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Summer May Be Ending, but Things Are Heating Up for Innate Immunity Drug Development: Featuring Top 10 Hot Targets in Neuro/Immunology

Key Message: Ahead of our ***3rd Annual Neuro/Immunology Day, which is scheduled for November 15-16,*** we are publishing a deep-dive featuring Top 10 emerging targets in the Neuro/Immunology (non-cancer) space. Over the past few decades, much of drug development has focused on targeting various components of adaptive immune system (e.g. interleukins). However, with the advancement of technologies that enhance our understanding of different components of innate immune cells, we are seeing a recent spike in drug development where companies are focusing on innate immunity targets across both neurological and non-neurological disease areas. Despite the excitement in this area, a common emerging challenge has materialized - many of these targets are hard to drug due to a lack of information regarding protein structure and molecular dynamics (e.g. conformational states, binding pockets, water solvation, etc). Nonetheless, new advancements in biophysical tools, artificial intelligence and molecular dynamics computer software are making the targeting of these elusive innate immunity targets possible. In this deep-dive, we have compiled a list of our top ten ***"hot targets"*** mostly in the innate immunity space, and we believe companies developing drugs against these targets, if successful, could create considerable long-term value. For each target we outlined: **(1)** its function, **(2)** tissue/cell expression, **(3)** link to human genetics, **(4)** biomarkers, **(5)** relevant indications, **(6)** challenges for drug development, **(7)** current drugs in the pipeline, and **(8)** our overall view on the target. Finally, we end our report with a short list of targets to keep an eye on - the next generation of "hot targets."

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The innate immunity space has been a hotbed of drug development recently; advancements in AI and protein structure elucidation could be the key to unlocking several of these elusive targets. Recently, there has been a spike in drug development in the innate immunity space across both neurological and non-neurological disease areas, highlighting the broad applicability of targets in this space. Despite the excitement in this area, a common emerging challenge has materialized - many of these targets are hard to drug due to a lack of knowledge of protein structures. A great example of this is NLRP3 - in the title of their 2020 review, McKee & Call referred to NLRP3/inflammasome as **"A riddle wrapped in a mystery inside an enigma,"** which says it all – the complexity and amount of unknown information surrounding NLRP3 (and many other innate immunity targets) make it an intriguing but extremely difficult target to pin down. But structures are just one piece of the molecular puzzle - proteins are often not static and are highly dynamic, cycling through many (sometimes dozens) of conformations, each with the potential for modifying potentially druggable binding pockets. Now with advancements in artificial intelligence (AI) and molecular dynamics computer software (protein structure elucidation, water solvation dynamics), targeting these elusive innate immunity targets is becoming a reality.

We have curated a list of our top ten hot innate immune targets, including targets that are neurology-focused, non-neurology focused, or have broad applicability across a number of diseases; we believe companies developing drugs against these targets, if successful, could create considerable long-term value. From an extensive (and growing) list of targets in the innate immunity space (and a few others worth mentioning), we have compiled a list of our top ten "hot targets" that we believe could create value in the long-term. For each target we outlined: **(1)** its function, **(2)** tissue/cell expression, **(3)** link to human genetics, **(4)** biomarkers, **(5)** relevant indications, **(6)** challenges for drug development, **(7)** current drugs in the pipeline and **(8)** our overall view on the target. These targets can be divided into three general groups (neurology, non-neurology targets or mixed) based on tissue expression and the indications

See pages 110 - 111 for analyst certification and important disclosures.

in which they are being developed - some are de-risked with ample clinical data (e.g. TKY2) while most are in early stages (Phase I or preclinical). Finally, we end our report with a short list of targets to keep an eye on - the next generation of "hot targets." Here is a summary on targets included in our report:

Our view on neurology-focused innate immunity targets. Below we highlight three hot targets that are enriched in the CNS and/or being developed for neurological indications. While we like all three targets, we note that applicability of **LRRK2** may be limited at this point to Parkinson's Disease or a subset of patients (familial Parkinson's Disease makes up ~2-3% or 20-30K of total Parkinson's patients in the U.S.) due to the strong link to human genetics. Additionally, we see considerable competition in the space as most companies developing LRRK2-based therapies are currently focusing in Parkinson's disease area. Similar to LRRK2, we generally like **PGRN** as a target based on its broad mechanism promoting CNS homeostasis but acknowledge the relatively limited spectrum of indications (e.g. FTD-GRN, genetic subsets of ALS and Progressive Supranuclear Palsy) in which PGRN may be suitable (and is currently being developed). A non-trivial challenge with PGRN lies in restoring levels within the physiological range - with PGRN, more is not always better. **TREM2 is a very attractive target** based on its critical role in supporting protective microglial functions in neurodegenerative conditions, and we think TREM2 has broad applicability across multiple neurological indications. However, due to increasing competition, we believe the most feasible strategy would be to carve out a niche in a rare microglial condition and then expand into larger indications like Alzheimer's. Most programs are developing activating antibodies, but **small molecule TREM2 activators could be game-changing**.

- **LRRK2:** a member of the leucine-rich repeat kinase family that controls intracellular vesicle trafficking and organelle maintenance including Golgi, endosomes and lysosomes and may regulate neurite maintenance and neuronal survival. Potential disease applications: *Parkinson's Disease*. Companies: *ALONC (Oncodesign SA), BIIB, DNLI, CERE, E-Scape (private), IONS, LLY.*
- **PGRN**: a growth factor expressed and secreted by several cells in the CNS (neurons, microglia, endothelial cells and astrocytes) which controls neurite outgrowth, neuronal survival, synapse number/function, and maintains microglial neuroinflammation and lysosomal protein degradation within physiological limits. Potential disease applications: *FTD-GRN, ALS caused by C9orf72 mutations, Progressive Supranuclear Palsy*. Companies: *ALEC, ALKS, Arkuda (private), DNLI.*
- **TREM2:** a cell surface receptor of the Ig superfamily mainly expressed on microglia in the CNS and peripheral macrophages, which promotes microglial: **(1)** chemotaxis/motility, **(2)** phagocytosis, and **(3)** survival, and proliferation (in a physiological context) and is crucial for promoting the disease-associated microglia (DAM) phenotype, a specific phenotypic subtype of microglia that may help protect against neurodegeneration. Potential disease applications: *Alzheimer's Disease, FTD, Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) and other rare microgliopathies.* Companies: *ALEC, DNLI.*

Our view on non-neurology innate immunity targets. Below we highlight four hot targets with high expression outside the CNS and/or being developed for indications affecting peripheral tissues. We like **c-KIT** as a target due to its potent control of mast cell survival/function and broad applicability across several inflammatory conditions in which mast cells play a key role (e.g. chronic urticarias, prurigo nodularis, asthma, etc.). CLDX is leading the space with their anti-c-KIT antibody CDX-0159 and have shown impressive clinical PoC in chronic inducible urticaria (CIndU) so far, but c-KIT-based therapies are likely to compete with anti-IgEs, especially in the allergic skin disease space. Selective Treg expansion through use of modified **IL-2 proteins** has gained steam recently based on the abundance of data showing clinical benefit from low doses of IL-2. We see applicability of this approach in Systemic Lupus Erythematosus (SLE), Ulcerative Colitis (UC) and potentially in Type 1 Diabetes (T1D) and think that the most promising data in patients so far (albeit early) have come from NKTR in SLE, but acknowledge MRK as a key player following their acquisition of Pandion. We think **IRAK4** presents a unique opportunity to address multiple inflammatory diseases, but potential for safety concerns around infections need to be monitored. PFE has the most advanced candidate (small molecule), but *we think the most efficient way to target IRAK4 could be KYMR's approach of selectively degrading IRAK4 to account for both kinase and scaffold functions*. We think **TYK2** is a very attractive target with broad applicability and clear differentiation from JAK inhibitors. BMY is the current leader in this space, but Esker, Nimbus, Ventus and Ventyx have interesting (and we believe competitive) programs in early stages.

- **c-KIT:** a receptor tyrosine kinase on the cell surface of innate immune cells, especially mast cells, which (through SCF binding) promotes mast cell: **(1)** differentiation, **(2)** migration and maturation, **(3)** survival and proliferation, and **(4)** FcεRI-dependent activation. Potential disease applications: *Urticarias, Atopic Dermatitis, Indolent systemic Mastocytosis, Asthma, Pancreatic/prostate/bladder cancers, COVID19, PAH, AML, Gastrointestinal Stromal Tumor (GIST), MDS, NSCLC, Hepatocellular carcinoma.* Companies: *AB-FR, CLDX, GOSS, TENX.*

- **IL-2 (for Treg expansion):** a multi-functional cytokine known for its ability to stimulate activity and proliferation of both pro-inflammatory T effector cells and immunosuppressive T cells (e.g. Tregs), depending on IL-2R isoform. Potential disease applications: *SLE, UC, Atopic dermatitis, Psoriasis.* Companies:*MRK, MRNA, NKTR, XNCR.*
- **IRAK4:** an intracellular dual function kinase/adaptor scaffold protein that mediates pro-inflammatory signaling in immune cells downstream of toll-like receptors (TLRs) and interleukin receptors. Potential disease applications: *AML, MDS, NHL, Atopic dermatitis, Hidradenitis suppurativa, Rheumatoid arthritis, IBD, Waldenstrom macroglobulinemia with MYD88 mutations, Rosacea.*Companies: *Evommune (private), KYMR, RIGL, SNY-US.*
- **TYK2:** a JAK family kinase that phosphorylates and activates STAT proteins downstream of multiple cytokine receptors (IL-23, IL-12, type I IFNs and IL-6) that regulates expression of cell proliferation, differentiation, and inflammatory genes. Potential disease applications: *IBD, psoriasis, psoriatic arthritis, lupus, Atopic dermatitis, psoriasis, psoriatic arthritis, alopecia areata, lupus, hidradenitis suppurativa, UC, CD, vitiligo, MS, T-ALL, ccRCC immunotherapy.*Companies: *BMY, Esker (private), GLPG/GILD, Nimbus (private), Ventus (private), Ventyx (private).*

Our view on innate immunity targets with broad applicability. Below we highlight three hot targets with a broad expression profile that are being developed for both CNS and non-CNS indications. **cGAS** is an interesting target with direct genetic links to several inflammatory disorders, but two factors preclude cGAS from being one of our top picks now: **(1)** a lot of the work done on this target is in relation to a downstream mediator STING, and **(2)** cGAS is a dynamic protein which would most likely require sophisticated protein structure/ molecular dynamics to target. That said, Ventus and Ventyx are active in this space with early programs that could overcome these two hurdles. ***We think NLRP3 is one of the most interesting targets,*** especially given its role as an endogenous danger sensor that integrates a host of signals, highlighting the broad applicability of NLRP3 inhibitors both in neurological and non-neurological indications. One major challenge with NLRP3 is a general lack of structural information (which just became available) and conformational dynamics; however, that has not stopped several companies from joining the growing pool of companies currently pursuing NLRP3. We think that development around this target will only accelerate as more sophisticated biophysical tools for in silico modeling come into play. **RIPK1** is a complex target due to its dual function of promoting both inflammation and pro-survival pathways; similar to PGRN, maintaining an optimal balance of RIPK1 signaling is key. The most straight forward approach would be to inhibit RIPK1 in a genetically-relevant disease (e.g. cleavage-resistant RIPK1-induced autoinflammatory syndrome or ALS) where RIPK1 is overactive, but most likely with the goal of not inhibiting RIPK1 completely.

- **cGAS:** intracellular DNA sensor that activates downstream mediator STING, eventually leading to expression of type I interferons (and other inflammatory mediators), pro-apoptotic genes and chemokines and induces autophagy. Potential disease applications: *Solid tumors, soft tissue sarcomas, head/neck cancer, melanoma, inflammation, autoimmunity, neuroinflammation.* Companies: *NOVN-SWX, Ventus (private), Ventyx (private).*
- **NLRP3:** an intracellular sensor protein that translates danger signals into an immune response by triggering assembly of a multiprotein complex (inflammasome), leading to release of IL-1β/IL-18 and to pyroptosis. Potential disease applications: *Gout, Heart failure, Osteoarthritis, NASH, IBD, CNS diseases, Liver and lung fibrosis, solid tumors, Hemophilia A and B, Multiple sclerosis, IBD, CAPS.* Companies: *ACIU, Invea (private), NodThera (private), NOVN, Olatec (private), ROG-CH, Ventus (private), Ventyx (private), ZyVersa (private).*
- **RIPK1:** a multi-domain intracellular kinase that signals downstream of TNF-α receptors to promote: **(1)** pro-survival gene expression, **(2)** RIPK1-dependent apoptosis, and/or **(3)** necroptosis (form of inflammatory cell death). Potential disease applications: *ALS, AD, MS, Psoriasis, UC, RA, Cutaneous lupus erythematosus, autoimmune and inflammatory diseases, CNS diseases.* Companies: *Boston Pharmaceuticals (private), DNLI, GSK, RIGL, SNY-US, LLY.*

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Featuring Top 10 Hot Targets In Neuro/Immunology

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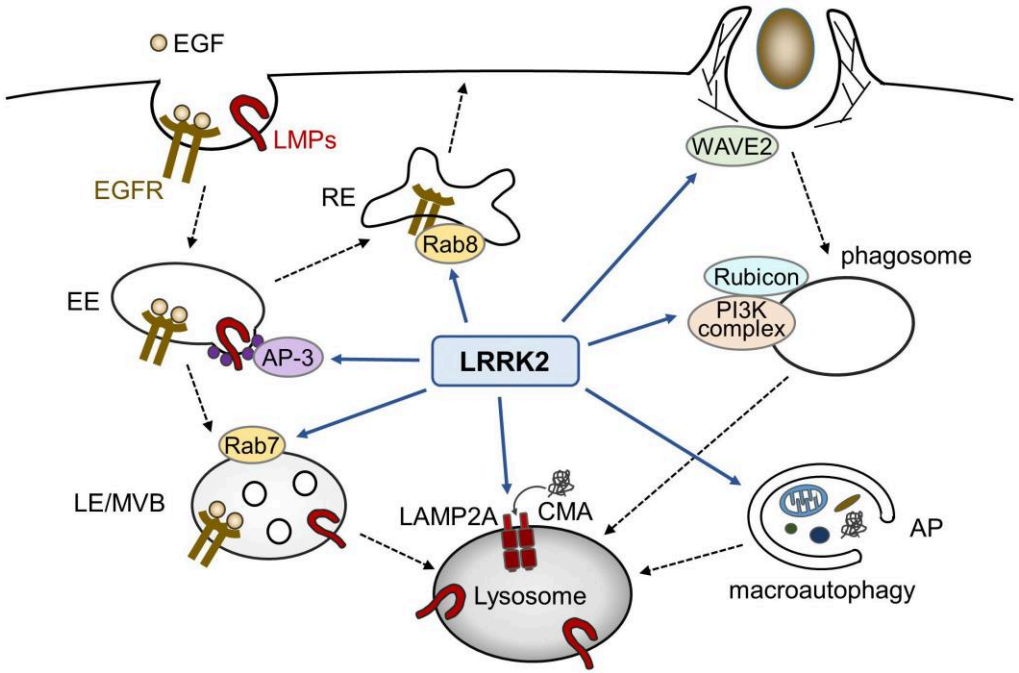
Table of Contents

__L__eucine __R__ich __R__epeat __K__inase 2 - LRRK2

What is LRRK2? (1/2) – LRRK is a kinase involved in autophagy regulation and is commonly linked to genetic Parkinson's disease

Leucine Rich Repeat Kinase 2 (LRRK2) is a member of the leucine-rich repeat kinase family, and most commonly studied in relation to its genetic linkage to Parkinson's disease.

- The protein is present largely in the cytoplasm but also associates with the mitochondrial outer membrane.
- LRRK2 interacts with the C-terminal R2 RING finger domain of parkin, and parkin interacts with the COR domain of LRRK2. Parkin is a component of a multiprotein E3 ubiquitin ligase complex which in turn is part of the ubiquitin-proteasome system that mediates the targeting of proteins for degradation.
- Expression of mutant LRRK2 induces apoptotic cell death in neuroblastoma cells and in mouse cortical neurons.
- Accumulating evidence suggests that LRRK2 regulates intracellular vesicle trafficking and organelle maintenance including Golgi, endosomes and lysosomes.
- LRRK2 regulates neurite maintenance and neuronal survival. Neurons that express disease-associated mutant forms of LRRK2 display reduced neurite process length and complexity, tau-positive inclusions with lysosomal features, and ultimately apoptotic cell death. In contrast, neurons deficient in LRRK2 harbor extended neuritic processes with increased branching (MacLeod et al, 2006).

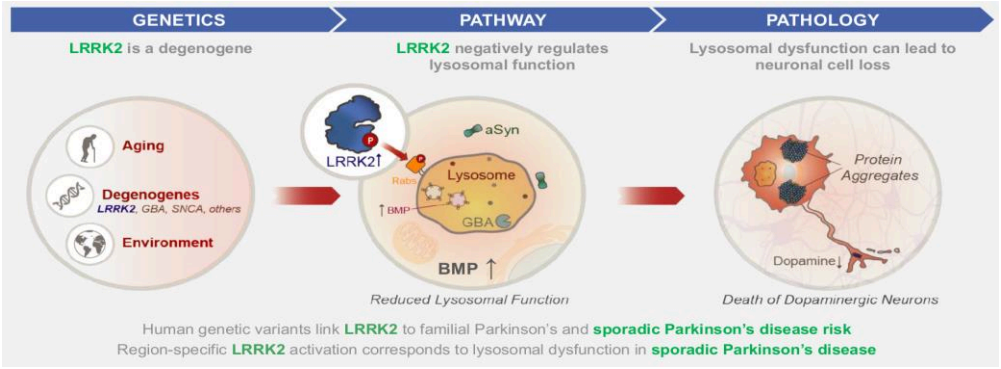


Source: Kuwahara & Iwatsubo, 2020; accessed on pubmed.gov

What is LRRK2? (2/2) – Dysfunction in LRRK2 is linked to PD

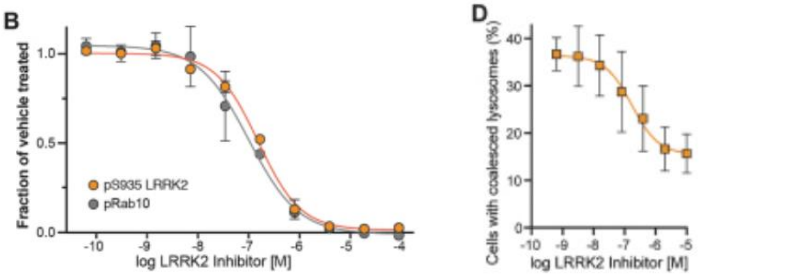
- LRRK2's physiological role involves maintaining a healthy cellular environment by regulating: **(1)** vesicular trafficking, **(2)** autophagy, **(3)** mitochondrial function and **(4)** lysosomal function through modification of Rab proteins.
- LRRK2 phosphorylates Rabs 8 and 10 which are thought to regulate lysosome size and excretion of digested contents.
  - Increased levels of LRRK2 lead to hyperphosphorylated Rab 8/10 and lysosomal dysfunction (but the mechanism is not fully understood), which can contribute to neurodegeneration and the formation of Lewy bodies, a central pathology of Parkinson's disease.
- Inhibition of LRRK2 activity may slow the progression of Parkinson's disease in patients with and without known genetic risks based on restoration of lysosomal function.
  - Reducing LRRK2 activity (based on pRab10) with a small molecule (DNLI's DNL201) can abrogate lysosomal dysfunction, as assessed by lysosome size and cellular distribution.
  - Notably, ~50% reduction in LRRK2 activity led to ~42% decrease in lysosomal abnormalities in cells. However, excessive inhibition of LRRK2 could also end up in lysosomal (and other cellular) defects, highlighting the importance of dose-finding and the potential for AEs with high drug exposure.

LRRK2 contribution to PD pathology



Increased activity of mutant LRRK2 (e.g. G2019S) can lead to hyperphosphorylation of Rabs which interrupts normal lysosomal degradation and may contribute to accumulation of α-synuclein and Lewy bodies in PD (although direct mechanistic evidence is lacking). Aside from lysosomes, overactive LRRK2 may also contribute to PD pathology through: (1) impaired mitophagy, (2) centrosomal defects and (3) α-synuclein propagation.

LRRK2 inhibition reduces lysosomal dysfunction



LRRK2 activity **Lysosomal dysfunction**

Based on DNLI's studies, inhibiting LRRK2 ~50% on average should normalize LRRK2 kinase activity and show therapeutic benefit (IC_{50} for LRRK2 leads to ~42% decrease in lysosomal dysfunction in cells). Similar to PGRN, too little activity of LRRK2 can be detrimental as several studies have shown an accumulation of enlarged, dysfunctional lysosomes in LRRK2 knockout cells and animals – an important consideration for therapeutic window and safety margins.

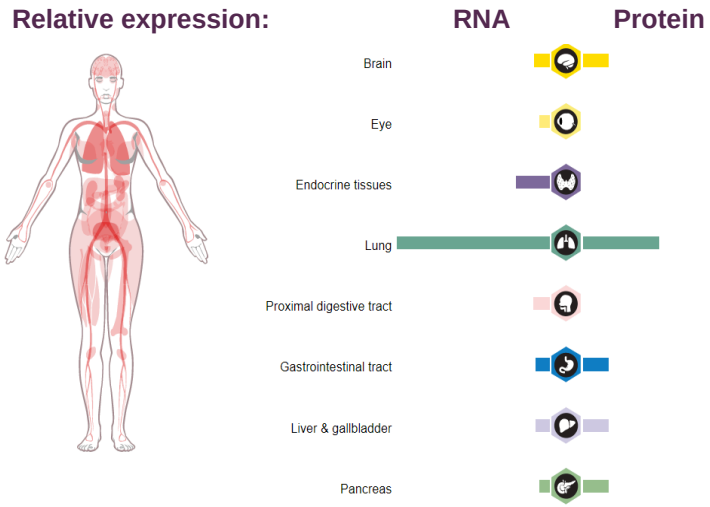
Source: DNLI company presentations, Kuwahara & Iwatsubo 2020

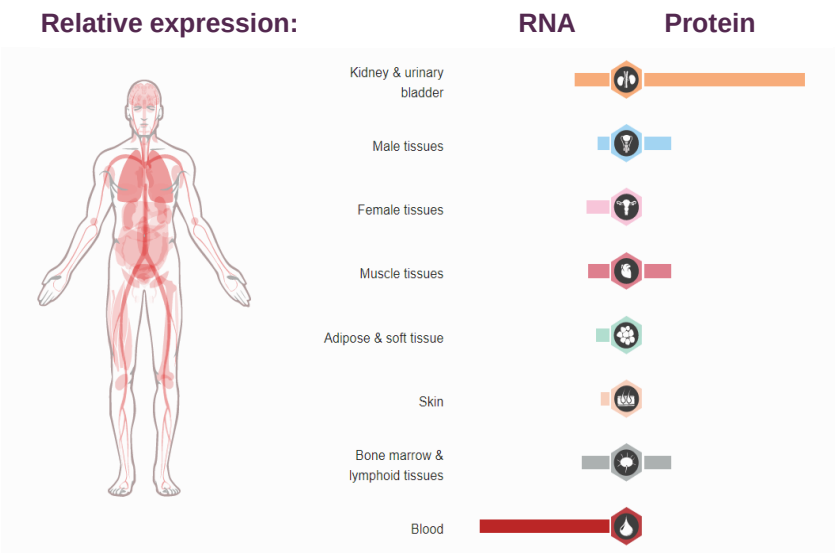
See pages 110 - 111 for analyst certification and important disclosures.

Where is LRRK2 enriched? (1/1) – LRRK2 is expressed in the brain but also enriched in peripheral tissues, like kidney and lung

- **LRRK2** protein is mainly expressed in kidney/urinary tissues, lungs, and the brain.
  - Lower levels of expression are observed in the GI tract, liver, pancreas, muscles and bone marrow
  - LRRK2 mRNA has been detected in a variety of cell types including blood/immune cells, epithelial cells (e.g. alveolar type 2 cells in the lung and proximal tubular cells in the kidney) and certain types of neuronal cells
  - Interestingly, LRRK2 is a very dynamic protein in the cell, being located in cytoplasm, but can translocate and associate with the endoplasmic reticulum, mitochondria, the nucleus, peroxisomes and maybe even the extracellular space, highlighting the many functions of this kinase

LRRK2 tissue expression



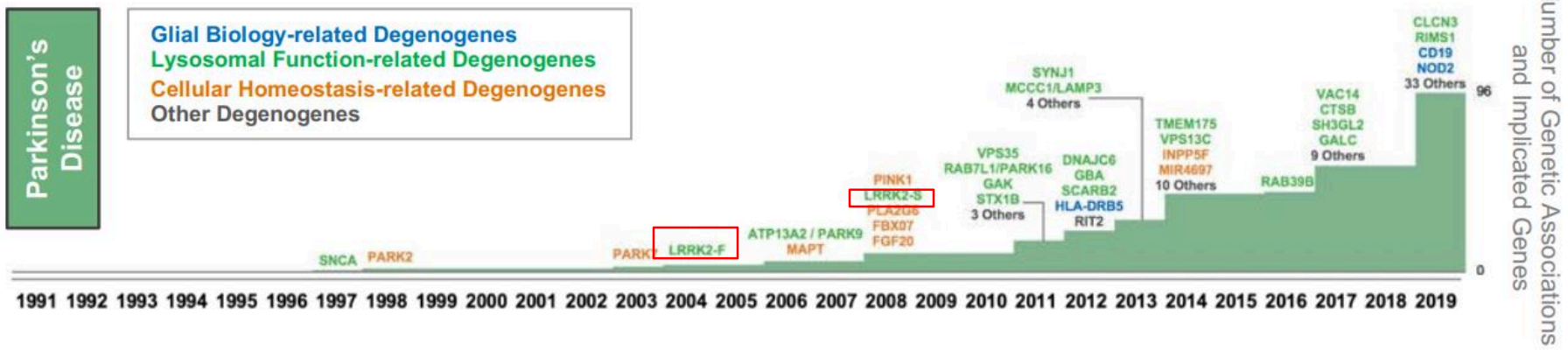


Source: Uhlen et al. 2015, Thul et al. 2017, https://www.proteinatlas.org/ENSG00000188906-LRRK2/tissue

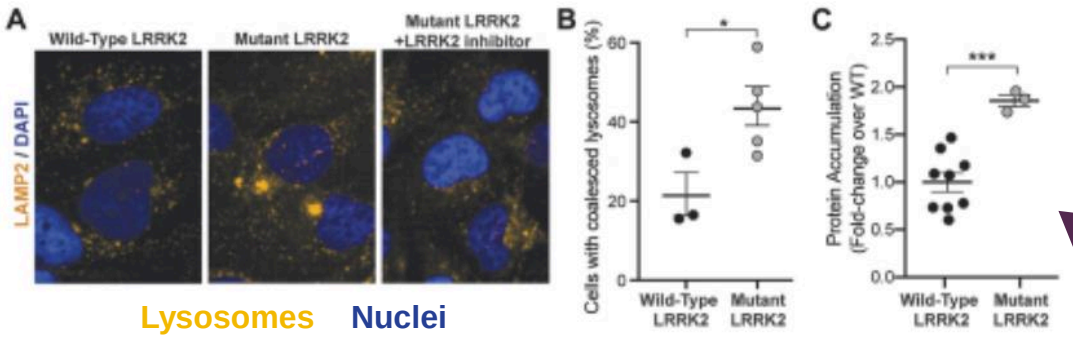
Is there a genetic connection between LRRK2 and disease? (1/1) – LRRK2 is the most common genetic risk factor for Parkinson's disease

- **LRRK2** is the most common genetic risk factor for Parkinson's disease and the most frequent cause of familial Parkinson's, representing 2-3% (~20k – 30k) of total Parkinson's disease patients in the U.S.
- LRRK2 is a kinase that controls lysosomal function, which can be dysregulated in PD.
  - The most common LRRK2 mutation (G2019S) results in increased kinase activity and lysosomal dysfunction, which leads to neurodegeneration.
  - Six additional LRRK2 mutations have been documented that result in either higher than normal kinase expression or activity.
  - LRRK2 is one of several lysosomal function-related genes (green text below) that have been associated with increased risk of Parkinson's disease, shedding light on the importance of lysosomal protein degradation as both a major contributing pathophysiological mechanism underlying PD and a hot therapeutic target.

LRRK2 as a genetic risk factor in PD



G2019S mutation disrupts lysosomal function

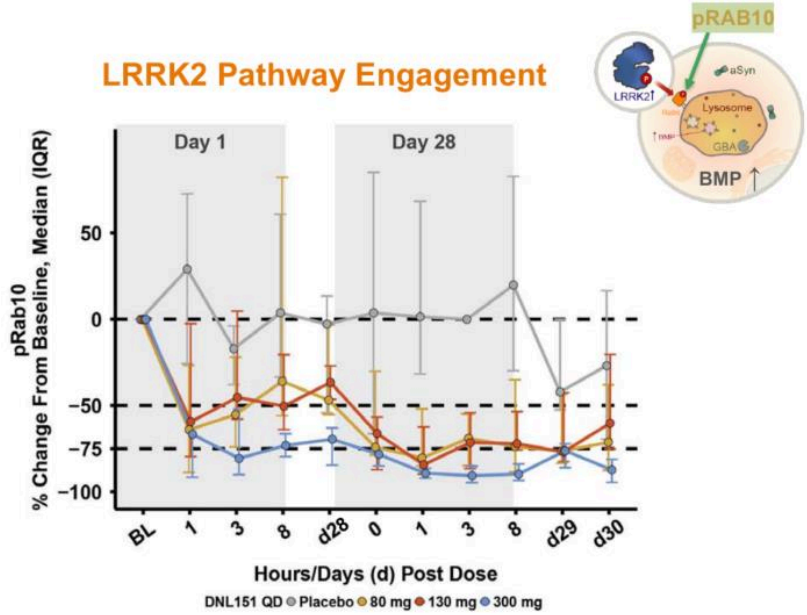


Cells expressing the pathogenic G2019S LRRK2 mutation showed an accumulation of lysosomes (via LAMP2 staining in orange, A-B) and a buildup of cellular protein (C) indicative of insufficient lysosomal function. These data suggest that excessive LRRK2 activity associated with the pathological G2019S mutation may promote disease in part by disrupting lysosomal function.

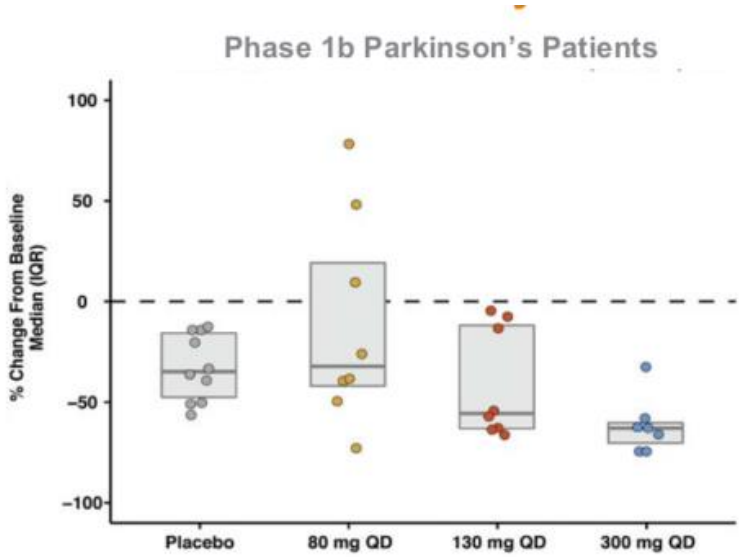
Source: DNLI company presentation

Are there biomarkers for LRRK2? (1/1) – Rab10 phosphorylation is a validated biomarker for LRRK2 activation

- Both Rab10 and Rab8 have been identified as LRRK2 substrates with a potential role in endolysosomal function and lysosomal homeostasis and can be used to measure LRRK2 kinase activity.
  - Ysselstein, 2019 found that by evaluating neurons derived from patients with LRRK2 mutations GCase activity was reduced in the dopaminergic neurons and identified a direct role of LRRK2 on regulation of GCase activity through Rab10 phosphorylation
  - Evaluating pRab10 or other substrates of LRRK2 kinase activity are attractive biomarkers for potential drug target engagement.
  - Increased activity of mutant LRRK2 (e.g. G2019S) can lead to hyperphosphorylation of Rabs which interrupts normal lysosomal degradation and may contribute to accumulation of α-synuclein and Lewy bodies in PD.



In DNLI's Phase Ib study for DNL151, the drug showed robust target and pathway engagement as depicted by both LRKK2pS935 levels and pRab10 levels, both of which are significantly reduced compared to placebo. 300mg of DNLI151 reduced pRab10 from baseline >75%



The drug also reduced the BMP 22:6 concentration in a dose-dependent fashion providing peripheral evidence supporting improvement of lysosomal function. BMP are elevated during reduced lysosomal function and therefore, showing reduction of these after LRRK2 inhibition demonstrates target engagement.

Source: DNLI company presentation; Ysselstein, 2019; Guggenheim Securities, LLC

What diseases is LRRK2 involved in? (1/1) – Mutations in LRRK2 cause Parkinson's disease

Indications	Mechanism of action	Strength of evidence
Parkinson's disease	Increased activity of mutant LRRK2 (e.g. G2019S) can lead to hyperphosphorylation of Rabs which interrupts normal lysosomal degradation and may contribute to accumulation of α-synuclein and Lewy bodies in PD (direct mechanistic evidence is lacking); overactive LRRK2 may also contribute to PD pathology through: (1) impaired mitophagy, (2) centrosomal defects and (3) α-synuclein propagation	**Strong** – direct human genetics link; ample pre-clinical data showing LRRK2 inhibitors penetrating BBB and providing neuroprotective effects *in vitro* and *in vivo*; some clinical validation with DNLI's Phase Ib study of DNL151, the drug showed robust target (LRKK2pS935) and pathway (pRab10) engagement and dose-dependent reduction of BMP 22:6, suggesting improved lysosomal function; however, no clinical efficacy data in PD patients yet
Crohn's disease	Exact mechanism not known, but data suggest that LRRK2 may regulate inflammatory response of immune cells in PD and CD; LRRK2 mRNA is increased in inflamed CD intestinal tissue vs. healthy tissue mainly attributed to changes in macrophages, B cells, and dendritic cells in the lamina propria; LRRK2 M2397T variant exhibited hyperresponsiveness to IFNγ compared to healthy controls	**Weak** – Direct link to human genetics based on GWAS; not much pre-clinical data directly testing role of LRRK2 in CD and most information comes from comparative studies between CD and PD; some clinical evidence with higher levels of LRRK2 in inflamed colon tissue from CD patients, but no LRRK2 inhibitors currently being developed for CD

Source: DNLI company presentations, Chen et al. 2018, Herrick & Tansey 2021, Barrett et al. 2008

What are the challenges in targeting LRRK2? (1/1) – systemic exposure (and LRRK2 inhibition outside of the brain) could be a key safety issue

LRRK2 is expressed in other tissues outside of the brain (e.g. kidney, lungs) and is actually expressed at higher levels in these tissues compared to the brain. Both WT and mutant forms of LRRK2 can contribute to PD. Two major factors to consider when targeting LRRK2 are: (1) Brain penetration vs. systemic exposure, and (2) targeting WT vs. mutant LRRK2. Given LRRK2's expression profile (and the fact that LRRK2 inhibition may interrupt monocyte maturation), hematological safety issues could arise if systemic exposure is too high. However, systemic inhibition of LRRK2 may be advantageous in the context of a constitutively active LRRK2 mutant, a target that would most likely would require both a precision medicine approach and sufficient structural guidance and in silico modeling to develop a specific inhibitor.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Brain penetrant vs. systemic LRRK2 inhibition	LRRK2 is highly expressed in tissues outside of the brain; LRRK2 inhibition may block maturation of monocytes, raising potential safety concerns for a molecule that inhibits LRRK2 outside of the brain	Either administer directly to brain, or develop an orally available inhibitor with a high proportion of brain penetrance, limiting systemic exposure	Intrathecal injection may be most suitable for anti-sense approaches (IONS), but for oral compounds limiting systemic exposure may be difficult
Targeting WT vs. mutant LRRK2	Pathogenic mutations can occur in different regions of the LRRK2 protein, making the design of a specific compound for a particular mutation challenging without knowledge of protein structure/conformational dynamics	Iterative in silico modeling utilizing LRRK2 protein structure and AI to provide insight on the relationship between a particular mutation and protein conformations/available binding pockets	Precision medicine-based approaches targeting mutant LRRK2 could provide a very efficacious therapy for subsets of PD patients; disease associated with mutant LRRK may be a situation where systemic inhibition of LRRK2 could be beneficial

Bottom line: In our view, brain penetrance (vs. systemic exposure) could be a key issue for PD associated with WT LRRK2, and although LRRK2 mutations only contribute to a minority of PD cases, a precision medicine approach with a specific inhibitor could be a valuable addition along with WT LRRK2 inhibitors to the PD market

Source: DNLI company presentations, Chen et al. 2018, Guggenheim Securities, LLC research

Current programs targeting LRRK2 (1/2)

LRRK2 is a very hot target especially in Parkinson's Disease, with 6 companies actively pursuing LRRK2 (all companies listed in the table on the next page). Our highlights:

- ***ALONC*** (along with Servier) is working on an undisclosed small molecule inhibitor of LRRK2 for PD (IND-enabling studies)
- ***Arrien Pharmaceuticals*** is developing ARN-1104, a next-gen, oral, CNS-penetrant selective small molecule inhibitor of LRRK2 in PD (also in IND-enabling studies)
- ***CERE*** has an undisclosed potent and selective LRRK2 kinase inhibitor for PD (pre-clinical stage)
- ***DNLI*** (in collaboration with BIIB) are developing DNL151, a CNS-penetrant selective small molecule LRRK2 inhibitor, in PD (Phase I/Ib completed)
- ***E-Scape*** is developing the G2019S mutant-selective LRRK2 inhibitor ESB5070 in PD (IND-enabling studies)
- ***IONS*** in collaboration with BIIB is developing ION859, an intrathecally-administered anti-sense drug targeting LRRK2 mRNA, in PD (currently in Phase I)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting LRRK2 (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
Arrien	Private		ARN-1104	Next-generation, orally available, brain penetrant, selective small molecule LRRK2 inhibitor	Parkinson's Disease (PD)	Pre-clinical (IND-enabling studies)
Cerevel	CERE	3684.0	Not disclosed	Highly potent and selective LRRK2 kinase inhibitor	Parkinson's disease	Pre-clinical
Denali (Biogen)	DNLI	6438.4	DNL151	Potent, selective, central nervous system–penetrant small molecule LRRK2 kinase inhibitor	Parkinson's disease	Phase I/Ib completed
E-Scape	Private		ESB5070	A mutant-selective LRRK2 G2019S kinase inhibitor	Parkinson's disease (w/ G2019S mutation)	Pre-clinical (IND-enabling studies)
Ionis (Biogen)	IONS	5548.5	ION859 (BIIB094)	Intrathecal anti-sense drug targeting LRRK2 mRNA, leading to mRNA degradation and decreased levels of LRRK2 protein	Parkinson's disease	Phase I
Oncodesign (Servier)	ALONC	72.9	Undisclosed	Small molecule inhibitor of LRRK2	Parkinson's disease	Pre-clinical (IND-enabling studies)

Note: all market cap figures in $ except for ALONC in €

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on LRRK2 (1/1) – LRRK2 is a viable target for PD, but potential AEs due to systemic LRRK2 inhibition may raise safety issues

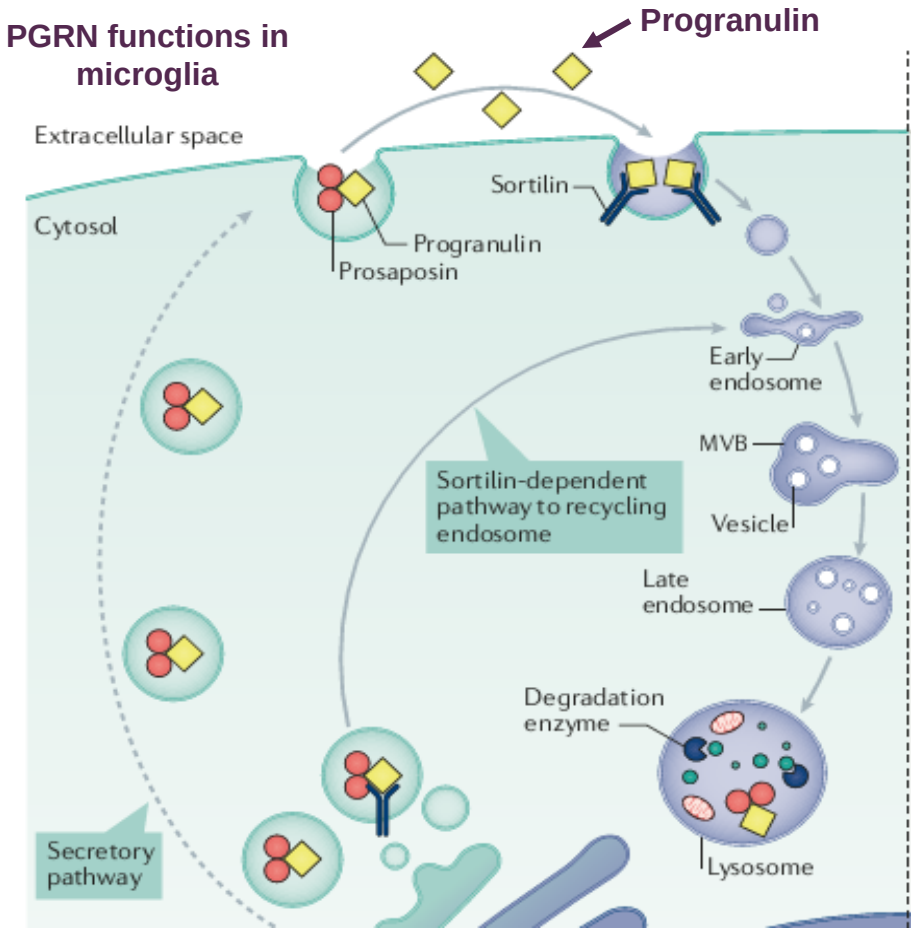
Target factor	Strength of evidence	GS comments
Link to human genetics	**STRONG**	LRRK2 is the most common genetic risk factor for PD and the most frequent cause of familial Parkinson's; most common LRRK2 mutation (G2019S) results in increased kinase activity and lysosomal dysfunction; also a genetic link to CD
CNS target enrichment	**WEAK**	LRRK2 is expressed in several tissues outside of the brain including kidney, lung and immune cells; LRRK2 expression is higher in kidney and lungs vs. brain; crossing BBB critical for LRRK2 inhibitors
Mechanism of action	**MODERATE**	Strong connection between LRRK2 and lysosomal dysfunction (but the mechanism is not fully understood), which can contribute to neurodegeneration and the formation of Lewy bodies, a central pathology of PD; possible link between LRRK2 and inflammation but not much data (especially re: CD)
Biomarkers	**STRONG**	DNLI's Phase Ib study of DNL151, the drug showed robust target (LRKK2pS935) and pathway (pRab10) engagement and dose-dependent reduction of BMP 22:6, suggesting improved lysosomal function
Safety	**MODERATE**	Like PGRN, too little activity of LRRK2 can be detrimental as several studies have shown an accumulation of enlarged, dysfunctional lysosomes in LRRK2 knockout cells and animals; DNLI's DNL151 was generally well tolerated with no serious AEs but two patients discontinued treatment due to hypotension/dizziness (no clinically meaningful changes in pulmonary or renal function)
Clinical PoC	**WEAK**	Most programs are in preclinical stage; DNLI's DNL151 showed target/pathway engagement in a Phase Ib, but no clinical efficacy data yet

Source: DNLI company presentations, clinicaltrials.gov, Guggenheim Securities, LLC research

See pages 110 - 111 for analyst certification and important disclosures.

Progranulin - PGRN

What is progranulin? (1/2) – Progranulin (PGRN) is a CNS growth factor that balances microglia activation, inflammation and lysosomal protein degradation



PGRN is trafficked to the lysosome in microglia via two main mechanisms: **(1)** binding to the sortilin 1 (SORT1) receptor (*genetic studies have identified it as a major negative regulator of PGRN levels in plasma and the brain*), or **(2)** binding to prosaposin proteins which facilitates a mannose-6-phosphate receptor-mediated trafficking to the lysosome

- **Progranulin (PGRN)** is a growth factor expressed and secreted by several cells in the CNS, including neurons, microglia, endothelial cells and astrocytes
  - PGRN controls neurite outgrowth, neuronal survival, synapse number/function, and maintains microglial neuroinflammation and lysosomal protein degradation within physiological limits
  - Secreted extracellular PGRN has two known fates: **(1)** cleavage and release of granulins, or **(2)** receptor binding, cellular import and trafficking to the lysosome (via two main pathways) where it regulates protein degradation, particularly in microglia as a critical later step in the phagocytic process
  - *While much about PGRN signaling is not well known, PGRN and granulins seem to have opposing effects, suggesting that a defined balance between PGRN/granulins is necessary for optimal physiological control*

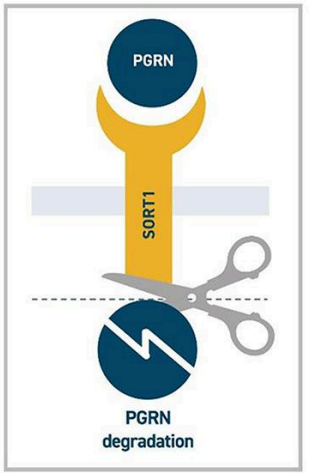
Source: Company presentation, Kao et al. 2017, Chitramuthu et al. 2017

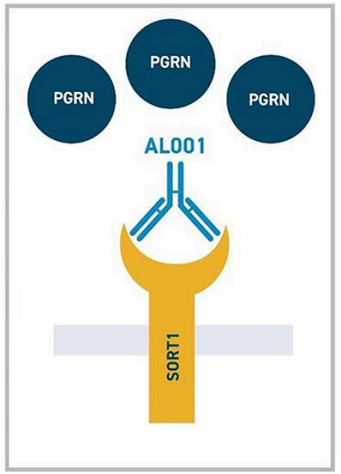
What is progranulin? (2/2) – A delicate balance between PGRN/granulins is necessary to properly balance inflammation, microglial activation and lysosomal function

PGRN must be maintained within a narrow range for optimal physiological function

PGRN is a double-edged sword – too little expression can lead to neurodegeneration but too much PGRN over time may contribute to malignancies (e.g. gliomas). Therefore, an approach like ALEC's AL001 (a monoclonal antibody that inhibits the SORT1 receptor to reduce the degradation of progranulin; right figure) that taps into an endogenous mechanism to provide physiological increases in PGRN would be an ideal approach.

- PGRN and granulins seem to have opposing effects, suggesting that a defined balance between PGRN/granulins is necessary to properly balance inflammation, microglial activation and lysosomal function.
- Based on this delicate balance, it is not surprising that either too little or excessive PGRN could be harmful
  - ***Too little PGRN:*** unresolved neuroinflammation, dystrophic neurons, and lysosomal dysfunction that impairs clearance of protein aggregates by microglia that can directly contribute to pathology
  - ***Too much PGRN:*** can lead to cancers, including gliomas



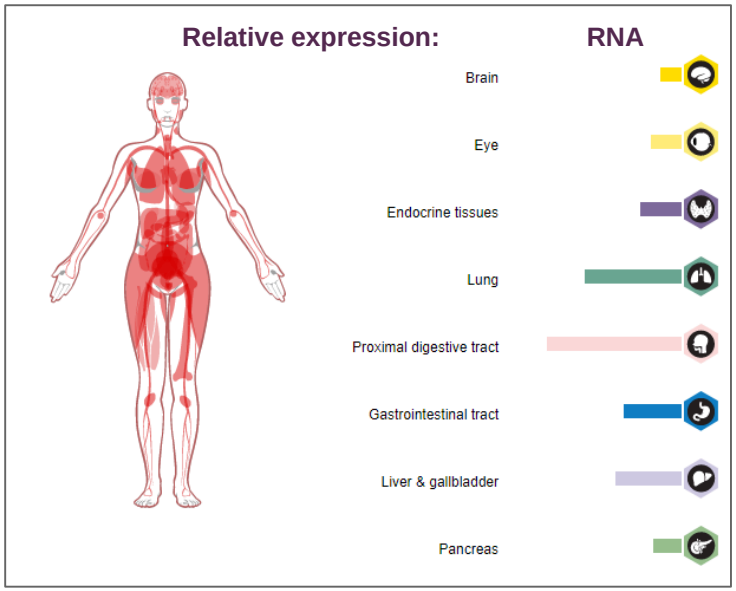


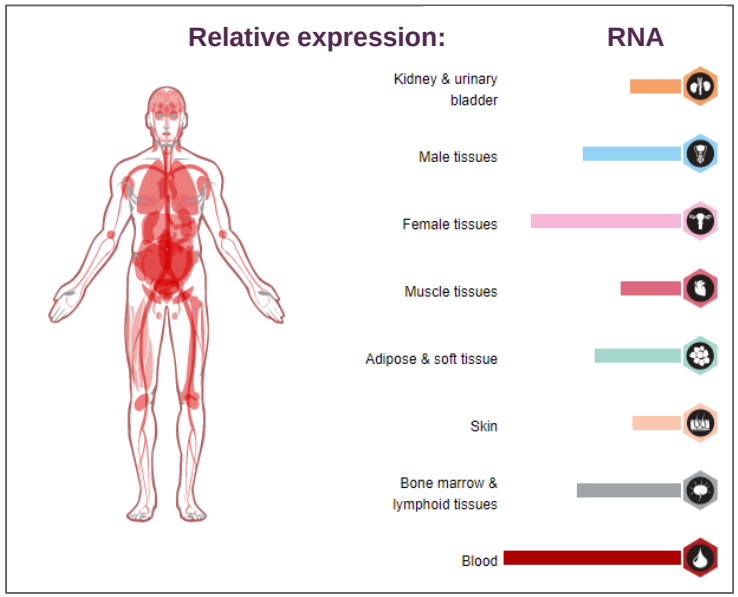
Source: Alector presentation, Kao et al. 2017, Chitramuthu et al. 2017

Where is progranulin enriched? (1/1) – PGRN (mRNA) is widely expressed in multiple tissues across the body

- GRN (gene encoding PGRN) mRNA is expressed in most tissues of the human body, with high expression in the lung, proximal GI tract, reproductive tissues, bone marrow and in the blood
  - PGRN is expressed in a subset of neurons (cerebral cortical neurons, cells in the hippocampus, Purkinje
  - cells of the cerebellum, and motor neurons)
  - PGRN is strongly expressed in myeloid cells (neutrophils, macrophages, and microglia) as well as in basal keratinocytes in the skin and in enterocytes of the villus crypt in the intestine.
  - In some cells, PGRN expression is very low at baseline but can increase dramatically upon tissue injury (e.g. fibroblasts)

PGRN tissue expression





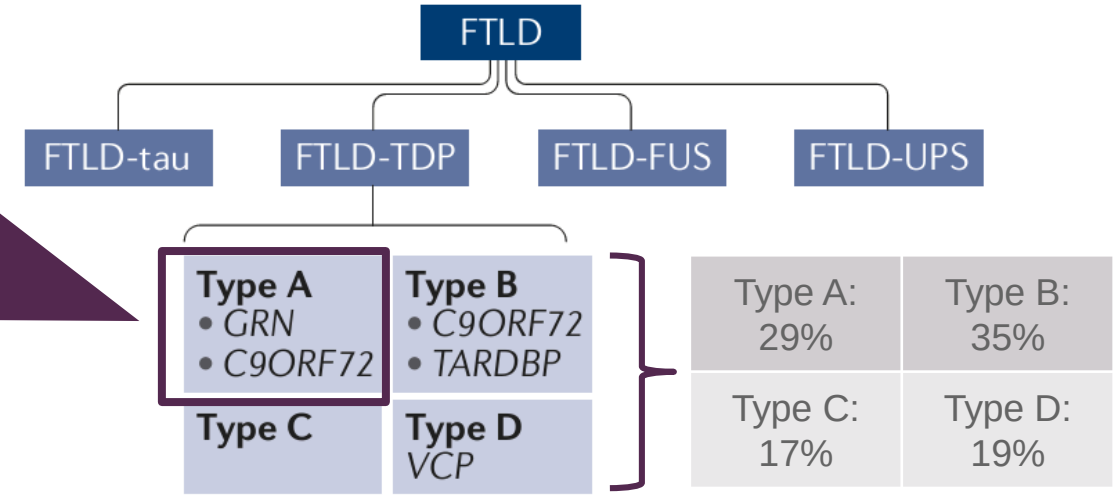
While GRN mRNA can be found in most tissues, protein expression is less well established (no consensus protein data were available from Human Protein Atlas), but has been detected in several cell types within the CNS.

Source: McKee & Coll 2020, Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000030582-GRN/tissue), Bateman et al. 2018

Is there a genetic connection between progranulin and disease? (1/1) – mutations in the GRN gene accounting for ~29% of FTD-TDP

- Frontotemporal dementia (FTD) is a clinical condition characterized by progressive neurodegeneration resulting in cognitive changes in executive functions, language and behavior.
- On a cellular level, FTLD is linked to the accumulation of misfolded proteins in neurons and/or glia and can be classified into four main subtypes based on the particular protein: (1) tau (FTLD-tau), (2) TDP43 (FTLD-TDP), (3) FUS (FTLD-FUS) or (4) no definitive protein but with evident problems in the ubiquitin proteasome system (FTLD-UPS).
- FTLD-TDP accounts for ~50% of all FTLD, and TDP43 accumulates in most patients with ALS.
  - FTLD-TDP can be further sub-divided into four categories: (1) Type A (caused by mutations in *GRN* or *C9ORF72),* (2) Type B (caused by mutations in *C9ORF72* or the TDP43 encoding gene *TARDBP*), (3) Type C or (4) Type D (caused by mutations in *VCP*). Patients with *GRN* mutations usually present with behavioral variant FTD (bvFTD; apathy, irritability, social withdrawal, impulsive behaviors) or primary progressive aphasia (PPA; decreased fluency and difficulty finding words).
  - Type A FTLD associated with GRN mutations (FTD-GRN) represents ~29% of FTLD-TDP cases and results in decreased levels of the encoded protein progranulin.

Mutations in the GRN gene (p.Thr272fs) have also been linked to Progressive Supranuclear Palsy (PSP), but the role PGRN plays in the underlying pathology is less well understood compared to FTD-GRN. Most PGRN programs are focused on FTD-GRN, but Alzprotect's Ezeprogind is currently in a Phase IIa for Progressive Supranuclear Palsy

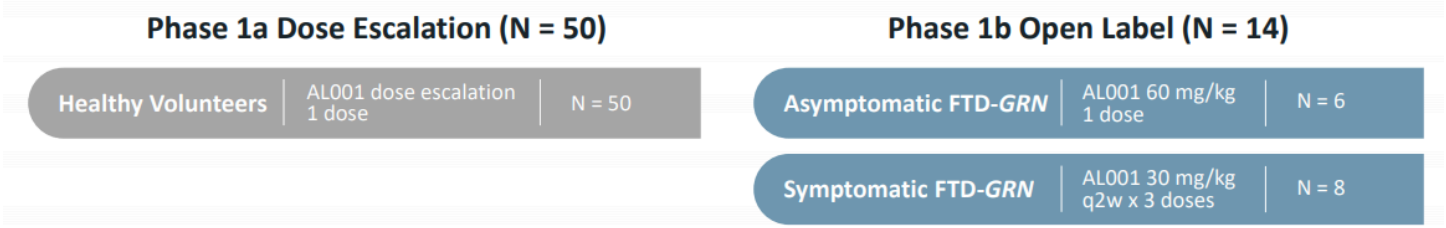


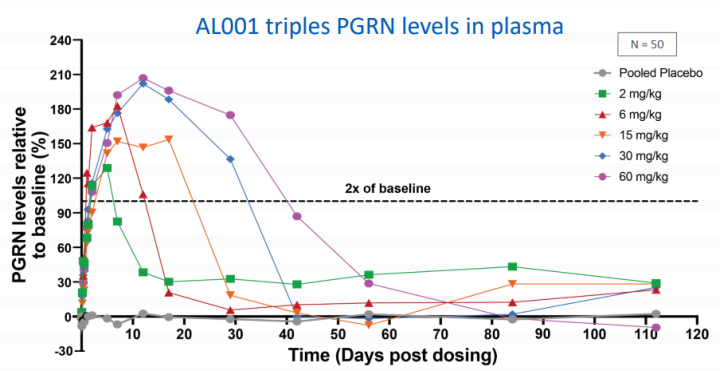
Prevalence of FTLD-TDP subtypes

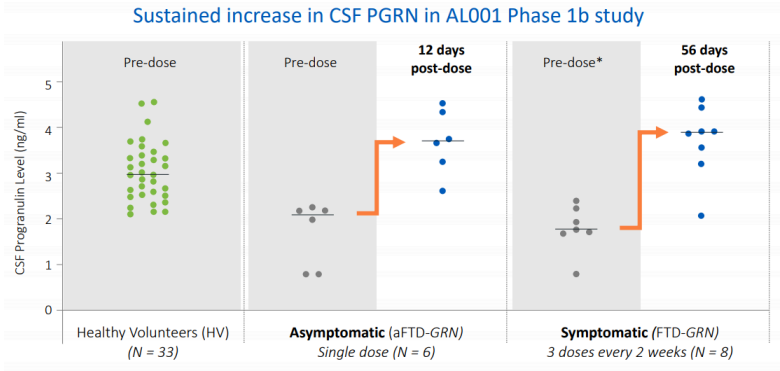
Source: Company reports, Kao et al. 2017, Panza et al. 2020, Tremolizzo et al. 2011

Are there biomarkers for progranulin? (1/1) – PGRN can be directly measured in plasma and CSF of FTD patients

- In ALEC's Phase Ia dose escalation study in healthy volunteers (n = 50), AL001 dose-dependently increased plasma PGRN levels in healthy volunteers up to 3x above baseline levels and maintained PGRN above 2x baseline levels for ~40 days after 60mg/kg dose.
- In an open-label Phase Ib with FTD-GRN patients (n = 14), AL001 was able to restore CSF PGRN levels in the CSF (~80% increase) to within the normal range of healthy volunteers in both asymptomatic (n = 6) and symptomatic (n = 8) patients (more on Phase I study on next page).
- Importantly, AL001 ***consistently increased PGRN in both the plasma and the CSF of HV and patients, which suggests that plasma PGRN may be a suitable biomarker for target***







Source: ALEC company reports, clinicaltrials.gov

What diseases is progranulin involved in? (1/1) – Mutations in PGRN cause FTD-GRN and may contribute to ALS and PSP

PGRN (mainly mutant forms) has been implicated in a small group of neurodegenerative diseases including FTD-GRN and a subtype of ALS. Healthy individuals have two normal copies of the GRN gene (encodes PGRN) that together produce healthy levels of PGRN. Mutations in both copies of the GRN gene lead to a neurodegenerative disease called neuronal ceroid lipofuscinosis, characterized by childhood dementia, vision loss, and epilepsy. Heterozygous mutations in (one copy of) the GRN gene lead to a ~50-70% decrease in the level of PGRN and consequently lead to the development of FTD (90% probability). Human genetic studies have shown that mutations in GRN, that lead to mild decreases in PGRN increase the risk for Alzheimer's disease and Parkinson's disease, making PGRN a significant risk gene for these disorders as well. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
FTD-GRN	Mutations in GRN gene (encoding PGRN) lead to lower PGRN protein levels, which can contribute to unresolved neuroinflammation, dystrophic neurons, and lysosomal dysfunction that impairs clearance of protein aggregates by microglia that can directly contribute to cognitive and behavioral symptoms observed in FTD pathology	**Strong** – direct human genetics link; abundant pre-clinical MoA work that suggests that restoring PGRN can have therapeutic benefit, but exact role of PGRN in the CNS not well defined; good clinical PoC with ALEC's AL001 achieving peak plasma PGRN levels ~95ng/mL in FTD-GRN patients (normal range ~72-180ng/mL) and favorable safety profile in Phase Ia/b and showed sustained 2-2.5-fold elevations of PGRN comparable to normal controls and 47% slowing of clinical progression in a Phase II trial
ALS/FTD caused by *C9orf72* repeats	Repeat expansions in the C9orf72 gene lead to loss of function of the C9orf72 protein, which leads to multiple downstream cellular effects including: (1) dysfunctional RNA metabolism, (2) inefficient lysosomal function, (3) altered energy metabolism and (4) altered neuronal function.	**Weak** – genetic component but in a separate gene; MoA is not clear due to conflicting reports on how C9orf72 expansions affect PGRN levels; not much clinical validation to this point – ALEC in Phase II but not much C9orf72-specific data yet
Progressive Supranuclear palsy	In one patient case, the p.Thr272fs mutation in GRN gene lead to supranuclear ophthalmoplegia, dysphagia, dysarthria, dysphonia, and a shuffling gait. PGRN levels were not measured in this patient.	**Weak** – clear (but rare) genetic link between PGRN and PSP; MoA not defined, but may be similar to that in FTD-GRN; not much clinical PoC for targeting PGRN in PSP

Source: ALEC company presentations and website, Arrant et al. 2017, Lee et al. 2014, Miyakawa et al. 2020, clinicaltrials.gov, Balendra & Isaacs, 2018, Dols-Icardo et al. 2012, Tremolizzo et al. 2011

What are the challenges in targeting progranulin? (1/1) – Increasing PGRN by intervening at the protein level may be the most promising approach

There are currently three main approaches to targeting PGRN: **(1)** driving expression from the intact GRN allele (ALKS, possibly Arkuda but MoA not fully known), **(2)** blocking SORT1-mediated PGRN recycling (ALEC), and **(3)** adding back exogenous PGRN (DNLI). Major challenges here center on specificity of gene transcription, achieving enough PGRN increase to therapeutic benefit but not enough to elicit AEs, immunogenicity and crossing the blood brain barrier (for exogenous PGRN).

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Driving expression from intact GRN allele	Specificity to GRN gene; difficult to titrate transcription of GRN to avoid safety issues with too much PGRN; potential to also increase granulins which can functionally oppose PGRN	Bi-specific drugs that could increase GRN gene specificity and help reduce PGRN > granulin conversion	In our view, this approach is possible but may be very challenging since the regulation of GRN transcription especially in the context of FTD-GRN is not well understood
Blocking SORT1	Blocking SORT1 may also alter levels of other SORT1 cargo and could interrupt PGRN trafficking to the lysosome	Pre-clinical MoA and dose titration to minimize non-PGRN effects and understand the SORT1-independent effects of PGRN	Blocking cellular import and degradation of PGRN is more likely to achieve therapeutically-relevant (and safe) levels of PGRN and is easier to titrate vs. a compound acting at the gene level
Exogenous PGRN replacement	Immunogenicity; crossing BBB; potential disruption of natural PGRN production from intact allele	Utilize delivery technology to help fully human PGRN protein cross BBB	This approach can help increase PGRN in the brain, but how exogenous PGRN may affect endogenous PGRN pathways/regulation is not known; may be harder to achieve physiological levels of PGRN

Bottom line: In our view, given that increasing PGRN from the intact allele is mainly achieved through non-specific HDAC inhibitors, the two approaches most likely to achieve efficacious and safe increases in PGRN are: (1) blocking SORT1 to increase endogenous PGRN, or (2) replacing PGRN via exogenous protein administration with technology to maximize BBB penetration.

Source: ALEC company presentations, ALKS company presentations, Guggenheim Securities, LLC research

Current programs targeting progranulin (1/2)

The **PGRN space** is rapidly growing, with 5 companies actively pursuing the target (all companies listed in the table on the next page). Some of our highlights from a neuro/inflammation perspective:

- ***ALEC*** is developing AL001, an anti-SORT1 antibody that increases PGRN via blockade of PGRN degradation, in FTD-GRN and ALS caused by C9orf72 mutations (currently in Phase III)
- ***ALKS*** has an HDAC inhibitor (RDC-274307) that increases PGRN expression from the normal allele in a manner that may depend on GRN gene methylation patterns (preclinical stage)
- ***Alzprotect*** is the only company developing a small molecule (Ezeprogind, AZP2006) that increases PGRN secretion for Progressive Supranuclear Palsy (currently in a Phase IIa)
- ***Arkuda*** is developing ARKD-102 as a small molecule PGRN expression and lysosomal function booster (MoA not fully known) in FTD-GRN (currently in preclinical stage)
- ***DNLI*** is developing DNL593 (PTV:PGRN), a PGRN protein linked to a transferrin receptor binding transport vehicle (TV) facilitating blood brain barrier crossing, in FTD (currently in pre-clinical studies)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting progranulin (2/2)

Company	Ticker	Market Cap ($MM)	Drug	Mechanism of Action	Indications	Development Phase
Alector	ALEC	2220.8	AL001	Anti-SORT1 antibody, blocks degradation of PGRN, increasing PGRN levels	FTD-GRN, ALS caused by C9orf72 mutations	Phase III
Alkermes PLC	ALKS	4615.7	RDC-274307	HDAC inhibitor that increases PGRN expression from normal allele (MoA not well defined but may depend on maintaining certain histone acetylation patterns in GRN gene)	FTD	Preclinical
Alzprotect	Private	-	EZEPROGIND (AZP2006)	Small molecule that increases secretion of PGRN	Progressive Supranuclear Palsy	Phase IIa
Arkuda	Private	-	ARKD-102	Small molecule that increases PGRN levels to boost lysosomal function (exact MoA not known, but not via SORT1 blockade)	FTD-GRN	Preclinical (IND 1H22)
Denali	DNLI	6417.1	DNL593 (PTV:PGRN)	PGRN protein linked to transferrin binding transport vehicle (PTV) allowing PGRN protein to cross BBB	FTD	Preclinical (IND late 2021)

Note: all market cap figures in $

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on progranulin (1/1) – PGRN is a viable target for FTD, but broad tissue distribution and unclear MoA could complicate other indications

Target factor	Strength of evidence	GS comments
Link to human genetics	**STRONG**	LOF mutations lead to FTD-GRN, with some evidence that repeat expansions in the C9orf72 gene may lead to ALS or FTD with PGRN involvement but not clear for those indications
CNS target enrichment	**WEAK**	Although no consensus exists on protein levels, PGRN mRNA is found throughout the brain – and the rest of the body
Mechanism of action	**STRONG**	In FTD, there is a fairly clear mechanism for how lower PGRN levels lead to neuroinflammation, dystrophic neurons, and lysosomal dysfunction that impairs clearance of protein aggregates by microglia that can directly contribute to cognitive and behavioral symptoms observed in FTD pathology; not much clarity from the C9orf72 perspective
Biomarkers	**STRONG**	PGRN can be measured in both plasma and CSF, and data from ALEC suggest that their anti-SORT1 Ab can increase PGRN levels in patients back to normal, but whether this correlates with clinical improvement is yet to be determined
Safety	**MODERATE**	Safety could become an issue especially since PGRN is expressed everywhere, PGRN can be converted into granulins with opposing actions, and PGRN needs to be within a defined range to avoid AEs; that said, ALEC has not yet seen any serious safety issues but did report 5 falls in their Phase II (not clear if drug related)
Clinical PoC	**MODERATE**	Most programs are early, but ALEC's AL001 achieved peak plasma PGRN levels of ~95ng/mL in FTD-GRN patients (normal range ~72-180ng/mL) and favorable safety profile in their Phase I trial; 2-2.5-fold elevations of PGRN comparable to normal controls and 47% slowing of clinical progression in a Phase II trial

Source: ALEC company presentations, Guggenheim Securities, LLC

__T__riggering __R__eceptor __E__xpressed On __M__yeloid Cells __2__ - TREM2

What is TREM2? (1/1) – TREM2 is a cell surface receptor expressed on microglia that promotes microglial chemotaxis, phagocytosis and survival

Triggering Receptor Expressed On Myeloid Cells 2 (TREM2) is a cell surface receptor of the Ig superfamily mainly expressed on microglia in the CNS and peripheral macrophages. ***TREM2 is an essential microglia sensor that mediates responses to environmental signals to maintain brain homeostasis.***

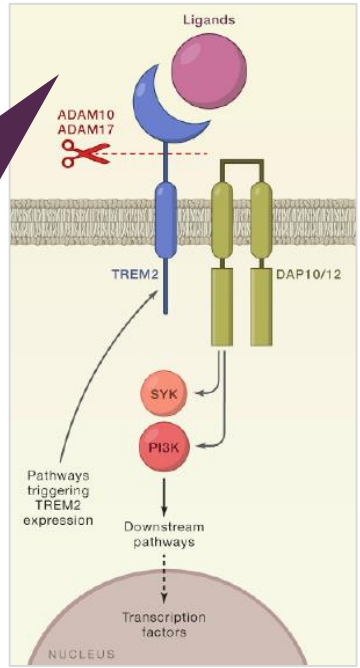
Physiological function

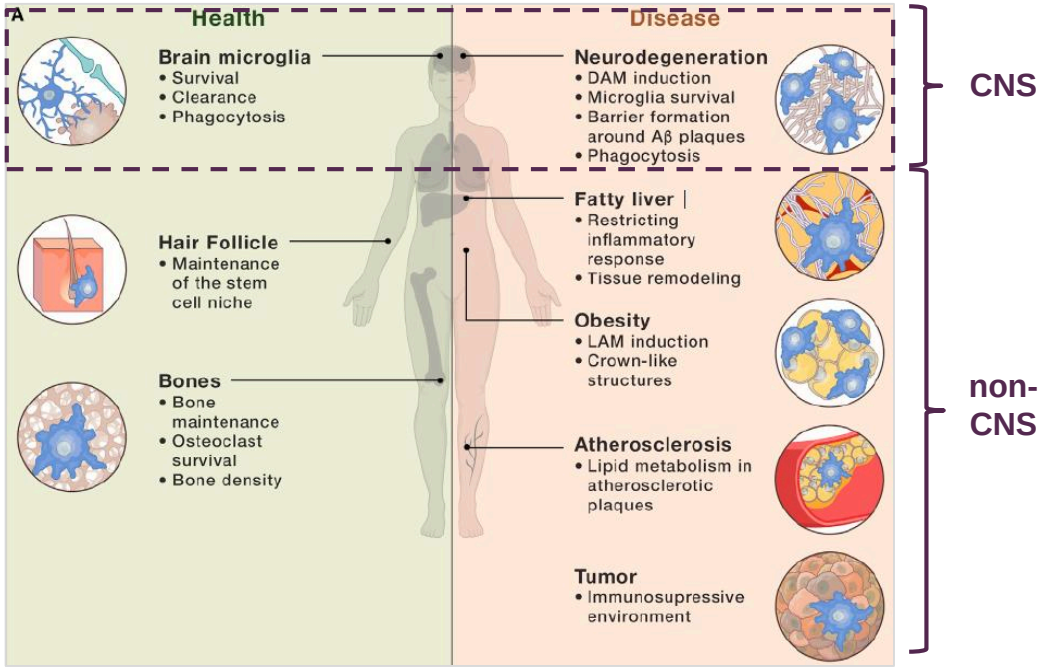
- Binding of ligands (e.g. DNA, lipoproteins, phospholipids) to TREM2 promotes microglial: **(1)** chemotaxis/motility, **(2)** phagocytosis, and **(3)** survival, and proliferation.
- TREM2 also helps maintain stem cell niche of the hair follicle and promotes osteoclast survival to sustain bone density.

Pathological function

- TREM2 is vital for the disease-associated microglia (DAM) phenotype, a specific phenotypic subtype of microglia that may help protect against neurodegeneration.
  - TREM controls several critical functions of microglia in the context of AD: **(1)** removal of cellular debris and protein aggregates, **(2)** forming protective barriers around plaques preventing cellular damage caused by free Aβ protein, and **(3)** curbing inflammation.
- TREM2 has also been linked to restricting inflammation in fatty liver disease, adipose tissue remodeling and limiting metabolic dysfunction in obesity, and are thought to be protective in atherosclerosis through anti-inflammatory and lipid oxidation functions.

TREM2 signals through DAP10/12 and SYK/PI3K to control microglia chemotaxis/motility, phagocytosis, survival and proliferation in both transcription-dependent and transcription-independent ways



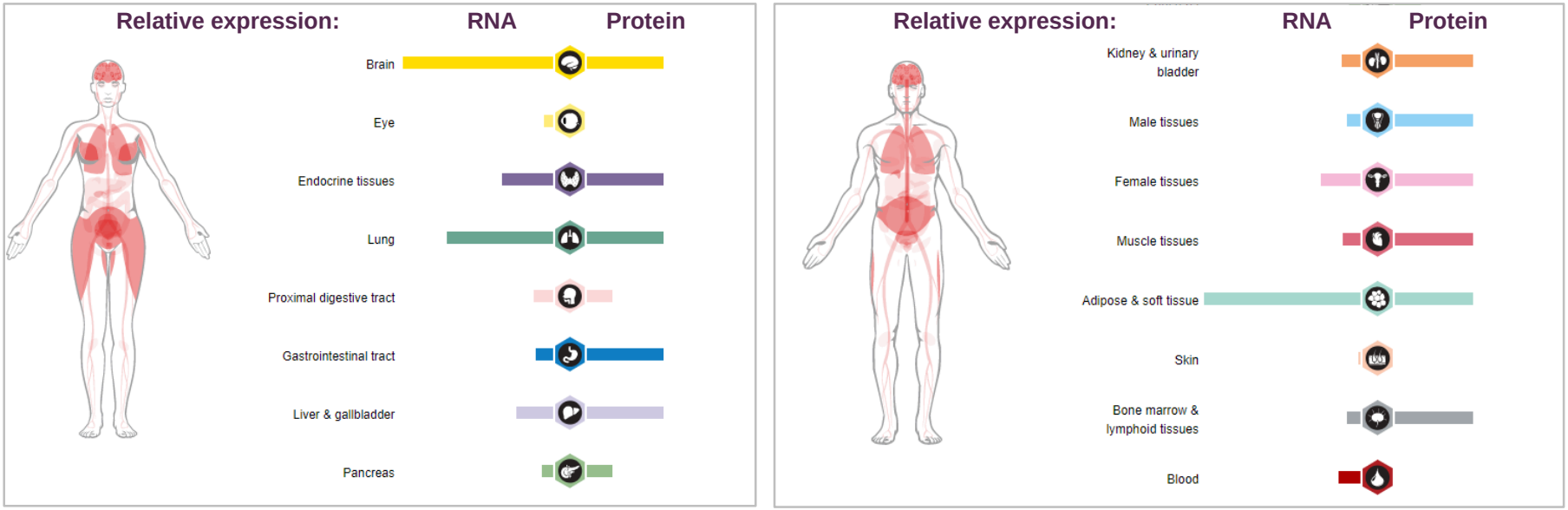


Source: Hansen et al. 2018, Keren-Shaul et al. 2017, Deczkowska et al. 2020

Where is TREM2 enriched? (1/1) – TREM2 is highly expressed in microglia and macrophages

- TREM2 is mainly expressed on the cell surface of **microglia and macrophages**, according to the Human Protein Atlas.
- Whether in the CNS or the periphery, TREM2 seems to have a protective role in the context of diseases due in part to its role in restraining inflammation, but similar to NLRP3 the nuances between TREM2 function across different macrophage populations is not well defined.
  - Three key factors to consider based on the broad expression of TREM2 are: **(1)** how TREM2 function may differ among in different macrophage sub-populations across tissues, **(2)** the location of TREM2 relevant for therapeutic intervention in a particular disease (e.g. CNS for neurodegenerative disease vs. adipose for metabolic disease), and **(3)** whether specific drug delivery and/or administration modalities are needed to engage TREM2 in a specific tissue or if whole-body engagement of TREM2 is sufficiently efficacious and safe.

TREM2 tissue expression



While TREM2 mRNA (bar on left side) and protein (bar on right side) can be detected in most tissues in the human body (except lower expression in the eye, skin, pancreas and proximal GI tract), it is thought that most of the TREM2 expression is attributed to resident macrophages (and other innate immune cells) in these tissues (e.g. Kupffer and Hofbauer cells)

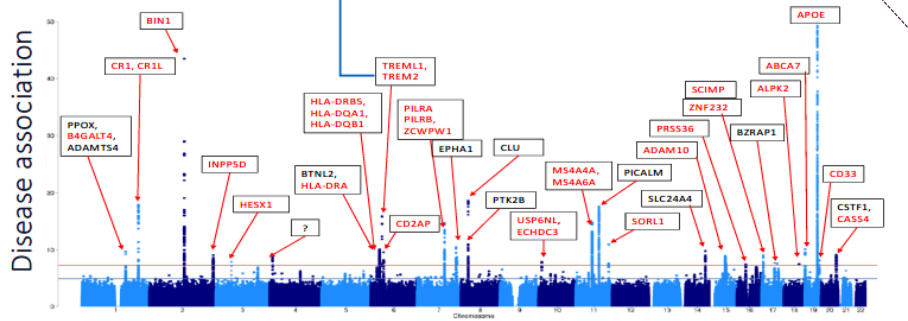
Source: McKee & Coll 2020, Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000095970-TREM2/tissue)

Is there a genetic connection between TREM2 and disease? (1/1) – TREM2 has the second strongest genetic link to AD

- Multiple GWAS studies have found a strong genetic link between TREM2 variants and risk of late-onset AD, implicating TREM2 mutations as a potential cause of AD.
  - The R47H mutation in TREM2 (which disrupts ligand binding and dampens TREM2 signaling) was found to confer a significant risk of AD (odds ratio of 2.92) in an Icelandic population (n = 2261).
  - R47H may prevent microglia from properly handling buildup of Aβ protein leading to neuronal dysfunction and cell death
- Key points of genetic evidence for TREM2 in AD are: (1) homozygous TREM2 loss of function may lead to early neurodegeneration with shortened lifespan (e.g. the leukodystrophy Nasu-Hakola Disease), (2) heterozygous loss of TREM2 function can triple risk of developing AD, and (3) a SNP that increases TREM2 expression protects against AD.

TREM2 loss-of-function mutations lead to disease while TREM2 overexpression protects against disease, suggesting that TREM2 activation could be a viable therapeutic approach

TREM2



Key evidence for genetic link between TREM2 and AD

- TREM2 homozygous loss of function may cause neurodegeneration by age 40, with a lifespan of ~10 years following diagnosis
- TREM2 heterozygous loss of function increases risk for AD by 3x
- A SNP (rs9381040) associated with increased TREM2 expression is protective against AD

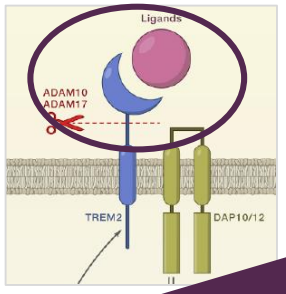
Source: ALEC company presentation, Jansen et al. 2019, Jonsson et al. 2013, Hansen et al. 2018

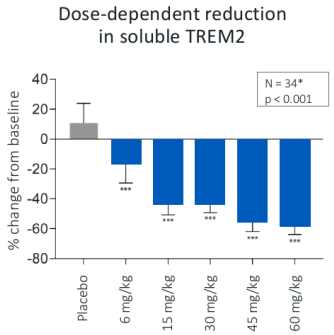
Are there biomarkers for the TREM2? (1/1) – Soluble TREM (sTREM2) and soluble CSF1R (sCSF1R) are TREM2 biomarkers

sTREM – direct biomarker

- sTREM2 is formed as a proteolytic biproduct of TREM2 cleavage by ADAMs 10 and 17
- sTREM2 correlates with concentration of free/bound transmembrane TREM2, where a reduction in sTREM2 corresponds to a higher level of receptor occupancy and lower level of free receptors
- sTREM2 is considered a direct biomarker for target engagement of transmembrane TREM2 and for microglia activation (and possibly neuron injury)

sTREM2 (cleavage)



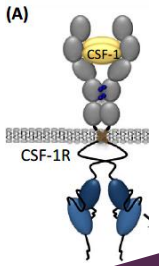


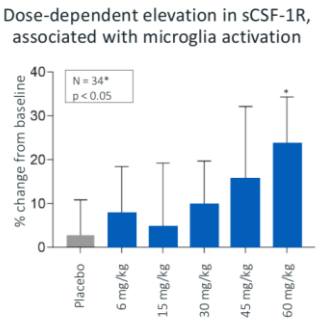
ALEC's TREM2 activating Ab AL002 showed ~60% reduction in sTREM2 at 60mg/kg in a Phase I HV trial; sTREM2 may have a separate biological function but not much is known at this point

sCSF1R – indirect biomarker

- CSF1R signaling is required for viability of microglia and is critical for differentiation and proliferation
- sCSF1R is mainly produced through mRNA splicing and may increase as a compensatory response to CSF1R activation
- sCSF1R is considered an indirect marker of TREM2 activation and more directly correlates with macrophage activation

sCSF1R (mRNA splicing)





ALEC's TREM2 activating Ab AL002 showed ~25% increase in sCSF1R at 60mg/kg in the same Phase I HV trial, but the data were more variable compared to sTREM2 and little is known about sCSF1R production

Source: ALEC company presentation, Deczkowska et al. 2020, Chitu et al. 2016, Barreda et al. 2005, Guggenheim Securities, LLC research

What diseases is TREM2 involved in? (1/1) – TREM2 plays a protective role in numerous CNS and non-CNS diseases

TREM2 activity has been implicated in a handful of indications, mainly neurodegenerative and metabolic diseases. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
Nasu-Hakola Disease	Homozygous LOF mutations in TREM2 completely block ligand binding resulting in: (1) changes in microglial gene expression and phenotype, (2) disrupted regulation of bone formation and synaptic plasticity, and (3) clinical symptoms (progressive pre-senile dementia and recurrent bone fractures); exact MoA connecting receptor to symptoms not known	**Moderate** - defined human genetics link (may also include TYROBP mutations); clear MoA link based on physiological function of TREM2, but exact MoA relating loss of receptor function to clinical symptoms not known; not much clinical validation as there are no approved drugs and no disclosed drugs in development
Alzheimer's Disease	Mutations (e.g. R47H) decrease ligand binding and receptor signaling which: (1) interrupts regulation of neuroinflammation, (2) alters compaction and clearance of amyloid, and (3) promotes neuronal damage. These changes are thought to be closely linked to the cognitive decline in AD.	**Strong** – defined human genetics link (2nd strongest in AD), robust pre-clinical data showing altered microglial regulation of inflammation and amyloid interactions/clearance in AD models; some clinical validation with concordance of MoA (pre-clinical and patients) and promising PD data from ALEC's AL002 Phase I HV study
Atherosclerosis	Macrophages highly expressing TREM2 have a unique lipid metabolic profile and selectivity migrate to atherosclerotic plaques (and not in healthy aortas), but exactly what these macrophages are doing is not well established	**Weak** – not much genetic evidence; pre-clinical data are not definitive and contradictory; some clinical evidence, with TREM2 expression detected in human lesional macrophages
Obesity/NASH	TREM2 is essential for induction of the lipid-associated macrophage (LAM) phenotype in obese adipose tissue and controls inflammation, adipocyte size, cholesterol levels and glucose metabolism in obese mice	**Moderate** – not much genetic evidence; solid pre-clinical data but MoA may depend on obesity stage; clinical evidence - TREM2 in human adipose macrophages and LAMs associated with BMI

Source: Jadhav et al. 2020, Deczkowska et al. 2020, Cochain et al. 2018, Jaitin et al. 2019

See pages 110 - 111 for analyst certification and important disclosures.

What are the challenges in targeting TREM2? (1/1) – Complexity of TREM2 signaling and broad tissue expression represent hurdles in drug development

TREM2 may be a hot target but drugging this receptor may not be easy. TREM2 is a complex receptor that exhibits different signaling modes across a spectrum of receptor activity. So, how much activity is the right level and how do you achieve this? Currently, there are two primary approaches to targeting (at this point activating) TREM2: (1) antibodies and (2) small molecules. While antibodies offer potency and specificity, antibodies could lead to over-activation or under-activation depending on how the natural ligands interact with TREM2, which could lead to lower efficacy and higher AEs. Small molecules offer the option for precise pocket binding (e.g. allosteric) but may not be as potent as antibodies and may not activate TREM2 the same way as an antibody. In our view, both could work but there are significant hurdles to overcome.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Activating antibody	Spectrum of TREM2 signaling with different cellular effects based on degree of activation; TREM2 binds to several ligands (many not well defined); antibodies could lead to under- or over-activation leading to lower efficacy and/or undesired AEs; delivery to right tissue	Incorporate structure/function studies for ligand-competitive vs. non-competitive binding; titration of TREM2 activity and correlation with signaling outcomes; utilize tissue targeting technology (e.g. for CNS delivery)	In general, maxing out activity for TREM2-activating antibodies should be sufficient to activate microglia in neurodegenerative indications; whether chronic activation of microglia (DAMs) in a TREM2-dependent manner is beneficial in the long-term, is not known
Small molecule activator	More potential for off-target effects (e.g. binding to other Ig superfamily receptors); potentially lower potency compared to antibody; ligand competitive compounds may have to compete with several ligands while allosteric molecules may not engage all functions of TREM2	Structure-guided medicinal chemistry to build compounds that bind to the right domain of TREM2 (and only TREM2, if that is desired)	Antibodies are already in the clinic and could provide important PoC for TREM2, but small molecules would be more convenient (oral dosing possible); small molecules may have to be as potent as antibodies which could create a pre-clinical bottleneck requiring a sufficiently large compound library

Bottom line: In our view, both antibody and small molecules can be successful approaches for targeting TREM2, and antibodies (further in development) will provide important PoC for next-gen small molecule activators but in either case not enough long-term data exist to suggest whether chronic microglial activation is: (1) maximally efficacious, and (2) safe.

Source: Deczkowska et al. 2020, Konishi & Kiyama 2018, ALEC company presentations, Guggenheim Securities, LLC research

Current programs targeting TREM2 (1/2)

TREM2 is still a relatively untapped hot drug target in the innate immunity space, with two companies actively pursuing the target (all companies listed in the table on the next page). Some highlights from our end:

- ***ALEC*** is developing (in collab with ABBV) AL002, a humanized and IV-administered TREM2-activating antibody in AD (currently in Phase II)
- ***DNLI*** is developing DNL919, a TV-enabled (transferrin receptor binding) antibody designed to cross the blood-brain barrier and activate TREM2 signaling in microglia in Alzheimer's Disease (AD) and FTD (currently in preclinical stage)

Source: Foulds et al. 2015, Konishi & Kiyama 2018, AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting TREM2 (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
Alector (Abbvie)	ALEC	2257.2	AL002	AL002, is a humanized, TREM2 activating, monoclonal antibody (IV admin) that induces microglial proliferation, increases microglial survival and decrease dystrophic neurites, and may work regardless of genetic variant (normal vs. disease risk variant) of TREM2	Alzheimer's disease	Phase II
Denali	DNLI	6438.4	DNL919 (ATV-TREM2)	DNL919 is a TV-enabled antibody designed to modulate TREM2 signaling and thereby normalize microglial function	Alzheimer's disease, FTD	Preclinical (IND-enabling studies)

Note: all market cap figures in $

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on TREM2 (1/1) – Despite broad expression profile, TREM2 has the potential to be a strong target in neurodegenerative diseases

Target factor	Strength of evidence	GS comments
Link to human genetics	**STRONG**	Homozygous LOF mutations lead to Nasu Hakola disease (along with mutations in TYROBP gene), while heterozygous LOF mutations have the 2nd strongest link to increased risk of AD; variants with increased TREM2 expression are protective in neurodegeneration
CNS target enrichment	**WEAK**	TREM2 is present not only in microglia of the brain but also in peripheral macrophages in most tissues (especially in lung and adipose); tissue-specific functions and long-term safety of chronic microglial activation is not yet known
Mechanism of action	**STRONG**	Strongest in AD; genetic decrease in ligand binding and receptor signaling: (1) interrupts regulation of neuroinflammation, (2) alters compaction and clearance of amyloid, and (3) promotes neuronal damage; these changes are thought to be closely linked to the cognitive decline in AD.
Biomarkers	**STRONG**	TREM2 has both direct (sTREM2, target engagement) and indirect (sCSF1R, microglial activation) biomarkers that are closely linked to the receptor biology and may correlate with some clinical parameters (sTREM2 may be marker of neuronal damage)
Safety	**MODERATE**	Due to broad expression of TREM2 in both CNS and non-CNS tissues, safety could be an issue; ALEC has not seen any serious AEs in their Phase I trial of AL-002 so far (more data coming late July), but long-term safety is still a major question
Clinical PoC	**MODERATE**	DNLI's program is in preclinical stage, but ALEC has produced important PoC in their Phase I showing that AL002 can activate TREM2 and microglia in humans, but signs of clinical efficacy are still lacking (and may not come until 2023)

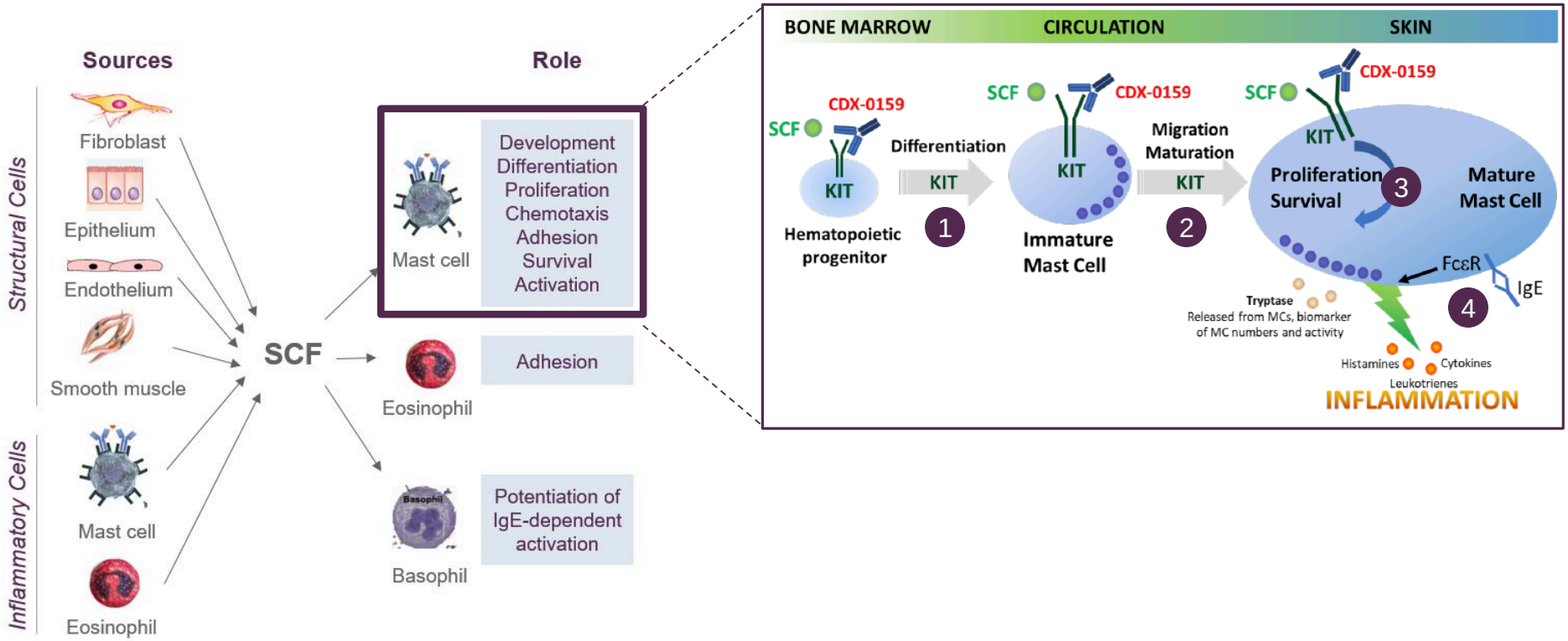
Source: Hansen et al. 2018, ALEC presentations, clinicaltrials.gov, Guggenheim Securities, LLC research

Table of Contents

c-KIT

What is c-KIT? (1/1) – c-KIT is a cell surface receptor tyrosine kinase that is critical for survival, differentiation and activation of mast cells

- **c-KIT** is a receptor tyrosine kinase on the cell surface of innate immune cells, especially mast cells
  - C-KIT is related to the CSF1R/PDGF type III receptor subfamily, with four receptor isoforms in humans.
  - The main ligand of c-KIT is stem cell factor (SCF), a critical local growth factor for mast cells that is produced by both structural cells (e.g. fibroblasts and epithelial cells) and inflammatory cells (e.g. mast cells and eosinophils)
  - SCF signaling through c-KIT promotes mast cell: (1) differentiation, (2) migration and maturation, (3) survival and proliferation, and (4) FcεRI-dependent activation.
  - Many innate immune cells express c-KIT besides mast cells (more on next page)

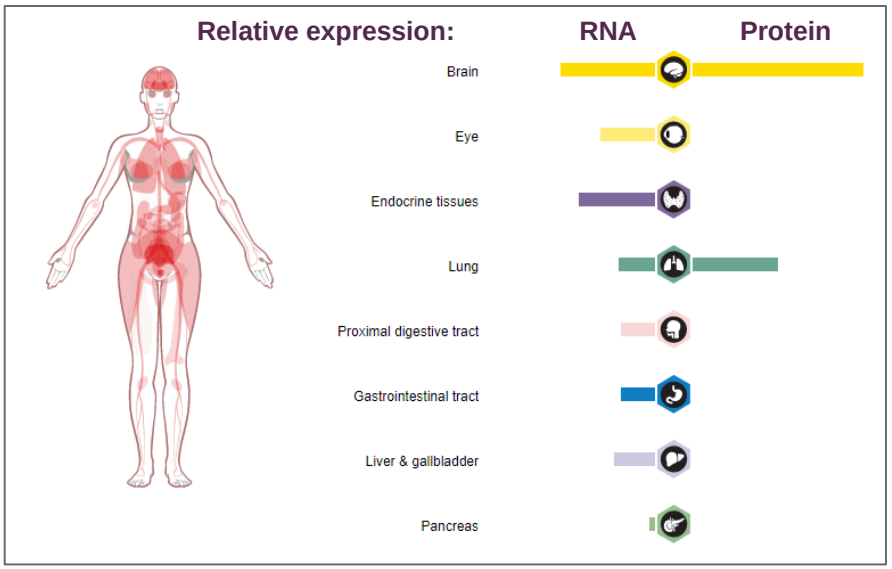


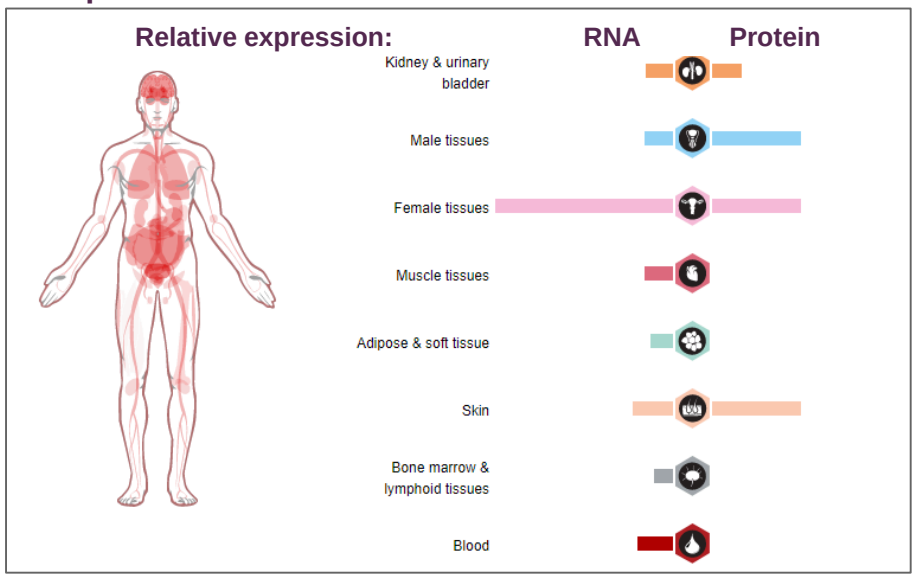
Source: ALLK company presentation, CLDX company presentation, Silva et al. 2006, Alex & Frangogiannis 2018, Altrichter et al. 2020, Islam & Luster, 2012, Guggenheim Securities, LLC research

Where is c-KIT enriched? (1/1) – c-KIT is highly expressed in the brain but can be found in several peripheral tissues as well, mainly in tissue granulocytes

- c-KIT is mainly expressed on the surface (plasma membrane) of innate immune cells including mast cells, eosinophils, basophils, melanocytes, and germinal cells and can be measured in multiple tissues, with protein highly expressed in brain and moderate expression in lung, reproductive organs, and the skin
  - Most of the expression seems to be due to granulocytes in the tissue
  - Some non-granulocyte cells (e.g. lung alveolar cells, melanocytes, endothelial cells) also express low levels of c-KIT
- c-KIT expression and function is fairly well known for mast cells and eosinophils, but the role SCF/c-KIT plays in the development and/or physiological function in other cell types is not as well defined

c-KIT tissue expression



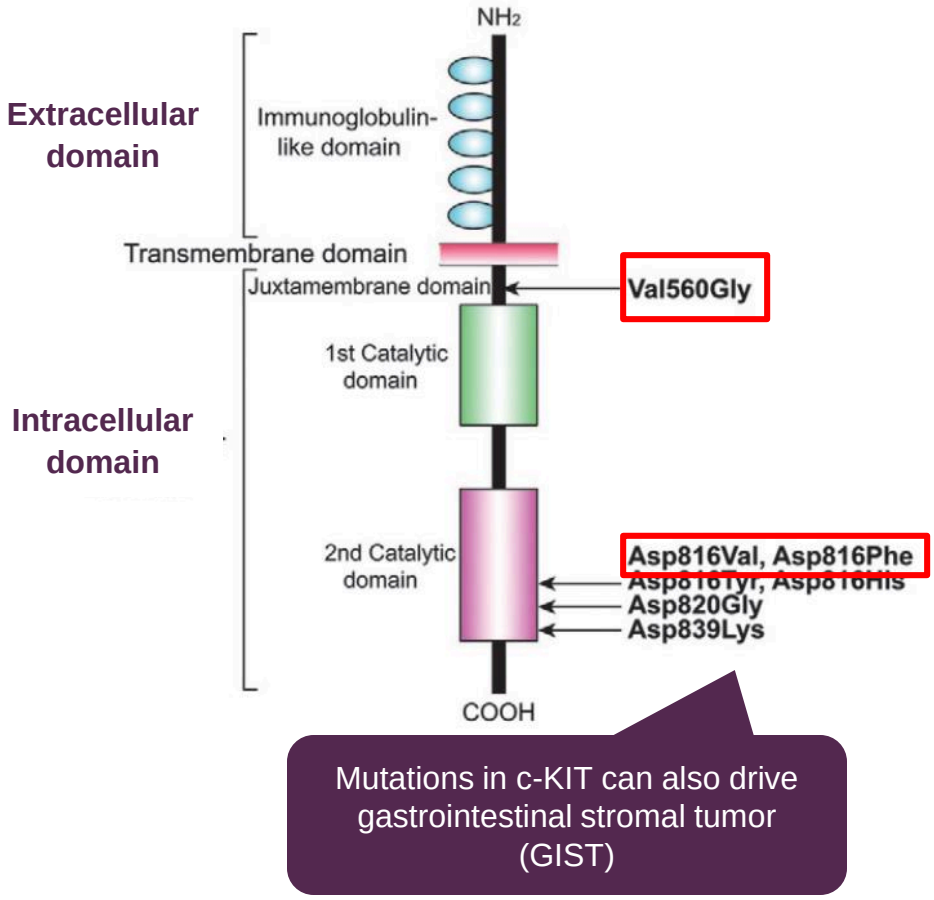


While c-KIT mRNA (bar on left side) can be detected in most tissues in the human body c-KIT protein (bar on right side) is mainly found in the CNS, lung, skin and reproductive organs. It is thought that most of the c-KIT expression is attributed to granulocytes in these tissues, but c-KIT can also be detected in type 2 alveolar cells in the lung, melanocytes and some endothelial cells.

Source: Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000157404-KIT/tissue)

Is there a genetic connection between c-KIT and disease? (1/1) – GOF mutations in c-KIT cause mastocytosis

c-KIT mutations contributing to mastocytosis



Mutations in c-KIT can also drive gastrointestinal stromal tumor (GIST)

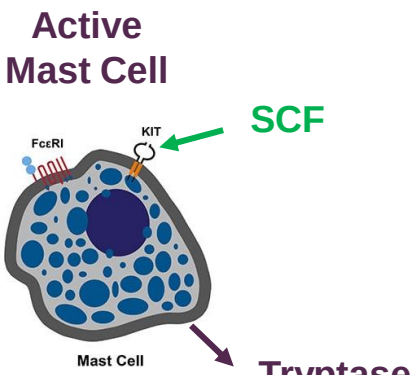
- **Mastocytosis** comprises a group of skin/hematological disorders characterized by hyperproliferation of mast cells in various organs (e.g. skin, bone marrow, liver, spleen, and lymph nodes)
  - Mastocytosis can be cutaneous (restricted to skin) or systemic (involving bone marrow)
- Mastocytosis can be caused by several gain-of-function (GOF) mutations in c-KIT in either the juxtamembrane or catalytic domains
  - *Asp816Val* and *Val560Gly* both contribute to adult-onset disease
  - *Asp816Val* and *Asp816Phe* both contribute to childhood-onset disease
    - All three mutations ***lead to constitutive c-KIT activation which directly contributes to the hyperproliferation of mast cells*** that underlies the lesions that characterize mastocytosis

Source: Yanagihori et al. 2005, BPMC company presentations, Guggenheim Securities, LLC research

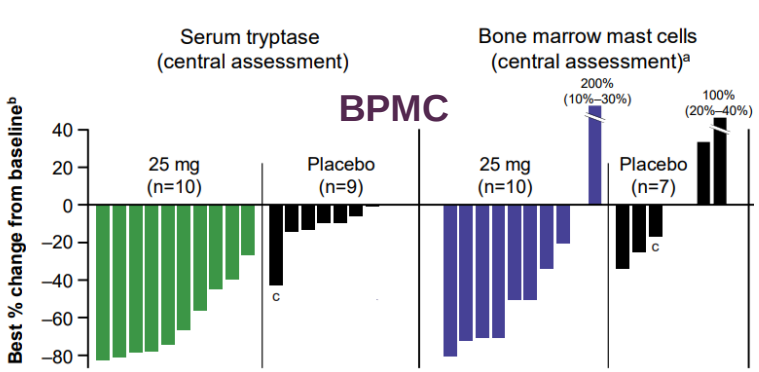
Are there biomarkers for c-KIT? (1/1) – Serum tryptase is a clinically validated biomarker for mast cell activation

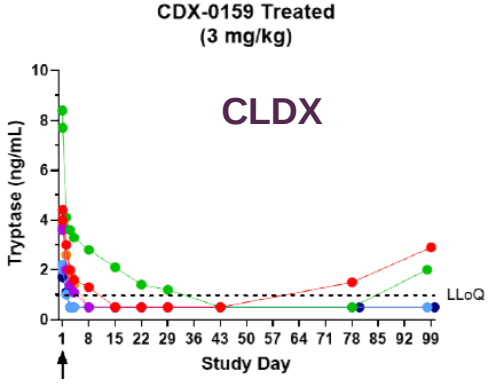
Marker	Relative specificity to mast cell activation	Limitations
Tryptase	**Most specific marker**	**Must be measured within 4hrs of symptoms**
Urinary histamine metabolites	Fairly specific for mast cell activation	Can be influenced by diet or bacterial infection; no established activation threshold values
Urinary prostaglandin D_2/metabolites	Not specific to mast cells	No established activation threshold values; requires a second validation marker
Urinary leukotriene E_4	Not specific to mast cells	Relatively little clinical evidence

- **Serum tryptase is viewed as a good biomarker for c-KIT activity and mast cell activation**
- Recombinant SCF injections dose-dependently increased serum tryptase in subjects
- Elevated serum tryptase is associated with clinical signs of mast cell related disease (fatigue, flush, and edema)
- Anti-c-KIT antibodies (BPMC, CLDX) decreased serum tryptase levels in patients which were associated with improvement in clinical scores (BPMC)



Anti-c-KIT antibodies reduce serum tryptase and mast cell numbers in humans





Source: CLDX company presentations, BPMC company presentations, Guggenheim Securities, LLC

What diseases is c-KIT involved in? (1/1) – Both WT and mutant c-KIT play a vital role in mast cell driven diseases of the skin, lungs, GI tract and CNS

c-KIT (both WT and mutant) has been implicated in many indications, including both allergic and non-allergic chronic diseases of the skin, lungs, GI tract and the CNS. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
Mastocytosis	GOF mutations in c-KIT drive mast cell hyperproliferation which directly results in skin lesions and bone marrow issues	**Strong** – direct human genetics link; mast cell activation observed at site of lesions; BPMC's Avyakit (avapritinib) approved for advanced systemic mastocytosis
Chronic urticarias (CSU, CIndU)	Allergens and other stimulatory molecules (e.g. SCF, IL-33) activate IgE-bound mast cells leading to MC degranulation releases histamine (and others) promoting vasodilation, vascular permeability and inflammatory cell infiltration and directly contributes to pain, itch and the tissue damage underlying wheals characteristic of chronic urticarias	**Strong** – not much genetic involvement since overactivation of WT c-KIT drives mast cell activity; clear MoA and localization of mast cells and molecular mediators of inflammation at sites of wheals in humans; clinical PoC from CLDX's CDX-0159 in CIndU (95% complete response rate)
Allergic asthma	Histamine and proinflammatory cytokines secreted by airway mast cells promote bronchoconstriction and airway remodeling; mast cell burden correlates with disease severity, asthma phenotype, and airway hyperresponsiveness	**Strong** - not much genetic involvement since overactivation of WT c-KIT drives mast cell activity; clear MoA linking mast cells to bronchial hyperresponsiveness; clinical PoC from AB-FR's masitinib Phase III (35% reduction in severe asthma exacerbations)
Gastrointestinal stromal tumor (GIST)	GOF mutations in c-KIT stimulate proliferation of both mast cells and of interstitial cells of Cajal in the gut, driving tumorigenesis	**Strong** – clear human genetics link; direct MoA connecting c-KIT in ICCs and mast cells to tumor growth; some clinical PoC with COGT's CGT9486 pushing mPFS to 11 months
ALS	Mast cells can cross BBB and release neuropeptides/histamine, activate microglia and promote inflammation/neuronal dysfunction	**Moderate** – no clear genetic link; MoA linking mast cells to pathology but not clear; clinical evidence of mast cell involvement in ALS patients

Source: Yanagihori et al. 2005, BPMC company presentations, CLDX company presentations, Guggenheim Securities, LLC research, Lee-Fowler et al. 2012, AB-FR company presentations, Pittoni et al. 2011, Jones et al. 2019

What are the challenges in targeting c-KIT? (1/1) – Targeting the WT c-KIT receptor or a mutant receptor will depend on the pursued indication

There are two high level approaches to targeting the c-KIT receptor: (1) the normal WT receptor which carries out normal physiological functions on mast cells, basophils, eosinophils, etc. and (2) mutant forms of c-KIT specifically linked to certain diseases including the Asp816Val mutation that drives mastocytosis. Each approach has its challenges – WT receptor inhibition could lead to AEs (especially in the bone marrow) and mutant receptor blockade requires resource- and time-intensive SAR studies cross-referenced to mutant vs. WT receptor structures. Within both approaches, antibodies and (more commonly) small molecules can be used – with the common caveat that antibodies could be more specific than small molecules that often hit more than one (and up to 7) other kinases. In our view, both can be successful, depending on the indication pursued.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
WT receptor inhibitor	Broad applicability, but potential for interrupting normal physiological function of c-KIT, especially in the bone marrow	Target antibody specifically to diseased tissues where mast cells are located	Tissue targeting could be very labor- and time-intensive; thus far, benefit/risk profile seems favorable with no serious bone marrow complications (based on Phase I CLDX safety data)
Mutant receptor-specific inhibitor	More specific to a genetically defined receptor/indication combo, but would require intensive medicinal chemistry, SAR studies and high-resolution c-KIT structures	Screening in cell lines with clinically relevant mutations to facilitate iterative SAR studies	This approach is best suited for indications with a clear genetic link to c-KIT (e.g. mastocytosis), as evidenced by the recent FDA approval of BPMC's mutant KIT inhibitor Avyakit (avapritinib)

Bottom line: In our view, both approaches can be successful: (1) WT receptor may be a better target for indications with a less defined or more complex genetic component (e.g. urticarias), and (2) mutant receptors may be a better target in indications with a strong genetic link to disease (e.g. mastocytosis) to maximize efficacy and minimize the chances of AEs from blocking the normal, physiological functions of WT c-KIT

Source: CLDX company presentations, BPMC company presentations, Da Silva et al. 2006, Guggenheim Securities, LLC research

Current programs targeting c-KIT (1/2)

The **c-KIT space** is a crowded landscape, with 14 companies actively pursuing the target (all companies listed in the table on the next page). Some of our highlights from a neuro/inflammation perspective:

- *AB-FR* is developing masitinib, which blocks mast cell proliferation through inhibition of c-KIT/Lyn/Fyn kinases, in a host of indications but including ALS, MS and AD (ALS: Phase III, MS/AD: Phase II/III)
- *CLDX* is developing CDX-0159, an antibody that blocks SCF binding to WT c-KIT reducing the overall mast cell population, in chronic (spontaneous and inducible) urticarias (currently in Phase Ib)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting c-KIT (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
AB Science	AB-FR	570.8	Masitinib	Blocks mast cell activation and proliferation by inhibiting wild-type c-Kit, Lyn and Fyn tyrosine kinases	ALS, MS, AD, Indolent systemic mastocytosis, asthma, pancreatic/prostate cancers, COVID19	Phase III (ALS, ISM); Phase II/III (MS, AD, asthma, cancers); Phase I/II (COVID-19)
Apollomics	Private		APL-102	APL-102 inhibits both receptor tyrosine kinase (RTKs) and serine/threonine-kinases, including: VEGFRs, PDGFRs; MAPK pathway via B-RAF and C-RAF; RET, CSF1R, DDR1 and c-KIT.	Oncology (solid tumors)	Pre-clinical
Aveo Pharmaceuticals Inc	AVEO	213.5	Tivozanib (AV-951)	Tivozanib inhibits VEGFR1, 2 and -3 at picomolar concentrations (IC50 of 0.21, 0.16 and 0.24 nM respectively), and inhibits c-Kit and PDGFR at 10-times higher concentrations (IC50 of 1.63 and 1.72 nM respectively)	Hepatcellular Carcinoma	Phase II
Blueprint Medicines	BPMC	5545.8	Ayvakit (avapritinib), BLU-263	Potent inhibitor of the constitutively active D816V mutant KIT (also inhibits WT KIT) and PDGFRA; BLU-263 is a next-gen inhibitor		Ayvakit: approved (GIST, Advanced SM), Phase II (Non-advanced SM); BLU-263: Phase II/III (Non-advanced SM)
Celldex	CLDX	2099.1	CDX-0159	Blocks binding of SCF to c-KIT receptor on mast cells, depriving mast cells of key growth factor and ultimately reduces number of mast cells	Chronic spontaneous urticaria (CSU; cold-induced and symptomatic dermographism), Chronic Inducible Urticaria (CIndU)	Phase Ib
Cogent Biosciences Inc (Unum Therapeutics)	COGT	309.2	CGT9486	Specifically targets constitutively active D816V KIT mutant receptor that drives abnormally high proliferation of mast cells	Systemic mastocytosis, gastrointestinal stromal tumor (GIST)	Phase I/II (GIST); Phase II in advanced SM (coming in 1H21) and Phase II in non-advanced SM and GIST (coming in 2H21)
Gilead	GILD	88870.1	GS-0174	Blocks c-Kit to deplete host hematopoietic stem cells, with the goal of minimizing adverse events associated with HSC transplants	Transplant conditioning regimen	Phase Ia
Gossamer	GOSS	668.8	Seralutinib (GB002)	Inhaled inhibitor of PDGFR, CSF1R and c-KIT	PAH	Phase II
Jiangsu Hengrui Pharmaceuticals Co Ltd	600276-CN	354652.3	Famitinib	Orally available small molecule RK that inhibits c-Kit, VEGFR2, PDGFR, VEGFR3, Flt1 and Flt3, eliciting anti-tumor and anti-angiogenesis effects	CRC, GIST	Phase III
Magenta Therapeutics Inc	MGTA	386.5	MGTA-117	MGTA-117, which is an anti-CD117 antibody conjugated to an amanitin payload which depletes HSCs and leukemia cells (that overexpress c-KIT) for preconditioning of HSCT in AML and MDS	AML, MDS	Preclinical
Mirati Therapeutics Inc	MRTX	7241.2	Sitravatinib	Sitravatinib is a receptor tyrosine kinase inhibitor (TKI) that targets multiple closely related receptor tyrosine kinase pathways including VEGFR, PDGF receptor (PDGFR), c-KIT, MET, and the TAM family of receptors (TYRO3, AXL, and MER)	NSCLC, Bladder cancer	Phase II (Bladder); Phase II/III (NSCLC)
Poseida	PSTX	545.7	anti-cKIT CAR-T	CAR-Ts against c-KIT as a safer preconditioning regimen for hematopoietic stem cell transplantation in patients with AML	AML	Preclinical
Shenzhen Chipscreen Biosciences Co., Ltd.	688321-CN	16519.2	Chiauranib	Oral small molecule that inhibits multiple kinases (VEGFR2, VEGFR1, VEGFR3, PDGFRa and c-Kit), Aurora B, CSF-1R	Progressed/Relapsed Small-cell Lung Cancer After 2 Lines Chemotherapy	Phase III
Tenax Therapeutics	TENX	39.1	Reformulation of imatinib	Imatinib has been shown to specifically inhibit ABL, PDGFR, and KIT kinases, and PDGFR is important for proliferation of smooth muscle cells in PAH pathophysiology	PAH	Pre-clinical with Phase I coming in 2H21

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Note: all market cap figures in $ except for AB-FR in € and 600276-CN and 688321-CN in CN ¥

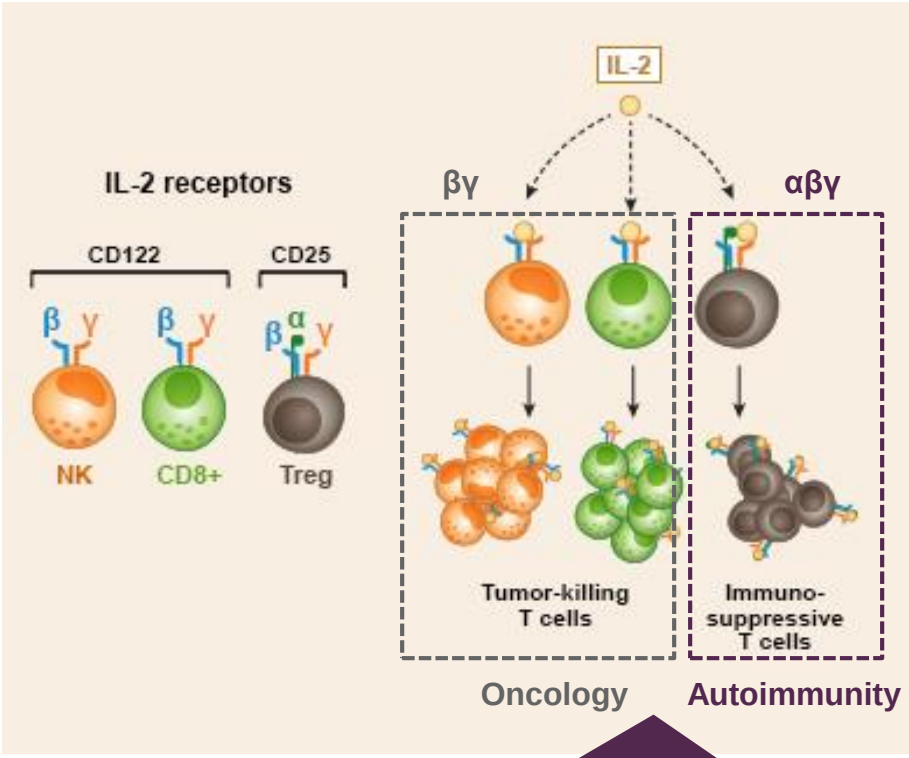
Our view on c-KIT (1/1) – c-KIT is a genetically and clinically validated target for mast cell-driven disease

Target factor	Strength of evidence	GS comments
Link to human genetics	**STRONG**	GOF mutations are directly linked to mast cell hyperproliferation that underlies the clinical symptoms of mastocytosis and GIST
CNS target enrichment	**WEAK**	By virtue of its cellular expression, c-KIT is expressed in several tissues outside of the brain (including skin), but we think that this is an *advantage* that expands the realm of relevant c-KIT indications
Mechanism of action	**STRONG**	Mastocytosis provides clinic PoC for the importance of SCF/Kit signaling for mast cell proliferation, survival and activation. In urticarias, mast cells and the effector molecules released when activated are present in human skin lesions, suggesting direct involvement
Biomarkers	**STRONG**	Serum tryptase is a clinically validated biomarker for mast cell activation that is associated with mast cell number and clinical symptoms (BPMC's avapritinib in mastocytosis); mast cell release of tryptase is due in part to c-KIT activation
Safety	**MODERATE**	Most safety signals in the clinic have been benign so far, with mild IRRs; bone marrow-associated AEs are a concern with the importance of c-KIT for maturation of mast cells in the bone marrow environment, but no serious AEs observed to date by CLDX in CIndU
Clinical PoC	**STRONG**	Strong PoC for mastocytosis (BPMC's avapritinib approved as Avyakit); early PoC by CLDX in mast cell-driven urticarias with impressive 95% overall CR rate in Phase Ib CIndU trial

Source: CLDX company presentations, BPMC company presentations, Guggenheim Securities, LLC

*Inter**l**eukin-**2** IL-2 (Treg expansion)*

What is IL-2? (1/2) – IL-2 is a cytokine that stimulates both T effector and T reg cells depending on IL-2 receptor isoform engagement



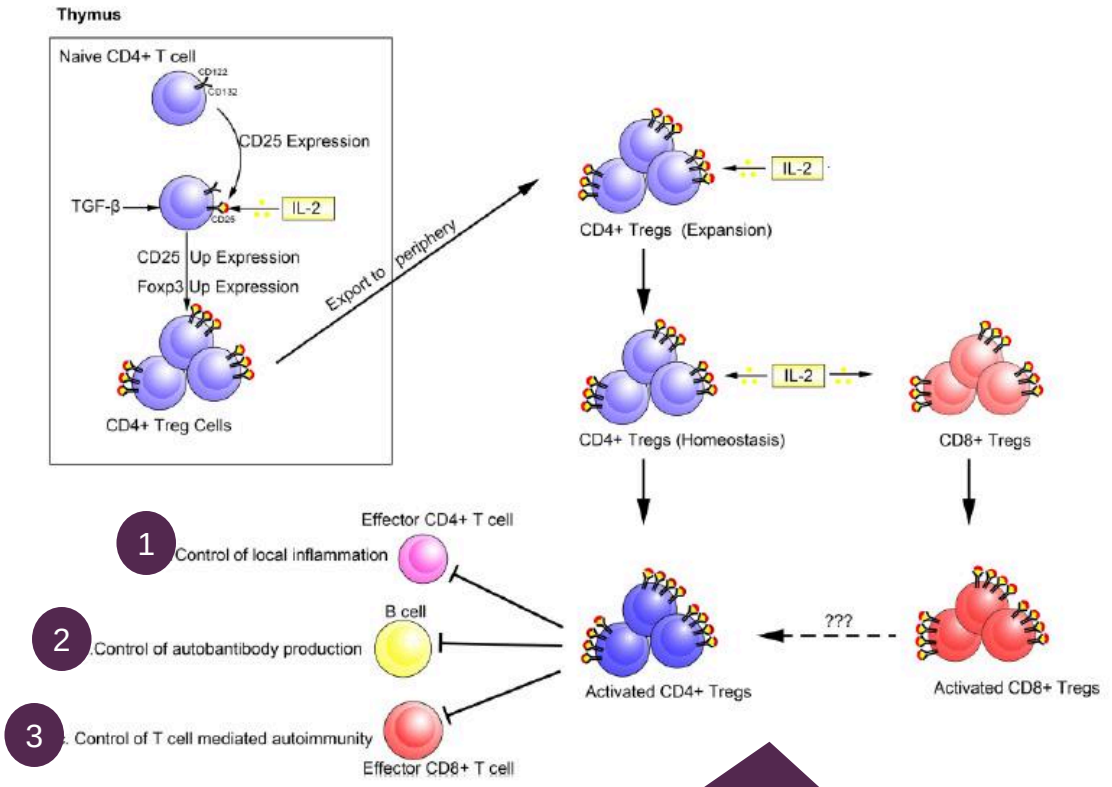
By tuning IL-2 receptor activation, it may be possible to toggle the IL-2 switch between βγ-mediated tumor suppression in oncology indications and αβγ-mediated Treg expansion and rebalancing of the immune system in autoimmune diseases. In this report, we will focus on approaches specifically expanding Tregs, instead of the "non-alpha" approaches in cancers.

Interleukin-2 **(IL-2)** is a multi-functional cytokine known for its ability to stimulate activity and proliferation of both pro-inflammatory T effector cells and immunosuppressive T cells (e.g. Tregs)

- IL-2 is produced by T cells and dendritic cells, which can act in a paracrine fashion to promote expansion of both CD8+ T cells/NKs and Tregs
- T effector cells (NK, CD8+ cells) express the β and γ isoforms of the IL-2 receptor on the cell surface, which drive expansion of NK, CD8+ cells
- Tregs have a trimeric IL-2 receptor consisting of α, β and γ isoforms, which drive expansion of Treg subsets
- The αβγ IL-2 receptor trimer has a higher affinity for IL-2 compared to the βγ dimer
- Low doses of IL-2 have been shown to preferentially activate Tregs in autoimmune conditions

Source: NKTR company presentation

What is IL-2? (2/2) – IL-2 is a key regulator of Treg development, stability, and function

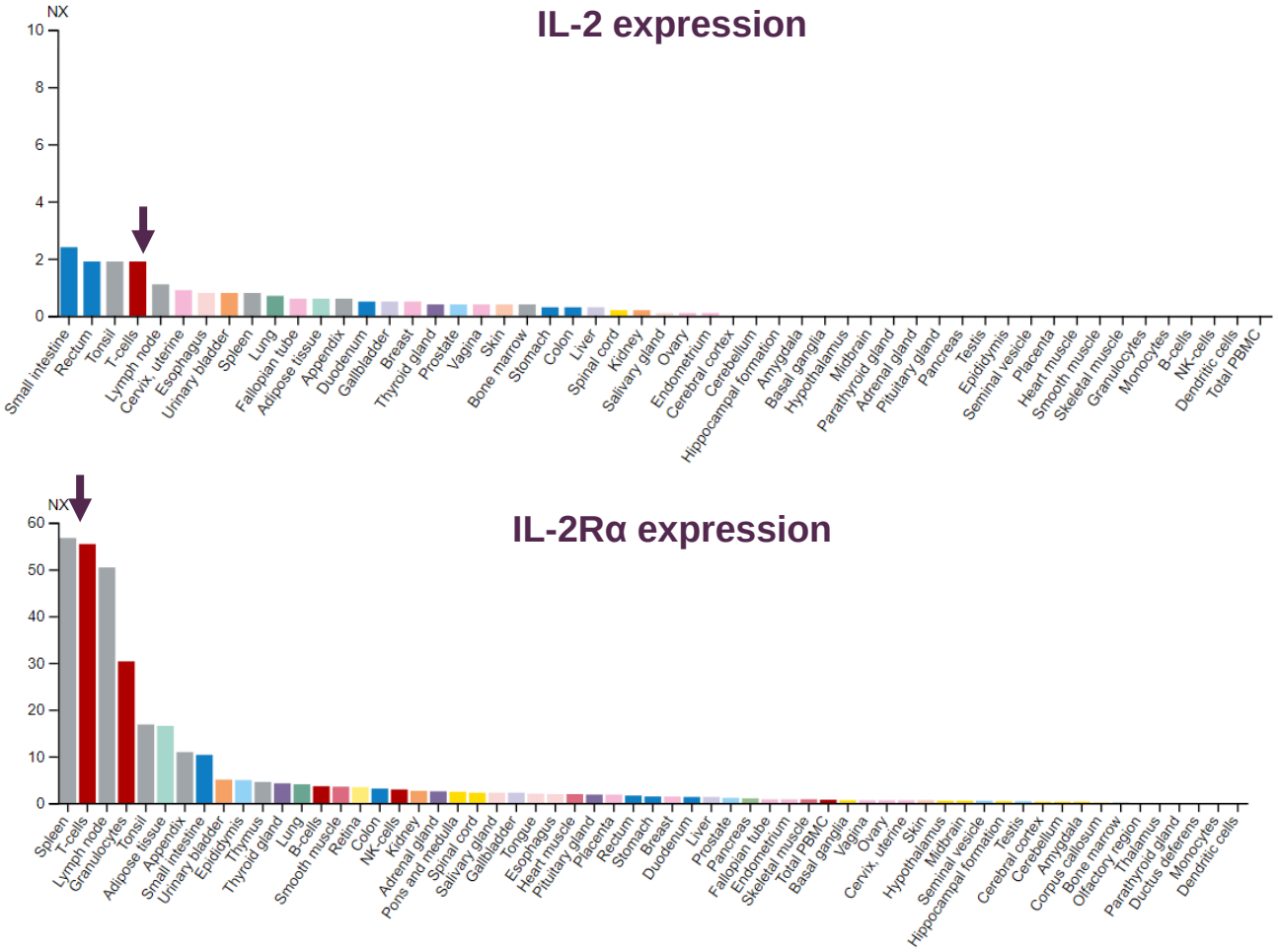


- In the thymus, IL-2 promotes maturation of CD4+ Tregs through STAT signaling
- Mature CD4+ Tregs exit the thymus and can respond to IL-2 due in part to a feed forward loop of IL-2-mediated expression of CD25 (IL-2Rα), forming activated CD4+ Tregs
- Activated CD4+ Tregs (and CD8+ through a less well-known MoA) exert immunosuppressive functions through:
    1. Control of local inflammation
    2. Control of autoantibody production
    3. Control of T cell autoimmunity

Clinical data suggest that low-dose IL-2 treatment can expand Treg populations in humans in multiple indications, and even lead to clinical benefit in some patients with graft-versus-host disease (GVHD), but the clinical effects of Treg expansion in autoimmunity need to be verified in randomized controlled clinical studies

Source: Ye et al. 2018

Where are IL-2/IL-2Rα enriched? (1/1) – While IL-2 has a diffuse expression profile, IL-2Rα is expression in T cells/granulocytes

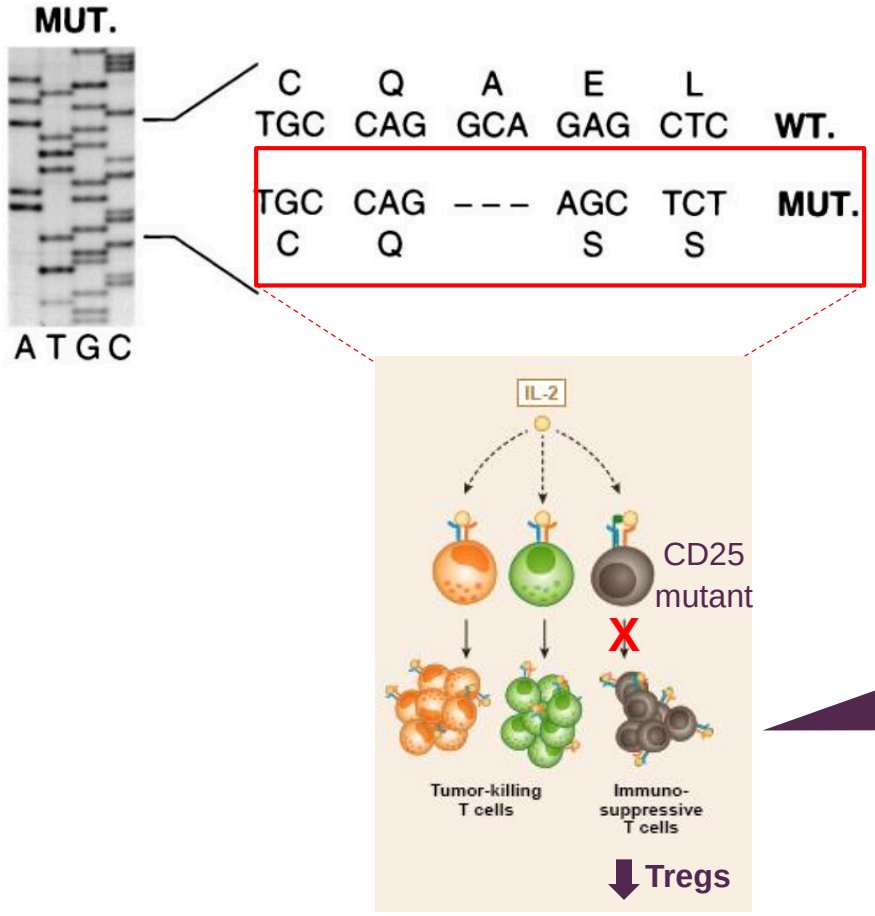


- **IL-2** is expressed across a number of cells/tissues including small intestine, rectum, tonsils, and T-cells (arrows)
  - IL-2 is a secreted protein and may be found in far more tissues than listed here
- **IL-2Rα** shows a more extensive and enriched expression profile, with high expression in the spleen, T cells, lymph node, granulocytes, tonsils and adipose tissue
  - IL-2 and IL-2Ra expression are both expressed at high levels in T cells, the main cell type targeted in autoimmunity

Source: Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000109471-IL2/tissue; https://www.proteinatlas.org/ENSG00000134460-IL2RA/tissue)

Is there a genetic connection between IL-2 and disease? (1/1) – Mutations in IL-2Rα deplete Tregs and promote autoimmunity

IL-2Rα deletion mutants result in autoimmunity driven by lack of CD4+CD25+ Tregs

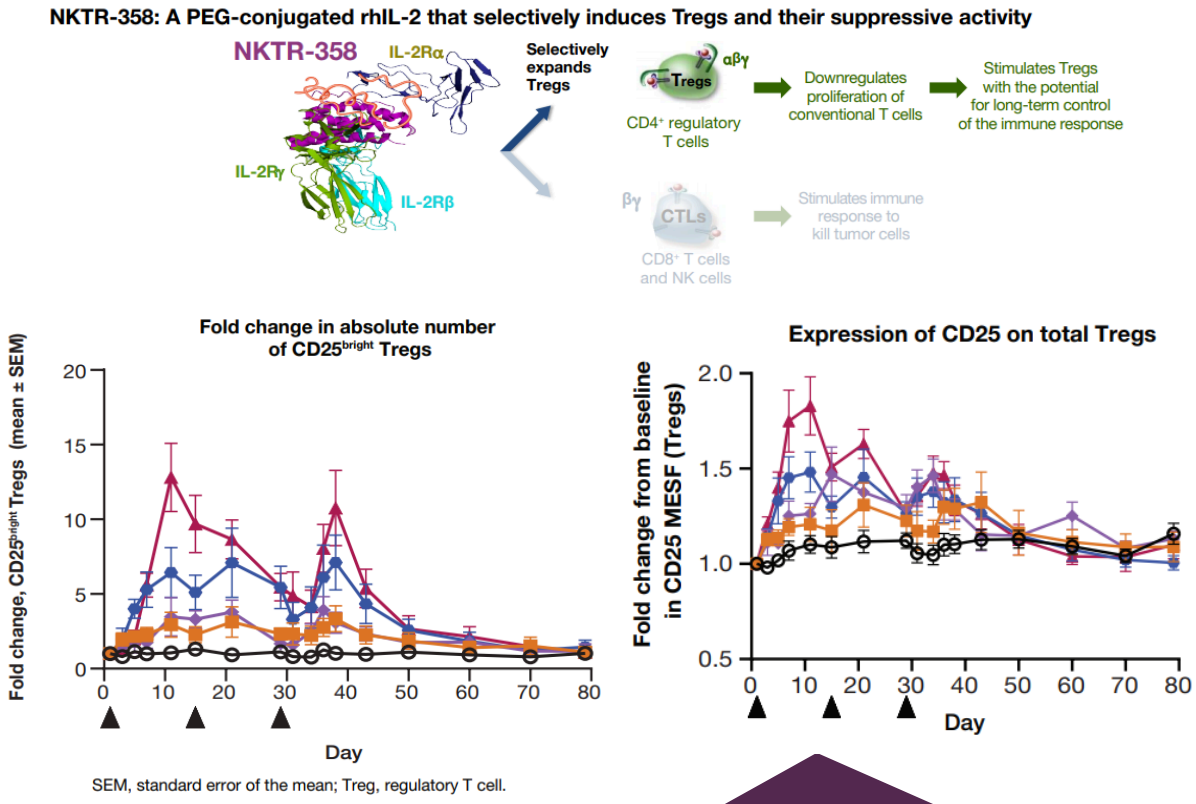


- A truncation mutation in IL-2Rα leads to a depletion of CD4+CD25+ Tregs and a multi-tissue autoimmune disorder
  - No detectable CD25 (IL-2Rα) expression on T cells
  - Excessive T cell infiltration observed in lung, liver, gut and bone

GWAS studies have also identified associations between SNPs in CD25 and Type 1 Diabetes, Grave's disease, MS and RA. In fact, levels of soluble CD25 are lower in individuals with T1D susceptibility alleles, and a lack of IL-2 signaling contributes to pancreatic autoimmunity driving T1D (but this is mainly supported by pre-clinical mouse studies)

Source: Sharfe et al. 1997, Wang et al. 2009, NKTR company presentation

Are there biomarkers for IL-2? (1/1) – Quantification of Tregs provides a direct biomarker for IL-2-mediated actions



The most clinically validated biomarker for IL-2-mediated Treg expansion is the **quantification of Treg populations** from patients.

- NKTR's recombinant human IL-2 NKTR-358 that selectively stimulates Tregs led to a dose-dependent increase in $CD25^{bright}$ (highly expressing CD25) Tregs in a Phase Ib MAD study in SLE patients
- Proliferation of Tregs was also accompanied by dose-dependent increases in markers of Treg activation (e.g. CD25, Helios, CTLA-4), suggesting Treg activation markers could be an alternative biomarker

$CD25^{bright}$ Tregs are a subset of Tregs that express CD25 (IL-2Ra) at high levels and are thought to have the most potent immunosuppressive capacity. However, whether reductions in these Tregs is correlated with improvements in clinical endpoints is not well known at this point.

Source: NKTR ACR 2020 poster

What diseases is IL-2 involved in? (1/1) – Deficient IL-2 signaling and low Treg numbers contributes to multiple peripheral inflammatory disorders

IL-2 has been implicated in a number of (mainly) peripheral inflammatory diseases. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
SLE	IL-2 production is decreased in SLE patients, which is thought to reduce Treg number and control of autoreactive T cell clones and disrupt CD8+ T cell cytotoxicity, leading to inflammatory imbalances; Treg number may inversely relate to disease severity	**MODERATE** – no clear genetic link; moderately strong MoA but also involve IL-15/IL-21; strong clinical validation from low-dose IL-2 studies and NKTR's Phase I showing dose-dependent expansion of Tregs and improvement in CLASI-A scores
UC	Deficiencies in Tregs contribute to intestinal inflammation in UC; IL-2-deficient mice present with colitis characterized by a high number of activated T and B cells, elevated immunoglobin secretion, anti-colon antibodies, and aberrant expression of class II major histocompatibility complex molecules	**MODERATE** – some genetic evidence (mainly murine genetics but IL2RA gene duplication can drive colitis); strong preclinical data showing low-dose IL-2 ameliorates murine colitis; some clinical validation with low-dose IL-2 (NCT02200445) but no clear dose-dependency on clinical remission
T1D	Lower than normal levels of IL-2 in T1D can lead to apoptosis of Tregs (a hallmark of disease onset); lack of adequate IL-2 leads to Treg deficiency and activated autoreactive T cells that drive inflammation in pancreatic islets responsible for insulin secretion	**MODERATE** – some evidence for both direct (IL-2) and indirect (FOXP3, Treg marker) gene involvement; strong preclinical data suggesting a key role for IL-2/Tregs in T1D with multiple studies showing benefits of low-dose IL-2 treatment; moderate clinical evidence demonstrating Treg expansion in T1D patients, but glucose control capacity and dependence on residual insulin secretion in T1D is not yet known
Atopic Dermatitis	Increased numbers of CD8+ T effector cells are present in the skin at sites of IgE production and eosinophilia, suggesting an imbalance between T effector/Tregs, but high dose IL-2 can induce severe itch in humans	**WEAK** – no consensus on genetic link between IL-2 and AD; conflicting MoA/clinical evidence (high dose IL-2 can drive itch in AD, but IL-2 can ameliorate itch in refractory AD patients); role of IL-2 in AD not clear

Source: Lieberman & Tsokos 2010, Dixit et al. 2021, Goettel et al. 2019, Sadlack et al. 1993, Joosse et al. 2021, Hulme et al. 2012, Dwyer et al. 2016; Heywood et al. 1995, Hsieh et al. 1991, clinicaltrials.gov

What are the challenges in targeting IL-2/IL-2Rα? (1/1) – Recombinant IL-2 administered at controlled low doses could be most efficient Treg booster

There are two high level considerations when considering targeting the IL-2/IL-2Rα axis: (1) recombinant protein vs. mRNA, and (2) low vs. high dose IL-2. While both recombinant protein and mRNA approaches are likely to efficiently increase IL-2 levels in patients, mRNA-based approaches may be harder to tightly control IL-2 levels, an important consideration when most data suggest that clinical benefit derives from lower doses. However, "lower doses" could mean different things for different people, possibly requiring a precision medicine approach to further understand the variability in baseline IL-2 levels and how much IL-2 would be enough.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Recombinant protein vs. mRNA	mRNA approach relies on endogenous translation mechanisms; may be harder to tightly control IL-2 levels with mRNA-based therapeutic	Maintaining lower dose levels in the therapeutic Treg expansion range may be more feasible with recombinant protein	For now, dosing with recombinant protein may be easier to establish dose thresholds and minimize risk of over-dosing, especially with mutein versions that increase affinity towards IL-2Rα vs. IL-2Rβ isoforms
Low-dose vs. high dose	An optimal IL-2 dose may be difficult to predict for a heterogeneous patient population; adjunct therapy may be needed to boost Treg expansion and improve outcomes	Adopt a precision medicine approach to stratify patients based on IL-2 levels; start evaluating correlations between IL-2 levels and disease progression/clinical benefit	The therapeutic window for "low dose" IL-2 may have to be determined on an indication-by-indication basis, and in some cases on a patient-by-patient basis, introducing the need for some level of precision medicine; theoretically safety issues should be mitigated with mutein versions that are more selective for α vs. β

Bottom line: In our view, the most effective and safest approach to boosting Treg number and function in autoimmune disorders is currently a recombinant IL-2 mutein approach coupled with a precision medicine-guided dosing scheme that maps out the heterogeneity in IL-2 among patient populations across indications and informs minimum required IL-2 doses for therapeutic benefit

Source: Ye et al. 2018, Dwyer et al. 2016, MRNA company press release, Guggenheim Securities, LLC research

Current programs targeting IL-2 (1/2)

All four of the current **IL-2** programs focusing on autoimmunity are developing modified IL-2 proteins (three recombinant and one mRNA-based) in autoimmune indications including SLE and UC. Highlights from our end:

- ***MRK*** recently acquired Pandion Therapeutics and now has the IL-2 mutein PT101, currently being developed in SLE and UC (Phase I)
- ***MRNA*** is taking a unique approach and developing mRNA-6231 (LNP-based mRNA drug encoding IL-2 mutein) in undisclosed autoimmune diseases (Phase I)
- ***NKTR*** in collab with LLY is developing NKTR-358 (PEG conjugates of native IL-2) for SLE and UC (Phase II) and atopic dermatitis and psoriasis (Phase Ib)
- ***XNCR*** is developing their IL-2-Fc fusion protein XmAb564 in undisclosed autoimmune diseases (Phase I)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting IL-2 (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
Merck	MRK	192485.4	PT-101 (via Pandion Therapeutics acquisition)	IL-2 mutein fused to a protein backbone that selectively activates and expands Tregs	SLE, UC	Phase I
Moderna	MRNA	157995.1	mRNA-6231	Lipid nanoparticle-encapsulated mRNA-based therapeutic encoding mutein human interleukin 2, fused to human serum albumin	Autoimmune diseases	Phase I
Nektar Therapeutics (Eli Lilly)	NKTR	2628.4	NKTR-358	First-in-class, composition of stable PEG conjugates of native IL-2 designed to selectively stimulate Treg cell function; preferentially binds to the high affinity trimeric receptor on T regs which decreases number and function of T effector cells	SLE, UC, Atopic dermatitis, Psoriasis	Phase II (SLE, UC), Phase Ib (atopic dermatitis and psoriasis)
Xencor Inc	XNCR	1859.9	XmAb564	Monovalent IL-2-Fc fusion protein with reduced binding affinity for IL-2Rβ and increased binding affinity for IL-2Rα	Autoimmune diseases	Phase I

Note: all market cap figures in $

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on IL-2 (1/1) – Selectively increasing Tregs with IL-2 may be a promising approach to rebalancing the immune system in autoimmune disorders

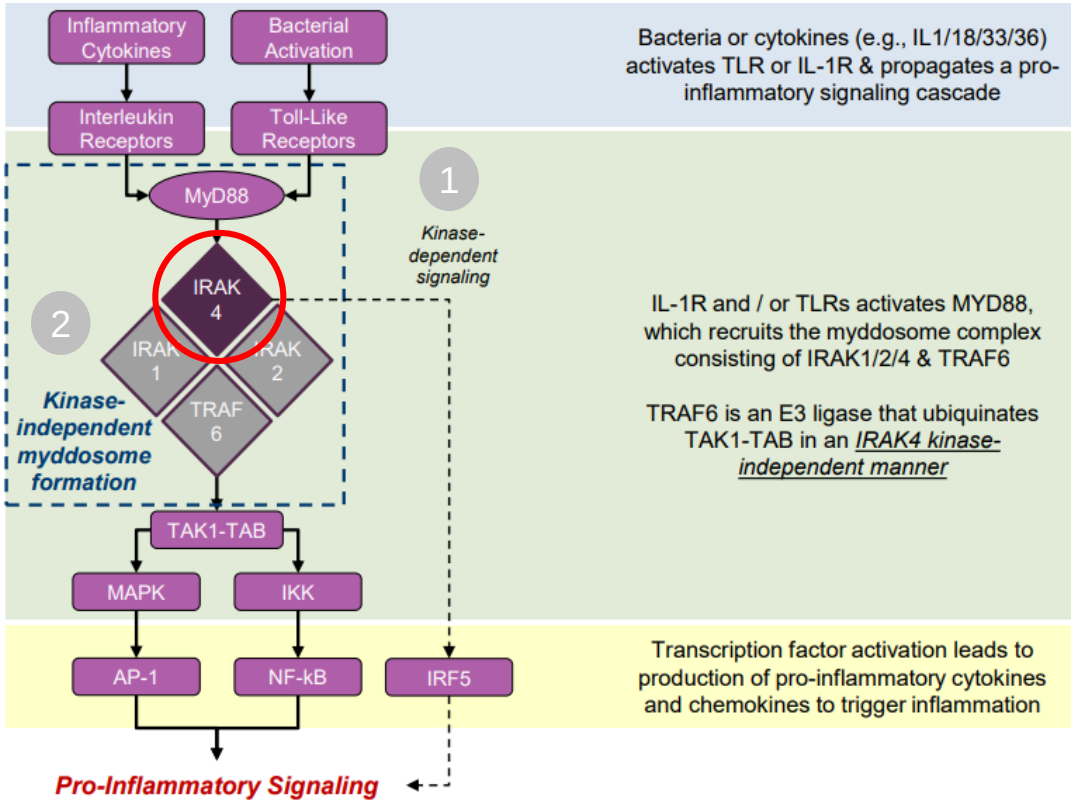
Target factor	Strength of evidence	GS comments
Link to human genetics	**MODERATE**	Mutations in either IL-2 or IL-2Rα have been linked to a few indications (e.g. UC, T1D), but majority of evidence comes from mouse studies of IL-2-deficient mice and other preclinical models
CNS target enrichment	**WEAK**	While IL-2 has a diffuse expression profile, IL-2Rα is expression in T cells/granulocytes in the periphery; no clear enrichment in the CNS
Mechanism of action	**MODERATE**	In most cases (except AD), there is a strong preclinical MoA connecting lower IL-2 levels with Treg deficiency that contributes to autoimmunity and disease progression
Biomarkers	**STRONG**	Quantification of patient Tregs provides a clinically-validated (so far in SLE), direct biomarker for IL-2-mediated actions
Safety	**MODERATE**	Most clinical benefit has been observed with low dose IL-2, with higher doses of IL-2 engaging the proliferation of NK/CD8+ cells that could drive inflammation; more selective IL-2 therapies (e.g. muteins), could mitigate safety concerns, but therapeutic window could vary depending on patient and/or indication heterogeneity, introducing the risk of AEs if patients are dosed too high
Clinical PoC	**MODERATE**	NKTR's NKTR-358 increased Tregs and improved clinical symptoms in SLE patients (Phase I); some clinical PoC in UC (but dose threshold for clinical remission not clear) and in T1D (but effects on glycemic control not yet reported)

Source: NKTR company presentations, Lieberman & Tsokos 2010, Dixit et al. 2021, Goettel et al. 2019, Sadlack et al. 1993, Joosse et al. 2021, Hulme et al. 2012, Dwyer et al. 2016, clinicaltrials.gov, Guggenheim Securities, LLC

Interleukin-1 Receptor–Associated Kinase 4 - IRAK4

What is IRAK4? (1/1) – IRAK4 is a key component of the myddosome complex, which mediates pro-inflammatory immune cell signal transduction

Dual functions of IRAK4 drive inflammatory signaling



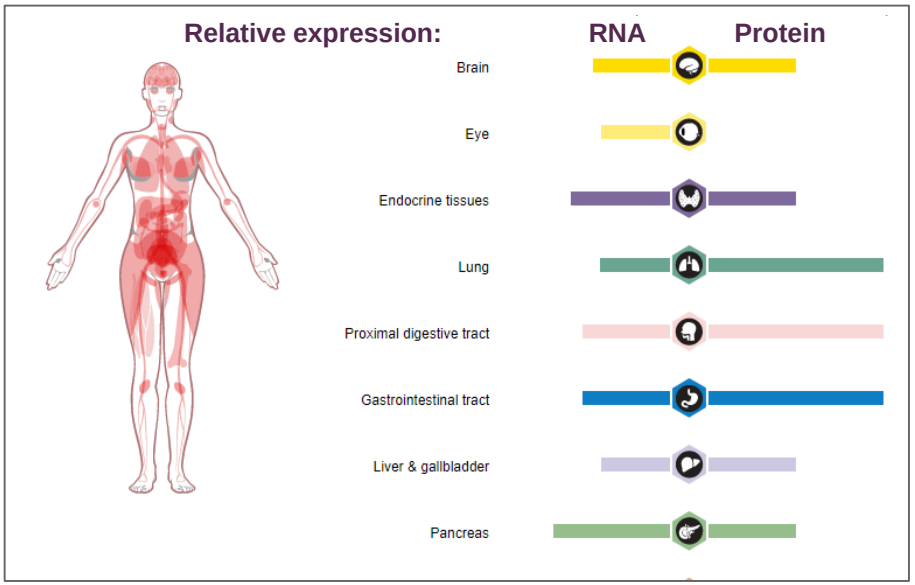
- **Interleukin-1 receptor–associated kinase 4 (IRAK4)** is an intracellular dual function kinase/adaptor protein that mediates pro-inflammatory signaling in immune cells downstream of toll-like receptors (TLRs) and interleukin receptors.
- TLRs and interleukin receptors are cell surface receptors that recognize microbial or endogenous danger signals (e.g. cytokines) and signal through the adaptor protein MyD88.
- MyD88 signaling occurs through formation of a large oligomeric complex containing IRAKs 1, 2, and 4 (called the myddosome).
    - IRAK4 can function as: **(1) a *kinase*** to activate the transcription factor IRF5, which increases transcription of pro-inflammatory cytokines, and **(2) a *scaffold*** that allows docking and activation of TRAF6 which ultimately leads to NFκB- and AP1-mediated pro-inflammatory gene expression.

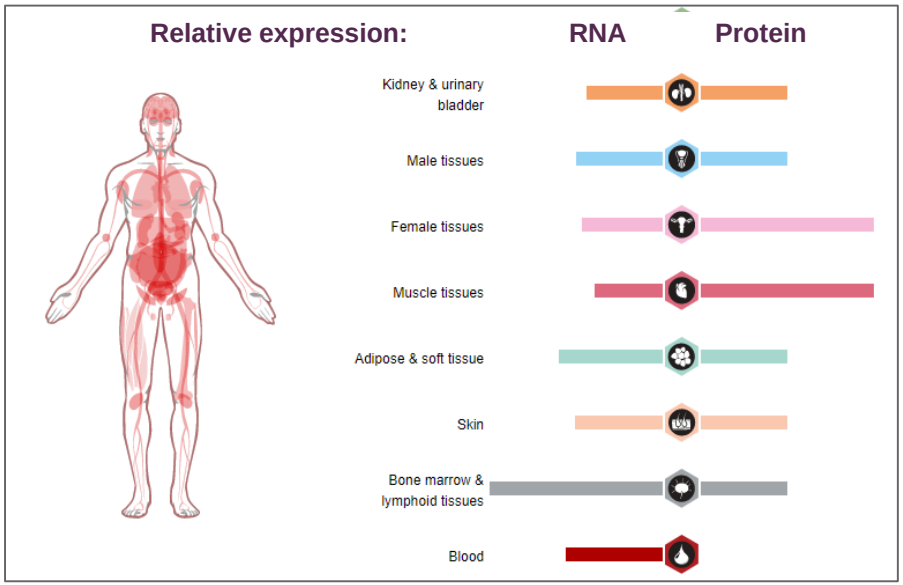
Source: Guggenheim Securities, LLC Analysis; Kymera SEC filings; De Nardo 2018, https://www.bu.edu/nf-kb/gene-resources/target-genes/

Where is IRAK4 enriched? (1/1) – IRAK4 is globally expressed in immune and non-immune cells inside and outside of the CNS

- IRAK4 is found in most tissues in the human body with the highest expression in the lung, GI tract, and reproductive tissues
  - IRAK4 protein is undetectable (or at least at very low levels) in the eye and in the blood
  - Although most prominently studied in immune cells, IRAK4 mRNA is found in both immune cells (e.g. T-cells, macrophages) and non-immune cells (e.g. neurons, epithelial cells in the kidney and fibroblasts)

IRAK4 tissue expression



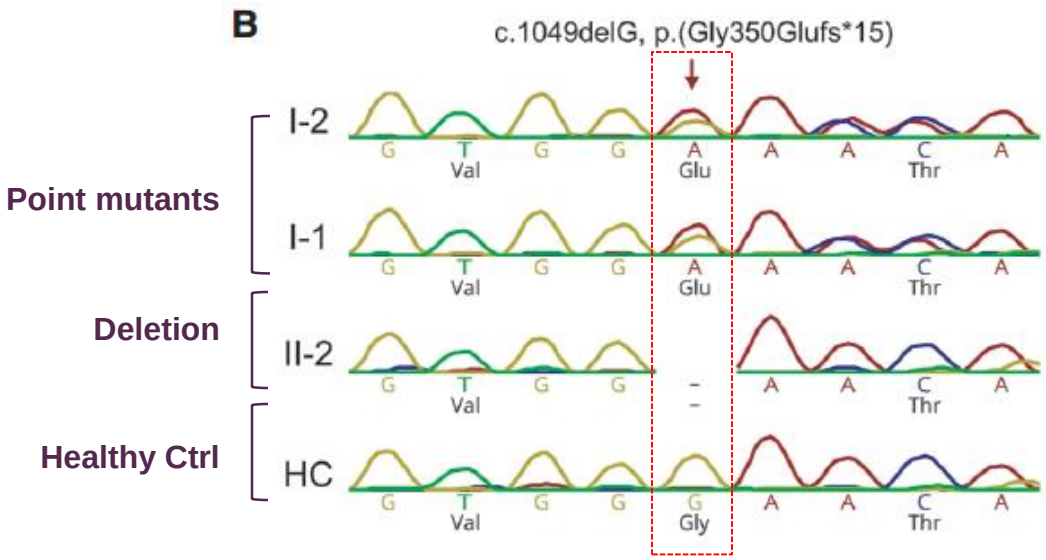


IRAK4's global expression profile has both benefits and risks: ***Benefit –*** IRAK4 could be broadly targeted across multiple CNS and non-CNS inflammatory diseases***; Risk –*** expression outside of immune cells raises the possibility that IRAK4 inhibition could disrupt normal functions of non-immune cells (e.g. neurons or ductal cells in the kidney) and thus lead to safety concerns.

Source: Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000198001-IRAK4/tissue),

Is there a genetic connection between IRAK4 and disease? (1/1) – Mutations in IRAK4 cause IRAK4 deficiency, an inborn error of immunity

IRAK4 gene sequence



Other IRAK4 mutations have also been linked to IBD and hepatocellular carcinoma

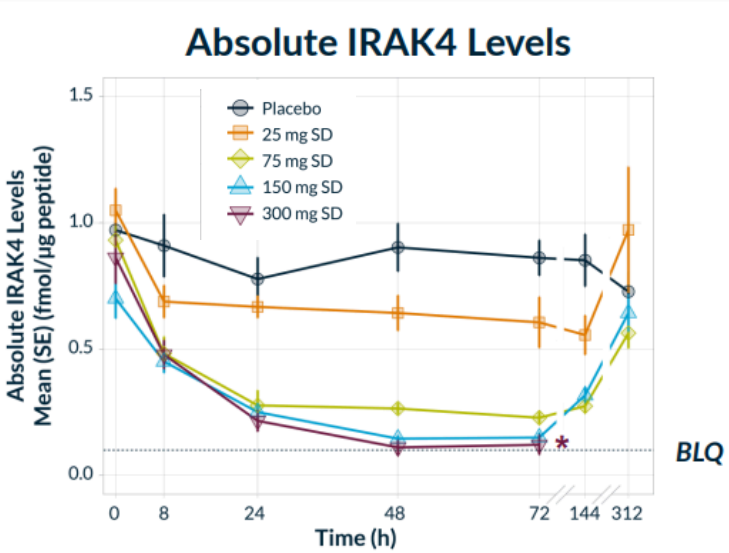
- **IRAK4 deficiency** is an autosomal recessive inborn error in immunity that is caused by insufficient inflammatory response to infection from pyogenic bacteria, particularly Streptococcus pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa
- IRAK4 deficiency is caused by mutations in the IRAK4 gene that leads to a loss of IRAK4 protein
    - Loss of IRAK4 protein blunts TLR signaling and therefore hinders the immune response to pathogens, such as bacteria

Source: Jia et al. 2020, Candan et al. 2019, Wang et al. 2018, Guggenheim Securities, LLC research

Are there biomarkers for IRAK4? (1/1) – Biomarkers for IRAK4 depend on the therapeutic approach

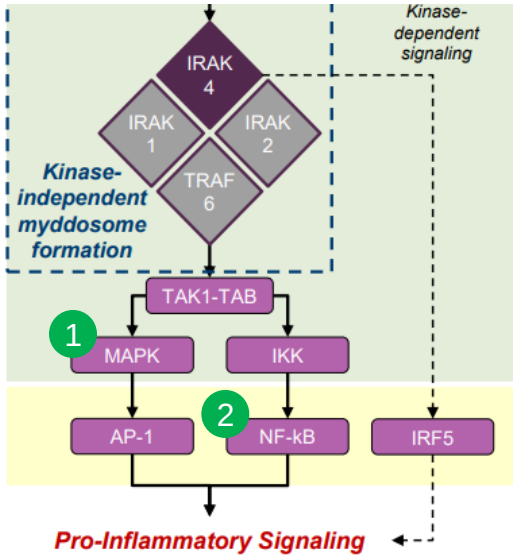
Approach 1: IRAK4 degradation

- Putative biomarker: IRAK4 protein levels in PBMCs (see KYMR's Phase I data below)
- Strengths: Direct measure of target engagement and easily accessible (circulating blood cells)
- Limitations: Correlation with clinical benefits TBD, total protein levels also subject to transcriptional/translational regulation independent of drug



Approach 2: Kinase inhibition

- Putative biomarkers: (1) downstream signaling markers (e.g. MAPK activation), or (2) NFκB target genes
- Strengths: direct downstream marker of IRAK-mediated signaling
- Limitations: Several upstream kinases converge on MAPK/NF-kB, and NF-kB regulates many genes (inflammatory and non-inflammatory)



Source: KYMR company presentations, Guggenheim Securities, LLC

What diseases is IRAK4 involved in? (1/1) – IRAK4 contributes to several inflammatory diseases, mainly through TLR signaling in innate immune cells

IRAK4 has been implicated in many inflammatory diseases and cancers. In the table below, we highlight the major inflammatory indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
Rheumatoid arthritis	Overproduction of inflammatory cytokines (e.g. TNF-α, IL-1 and IL-6) promotes angiogenesis migration of lymphocytes to the synovium, bone remodeling and activation of additional immune cells that contributes to chronic synovitis	**MODERATE** – Not a clear genetic association; strong preclinical data showing clear MoA implicating TLR/IRAK4 signaling in RA; early PoC by RIGL showing robust reduction in cytokine production in response to a LPS challenge in humans, but not much data in RA patients yet and PFE in Phase II
Atopic dermatitis	Increased TLR signaling in both immune cells and in keratinocytes promotes TH1/TH17 immunity that contributes to skin lesions (much like RA)	**MODERATE** – No direct genetic connection between IRAK4 and AD; clear MoA connecting TLR signaling to immune cell infiltration and skin damage (similar MoA as RA); not much clinical PoC, positive readthrough from KYMR, RIGL
Hidradenitis suppurativa	Overproduction of inflammatory cytokines (e.g. IL-1β) that signal through IRAK4 promote immune cell accumulation at painful purulent skin lesions and progressive destruction of skin architecture	**MODERATE** – Not a clear genetic association; strong preclinical data showing clear MoA implicating TLR/IRAK4 signaling in HS; early PoC by KYMR showing ~85% reduction in IRAK4 protein in Phase I HV study but no data in HS patients yet
Lupus	Excessive TLR7/TLR9/IRAK4 signaling contributes to: (1) B cell-mediated autoantibody production, and (2) increased production of type I IFNs from pDCs	**WEAK** – No clear genetic association; strong preclinical MoA data but other IRAKs (IRAK2) may be involved indicating redundancy; not much clinical PoC
IBD	May contribute to reduced innate immunity driving resistance to anti-TNF therapies; IRAK1 may play bigger role in actively driving gut inflammation	**MODERATE** – IRAK4 variants increase risk of IBD; MoA not as clear (may contribute to TNF resistance, but IRAK1 seems to drive gut inflammation); no clinical PoC

Source: KYMR company presentations, Ellen Witte-Händel et al. 2019, RIGL company presentations, Wiese et al. 2020, Sun et al. 2019, Dudhgaonkar et al. 2017, Boumiza et al. 2020, Candan et al. 2019, Heiseke et al. 2015, Baird et al. 2016

What are the challenges in targeting IRAK4? (1/1) – Targeted degradation of IRAK4 protein inhibits both kinase and scaffold functions of IRAK4

There are two high level approaches to targeting IRAK4: (1) inhibiting the kinase function of IRAK4 (mainly binding the kinase domain via small molecules), and (2) targeted protein degradation to decrease IRAK4 protein (inhibiting both kinase and scaffold functions of IRAK4). The first approach could have issues with specificity against other IRAKs (which share a decent amount of sequence similarity). The second approach carries the risk of degrading other off-target proteins and potentially depends on the fidelity of the cell's own protein degradation system which could be comprised in certain indications.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
IRAK4 kinase inhibition	Specificity to IRAK4 vs. other IRAKs, only inhibiting one function of IRAK4, leaving IRAK4 scaffold function and MAPK/NF-kB signaling intact	Use combo therapies to also inhibit downstream of IRAK4 scaffold functions	Potential for overlap with other IRAKs may provide added efficacy or increase the odds for AEs, depending on the indication
IRAK4 protein degradation	Ensuring specific degradation of IRAK4 without degrading highly similar IRAKs (e.g. IRAK1); potential overload of proteasomal system causing cellular stress and inflammation	Use structure-guided modeling to harness cell's own protein degradation system (ubiquitin proteasome system) to specifically degrade IRAK4	This approach is more likely to achieve selective IRAK4 inhibition and drive maximal anti-inflammatory efficacy by blocking both kinase and scaffold functions

Bottom line: In our view, targeted protein degradation is the most feasible and most promising therapeutic strategy for targeting IRAK4, given the importance of the scaffold function for driving inflammation (a signaling arm that is left untouched by small molecule kinase inhibitors).

Source: KYMR company presentations, Guggenheim Securities, LLC research

Current programs targeting IRAK4 (1/2)

IRAK4 has become a popular target with 10 companies pursuing this target across multiple indications (many in cancers), with most companies developing kinase inhibitors. Our highlights from the neuro/inflammation side:

- ***Evommune*** has a small molecule dual IRAK4/TrkA for rosacea and atopic dermatitis (pre-clinical)
- ***KYMRA*** (in collab with SNY-US) is developing KT-474 a differentiated targeted degrader of IRAK4 for atopic dermatitis, hidradenitis suppurativa and rheumatoid arthritis (Phase I)
- ***RIGL*** is developing the dual IRAK4/IRAK1 inhibitor in MDS, RA, lupus and psoriasis (Phase I)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting IRAK4 (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
Bayer AG	BAYN-DE	47122.0	Two undisclosed compounds	IRAK4 inhibitors	Undisclosed	Phase I
Curis Inc	CRIS	710.8	CA-4948	Small molecule IRAK4 inhibitor that specifically targets the oncogenic long form of IRAK4 that drives increased TLR/MyD88/NFκB signaling	AML, MDS, NHL	Phase I (AML/MDS), Phase II (NHL)
Emmaus Life Sciences Inc (Kainos Medicine, Inc.)	EMMA	74.0	KM10544	IRAK4 inhibitor (exact MoA not disclosed)	Waldenstrom macroglobulinemia with MYD88 mutations	Emmaus leading pre-clinical/clinical development of Kainos compound
Evommune (LLY's Dermira)	Private	-	Undisclosed compound	Small molecule dual IRAK4/TrkA inhibitor; blocks both IRAK4-mediated signaling downstream of TLRs and IL-1R and TrkA (NGF receptor)-mediated angiogenesis and vasodilation, upregulation and heightened sensitivity of TRPV1 on nerves. These two pathways contribute to pathophysiology of atopic dermatitis, asthma, Behçet's disease, conjunctivitis, and papulopustular rosacea.	Rosacea, Atopic dermatitis	Pre-clinical
Gilead Sciences Inc	GILD	88870.1	GS-5718	Oral, small molecule IRAK4 inhibitor that blocks TLR/IL-1R signaling	IBD, RA, Lupus	Phase I
Kymera Therapeutics Inc (Sanofi)	KYMR	2805.7	KT-474	KT-474 blocks TLR/IL-1R-mediated inflammatory signaling by targeting IRAK4 for degradation via ubiquitin proteasome and is thought to be superior to IRAK4 kinase inhibitors by abolishing both the kinase and scaffolding functions of IRAK4	Atopic dermatitis, Hidradenitis suppurativa, Rheumatoid arthritis	Phase I
Pfizer Inc	PFE	264434.9	PF-06650833	Small molecule inhibitor of IRAK4, blocking TLR/IL-1R signaling	RA, HS	Phase II RA (in combo with ritlecitinib); Phase II HS (in combo with brepocitinib and PF-06826647)
Rigel Pharmaceuticals Inc	RIGL	705.6	R835	Dual inhibitor of IRAK1 and IRAK4; R835 blocks IL-23 production and TH17 cell differentiation in response to TLR and IL-1R signaling. TLRs and IL-1Rs play a critical role in inflammatory conditions including psoriasis, rheumatoid arthritis, lupus and gout (among others).	Immune diseases (e.g. MDS, psoriasis, RA, lupus, etc.)	Phase I
Sanofi SA (Kymera)	SNY-US	128806.6	Undisclosed molecule	IRAK4 degrader - same MoA as above	Undisclosed indications	Pre-clinical
TG Therapeutics Inc (Ligand Pharma)	TGTX	3209.4	Undisclosed	IRAK4 inhibitor (exact MoA not disclosed)	Undisclosed	Pre-clinical

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Note: all market cap figures in $ except for BAYN-DE in €

Our view on IRAK4 (1/1) – IRAK4 presents an opportunity to address multiple inflammatory diseases but infections and tissue distribution could present challenges

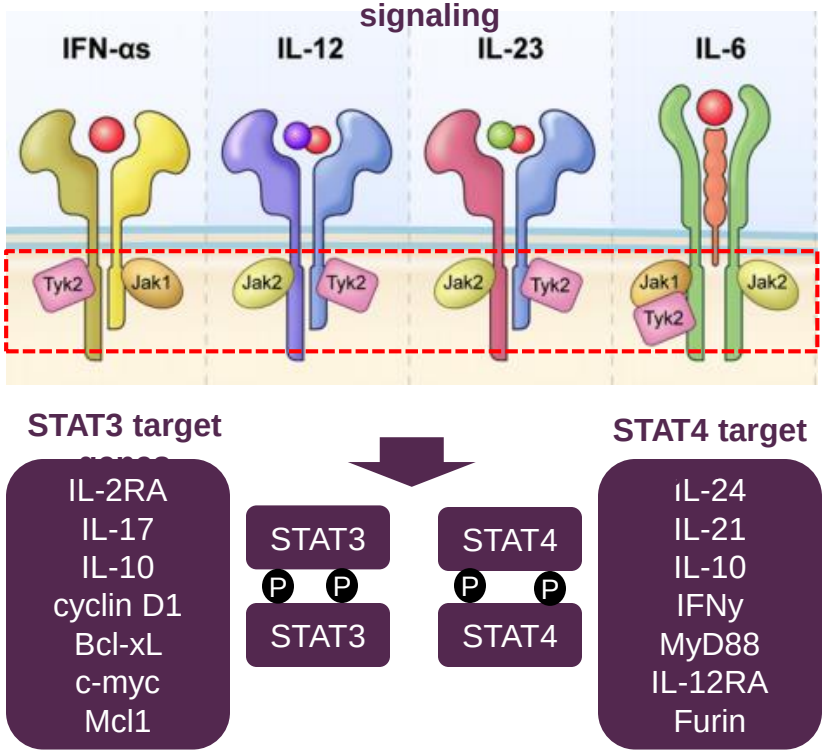
Target factor	Strength of evidence	GS comments
Link to human genetics	**MODERATE**	LOF mutations in IRAK4 can lead to increased susceptibility to bacterial infections in IRAK4 deficiency; IRAK4 variants are associated with increased risk of IBD; not much connection to other diseases currently being pursued
CNS target enrichment	**WEAK**	IRAK4 is found in most tissues in the human body with the highest expression in the lung, GI tract, and reproductive tissues (in both immune and non-immune cells)
Mechanism of action	**STRONG**	In most cases, there are strong preclinical data connecting TLR/IRAK4 signaling to inflammation, immune cell infiltration and clinical symptoms (e.g. joint damage or skin lesions)
Biomarkers	**MODERATE**	Depends on the therapeutic approach to targeting IRAK4; for protein degradation IRAK4 protein levels provide a good indication of target validation (but clinical relevance TBD), but downstream signaling/gene expression for kinase inhibition may not provide the clearest indication of IRAK4 activity, especially in humans
Safety	**MODERATE**	IRAK4 deficiency leads to increased infections, which could be an issue regardless of therapeutic approach; IRAK4 is expressed in most tissues, so there could be other off-target effects; no serious issues observed so far in KYMR's Phase I HV study
Clinical PoC	**MODERATE**	Most programs are early; KYMR and RIGL have early PoC in humans mainly validating mechanistic relevance, but clinical efficacy is still lacking; PFE is in Phase II

Source: CLDX company presentations, BPMC company presentations, Guggenheim Securities, LLC

Tyrosine Kinase 2 - TYK2

What is TYK2? (1/1) – TYK2 is a JAK family kinase that activates STAT proteins and a diverse downstream transcriptional program

TYK2-associated receptors and signaling



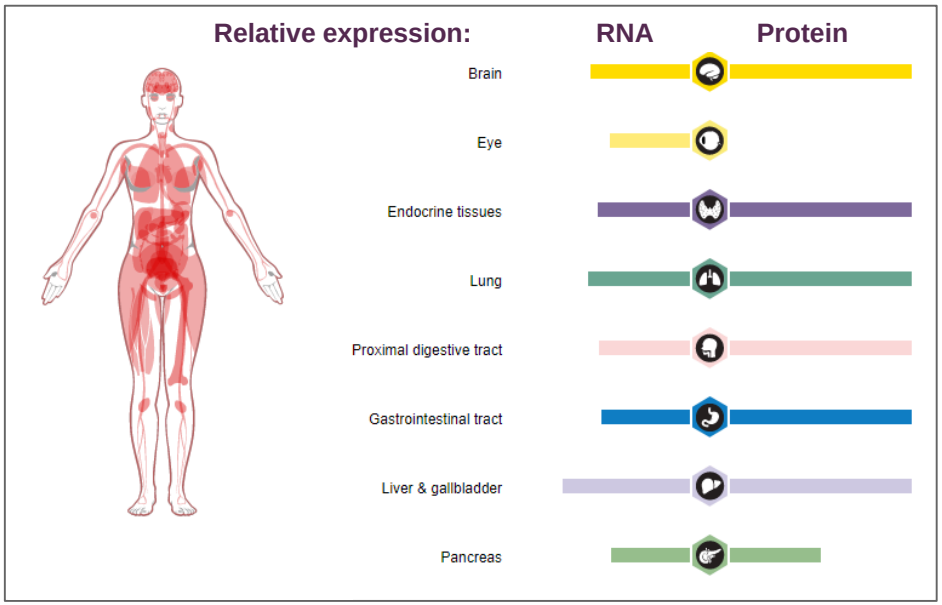
- **Tyrosine kinase 2 (TYK2)** is a JAK family kinase that phosphorylates and activates STAT proteins downstream of multiple cytokine receptors (IL-23, IL-12, type I IFNs and IL-6).
- TYK2 activates STATs 3 and 4, inducing dimerization and transcriptional activity.
    - STATs drive expression of a diverse set of genes influencing cell proliferation, differentiation, and inflammation (cytokines, chemotaxis, cell adhesion) that play an important role in several auto-immune disorders (more on next page).
    - Blocking STAT activation by targeting TYK2 upstream has the potential to address multiple aspects of inflammatory diseases beyond cytokine activity/expression

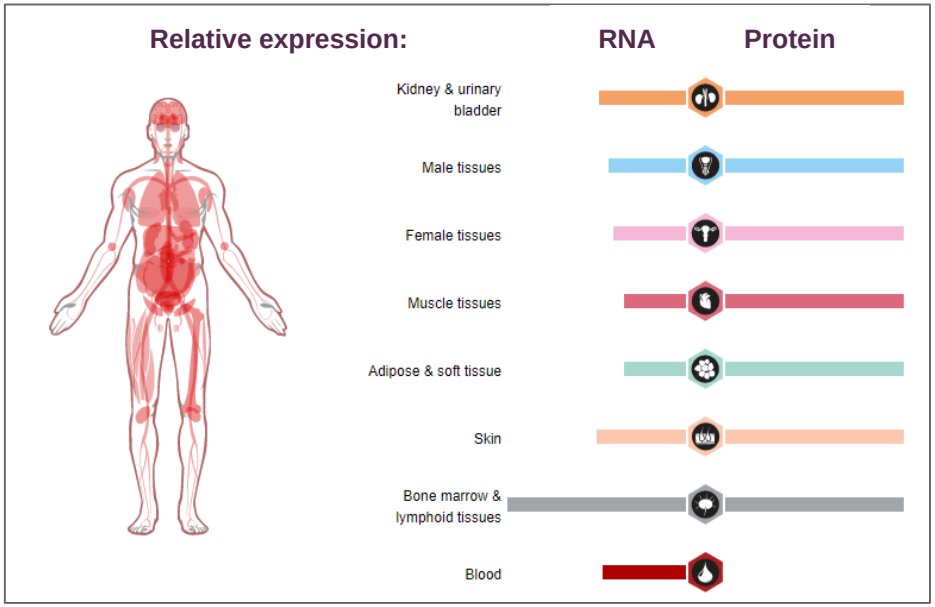
Source: Diogo et al. 2015, O'Shea & Plenge 2012, Wang & Sun 2014, Good et al. 2009

Where is TYK2 enriched? (1/1) – TYK2 is globally expressed at uniformly high levels in all tissues minus the eye and blood

- TYK2 is expressed in most tissues in the human body, with protein detected in all listed tissues on Human Protein Atlas except in the eye and blood
- TYK2 mRNA is detected both in immune (e.g. macrophages, T cells) and non-immune cells (e.g. cardiomyocytes, distal tubular cells)

TYK2 tissue expression





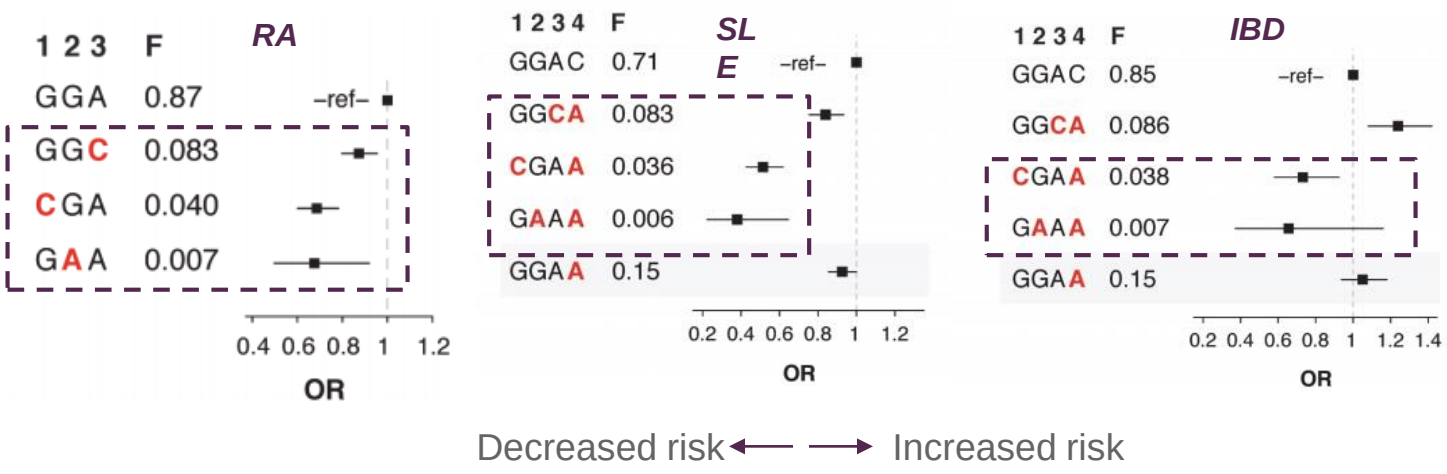
Unlike many of the other targets, TYK2 (according to Human Protein Atlas) is not just expressed across many tissues but exhibits high expression in most tissues and shows much less variability. This tissue distribution could make TYK2 an attractive target across a host of CNS/inflammatory indications, but also could carries some risk for off-target effects due to the lack of enrichment in any particular tissue.

Source: Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000105397-TYK2/tissue)

Is there a genetic connection between TYK2 and disease? (1/1) – Multiple TYK2 variants are associated with protection against RA, SLE and IBD

- Human genetics studies have mapped out three variants of TYK2 that protect against rheumatoid arthritis and systemic lupus erythematosus and two of these three variants also protect against IBD.
- The degree of protection seems to be disease-specific, with OR ranging from 0.4-0.9 (GGCx, CGAx, xGAA and GAAx variants) for RA and SLE and 0.6-0.7 (CGAA and GAAA variants) in IBD, but notably the GGCA and GGAA variants showed no protective effects (in fact a slight risk increase).
    - Therefore, there seems to be a more genetic evidence of protection in RA and SLE.

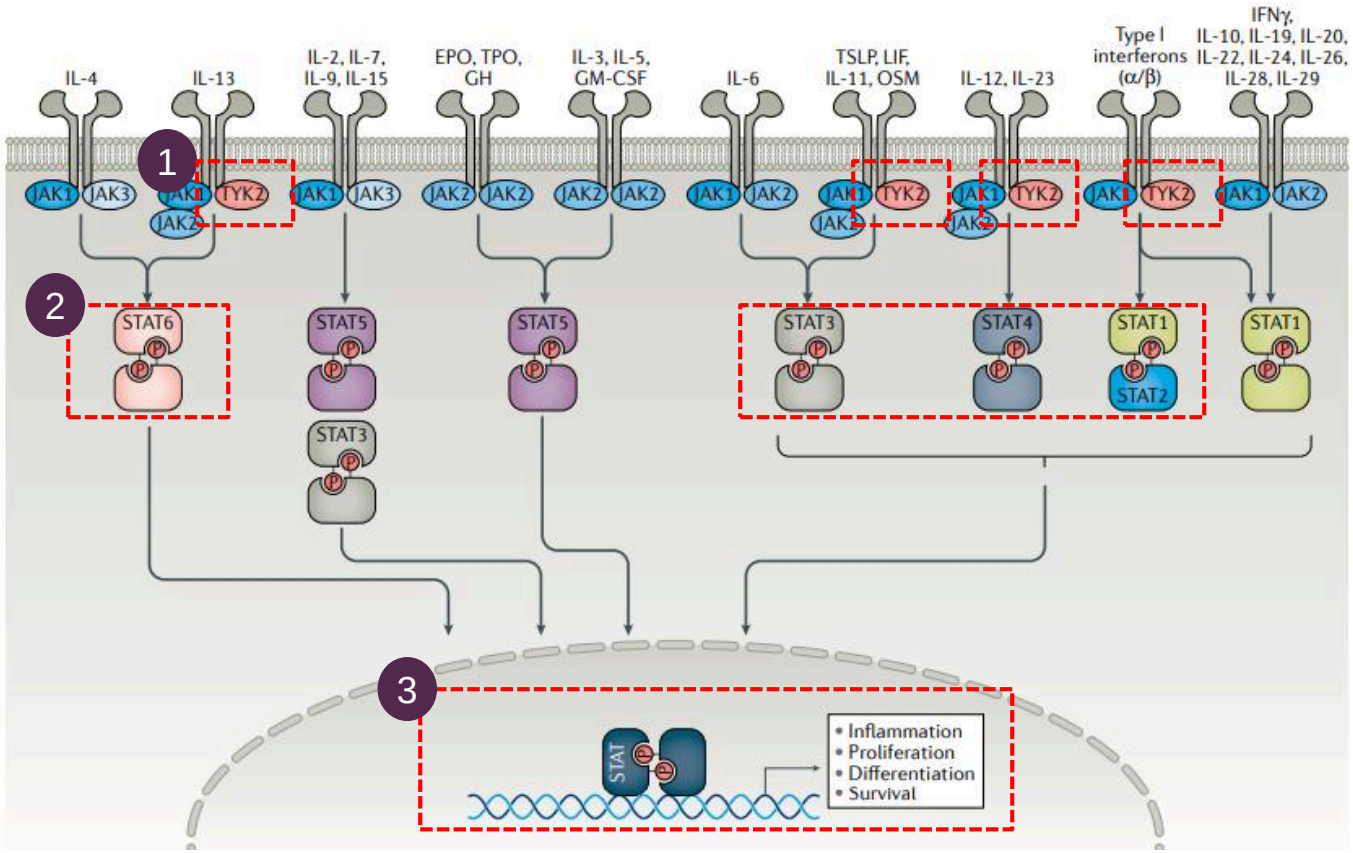
Protective variants of TYK2



Decreased risk ⟷ Increased risk

Source: Diogo et al. 2015, O'Shea & Plenge 2012, Wang & Sun 2014, Good et al. 2009

Are there biomarkers for TYK2? (1/1) – Few TYK2-specific biomarkers currently exist due to regulatory overlap with JAKs



- Putative TYK2 biomarkers are based on the downstream signaling/transcriptional activity and may include: **(1)** *TYK2 phosphorylation at Tyr-1054 and Tyr-1055*, **(2)** *STAT activation* (STATs 1,3,4 and 6) or **(3)** *STAT target genes*
  - These can be measured in circulating PBMCs as a clinically accessible measure in patients
- While ***TYK2 phosphorylation is specific***, STAT activation and STAT target genes are ***not target-specific to TYK2*** often overlapping with JAK1 and/or JAK2 signals

Source: Zarrin et al. 2021, Keiper 2021, https://www.reactionbiology.com/, Guggenheim Securities, LLC

What diseases is TYK2 involved in? (1/1) – TYK2 is a genetically validated target driving Th1/Th17 immunity in multiple inflammatory diseases

TYK2 has been implicated in many inflammatory indications of the skin, joints and GI system. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
Rheumatoid Arthritis	TYK2 signaling drives production of Th1/Th17-related cytokines and proteinases and infiltration of macrophages and neutrophils into joints, underlying destruction of cartilage and bone	**MODERATE** – genetic variants reduce risk of RA; clear and robust preclinical MoA data; not much clinical validation yet, most RA programs are preclinical
Psoriasis	IL-23/IL-12 signaling through TYK2 (and IL-17 independently of TYK2/JAKs) is thought to: (1) induce proliferation/differentiation of Th1/Th17 cells, (2) promote migration of T cells, neutrophils and DCs to the skin lesions, (3) increase IFN-y which sensitizes keratinocytes and (4) promote keratinocyte hyperplasia via IL-19/IL-36/IL-22	**MODERATE** – genetics are unclear as I684S variant impairs TYK2 activity but is associated with autoimmune disease; clear and multi-modal MoA connecting TYK2/JAKs to inflammation and skin damage, but of note IL-17 does not activate the JAK–STAT pathway; strong clinical validation, with BMY's deucravacitinib showing PASI 75 of 58.7% (deucra) vs. 12.7% (pbo) and 53.6% (deucra) vs. 9.4% (pbo) across two Phase III trials
IBD	TYK2 signaling promotes gut inflammation via production of such Th1-promoting cytokines and is TYK2 is required for the expansion and maturation of Th17 cells through activation of IL23R-STAT3 signaling; TYK2 signaling mainly in T cells is thought to drive colitis in mice	**MODERATE** – strong genetic link with multiple variants protecting against IBD; robust pre-clinical MoA data connecting TYK2 in T cells with gut inflammation and GI tract damage; not much clinical validation yet as PFE's Phase II studies in UC and CD are enrolling
Systemic Lupus Erythematosus	IFN-α binding to its receptor on macrophages activates Tyk2, which stimulates IRF3/IRF5-dependent production of IFN-I and IFN-inducible genes; TYK2-mediated signaling by IL-23, IL-12, and type I IFNs drive the functions TH17, TH1, B, and myeloid cells critical in the SLE pathobiology	**MODERATE –** strong genetic link with multiple variants protecting against SLE; strong pre-clinical MoA data with TYK2 inhibitors *in vivo;* not much clinical validation, but BMY's deucra showed dose-dependent reduction in IFN-stimulated genes in blood of HVs in their Phase I study

Source: Ishizaki et al. 2011, Li et al. 2013, De Vries et al. 2021, Shao & Cohen 2014, Burke et al. 2019

What are the challenges in targeting TYK2? (1/1) – Allosteric TYK2 inhibition may offer an attractive alternative that could maximize selectivity over JAKs

There are two high level approaches to targeting TYK2: (1) inhibiting the kinase function of TYK2 (mainly binding the kinase domain via small molecules), and (2) allosteric inhibition of TYK2 by binding to a site distinct from the active kinase domain. The first approach could have issues with specificity against JAKs and known safety issues with JAKi (TYK2 is part of the JAK family). The second approach carries the risk of subpar efficacy if allosteric inhibition does not achieve the same potency of inhibition as direct kinase domain targeting.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Kinase domain inhibition	Specificity to TYK2 vs. JAKs (e.g. JAK1); chance for similar safety profile as JAKi's due to possible lack of specificity	Structure-guided medicinal chemistry to maximize TYK2 specificity	Potential for overlap with JAKs may provide added efficacy or increase the odds for AEs, depending on the indication; structure and molecular dynamics could help increase specificity
Allosteric inhibition via JH2 pseudokinase domain	Potential for lower-than-expected efficacy if not all activity blocked by an allosteric compound; (lower) chance of safety issues since TYK2 is globally expressed	Comparative studies of allosteric vs. kinase domain inhibitor to understand efficacy thresholds	This approach is more likely to achieve selective TYK2 inhibition and drive maximal anti-inflammatory efficacy while limiting AEs; binding pocket dynamics could more complex than previously thought, which could be elucidated with protein structure/molecular dynamics

Bottom line: In our view, inhibiting TYK2 via allosteric binding (if binding to the right site, as elucidated with computational means) can drive meaningful efficacy through robust anti-inflammatory effects while minimizing (but not necessarily removing) safety concerns (e.g. cytopenia, cardiovascular disease, malignancies) that have arisen with JAKi.

Source: Keiper 2021, O'Shea & Plenge 2012, Guggenheim Securities, LLC research

Current programs targeting TYK2 (1/2)

Most of the 9 current **TYK2** programs are focused on psoriasis, lupus and IBD, three indications with an established genetic connection tying TYK2 variants to changes in risk of disease. Some highlights from our end:

- ***BMY*** has the oral TYK2 inhibitor deucravacitinib in later stage development for psoriasis, psoriatic arthritis, lupus nephritis, SLE, and IBD (Phase III for psoriasis completed, Phase II for other indications)
- ***Esker*** is developing their TYK2 inhibitor ESK-001 in psoriasis (Phase I) and undisclosed autoimmune disorders (pre-clinical)
- ***GLPG*** (in collab with GILD) is developing two TYK2 inhibitors: GLPG3667 (reversible TYK2 kinase domain inhibitor in Phase Ib for psoriasis) and GLPG3121 (JAK1/TYK2 dual inhibitor in Phase I for inflammatory diseases)
- ***Nimbus*** (working with BMY) has an undisclosed selective TYK2 inhibitor that hits the JH2 pseudokinase domain for psoriasis (Phase Ib)
- ***PFE*** has the small molecule JAK1/TYK2 inhibitor brepocitinib being developed in a host of dermatological indications (topical admin for atopic dermatitis), lupus and IBD (Phase II in combo with either PF-06650833/PF-06826647 or ritlecitinib)
- ***Ventus*** also has a TYK2 inhibitor (pre-clinical), but not much has been disclosed on the molecule or indications pursued
- ***Ventyx*** is developing VTX-958, a differentiated allosteric inhibitor of TYK2, for IBD, psoriasis, psoriatic arthritis and lupus (Phase I)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting TYK2 (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
Bristol Myers Squibb (Celgene)	BMY	148770.3	Deucravacitinib	Oral, selective TYK2 inhibitor	Psoriasis, psoriatic arthritis, lupus nephritis, systemic lupus erythematosus, CD, UC	Phase III (psoriasis), Phase II (psoriatic arthritis, lupus nephritis, systemic lupus erythematosus, CD, UC)
Esker	Private	-	ESK-001	Selective TYK2 inhibitor (MoA not fully known)	Psoriasis, autoimmune disorders	Phase I (psoriasis), Pre-clinical (autoimmune)
Galapagos NV (Gilead)	GLPG	3268.9	GLPG3667	Reversible and selective TYK2 kinase domain inhibitor	Psoriasis	Phase Ib
			GLPG3121	Selective JAK1/TYK2 inhibitor	Inflammatory indications	Phase I
InnoCare Pharma Limited	33C.KY	32992.7	ICP-332, ICP-488	332 is a small-molecule inhibitor of TYK2, and 488 is a small molecule binder of the pseudokinase domain (Janus Homology 2 or JH2) of TYK2	Psoriasis, IBD and SLE	Pre-clinical (IND accepted for 332)
Nimbus Therapeutics (BMS)	Private	-	Undisclosed	Potent, selective allosteric TYK2 inhibitor that interacts with the TYK2 JH2 pseudokinase domain	Psoriasis	Phase Ib
Pfizer, Inc.	PFE	264434.9	Brepocitinib (PF-06700841)	Small molecule JAK1/TYK2 inhibitor (topical for AD, psoriasis)	Atopic dermatitis, psoriasis, psoriatic arthritis, alopecia areata, lupus, hidradenitis suppurativa, UC, CD, vitiligo	Phase II (in combination with: PF-06650833 and PF-06826647 for HS; ritlecitinib for UC, CD and Vitiligo)
Sareum Holdings PLC	SAR.GB	300.1	SDC-1801, SDC-1802	Selective, small molecule inhibitors of TYK2/JAK1	Psoriasis, RA, Lupus, IBD, MS (1801); T-ALL, ccRCC, immunotherapy (1802)	Pre-clinical
Ventus	Private	-	Undisclosed	Undisclosed	Undisclosed	Discovery
Ventyx	Private	-	VTX-958	Selective allosteric TYK2 inhibitor, dampening type I interferon responses, IL-12/IL-23 signaling	IBD, psoriasis, psoriatic arthritis, lupus	Phase I

Note: all market cap figures in $ except for GLPG in €, 33C.KY in HKD, and SAR.GB in £

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on TYK2 (1/1) – TYK2 is an attractive target for multiple inflammatory diseases with the potential for differentiation vs. JAKi

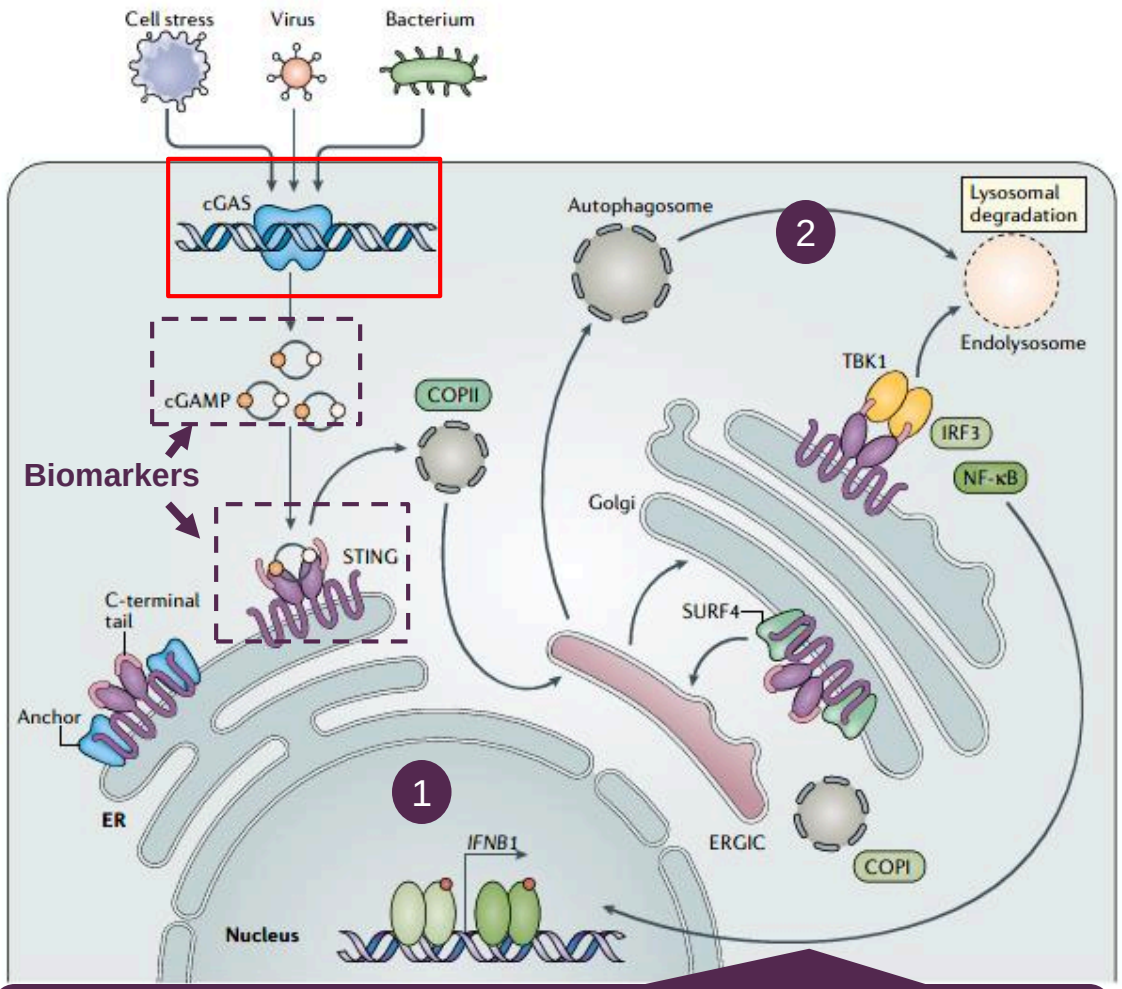
Target factor	Strength of evidence	GS comments
Link to human genetics	**STRONG**	TYK2 variants have been shown to be protective across at least three indications (RA, SLE and IBD)
CNS target enrichment	**WEAK**	TYK2 is globally expressed both in immune and non-immune cells, which could be an important factor for both efficacy and safety
Mechanism of action	**STRONG**	Across multiple indications, TYK2 controls cytokine-mediated Th1/Th17 cell proliferation, cell infiltration into relevant tissues and tissue damage that directly relates to clinical symptoms
Biomarkers	**MODERATE**	Measuring phosphorylated TYK2 is the most direct measure of TYK2 activation (which could be measured in patient PBMCs), but associations between phospho-TYK2 and clinical outcomes in RA, SLE or IBD are TBD
Safety	**MODERATE**	In theory, specific targeting of TYK2 (especially via allosteric approach) *should* mitigate some of the safety issues (cytopenia, cardiovascular complications, malignancies), but there is a chance for some similar safety issues based on: (1) similarity of TYK2 to JAKs, and (2) broad tissue distribution of TYK2
Clinical PoC	**STRONG**	**BMY** (Phase III for psoriasis and Phase II for psoriatic arthritis, lupus nephritis, systemic lupus erythematosus and IBD) and **PFE** (Phase II for brepro combo therapies in HS, IBD and Vitiligo) are in advanced clinical development; several approved medications (e.g. JAKi) for RA and psoriasis that signal through some of the same pathways in which TYK2 participates

Source: Diogo et al. 2015, O'Shea & Plenge 2012, Wang & Sun 2014, Good et al. 2009, Keiper 2021, Burke et al. 2019, BMY and PFE company presentations, Guggenheim Securities, LLC

Table of Contents

__C__yclic __G__MP–__A__MP __S__ynthase - cGAS (a brief introduction)

What is cGAS, where is it expressed and are there biomarkers? (1/1) – cGAS is a widely-expressed DNA sensor promoting a powerful innate immune response that can be tracked via cGAMP/pS366-STING



cGAS is expressed in most tissues, mainly in blood/immune cells, but cGAS has also been detected in certain epithelial cells and fibroblasts.

- **cGAS** is an intracellular sensor of both microbial and endogenous DNA that mediates activation of a powerful inflammatory response
  - Activates downstream mediator STING, which leads to two major outcomes: **(1)** IRF-3 and NF-kB-mediated gene expression, and **(2)** activation of autophagy.
  - cGAS activation leads to expression of type I interferons (and other inflammatory mediators), pro-apoptotic genes and chemokines
  - STING activation also promotes autophagy via an unknown MoA which serves to both activate a protective self death program and to regulate STING localization/activation
- **Putative biomarkers** of cGAS/STING are: (1) cGAMP leves, and (2) pS366-STING

Source: Decout et al. 2021, Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000164430-CGAS/tissue)

What diseases is cGAS involved in and is there a link to human genetics? (1/1) – cGAS (and STING) are involved in a wide array of both CNS and non-CNS inflammatory diseases

cGAS has been implicated in a number of inflammatory diseases from CNS to metabolic to autoimmune. As noted by Decout et al. 2021, the table below highlights the major indications and the link to the cGAS/STING pathway.

Table 1. cGAS/STING and inflammatory diseases

Type of disease or condition	Specific disease	Link to cGAS–STING pathway	Refs
Monogenic autoinflammatory syndromes	STING-associated vasculopathy with onset in infancy (SAVI)	Disease caused by GOF mutations in *STING1*	113,114
	Aicardi–Goutières syndrome (AGS)	Disease associated with perturbation of nucleic acid metabolism. Pathology due to defects in a subset of AGS genes is rescued in cGAS-deficient or STING-deficient mice	125–127, 192–194
	Familial chilblain lupus	Disease can be caused by *STING1* GOF mutation	195
	COPA syndrome	Pathology reduced in STING-deficient mice or mice treated with a STING inhibitor and in patient cells upon STING suppression	37,38, 133,134
Autoimmune diseases	Systemic lupus erythematosus	Subset of patients have elevated cGAMP levels. Pathology of certain mouse models, which display a lupus-like phenotype, can be rescued in STING-deficient mice	135,136,140
	Rheumatoid arthritis	Reduced cytokine expression in patient cells following cGAS or STING knockdown	196
Neurological disorders	Ischaemic brain injury	Pathology reduced in mouse models treated with inhibitory oligonucleotide A151	197
	Parkinson disease	Pathology reduced in STING-deficient mouse models	91
	General neurodegeneration	Reduced inflammation markers seen in a STING-deficient mouse model	148
	Huntington disease	Cytokine expression within patient cells reduced upon cGAS depletion	147

Table 1. cGAS/STING and inflammatory diseases (cont'd)

Neurological disorders	Amyotrophic lateral sclerosis and frontotemporal dementia	Protection in STING-deficient mice or in mice treated with a STING inhibitor. Reduced type I interferon expression in patient cells treated with a STING or cGAS inhibitor	101,145
	Age-dependent macular degeneration	Protection in cGAS-deficient and STING-deficient mouse models	198
	Traumatic brain injury	Reduced neuroinflammation seen in STING-deficient mice	207
Metabolic diseases	Nonalcoholic steatohepatitis	Protection seen in STING-deficient mice	199
	Alcoholic liver disease	Protection in STING-deficient mice	60
	Acute pancreatitis	Protection seen in cGAS- or STING-deficient mouse models	200
Inflammatory diseases	Silica-induced fibrosis	Pathology reduced in STING-deficient mice	201
	Sepsis	Protection seen in STING-deficient mice	202,203
Cardiovascular diseases	Myocardial infarction	Protection in cGAS-deficient or STING-deficient mice	81,204
	Chronic heart failure	Protection when cGAS is inhibited (via an AAV vector)	205
Cancer	Colorectal cancer	Protection in STING-deficient mouse model	206
	Skin cancer	Protection in STING-deficient mice	149
	Metastases	Protection seen with STING-deficient tumour cells	51
Senescence and ageing	Senescence	Protection against senescence seen in cGAS-deficient or STING-deficient cells or mice	58,155,156
	Ageing	Ageing-associated inflammation reduced in STING-deficient cells	105,157

AAV, adeno-associated virus; cGAMP, 2′3′ cyclic GMP–AMP; cGAS, cyclic GMP–AMP synthase; GOF, gain of function; STING, stimulator of interferon genes.

Link to human genetics: despite being associated with a number of diseases, the link with human genetics is mainly through STING. STING1 GOF mutations can lead to SAVI or a familial form of lupus.

Source: Decout et al. 2021

Current programs targeting cGAS (1/1)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
F-Star	FSTX	129.9	SB 11285 (STING agonist)	Next generation cyclic dinucleotide-based STING agonist	Head/neck cancer, melanoma	Phase I
IFM Therapeutics (Novartis)	Private	-	Undisclosed cGAS/STING inhibitors	Block STING-induced cytokine expression	Inflammation, autoimmunity, neuroinflammation and oncology	Discovery
Mersana	MRSN	893.4	XMT-2056 (STING agonist)	ADC that selectively delivers a STING agonist to tumor cells	Oncology	Pre-clinical
Nanobiotix	NANO-FR	386.4	NBTXR3	Nanoparticles injected into tumors are activated by radiation which lead to oxidative stress and cGAS/STING activation	Soft Tissue Sarcomas	Phase III
Onxeo	ALONX-FR	53.2	OX401 (indirect activation of cGAS/STING through PARP)	Blocks PARP function, which increases DNA damage which stimulates cGAS/STING-mediated anti-tumor immunity	Oncology	Pre-clinical
Tempest	Private	-	TREX1 inhibitor (indirect inhibition of cGAS/STING)	Inhibits the TREX1 exonuclease which leads to activation of STING, increased IFN (and other cytokines) which promotes anti-tumor immunity	Solid tumors	Lead optimization
Ventus	Private	-	Undisclosed	Unknown	Undisclosed	Pre-clinical
Ventyx	Private	-	Undisclosed	Unknown	Undisclosed	Discovery

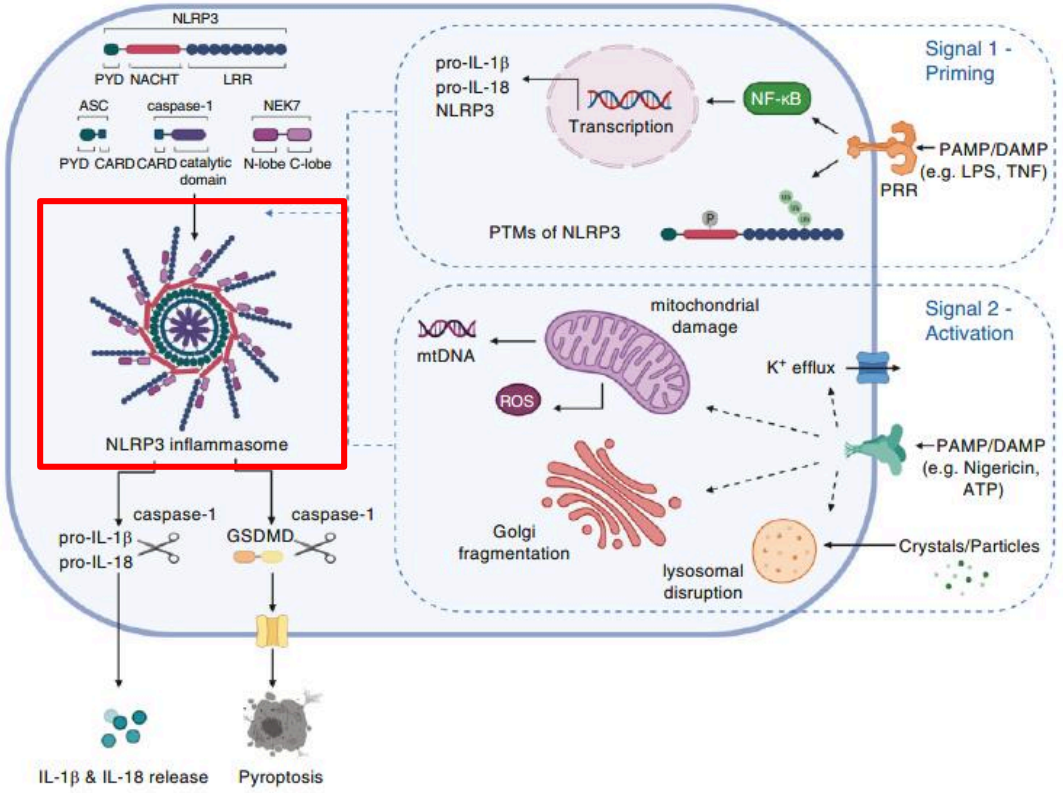
Note: all market cap figures in $, except ALONX-FR and NANO-FR in €

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

__N__OD-, __LR__R- and Pyrin Domain-Containing __P__rotein 3 - NLRP3/Inflammasome

What is the inflammasome? (1/2) – The inflammasome is a key component of innate immunity

- **Inflammasomes** are multi-protein complexes in the cytoplasm of all cells that act as an endogenous front line molecular security system that initiates an inflammatory cascade in response to danger signals, either extracellular (e.g. pathogens) or intracellular (e.g. beta-amyloid, crystals).
- There are multiple subtypes of inflammasome – one of the most studied (and one of the hottest drug targets) is the **NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)** inflammasome.
- NLRP3 is an intracellular sensor protein that translates danger signals into an immune response by triggering assembly of a multiprotein complex that results in the release of the potent pro-inflammatory cytokines IL-1β and IL-18, pyroptosis (a form of cell death) and amplifies immune responses.
- NLRP3 inflammasome activation involves two steps: (1) priming and (2) activation (more on next page).

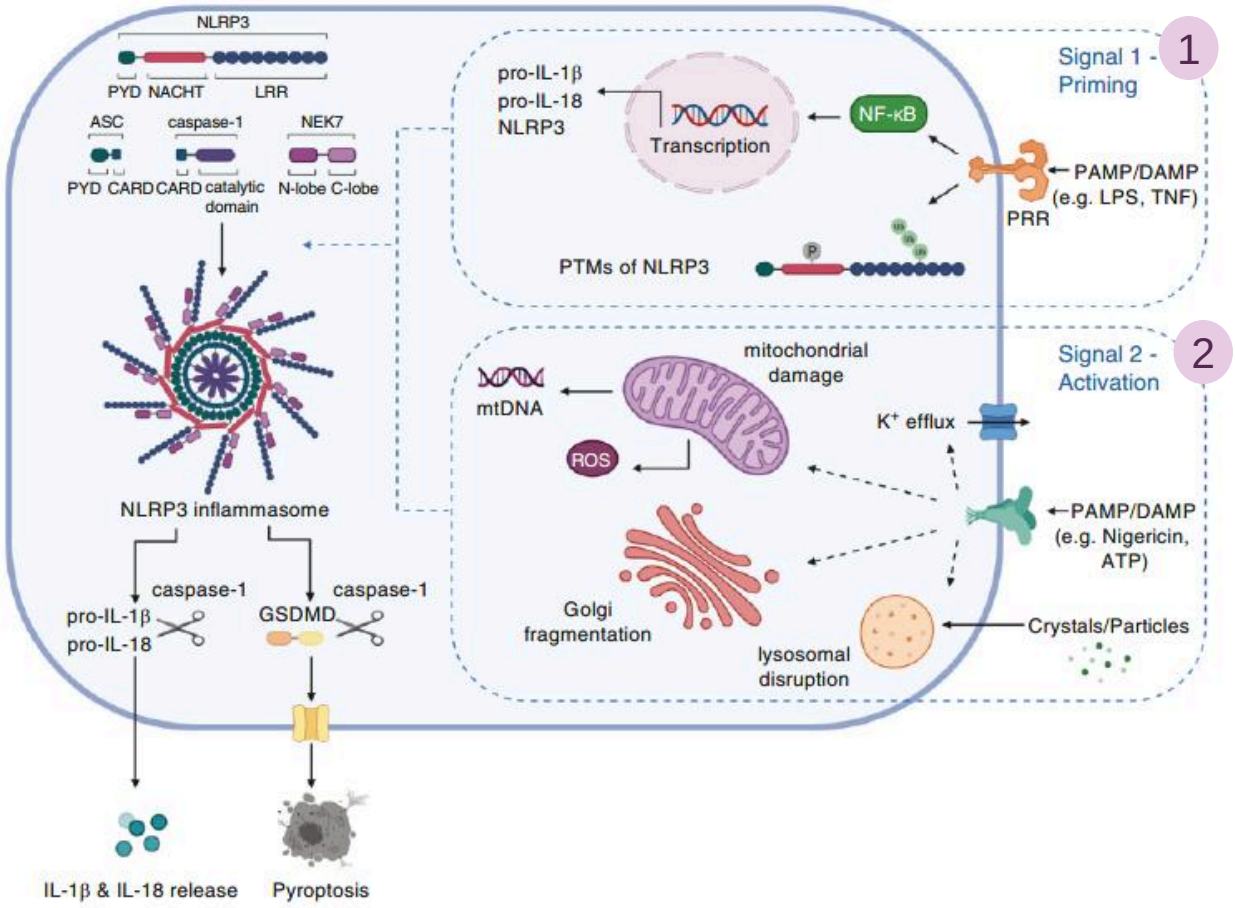


Source: McKee & Coll 2020

See pages 110 - 111 for analyst certification and important disclosures.

What is the inflammasome? (2/2) – NLRP3 inflammasomes are activated in a two-step process

Priming and activation of inflammasomes



1

Priming:

- Binding of pathogen- or danger-related signals (e.g. LPS, TNF) to pattern recognition receptors (e.g. TLRs).
- Activation of these receptors: (1) upregulates the transcription of pro-forms of the cytokines IL-1β and IL-18, and (2) results in post-translational modifications necessary for full inflammasome assembly/activation.

2

Activation:

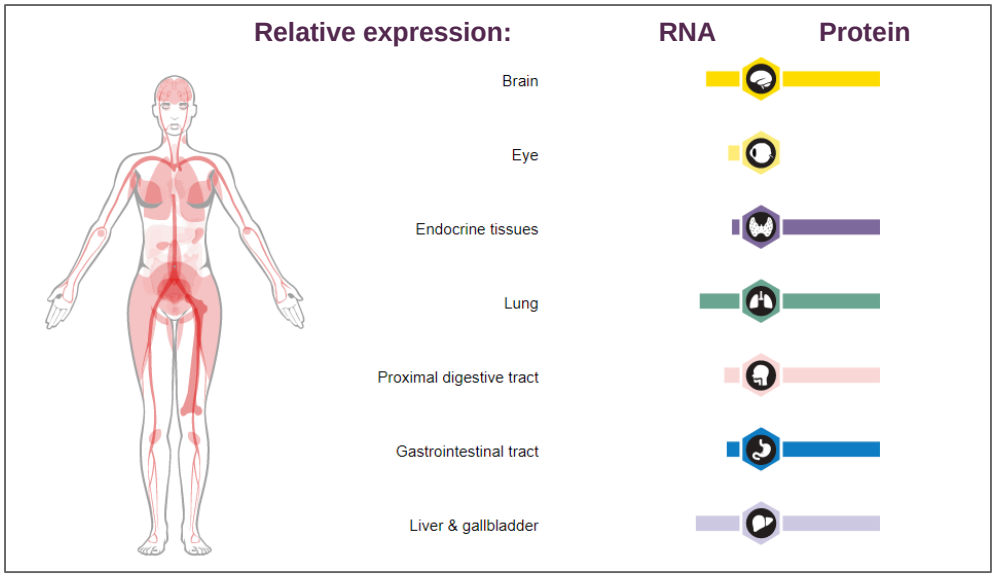
- Multiple stimuli (e.g. bacterial toxins, or crystals/particulates) trigger intracellular signals promoting reactive oxygen species and mito DNA release.
- These signals lead to inflammasome formation via NLRP3 oligomerization/interaction with the adapter protein ASC.
- Multiple ASC units build a platform for the recruitment and activation of caspase-1 (cleaves pro-IL-1β, pro-IL-18, and GSDMD that cause inflammation and pyroptosis).

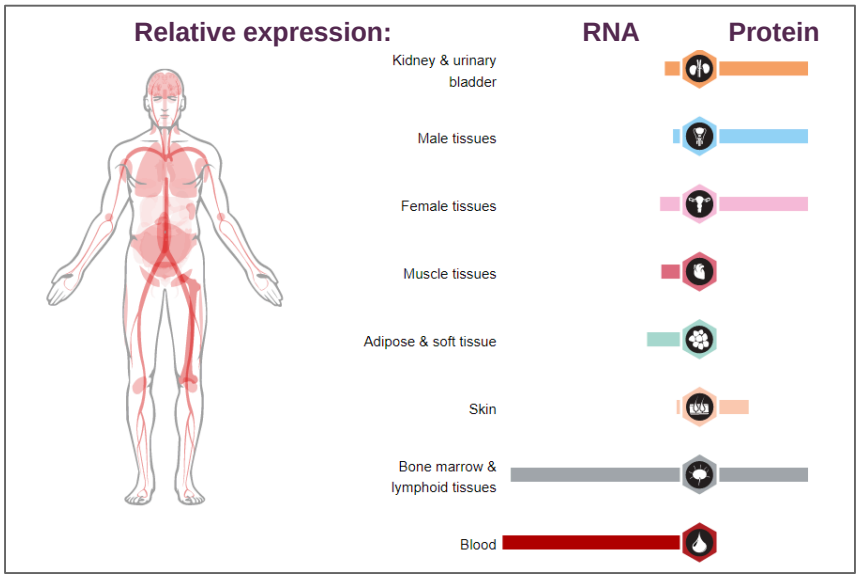
Source: McKee & Coll 2020

Where are inflammasomes enriched? (1/1) – NLRP3 is highly expressed in macrophages and can be detected in most tissues in the human body

- The NLRP3 inflammasome exists mainly inside (cytoplasm) of most innate immune cells, with high expression in **macrophages** and is detected in most tissues (both in the brain and in peripheral tissues), according to the Human Protein Atlas
- It is likely that different macrophages (e.g. microglia vs. peripheral) have different NLRP3 regulation or other NLRP isoforms that make up unique inflammasomes tailored to the immune response in that environment
    - One challenge (highlighted on the next page) that arises is understanding the different characteristics among these different inflammasomes
        - Structure and function (activation/priming) may not be exactly the same across inflammasomes in different innate immune cells
        - For example, targeting NLRP3 in microglia may not have the same effects as in macrophages that reside in liver (Kupffer cells)

NLRP3 tissue expression



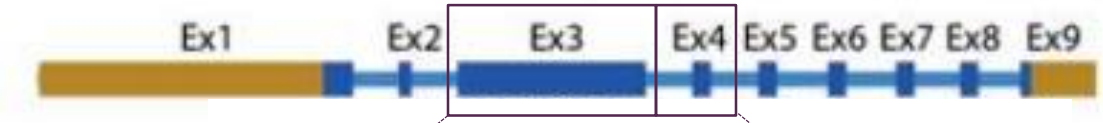


While NLRP3 mRNA (bar on left side) and protein (bar on right side) can be detected in most tissues in the human body (except lower expression in the eye, muscles and adipose), it is thought that most of the NLRP3 expression is attributed to resident macrophages (and other innate immune cells) in these tissues (e.g. Kupffer cells in the liver)

Source: McKee & Coll 2020, Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000162711-NLRP3/tissue)

Is there a genetic connection between NLRP3 and disease? (1/1) – GOF mutations in NLRP3 cause cryopyrin-associated periodic syndromes (CAPS)

NLRP3 gene structure



Mutations causing CAPS

Exon 3: R260W, L264H, E304K, A352V, F523C, L632F, R260P, D303N, L305P, T436I, G569R, M659K, R260L, D303G, T348M, A439V, E627G

Exon 4: G755R

Inflazome's (acquired by Roche) inzomelind (a brain-penetrant NLRP3 inhibitor) has already generated positive POC in CAPS.

- **Cryopyrin-associated periodic syndromes (CAPS)** is group of inflammatory diseases, characterized by recurrent episodes of systemic inflammatory attacks without infections or underlying autoimmune disease
  - CAPS encompasses three disorders: CINCA, Muckle-Wells syndrome, and familial cold urticaria
- CAPS is caused by autosomal dominant gain-of-function (GOF) mutations in NLRP3, leading to increased secretion of IL-1β and IL-18 and systemic inflammation
  - ~170 variants (most mutations in exon 3 and 4) have been linked with CAPS

Source: Izawa et al. 2012, Infevers database (https://infevers.umai-montpellier.fr/web/search.php?n=4)

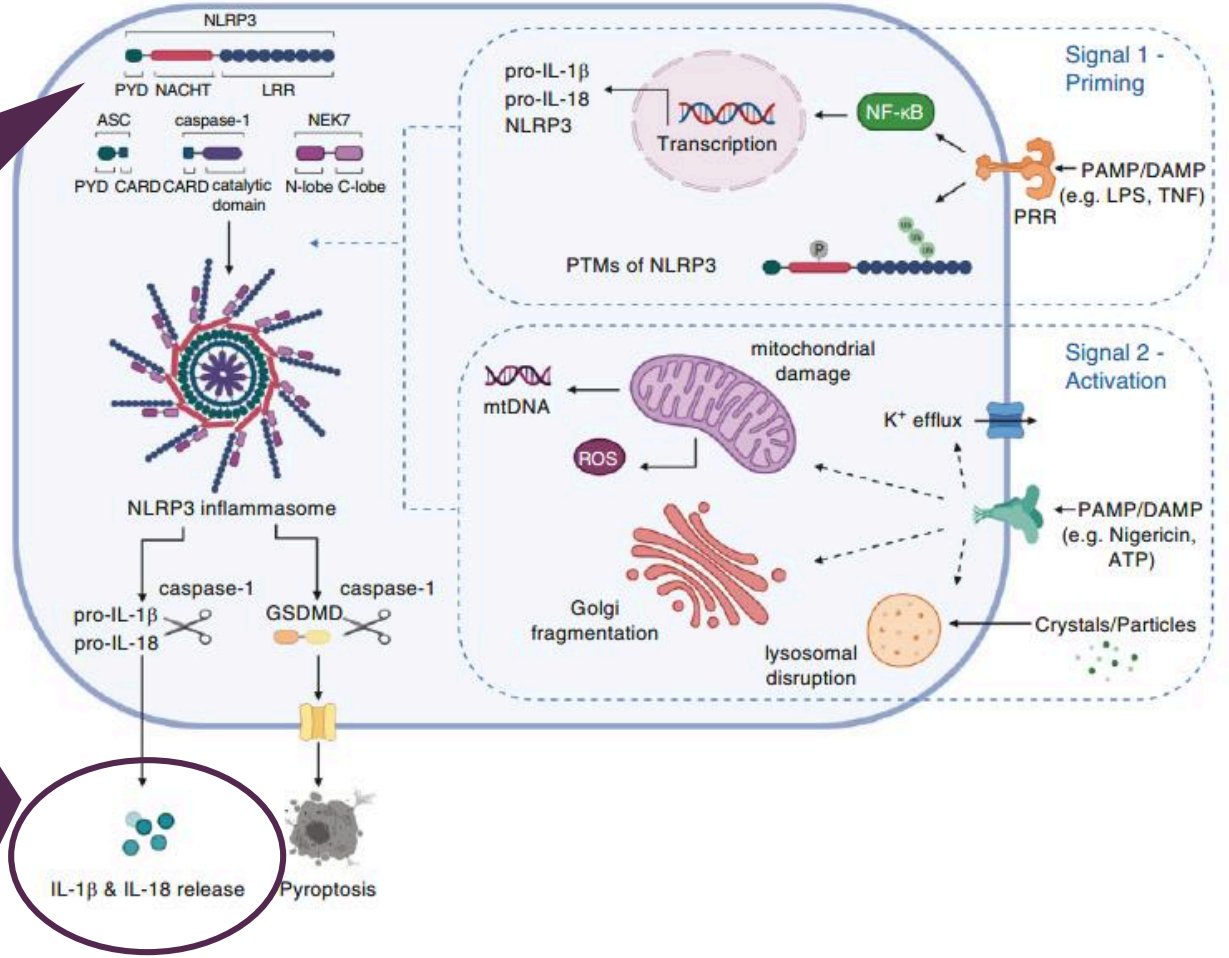
Are there biomarkers for the NLRP3 inflammasome? (1/1) – IL-1β and protein kinase D phosphorylation are putative biomarkers to measure NLRP3 activation

Protein Kinase D Phosphorylation

- Protein kinase D (PKD) auto-phosphorylation is a novel, putative biomarker for NLRP3 activation
- PKD phosphorylates NLRP3 which is important for allowing NLRP3 to assemble the inflammasome complex

IL-1β expression

- The cytokine IL-1β is the most commonly used marker for NLRP3 inflammasome activation (mainly pre-clinical) given the downstream conversion of pro-IL-1β to mature IL-1β
- Higher levels of IL-1β observed in a genetically driven NLRP3 syndrome (CAPS) supports IL-1β as biomarker
- However, we note that inflammasomes are not the only source of IL-1β and that processing of pro-IL-1β may be influenced by other inflammasome-independent factors



Source: Heiser et al. 2021

What diseases is NLRP3 involved in? (1/1) – NLRP3 inflammasome activation contributes to both CNS and peripheral diseases

NLRP3 inflammasome activation has been implicated in a host of indications, from auto-immune to neurodegenerative to metabolic. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
Cryopyrin-associated periodic syndromes (CAPS)	Gain-of-function mutations in NLRP3 drive activation of NLRP3 inflammasomes, excessive production of IL-1β/IL-18 that contribute to rash, fever, myalgia, conjunctivitis and headache	**STRONG** - defined human genetics link; clinical validation with canakinumab (IL-1β blocker from NVN-SWX) already approved in CAPS. ***More importantly, Inflazome's (acquired by Roche) inzomelid (a brain-penetrant NLRP3 inhibitor) has already generated positive POC in CAPS.***
Gout	Monosodium urate crystals (which cause gout) activate NLRP3 inflammasome and increase IL-1β/IL-18 which can drive neutrophil-mediated joint swelling and pain	**STRONG** – not much genetic evidence, but crystals are direct activator of NLRP3 which is known to promote neutrophil infiltration into joints; clinical validation (canakinumab approved in Europe)
Atherosclerosis	Cholesterol crystals and oxidized LDL can activate NLRP3, which can directly promote foam cell formation and lesion development	**MODERATE** – not much genetic or clinical evidence, but clear pre-clinical link between NLRP3 activation and lesion development
Parkinson's Disease	α-synuclein can activate NLRP3 inflammasomes in brain microglia, contributing to neuroinflammation	**MODERATE** – robust pre-clinical data with evidence of NLRP3 activation in brains of PD patients, but minimal clinical precedence
Alzheimer's Disease	Amyloid-β activates NLRP3 inflammasome in microglia, and IL-1β is linked to cognitive impairment	**MODERATE** – robust preclinical data with evidence of NLRP3 activation in brains of AD patients, but minimal clinical precedence
Non-alcoholic steatohepatitis (NASH)	MoA not completely known; NLRP3 and NLRP6 inflammasomes may interact with gut microbiome to influence TNFα expression in liver	**WEAK** – conflicting preclinical data, with unclear MoA and little clinical validation

Source: Mullard 2019, Booshehri & Hoffman 2019, Bai et al. 2021, Gordon et al. 2018, Heneka et al. 2012, Henao-Mejia et al. 2012, Mridha et al. 2017

See pages 110 - 111 for analyst certification and important disclosures.

What are the challenges in targeting NLRP3 inflammasomes? (1/1) – NLRP3 complexity highlights the need for structure-guided drug development

Targeting NLRP3 is easier said than done and comes with challenges. In the title of their 2020 review, McKee & Coll referred to NLRP3/inflammasome as a ***"A riddle wrapped in a mystery inside an enigma,"*** which says it all – the complexity and amount of unknown information surrounding NLRP3/inflammasomes make it an intriguing but extremely difficult target to pin down. While several approaches exist to inhibiting NLRP3/inflammasomes (outlined in the table below), many are plagued by the lack of knowledge concerning the structure of individual proteins (NLRP3), how these proteins oligomerize into the inflammasome and how this structure/function changes when you alter inflammasome activity or introduce an inhibitory/activating compound. Cracking the structural code of NLRP3-formed inflammasomes could unravel the enigma and rapidly expand the inflammasome's therapeutic potential.

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Direct NLRP3 inhibition	Very little NLRP3 structural data; structure/function could vary by cell/tissue	Elucidate NLRP3/inflammasome structures	Very labor- and time-intensive – need to consider protein conformations; if successfully executed, potential to expand inflammasome market
Inhibiting downstream cytokines (e.g. IL-1β)	Potential off-target effects and broad immunosuppression; inflammasomes are not the only source of IL-1β	More direct targeting of NLRP3/inflammasomes	In the CANTOS trial, NOVN-SWX's IL-1β blocker canakinumab showed pbo-adjusted reductions in non-fatal MIs (15%) and cancer mortality (50%) but led to higher incidence of fatal infections
Augmenting post-translational modifications	PTMs are residue-specific and can either activate/inhibit depending on the protein and context	PTM structure/function dynamics to guide design of a site-specific inhibitor	While this is possible, most kinases/deubiquitinases have multiple substrates, which could lead to off-target effects
Manipulating protein-protein interactions	NLRP3 is regulated by many binding proteins, the binding sites/dynamics of which are largely unknown	Elucidate NLRP3/inflammasome structures and sites of regulator binding	Blocking binding of activating proteins requires clear NLRP3 structural insights

Bottom line: In our view, the key to unlocking NLRP3 as a target is ***gaining clear insights into protein structure and dynamics*** in order to facilitate precision inflammasome drug development

Source: McKee & Coll 2020, Mullard 2019, NVS company presentations, Guggenheim Securities, LLC research

Current programs targeting NLRP3 inflammasomes (1/2)

The **NLRP3 inflammasome** is one of the hottest drug targets in the innate immunity space, with 12 companies actively pursuing the target (all companies listed in the table on the next page). Some highlights from our end:

- ***ACIU*** has biologics targeting NLRP3 in orphan CNS/non-CNS
- ***BMY*** is an active player in the space, developing the small molecule NLRP3 *activator* (instead of inhibitor) BMS-986299 for solid tumors (Phase I)
- ***Invea*** is working on a first-in-class pan-inflammasome inhibitor that the company wants to develop for GI disorders. The compound is currently in preclinical development and is believed to be a peptidomimetic inhibitor of PYCARD (often referred to as ASC, apoptosis-associated speck-like protein containing CARD).
- ***Nodthera*** is working on multiple small molecule NLRP3 inhibitors (brain penetrant and peripherally acting). Lead molecule, NT-0796 is in early clinical development. Indications of interest include gout, Parkinson's, and other inflammatory disorders
- ***Novartis*** is active in the NLRP3 space, with multiple assets from the acquisition of IFM, including IFM2427 which is in development for NASH, IBD, CNS diseases (development stage unknown)
- ***Olatec*** is developing the NLRP3 inhibitor dapansutrile (oral and topical) in Gout (oral, Phase IIa), heart failure (oral, Phase Ib) and osteoarthritis (topical, Phase II)
- ***Roche*** is very active in the NLRP3 space and, through their acquisition of Inflazome, now has full access to Inflazome's portfolio of orally available NLRP3 inhibitors including RG6418 (Somalix) for peripheral inflammatory diseases (Phase I) and inzomelid for CAPS and neurodegeneration (Phase I for CAPS)
- ***Ventus*** has two compounds VEN-4099 and VEN5695 which are small molecules specifically designed to inhibit the oligomerization of NLRP3, being developed for innate immunity indications (pre-clinical)
- ***Ventyx*** is developing the NLRP3 inhibitor ZMG-2735 for undisclosed indications (pre-clinical stage)
- ***ZyVersa*** has biologics targeting multiple sclerosis

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting NLRP3 inflammasomes (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
AC Immune	ACIU	495.5	Undisclosed anti-NLRP3/ASC antibody, NLRP3/ASC morphomer	Biologics that block both NLRP3 and the adaptor protein ASC	Orphan neuro indication, non-CNS indications	Pre-clinical
Bristol Myers Squibb	BMY	148770.3	BMS 986299	Small molecule NLRP3 agonist	Solid tumors	Phase I
Invea	Private	-	INVA8003	Small molecule against PYCARD	GI disorders	Pre-clinical
Nodthera	Private		NT-0796	Small molecule NLRP3 inhibitor	Gout, OA, Parkinson's	Phase I
Novartis	NOVN-SWX	190701.3	IFM2427	Small molecule NLRP3 inhibitor	NASH, IBD, CNS diseases	Unknown
Olatec	Private	-	Dapansutrile	Selective NLRP3 inflammasome inhibitor (oral and topical)	Gout, Heart failure (oral); Osteoarthritis (topical)	Phase IIa (gout), Phase Ib (HF), Phase II (OA)
Roche (Inflazome)	ROG-CH	313428.4	Somalix (RG6418), Inzomelid	Potent, selective, oral NLRP3 inflammasome inhibitors (Inzomelid is brain-penetrant)	Inflammatory diseases, CAPS, neurodegeneration	Phase I
TWi Pharmaceuticals, Inc.	Private	-	AC-201	Oral compound that targets caspase-1/ICE (IL-1ß-converting enzyme), IL-1, NLRP3/Inflammasome and URAT1	Hemophilia A and B	Phase II
Ventus	Private	-	VEN-4099 VEN-5695	Small molecules designed to inhibit formation of NLRP3 ring oligomers, preventing the ramping up of inflammation at its source	Innate immunity	Pre-clinical
Ventyx	Private	-	ZMG-2735	Targets NLRP3 to regulate downstream IL-1β cytokine	Not disclosed	Pre-clinical
Zydus Cadila	532321-IN	557221.7	ZYIL-1	Oral small molecule inhibitor of NLRP3	IBD, CAPS	Phase I
ZyVersa (InflamaCORE)	Private	-	IC-100	mAb that blocks ASC, which inhibits inflammasome formation, activation, and initiation of the inflammatory response	Multiple sclerosis	Pre-clinical

Note: all market cap figures in $ except for ROG-CH and NOVN-SWX in CHF and 532321-IN in INR

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on NLRP3 (1/1) – NLRP3 is a genetically-validated target with a strong mechanistic link across multiple CNS and non-CNS indications

Target factor	Strength of evidence	GS comments
Link to human genetics	STRONG	CAPS is an example where genetic over-activation of NLRP3 drives disease; indirect readthrough to other NLRP3-associated inflammatory disorders in which increased NLPR3 activity due to endogenous activators (e.g. protein aggregates)
CNS target enrichment	WEAK	NLRP3 inflammasomes are present in innate immune cells, including microglia of the brain but also in peripheral macrophages in most tissues. It is still unknown whether the structure/function of inflammasomes in the CNS are the same as in the periphery.
Mechanism of action	STRONG	Pre-clinical data provide a link between NLRP3 and the pathophysiology of at least 6 indications (including genetically validated CAPS); upstream inhibition (vs. downstream IL-1β blockade) may be most beneficial in CNS/inflammatory diseases but may require adequate structural insights to guide drug development
Biomarkers	MODERATE	Both IL-1β and PKD auto-phosphorylation are candidate biomarkers and seem to correlate with inflammasome activation, but IL-1β processing/localization may be indication-specific and inflammasome-independent. PKD also regulates more than just inflammasome activation, which may make phospho-PKD levels difficult to interpret
Safety	MODERATE	NLRP3 inhibition should NOT increase infection rates (unlike broad-based anti-inflammatories) since pathogen sensing by other non-NLPR3 inflammasomes should not be altered. However, this favorable safety profile may be muted by the potential for unforeseen AEs due to differences in CNS vs. peripheral inflammasomes.
Clinical PoC	MODERATE	Most programs are early stage (pre-clinical or Phase I), but Olatec produced positive Phase Ib data in HF with dapansutrile and Inzomelid has produced positive PoC in CAPS

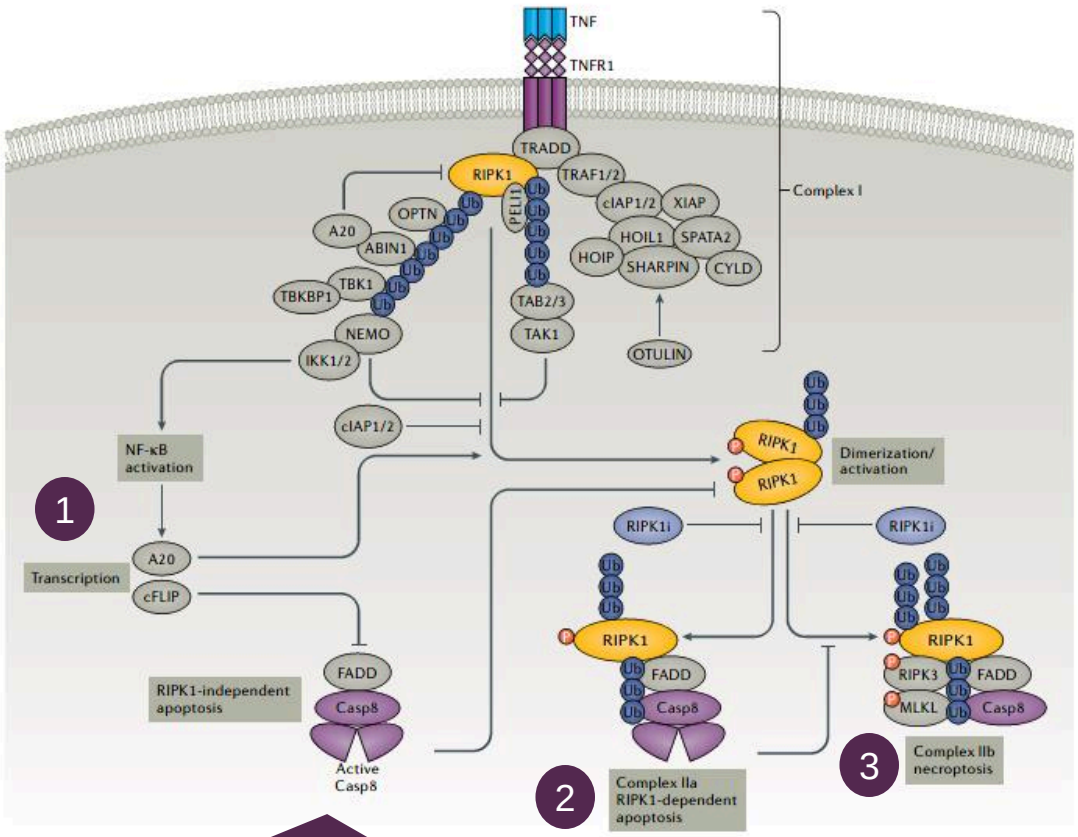
Source: Ranson et al. 2019, Heiser et al. 2021, Olatec press release, Guggenheim Securities, LLC

See pages 110 - 111 for analyst certification and important disclosures.

Receptor-Interacting Protein Kinase 1

- RIPK1

What is RIPK1? (1/1) – RIPK1 is a scaffold/kinase downstream of TNF-α receptor that controls the balance between cellular life and death



RIPK1 also has a scaffold function that primarily supports NF-kB-mediated pro-survival pathways, in contrast to its kinase activity which mainly drives inflammation and cell death (apoptosis or necroptosis).

- **R**eceptor-**I**nteracting **P**rotein **K**inase **1 (RIPK1)** is a multi-domain intracellular kinase that signals downstream of TNF-α receptors (mainly TNFR1, but also TNFR2)
  - TNF-α binding to TNFR1/2 induces formation of a large signaling complex (Complex I) including RIPK1, TRAF2, and E3 ubiquitin ligases, with RIPK1 serving as a scaffold.
  - RIPK1 is highly regulated by post-translational modifications (e.g. ubiquitination, phosphorylation) and by caspase cleavage.
  - RIPK1 deubiquitination and kinase activation leads to formation of a cytosolic signaling complex (Complex II).
  - RIPK1 signaling/scaffold functions promote: **(1)** pro-survival gene expression (scaffold), **(2)** RIPK1-dependent apoptosis (kinase function), and/or **(3)** necroptosis (form of inflammatory cell death; via kinase function).

Source: Degterev et al. 2019

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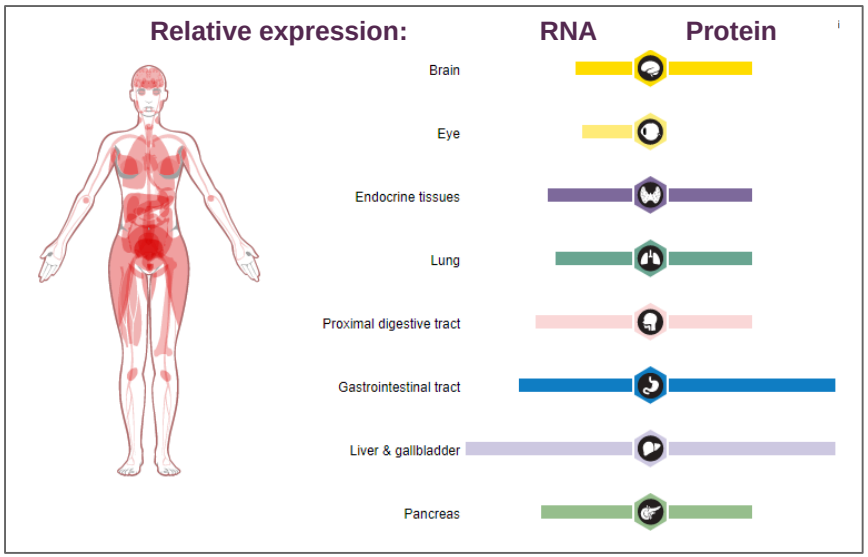
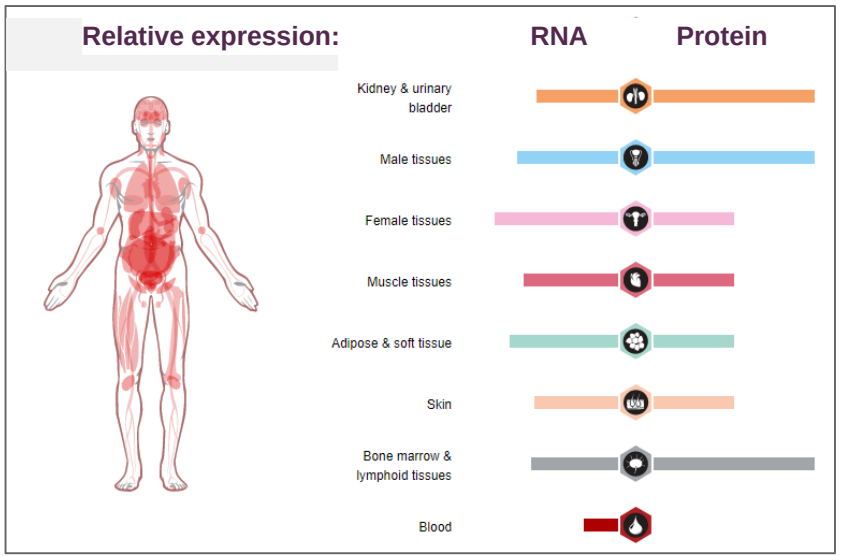
Where is RIPK1 enriched? (1/1) – RIPK1 is a globally expressed kinase

RIPK1 is widely expressed in most tissues of the human body

- RIPK1 protein is detected in moderate amounts in the brain, but the highest relative levels are measured in the GI tract, liver and gallbladder, kidney and urinary bladder, male reproductive tissues and bone marrow/lymphoid tissues
- Within these tissues, RIPK1 (at the mRNA level) is also broadly expressed across multiple cell types, but interestingly exhibits lower expression in germ cells

RIPK1 tissue expression





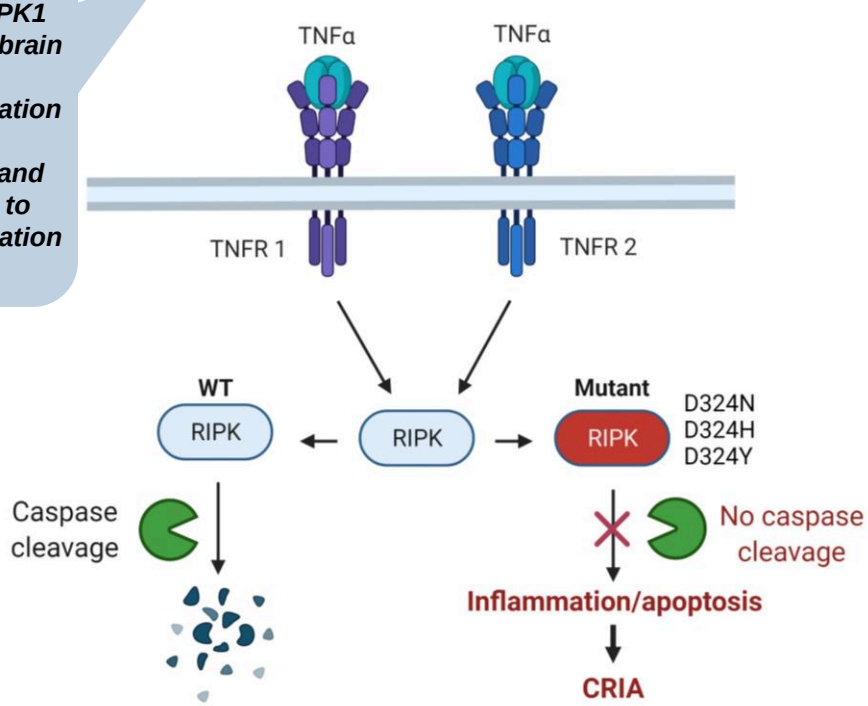
On a subcellular level, RIPK1 is detected throughout the cellular cytoplasm, but notably has not been detected in other organelles involved in the downstream consequences of RIPK1 signaling (e.g. nucleus or mitochondria), indicating that RIPK1 is an important upstream regulator of these pathways but may not be directly and/or proximally involved in the gene expression (nucleus) and apoptosis (mitochondria). RIPK1 may also have cell-specific functions.

Source: Uhlen et al. 2015, Thul et al. 2017, Human Protein Atlas (https://www.proteinatlas.org/ENSG00000137275-RIPK1/tissue)

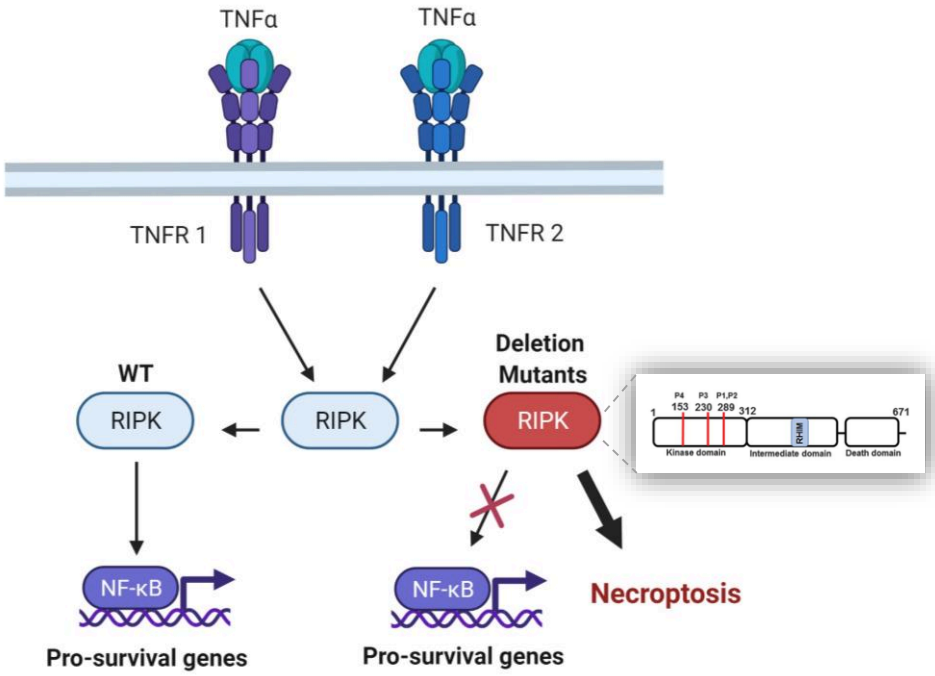
Is there a genetic connection between RIPK1 and disease? (1/1) – GOF mutations cause autoinflammatory syndrome, while LOF mutations increase risk of IBD

Increased RIPK1 activity in the brain drives neuroinflammation and cell necroptosis and contributes to neurodegeneration

RIPK1 GOF mutations can drive autoimmune disease



RIPK1 LOF mutations increase risk of early-onset IBD



Heterozygous GOF mutations (D324N, D324H and D324Y) that prevent caspase 8-mediated cleavage (and inhibition) of RIPK1 result in the autoinflammatory syndrome **cleavage-resistant RIPK1-induced autoinflammatory syndrome (CRIA),** characterized by hypersensitivity to TNF-mediated apoptosis/necroptosis and splenomegaly, hepatomegaly, ulcers and arthralgia (among several other symptoms)

Rare homozygous LOF mutations (mainly deletions in the kinase domain) that completely inhibit RIPK1 impair pro-survival signaling and drive excessive compensatory necroptosis, resulting in **immunodeficiency with recurrent infections, early-onset inflammatory bowel disease, and progressive polyarthritis**

Source: Lalaoui et al. 2019, Mifflin et al. 2020, Cuchet-Lourenço et al. 2018, Li et al. 2019, Guggenheim Securities, LLC research, images created with BioRender.com

Are there biomarkers for RIPK1? (1/1) – RIPK1 phosphorylation is a clinically validated and selective biomarker for RIPK1 activation

Biomarker	Indications	Rationale	GS comments
S166 RIPK1 phosphorylation	**All RIPK1-relevant indications**	**Phosphorylation of S166 is a key step in activating RIPK1-mediated apoptosis/necroptosis**	**Phase Ia HV data from DNLI's DNL104 showed ~80% reduction in S166 RIPK phosphorylation in human PBMCs *ex vivo*; most direct marker of RIPK1 activity and not indication-specific**
MIP-1α	All RIPK1-relevant indications	Expression of the cytokine MIP-1α is driven by RIPK1	Phase Ia HV data from GSK's GSK2982772 showed ~80% reduction in MIP-1α, which was not dose-dependent but time dependent; direct but not most specific biomarker
Lipids	Alzheimer's disease (AD)	RIPK1 activation in AD leads to increased expression of Ch25 (encodes cholesterol 25-hydroxylase) which regulates levels of 25-hydroxycholesterol	Not the most direct or clear biomarker; would need to specifically monitor this lipid (which is dynamically regulated by multiple metabolic pathways)
Cystatin F	Alzheimer's disease (AD)	RIPK1-mediated DAM phenotype characterized by cystatin F upregulation in microglia in AD	More specific than lipids, but would mainly be useful for late-stage disease and unclear if upregulated in more clinically accessible cells (e.g. PBMCs)
Phosphorylation of hMLKL	Drug-induced liver injury	MLKL mediates necroptosis downstream of RIPK1	Biomarker for necroptosis signaling; requires IHC of tissue biopsies possibly limiting clinical applicability

Bottom line: There are several applicable biomarkers for RIPK1 inhibition that are disease-specific, but many are not selective for RIPK1 activity, leaving ***S166 RIPK1 phosphorylation as the most specific (and clinically validated) RIPK1 biomarker***

Source: Degterev et al. 2019, He et al. 2016, Grievink et al. 2019, Mifflin et al. 2020, Weisel et al. 2017

What diseases is RIPK1 involved in? (1/1) – RIPK1 has genetic ties to several diseases and could be a viable target inside and outside of the brain

RIPK1 has been implicated in a number of CNS and peripheral inflammatory diseases ***and the therapeutic goal is to restore the balance of R1PK1, depending on the disease***. In the table below, we highlight the major indications, MoA, and the strength of evidence for each.

Indications	Mechanism of action	Strength of evidence
CRIA	Heterozygous GOF mutations in RIPK1 prevent caspase 8-mediated cleavage (and inhibition) of RIPK1, resulting in extensive TNF-mediated apoptosis/necroptosis that drives splenomegaly, hepatomegaly, ulcers and arthralgia	**MODERATE** – clear link to human genetics; preclinical MoA data are strong but are complicated by cell-specific effects on inflammatory cell death; patient cells show activation of RIPK1, but syndrome discovered relatively recently with little clinical data
ALS	LoF mutations in the OPTN and TBK1 genes, lead to increased RIPK1 expression/activity and RIPK1-mediated necroptosis of motor neurons, contributing to familial ALS/FTD	**STRONG** – clear (indirect) genetic link; strong preclinical data showing benefit of RIPK1 inhibition in ALS mouse models; increased RIPK1 activation in ALS patient spinal cords, but clinical data sparse (DNLI in Phase I)
Alzheimer's disease (AD)	Overactivation of RIPK1 (cause not known) may contribute to neuroinflammation (via cystatin F among others) and drive white matter loss in AD; necroptosis signaling correlated with neuronal loss in AD	**MODERATE** – somewhat ambiguous (indirect) genetic link; strong preclinical data showing benefit of RIPK1 inhibition in AD mouse models; increased RIPK1 activation in post-mortem AD patient brains, but clinical data sparse (DNLI in Phase I)
IBD	LOF RIPK1 mutations impairs NF-κB/MAPK signaling, but increases RIPK3/MLKL-mediated necroptosis	**WEAK** – strong link to human genetics; paradoxical preclinical data suggesting increased necroptosis but decreased cytokine expression; not much clinical data (GSK's compound is preclinical)
Cutaneous Lupus Erythematosus	In SLE, complement can activate RIPK1, which plays an integral part in neutrophil NETosis (neutrophil extracellular traps [NETs]), leading to the release of autoantigens from neutrophils and autoimmune pathology	**MODERATE** – indirect genetic link through RIPK1 regulators; strong mechanistic preclinical data involving neutrophils but for SLE not specifically in CLE; some target de-risking based on known role in SLE, but no clinical data yet (SNY-US in CLE Phase II)

Source: Mifflin et al. 2020

What are the challenges in targeting RIPK1? (1/1) – RIPK1 kinase inhibition could maximize efficacy/safety but targeted delivery could play a key role

There are two high level approaches to targeting RIPK1: **(1)** allosteric inhibition of the RIPK1 kinase function with a small molecule, and vs. leveraging protein degradation platforms already used for other targets (e.g. IRAK4) to reduce overall RIPK1 protein levels, and **(2)** systemic vs. targeted delivery of drug. ***While reducing overall protein levels is desired in some cases (IRAK4), kinase inhibition may be preferred in this context given the pro-survival signaling mediated through RIPK1 scaffold functions.*** Although, systemic administration of a small molecule inhibitor would be more straight forward, this approach could lead to unwanted AEs since RIPK1 function can vary widely depending on the cell/tissue. ***Location matters with RIPK1.***

Therapeutic strategy	Major challenges	Potential solutions	GS comments
Protein degradation vs. kinase inhibition	RIPK1 exerts pro-survival signals through scaffold and pro-death signals via kinase; protein degradation may negate beneficial pro survival pathways	Focus on kinase inhibition, which has been achieved by efficient targeting of hydrophobic, allosteric pocket on RIPK1	Contrary to IRAK4, the most effective (and reasonably achievable) way to inhibit RIPK1 is to block kinase function while leaving scaffold function intact
Tissue delivery (systemic vs. targeted)	RIPK1 is expressed in all tissues, and systemic administration may lead to AEs especially due to cell-specific functions of RIPK1	Employ delivery technology to selectively target RIPK1 in the CNS or in the periphery	Given the complexity of RIPK1 signaling, tissue-targeted (at least CNS vs. periphery) could be crucial to balance efficacy and safety

Bottom line: In our view, the most effective and safest (and currently the most common) way to inhibit RIPK1 is a potent, selective kinase inhibitor (mainly through binding to well-characterized allosteric site) that is targeted to the general area of the body affected by disease, in order reduce safety issues that may arise from inhibiting RIPK1 in non-diseased tissues

Source: Mifflin et al. 2020, Guggenheim Securities, LLC research

Current programs targeting RIPK1 (1/2)

All of the five current **RIPK1** programs are developing small molecule kinase inhibitors in larger neuro/inflammatory diseases like Alzheimer's, ALS, psoriasis, UC and lupus. Some highlights from our end:

- ***Boston Pharmaceuticals, Inc.*** has a small molecule RIPK1 inhibitor (BOS-421) in development for neurodegeneration (Pre-clinical)
- ***DNLI*** in collab with SNY-US is developing the brain-penetrant small molecule RIPK1 inhibitor DNL-788 for ALS, AD and MS (Phase I)
- ***GSK*** is developing their small molecule RIPK1 inhibitor GSK 2982772 for psoriasis (Phase I), UC and RA (Pre-clinical)
- ***RIGL*** in collab with LLY is developing two small molecule inhibitors of RIPK1: R552 for autoimmune/inflammatory diseases (Phase I) and an undisclosed CNS-penetrant compound for CNS diseases (Pre-clinical)
- ***SNY-US*** is developing the peripherally-restricted small molecule inhibitor of RIPK1 SAR 443122 in cutaneous lupus erythematosus (Phase II) and other inflammatory indications (Phase I)

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Current programs targeting RIPK1 (2/2)

Company	Ticker	Market Cap (MM)	Drug	Mechanism of Action	Indications	Development Phase
Boston Pharmaceuticals, Inc.	Private	-	BOS-421 (GSK-3502421)	Small molecule inhibitor of RIPK1	Neurodegeneration	Pre-clinical
Denali (Sanofi)	DNLI	6438.4	DNL-788	Potent, selective and brain-penetrant small molecule inhibitor of RIPK1	ALS, AD, MS	Phase I
GSK	GSK	73772.4	GSK 2982772	Oral, allosteric small molecule inhibitor of RIPK1	Psoriasis, UC, RA	Phase I (Psoriasis), Pre-clinical (UC, RA)
RIGL (LLY)	RIGL	705.6	R552 and undisclosed CNS-penetrant compound	RIPK1 inhibitor	Autoimmune and inflammatory diseases; CNS diseases	Phase I completed; Phase II initiation in 2021 (R552); Pre-clinical (undisclosed compound)
Sanofi SA	SNY-US	128806.6	SAR 443122	Small molecule inhibitor of RIPK1	Cutaneous lupus erythematosus, inflammatory indications	Phase I, Phase II (cutaneous lupus erythematosus)

Note: all market cap figures in $ except for GSK in £

Source: AlphaSense, FactSet, Biomedtracker, Guggenheim Securities, LLC research

Our view on RIPK1 (1/1) – RIPK1 may be a strong target from an efficacy standpoint, but safety could be a hurdle to overcome

Target factor	Strength of evidence	GS comments
Link to human genetics	**STRONG**	Both LOF and GOF variants in RIPK1 (CRIA, IBD) and RIPK1 regulators (MS, RA, IBD, ALS/FTD) have been shown to be implicated in multiple indications
CNS target enrichment	**WEAK**	RIPK1 is widely expressed in most tissues and cell types with documented cell-specific function, which could be an important factor for both efficacy and safety
Mechanism of action	**STRONG**	Across multiple indications, RIPK1 controls the balance between pro-survival signaling and inflammatory cell death that directly contributes to clinical symptoms
Biomarkers	**MODERATE**	Measuring phosphorylated RIPK1 is the most direct measure of RIPK1 activation (which has been clinically validated in patient PBMCs), but there are also disease-specific PD markers that may be combined with RIPK1 activity for a more robust biomarker panel
Safety	**MODERATE**	In theory, concentrating the drug in the desired site of action (CNS vs. periphery) *should* mitigate some of the safety issues that could arise with systemic RIPK1 inhibition, but there is still a chance for some safety issues, since a CNS-penetrant molecule would most likely still end up in lower levels in the periphery (DNLI saw post-dose liver toxicity in 37.5% of subjects with CNS-penetrant DNL104 in Phase I)
Clinical PoC	**MODERATE**	In a Phase Ia HV study, **DNLI** showed ~80% RIPK1 inhibition in subject PBMCs with DNL104 a precursor to DNL788 (but saw liver tox); in their Phase I HV study **GSK** showed >90% target engagement and ~80% reduction in the RIPK1-induced cytokine MIP-1α with GSK 2982772; limited data in patients yet

Source: Grievink et al. 2019, Mifflin et al. 2020, Weisel et al. 2017, Guggenheim Securities, LLC

Table of Contents

Hot target watchlist – the next generation of "hot targets"

Hot targets watchlist (1/1) – Emerging targets to keep an eye on; structural elucidation likely needed for successful development

Target	What is it?	GS comments
ALPK1	α-protein kinase with strong genetic links to human inflammatory diseases, but the function is not well understood	Beyond finding a suitable candidate drug for this target, development may be hindered by a lack of defined function, making biomarker and PD marker validation difficult
AIM2	Another inflammasome sensor protein that is activated in the presence of viral and bacterial double-stranded DNA	Possible to leverage learnings from NLRP3 discovery, but AIM2 is mechanistically different than NLRP3, requiring an understanding of the underpinnings of these differences
cGAS	Key intracellular sensor of DNA that initiates a STING-mediated inflammatory cascade	cGAS is a very dynamic protein; efficient targeting most likely will require deep insights on protein structure and dynamics
Gasdermin D	Pore-forming protein downstream of NLRP3 inflammasomes that causes inflammation and cell death (pyroptosis)	Complex and dynamic protein; needs to be cleaved by caspase 1 to form pores at plasma membrane; we think is another target for which protein structures/molecular dynamics could be key
ILT7	Receptor selectively expressed on pDCs that coordinates with FcεRIγ to inhibit innate immune functions of pDCs	Some ILTs can activate innate immunity; FcεRIγ can interact with several receptors on pDCs; structure-guided design to ensure selective ILT7 agonism could be vital for development
MyD88	Adaptor protein downstream of IL-Rs and TLRs that recruits the myddosome signaling complex (IRAK1/2/4 and TRAF6)	A difficult target, given the multiple binding sites with different signaling proteins; may need a molecule that locks MyD88 in a conformation that reduces binding of multiple myddosome components
OX40	T cell co-stimulatory molecule (TNFR family member) that mediates the survival/ expansion of CD4+ and CD8+ T cells; also controls effector and memory T cells	MoA seems context dependent – OX40 can strongly promote the induction of Th1, Th2, and Th9 cells and/or can inhibit the generation of Foxp3+ Tregs
STATs	Transcription factors downstream of JAKs and TYK2 that control cell proliferation, differentiation, and inflammation	Interesting targets, but given the broad transcriptional regulation of each STAT isoform, could introduce safety issues

Source: AlphaSense, Decout et al. 2021, McKee & Call 2020, Mambwe et al. 2019, Fu et al. 2020, Williams et al. 2019, Cao et al. 2006, Cao & Bover 2010, Guggenheim Securities, LLC research

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Source: FactSet, AlphaSense

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