NeuroDetective®
INTERNATIONAL
Expert Neuroscience Research, Advancing Drug Development

ALZHEIMER'S MODELS

Alzheimer's disease is characterized by both behavioral and histopathological symptoms that develop with age, and NDI offers animal models that capture these different aspects. Especially comprehensive are two naturally occurring aged-animal models that exhibit AD-like cognitive, non-cognitive, as well as histopathological symptoms.

AGED BEAGLES

Background

- Beagles develop beta amyloid accumulations, starting around 8 years of age.
- The predominant form of beta amyloid is the 42-peptide molecule, which is also the predominant form in humans.
- Beta amyloid also accumulates in the vascular system.
- Development of beta amyloid is structure specific, starting first in prefrontal cortex.
- Aβ deposition increases progressively. By 11 years of age, over 80 percent of these animals have Aβ deposition in prefrontal and entorhinal cortex.

Behavior testing (Cognition)

- Acquisition of a visuospatial memory task shows progressive deterioration with age (Delayed-Non-Matching to Position Task).
- Allocentric spatial ability decreases with age (Landmark Discrimination Task).
- Control tests are procedural learning and egocentric spatial learning tasks, which show little age sensitivity.
- Complex discrimination learning and reversal learning tasks are also age sensitive (Oddity Task and Discrimination Reversal Tasks).

Behavior testing (Non- Cognitive Behaviors)

- General activity is lessened (Open Field Test).
- Specific exploratory behavior is diminished (Curiosity Task).
- Social behavior is reduced (Human Interaction Task).
- Sleep-Wakefulness rhythms are disrupted.

Neuropathological Assessment

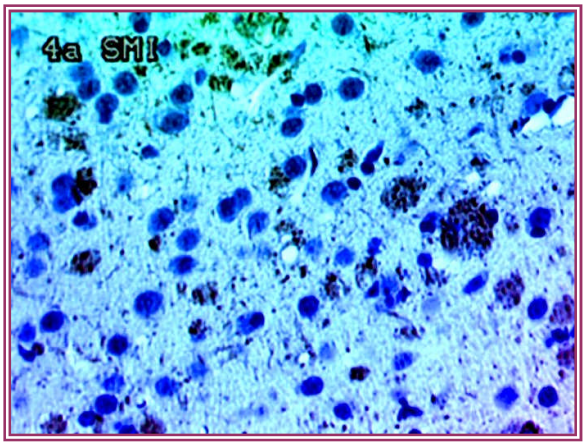
- Immunohistochemical staining for beta amyloid deposition
- Counts of apoptotic neurons
- Measurement of brain volume (MRI)

Compounds we have tested in the aged beagle model:

- **Cholinesterase inhibitors**
- **Nicotine receptor agonists**
- **Muscarinic receptor modulators.**
- **Glutamate antagonists**
- **Estrogen receptor agonists/antagonists**
- **Calcium channel blockers**
- **Vitamins**
- **Anti-oxidants**

FBN/F1 AGED RAT

Both males and females of the FBN/F1 hybrid rat strain progressively develop specific cognitive impairments during aging, in a manner characteristic of the development of human cognitive deficits in dementia. The order in which these deficits develop is: (1) an attention deficit (seen in a T-maze test and in a modification of the Barnes maze), (2) a memory deficit (seen in the moving-platform version of the watermaze test), (3) a learning deficit (seen in the classic Morris version of the watermaze), and (4) a global cognitive impairment (seen in the foraging portion of the modified Barnes maze task). Importantly, these impairments in cognition are detetectable before motor impairments develop, which in other aged rat strains occurs in parallel with age-related behavioral impairments and compromises the "cognitive" interpretation of those behavioral impairments. In addition the FBN/F1 strain displays age-related increases in ubiquitin expression in specific brain regions implicated in its cognitive impairments, making it a model for an early, pro-AD state characterized by elevated inflammatory responses and gradual cognitive loss.

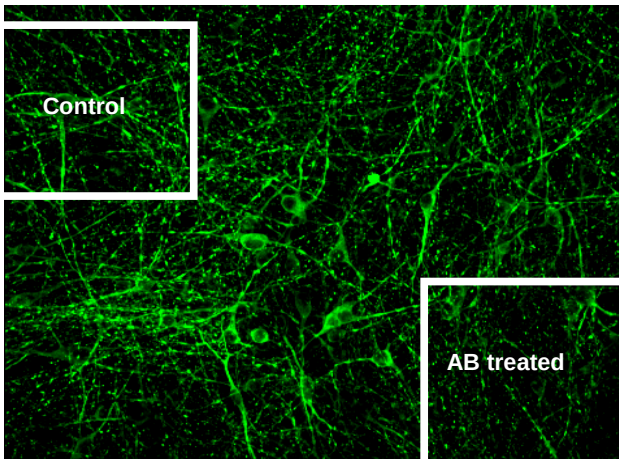


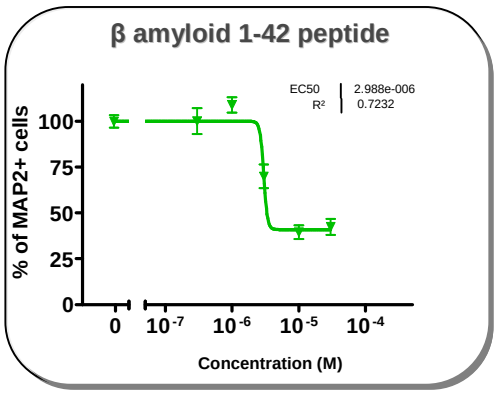
Increased ubiquitin staining in entorhinal cortex of 32-month-old FBN rat. Density of staining correlates with extent of short-term memory deficit.

IN VITRO AD ASSAYS

Aβ-induced neurotoxicity (mesencephalic cells)

We have developed a novel in vitro assay for screening potential neuroprotective agents, that uses mesencephalic neurons and MAP2 (neuron-specific) quantification. An additional capability of this assay is detection of neurotrophic as distinct from neuroprotective effects. The cultures contain dopaminergic neurons taken from embryonic rat mesencephalon, which fully differentiate in vitro, and survive for at least 30 days.





AB-INDUCED NEUROTOXICITY (NT2N CELLS)

This assay is useful for screening compounds that interfere with APP processing. The formation of intracellular Aβ is measured in NT2N cells that have differentiated into neurons. NT2N cells are used because they appear to process APP in ways similar to human neurons.

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