Washington University in St. Louis
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SELECTIVE RANK LIGAND TO TREAT OSTEOPOROSIS

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Selective RANK ligand to treat osteoporosis

Disease indication - Osteoporosis, skeletal metastasis, and potentially rheumatoid arthritis, psoriasis, acute myeloid leukemia, and breast cancer

Drug format – Engineered Protein

Research stage and Preliminary data – Proof of concept in vitro and in vivo

- Inventors have demonstrated that this protein (mutant RANKL) inhibits osteoclast (cells that break down bone) formation in vitro and bone resorption in vivo (mice).

Target – Receptor Activator of NF-κB (RANK) and potentially other tumor necrosis factor (TNF) superfamily receptors, such as TNFR1 and DR5.

Background – Current antibody treatments for osteoporosis prevent bone loss and osteoclast formation by binding the RANK ligand (RANKL) and thereby inhibiting RANKL/RANK interactions. However, this completely removes RANKL for 7-9 months which leads to increased infection and off-target effects. For example, binding between osteoprotegerin (OPG) and RANKL suppresses osteoclast formation, but is inhibited by antibody treaments. Thus, there is a need for treatments that selectively target RANKL/RANK interactions, without affecting other pathways.

Keywords – osteoporosis, bone loss, skeletal metastasis, Receptor Activator of NF-κB, Tumor Necrosis Factor, TNF-Related Apoptosis-Inducing Ligand

Mode of action – Unlike antibody treatments for osteoporosis, researchers in Dr. Steven Teitelbaum's laboratory genetically engineered a mutant RANKL protein that prevents bone loss by **selectively** inhibiting RANK activation. This inhibition occurs in two ways. First, the mutant RANKL protein preferentially binds to RANK and not to OPG to avoid detrimental off-target effects. Second, it prevents osteoclast formation and bone loss by inhibiting RANK signaling.

Furthermore, RANKL is a member of the TNF superfamily and drugs that target this class of molecules are fraught with off-target effects from non-specific interactions. The methods used to engineer the mutant RANKL could potentially be generalized to create additional therapies directed toward other TNF superfamily receptors (such as TNFR1 for rheumatoid arthritis and psoriasis or DR5 for acute myeloid leukemia and breast cancer).

Competitive edge –

- **Selective inhibition** – Mutant RANKL does not interact with OPG, leading to less off-target effects

and potentially less risk for infection
- **Potential platform to target other TNF superfamily receptors** – Genetic engineering method could be generalized to generate therapeutics that selectively inhibit other pathological TNF superfamily pathways

Publication – Warren, J. T., Nelson, C. A., Decker, C. E., Zou, W., Fremont, D. H., & Teitelbaum, S. L. (2014). Manipulation of receptor oligomerization as a strategy to inhibit signaling by TNF superfamily members. *Science Signaling*, *7*(339), ra80.

Patent status – Patented

- Oligomers for TNF superfamily inhibition (US Patent No. 9,914,761)
- Additional Patent Application Pending

Web Links – Steven Teitelbaum Lab Website