Parkinson's Disease Research in Mouse Model

Technology #2131

“Lead Inventor: Andreas Kottmann, Ph.D. Parkinson’s Disease Screening, Treatment Tested in Mouse Models

This mouse model is based on the conditional ablation of Sonic hedgehog (Shh) from mesencephalic dopaminergic (DA) neurons which causes an adult onset, progressive phenotype that recapitulates multiple aspects of the core pathologies of Parkinson’s disease (PD): While the basal ganglia are structural and functional unaffected in young adults in this novel model, animals develop late life onset and then progressively (1) hypokinesia and bradykinesia, then gait and eventually postural abnormalities (face validity), (2) degeneration of dopaminergic neurons of the substantia nigra pars compacta resulting eventually in reduction of dopamine availability in the striatum (construct validity) (3) responsiveness to drugs of proven efficacy in the management of PD (that is both dopamine substitution and anti-cholinergic pharmacology) which ameliorate acutely the gait abnormalities (predictive validity) (4) alterations in expression of many “PD associated disease genes” in the striatum and ventral midbrain (genetic validity).

Longitudinal analysis of neurochemical, cell morphological, cytological and pharmacological measures and gene expression establishes a stereotypic progression of pathological alterations that involves first the striatum and secondarily DA neurons of the ventral midbrain. The recombinant alleles necessary for the conditional ablation of Shh were backcrossed for more than 18 generations into C57B/6 resulting in a model in which the pathological features appear like “clockwork” in a temporally highly predictable manner. Hence, our model appears both highly relevant to the study of the etiology of PD and very amenable to the utilization of post genomic technologies for the discovery and validation of novel targets. Additional the model provides for the in vivo selection of candidate drugs of disease modifying potency. As proof of this utility we have successfully profiled dynamic alterations in trophic factor expression and “PD associated disease genes” in the basal ganglia.

Further experimentation based on our paradigm seems to offer insights into three enigmas in understanding PD pathogenesis:

a) What are the molecular and mechanistic underpinnings of the linked dopaminergic and striatal dysfunction?
b) How do multiple risk factors conspire to undermine structural homeostasis?
c) How is aging linked to the mechanism(s) that allow the spread of pathology through most of the population of DA neurons causing their extensive degeneration in sporadic PD?

Applications:
This model can be used for screening and/or validating drugs in vivo with:
• Neuroprotective potential (prior to cell death – disease modifying agents)
• Symptomatic treatment (after manifestation of PD)
• Identification and validation of novel drug targets

Licensing Status: Available for Licensing and Sponsored Research Support

Inventors

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