TARGETS TO THERAPIES: A NEW TARGET DE-RISKING INITIATIVE AT MJFF

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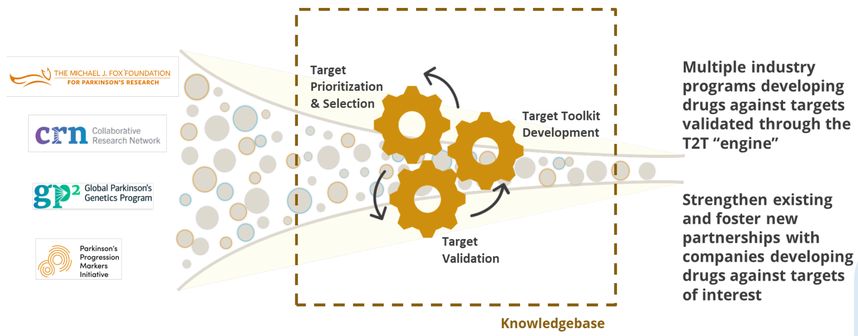
Targets to Therapies (T2T) Program

The T2T collaborative initiative seeks to identify targets with the most promising clinical potential and support their de-risking and relevant tool development, to enable rapid therapeutic development. The ultimate goal of T2T is to speed translation of promising biology into therapeutic pipelines. Our approach includes establishing a community of academic researchers, industry researchers and investors from the program's inception to enhance the likelihood of success. T2T is not focused on advanced targets such as LRRK2, GBA, SNCA, NLRP3, Parkin/PINK1.



Multiple industry programs developing drugs against targets validated through the T2T "engine"

Strengthen existing and foster new partnerships with companies developing drugs against targets of interest

T2T Program Governance & Prioritization & Selection Core

In 2024, we launched T2T by establishing our governance committee to guide us on our strategy and vision for the initiative. We also established our Prioritization and Selection (P&S) Core to help us prioritize and nominate targets for validation efforts through additional MJFF investments. This core is led by Darryle Schoepp, Virginie Buggia-Prevot and Steven Braithwaite and consists of a network of advisors with drug development expertise from large and small biopharmaceutical companies, venture capital groups, academic and nonprofit institutes to define a framework for prioritizing PD-relevant, potentially druggable targets.

GOVERNANCE COMMITTEE

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John Dunlop, *Aliada Therapeutics*
Stacie Weninger, *F-Prime*
Karoly Nikolich, *Stanford University*
Rob Malenka, *Stanford University*
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Sonya Dumanis, *Coalition for Aligning Science*
Todd Sherer, *MJFF*
Brian Fiske, *MJFF*
Michelle Durborow, *MJFF*
Sohini Chowdhury, *MJFF*

PRIORITIZATION & SELECTION COMMITTEE

Virginie Buggia-Prevot | **Darryle Schoepp** | **Steven Braithwaite**

Subject Matter Experts

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Ben Logsdon, *Cajal Neuroscience*
Bruce Leuchter, *Neurvati/Blackstone Life Science*
David Stone, *Cerevel Therapeutics*
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Steve Wood, *Neuron23*
Tina Schwabe, *Nine Square Therapeutics*
Tom Otis, *Lario Therapeutics*

Support Team

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Pooja Mukherjee, *UC Berkeley*
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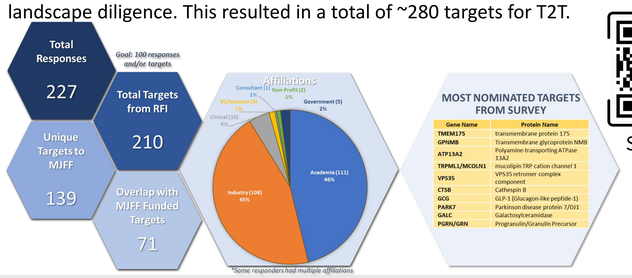
Kushan Chowdhury, *UCLA*
Joshua Crapser, *Stanford University*
Rita Marreiros, *Chan Zuckerberg Biohub*
Shima Rastegar, *UCSF*
Nicolás Wiggenhauser, *Stony Brook Univeristy*
Wendy Hung, *UCSF*

Step 1: Target Landscape Analyses

MJFF deployed a survey to the PD research community to bolster our internal target landscape diligence. This resulted in a total of ~280 targets for T2T.



MOST NOMINATED TARGETS FROM SURVEY

Gene Name	Protein Name
TMEM175	transmembrane protein 175
GPNMB	Transmembrane glycoprotein NMB
ATP13A2	Polyamine-transporting ATPase 13A2
TRPML1/MCOLN1	mucolipin TRP cation channel 1
VPS35	VPS35 retromer complex component
CTSB	Cathepsin B
GCG	GLP-1 (Glucagon-like peptide-1)
PARK7	Parkinson disease protein 7/DJ1
GALC	Galactosylceramidase
PGRN/GRN	Progranulin/Granulin Precursor

SCAN ME

Step 1: Target List February 2024

Step 2: Light Scorecard & Initial Prioritization

As a first step, we defined the ideal portfolio for the first iteration of this program:

- ✓ Focus on disease modifying targets
- ✓ Maintain diversity across disease relevant pathways
- ✓ Establish a diverse target portfolio based on the "stage of advancement"
  - ❖ **Stage 1:** No tool compounds
  - ❖ **Stage 2:** Tool compounds available
  - ❖ **Stage 3:** Clinical assets available (CNS and non-CNS)
- ✓ Developed a light scorecard to narrow down the targets to ~59 targets

Light scorecard heatmap

			LIGHT SCORE CARD					SAFETY CATEGORIES		
Real Gene ID	Protein Name	Stage of advancement (updated 4/25/24)	Genetics	Target MOA in PD	Target Biology in Patient Samples	Druggability	Expression in relevant tissue in PD	Human phenotypes associated with genetic mutations at the target locus	Human liabilities based on clinical trials	Adverse effects in preclinical models, including CNS
			5	4	3	2	1			
			Go to "Primary Data Sources" tab to get details on accessing primary data for each category							
TMEM175	transmembrane protein 175	Stage I	2	2	2	1	2	no	not stage II	yes&CNS
CTSB	Cathepsin B	Stage III	2	2	2	1	2	yes	no	not stage I or II
CD38	CD38	Stage III	2	1	2	2	2	no	yes	not stage I or II
GPNMB	Transmembrane glycoprotein NMB	Stage I	2	2	2	1	1	yes	not stage III	yes
VPS13C	vacuolar protein sorting 13 homolog C	Stage I	2	1.5	2	0.5	2	yes	not stage III	yes
VPS35	VPS35 retromer complex component	Stage I	2	1.5	2	0.5	2	yes	not stage III	yes&CNS
PARK7	Parkinson disease protein 7/DJ1	Stage I	2	1.5	1.5	1	2	yes	not stage III	yes&CNS
MAPT	microtubule associated protein tau	Stage III	1	1.5	1.5	2	2	yes	yes	not stage I or II
NFE2L2	NFE2 Like BZIP Transcription Factor 2; NRF2	Stage III	0	2	2	2	2	no	no	not stage I or II
PARP1	Poly(ADP-ribose) polymerase 1	Stage III	0	2	2	2	2	no	yes	not stage I or II
ATP13A2	Polyamine-transporting ATPase 13A2; ATPase Cation Trasporting 13A2	Stage I	2	2	0.5	1	2	yes	not stage III	yes&CNS
FYN	FYN Proto-Oncogene, Src Family Tyrosine Kinase	Stage III	1	1.5	1	2	2	no	no	not stage I or II
DNAJC6	Dnal Heat Shock Protein Family (Hsp40) Member C6/Park19; Auxilin	Stage I	2	1.5	0.5	1	2	yes	not stage III	yes&CNS
SYNJ1	synaptojanin-1	Stage I	2	1	1	1	2	yes	not stage III	yes&CNS
KLK6	Kallikrein Related Peptidase 6	Stage I	0	2	2	1	2	yes	not stage III	yes&CNS
LAMP2	Lysosome associated membrane protein 2 A isoform; receptor and transport channel	Stage I	0	2	2	1	2	yes	not stage III	yes

	ENDOLYSOSOME	PROTEIN AGGREGATION	MITOCHONDRIA	INFLAMMATION	OTHER
Stage I. Targets with **no tool compounds** (29)	VPS13C, VPS35, ATP13A2, PSAP, RILPL1, SCARB2, SPTLC2, Rab32, GBAP1, SYNJ1, GPNMB	FBOXO7, DNAJC13, PAM, EIF2AK1	KANSL1, BECN1, ZNF746, CACNA1D, GPR37, USP15	DNAJC6, KLK6, HLA-DRB5, RIT2, NLRP12, CD84, NOD2	TMEM230
Stage II. Targets with **reliable tool compounds** (11)	TMEM175, TFEB, TRPML1, SMPD1	AIMP2	PARK7, STING1, NRFA2, TRAP1, mPTP	CDK5	
Stage III. Targets with promising **clinical assets** (19)	CTSB, GRN, NPC1, GALC, CSNK2B	MAPT, OGA, PARP1, TGM2, DYRK1A,	GCG, NFE2L2, HMOX1, USP30, SOD1	CD38, FYN, TLR2, TREM2	

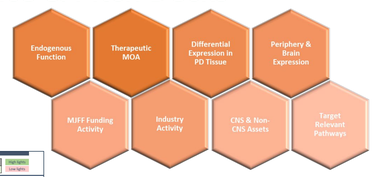
The 59 prioritized targets cover key Parkinson's disease-associated pathways and are at various stages of the discovery pipeline.

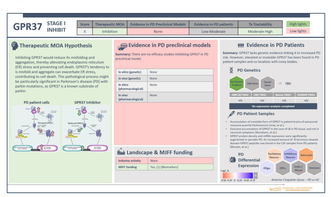
Step 2: Light Scorecard May 2024

Step 3: Deep Scorecard Summer 2024

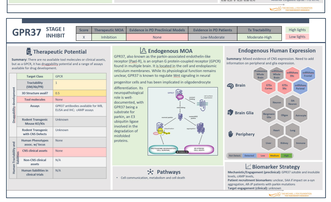
Step 3: Deep Diligence & Pitch Decks

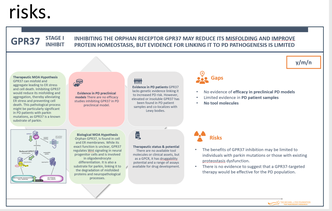
A deeper diligence was conducted on the light scorecard categories and deep scorecard categories were generated.





The information from the deep diligence was utilized to populate target "pitch decks" that summarizes information around a target and highlights the gaps and risks.





Step 4: Target Selection October 2024

Step 4: Target Selection

At the second in-person workshop held on October 15-16, 2024, the P&S committee met to review the target pitch decks and rank order the targets based on feasibility of validating the target over the next 2-3 years and impact. At this workshop, we also revealed the prototype for the target knowledgebase.

Step 5: Target Validation

Our 2025 goals include:

- ✓ Developing and implementing validation strategies for selected targets, including developing target relevant toolkits
- ✓ Publishing a perspective on T2T that outlines our approach and shares all T2T outputs
- ✓ Releasing Knowledgebase to the community