## Chinese traditional medicine is characterized by inducing multi-target effects

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**Abstract**: In the past decades, single target drugs showed less therapeutic action and more side effects in treatment of complicated diseases such as tumor, AIDS, inflammation, diabetes, stroke and neurodegenerative disorders. The reason for this is that complicated diseases have multiple pathogenesis and multiple genes or pathological changes occur in many organs or in different kinds of cells. Therefore, scientists of worldwide hope to develop multi-target drugs recently traditional Chinese medicine (TCM) and their many effective components are characterized by inducing multi-target effects, the following 2 components isolated from TCM were proved in our laboratory to have multi-target effects which benefit complicated diseases. Anti-stroke drug-salvianolic acid B (Sal B): In MCAO rats, Sal B was shown to have many biological activities. Firstly, Sal B could past through blood-brain barrier (BBB) and could repair damage of BBB induced by cerebral ischemia. Secondly, Sal B improved blood flow in ischemic hemisphere with no steal blood and without hypotention, inhibited platelet aggregation a thrombosis but no hemorrhagic risk. More importantly, Sal B could inhibit three risk factors-intracellular $Ca^{2+}$ overload, excessive regeneration of free radicals, excitotoxicity which aggravate ischemic brain injuries. Thirdly, Sal B activated organism protective mechanism such as increasing neurogenesis, angiogenesis, and many anti-oxidative substances and improving energy supply. Taking all these results we believe that sal B is a good anti-stroke agent. Anti-dementia drug-(-) clausenamide: (-) Clausenamide is a novel compound isolated from clausena lansium (Lour) which is the first chiral compound having anti-dementia effect in recent years. As the content in the plant is very low, after long term of effort this compound now been chemically synthesized by our institute and the production are has reached semi-industry scale that satisfies the demand for clinical trial and hereafter therapeutic use. For pharmacology, (-) clausenamide improved cognition and inhibited Aβ pathogenesis including inhibition of Aβ toxicity and tau hyperphosphorylation. According to the new theory "Synaptic loss=AD", a good anti-dementia drug must be able to improve synaptic plasticity and promote synaptogenesis. Fortunately, (-) clausenamide happened to be such compound. As proved in our study that (-) clausenamide increased synaptic plasticity both in efficacy and structure. For latter, (-) clausenamide increased synaptic density and expression of growth associate protein (GAP-43) in the brain significantly. Now (-) clausenamide has been developed to phase Ⅱ of clinical trial.

**Key words**: neurodegenerative disorders; traditional Chinese medicine; clausenamide
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## IUPHAR, Guide to pharmacology and natural products

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**Abstract**: The pharmaceutical industry has struggled to provide new drugs for stroke and neurodegenerative disease using classical medicinal chemistry approaches. However there is a disconnect between single molecular targets and such severe diseases. Life style changes, particularly exercise, and some natural products, may extend life span: but what are the molecular targets? IUPHAR has built a database of the molecular targets within the human genome which is freely available, with gold standard ligands: the IUPHAR/BPS GuidetoPHARMACOLOGY (GtoP) database (see GuideToPharmacology.org). The database is unique containing information reviewed by the >90 NC-IUPHAR expert committees

with their publications (H-index 72). These expert committees consider features beyond the capability of machine-based data trawling, such as what we know and don't know, variables affecting drug receptor affinity, the crucial challenges of multiple gene products, alternative splicing, epigenetics, allostery, disease and drug ontologies. The database is being actively promoted worldwide by the main pharmacological societies, resulting in a large international user-base. This can now be extended to the molecular targets of natural products. Natural products also markedly affect cellular metabolism and I will also cover how recent human evolution selected certain molecular pathways, allowing metabolomics analysis to develop new directions for the treatment of neurodegenerative disease. IUPHAR can be a partner in developing new therapeutic paradigms, by expert assessmentof complex research areas at clinical and preclinical levels. This is a unique cooperative international initiative.

**Key words**: pharmacology; molecular targets; natural products

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# INVITED LECTURES

## Small molecule modulators of lysine acetyltransferases from natural sources: Implication in therapeutics

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**Abstract**: The altered function of any epigenetic modification also causally affects the physiological homeostasis in different pathophysiological conditions such as cancer, neurodegenerative disorders, diabetes, asthma, COPD etc. Among the different epigenetic enzymes we focus on three important classes: lysine acetyltransferases, arginine methyltransferases and aurora kinases in the context of cancer and neurodegenerative diseases. Our laboratory has discovered several small molecule modulators of these enzymes, which may serve as lead scaffolds to design new generation therapeutics. We have shown that specific as well as broad spectrum inhibitors of lysine acetyltransferases repress the oral, liver as well as prostate cancer progression in the xenografted animal model system. Furthermore, we have shown that one of the p300 specific inhibitors discovered in our laboratory potently inhibit the multiplication of HIV in a cellular system. By using a novel histone acetyltransferase activator molecule, we find that p300/CBP mediated acetylation of histones is an important inducing factor for robust neurogenesis; which presumably contributes to long-term spatial memory. Remarkably, the p300/CBP activator treatment efficiently enhances the memory of Tau mice almost to the normal level. The molecular basis of this phenomenon is being understood.

**Key words**: lysine acetyltransferases; arginine methyltransferases; aurora kinases

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## Natural product inspired drug discovery

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**Abstract**: Natural products or natural product derived drugs comprised 32% of small molecule approved drugs between 1981 and 2010. In the same period of time, 16% of small molecule approved