The overarching aim of our seedling effort was to de-risk the idea that viruses could be engineered into therapeutics, known as Therapeutic Interfering Particles (‘TIPs’), using the virus HIV as a model system. By engineering TIP prototypes that were shown to reduce HIV levels >10X in cell-culture—while having no effect on the viability of healthy, uninfected cells—we directly achieved this aim (Aim I of our proposal). The secondary aim (Aim II) of the proposal was to demonstrate, via mathematical modeling, that engineered TIPs could have indefinite, population-scale impact. To achieve this aim, we developed novel multi-scale models that connected the measured within-cell TIP dynamics achieved in Aim I with the predicted population-scale impact of these TIP prototypes on HIV prevalence levels. We further calculated cellular design constraints (e.g., genomic RNA expression levels) to guide the development of TIPs with predicted population-scale efficacy. Finally, we demonstrated the evolutionary robustness of TIPs against a key route of HIV mutational escape. Our modeling results de-risking the TIP approach were published in PLoS Computational Biology this past year.

N/A as all established goals and metrics of success were achieved.

Our seedling successes in (experimentally and computationally) demonstrating the feasibility of the TIP therapeutic concept have led to the now community-wide DARPA Intercept Program. We will be continuing to develop, test and transition TIPs as part of that program.