NAME

STAGE I, II, III
TX DIRECTION

HIGH LEVEL SUMMARY OF THE THERAPEUTIC POTENTIAL OF THE TARGET, HIGHLIGHT KEY GAPS AND/OR RISKS

Rank Order from Summary Slide

De-Risking Strategy & Success Criteria (within 3 years)

yes/maybe/no

Gap	De-Risking Goal	Key Experimental Approach	Risk	Exit/Success Criteria (Optional)
Gap 1:	…	▪ Experimental Approach (if applicable) ▪ Assay/Sample Type ▪ Model	X Risk… (Consider time & feasibility)	✓ Validation of… (Consider impact/strength of data package)
Gap 2:	…	▪ Experimental Approach (if applicable) ▪ Assay/Sample Type ▪ Model	X Risk…	✓ Validation of…
Gap 3:	…	▪ Experimental Approach (if applicable) ▪ Assay/Sample Type ▪ Model	X Risk…	✓ Validation of…

GUARD RAILS FOR FILLING ON THE VALIDATION SLIDE

1. **List all critical gaps:** Overview of key, addressable gaps to de-risk target in PD model or patient population (list available on slide 3 of target pitch decks)
2. **Rank the gaps** based on impact and feasibility to address in 2-3 years
3. **Outline** your derisking goal.
4. **Use the checklist** to guide key experimental approaches.
   - Do we need to conduct **in vivo** experiments?
   - Do we need **in vitro** experiments?
   - Is there a need to **create or find** a new tool molecule?
   - Should existing tool molecules be **improved**?
   - Do we need to analyze more **patient data**?
   - Is additional **genetic analysis** required?
   - Are any **critical tools, mouse models, assays, biomarkers**, needed?
5. **Risks** or obstacle of experimental approach
6. **Exit/Criteria** for a successful outcome

GPR37 STAGE I INHIBIT — INHIBITING THE ORPHAN RECEPTOR GPR37 MAY REDUCE ITS MISFOLDING AND IMPROVE PROTEIN HOMEOSTASIS, BUT EVIDENCE FOR LINKING IT TO PD PATHOGENESIS IS LIMITED

Rank Order from Summary Slide

De-Risking Strategy & Success Criteria (within 3 years) — y/m/n

Gap	De-Risking Goal	Key Experimental Approach	Risk	Exit/Success Criteria (Optional)
Gap 1: No evidence of **efficacy in preclinical PD models**	Genetic modulation of GPR37 in preclinical PD models	▪ Make KO of GRP37 ▪ Cross GPR37 KO with a parkin model (endpoints behaviour, insoluble GPR37) ▪ Cross GPR37 KO with a-syn models (determine if role of GPR37 is parkin specific)	X Risk: as role of GPR37 is limited. **There is no evidence to suggest that GPR-37 would be effective for the PD population.** X Time risk, as would need to generate animals	✓ Validation of efficacy of GPR37 inhibition (via genetic modulation) in parkin and a-syn PD associated models.
Gap 2: **No tool molecules**	Development and validation of preclinical pharmacological tools to measure GPR37	▪ *In vitro* assay: cAMP assays (unclear if GPCR subtype is established), insoluble GPR37 ▪ *In vivo model & assay:* Consider using parkin and a-syn models with similar PD associated endpoints, and GPR37 soluble and insoluble levels.	X Risk: Developing a brain penetrant GPR37 inhibitor could be challenging.	✓ Validation of efficacy of GPR37 inhibition (via pharmacological modulation) in parkin and a-syn PD associated models.
Gap 3: Limited evidence in **PD patient samples**	Assessment of GPR37 levels in PD patient CSF samples	▪ Validate presence of soluble and insoluble GPR37 in PD patient CSF samples ▪ Validate DE of GPR37 in PD patient cohorts (parkin and sporadic PD) CSF samples	X Risk: Levels of GPR37 maybe variable in PD patients. DEG levels could be limited to sub-cohort of PD patients (**Parkin mutation or those with proteostasis dysfunction**).	✓ Demonstrated robust modulation of GPR37 levels in PD patient CSF

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- During the discussion, MJFF team members and BCBA scientists have been assigned the role of filling out the slide.
- Core member will carry out the presentation on day 2.