C-Abl Inhibition; A Novel Therapeutic Target for Parkinson's Disease

By: Abushouk, Al (Abushouk, Abdelrahman Ibrahim)[1,2]; Negida, A (Negida, Ahmed)[1,3]; Eishenawy, RA (Eishenawy, Rasha Abdelsalam)[1,4]; Zein, H (Zein, Hossam)[1,4]; Hammad, AM (Hammad, Ali M)[1,5]; Menshawy, A (Menshawy, Ahmed)[1,6]; Mohamed, WMY (Mohamed, Wael M. Y)[1,7,8]

Abstract
Parkinson’s disease (PD) is the most prevalent movement disorder in the world. The major pathological hallmarks of PD are death of dopaminergic neurons and the formation of Lewy bodies. At the moment, there is no cure for PD; current treatments are symptomatic. Investigators are searching for neuroprotective agents and disease modifying strategies to slow the progress of neurodegeneration. However, due to lack of data about the main pathological sequence of PD, many drug targets failed to provide neuroprotective effects in human trials. Recent evidence suggests the involvement of C-Abelson (c-Abl) tyrosine kinase enzyme in the pathogenesis of PD. Through parkin inactivation, alpha synuclein aggregation, and impaired autophagy of toxic elements. Experimental studies showed that (1) c-Abl activation is involved in neurodegeneration and (2) c-Abl inhibition shows neuroprotective effects and prevents dopaminergic neuronal death. Current evidence from experimental studies and the first in-human trial shows that c-Abl inhibition holds the promise for neuroprotection against PD and therefore, justifies the movement towards larger clinical trials. In this review article, we discussed the role of c-Abl in PD pathogenesis and the findings of preclinical experiments and the first in-human trial. In addition, based on lessons from the last decade and current preclinical evidence, we provide recommendations for future research in this area.

Keywords
Author Keywords: Alzheimer’s disease; c-Abelson; nilotinib; Parkinson’s disease; tyrosine kinase inhibitors; neurological diseases

Keywords Plus: TYROSINE KINASE INHIBITOR; ALPHA-SYNUCLEIN; OXIDATIVE STRESS; PKC-DELTA; CLINICAL PHARMACOKINETICS; PROTECTIVE FUNCTION; AMYLOID CLEARANCE; S-NITROSYLATION; NEURONAL LOSS; LEWY BODIES

Author Information
Reprint Address: Negida, A (reprint author)
Zagazig Univ, Fac Med, Zagazig 44519, El Shakra, Egypt.

Addresses:
1. **Psychiatric disorders among Egyptian pesticide applicators and formulators**
   By: Amr, MM; Halim, ZS; Moussa, SS
   ENVIRONMENTAL RESEARCH Volume: 73 Issue: 2 Pages: 193-199 Published: 1997
   Times Cited: 51

2. **Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies**
   By: Baba, M; Nakajo, S; Tu, PH; et al.
   AMERICAN JOURNAL OF PATHOLOGY Volume: 152 Issue: 4 Pages: 879-884 Published: APR 1998
   Times Cited: 1,018

3. **Activation of tyrosine kinase c-Abl contributes to alpha-synuclein-induced neurodegeneration**
   By: Brahmachari, Saurav; Ge, Preston; Lee, Su Hyun; et al.
   JOURNAL OF CLINICAL INVESTIGATION Volume: 126 Issue: 8 Pages: 2970-2988 Published: AUG 2016
   Times Cited: 11

4. **Adverse events associated with tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia**
   By: Breccia, Massimo; Colafigli, Gioia; Molica, Matteo; et al.
   EXPERT OPINION ON DRUG SAFETY Volume: 15 Issue: 4 Pages: 525-533 Published: APR 2016
   Times Cited: 5

5. **The role of comorbidities in chronic myeloid leukemia**
   By: Breccia, Massimo; Alimena, Giuliana
   LEUKEMIA RESEARCH Volume: 37 Issue: 7 Pages: 729-730 Published: JUL 2013
   Times Cited: 4

6. **Linked Clinical Trials - The Development of New Clinical Learning Studies in Parkinson's Disease Using Screening of Multiple Prospective New Treatments**
   By: Brundin, Patrik; Barker, Roger A.; Conn, P. Jeffrey; et al.
   JOURNAL OF PARKINSONS DISEASE Volume: 3 Issue: 3 Pages: 231-239 Published: 2013
   Times Cited: 11