**Fall 2022 Request for Applications**

**Translational Pipeline Program**

#### **Pre-PROPOSAL TEMPLATE**

*Please use the following template to create an executive summary of your experimental plan and upload a PDF copy with your online submission. Text should be no smaller than 11-pt font and not exceed* ***2 pages, including optional references,*** *but not including the optional Therapeutic Profile Template****.*** *You may delete the instructional text in each box below to save space.*

Principal Investigator:

Institution/Company:

Project Title:

I plan to request biospecimens from MJFF for use in this project. (If yes, please download and complete the separate Biospecimen Request Pre-proposal Form.)

|  |  |
| --- | --- |
| THERAPEUTIC | Describe the specific therapeutic being developed, or that would be developed provided the specific biological target is validated as a therapeutic target in PD, whether it is intended to: alter the course of disease progression, address motor or non-motor symptoms of Parkinson’s, or treat complications of therapeutic liabilities, mode of action and how the therapeutic was identified. Please identify the strengths and weaknesses of the proposed therapeutic.  Describe the current stage of development of your proposed therapeutic/tool (e.g., high throughput screening, hit-to-lead, lead optimization, or preclinical drug candidate nomination) and discuss relevant data (preclinical and/or clinical) that justifies the progression of the therapeutic/tool to the next development stage (e.g., bioavailability, PK/PD relationships, safety).  As guidance, and for pharmaceutical compounds only, you can refer to the Therapeutic Template Profile below to describe the chemical matter. Studies to collect gaps in the data can be proposed as part of your application. |
| TARGET | Indicate the biological target and hypothesized mechanism by which it regulates PD pathogenesis and/or symptoms. For novel targets, indicate how the target is associated with human PD condition (e.g., expression changes, genetic association) and indicate any prior evidence of the beneficial effects of the target manipulation in any neurodegenerative model. |
| DEVELOPMENT PLAN | Describe and justify the proposed study(ies) that you wish to complete to move the proposed target/therapeutic forward. How do these studies fit into the big picture of developing a therapeutic for patients? Please describe any biomarker plan associated with the proposed therapy (e.g. pharmacodynamics biomarkers; exploratory biomarkers; efficacy biomarkers); If using a tool compound to validate a target, provide information detailing compound’s potency and selectivity for the target. |
| IP/PATENT LANDSCAPE | Describe any intellectual property considerations and/or restrictions that may impact further advancement of the target/therapy. |
| IMPACT | Indicate how a successful outcome of the proposed plan would lead to future development efforts, including ultimate goals and estimated timeline for moving the target and/or therapeutic into the next stage of development. |
| SAMPLE SIZE AND RECRUITMENT | FOR CLINICAL PRE-PROPOSALS ONLY:  Estimate approximate sample size and number of sites needed for recruitment. Describe how you will recruit and retain a representative population within the study’s proposed timeline. A representative population may refer to a diversity of race, ethnicity, gender, age, abilities/disabilities, sexual orientation, socioeconomic status, geographic region, or disease duration (if relevant). In your response consider your sampling frame rather than site catchment area. |
| DIVERSITY, EQUITY, INCLUSION | Please describe how you intend to incorporate diversity considerations in your proposed plan. (e.g. more diverse patient populations in clinical trials, or more diverse sample selection in pre-clinical studies). |

#### Therapeutic Profile Template (FOR pharmacological THERAPEUTIC DEVELOPMENT/clinical ONLY)

Please see below the Therapeutic Profile Template, which can be used to describe your proposed therapeutic drug/tool compound, including PK/PD, safety, and efficacy data. This template is **not** required at the pre-proposal stage, but you may choose to provide this information if available. **Provided you are invited to submit a full proposal, you will be asked to complete the template and submit it as part of the full proposal.** Please use the following information as guidance to inform you of the relevant experiments eventually needed for the advancement of the proposed therapy.

CHEMICAL PROPERTIES

|  |  |  |
| --- | --- | --- |
|  | Series 1 | Series 2 |
| MW |  |  |
| TPSA |  |  |
| cLogP |  |  |
| eLogD (preferred shaker flask method) |  |  |
| Number of hydrogen bond donors |  |  |
| Number of hydrogen bond acceptors |  |  |
| MPO score |  |  |
| Does it contain a(n) Thiol |  |  |
| Does it contain a(n) Acid |  |  |
| Does it contain a(n) Basic amine |  |  |
| Does it contain a(n) Hydroxy amine |  |  |
| Can they form covalent adducts? |  |  |
| Any structural alerts? |  |  |
| Any chiral centers? |  |  |
| If so, can they be racemized at physiological pH? |  |  |
| Is there obvious SAR? |  |  |
| How many hits have been synthesized to date? From many different structure classes? |  |  |
| How many leads have been synthesized to date? From many different structure classes? |  |  |
| Additional information |  |  |

IN VITRO/IN VIVO ADME & PK

|  |  |  |
| --- | --- | --- |
|  | Series 1 | Series 2 |
| In vitro microsomal stability: Human, mouse, rat, dog, and/or cyno T1/2; CL |  |  |
| Microsome Stability: Human T1/2; Cl (%remaining after 60mins) |  |  |
| Formulation used for IV/PO |  |  |
| In vivo rodent/ In vivo NHP PK |  |  |
| IV T1/2; CL; Vdss |  |  |
| PO Dose/Cmax |  |  |
| F% (at X mg/kg) |  |  |
| CACO2 or MDCK permeability/efflux |  |  |
| Brain/Plasma concentration; Timepoint |  |  |
| In vivo Brain/Plasma AUC ratio |  |  |
| In vivo Unbound Brain/Unbound Plasma AUC ratio |  |  |
| In vivo total and unbound brain concentration (at timepoint X) |  |  |
| Homogenate Brain Fraction unbound (Fub) |  |  |
| Plasma protein binding |  |  |
| Brain protein binding |  |  |
| Additional Information |  |  |

THERAPEUTIC CHARACTERISTICS

IS THERE A PK/PD RELATIONSHIP?

|  |
| --- |
| Click here to enter text. |

ADDITIONAL PK INFORMATION (please discuss the following: Dose(s), Route(s) of Administration, Species, Tissues; ie. Brain, CSF, plasma, Time pointes tested) PLEASE ATTACH ANY DATA/GRAPHS THAT MAY SUPPORT THIS INFORMATION ON PAGE 3

TARGET ENGAGEMENT MARKERS SELECTED:

SAFETY PHARMACOLOGY

SAFETY PHARMACOLOGY ☐Not Tested ☐NOEAL at Click or tap here to enter text. Mg/kg Click or tap here to enter text.

hERG SIGNAL ☐ Yes ☐ No

PREVIOUS CLINICAL EXPERIENCE WITH THERAPEUTIC

EXPERIENCE IN HUMANS: NON-PD:

*INDICATE DISEASE:*

EXPERIENCE IN HUMANS: PD:

DOSE RATIONALE JUSTIFICATION: (Please reference the page number in or section in the IB or discuss selection based on safety, receptor coverage, etc)