# Interprotein<sup>®</sup>

# Small molecule TNF-α inhibitor

#### **Concept:**

- We identify orally active compounds that bind to TNF $\alpha$  and inhibit interaction between TNF- $\alpha$  and TNFRII.
- Such compounds can be alternatives to anti-TNFα antibodies and soluble TNF- α receptors, and anti-TNF-α therapy can be extended beyond current segments treated with antibodies and/or soluble receptor.

Acquisition of

co-crvstal

structure

data (TNFa/S-

0286)

## **Research history:**

Identification of small molecule binding site and selection of hit candidates by INTENDD<sup>®</sup>/SBSG<sup>®</sup> Identification of hit compounds by cellfree and cell-based assay systems Synthesis and evaluation of newly designed compounds

Further design based on co-crystallography data (supported by INTENDD®/SBSG®)

Increase in potency (around 10-fold from S-0286

#### Present status and future scope:

- Multiple active compounds have been identified based on co-crystal structure data (Table 1).
- Selected compounds were tested for *in-vivo* PK (i.p.) and showed relatively high plasma concentrations.
- We seek a partnership with a pharmaceutical or biotech company (licensee or collaboration partner) to examine *in vivo* pharmacological efficacy using various types of TNFα-related models and to identify lead compounds.

### Table 1: In vitro activities of representative compounds

Compound	S-0286	S-0660	S-0765	S-0871	S-0922	S-0988	S-0999	Sunesis	UCB
Cell- free assay (IC <sub>30</sub> , μM)									
TNFα-TNFR binding in AlphaScreen assay	2.6	0.54	0.75	0.82	0.28	0.46	0.24	5.4	0.37
Cell-based assay (IC <sub>50</sub> , μM)									
hTNFα-induced NFκB activation in Hela cells	8.5	1.2	1.4	0.95	0.52	2.2	1.2	2 - 6	1.4
hIL-1β-induced NFκB activation in Hela cells	43	>30	> 30	>30	> 30	28	> 30	10-30	>10
mTNFα-induced IL-6 production in C2C12 cells	Not tested	Not tested	Not tested	Not tested	0.69	1.7	1.7	Not tested	Not tested