A Quantitative Systems Pharmacology Platform of Brain and Serum Progranulin (PGRN) to Investigate Targets in Frontotemporal Dementia (FTD)

Christina M. Friedrich1, James Soper1, Colleen M. Witt1, Meghan M. Pryor1, Lauren Martens2, Dooyoung Lee2, Kelley Larson2, Matthew Townsend2, Cuyue Tang2, Holger Patzke2, Gerhard Koenig2

(1) Rosa & Co., LLC, CA, USA; (2) FORUM Pharmaceuticals Inc., MA, USA

Introduction

Frontotemporal dementia (FTD) is the second most common form of neurodegenerative dementia, characterized by extensive neuronal loss, TDP-43 pathology, and gliosis

FTD can be caused by loss of function mutations in the PGRN gene that results in a haploinsufficiency of the progranulin (PGRN) protein

Restoration of normal PGRN levels is a therapeutic strategy of interest, and plasma PGRN is of interest as a possible biomarker

It is unclear which pool of PGRN (e.g., intra- vs. extracellular) should be increased to achieve optimal therapeutic efficacy, and which functional pathway should be targeted

Objectives

- Elucidate and document PGRN production, uptake, clearance, and transport in the brain and periphery
- Formulate hypotheses for unknown or uncertain aspects of PGRN life cycle
- Identify experiments to test hypotheses, resolve uncertainties, identify/prioritize potential targets
- Support development of therapies designed to restore the expression and distribution of PGRN

Methods

- Explore the role of PGRN in FTD by collaborating on the development of a PGRN PhysioMap, a qualitative, graphical model of PGRN's known and hypothesized functions
- Develop a PGRN PhysioPD™ research platform to quantitatively integrate public and proprietary data sets into a mechanistic representation of PGRN dynamics
- Reproduce key results in simulated experiments
- Facilitate identification of knowledge gaps, generation of hypotheses, and identification of assays to resolve uncertainties and test hypotheses

Results

- The PGRN PhysioMap was designed and curated by a multidisciplinary team from Rosa and FORUM to represent PGRN life cycle in brain, CNS, and periphery (Figure 3)
- For further analysis, dynamic modeling was performed in the PGRN PhysioPD Research Platform
- The systematic process of integrating information in the PGRN Platform led to insights, development of hypotheses, and identification of experiments to resolve uncertainty

Finding #1: PGRN protein in the brain is mostly stored in neurons

- Modeling confirmed that microglial supply most of the PGRN in the brain, but total neuronal secretion rate was also significant (Figure 4)
- Neurons take up more PGRN than microglia
- Because PGRN in neurons has a long intracellular half-life, it is expected that most of the PGRN measured in brain tissue is stored in neurons (Figure 5)
- This has important implications for interpreting PGRN protein measurements in brain

Finding #2: PGRN synthesized vs. taken up has very different intracellular half-life

- Cyclohexamide chase experiments suggested long intracellular half-life
- Blocking sortilin-mediated PGRN uptake increased extracellular PGRN concentration compared to control, but had no effect on intracellular PGRN levels in neurons
- The team formulated 5 hypotheses to explain the apparent contradiction (Figure 6)
- One hypothesis that is consistent with the given data is that there is a protected pool of PGRN inside the neuron that is subject to slow turn-over dynamics
- The team discussed specific experiments that could be used to test the hypotheses

Finding #3: Dynamic analysis suggests significant revision of plasma PGRN half-life

- The only available data suggested a 40 hour plasma PGRN half-life
- FORUM preclinical data showed that when PGRN production in CNS is increased, plasma concentration increases significantly (>20%) within 4 hours
- Dynamic modeling illustrated that this level of increase at 4 hours is inconsistent with a long plasma half-life (Figure 7)
- This suggests that caution should be used in interpreting serum PGRN as a biomarker for brain PGRN level, consistent with recent evidence

Conclusions

- The process of constructing the PGRN PhysioPD Research Platform produced novel insights and recommendations
- Several experiments were identified that could resolve knowledge gaps and test hypotheses identified by the team in the process of developing the Platform
- The PGRN PhysioPD Research Platform can be used to simulate the effects of modulating different targets on increasing PGRN in intracerebral and extracellular compartments in support of developing effective treatments for FTD
- PhysioPD research supports focused pharmaceutical R&D and reduces development risk

References


For more information about this work, please contact Christina Friedrich Rosa & Co LLC 665-784-0771 cfriedrich@rosaandco.com