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

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Objectives: Frontotemporal dementia (FTD), the second most common form of neurodegenerative dementia, is characterized by extensive neuronal loss, TDP-43 pathology, and gliosis. FTD can be caused by loss of function mutations in the *GRN* gene that results in a haploinsufficiency of the progranulin (PGRN) protein. Therapies are being developed to restore the expression and distribution of PGRN. Here, we describe the development of a PGRN PhysioPD™ Research Platform, a graphical and mathematical model of PGRN production, uptake, clearance, and transport in brain and periphery.

Methods: Platform development quantitatively integrated public and proprietary data sets into a mechanistic representation of PGRN dynamics. Key results were reproduced in simulated experiments.

Results: Platform development led to interesting insights, including:

1. Microglial PGRN production far exceeds neuronal PGRN production on a per cell basis, yet neuronal PGRN production *in vivo* contributes significantly to total brain PGRN concentration due to the higher numbers and longer PGRN intracellular half-life of neurons relative to microglial cells.
2. Modeling of two proprietary datasets revealed an apparent inconsistency in the intracellular half-life of PGRN in neurons. To reconcile the apparent conflict, the team formulated and tested hypotheses, revealing insights about neuronal PGRN production and uptake.
3. There are significant differences in PGRN dynamics in periphery vs. brain, suggesting that caution should be used in interpreting serum PGRN level as a biomarker for brain PGRN level. A recent study appears to support this modeling research insight (Wilke et al. Curr Alzheimer Res. 2016;13(6):654-62).

Conclusions: The PGRN PhysioPD Research Platform has proven useful to simulate the effects of modulating different targets and investigating drug effects on increasing PGRN for the treatment of FTD.