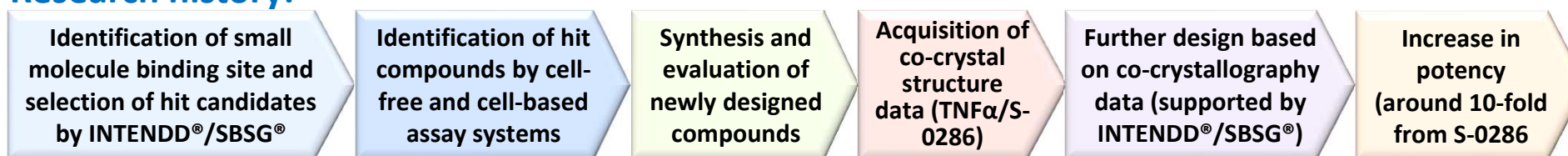


Small molecule TNF- α inhibitor

Concept:

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

Research history:



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 TNF α -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 (IC₃₀, μM)									
TNF α -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 (IC₅₀, μM)									
hTNF α -induced NF κ B activation in Hela cells	8.5	1.2	1.4	0.95	0.52	2.2	1.2	2 - 6	1.4
hIL-1 β -induced NF κ B activation in Hela cells	43	>30	> 30	>30	> 30	28	> 30	10-30	>10
mTNF α -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