Breaking the conventional barriers: Discovery of a molecule that progressed to phase-II human clinical trials

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Abstract:
The 'one drug, multiple targets' concept has gained attention of both the academic and the pharmaceutical industry in recent years. To achieve such goals concept of molecular hybridization was put forward wherein two or more distinct pharmacophores are covalently linked into a single molecule.[1,3] The development of such molecular frameworks with synthetic selectivity and economic viability is still a challenging task for the pharmaceutical industry. Drugs developed through this approach can be used for the cure of infectious diseases where treatment is limited to few drugs and the known drugs have limitations such as toxicity, pharmacokinetics, pharmacodynamic and drug resistance. The benefit of using molecular hybrid is to activate different or same targets by a single molecule, and increase the therapeutic efficacy and to improve the bioavailability. Molecular hybridization approach has resulted many drug candidates with improved activity profile and some of these compounds are in clinical trials.[4] We have utilized this concept in designing antimalarial molecules and many molecules with aminiquinoline and pyrimidine phamacohpore showed low nano molar activity. Later a massive multi-institutional collaboration was started and over 700 new molecules were studies for Nurr1 activation, a potential target for Parkinson disease model and identified 15 hits out of which 3 compounds have cleared pre-clinical trials and technology has been transferred to NURRON pharmaceuticals for further development.[5-8] These molecules activate the Nurr1 enzyme which is essential for the survival of the dopamine neurons, stops the aggregation of α-synuclein protein in the brain, and promotes autophagy. Systematic studies demonstrated that these compounds can cures the Parkinson induced mice model at 5 mg/kg body weight without any toxicity and recently one of the molecule has successfully cleared phase I human clinical trials and it has moved to human phase II clinical trials.

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