXED/POTENTIAL BENEFIT
Genetic knockout of NLRP3 increased mean lifespan in mice by 34% and maximum lifespan by 29% without a change in food intake or body weight [37]. Old NLRP3 knockout mice also had reduced levels of cholesterol, fasting glucose, IGF-1, lactate dehydrogenase, several liver enzymes, improved insulin sensitivity, and reduced leptin/adiponectin ratio. Serum IL-1β was not detected, but tissue levels of IL-1β and caspase-1 were reduced in knockout mice. There were no significant changes in other inflammatory markers such as TNFα, IL-6, and IL-8.

Old NLRP3 knockout mice had a reduced heart rate due to a lack of cardiac hypertrophy and reduced cardiac fibrosis [37]. Old NLRP3 knockout mice had other measures of improved cardiac fitness and fewer deaths from cancer, so the investigators still do not know the cause of death in these mice. Cardiac tissue from old NLRP3 knockout mice also had longer telomeres, fewer lipofuscin inclusions, though similar levels of senescent markers. There was a reduced expression of phosphorylated mTOR in old NLRP3 knockout mice and fewer autophagosomes, suggesting that autophagy may not be impaired in these mice.
Gene expression studies from the hearts of old NLRP3 knockout and WT mice suggested that the greatest difference in gene expression was increased expression of *Nampt*, the rate limiting step in NAD+ synthesis. After 15 weeks on a high fat diet, old NLRP3 mice had increased NAD+ levels and SIRT1 expression [37].

Genetic knockout of several components of the NLRP3 inflammasome (NLRP3 -/-; Asc -/-) improved several aspects of the aging phenotype including improved glucose levels, a reduction in IL-1β, improved thymic function, a reduction of bone-loss, a reduction of astrogliosis, an increase in BDNF, and improved cognition [38; 39].

In aged mice, treatment with MCC950 reduced glucose and IGF-1 levels and reduced the weight of fatty liver. It reduced cholesterol and triglycerides. It was reported to inhibit mTOR and induce autophagy in the liver [40].

It was reported that beta-hydroxybutyrate (BHB), but not acetoacetate, was an NLRP3 inhibitor by preventing K+ efflux and reducing ASC oligomerization and speck formation [41]. Administration of BHB or a ketogenic diet prevented activation of NLRP3.

Cardiovascular disease: POTENTIAL BENEFIT
NLRP3 activation is implicated in the pathophysiology of various cardiovascular diseases, including acute high-level elevation following ischemic injury, as well as sustained low-level activation in the context of chronic conditions such as heart failure, atherosclerosis, and hypertension [42]. The therapeutic window and dosing of prospective NLRP3 inhibitors may vary depending on the condition, though this remains to be determined in clinical testing. In male mice, NLRP3 was shown to play a role in age-related cardiac fibrosis [37].

Part of the rationale for NLRP3 inhibitors for cardiovascular disease stems from the results of the CANTOS trial, where the IL-1β antibody, canakinumab, reduced the risk of a second cardiovascular event.

Inflammation is a key feature of the pathophysiology of atherosclerosis. The uptake of oxidized LDL and cholesterol crystals can trigger the activation of the NLRP3 inflammasome in macrophages [43]. This facilitates their transformation into a pro-inflammatory phenotype which can elicit damage to vessel endothelial cells. Consequently, the inhibition of NLRP3 has been proposed as a therapeutic mechanism to mitigate vascular damage and slow progression in the context of atherosclerosis.

In a mouse model of atherosclerosis, 4-week treatment with MCC950 slightly reduced atherosclerotic plaque size and volume. It reduced macrophage plaque infiltration but had no effect on collagen content or the size of the necrotic core. VCAM1 and ICAM1, but not MCP-1, were also reduced [44]. Additionally, genetic elimination of multiple components of the NLRP3 inflammasome reduced atherosclerotic lesion size in multiple models of atherosclerosis [45].

In a mouse model of myocardial infarction (MI), 14-day treatment with MCC950 improved heart function, improved cardiac remodeling, and reduced myocardial fibrosis. MCC950 also reduced levels of cleaved IL-1β, NLRP3, and cleaved IL-18, and reduced the infiltration of inflammatory cells into the injured site [46].

RRx-001: In addition to its ability to inhibit the NLRP3 inflammasome, RRx-001 exerts a variety of other actions, including the induction of nitric oxide during hypoxic conditions. Preconditioning with RRx-001 (5 mg/kg 24 hours prior to ischemia) increased tissue perfusion and integrity during the reperfusion stage in a hamster model [47]. In addition to enhanced blood flow, there was a decrease in leukocyte adhesion in the vessels, indicative of a mitigation of the inflammatory response. This suggests that RRx-001 may be most beneficial as a preconditioning agent to prevent/mitigate vascular injury prior to surgeries that impact blood flow, such as coronary bypass. Additionally, it may help protect against chemotherapy-related cardiotoxicity.

Dapansutrile: Dapansutrile was tested in a randomized, double-blind Phase 1b trial (NCT03534297) at doses of 500, 1,000, or 2,000 mg/day (five oral capsules once, twice, or four times per day) for up to 14 days in patients with NYHA II–III defined systolic heart failure (n=30) [48]. The trial was not powered for functional endpoints, but trends of improvement were observed on exploratory measures. There were

improvements in left ventricular ejection fraction (from 31.5%, 95% CI 27.5 to 39% to 36.5%, 95% CI 27.5 to 45%) and in exercise time (from 570, 95% CI 399.5 to 627 seconds to 616, 95% CI 446.5 to 688 seconds) in the dapansutrile 2,000 mg cohort. Additional well-powered studies are needed to determine clinical benefit in this population. Further details on the efficacy of dapansutrile in preclinical models of heart failure are provided in the Dapansutrile report.

NT-0796: The CNS-penetrant NLRP3 inhibitor NT-0796 was tested in a Phase 1b/2a trial in 67 patients with obesity and elevated cardiovascular risk and elevated levels of the inflammatory marker CRP at baseline (NCT06129409). Full results have not yet been made available, but topline results were presented in a press release in June 2024. The 28-day study was conducted in-clinic with caloric intake limited to 2,000 kCal per day. The study met its primary endpoint, a significant reduction in plasma levels of the systemic inflammation marker hsCRP. The threshold of ≤2mg/L is considered the level of CRP reduction required to reduce cardiovascular risk. Less than 25% of participants in the placebo group achieved a reduction in CRP to ≤2mg/L by day 28, compared with more than 75% of participants treated with NT-0796. Body weight decreased in all subjects due to caloric restriction, but it was reported that the high-risk subjects treated with NT-0796 experienced the greatest placebo-adjusted decreases in body weight, which is consistent with preclinical studies (see below). Based on these results, Nodthera indicated that it plans to conduct a larger Phase 2 trial for this indication.

Obesity: POTENTIAL BENEFIT (primarily preclinical)
Systemic inflammation is a prominent feature of obesity and metabolic disease. Inflammation may contribute to the induction, maintenance, and complications of metabolic disease in a variety of ways. In mice, NLRP3 deficiency protected against metabolic impairment in the context of a high-fat diet [49]. These mice had lower rates of cardiac hypertrophy and liver steatosis, as well as better insulin sensitivity during aging, likely contributing to the increased lifespan of the NLRP3 deficient mice, relative to wildtype mice fed a high fat diet.
Inflammatory pathways may impact the regulation of energy homeostasis in the brain. CNS-penetrant NLRP3 inhibitors have shown benefit in preclinical models of obesity, through a decrease in food consumption and body weight. The effect appears to be at least partially mediated through a reduction in NLRP3-medited inflammatory signaling in the hypothalamus, the region of the brain involved in the regulation of appetite. Notably, the effect appears to be distinct from the mechanism of appetite mitigation observed with GLP-1 agonists, such that the two agents could potentially be used together to offer superior clinical benefits.

NT-0796 and NT-0249: The CNS-penetrant NLRP3 inhibitors from NodThera, NT-0249 and NT-0796 were tested in diet-induced obesity mouse models. These drugs have a short half-life in mice, so they were administered three times per day in order to achieve > 50% brain target cover throughout the 28-day studies [8]. The driver for weight loss with these NLRP3 inhibitors appears to be through a reduction in caloric consumption, as the degree of weight loss was similar to what was observed with caloric restriction. NT-0249 (100 mg/kg 3x/day, orally) led a reduction in body weight of 6.8% in C57Bl/6J mice, which was similar to the 7.4% weight loss observed in the calorie restricted mice, but less than the 14.3% reduction observed with the GLP-1 agonist, semaglutide (0.01 mg/kg). A similar pattern was observed using NT-0796 (100 mg/kg 3x/day, orally) which led to a 19.0% reduction in body weight in hCES1 mice, compared to a 16.9% reduction with caloric restriction, and a 21.5% reduction with semaglutide. Notably, significant reductions in food intake or body weight were not observed using these NLRP3 inhibitors in non-obese mice. The selective effect in obese rodents is thought to be related to a reduction in aberrant NLRP3-driven inflammatory activity within the hypothalamus, allowing for better regulation of energy homeostasis. Treatment with these CNS-penetrant NLRP3 inhibitors was associated with a reduction in levels of the activated glial marker GFAP in regions of the hypothalamus involved in energy homeostasis, including the arcuate nucleus and dorsomedial hypothalamus.
A reduction in body weight was also observed in a clinical trial testing NT-0796 in obese subjects, as described in the Cardiovascular section (press release).

VTX3232: In a diet-induced obesity mouse model using a high fat diet, treatment with the CNS-penetrant NLRP3 inhibitor VTX3232 (20 mg/kg BID orally) for 28 days led to a reduction in food intake and body weight by approximately 9%, but was modest relative to the reduction of 16% seen with the GLP-1 agonist, semaglutide (10 ug/kg/day s.c.) (Corporate Presentation). This was accompanied by a reduction in plasma levels of the inflammatory markers IL-1β, IL-6 and fibrinogen, though reductions were greater with semaglutide. However, the combination of VTX3232 with semaglutide led to greater reductions in caloric intake, body weight, and inflammatory biomarkers, including IL-1β, IL-6, fibrinogen, and PCSK9, relative to either drug alone. There was also a greater reduction in liver steatosis with the combination. Changes in body composition were not seen with either drug as a monotherapy, but a shift toward a lower fat mass relative to lean mass was observed with the combination of VTX3232 with semaglutide.
Based on the results from these preclinical studies, Ventyx Biosciences is planning a proof-of-concept Phase 2a trial in obese participants testing VTX3232 (40 mg/day, orally for 28 days).

Cancer: POTENTIAL BENEFIT WITH RRX-001; CONTEXT DEPENDENT

The role of NLRP3 in cancer is controversial. Given the inflammatory nature of many cancers, NLRP3 is often upregulated, and IL-1 is implicated in tumor development and progression. However, the impact of NLRP3 appears to be cancer-type and context dependent [50].
For example, one preclinical study suggested that NLRP3 knockout may exacerbate liver cancer metastasis [51], while an *in vitro* study suggested NLRP3 knockout or inhibition of NLRP3 can reduce metastasis [52].

The NLRP3 inhibitor RRx-001 has been clinically tested and exhibited signs of efficacy in numerous Phase 3 trials for various cancer indications, RRx-001 may be uniquely suited for cancer indications relative to other NLRP3 inhibitors because, as an electrophilic compound, it targets multiple cancer- associated pathways [5].
RRx-001 forms covalent adducts with thiol sulfurs, which can deplete cellular stores of cysteine, thioredoxin, and glutathione [4]. This can result in cytotoxic oxidative stress in tumor tissue, but a protective hormetic effect in healthy tissue. RRx-001 can have direct anti-tumor effects when injected intratumorally or given by hepatic artery infusion due to the modification of proteins involved in cell proliferation, cell cycle regulation, and cell components [4]. It can also induce damage to tumor cells via indirect mechanisms when administered intravenously through the generation of reactive oxygen species/reactive nitrogen species (ROS/RNS), the formation of inflammatory foam cell macrophages, and vascular normalization [4]. RRx-001 reacts with sulfhydryl groups in red blood cells (RBCs), which can increase their oxygen affinity, leading to enhanced oxygen delivery to hypoxic regions of the tumor. This can lead to changes in vascular dynamics as RRx-001-bound RBCs can promote the redistribution of blood flow in a manner that induces the pruning of the dysfunctional vasculature with a more even oxygen distribution [4].
RRx-001 can also impact immune cell dynamics. The RRx-001-bound RBCs increase expression of vascular adhesion molecules, leading to their uptake by tumor associated macrophages [4]. The oxidized contents of the RBCs are then released within the tumor, resulting in oxidative cytotoxicity. The RBC-laden tumor associated macrophages develop an M1-like foam cell profile which can inhibit the tumor growth promoting transcription factor, MYC, and in turn lead to the reduction in the expression of the immune checkpoint, CD47, ultimately stimulating immune antitumor activity.
In addition to its antitumor effects, RRx-001 also exerts protective effects on healthy tissue, which may reduce the damage related to chemotherapy or radiotherapy [4]. This stems from its hormetic effects in inducing endogenous protective/repair pathways, such as the Nrf2 antioxidant system. The release of microvesicles derived from damaged RBCs, following RRx-001 reactivity induces a low level of oxidative stress sufficient to induce protective antioxidant pathways.

Through these various mechanisms, RRx-001 has shown benefit in a variety of Phase 1, 2, and 3 trials in over 300 cancer patients to date, as a monotherapy, or in combination with other anticancer agents to enhance their efficacy and/or mitigate side effects [5]. Findings from some of the most notable studies are described below.

Small cell lung cancer (SCLC): RRx-001 was tested in the open-label Phase 2 QUADRUPLE THREAT trial (NCT02489903) in 26 patients with previously treated SCLC [53]. Participants were treated with RRx-001 at a dose of 4 mg administered intravenously on a weekly basis followed by a rechallenge with a platinum doublet, which consists of cisplatin/carboplatin plus etoposide. In the intention-to-treat (ITT) population, one patient (3.8%) had a complete response, six (23.1%) had partial responses, and seven (26.9%) had stable disease on platinum plus etoposide. During a median follow-up of 7.3 months, ranging from 1.5 to 30.1 months, the median overall survival was 8.6 months (95% CI 5.8 to not reached). Clinical response to the reintroduced platinum doublet was found to be associated with a decrease in PD-1 expression on circulating tumor cells following treatment with RRx-001, with an approximately 92.8% accuracy for predicting clinical outcome [54]. The original version of the Phase 3 REPLATINUM trial [55] (NCT03699956) was terminated by the study sponsor in favor of a new global Phase 3 study (NCT05566041).

Colorectal Cancer: A gain of function SNP (Q705K) in NLRP3 was found to be a prognostic factor for disease progression and poor survival in colorectal cancer [5]. In the Phase 2 ROCKET trial, RRx-001 was tested in combination with the chemotherapeutic irinotecan, compared to the tyrosine kinase inhibitor, regorafenib as a third- or fourth-line therapy in 34 patients with colorectal cancer [56]. Notably, numerous patients had previously tried using irinotecan alone or in combination with other agents without success. The combination of RRx-001 with irinotecan was associated with a trend toward longer overall survival (8.6 months vs 4.7 months), and a significant increase in progression free survival (6.1 months vs 1.7 months; Hazard Ratio [HR]: 0.24, 95% CI 0.09 to 0.61; p=0.003), compared with regorafenib. Five (out of 24) patients taking RRx-001 experienced partial responses (20.8%), with no complete or partial responses in the regorafenib group.

Glioblastoma: As a brain-penetrant molecule, RRx-001 was tested in 16 patients with newly diagnosed glioblastoma in the Phase 1 G-FORCE-1 trial [57]. Participants received RRx-001 followed by fractionated radiotherapy and temozolomide. The rate of disease control was 68.8%, based on three partial responses, and eight cases of disease stabilization. The median overall survival duration was 21.9 months (95% CI 11.7 to NA), which is longer than the 14.6-month survival previously reported for radiotherapy plus temozolomide in this population.

Brain metastases: In the Phase 1/2 BRAINSTORM trial, 28 patients with brain metastases received RRx-001 in combination with whole brain radiation therapy [58]. Among the 22 evaluable patients, the median survival duration was 5.2 months (95% CI 4.5 to 9.4). A decrease in fractional plasma volume (Vp) on DCE-MRI following RRx-001, was associated with a subsequent reduction in tumor volume at one and four months, suggestive of anti-angiogenic activity and a possible synergistic effect between RRx-001 with radiation.
Oral mucositis: RRx-001 was granted orphan drug status for acute radiation syndrome. Oral mucositis is one of the most common toxicities associated with radiation used for head and neck cancers. In the Phase 2a PREVLAR trial, 46 patients were treated with RRx-001 (4 mg infusions) prior to receiving cisplatin-based chemoradiotherapy. RRx-001 pretreatment did not reduce the incidence of developing severe oral mucositis in this study [59].

Myeloid diseases: The NLRP3 inhibitor, DFV890, in clinical development by Novartis, will be tested in adult patients with myeloid diseases in an open-label, Phase 1b, multicenter study (NCT05552469) [60]. DF890 will be tested twice per day for a minimum of 24 weeks in high and low doses in approximately 80 patients.

Autoimmune disease

Cryopyrin-associated periodic syndromes (CAPS): POTENTIAL BENEFIT
CAPS represents a group of rare autoinflammatory conditions caused by gain-of-function mutations in the NLRP3 gene, CIAS1, which encodes for the NLRP3 inflammasome protein, also known as cryopyrin [61]. Current standard of care involves treatment with anti-IL-1 antibodies, but some patients only achieve a partial response, due to NLRP3-driven inflammatory responses mediated by factors other than IL-1. Several companies have tested their NLRP3 inhibitors in this population in proof-of-concept studies.
DFV890: The NLRP3 inhibitor, DFV890 was tested in an open-label Phase 2 study in four patients with the familial cold autoinflammatory syndrome (FCAS) form of CAPS (NCT04868968). DFV890 was administered in the form of film-covered tablets at a dose of 100 mg BID for three days and 100 mg on the morning on the fourth day. A cold challenge was performed at baseline and on day four. The primary outcome was the ratio of fold change from pre-challenge to the highest post-challenge value of white cell count between treatment and baseline. Based on the results posted on the ClinicalTrials.gov record, the geometric least squares mean for the ratio of fold change was 0.82 (90% CI 0.56 to 1.21). There were also improvements noted on the Physician global assessment of autoinflammatory disease activity

scores and Patient's global assessment of disease activity scores, with a shift from activity in the minimal to mild range (scores 1-2) towards the absent to minimal range (scores 0-1).

VTX2735: The peripheral NLRP3 inhibitor VTX2735 has been shown to maintain inhibitory activity toward NLRP3 across a broad range of CAPS-related NLRP3 mutations. Compared with an IC_{50} of 2 nM toward LPS-induced IL-1β release in healthy human monocytes, the IC_{50} ranged from 14-166 nM for monocytes with the gain-of-function NLRP3 mutations (Corporate Presentation). As a result it was tested in a proof-of-concept Phase 2 trial in seven patients with FCAS, the most common form of CAPS (Press release). Five of the participants completed the study, as one withdrew consent after the first treatment period, and the other withdrew due to lack of efficacy (Corporate Presentation). The study involved two 14-day dosing periods, with a 14-day washout in between testing VTX2735 at 100 mg BID (n=2) or 150 mg BID (n=5), with a follow-up period up to 30 days. Disease activity was assessed through the Key Symptom Score (KSS) which is a scale ranging from zero to ten. During the first treatment period participants showed a mean reduction of KSS by 85%. Three participants had low KSS (<2.5) at baseline, which remained low, while the other five had high scores (>5) which dropped toward zero. One participant's symptoms rebounded during the withdrawal period, but fell dramatically again during the second treatment period. Similar trends were observed for inflammatory biomarkers, IL-6, high-sensitivity C-reactive protein (hsCRP), and serum amyloid A (SAA), such that levels remained low, or fell below the limit of detection in those with low levels at baseline, and levels fell to very low levels in those with elevated biomarkers at baseline, with evidence of rebounding during the withdrawal period in some participants. The low baseline levels in some participants are expected to stem from prior long-lasting treatments, such as anti-IL-1 antibodies (e.g. canakinumab).

ZYIL1: The oral NLRP3 inhibitor ZYIL1 was tested in an open-label proof-of-concept trial in three adult patients with the FCAS subtype of CAPS, with mild to moderate disease severity [62]. The patients were treated with ZYIL1 at a dose of 50 mg BID for seven days. ZYIL1 treatment was associated with reductions in blood-based inflammatory biomarkers from baseline, including plasma CRP (from 23.4 ±15.3 mg/L to 1.4 ±0.8 mg/L), plasma IL-6 (from 10.5 ±6.3 pg/mL to 6.3 ±3.6 pg/mL), SAA (from 217± 229.4 µg/mL to 12.4 ±1.9 µg/mL), and white blood cell count (from 8,500 ±350/µL to 5,630 ±250/µL), but had no significant effect on plasma IL-1β levels. Improvement was observed in disease activity based on a mean decrease of 9 points on the Physician Global Assessment Score, and mean decrease of 9.3 points on the Patient Global Assessment Score.

Emlenoflast: Full details of the study results have not been made available, but an open-label study assessing the potential efficacy of emlenoflast in CAPS patients as part of a Phase 1 trial reported in a press release that, following treatment, one CAPS patient showed clinical improvement from a CAPS-related flare within hours, and remission within days.

Selnoflast: Selnoflast was tested in an open-label study in CAPS patients to test preliminary efficacy as part of a Phase 1 trial, but results have not been made available.

Ulcerative colitis: UNCLEAR/NO CLEAR BENEFIT WITH SELNOFLAST
Selnoflast (RO7486967) was tested in a double-blind, placebo-controlled Phase 1b RCT in 19 adult patients with moderate to severe ulcerative colitis [63]. Selnoflast was administered as an oral dose of 450 mg once daily for seven days. The dose was selected to achieve 90% IL-1β inhibition in the plasma and colon tissue, based on dosing in a prior Phase 1 trial. While levels of selnoflast reached concentrations (5-20 µg/g) above the estimated IC_{90} (2.0 µg/mL or 1.94 µg/g) in the colon tissue, there were no meaningful differences in the expression of IL-1-related genes in sigmoid colon tissue, or in stool biomarkers. Robust IL-1β inhibition was observed *ex vivo* following whole blood stimulation with LPS. The clinical development of selnoflast for ulcerative colitis was terminated following the results of this study.

ZYIL1, an oral NLRP3 inhibitor from Zydus Lifesciences, is currently being tested in a randomized, double-blind Phase 2a trial in patients with mild to moderate ulcerative colitis resistant or intolerant to oral aminosalicylates (NCT06398808). ZYIL1 will be tested in 25 mg or 50 mg oral capsules for 12 weeks. The trial has an estimated completion date in late 2024.

Covid-19: POTENTIAL BENEFIT/UNCLEAR
Elevation of NLRP3 has been observed in the context of covid-19, particularly in lung tissues and fluids, and the signature of inflammasome activation was associated with disease severity and worse prognosis [64]. This activation is likely triggered by SARS-CoV2-related PAMPs. Sustained NRLP3 activation may contribute to covid-19-associated coagulopathy and immunothrombosis, via increased levels of the pro-inflammatory cytokines, IL-1 and IL-6 [64]. The inhibition of NLRP3 has been proposed as a method to mitigate the lung inflammation contributing to covid-19 pneumonia, and has been clinically tested. The potential benefit has been difficult to ascertain, as severe patients are generally treated with multiple anti-inflammatory agents. Additionally, there may be specific subpopulations that experience preferential benefit, and/or there may be an optimal therapeutic window of administration, which has yet to be determined.

DFV890: The oral NLRP3 inhibitor DFV890 was tested in an international (12 countries) Phase 2a RCT in 143 patients with covid-19 pneumonia and impaired respiratory function who had been diagnosed within seven days prior to randomization (NCT04382053) [65]. Participants received DFV890 at a dose of

50 mg BID orally or nasogastrically in combination with the standard of care, or standard of care alone for 14 days. The primary endpoint, the APACHE II score, a measure of disease severity based on laboratory values and patient signs, at day 14 or on day-of-discharge, was not met. The adjusted least-squares mean difference in APACHE II score was 0.11 (90% CI -2.0 to 2.3). CRP levels, a marker of systemic inflammation, decreased in both groups over time. Patients treated with DFV890 generally showed faster clearance of SARS-CoV2, with 76.4% showing clearance by day 7, relative to 57.4% in the standard of care group. A treatment effect with an inflammation modulating drug, such as NLRP3 inhibitors, may have been difficult to observe in this population, since the majority of participants were taking high-dose corticosteroids.

RRx-001: There are two case reports involving the successful use of RRx-001 in critically ill patients with covid-19-related respiratory failure who had exhausted other treatment options [66]. Both received 4 mg doses of RRx-001 intravenously twice weekly for two weeks. One patient was a 59-year-old male with hypothyroidism, type 2 diabetes, and hypertension, who experienced hemodynamic stabilization, a reduction in interstitial lung thickening on CT and be weaned off a cardiopulmonary bypass machine following RRx-001 treatment. The other patient, a 36-year-old male with morbid obesity, experienced clinical and radiographical improvement, allowing for discontinuation of chest tubes and tracheostomy.

Safety: Clinically tested NLRP3 inhibitors show a good safety profile to date, with no clear evidence of class related toxicities or increased infection risk, however, the trials have been short, so long-term safety remains to be established.

Types of evidence:

- Over a dozen clinical trials including >300 cancer patients for RRx-001
- 3 clinical trials for oral dapansutrile (Phase 1 healthy volunteers, heart failure; Phase 2 gout)
- 3 clinical trials for DFV890 (Phase 1 in healthy volunteers; Phase 2a covid-19, and CAPS)
- 1 clinical trial for emlenoflast (Phase 1 in healthy volunteers)
- 1 clinical trial for GDC-2394 (Phase 1 in healthy volunteers)
- 1 clinical trial for NT-0249 (Phase 1 in healthy volunteers)
- 3 clinical trials for NT-0796 (Phase 1 in healthy volunteers; Phase 1b Parkinson's, and obesity)
- 2 clinical trials for selnoflast (Phase 1 in healthy volunteers; Phase 1b ulcerative colitis)
- 1 clinical trial for VENT-02 (Phase 1 in healthy volunteers)
- 2 clinical trials for VTX2735 (Phase 1 in healthy volunteers; Phase 2a in CAPS)

- 1 clinical trial for VTX3232 (Phase 1 in healthy volunteers)
- 2 clinical trials for ZYIL1 (Phase 1 in healthy volunteers; Phase 2a in CAPS)
- Numerous preclinical studies

No reported safety issues have been reported from preclinical studies in animal models. IL-1β antibodies, such as anakinra and canakinumab, are potentially associated with severe infection risks. However, there are several redundant inflammasomes that all have anti-infective properties. Preclinical studies have suggested that NLRP3 may be important for resistance to a couple of infective agents (e.g. *Burkholderia pseudomallei, Toxoplasma gondii*).

Clinical development of MCC950 was terminated due to evidence of liver injury, including elevated liver enzymes during a Phase 1 trial in patients with rheumatoid arthritis. MCC950 has poor bioavailability and was dosed at high levels, which may have contributed to the toxicity [67]. Evidence from other studies suggest that this may be a drug-specific, rather than class-specific effect.

Dapansutrile (OLT1177): Dapansutrile has generally been safe and well-tolerated in the six clinical trials conducted thus far, three of which tested an oral formulation. There have been no serious treatment emergent adverse events (TEAEs). TEAEs have generally been mild, and resolved on their own. Dapansutrile has not been associated with changes in hematological parameters, vital signs, physical exams, laboratory chemistry, liver function tests, renal function, or blood pressure [48; 68].

DFV890: DFV890 was generally well-tolerated in a Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy volunteers (n=122) and a Phase 2a trial in patients with covid-19 (n=143), and an open-label trial in patients with CAPS (n=4).
In the Phase 1 SAD study conducted in Germany, 3 mg was chosen for the starting dose based on the IC_{50} and IC_{90} in plasma of 0.33 and 2.14 µM, respectively, and expectation that biological activity will require ≤75% inhibition of IL-1β release [6]. The highest selected dose, 600 mg, was expected to be below the NOAEL, based on preclinical toxicology studies. The Phase 1 study tested several different oral formulations of DFV890, including a crystalline suspension, crystalline tablets, encapsulated crystalline tablets, and a spray-dried dispersion (SDD) suspension. The crystalline tablets at a dose of 100 mg once-daily or 25 mg twice-daily were sufficient to maintain ~90% of the IL-1β release inhibition over 24 hours at steady state, based on an IC_{90} of 1,340 ng/mL (90% CI 1,,190 to 1490) in an *ex vivo* LPS stimulation assay. Ten percent of participants discontinued due to an adverse event, though adverse events were generally distributed between the active and placebo arms. Treatment emergent adverse events (TEAE)

occurred in 70% of participants in the DF890 arm (66 of 94 subjects) (70%) and in 75% of those in the placebo arm (21 of 28 subjects). The majority of adverse events were mild, and there were no serious adverse events. TEAEs of maculopapular skin rash and/or pruritus (10% of subjects) were considered potentially related to the study drug. Histopathological analysis of the rashes indicated they were primarily superficial with no immune cell infiltration. Non-clinically significant decreases in neutrophils and leukocytes were noted in some subjects which could potentially be related to the drug's mechanism of action. Additionally, there were no other clinically relevant findings reported on vital signs, ECG, or physical examination.
In the Phase 2a multinational trial in patients with covid-19, the proportion of patients reporting an adverse event was similar across the DFV890 and standard of care groups (58.6% vs 54.2%) [65]. The adverse events were primarily mild, and there were no drug-related serious adverse events.
In CAPS patients treated with DFV890, there were no serious adverse events (NCT04868968).

Emlenoflast: The oral, CNS-penetrant NLRP3 inhibitor, Inzomelid (IZD174), later named emlenoflast, was tested in a Phase 1 SAD and MAD trial (n=80) in healthy volunteers along with an open-label preliminary efficacy study in adult patients with CAPS (NCT04015076). Full study results have not been made available. A press release from the study sponsor, Inflazome, indicated that the drug showed good safety and tolerability, with dose proportional exposure that correlated with markers of target engagement.
A Phase 1 trial testing emlenoflast in patients with Parkinson's disease was withdrawn following the acquisition of the asset by Roche, who is instead developing another NLRP3 inhibitor, selnoflast, for this indication.

GDC-2394: The clinical development of GDC-2394 has been terminated due to safety concerns. GDC-2394 was developed as part of an effort to identify novel NLRP3 inhibitors that minimized the risk for liver injury that was observed with the first major NLPR3 inhibitor, MCC950 [69]. Renal toxicity was observed in cynomolgus monkeys stemming from compound precipitation, so efforts were made to improve the solubility of the compound [69].
In the Phase 1 SAD and MAD trial in healthy volunteers (n=67) conducted in New Zealand, the starting dose of 150 mg was selected based on safety margins identified in the study in cynomolgus monkeys, and the human equivalent dose of the NOAEL in monkeys was 193 mg/kg. GDC-2395 showed dose proportional exposure, minimal accumulation, as well as minimal CYP3A4 induction in a drug-interaction study [10]. It was generally well tolerated in SAD, MAD, and food interaction studies. The drug was not associated with any clinically meaningful, abnormal ECG or vital signs findings. However, all participants

in the drug interaction study (n=9) experienced adverse events. The most common were fatigue, headache, and rash. Two participants in the drug interaction study experienced grade 4 drug-induced liver injury which met the criteria for Hy's law (liver enzymes >3× the upper limit of normal and total bilirubin >2× upper limit of normal or clinical jaundice) that were classified as treatment related, but not stemming from a drug-drug interaction. Both recovered within three months. Another participant experienced a grade 2 elevation in alanine aminotransferase (ALT). Additionally, one participant in the MAD study experienced an asymptomatic elevation of ALT to 1.67 times the upper limit of normal. Due to the potential for liver toxicity, clinical development by Genentech was terminated.

NT-0249: The oral NLRP3 inhibitor has been tested in a Phase 1 trial in healthy volunteers. Details have not been made available, but topline results from a press release by the study sponsor, NodThera, indicate that it was safe and well-tolerated, with dose-proportional exposure in a SAD study. A separate press release indicated that NT-0249 also showed a good profile, suitable for once daily dosing, in the MAD study. While originally designated as a peripheral NLRP3 inhibitor, CSF sampling indicated that NT-0249 is CNS penetrant. Reductions in plasma inflammatory markers, including CRP and fibrinogen, were also observed.

NT-0796: The oral, CNS-penetrant NLRP3 inhibitor has been tested in a Phase 1 trial in healthy volunteers, a Phase 1b/2a trial in patients with Parkinson's disease, as well as a Phase 1b/2a trial in patients with obesity and elevated cardiovascular risk (NCT06129409). Full results have not been made available, but topline results of the studies have been released as part of press releases from the sponsor of these studies, NodThera. NT-0796 was reported to have good pharmacokinetic and pharmacodynamic profiles, with dose proportional exposure, including the inhibition of IL-1β and IL-18 in whole blood *ex vivo* stimulation assays. CSF sampling indicated good CNS exposure, to levels sufficient for anti-inflammatory activity in the periphery. It was generally well tolerated, with no evidence of abnormalities on liver function tests.
In mice (C57Bl/6), NT-0796 shows a brain-to-blood ratio of 0.79 following i.v. administration [7]. In preclinical safety assays, NT-0796 did not show any evidence of CYP enzyme inhibition, hERG inhibition, or genotoxicity [7].
NT-0796 was reported to be safe and well-tolerated in Parkinson's patients in a press release. Adverse events were primarily mild and transient, and there were no serious adverse events.
NT-0796 was also reported to be safe and well tolerated in obese subjects with cardiovascular risk in a press release. The reported adverse events were mild and transient, and there were no serious adverse events.

RRx-001 (nibrozetone): RRx-001 has been tested in over 300 patients to date in Phase 1, 2, and 3 trials for cancer indications [5]. It has been found to be generally safe and well-tolerated across studies. The only major toxicity associated with RRx-001 is sterile painful infusion phlebitis (vein inflammation) during intravenous administration which stems from the displacement of nitric oxide from its binding site on hemoglobin by RRx-001 (at the same site that RRx-001 interacts, β-cysteine 93) [4]. This side effect can be mitigated through the *ex vivo* incubation of RRx-001 with an aliquot of autologous whole blood prior to infusion, which has become the standard practice for RRx-001 administration in cancer clinical trials. Although RRx-001 binds to hemoglobin, it is not associated with anemia, as it binds to only a small population of red blood cells, and shows no evidence of hemotoxicity [4]. Because it is sequestered within the red blood cells it has minimal potential for systemic toxicity. RRx-001 does not interact (induce or inhibit) cytochrome P450 enzymes, and to date does not have any drug-drug interactions. No increases in infections have been observed. Additionally, RRx-001 has been tested in combination with radiation and chemotherapy, and is associated with lower levels of side effects relative to treatment with these cytotoxic agents alone [5].

Selnoflast: Originally called Somalix (IZD334), the oral, peripheral NLRP3 inhibitor selnoflast was reported to have good safety and tolerability in a Phase 1 trial (NCT04086602) (n=64) in healthy volunteers and CAPS patients based on a press release from the trial's sponsor, Inflazome. Full study results have not been made available.
The asset was subsequently acquired by Roche in late 2020, and tested in a Phase 1b trial at an oral dose of 450 mg/day for seven days in patients with ulcerative colitis. Selnoflast was well-tolerated in this study. Adverse events were primarily mild (grade 1), and there were no serious adverse events. The most common adverse events in the selnoflast arm were headache and dyspepsia, occurring in two participants each. Selnoflast was not associated with any clinically meaningful changes in clinical chemistry, liver function tests, urinalysis, ECGs, or vital signs.

VENT-02: The oral, CNS-penetrant NLRP3 inhibitor, VENT-02 was tested in a Phase 1 SAD and MAD study in healthy volunteers. According to topline data announced by the sponsor, Ventus Therapeutics, in April 2024, VENT-02 demonstrated full target engagement based on 100% inhibition of IL-1β in an *ex vivo* whole blood challenge assay. The half-life was consistent with once daily dosing. VENT-02 was present at significant concentrations within the CSF and was associated with reductions in inflammatory biomarkers, including hsCRP. VENT-02 was generally well-tolerated with no dose-limiting toxicities. Adverse events were primarily mild, with no serious adverse events. Moderate adverse events were

headache and nausea, which were only observed at a dose that is several times higher than the intended therapeutic dose.

VTX2735: The oral, peripheral NLRP3 inhibitor VTX2735 was reported to be well tolerated across all tested doses in a Phase 1 SAD and MAD trial in 72 healthy adult volunteers by the study sponsor, Ventyx Biosciences, in a Press Release. The study tested single doses up to 200 mg (15, 50, 100, and 200 mg) and multiple doses up to 200 mg for 14 days. Drug exposure was reported to be dose proportional, and correlated with biomarkers of target engagement, including suppression of IL-1β release in an *ex vivo* plasma stimulation assay, and reductions in levels of the inflammatory marker hsCRP. Adverse events were mild, and there was no dose-related trend in the frequency of TEAEs, and abnormalities on liver function tests.
In a proof-of-concept Phase 2a trial in patients with CAPS (n=7) treated with VTX2735 for a total of 28 days, over the course of two 14-day treatment periods, all adverse events were mild or moderate and resolved without drug cessation (Corporate Presentation). Overall, VTX2735 was generally well-tolerated in this population.

VTX3232: The oral, CNS-penetrant NLRP3 inhibitor VTX3232 was reported to be safe and well-tolerated by the study sponsor, Ventyx Biosciences in Phase 1 SAD (tested doses: 1, 3, 10, 20, 50, and 80 mg) and MAD (n=40) (tested doses: 1, 3, 10, 20, and 40 mg) studies in healthy volunteers (Corporate Presentation). VTX3232 showed dose-linear exposure, with 100% relative bioavailability and no food effect. VTX3232 shows good CNS partitioning, and daily dosing is sufficient to achieve CNS levels within the therapeutic range, based on IL-1β inhibition in *ex vivo* whole blood assays (IC_{50} = 2.7 nM). In the blood, the IC_{50} is reached with 3 mg doses, while the doses from 20-80 mg reached the IC_{90}. In the CSF, daily doses of 40 mg achieve levels above the IC_{90} for 24 hours. In plasma, doses ≥ 3mg reduce levels of the inflammatory markers hsCRP and IL-6 by 55% and 46%, respectively, which is in line with the level of reduction observed with anti-IL-1 therapy. In the CSF, a similar degree of IL-6 inhibition (~50%) was observed with doses of 40 mg. There were no CYP, hERG, or transporter interactions. All TEAEs were mild or moderate with no trends, and no dose-limiting toxicities.

ZYIL1: The oral, CNS-penetrant NLRP3 inhibitor ZYLI1 (usnoflast), in clinical development by Zydus Lifesciences, was tested in Phase 1 open-label SAD (n=30) and MAD (n=18) studies in healthy volunteers (NCT04731324; NCT0497218) [70]. The SAD study tested single doses of 25, 50, 100, 250, and 400 mg, while the MAD study tested the doses 12.5, 50, and 100 mg for 14 days. ZYIL1 had dose proportional exposure and limited accumulation with multiple dosing. The majority of subjects showed greater than

90% inhibition (IC_{90}) of IL-1β and greater than 70% inhibition of IL-18 in *ex vivo* blood assays at all tested doses, while there was no significant inhibition of IL-6 or TNF-α. One adverse event of a low white blood cell count occurred at the 250 mg dose in the SAD study. In the MAD study, there were 11 adverse events in six participants, including constipation, headache, pyrexia, glycosuria, nasopharyngitis, a decrease in neutrophil count, as well as increases in transaminases, alanine aminotransferase, and triglycerides, all of which resolved. There were no trends or dose-dependency to the adverse events. Most were of mild severity, while the increase in transaminases was moderate, which led to study discontinuation. The increase in triglycerides and decrease in neutrophil count were considered severe. There were no clinically relevant changes in the clinical laboratory, vital signs, physical examination, or ECG findings. Based on this study, an oral dose of 50 mg BID administered for seven days was selected for a pilot trial in patients with the FCAS form of CAPS (n=3). There were five TEAEs, none of which were considered related to ZYIL1 [62]. There were no clinically meaningful changes in vital signs, physical examination, ECG, and renal or liver function tests. There was no evidence of QTc prolongation.

Drug interactions: None known, but they may interact with other anti-inflammatory or immune modulating therapies.

Sources and dosing:
None of the NLRP3 inhibitors have been approved for use in any condition to date, and several are currently in clinical trials.
RRx-001, from EpicentRx, is generally administered intravenously, following incubation with autologous blood to mitigate side effects, at a dose of 4 mg/kg weekly in cancer trials. The other clinically tested NLRP3 inhibitors use oral formulations.
Dapansutrile, in clinical development by Olatec Therapeutics, has been tested at doses of 1,000 to 2,000 mg per day in gout and heart failure patients.
NT-0796, in clinical development by NodThera, was tested at a dose of 150 mg BID in Parkinson's disease patients.
VTX2735, in clinical development by Ventyx Biosciences, showed good safety at doses up to 200 mg in a Phase 1 study, as well as in doses of 100 mg BID and 150 mg BID in CAPS patients.
VTX3232, in clinical development by Ventyx Biosciences showed good safety at doses up to 80 mg, and doses of 40 mg showed good target engagement in the CNS. It is expected that 40 mg is the dose that will be used for CNS indications, including the planned trials in Parkinson's disease and obesity.

ZYIL1 (usnoflast), in clinical development by Zydus Lifesciences, showed good safety in doses of 100 mg/day in a Phase 1 study, and at 50 mg BID in CAPS patients. Ongoing trials are testing doses of 25 mg and 50 mg.

Research underway:
Several companies currently developing NLRP3 inhibitors for CNS diseases are at various stages of development.

Ongoing clinical trials

DFV890, an NLRP3 inhibitor in clinical development by Novartis is currently being tested in a Phase 1 trial in adult patients with myeloid diseases (NCT05552469) with an expected completion date in 2026, a Phase 2a proof-of-concept trial in patients with symptomatic knee osteoarthritis (NCT04886258) with an expected completion date in 2025, a Phase 2a randomized, placebo-controlled, double-blind trial in adult participants with coronary heart disease and elevated hsCRP (NCT06031844) with an expected completion date in 2025, and a Phase 2a randomized, placebo-controlled, double-blind trial in adult participants with coronary heart disease and clonal hematopoiesis of indeterminate potential (CHIP) (NCT06097663) with an expected completion date in 2026.

RRx-001, a pleiotropic NLRP3 inhibitor in clinical development by EpicentRx, is currently being tested in a controlled, open-label, global randomized Phase 3 trial with platinum chemotherapy versus platnium chemotherapy alone in patients with small cell lung cancer (REPLATINUM) (NCT05566041) with an expected completion date in 2025, and a randomized placebo-controlled Phase 2 trial of two schedules of RRx-001 for the attenuation of severe oral mucositis in patients receiving concomitant chemoradiation for the treatment of locally advanced squamous cell carcinoma of the oral cavity or oropharynx (head and neck cancer) (KEVLARx) (NCT05966194) with an expected completion date in 2025.

Senoflast (RO7486967), a peripheral NLRP3 inhibitor in clinical development by Roche, is currently being tested in a Phase 1b, adapative, randomized, double-blind, placebo-controlled, parallel design trial in patients with early idiopathic Parkinson's disease for up to 28 days (NCT05924243) with an expected completion date in 2025.

VENT-01 (NNC6022-0001), a peripheral NLRP3 inhibitor in clinical development by Novo Nordisk is currently being tested in a Phase 1 trial in healthy volunteers (NCT06336005) and has an expected completion date in 2024.

VTX3232, a CNS-penetrant NLRP3 inhibitor in clinical development by Ventyx Biosciences, is currently being tested in a Phase 2a open-label trial in early stage idiopathic Parkinson's disease for 28 days (NCT06556173) with an expected completion date in 2025.

ZYIL1, a CNS-penetrant NLRP3 inhibitor in clinical development from Zydus Lifesciences is currently being tested in a proof-of-concepet placebo controlled, randomized, double blind Phase 2 trial in ALS patients at a dose of 25 mg or 50 mg (oral capsules) for 12 weeks (NCT05981040) with an expected completion date in 2024, and in a Phase 2a randomized, double-blind, parallel group trial in patients with mild to moderate active ulcerative colitis resistant or intolerant to oral aminosalicylates at a dose of 25 or 50 mg (oral capsules) for 12 weeks (NCT06398808) with an expected completion date in 2024.

Planned clinical trials

NT-0796: Phase 2 trials are planned by the company NodThera testing NT-0796 in Parkinson's disease and in obesity (press release).

VENT-02: A Phase 1b trial in Parkinson's disease testing VENT-02 is planned by the company Ventus Therapeutics (press release).

VTX2735: A Phase 2 trial in pericarditis is planned by the company Ventyx Biosciences (press release).

VTX3232: A Phase 2a trial in patients with obesity with cardiovascular risk factors, likely dosed at 40 mg/day, orally for 28 days, is planned by the company Ventyx Biosciences (press release).

ZYIL1: A Phase 2 trial in Parkinson's disease has also been approved, but not yet registered (press release).

Search terms:
Pubmed, Google: NLRP3 inhibitor

- neurodegeneration, Alzheimer's disease, aging, lifespan, inflammation, cardiovascular, obesity, cancer, safety, clinical trials

Websites:

- Clinicaltrials.gov
- PubChem (Dapansutrile; RRx-001; Selnoflast; Emlenoflast; Usnoflast)
- Drugbank.ca (Dapansutrile; DFV890; RRx-001)

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