p-377

Friday

Characterization of ARK-1252, a novel small molecule enhancer of progranulin for the treatment of frontotemporal dementia

Jean-François Blain, Christopher Holler, Angela Chen, Morgan Brand, Anna Alves, Giuseppe Astarita, Jerusha Brendel, Richard Gallegos, Gennifer Greenberg, Shawna Henry, Gerhard Koenig, Stephanie McTighe, Xiaowen Peng, John Ross, Bonne Thompson, Katherine Watters, Mary Wozniak, James Lanter, Raymond Hurst, Duane Burnett

State of the art: Heterozygous mutations in *GRN* that lead to haploinsufficiency of the progranulin (PGRN) protein cause the fatal neurodegenerative disease frontotemporal dementia (FTD-*GRN*). Complete loss of PGRN, on the other hand, leads to an early onset lysosomal storage disorder, indicating a critical role for PGRN in the lysosome. Although its exact function is unknown, PGRN is both secreted and trafficked to the lysosome where it is processed into granulins and is reported to modulate the activity of lysosomal enzymes. Currently there are no treatments for FTD-*GRN* but restoring PGRN to normal levels is a promising therapeutic strategy. **Methodology:** We performed a small molecule screen in BV-2 cells and identified novel compounds that increase progranulin secretion. After extensive characterization, one molecule was fully characterized to progress to pre-IND studies. **Results:** Compounds were identified and optimized for the ability to increase PGRN secretion from BV-2 cells. The development candidate described herein shows about 100-fold improvement in potency from the initial screening hit. Importantly, we found that the lysosomal pathway was engaged as demonstrated by the change in specific biomarkers (granulins, saposins, lipids). In addition to potency, this compound was chosen based on its excellent CNS drug-like properties, including PK and CNS penetration. Moreover, it showed excellent *in vitro* selectivity and safety profile. Finally, we established an exposure-response relationship for PGRN changes in the CSF of non-human primates, demonstrating a good *in vitro-in vivo* correlation. **Conclusion:** Overall, these data support the further development of ARK-1252 for the treatment of FTD-*GRN*.

Conflicts of interest

All authors are employees of Arkuda Therapeutics.