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Novel Modality of GSK-3 Inhibition For Treating Neurodegeneration

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Neurodegenerative disorders spread over millions of people worldwide and are one of the greatest threats to public health. The prevalence of these disorders is expected to grow exponentially within the next few decades due to the increase in aging population and life span with a resultant enormous social and financial burdens. There is no adequate therapies to these disorders. Therefore, there is an urgent need to accelerate the discovery and development of effective treatments.

Although neurodegenerative disorders are broad ranging and highly complex, they may share overlapping mechanism and common targets for therapeutic interventions. Glycogen synthase kinase-3 (GSK-3) is recognized as an important target in this respect. Since its discovery as a key regulator of glycogen metabolism[1], GSK-3 emerged as a multi-tasking kinase involved in multiple cellular processes. In recent years, it became evident that GSK-3 plays key roles in neurological disorders through its ability to alter behavior, cognitive functions, and neuron cell survival[2-6]. Indeed, many targets controlled by GSK-3 are critically involve in neuron deterioration and disease progression. These include, for example, the microtubule associate protein tau[7], pro-inflammatory factors[8], heat shock proteins[9], brain derived neurotrophic factor BDNF[10] and Wnt signaling pathway[11]. Worth mentioning is our recent findings that linked GSK-3 with impaired cellular clearance through negative regulation of autophagy and lysosomal activity[12]. Inefficient autophagy is coupled with accumulation and formation of typical neurotoxic aggregates in neurodegeneration conditions[13,14]. Altogether, this raise the paradigm that GSK-3 inhibition is a potent and beneficial therapeutic for neurodegeneration .

Development and design of specific inhibitors of protein kinases is a focus of many drug discovery programs. Most protein kinase inhibitors developed so far are small molecules that compete with the ATP binding site of the kinase. This type of inhibition, although powerful, often has limited specificity because the ATP binding site is highly conserved among protein kinases[15,16]. Indeed, clinically approved ATP competitive drugs are noted to carry with them the risks for severe side effects due to specificity issues and for being ineffective against drug resistance mutations[17-20]. Thus, it was clear to us that a different type of GSK-3 inhibitors that do not bind (exclusively) to its ATP binding site is a favorable choice for clinical practice.

To fulfill this requirement we focused our attention on developing substrate competitive inhibitors (SCIs) for GSK-3. These compounds are short peptides that mimic substrate sequences and bind to the substrate-binding cavity of the kinase[21]. SCIs are considered specific because the substrate binding site is less conserved among the protein kinase family[15,16], in addition, they are expected to be less prone to drug-induced resistance due to the their large binding surface. We further

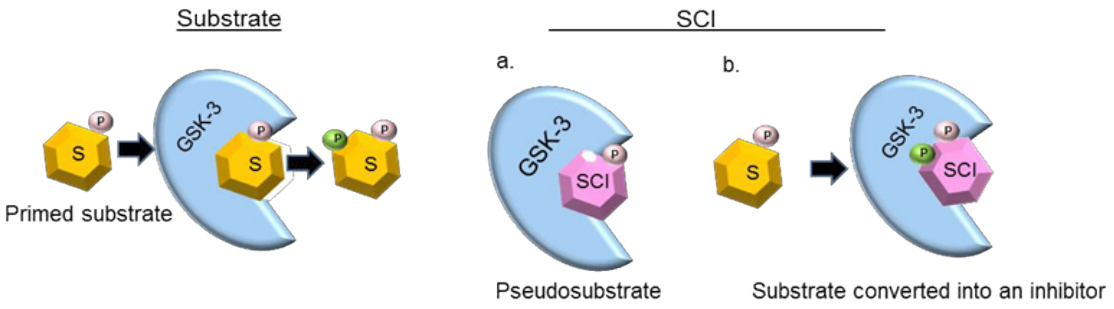

Fig. 1. GSK-3 SCIs. The primed substrate is phosphorylated by GSK-3 and dissociates from the enzyme (left panel). The pseudosubstrate SCI is a mutated substrate that can not be phosphorylated (a). The' substrate converted into an inhibitor' SCI is a substrate that upon phosphorylation remains in the substrate binding cavity (b). In both cases (a) and (b) SCIs prevent the binding of the physiological substrates to the kinase.

showed that it is possible to optimize the potency of GSK-3 SCIs by strengthening their interactions with the GSK-3-substrates binding site using computational and biological approach[22]. The first generation of GSK-3 SCIs function as pseudo- substrates[23], namely, they are 'phosphorylated invalid' substrates[24] (Fig. 1). Recently, we discovered a new type of SCI termed 'substrate converted into an inhibitor'[25]. The discovery was unexpected as we found that when we turn the pseudosubstrate back to a substrate it functions as an inhibitor. Namely, the inhibitor is a 'real' substrate, it binds to GSK-3, and upon phosphorylation (by the kinase) it turns *in-situ* into a potent inhibitor (Fig. 1). Thus, in contrast to 'normal' substrates that will immediately dissociate from the enzyme after being phosphorylated, phosphorylation of the 'substrate converted into an inhibitor' will result in a tighter binding to the kinase[25]. In fact, the 'substrate converted into an inhibitor' differs from the original sequence composition of the natural substrate in at least two positions. These simultaneous changes are key for its accompanied behavior as an inhibitor.

The use of GSK-3 SCIs indeed provided proof of concept. Treatment with GSK-3 SCIs improved Alzheimer's brain pathology and reversed cognitive decline[12,25]. They improved clinical symptoms in multiple sclerosis mouse model[26], and enhanced cognitive skills in FMRP-/- mice that represent Fragile X syndrome[27].

There are several advantages of the new modality of 'substrate converted into an inhibitor'. First, the strict requirement for being phosphorylated increases specificity, thus, limiting off target effects, Second, the inhibitor is effective only toward active GSK-3 sparing the inactive GSK-3 population 'unharmed' by the inhibitor. Third, the design of this type of inhibitor may be applied to many other protein kinases.

In summary, inhibition of GSK-3 has been considered a promising therapeutic approach for treating several neurodegenerative disorders including Alzheimer's and Parkinson's disease, depressive behavior, autism, and Huntington's disease. However, none of the GSK-3 inhibitors that were developed reached the market. Our suggestion is that 'correct' inhibition of GSK-3 is the key for a successful use of such inhibitors. Hence, the different inhibition modality based on substrate competition and, in particular, the type of 'substrate converted into an inhibitor' described here is a potential approach for fruitful treatment in the clinic.

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