

The Emory-Sage-SGC-JAX TREAT-AD Center: Systematic target prioritization and tool generation for emerging Alzheimer's disease targets

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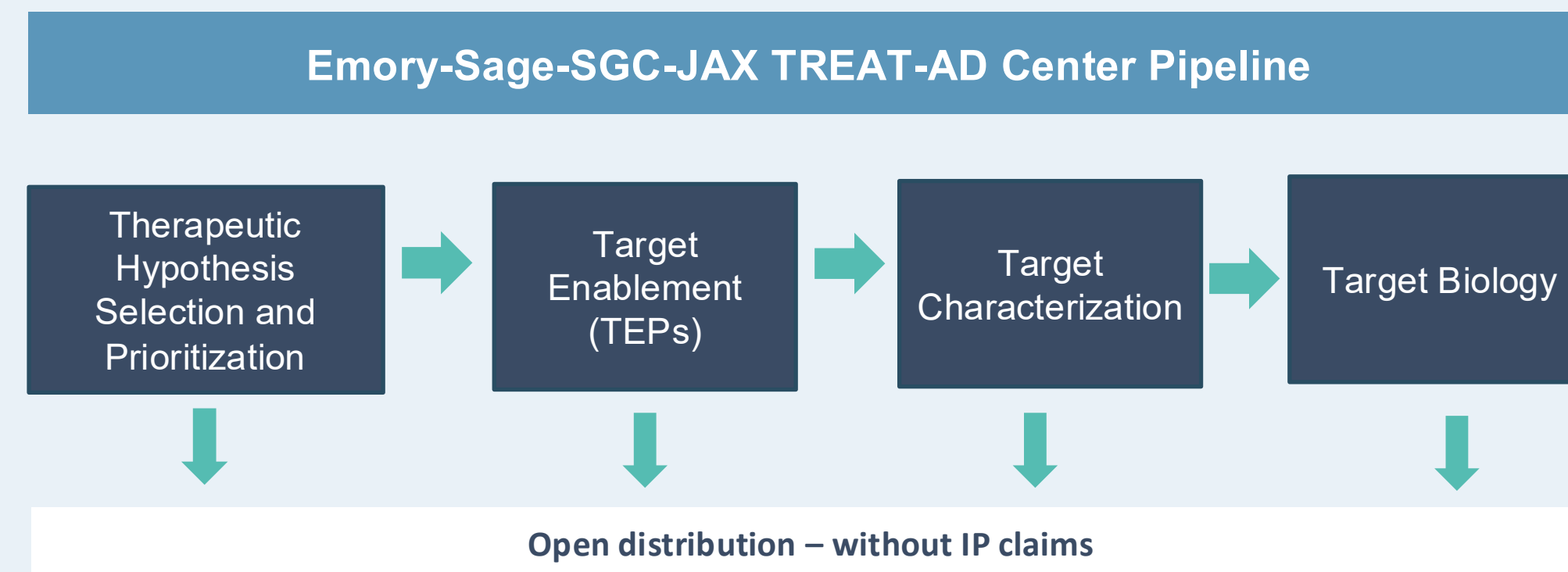


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INTRODUCTION

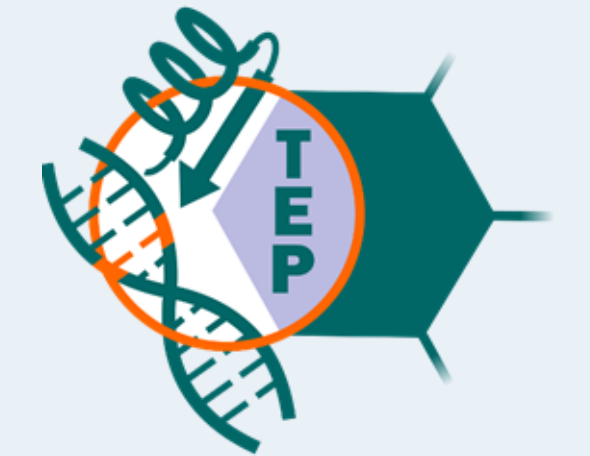
Abstract. The drug development landscape for Alzheimer's disease (AD) remains critically underpopulated, owing not only to the complexity and heterogeneity of the disease, but also to the historically narrow range of molecular targets and biological hypotheses explored for therapeutic intervention. **The Emory-Sage-SGC-JAX TREAT-AD Center is specifically focused on diversifying and reinvigorating the early drug discovery pipeline.** Its primary objective is to identify, prioritize, and de-risk understudied AD targets, with a sustained emphasis on experimental tool development and the timely, transparent dissemination of all resulting data, knowledge, and resources to the broader research community.

To this end, the Emory-Sage-SGC-JAX TREAT-AD Center adopted the concept of a **target enabling package (TEP)** to bridge the gap between target discovery and new therapeutics and to stimulate drug discovery by catalyzing investigation across the field for potential therapeutic pathways. *Our aim is to allow for rapid exploration of emerging therapeutic hypotheses and novel AD therapeutic targets and initiate early-stage drug discovery campaigns against the enabled targets.*



Target Enabling Packages (TEPs):

The Center develops and openly disseminates TEP resources that can enable independent evaluation by independent research teams and foster collaborations. By providing validated resources for emerging AD targets with no restrictions we aim to test hypothesis and derisk targets quickly.



A TEP report may include a variety of TEP components such as:

- Knockout cell lines
- Validated antibodies
- Purified protein
- Crystal structures
- Biochemical assays
- Biophysical assays
- Target engagement assays
- Functional modulators

✓ TEP Component	100
✓ TEP Report	62

RESULTS

Target ID and Prioritization

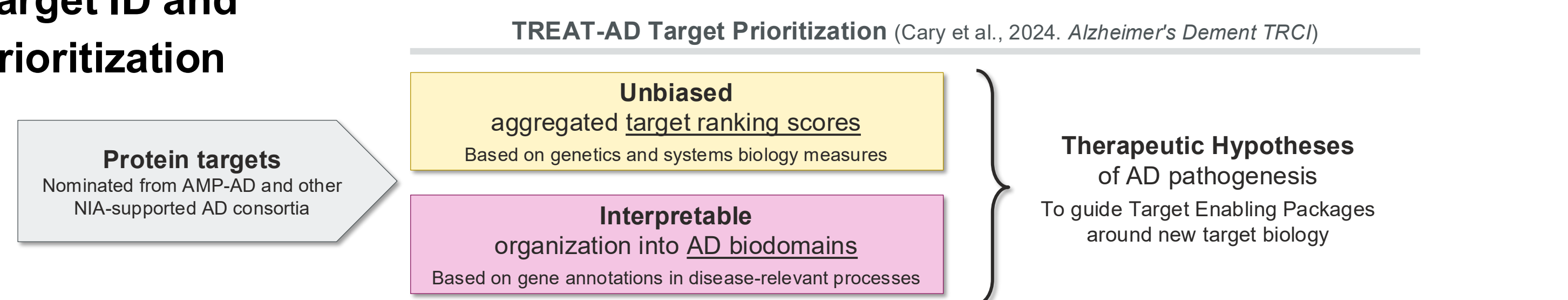
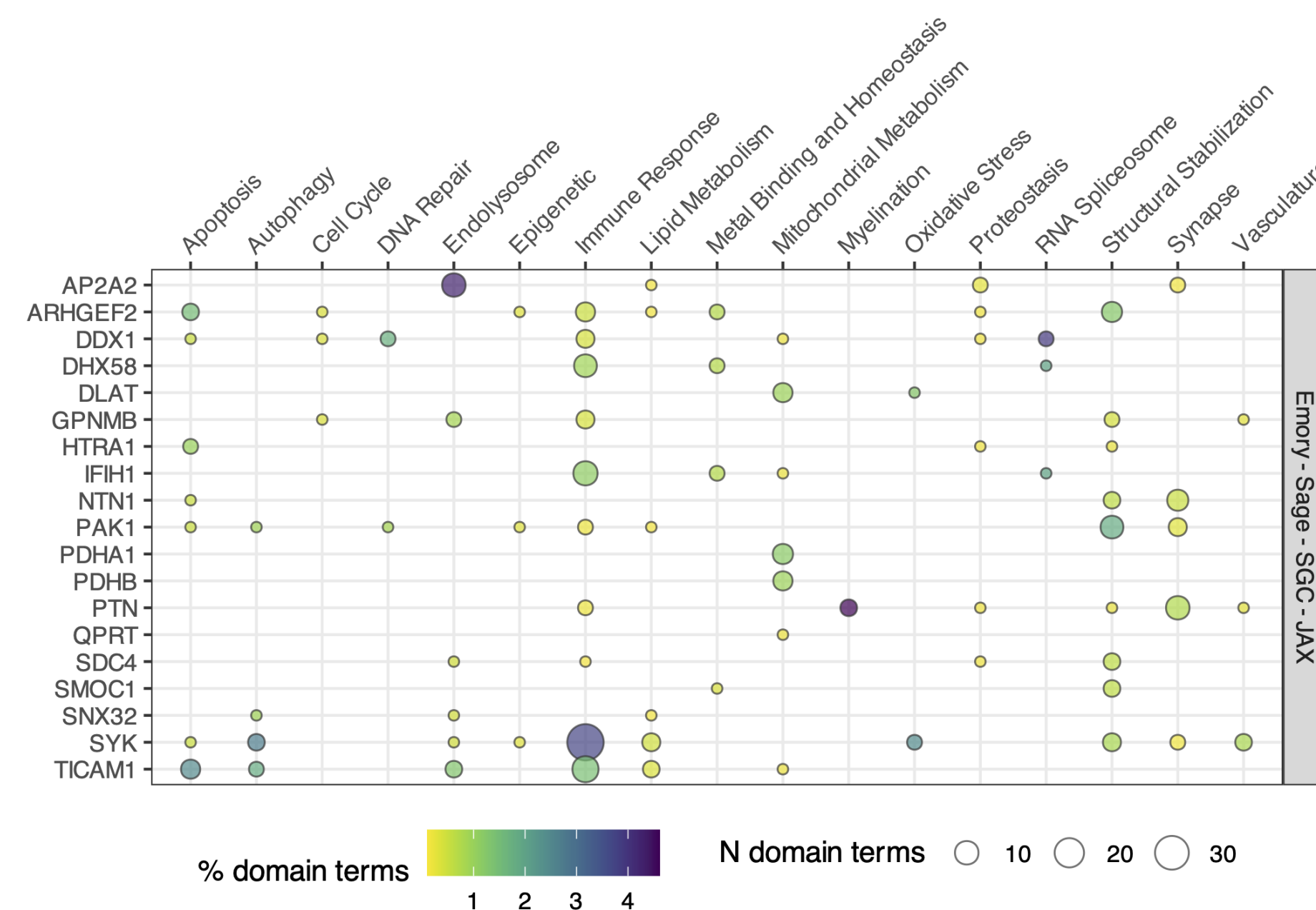


Figure 1. The target portfolio was assembled by evaluating prioritized understudied proteins by the AMP-AD consortium and additional NIA-supported AD consortia. Nominated targets were evaluated by calculating an unbiased AD risk score and then mapped to 19 biological domains ("biodomains") that describe and codify the different processes that are dysregulated in AD and prioritized based on multiple lines of evidence for overall AD-risk. Targets that meet criteria for development are evaluated to identify a set of experimental reagents necessary for hypothesis testing.

Target Enablement

Our Center develops and distributes experimental tools and reagents (TEPs) for emerging AD targets to enable the community to pursue independent studies.

Figure 2. Biological domain annotations of representative TREAT-AD targets are indicated with points for 17 representative biodomains. The size of the point indicates the number of biodomain GO terms to which the target is annotated, and the color indicates the percent of all GO terms in the biodomain that this number represents.



Target Characterization and Target Biology

Our Center uses validated probes developed from TEPs to generate target and therapeutic hypothesis-relevant biological data (Target Characterization) to guide future collaborative target validation and hypothesis testing (Target Biology), lead target is PAK1 (PMID: 41451871).

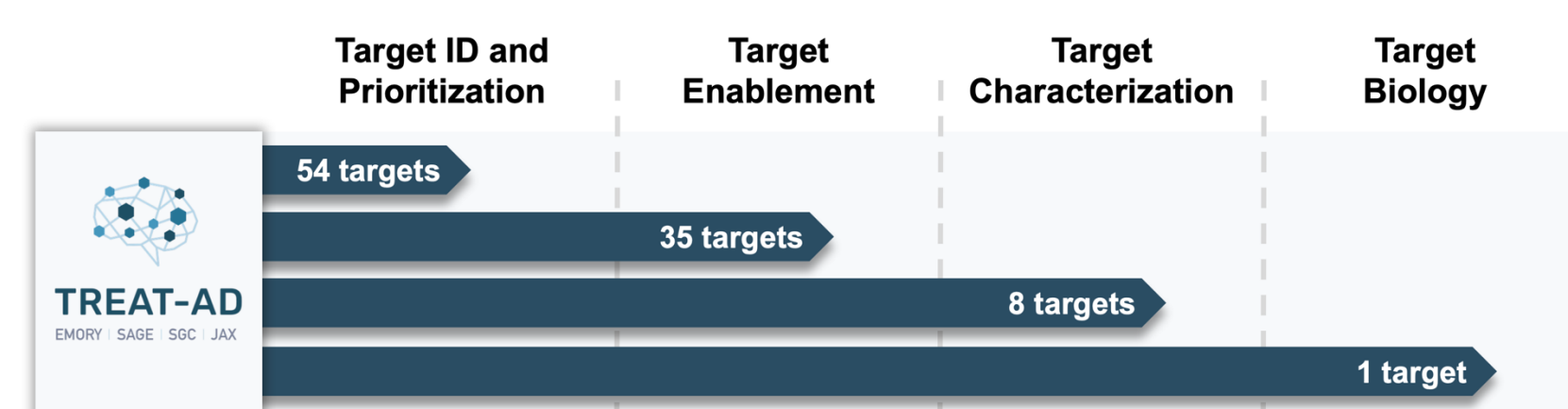
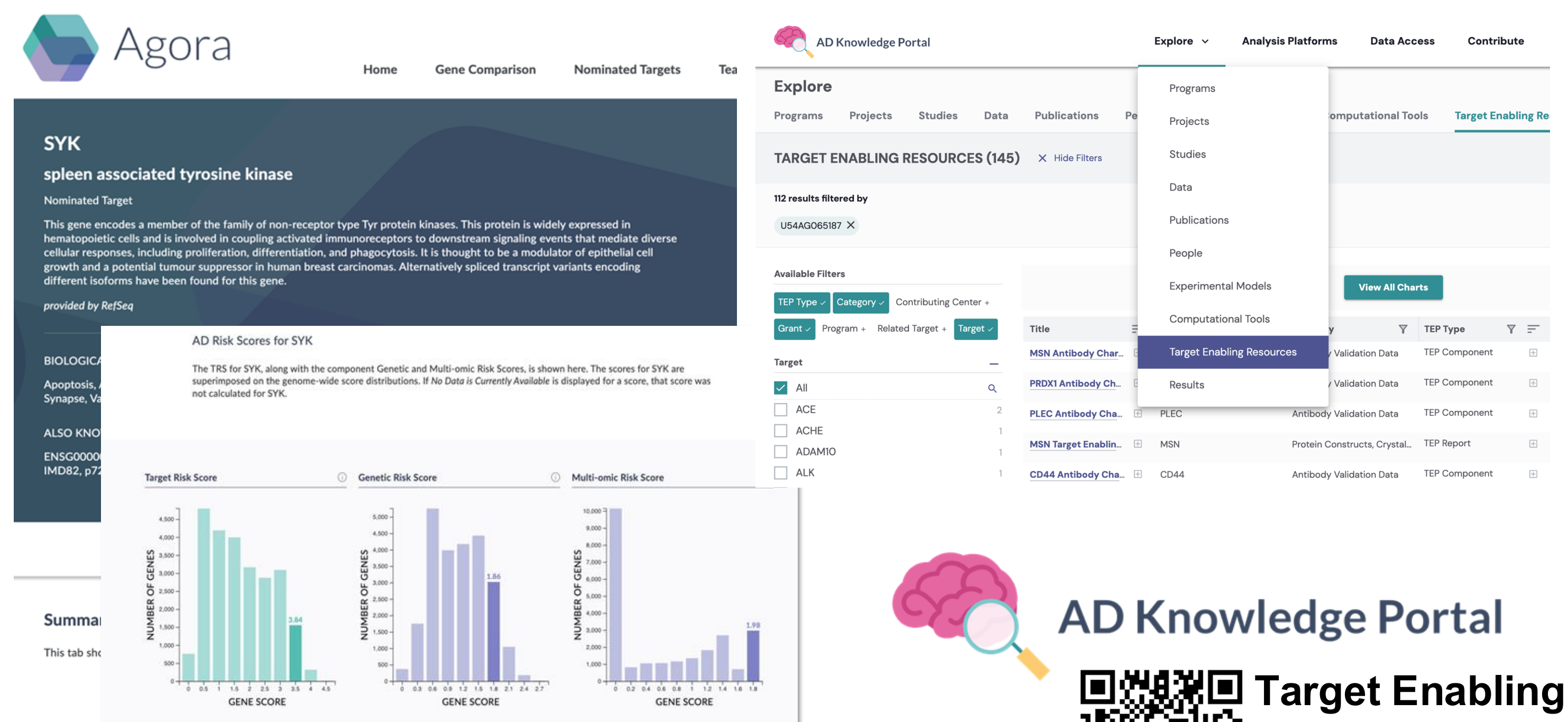


Figure 3. Overall center pipeline across workstreams with total number of targets being worked on. The full portfolio can be found on treatad.org

Data and Tool Dissemination

Target informatics, including the AD Risk Scores and Biological Domains, are shared on Agora results explorer. Available TEPs, TEP components, biodomains, associated GO terms, and annotated genes are openly shared with the scientific community through the AD Knowledge Portal.



CONCLUSIONS

The open drug discovery approach of TREAT-AD is aimed to de-risk potential AD targets, catalyzing robust and independent evaluation of a diverse portfolio of promising yet untested AD therapeutic hypotheses. We have prioritized more than 50 understudied targets for TEP development. All data, protocols, reagent sets, and chemical tools are being made widely available on the AD Knowledge Portal.



Target Portfolio

The full TREAT-AD target portfolio and progress dashboard can be found on <https://treatad.org/data-tools/target-dashboard/>

CONTACT US: Interested in collaborating? Reach out to us at treatad.info@sagebionetworks.org

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