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EDITORIAL

# Could cancer drugs be repurposed for use in Parkinson's and Alzheimer's?

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Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common neurodegenerative diseases with no known cure. The wealth of knowledge learned about molecular mechanisms of cancer and available treatments can be used to the advantage of neuroscientists to develop therapies for neurodegeneration. It may be non-obvious to scientists that cancer drugs which kill tumors can also be used to stop neuronal death. Repurposing of cancer drugs for use in PD and AD challenges the dogma that may often discount the critical importance of empirical evidence in science. Cancer drugs kill metastasis, but they may also exploit molecular mechanisms to achieve opposite outcomes in neurodegeneration [1]. Autophagy is a quality control mechanism shared by mitotic and post-mitotic cells, and it can clear oncogenes and reduce accumulation of toxic proteins in cancer and neurodegeneration, respectively.

Accumulation of toxic proteins, including alpha-synuclein (Lewy bodies), beta-amyloid plaques, Tau tangles, and TDP-43 are considered culprits in neurodegeneration and are often used as probable molecular biomarkers to predict disease progression. Neuronal degeneration also significantly alters neurotransmitters, that is, dopamine and acetylcholine. Progression of neurodegeneration is thought to be mediated via a prion-like mechanism [2], suggesting similarities with malignant tumors that spread by cellular contiguity or metastasize via blood and/or humoral transport. In neurodegeneration, accumulation of neurotoxic proteins may be the result of failure of clearance mechanisms via the proteasome or autophagy [3]. Autophagy is the cell's 'garbage disposal machine' that degrades toxic proteins, thus promoting neuronal survival. Preservation of neurons also maintains neurotransmitters that are necessary for normal cognitive, motor and other functioning.

A major criticism of use of cancer drugs in neurodegeneration is low blood–brain barrier (BBB) penetration. We investigated a number of US FDA-approved cancer drugs, including nilotinib and bosutinib [4] that stimulate autophagy and are well tolerated for chronic myeloid (600–800 mg daily) leukemia (CML). Less than 25% of the CML dose shows significant motor and cognitive improvements and degradation of neurotoxic proteins in animal models [4]. In animals, a small amount of nilotinib or bosutinib (<5%) enters the brain and promotes autophagic degradation of neurotoxic proteins. Nilotinib and bosutinib peak in the mouse brain 4 h after intraperitoneal injection and wash out by 8 h [1,4]. The lower dose and short bio-availability (up to 8 h) of drugs in the brain may prevent side effects and induce pulsatile autophagic degradation of neurotoxic proteins in post-mitotic neurons; and may also provide a strategy to prevent prolonged activation of autophagy that can lead to apoptosis. In human, nilotinib peaks in the plasma and cerebrospinal fluid (CSF) at 2 h ($T_{max}$) after dosing with 150 or 300 mg nilotinib. Nilotinib is not detected in the CSF ($t_{1/2}$ ~ 1.8) 3 h after dosing suggesting short bioavailability compared to plasma $t_{1/2}$ = 12.4 [5]. The CSF:plasma concentration of nilotinib is 12% and 5% after dosing with 300 and 150 mg nilotinib, respectively, but both doses yield similar motor, cognitive and biomarker effects, including 30% inhibition of CNS target [5]. Taken together these data suggest that low brain concentration and short CNS bioavailability of cancer drugs may be advantageous as some cancer drugs may induce vasogenic edema, accelerate cell loss, and exacerbate inflammation. Low CSF drug concentration may not predict the desired clinical outcomes or sufficient concentration for CNS target engagement. For example, L-Dopa has been used for several decades as the most effective treatment for PD and this drug is extensively metabolized in the gastrointestinal tract or during its first passage through the liver, so relatively little arrives in the blood as intact L-Dopa and a scant (<1%) amount enters the brain [6]. Hypothetically, the small concentration of brain L-Dopa may be considered insufficient to produce favorable clinical outcomes. However, despite the low brain level, L-Dopa is still the most effective therapy for PD so far. In addition, plasma pharmacokinetics and pharmacodynamics may be meaningless for efficacy in neurodegenerative diseases because target engagement is often tested in human plasma (not CNS) or animal plasma and brain tissue. Donepezil (Aricept), the most common therapy for mild–moderate AD is known to inhibit rat brain acetylcholinesterase (AChE) at a minimal effective dose of 0.625 mg/kg and it can inhibit 50% ($ID_{50}$) of brain AChE at 2.6 mg/kg. On the contrary, the $ID_{50}$ value of donepezil to inhibit plasma AChE is much higher at 37 mg/kg [7]. These

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data suggest that no correlation may be accurately drawn between the action of drugs in the periphery and their potential effects in the brain. Therefore, cancer drugs penetration of the BBB and their efficacy or clinical relevance must be considered with experimental evidence.

There are currently around 50 tyrosine kinase inhibitors (TKIs) that are FDA-approved for cancer and my laboratory tested many commercially available compounds in models of neurodegeneration. It must be emphasized that these broad spectrum TKIs are not all equally created as some of them may share a common primary target, that is, Abelson, Src, KIT, etc., and produce different effects in the brain. Some Abelson inhibitors, including nilotinib and bosutinib reduce neurotoxic protein levels but other Abelson inhibitors increase the level of neuroinflammation, vasogenic edema, ischemia, and neuronal loss. In addition, there is no definitive disease biomarker that can be reliably measured to predict drug action in the brain, and if cancer drugs can induce autophagy and rescue neurons, then testing more cancer drugs is a strategic option to identify potential disease-modifying therapies. In a clinical study to test the effects of nilotinib in PD, we evaluated homovanillic acid (HVA) as a metabolite of dopamine based on experimental evidence from our preclinical work that shows threefold increase in brain dopamine after treatment with 10 mg/kg nilotinib for 3 weeks. These data initially raised skepticism as we could not explain the dopamine source in a mouse model that overexpresses human mutant A53T alpha-synuclein. However, these data translated to the clinical study when all patients on nilotinib began to show signs of motor and psychiatric side-effects of dopamine excess that necessitated lowering or discontinuation of dopamine replacement therapies after 48 weeks of nilotinib treatment. These data led to investigation of CSF HVA as a stable dopamine metabolite and the results showed a steady and stable increase of CSF HVA consistent with the clinical and pre-clinical results. Furthermore, because cancer drugs may have known targets and biochemical pathways, their use in neurodegeneration may help identify novel biomarkers of drug effects. Measurement of certain molecules as biomarkers of cell death like neuron-specific enolase (NSE) may not have been previously explored in PD or AD, but nilotinib treatment suggests that this molecule may serve as PD-related biomarker as

CSF NSE level was significantly reduced after nilotinib treatment in PD patients [5]. HVA and NSE could give an indication of either symptomatic or disease-modifying effects of nilotinib in neurodegenerative diseases.

Health economics may either promote or impede cancer drug repositioning. Reports of clinical trials failure in PD and AD contribute to the apprehension among scientists and patients about potential new therapies. This circumspection, although healthy, contributes to many roadblocks scientists face when repurposing a new drug, mainly via reduced governmental and non-governmental funding. More importantly, the majority of FDA-approved cancer drugs are under patent protection, raising the level of difficulty to get a marketed non-generic drug from pharmaceutical manufacturers due to caution that repositioning may uncover unknown or unexpected adverse effects that may impact drug sales. In addition, drug repositioning may face a significant hurdle when overall patent life triggers reformulation of existing FDA-approved drugs in order to garner a more profitable and prolonged patent life. This route not only prevents expediting treatments to patients but involves the risk of failure of a novel compound on safety or efficacy grounds. On the other side of the spectrum, it is estimated that it takes an average of 10years and $2.5 billion to develop a new drug (http://www.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf). Therefore, reducing the cost of research and development via repurposing cancer drugs that have known safety and tolerability profile can significantly expedite treatments to patients, alleviate caregiver burden and reduce the national socioeconomic cost.

Research and development are significantly shortened by repurposing FDA-approved cancer drugs for use in PD and AD. These drugs can rapidly advance to multicenter phase III clinical trials that may lead to FDA approval for use in neurological diseases. Cancer drugs represent a novel strategy and a potential disease modifying therapy for neurodegeneration, and they may have compelling preclinical mechanistic, human safety, and efficacy data. This opportunity represents a high-yield, short-term return on investment with the potential to alleviate the suffering of millions of patients. Expert opinions and hypotheses about the use of cancer drugs as neurotherapeutics must be subjected to rigorous scientific experimentation so empirical evidence can validate or reject the benefits of use of cancer drugs in PD and AD.

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C. Moussa has a patent application to use cancer drugs in neurodegeneration. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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