



NYU



# Engineered Progranulin: A Promising Therapeutic Approach for Autoimmune Diseases

**New efficacious TNF $\alpha$  inhibitors for the treatment of Rheumatoid arthritis and other autoimmune diseases.**

## Technology

Based on yeast 2-hybrid screens, Dr. Chuanju Liu and colleagues at NYU Langone Health showed that recombinant human Progranulin (PGRN) can inhibit TNF $\alpha$  by binding TNFR2 in a dose-dependent manner and discovered that PGRN acts as a physiological antagonist of TNF $\alpha$  signaling. Based on that observation, they engineered a recombinant PGRN peptide called Atsttrin (Antagonist of TNF/TNFR Signaling via Targeting to TNF Receptors) and showed that it inhibits TNF $\alpha$  signaling in a dose-dependent manner.

## Background

TNF $\alpha$ -TNFR signaling has received great attention owing to its position at the apex of the proinflammatory cytokine cascade and its dominance in the pathogenesis of various disease processes, and in particular, autoimmune disorders. TNF $\alpha$  blockers, including etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira), are effective anti-inflammatory therapies. Although treatment with these agents is highly effective in ameliorating disease and improving quality of life in some patients with moderate-to-severe disease, current TNF $\alpha$  inhibitors fail to provide effective treatment for up to 50% of Rheumatoid arthritis patients.

## Proof of Concept (POC) Data

As discussed in Tang et al. Science 2011, collagen-induced-Arthritis (CIA) model mice treated with rhPGRN or Atsttrin showed markedly reduced joint swelling, erythema, and gross deformity compared to PBS-treated controls. PGRN, Atsttrin, and etanercept effectively prevented the development of arthritis, based on decreased arthritis severity score and lower incidence of disease. Atsttrin was more effective than either rhPGRN or etanercept in this model and completely prevented the onset of inflammation. Histological and quantitative analysis of the tarsal joints revealed normal articular anatomy in the rhPGRN and Atsttrin treatment groups. Mice treated with rhPGRN or Atsttrin also had significantly decreased serum concentrations of proinflammatory cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-6, and COMP, and increased concentrations of anti-inflammatory cytokines IL-10 and IL-13, as compared to control mice.

Administration of Atsttrin once per week effectively inhibited or reversed disease progression in a dose-dependent manner in an early-established CIA model. Atsttrin was also more efficacious than current anti TNF $\alpha$  therapies, including etanercept (Enbrel) and adalimumab (Humira), in several preclinical inflammatory arthritis models.

## Technology ID

LIU02-03

## Category

Life Sciences/Biologics

Autoimmune Disease

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## Learn more



## Applications

Treatment of Rheumatoid arthritis, Crohn's disease, Pompe disease, Ulcerative colitis, and other autoimmune diseases

## Advantages

- Unlike Progranulin, Atsttrin does not possess oncogenic activity. May function as a tumor-suppressor (Tang and Liu, unpublished data)
- In addition to its ability to inhibit TNF/TNFR1-mediated inflammatory signaling, Atsttrin also directly activates TNFR2-mediated anti-inflammatory and protective pathways
- Has an approximately 10-fold higher binding affinity for TNFR2 and an approximately 18-fold lower affinity for TNFR1 when compared with TNF $\alpha$
- Selectively interacts with TNFR1 and TNFR2, with a higher binding affinity to TNFR2 suggesting that Atsttrin would potentially elicit fewer adverse events than PGRN
- Does not exhibit any cytotoxic effects, even at exceedingly high dosages in rhabdomyosarcoma A673/6 cells
- No overt toxicity or lethality related to Atsttrin administration was observed throughout the study
- All currently marketed anti-TNF therapies bind to the TNF $\alpha$  ligand, while Atsttrin binds to TNFR and not to TNF $\alpha$  itself. Atsttrin may be effective for patients who fail to respond to current TNFblockers

## Intellectual Property

- This technology is covered by 2 issued US patents: US8362218B2 and US9403891B2.
- The US8362218B2 application has also been issued nationally in Japan, China, and Europe

## References

1. Dr. Chuanju Liu, PhD, et al. , <https://science.sciencemag.org/content/332/6028/478.long>