

## SIGNIFICANCE

We believe this proposal is highly significant for three reasons. First, this proposal is rooted in the ReFRAME compound collection, a small-molecule repositioning library developed by our team [1]. The ReFRAME collection has several properties that will greatly contribute to the success and rigor of our proposal:

- *Largest open small-molecule repositioning set.* Comprised of 13,000 compounds, ReFRAME includes nearly all small molecules that have been FDA-approved, reached clinical development, or undergone significant preclinical profiling (**Figure 1**) [1]. The ReFRAME collection is significantly larger than other similar initiatives (e.g., [2–5]), which each contain 3000-4000 compounds.