In the previous blog we saw that numerous biopharmaceuticals are investing to explore the potential of NLRP3 inhibitors. After in-depth analysis of each asset and their potential development in various therapeutic areas, it is clear that these inhibitors are being explored in every possible immune mediated indication.
Let’s explore the potential of NLRP3 in each of the therapeutic areas.

**Neuroscience:**
Neuroinflammation, and its association with the progression of neurodegenerative illness, has been an important area of focus. These diseases are caused by various different underlying mechanisms, but NLRP3 inflammasome activation and dysregulation are common features of several neurodegenerative diseases. Several studies demonstrated that modulating NLRP3 inflammasome expression and activation delays the progression of neuroinflammation in a number of neurodegenerative disease models.1

Olatec Therapeutics’ NLRP3 inflammasome inhibitor OLT1177 pre clinically demonstrated that cognitive impairment was rescued in a mouse model of Alzheimer’s disease.2 A study conducted with MCC950 demonstrated that inhibiting the NLRP3 inflammasome with MCC950 promotes non-phlogistic clearance of amyloid-β and cognitive function in APP/PS1 mice.3 Another study of MCC950 in Parkinson model demonstrated that inhibition of inflammasome activation effectively mitigated motor deficits, nigrostriatal dopaminergic degeneration, and accumulation of α-synuclein aggregates. These findings highlight the potential of NLRP3 as a target for disease modifying treatments for Parkinson’s disease and Alzheimer’s disease.4 It will be interesting to note the effect of NLRP3 inhibitors in neurodegenerative diseases clinically.

**Broad Immunology:**
This category led by VTX2735 (Ventyx), NT-0796 (NodThera) and RG6418 (Roche) explores all molecules which are under development for the treatment of inflammatory diseases but specific indication has not been disclosed.

VTX2735 and NT-0796 are recruiting healthy subjects for PK/PD studies 5,6 whereas RG6418 is currently in phase 1 development for inflammation.7

**Pulmonology:**
Molecules under development for CRS due to COVID-19 and pulmonary inflammation are explored in this category. A study published on bioRxiv suggested that NLRP3 activation takes place early in the COVID-19 infection and initiates CRS. Hence, NLRP3 becomes a target to control the inflammatory cytokines causing CRS.8

Dapansutrile (Olatec) is in phase 2 study evaluating the safety and efficacy in moderate COVID-19 symptoms and evidence of early CRS.9 DFV890 (Novartis) is in Phase 2 study. Trial completion was reported in November 2021. However, results are not available yet. 10 Cadila Healthcare Limited has conducted two Phase 1 trials in healthy subjects to assess the safety, efficacy, PK and PD and their completions were reported in June 2021 and November 2021 respectively. Results have not been published yet. 11, 12

**Rheumatology**
Rheumatology category consists of the drugs under development for the treatment of CAPS (Cryopyrin-associated periodic syndrome) and Gout. CAPS is a group of rare, heterogenous autoinflammatory diseases related to the defect in the protein cryopyrin (NLRP3) which leads to interleukin 1β-mediated systemic inflammation. IL-1 targeted therapies like Kineret (anakinra), Ilaris (canakinumab) and Arcalyst (Rilonacept) are already approved for the treatment of CAPS.13 In an ex-vivo study it was found that MCC950 blocked constitutive activation of NLRP3 observed in the PBMCs of CAPS patients.14

A preliminary analysis reported by Inflazome for Inzomelid (Roche) showed that a patient with a confirmed NLRP3 mutation suffering from CAPS showed rapid clinical improvement within hours.15 After the acquisition of Inflazome by Roche, no further development has been reported for inzomelid in CAPS disease area.

DFV890 (Novartis) is in Phase 2 development for the treatment of FCAS patients and ZYIL1 (Cadila Healthcare) has initiated Phase 2 study in CAPS patients. 16,17

For Gout, oral formulation of dapansutrile (Olatec) was found to reduce joint inflammation induced by monosodium urate crystal gouty arthritis in mice.18 Phase 1 study results suggests that healthy subjects receiving 1000 mg of dapansutrile daily for 8 day exhibited neither adverse events nor biochemical changes. Dapansutrile decreased IL-18 levels by 60% and IL-18 by 70% at concentrations 100-fold lower in vitro than plasma concentrations safely reached in humans.19 Phase 2a study results demonstrated that between baseline and day 7, there was a mean reduction in patient-reported target joint pain of 82.1% (22.68; p=0.031) for the 100 mg/day group, 84.2% (16.33; p=0.016) for the 300 mg/day group, 68.9% (34.89; p=0.031) for the 1000 mg/day group, and 83.9% (15.44; p=0.008) for the 2000 mg/day
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group, compared to baseline. Of the 34 patients, 73.5% reported a total of 45 adverse events, most being metabolism and nutrition disorders and gastrointestinal disorders.20

Cardiovascular and Metabolism
Osteoarthritis, Heart Failure and unspecified cardiovascular diseases are included in this section. Dapansutrile (Olatec) preclinical results showed that the drug limits infarct size and prevents left ventricular systolic dysfunction when given within 60 minutes following ischemia reperfusion injury in the mouse. This preclinical data paved the way for a phase 1 study.21 Phase 1 study (NCT03534297) was conducted in patients with heart failure and reduced ejection fraction. In the dapansutrile 2000 mg cohort, improvements in left ventricular EF [from 31.5% (27.5-39) to 36.5% (27.5-45), P = 0.039] and in exercise time [from 570 (399.5-627) to 616 (446.5-688) seconds, P = 0.039] were seen.22

Clinical data is unavailable for determining the effect of NLRP3 inflammasome inhibitors in treating osteoarthritis, however Novartis is furthest ahead in this area with a Phase 2 study (NCT04886258) evaluating DFV890 in knee osteoarthritis. A review article highlighted the role of NLRP3 inflammasome in osteoarthritis in a preclinical setting. Dexmedetomidine demonstrated that NLRP3 inflammasome activation via NF-κB pathway results in improvement in pain symptoms and alleviated cartilage damage in a rat model. Curcumin in mice models demonstrated that inhibition of the release of inflammasome NLRP3 results in alleviation of cartilage damage. Icariin administration in rat model demonstrated that inhibition of LPS-induced activation of NLRP3 inflammasome and proptosis-related caspase-1 signaling pathway suppressed proptosis of rat chondrocytes and alleviated cartilage damage.23

Hepatology
No drug is in clinical development for NASH, while there are five drugs being evaluated preclinically. IFM-514 demonstrated that the specific NLRP3 antagonist IFM-514 has decreased fibrosis and inflammation in experimental murine model of NASH.24

A paper published in May 2021 demonstrated that Obeticholic acid (OCA) works in NASH by direct inhibition of NLRP3 inflammasome activation in macrophage, inhibition of inflammasome activation-elicited hepatic lipid accumulation and contributing to the amelioration of NASH.25

Dermatology
Drugs under development for the treatment of Atopic Dermatitis, Bullous Pemphigoid and Epidermolysis Bullosa. Preliminary genetic evidence points towards the innate immune system playing a role in AD pathogenesis. Significant positive association was showed by single nucleotide polymorphisms (SNPs) located in two inflammasome genes, CARD8 and NLRP3 in AD pathogenesis. Significant positive association was showed by single nucleotide polymorphisms (SNPs) located in two inflammasome genes, CARD8 and NLRP3 in AD pathogenesis.26

House dust mite allergen induced activation of inflammasome demonstrated that NLRP3 inflammasome may play an important role in the pathogenesis of Atopic Dermatitis.27 Another study further indicated the role of inflammasomes in the progression of atopic dermatitis. UV-B irradiation of the eye aggravates atopic dermatitis not only via adrenocorticotropic hormone but also via NLRP3 inflammasome in NC/Nga mice.28 No inflammasome inhibitor is in clinical development for the treatment of atopic dermatitis yet.

In the year 2019, TWi Pharma published the result of AC-203 in Bullous Pemphigoid showing topical ointment treatment of blistered skin lesions similar to the super-potent topical steroid clobetasol. The results of this experiment were presented at the Japanese Society for Investigative Dermatology annual meeting in Japan.29 In case of Epidermolysis bullosa it was found that AC-203 alleviates EB symptoms, reducing blister formation and accelerating wound healing, while also demonstrating a good safety profile. AC-203 has been granted Orphan Drug Designation and rare pediatric drug status by FDA.30

Gastroenterology
No inflammasome inhibitor is in clinical development for the treatment of inflammatory bowel disease. At American Chemical Society (ACS) 2018 meeting, IFM Tre presented the preclinical data of NLRP3 inflammasome in IBD, which demonstrated that NLRP3 inhibitors reduced disease severity in a number of well validated preclinical models of IBD. In addition to use as a monotherapy, NLRP3 inhibitors could be used as a combination therapy with other systemic immunosuppressive agents to enhance the efficacy without compromising on the safety in IBD treatment.31
Another preclinical study evaluating MCC950 published in 2018, demonstrated that in a spontaneous chronic colitis mouse model Winnie, MCC950 significantly suppressed release of proinflammatory cytokines IL-1β, IL-18, IL1-α, IFNγ, TNF-α, IL6, IL17, chemokine MIP1a and Nitric Oxide in colonic explants. MCC950 resulted in a significant decrease of IL-1β release and activation of caspase-1 in colonic explants and macrophage cells isolated from Winnie. These results provide evidence for a potential novel treatment option for IBD.32

**Ophthalmology**

NLRP3 inflammasome inhibitors under investigation for diabetic retinopathy and age-related macular degeneration are included here. Preclinical data of MCC950 in diabetic retinopathy mice model suggested that Mcc950 partially reversed hyperglycemia-induced vascular damage and reduced histological changes compared to DR mice. In the diabetic model (DM) group IL-1β production was significantly increased but pretreatment with MCC950 significantly reversed the changes. MCC950 plays a protective role in diabetic retinopathy.33

In 2021 a preclinical study demonstrated that fluoxetine (which is approved for the treatment of clinical depression as Prozac) directly binds NLRP3 protein and prevents NLRP3-ASC inflammasome assembly and activation. Fluoxetine also prevented the degeneration of retinal pigmented epithelium cells in an animal model of dry AMD.34

Xiflam (tonabersat) is a Connexin43 hemichannels blocker, which inhibited NLRP3 inflammasome activation in a human retinal explant model of diabetic retinopathy. InflammX therapeutics is planning to initiate a Phase 2 trial with Xiflam (tonabersat).35, 36

**Oncology**

An article published in September 2021 demonstrated that high expression of NLRP3 is linked to a poor prognosis in BC patients. These results suggest that NLRP3 and TLR4 could be two new good prognostic factors for BC patients. 37

Preclinical studies suggest that the NLRP3 agonists can activate NK-cells and initiate the priming of T-cells, which promotes tumor inflammation and enhances antitumor function 38, 39

A comprehensive pan-cancer analysis indicated that NLRP3 inflammasome may influence tumor immunity mainly by mediating tumor-infiltrating lymphocytes (TILs) and macrophages, and the effect of NLRP3 inflammasome on immunity is diverse across tumor types in tumor microenvironment.40

Olatec pharmaceuticals presented preclinical results showing Dapansutriple reduces tumor growth in a mouse model of melanoma. Study demonstrated that by inhibiting the maturation and secretion of IL-1β with the NLRP3 inhibitor, dapansutriple, the expansion of immune suppressor cells (such as myeloid-derived suppressor cells or MDSCs) is reduced; as such, the immune system’s antitumor activity is restored to eradicate the tumor in mice with melanoma.41
Company Specific Development Spectrum

Bio-pharmas are evaluating NLRP3 inhibitors in the areas of their interest. Only Novartis, Olatec, Ventyx and Immvention therapeutics are evaluating their inflammasome inhibitors in multiple indications.

Galderma is evaluating their NLRP3 inflammasome inhibitor in dermatology, Bacainn is evaluating BT032 and BT132 in pulmonology. Halia is evaluating NRK7-NLRP3 inhibitor in hepatology. Inflammasome therapeutics is evaluating kamuvudine in ophthalmology and neurology. TWi Biologics is evaluating in dermatology (bullous pemphigoid and epidermolysis bullosa).

Conclusion:

NLRP3 inflammasome clearly holds a lot of promise in treating multiple diseases ranging from neurodegenerative diseases to cancer. However, there isn’t much clinical data available except from a few drugs like dapansutrile (Olatec) and inzomelid (Roche).

Results from clinical trials would further shed light on the therapeutic potential of NLRP3 inflammasome inhibitors and provide insights into the safety of these novel therapies. Inflammasome inhibitors could potentially revolutionize the treatment paradigm given their convenient oral dosing and CNS penetrant effects, attracting a lot of investments.

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