



## 2020 IMPACT CIRCLE

### ***Natural Killer cells; one treatment to prevent cancer and aging***

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**Unmet Need:** Many compound-based anti-aging interventions are either too weak or have undesirable side effects that limit their use in healthy people. To have a REAL effect on health and lifespan in the healthy population we need to rethink medicine. We already have the technology to go beyond compounds by engineering immune cells to fight cancer in our bodies. Live cell interventions can potentially out-shine the performance of drug-based interventions and yet they have never been used in aging.

**Background:** Senescent cells are thought to drive aging. Innovative anti-aging interventions use senolytic drugs to kill senescent cells and consequently prevent aging and age-related disease. However, many of these senolytic drugs can also kill healthy non-senescent cells. This collateral damage constrains the use of these drugs in the healthy aging population. In addition, not all senescent cells are bad; “good” senescent cells can promote cancer cell killing. Killing bad senescent cells without killing good senescent cells requires an intelligent design beyond what these current drugs can do. Cytotoxic T-cells (T-cells) from the immune system can make such decisions and are already being infused into patients to kill cancer cells. Their immune cousins, natural killer cells (NKs), have also been proven to be safe cancer cell killers in FDA phase I clinical trials. NKs and T-cells can make “intelligent decisions” because they have special receptors that allow them to ask cells whether they are cancerous or not. The receptors on T cells and NKs are different; the ones in T cells are far smarter at “catching” cancer cells. However, only the receptors in NKs are able to ask questions about senescence. Fortunately, as of last year, scientists have been able to engineer T cell receptors into NKs to make them as smart at catching senescent cells as T cells are at catching cancer cells. This can potentially make them infallible at killing “bad” senescent cells without killing “good” senescent cells or non-senescent cells while also killing cancer cells.

**Novel Hypothesis:** NK cells engineered to express T cell receptors (TCR-NK) that are selective for senescent cells will provide improved treatment efficacy and safety over senolytic drugs and can double as an anti-cancer intervention.

**Proposal:** Engineer TCR-NKs and test them in cultured cells (*in vitro*) and in mouse (*in vivo*) models of aging and age-related diseases.

**Impact:** Live cell treatments based on NKs can potentially go far beyond what a synthetic or natural senolytic drug can for aging or age-related disease. This would represent a paradigm shift that could change our concept of modern medicine.

**Specialized Equipment Needs:** \$100k to cover expenses for 1-year research project including primary human cells, human cell lines, genetic engineering, compounds and mouse models.

