Design and discovery of novel LRRK2 inhbitors

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Abstract

The most common genetic causes of Parkinson's Disease (PD). The G2019S mutation is the most common inherited LRRK2 mutation, occurs in the kinase domain, and results in increased kinase activity. Increased Leucine Rich Repeat protein Kinase 2 (LRRK2) activity is hypothesized to cause PD in those who inherit GS-LRRK2, as well as other less common LRRK2 mutations, and possibly even contribute to the pathogenesis of sporadic PD in people without LRRK2 mutations. The clear advantage of these non-selective LRRK2 kinase inhibitors is their possible indication for all forms of PD. Unfortunately, multiple advanced compounds of this type of LRRK2 kinase inhibitor are accompanied by concerning untoward effects in lung and kidney (e.g., compounds developed by Genentech and Merck, GNE-7915 and MLi-2, respectively), calling into question the suitability of relatively non-selective LRRK2 kinase inhibitors for long-term treatment of older individuals. Furthermore, although these side-effects in lung and kidney have been reported to be reversible, the safety of long-term administration of such compounds is untested. We report the discovery and development of compound 38, an indazole-based, G2019S-selective (>2000-fold vs. WT) LRRK2 inhibitor capable of entering rodent brain (Kp=0.5) and selectively inhibiting G2019S-LRRK2. The compounds disclosed herein present a starting point for further development of brain penetrant G2019S selective inhibitors that hopefully reduce lung phenotype side-effects and pave the way to providing a precision medicine for people with PD who carry the G2019S mutation.

Biography

Robert K. Leśniak joined the Medicinal Chemistry Knowledge Center at Stanford ChEM-H in 2018 as a postdoctoral fellow. Before Stanford, he completed a postdoc with Professor Chris J Schofield FRS at the University of Oxford, designing novel antibiotics for the European gram-negative antibacterial engine (ENABLE) and UK Medical Research Council (MRC). Dr Leśniak also completed his DPhil under the guidance of Professor Schofield as a BHF-CRE studentship recipient, which involved the design and implementation of small molecules targeting Fe(II), 2-oxoglutarate dependent oxygenase enzymes involved in heart disease and cancer. In addition, work on small-molecule modulation of bacterial metallo-beta-lactamases to combat antibiotic resistance was also carried out. Dr Leśniak completed his MSci degree in chemistry at the University of Bristol, and worked at GlaxoSmithKline, North Carolina, developing inhibitors of bromodomains and histone acetyl-transferases. He is currently an instructor and medicinal chemist working with Professor Thomas Montine at the Stanford School of Medicine on the design of small molecules to treat neurodegeneration.

Publications

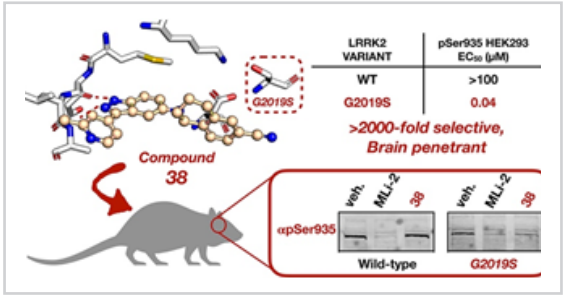
1. Discovery of G2019S-Selective Leucine Rich Repeat Protein Kinase 2 inhibitors with in vivo efficacy., R.K. Leśniak., R. J. Nichols, M. Schonemann, J. Zhao, C. R. Gajera, W. L. Fitch, G. Lam, K. C. Nguyen, M. Smith, T. J. Montine., Eur. J. Med Chem., 2021, 114080

2. Imitation of ⊠lactam binding enables broad-spectrum metallo-⊠lactamase inhibitors., J. Brem, T. Panduwawala, J. U. Hansen, J. Hewitt, E. Liepins, P. Donets, L. Espina, A. J. M. Farley, K. Shubin, G. G.Campillos, P. Kiuru, S. Shishodia, D. Krahn, R. K. Leśniak, et al., Nature Chemistry., 2021, 1-10.

3. High-Throughput Crystallography Reveals Boron-Containing Inhibitors of a Penicillin-Binding Protein with Di- and Tricovalent Binding Modes., H. Newman, A. Krajnc, D. Bellini, C. J. Eyermann, G. A. Boyle, N. G. Paterson, K. E. McAuley, R. K. Lesniak., et al., J Med Chem., 2021, 64, 15, 11379-11394.

4. Enantiomers of 2-Methylglutamate and 2-methylglutamine selectively impact mouse brain metabolism and behaviour., A. Wawro, C. Gajera, S. Baker, R. Leśniak, et. al., Scientific Reports, 2021 11 (1), 8138.

5. Enantiopmers of 4-aminopetanoic acid act as false GABAergic neurotransmitters ad impact mouse behaviour., A. Wawro, C. Gajera, S. Baker, R. Leśniak, et. al., Joural of Neurochemistry 2021 (published July 2021).



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