Small Molecule Activators of PP2A Suggests Controlled Tau Phosphorylation as a Novel Mode of therapy for Alzheimer's disease

Jagadeesh kumar.D[1], Mohammed Toufiq[1], Priya Narayan[1], and H Nagendra[1]

[1]Sir M Visvesvaraya Institute of Technology

July 2, 2020

Abstract

Alzheimer's disease (AD) is characterized by neurofibrillary tangles (NFTs), formed as a consequence of hyperphosphorylation of tau. The extent of phosphorylation of tau is regulated by protein phosphatases (PPs) like PP1, PP2A/Bα, PP2B and PP5. Interestingly, PP2A/Bα, is a major brain tau phosphatase which account for 70% of the dephosphorylation events in brain and, its activity is known to decrease by half under AD conditions. The down regulation of PP2A leads to hyperphosphorylation of Tau in the brains of AD patients. Hence, the process of reversal of tau phosphorylation needs to be achieved by the activation of PP2A, through specific molecules, as this could pave way towards development of novel therapeutics for AD. The key objective of the current study was thus to understand the affinities of various small molecules that could function as potential activators of PP2A. Molecules like Xylulose-5-Phosphate, Dihydroxy Phenylethanol, EGCG, Memantine, Sodium Selenate, Tetralone and Quinolone exhibit strong interactions across identified binding pockets of PP2A. The investigation not only confers that there could be more than one activation site in PP2A, but also offers clues as to how these molecules facilitate restoration of the phosphatases activity, thus proposing newer avenues for the treatment of AD.

Hosted file

`Proteins _Full Document_PP2A upload.pdf` available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

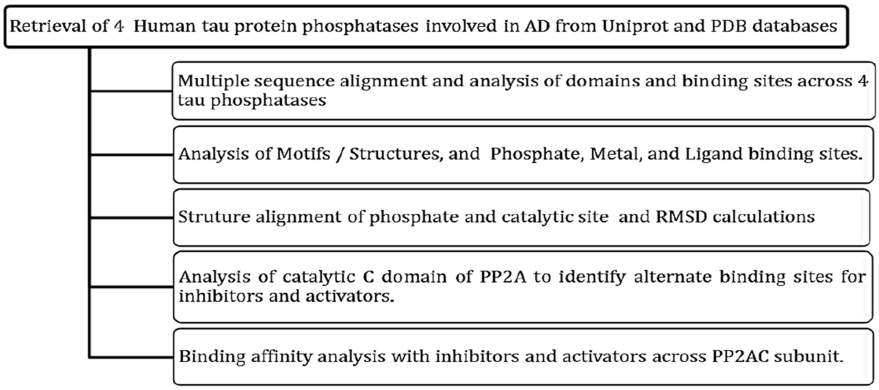
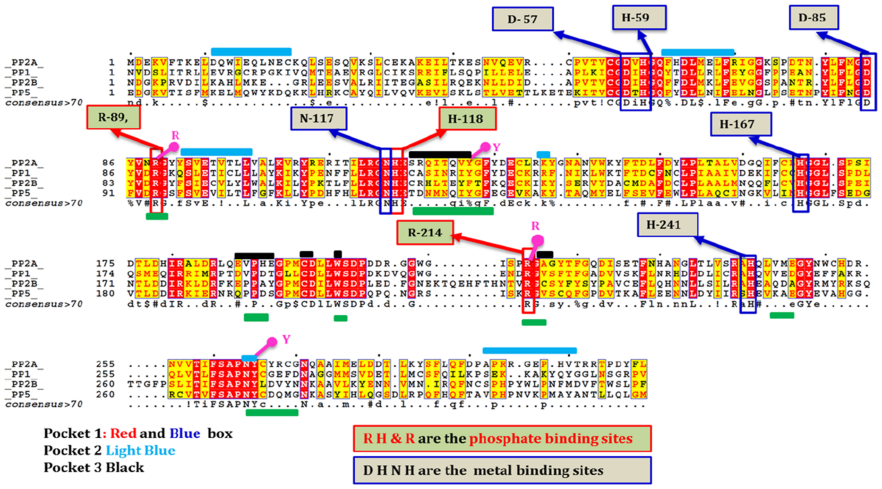
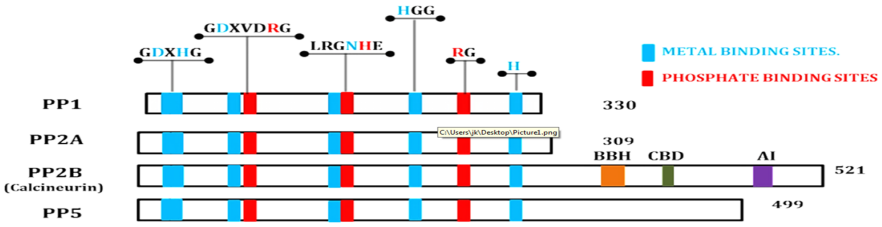
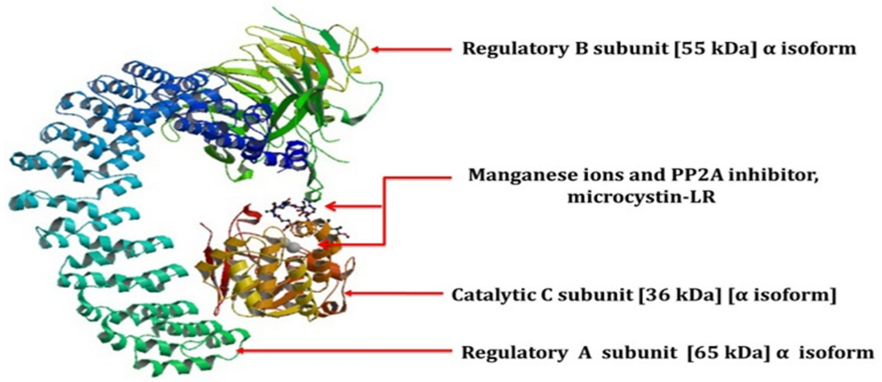
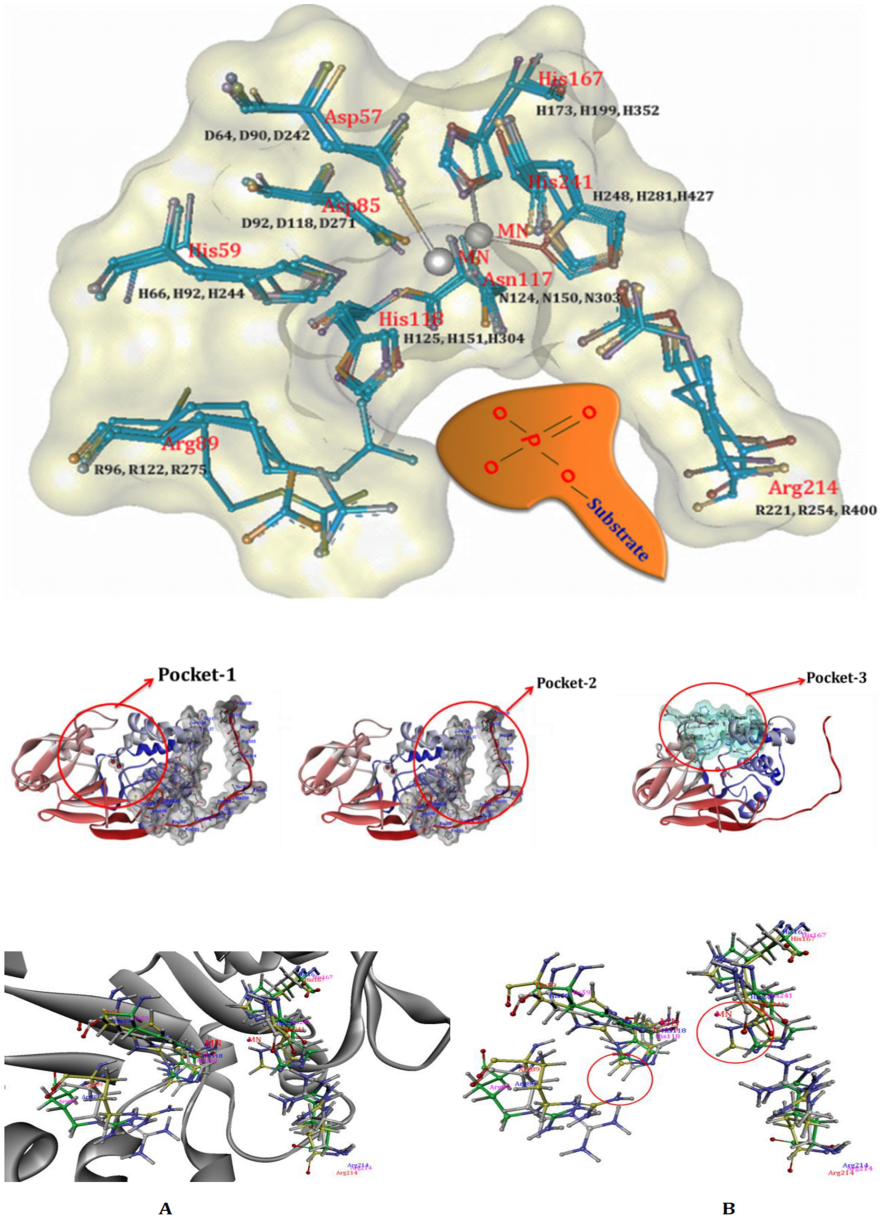


FIGURE 1: WORK FLOW CHART









Hosted file

Table I.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table II.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table III.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table IV.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table V.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table VI.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table VII.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table VIII.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table IX.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table X.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table XI.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table XII.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease

Hosted file

Table XIII.docx available at https://authorea.com/users/338916/articles/465295-small-molecule-activators-of-pp2a-suggests-controlled-tau-phosphorylation-as-a-novel-mode-of-therapy-for-alzheimer-s-disease