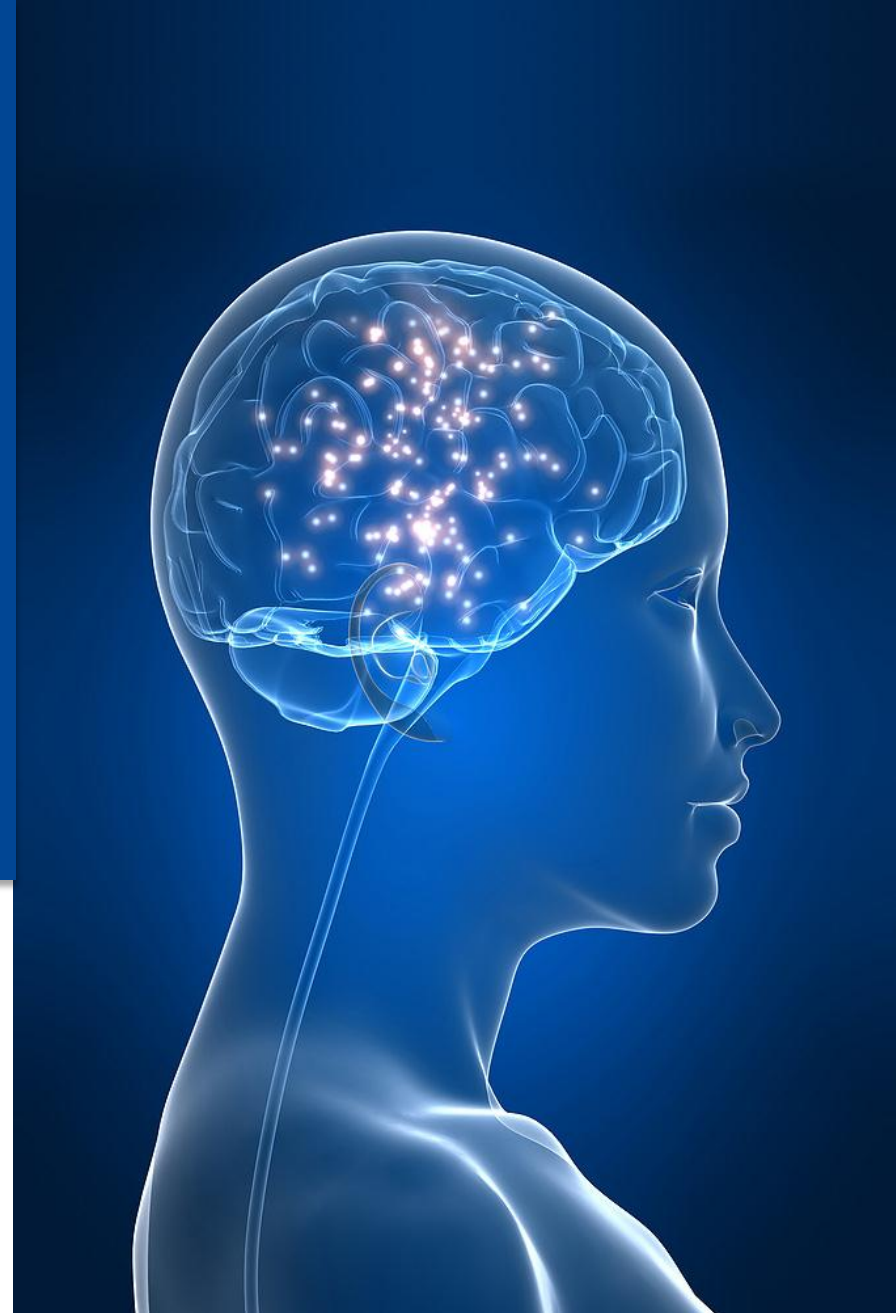


Stephen DeArmond
Lecture:
**Prionic Loops,
Dependence Receptors,
and a New Approach to
Alzheimer's Disease**

Dale E. Bredesen, M.D.
Augustus Rose Professor

Director, Easton Center for Alzheimer's Disease
Research

David Geffen School of Medicine, UCLA



30,000,000

patients in 2012

NAPA summit

160,000,000

patients in 2050

0

Cures

X Prize

Alzheimer's Disease (AD) Therapeutic Landscape

APPROVED

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Tacrine (Cognex)
- Memantine (Namenda)

- ↓ Ab production
- ↓ Aβ aggregation
- ↑ Aβ clearance
- ↓ Tau aggregation/phospho
- Cholinergic drugs
- Others

PHASE 3

- Solanezumab
- ELND005
- Bapineuzmab
- Valproate*
- Alzemed *
- Antioxidant
- Semagacestat*
- Statins
- Flurizan*
- Dimebon
- Rosiglitazone*
- EGCg
- Phenserine*

PHASE 2

- PBT2*
- AL-108*
- NIC5-15
- PF04360365
- Bryostatin-1
- Nicotinamide
- EHT-0202*
- NP12
- ACC001
- BMS708163
- Lithium*
- AN1792*
- ABT089*
- NGF
- CAD106
- AZD3480*
- SB742457
- Huperzine-A*
- PRX03140*
- EVP6124
- PUFA*
- MEM3454
- TTP448
- PF-04447943

PHASE 1

- GSK933776*
- AF102B*
- MABT5102A
- Talsaclidine
- UB311
- Begacestat
- R1450
- PF3084014
- V950
- CTS21166
- E2012*
- MK0752
- CHF5074

* Clinical Trial in AD terminated

Recent Clinical Trial Failures



The big problem with neurodegenerative disease

**Healthy
Brain**

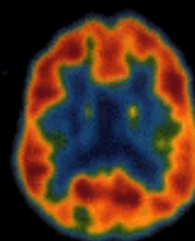


**Advanced
Alzheimer's**

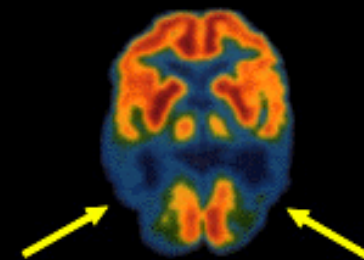
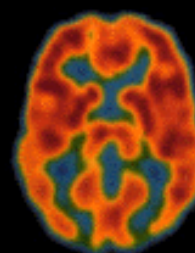
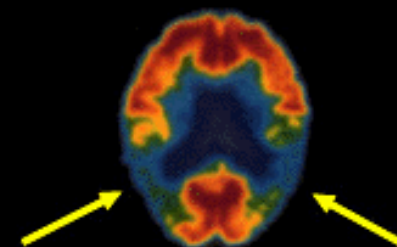


PET Scans:

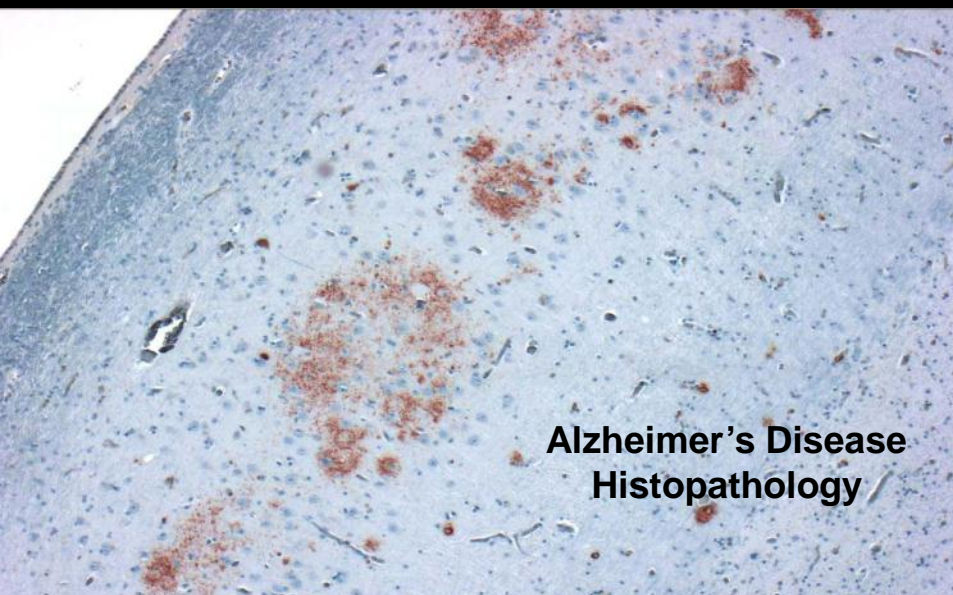
Normal



Alzheimer's



Crump Institute for Biological Imaging

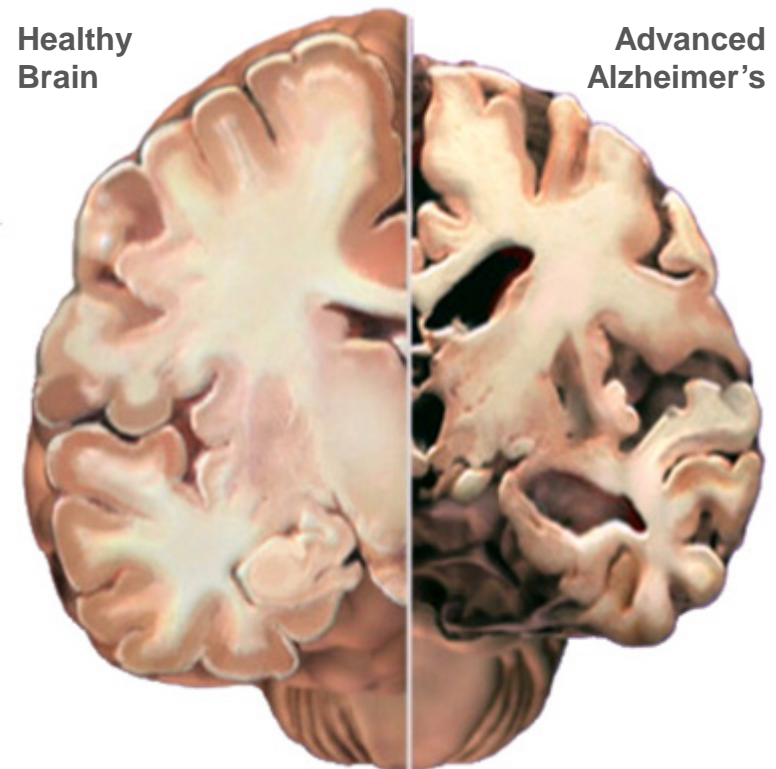


**Alzheimer's Disease
Histopathology**

The Status Quo: Alzheimer's is a disease of toxicity

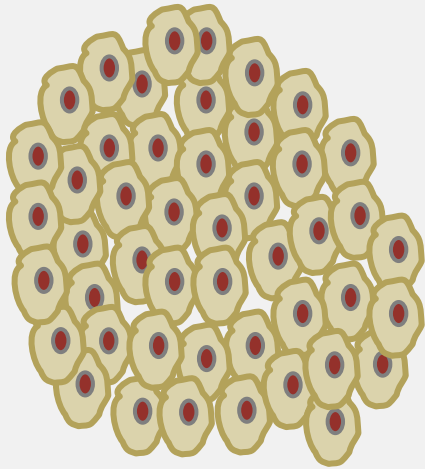
- Focus is on the chemical & physical effects of A β peptide:
 - Lysosomotropic detergent
 - Metal-binding peptide
 - Reactive oxygen species
 - Many other theories
- Approach reinforced by 50,000+ papers...all of which fail to answer key questions
- **Why do healthy brains produce A β peptide?**
- Recent results from transgenic mice

Physicochemical effect or signaling imbalance?

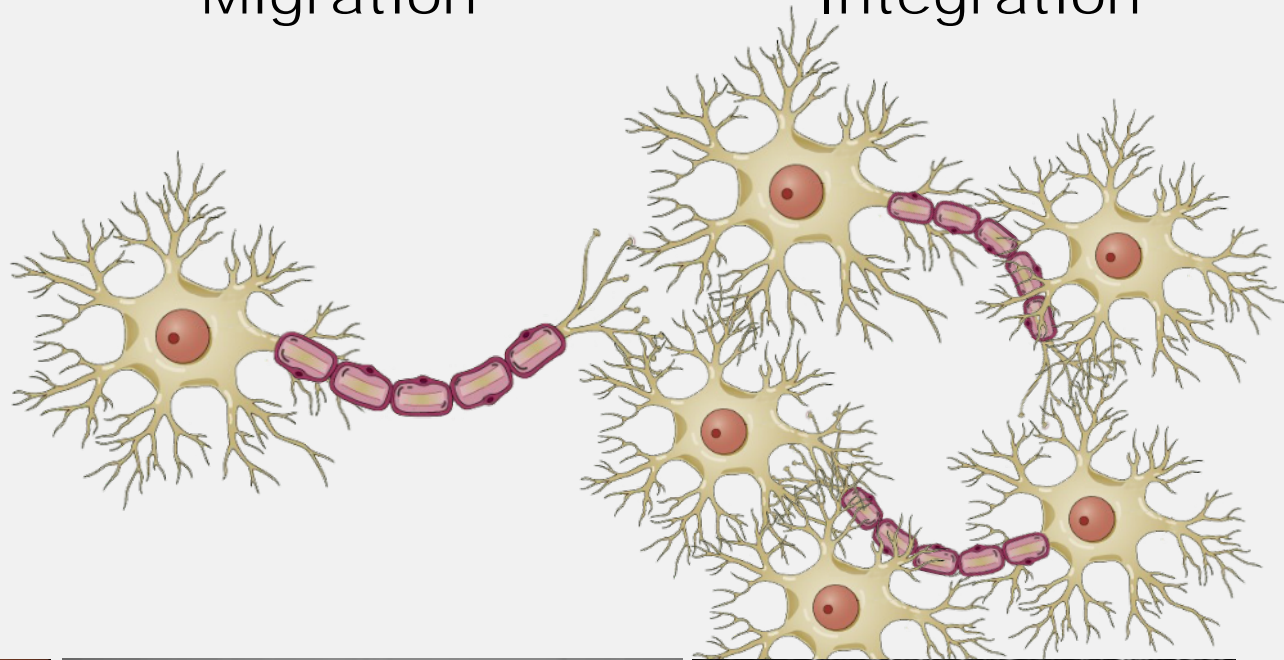


A New View of Alzheimer's Disease

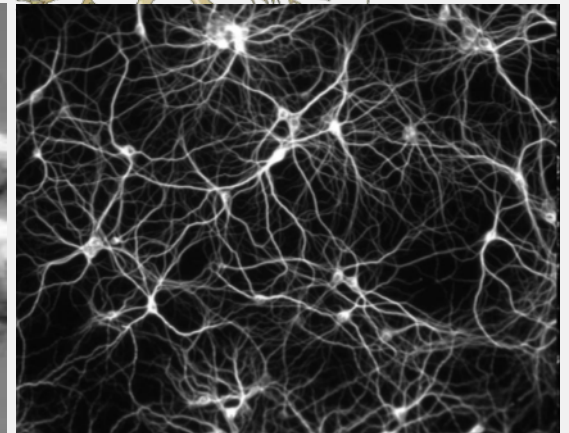
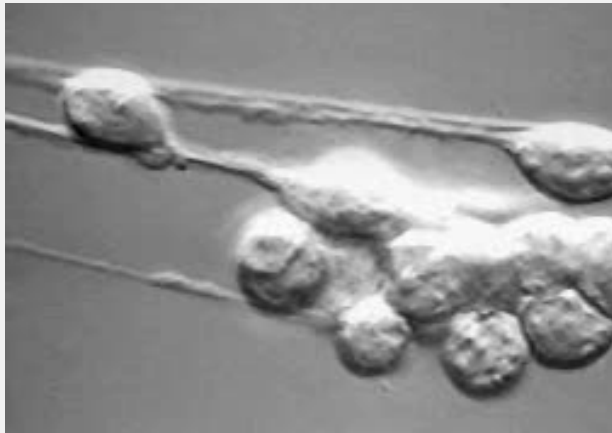
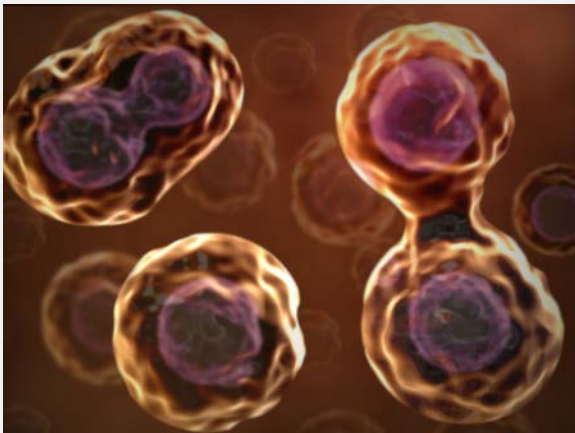
Proliferation



Migration

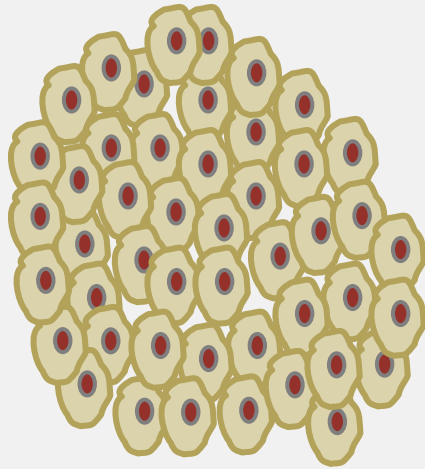


Integration

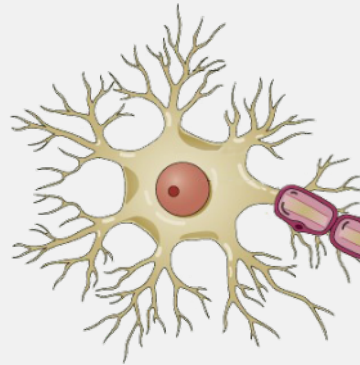


Cancer: imbalance in proliferation/survival vs. turnover

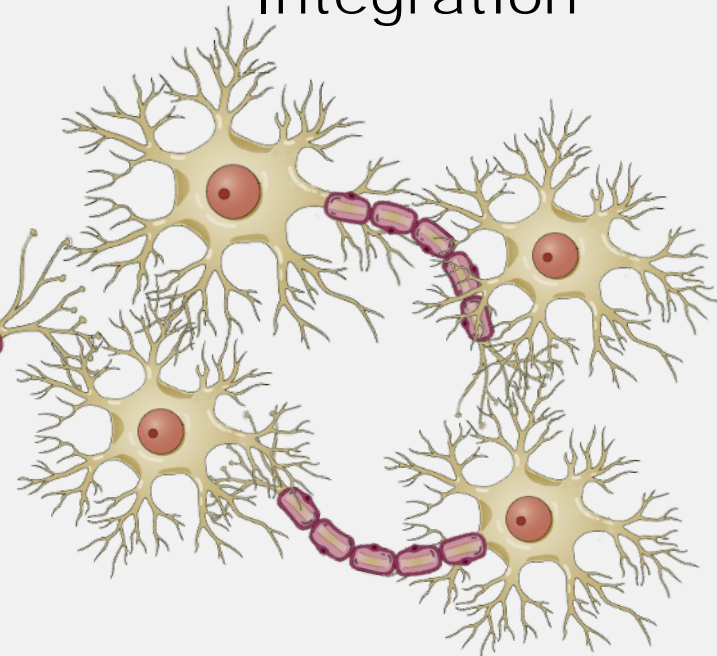
Proliferation



Migration

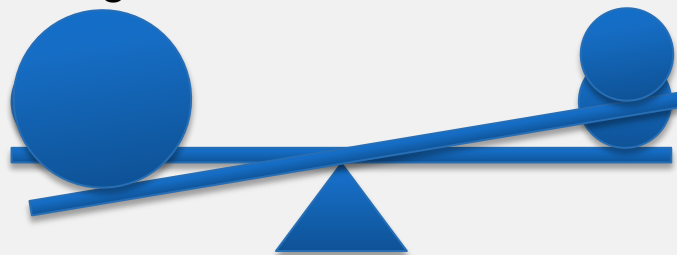


Integration

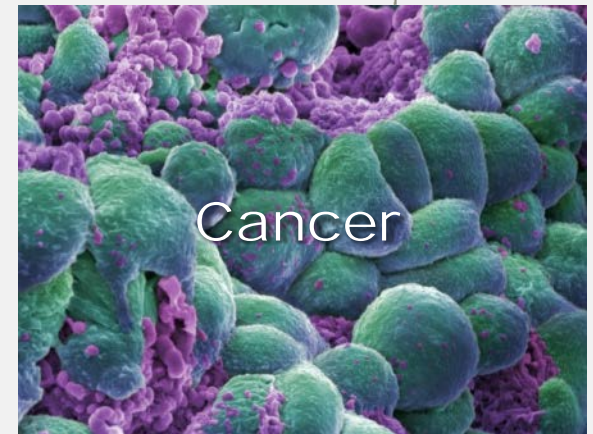


Oncogenes

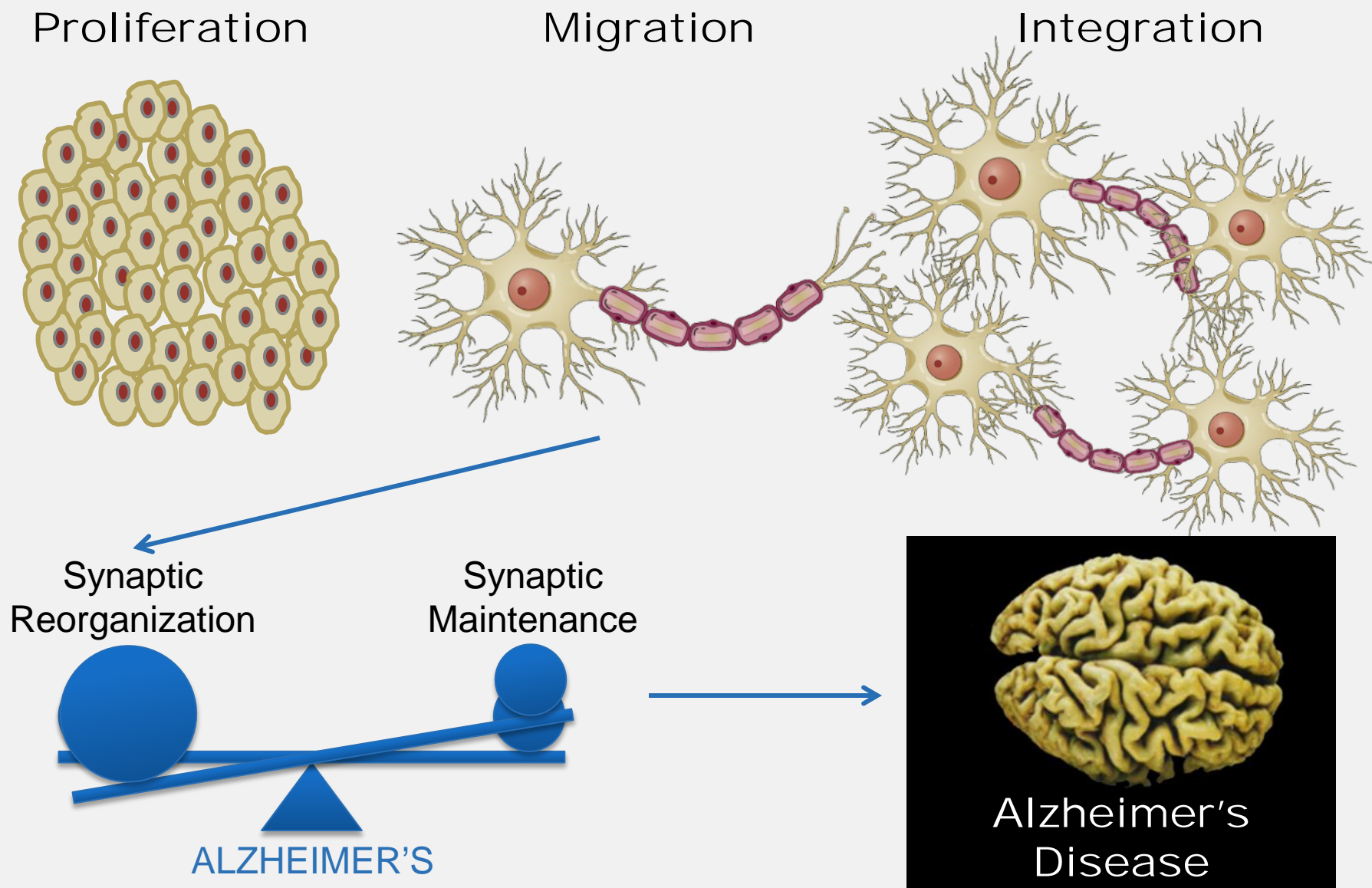
Tumor
Suppressor
Genes



CANCER



Alzheimer's disease: imbalance in plasticity



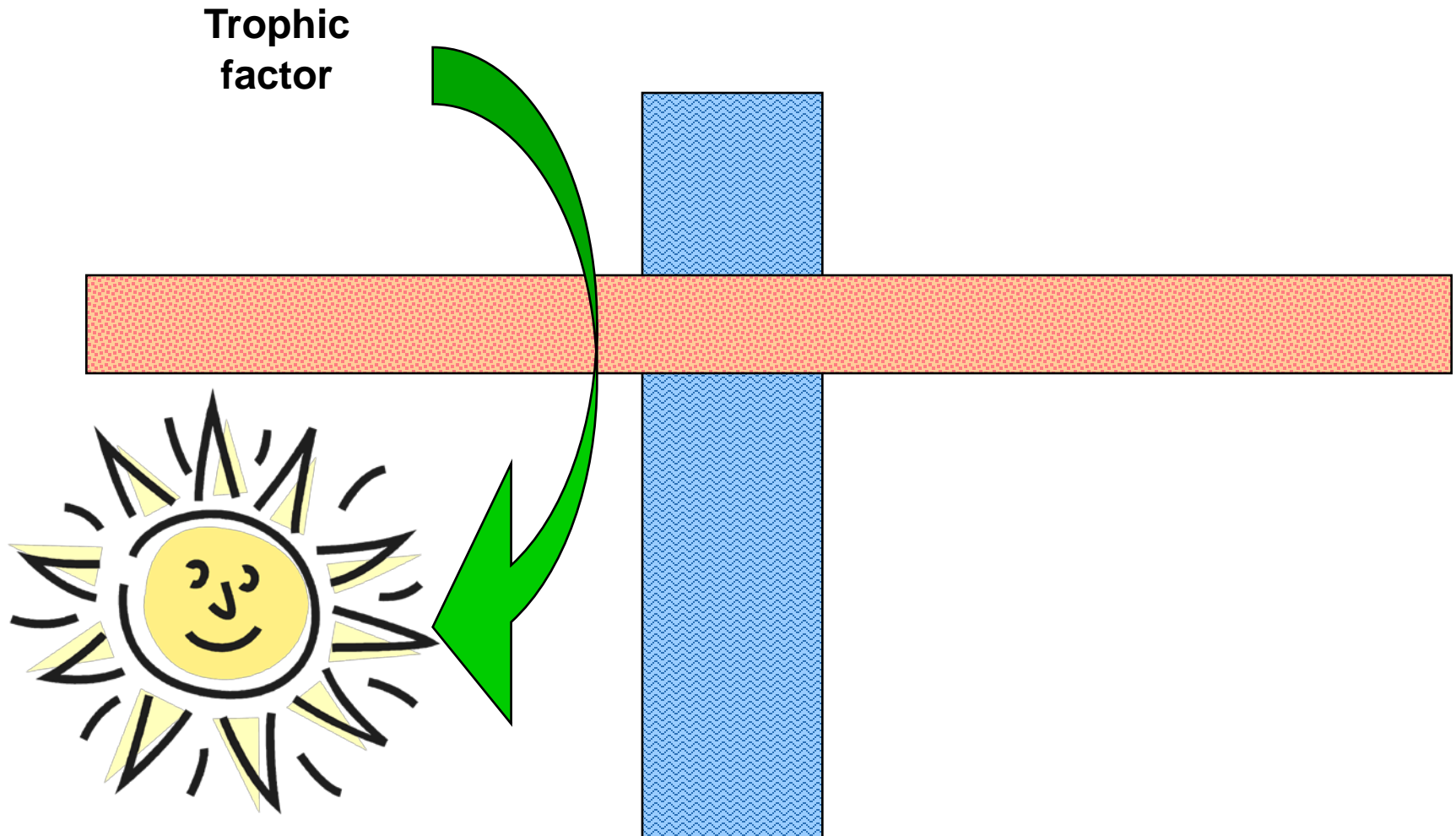
Back to basics: cellular dependence



• Rita Levi-Montalcini, the 1986 Nobel Prize, and the trophic factor hypothesis.

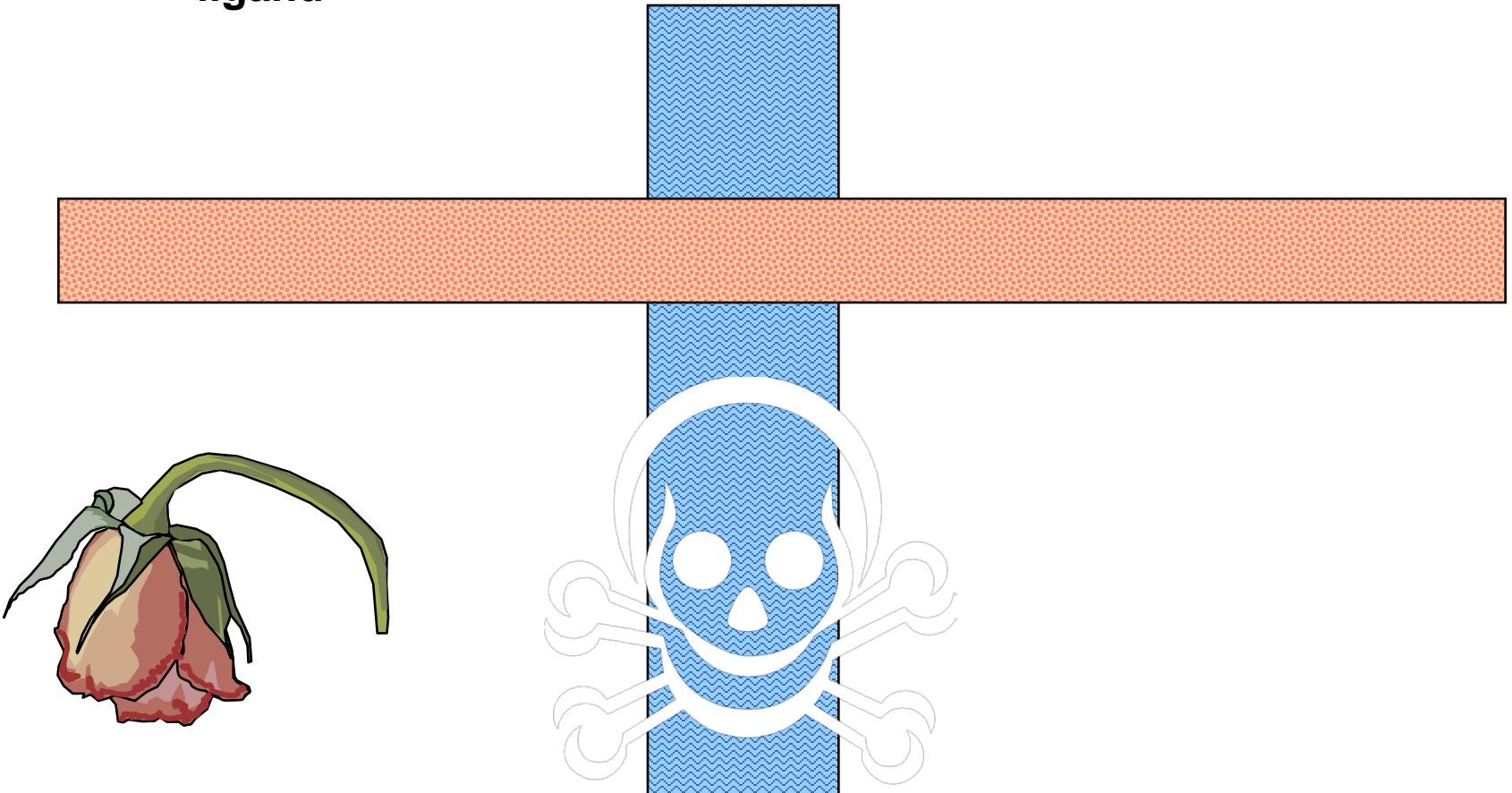
- It has been generally assumed that trophic factor withdrawal is associated with the loss of a positive survival signal, such as that associated with the phosphorylation of Akt.
- However, data accumulated over the past 20 years argue that there is a complementary cell death signal mediated by specific receptors, dubbed dependence receptors, activated by trophic ligand withdrawal but blocked by ligand binding.

Levi-Montalcini and the classic view

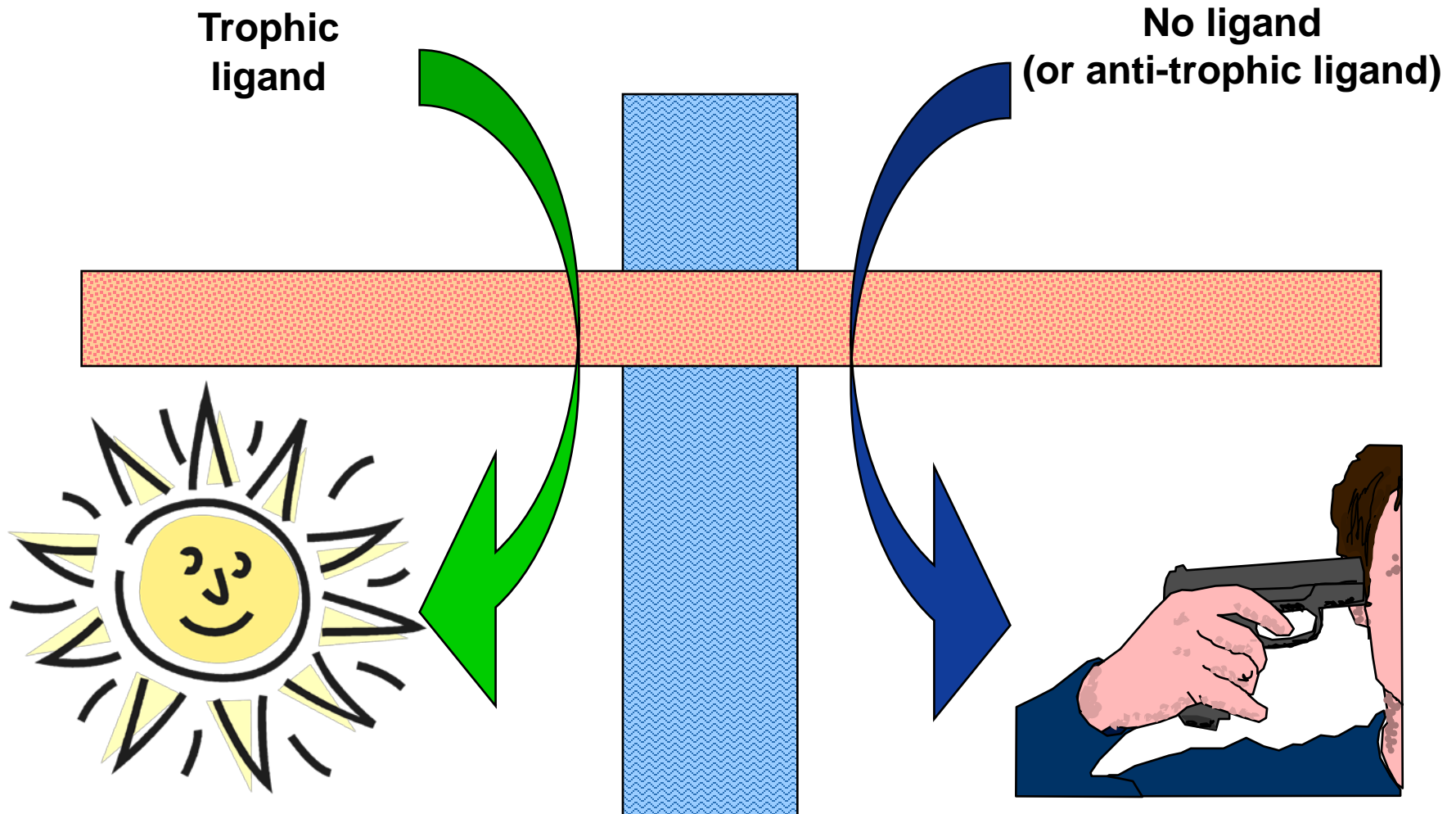


The old view: passive death

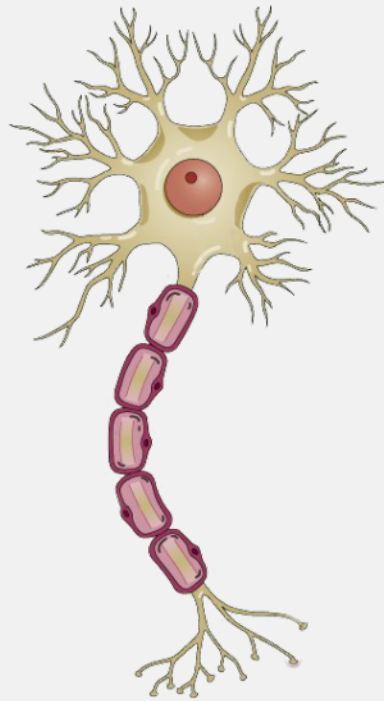
No trophic
ligand



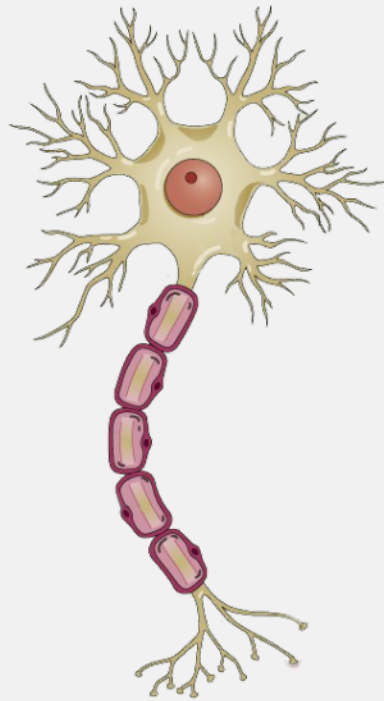
The Dependence Receptor Concept



An engineer's view of the neuron



An engineer's view of the neuron



Integration

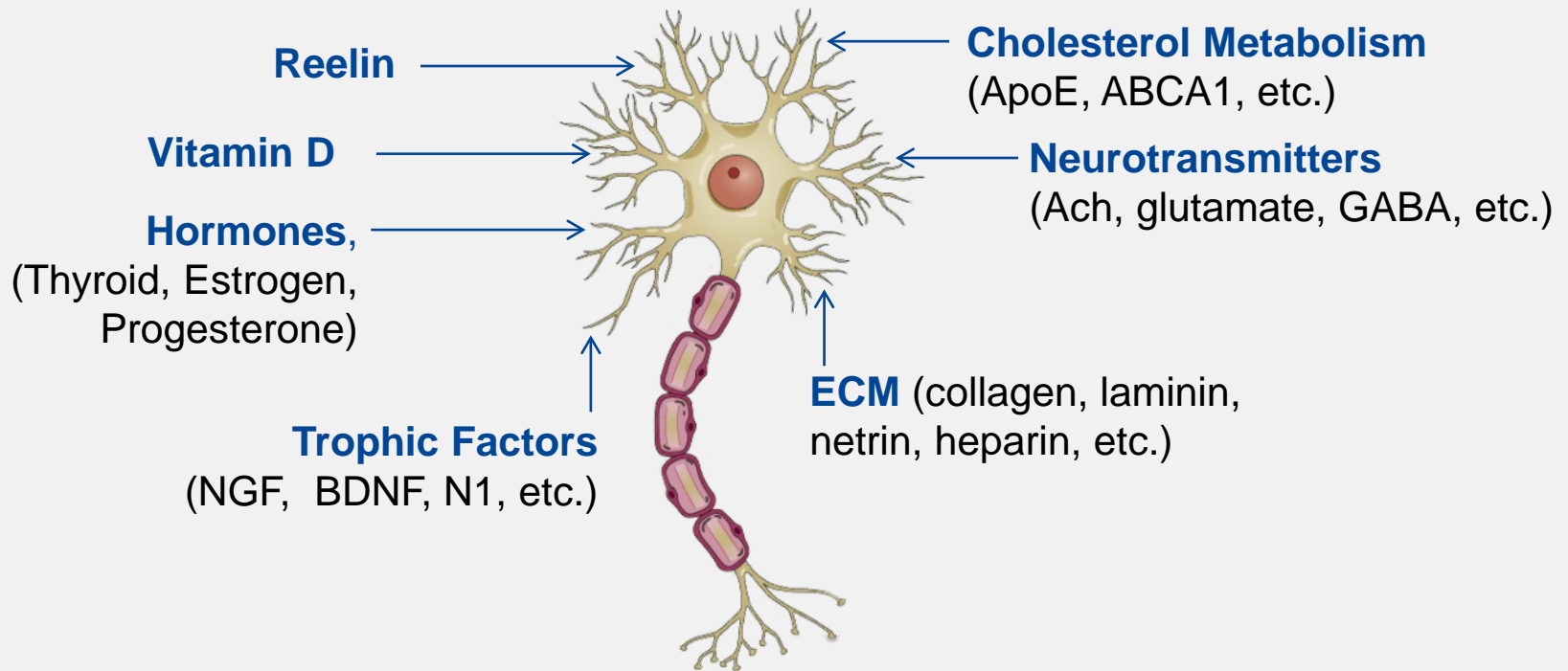
Analog \rightarrow digital

Electrical (chemical) input

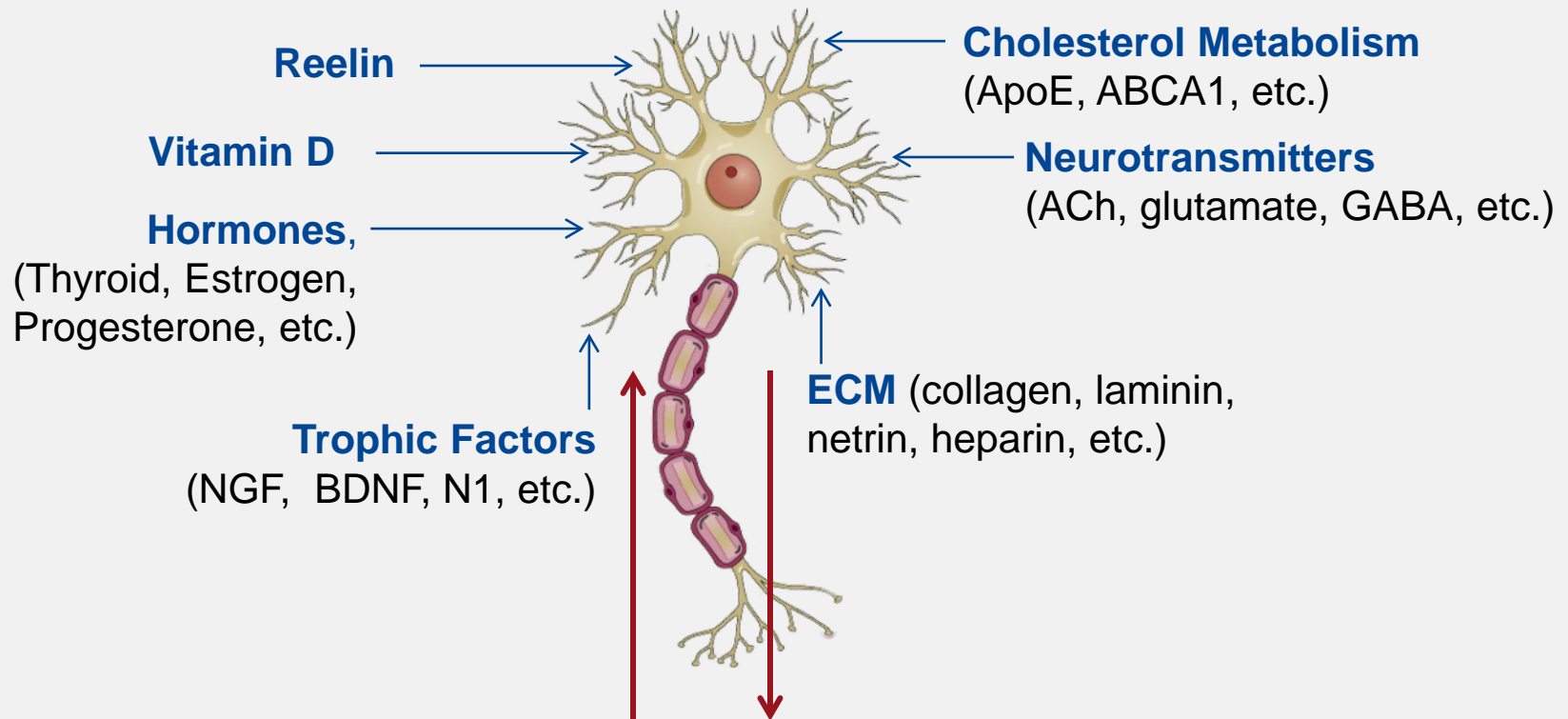
Via membrane conductance

Σ = Electrical input \rightarrow electrical output

Integration over anatomical vs. biochemical space



Integration over anatomical vs. biochemical space



Integration

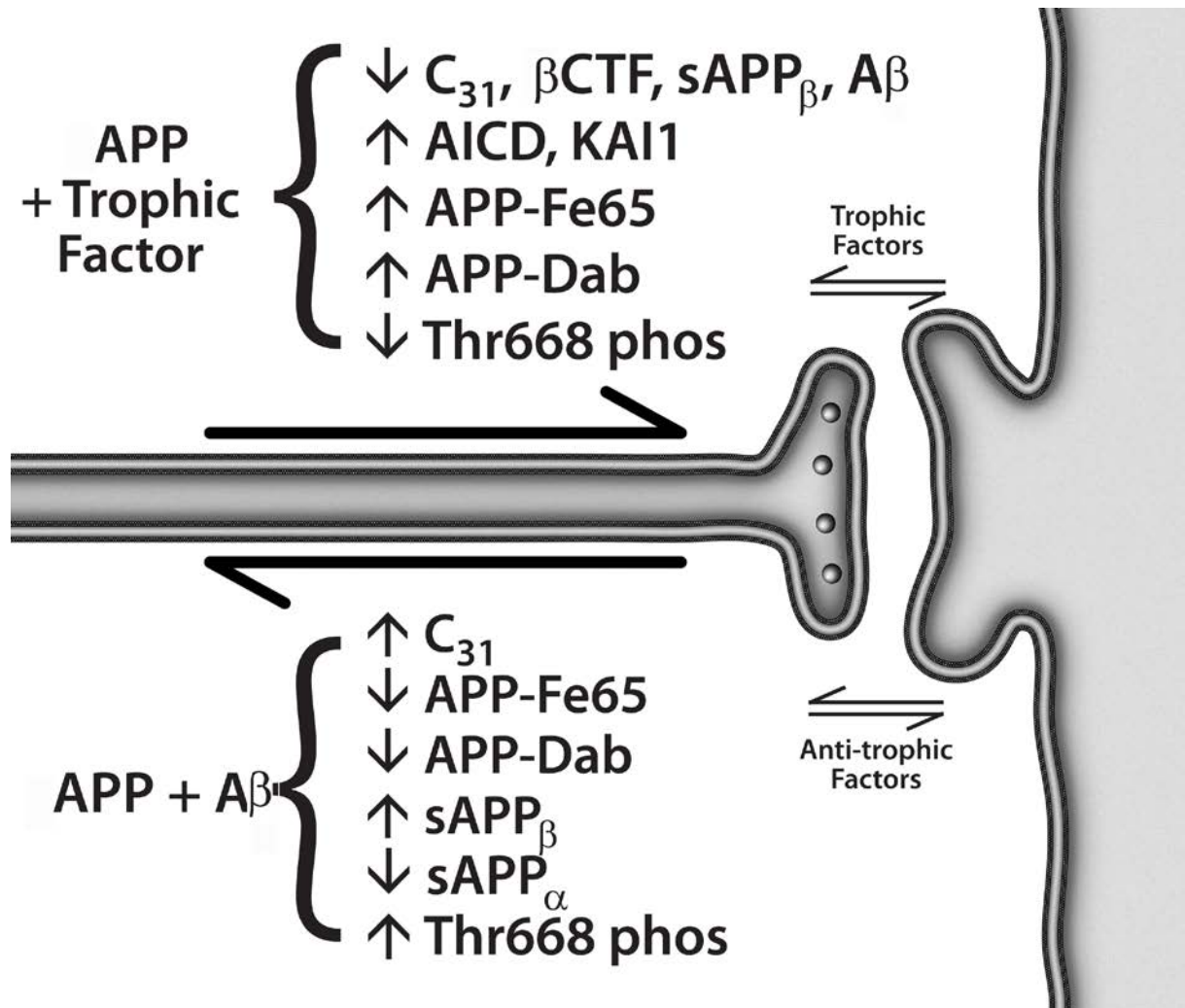
Analog → digital (slow) output

Receptor signaling input

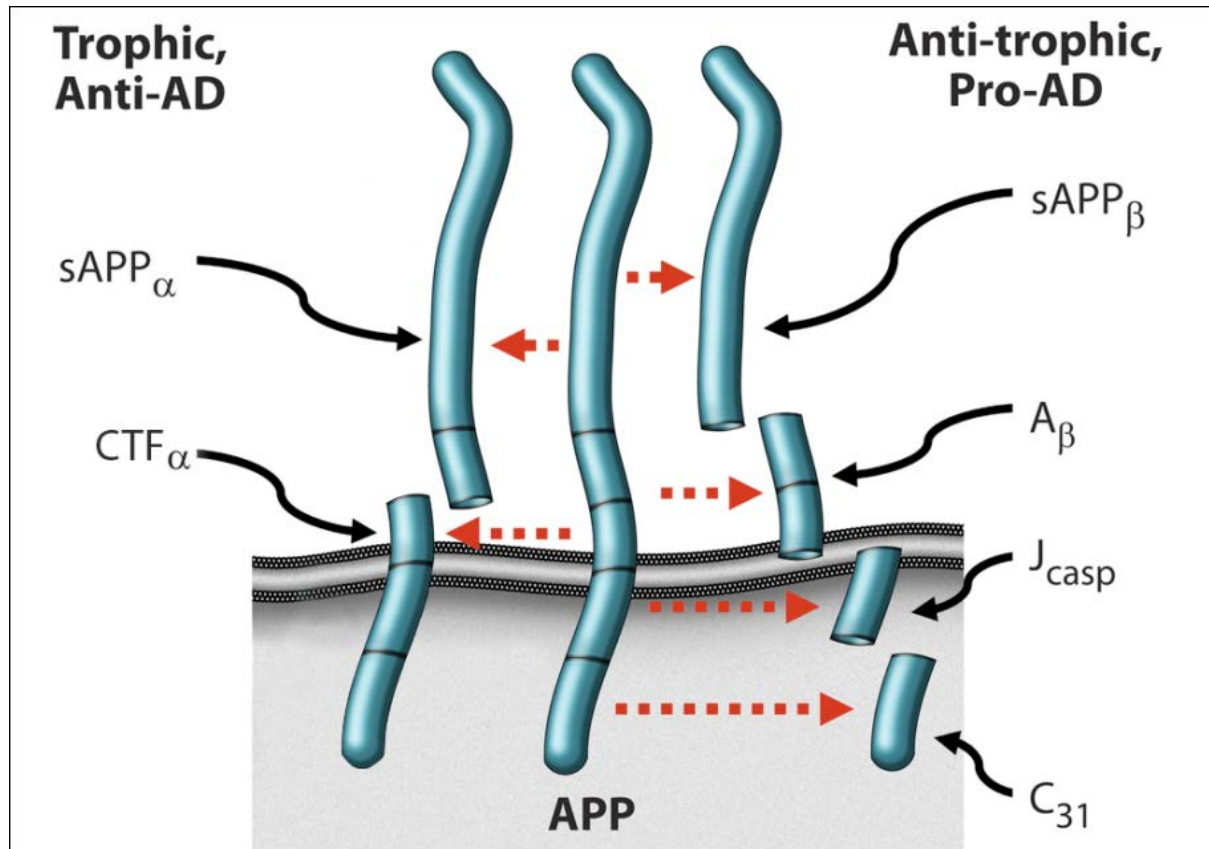
Via nuclei and cytoplasm

Σ = Chemical milieu input → morphogenetic output

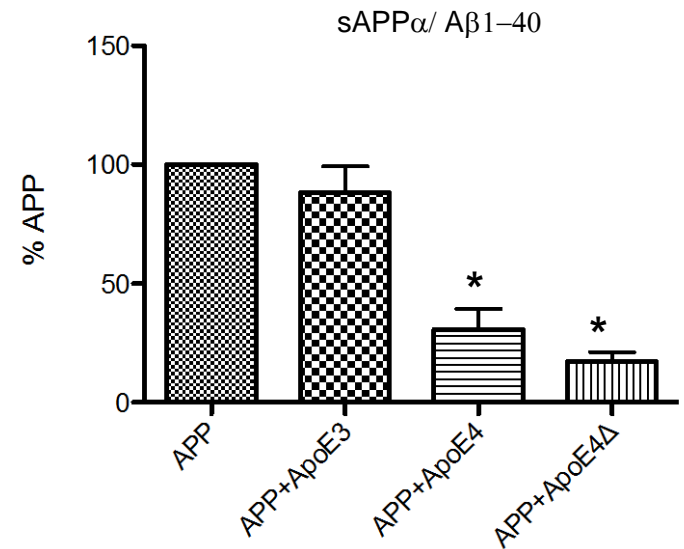
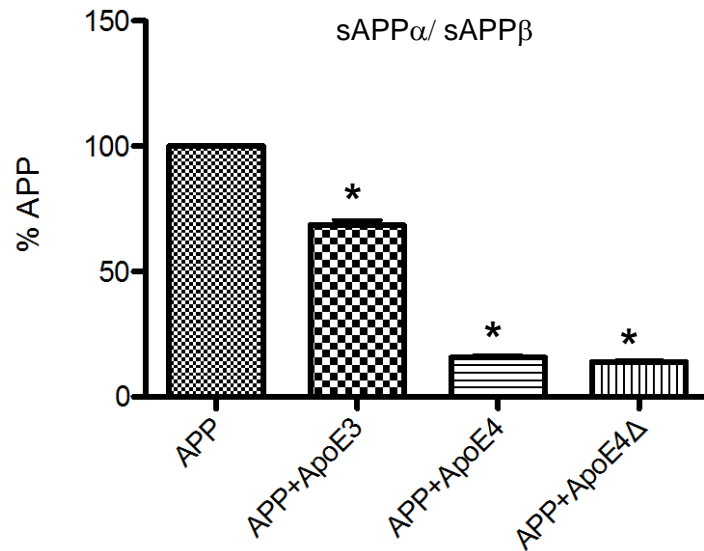
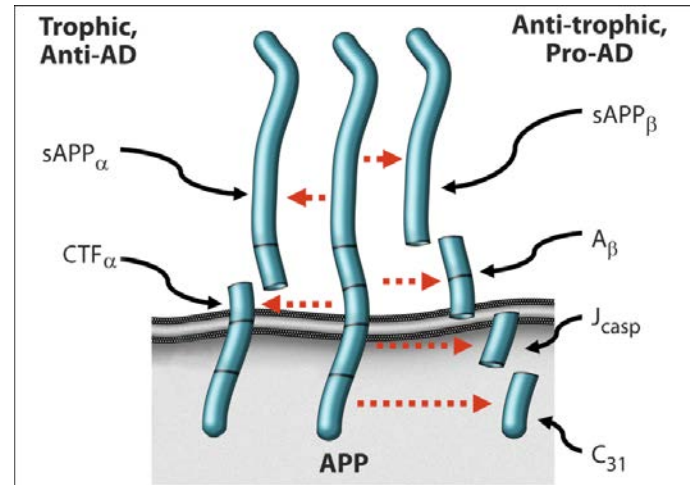
Synaptic element interdependence



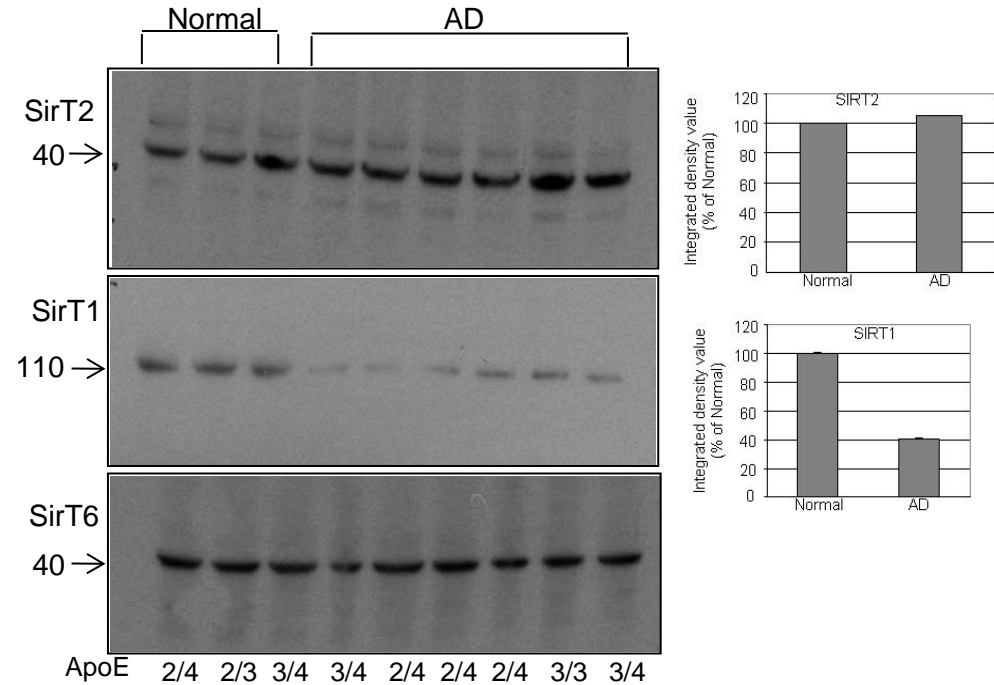
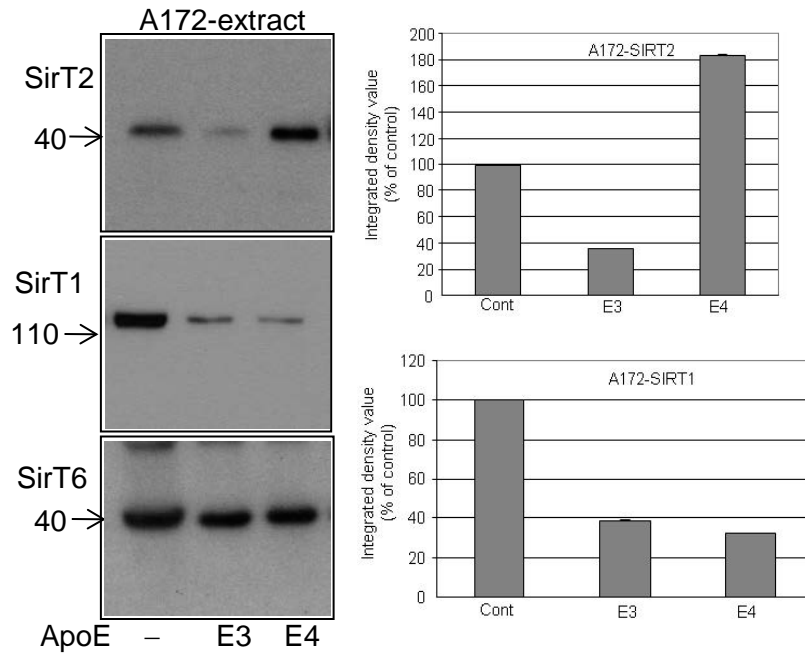
The readout: plasticity ratio (cf. HDL:LDL)



ApoE4 and plasticity ratio

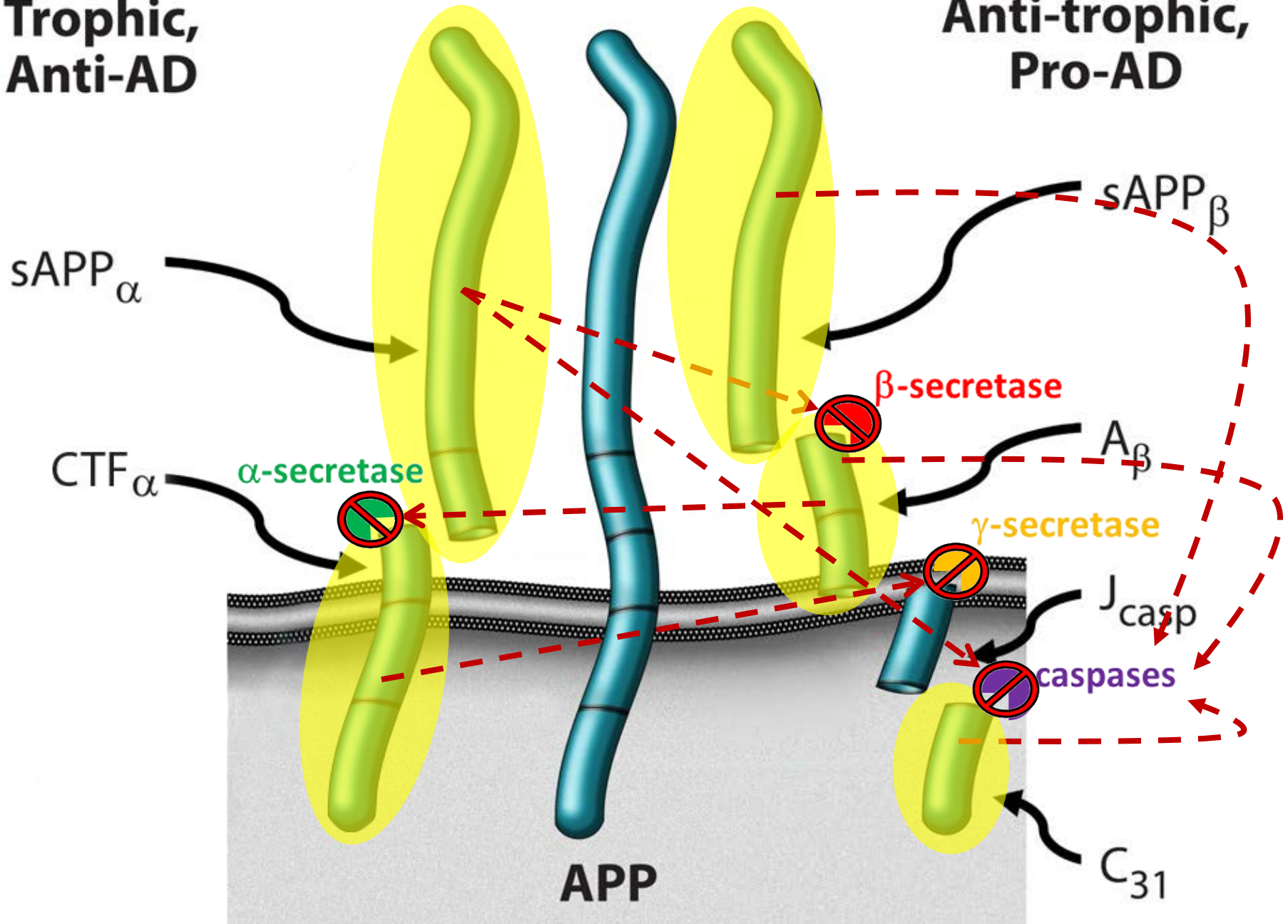


“Sirtuinversion”



**Trophic,
Anti-AD**

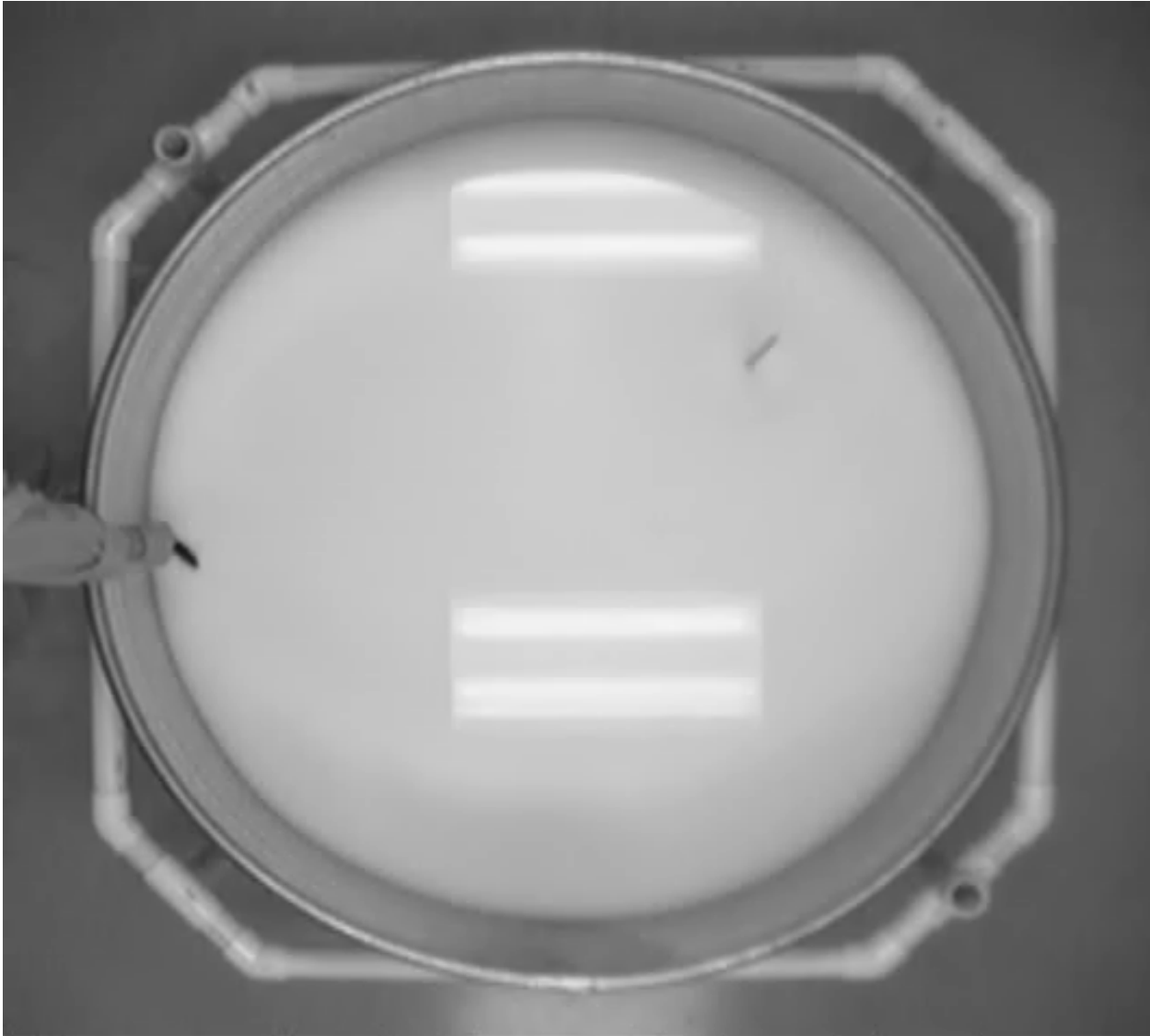
**Anti-trophic,
Pro-AD**



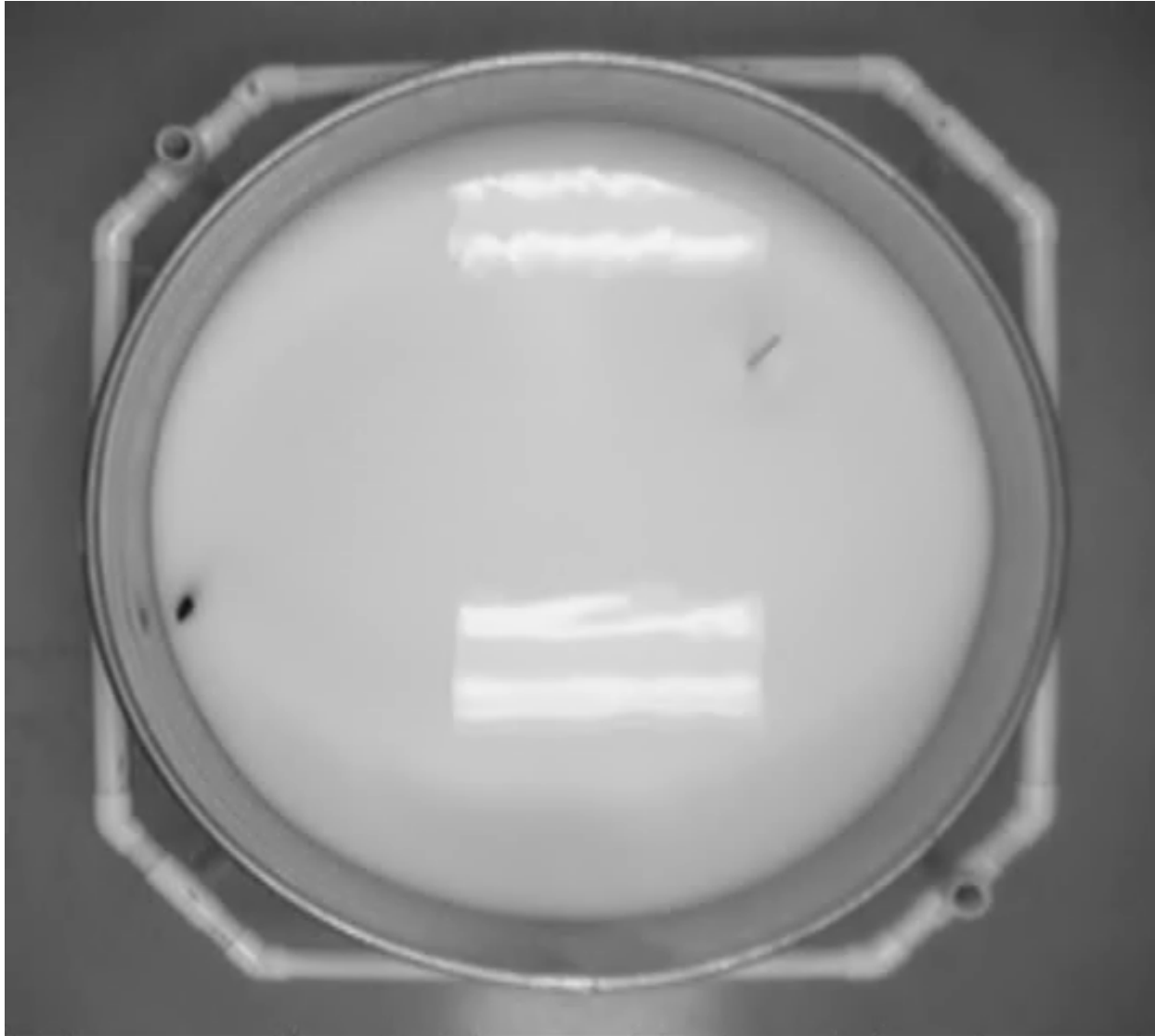
Normal mice can learn



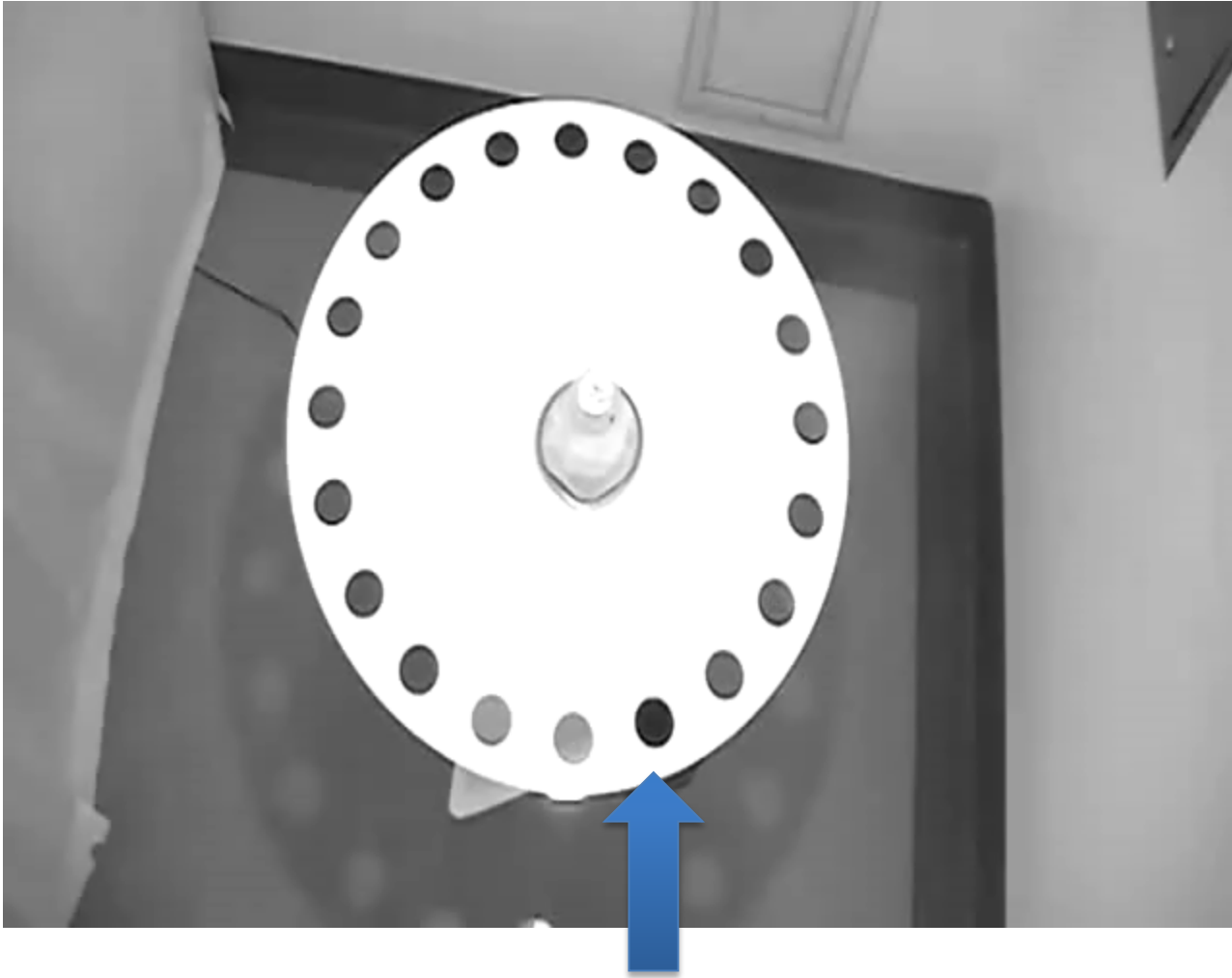
“Mouzheimer’s”



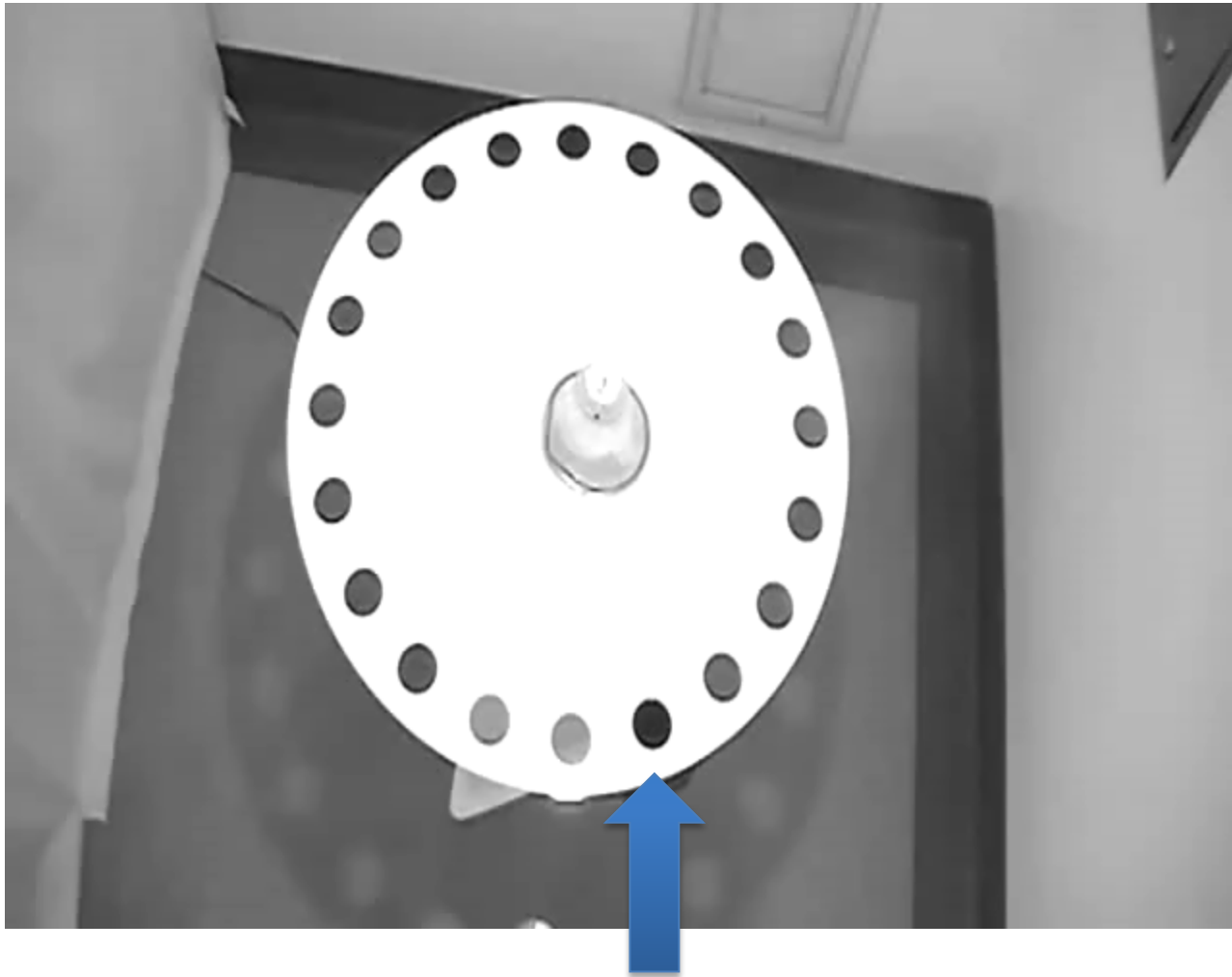
Mouzheimer's blocked



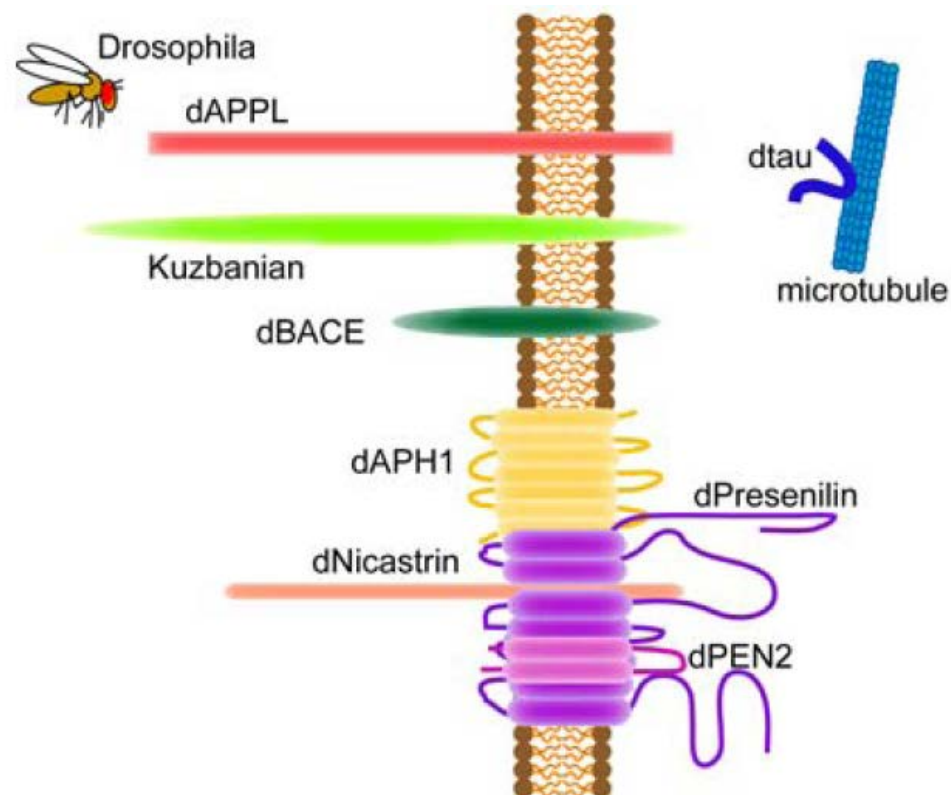
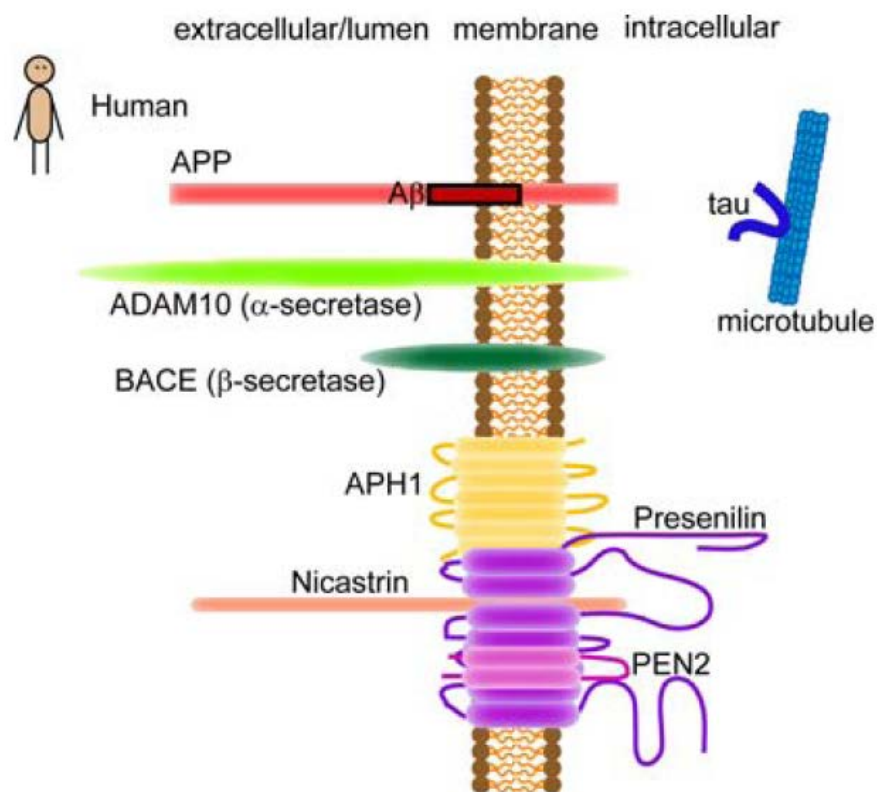
Normal mouse (trial #8)



“Mensa mouse”



Alzflymer's

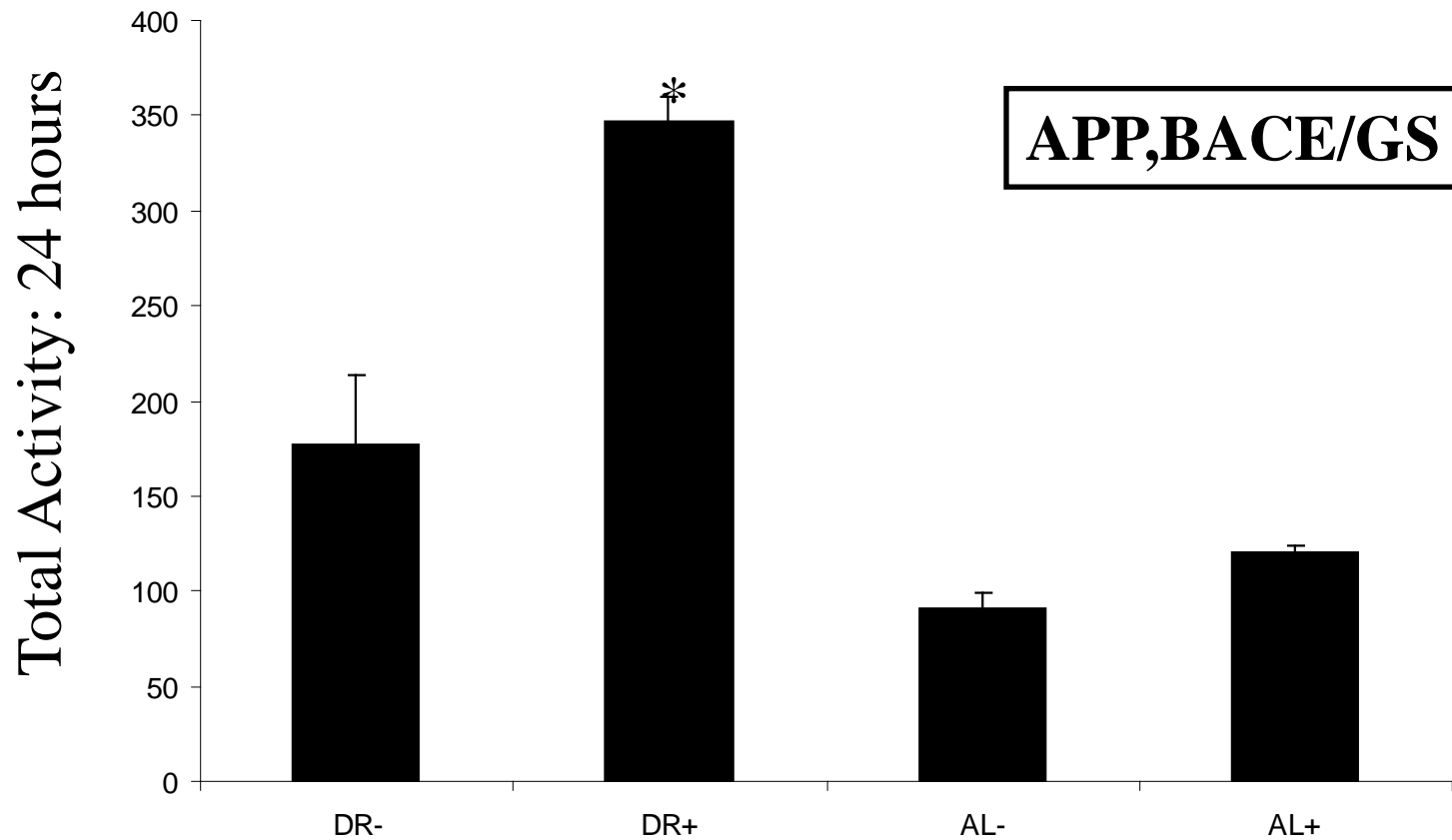


Alzflymer's

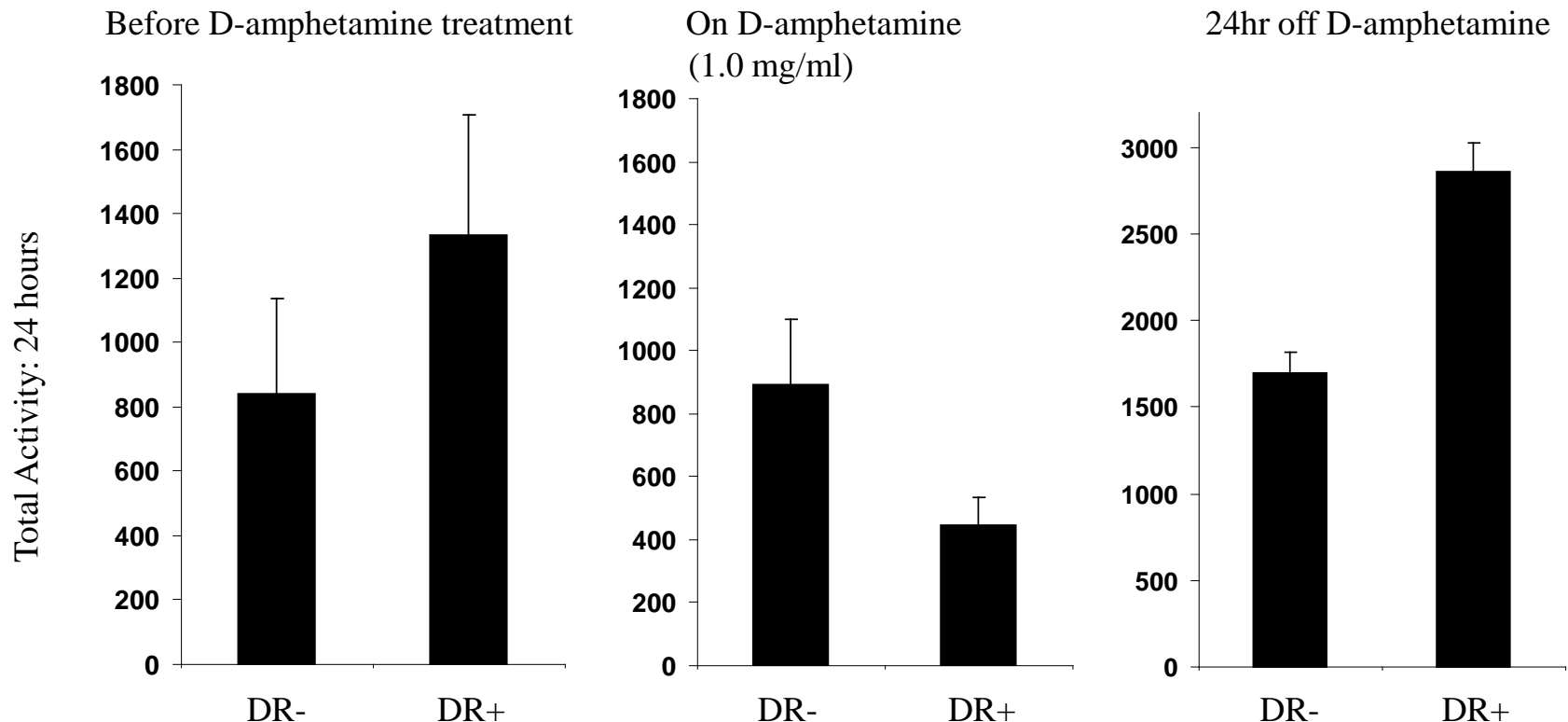
Left: Off Right: On



Activity Assay



Response to treatment with d-amphetamine



APP,BACE/GS

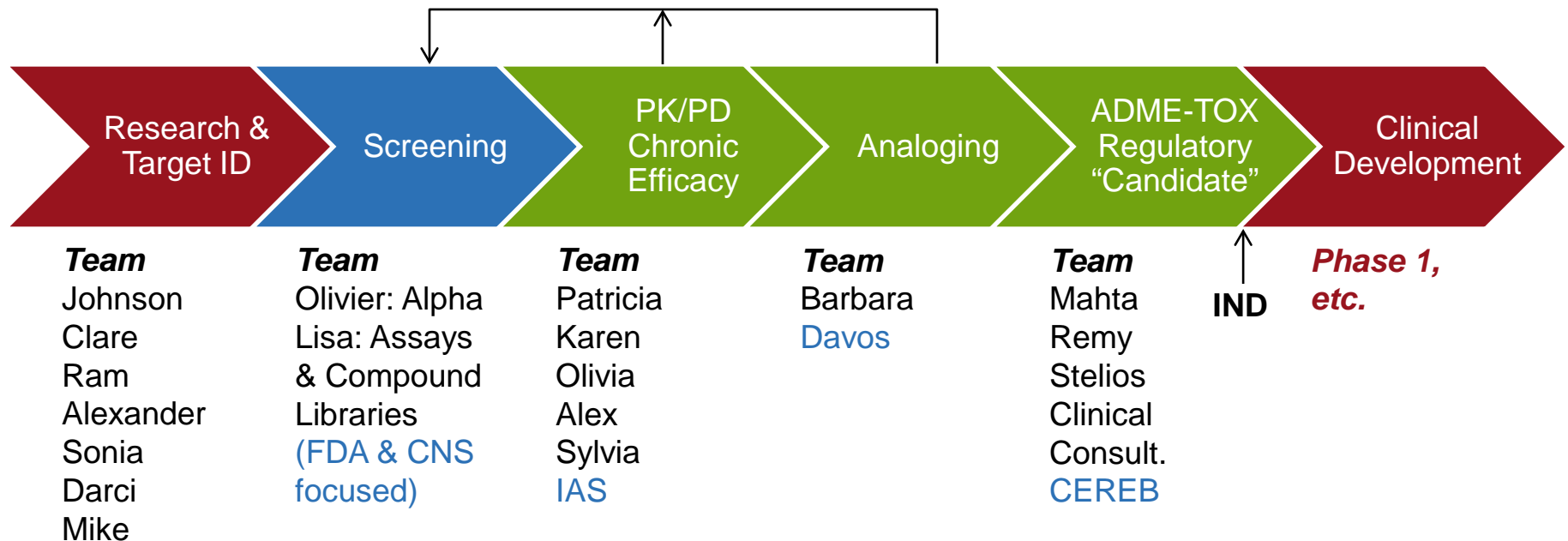
A *Drosophila* Hyperactivity Disorder (ADHD)

- Males >> Females.
- Exacerbated markedly by high CHO:protein diet.
- Reduced with aging.
- Associated with sleep/nocturnal dysrhythmic pattern.
- Reversibly responsive to d-amphetamine.
- “Paradoxical response” to d-amphetamine.

Research to Clinical Development BUCK INSTITUTE FOR RESEARCH ON AGING

Bench to Bedside

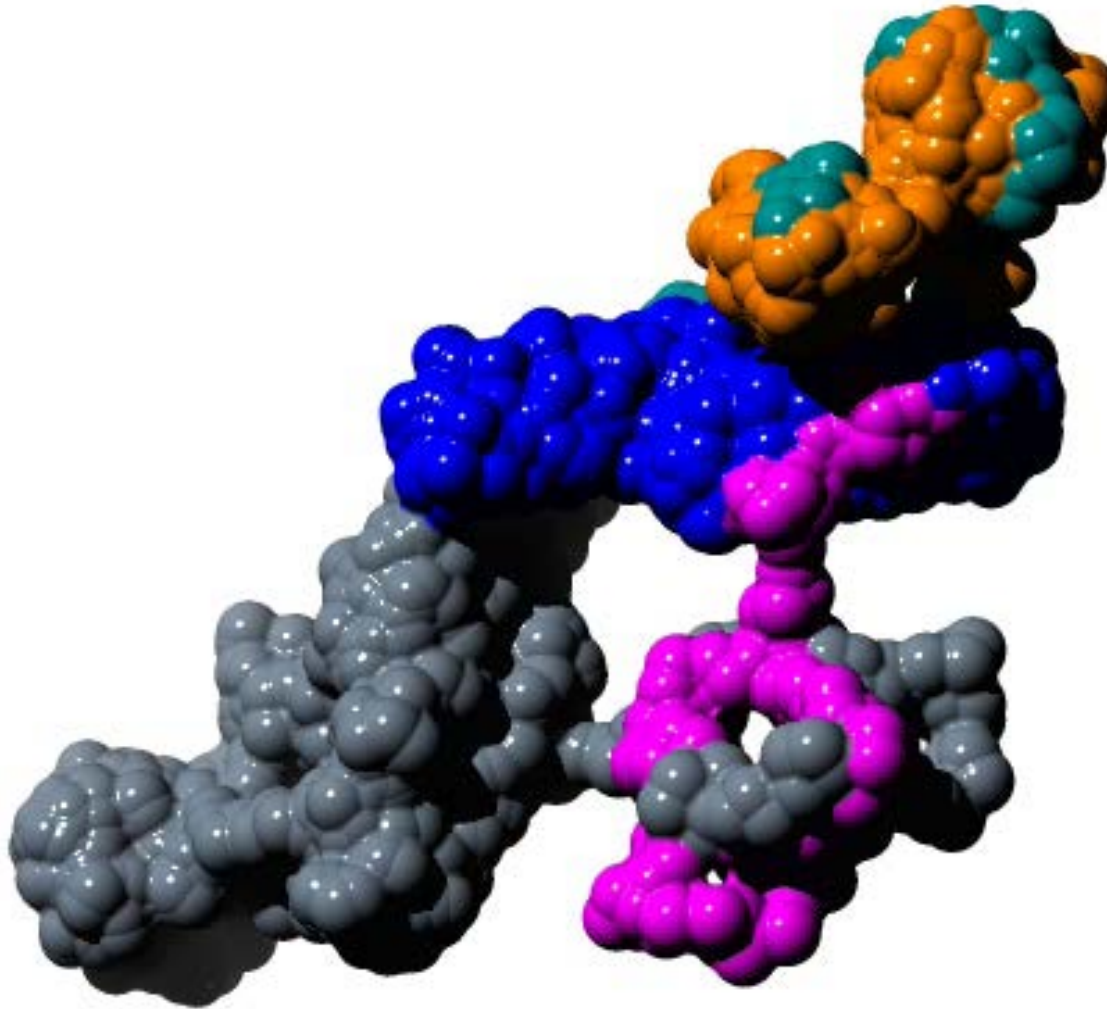
Alzheimer's Drug Development Network Varghese John, Ph.D., and Dale E. Bredesen, M.D.



Screening for Novel Therapeutics



APP forms homodimers



APP- Selective BACE Inhibitors (ASBIs)

- **Novel inhibitors that interact with the catalytic site of BACE & bind to the ectodomain of APP.**
- **Inhibitors are effective in \downarrow sAPP β & \downarrow A β 42 in cells transfected with APPwt but not APPsw.**
- **Exhibit selectivity for APP over NRG1 and PSGL1.**

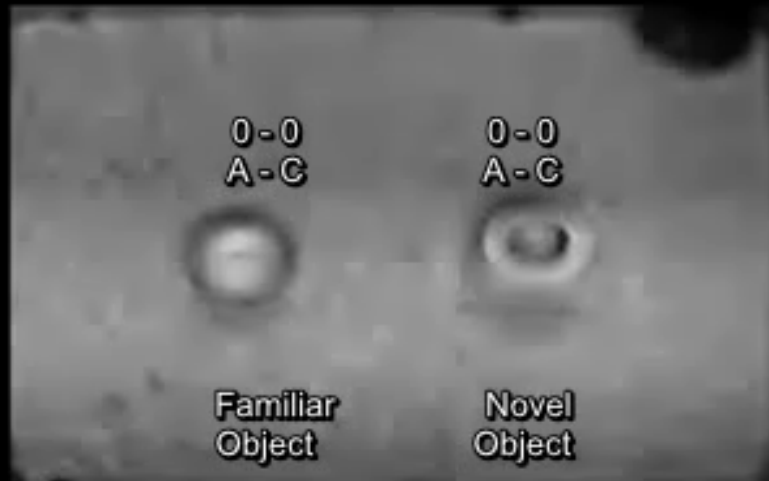
F03: Multiple Mechanisms Against Alzheimer's

- Reduces $A\beta$
- Increases $sAPP_{\alpha}$
- Blocks ApoE4 effect
- Improves LTP
- Blocks neuronal programmed cell death
- Excellent blood-brain barrier penetration
- High therapeutic index
- Markedly outperforms memantine and donepezil in Tg Mo

The text "F03" is centered within a light gray oval that has a blue border and a subtle drop shadow.

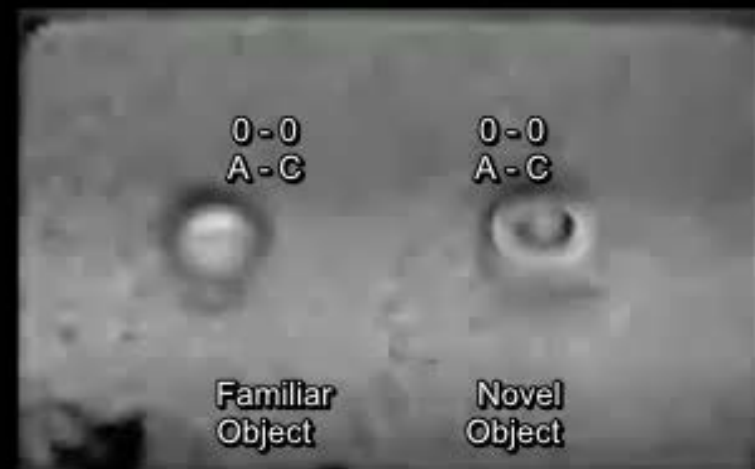
F03 restores novel object recognition completely

Normal Mouse



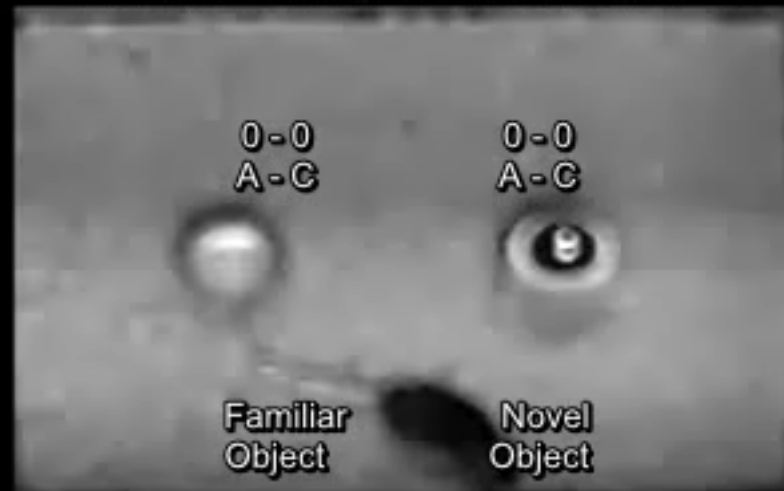
A=Attend . C=Climb

Alzheimer's Mouse



A=Attend . C=Climb

Alzheimer's Mouse after Treatment



A=Attend . C=Climb

A roof with 36 holes...



The first systems therapeutics clinical trial

- Systems Therapeutics (and U.S. case)
- F03
- Synaptik (multiple network-specific components)
- Computer-based assessment and memory training
- Sleep enhancement
- Exercise-induced BDNF increase
- AD-specific diet



Medicine



Synaptik



Nutrition
Guidance



Cognitive
Exercise



Physical
Exercise



Sleep Aid

First clinical trial is set for 2013

Summary

- Our model suggests that AD is fundamentally related to a plasticity balance, analogous to oncogene:tumor suppressor gene balance.
- In this model, AD results from a synaptoblastic:synaptoclastic imbalance that is metabolically induced, mediated by dependence receptors (including APP), and amplified by prionic loops.
- Therefore, one translational approach involves correcting this imbalance by targeting APP signaling directly.
- However, an optimal approach would include impacting multiple network components, as physiologically and as far upstream as possible.
- We have had initial success both pre-clinically and clinically with this approach, but much more proof is needed, as well as optimization of each network component therapeutic.

Is Alzheimer's disease incurable?

“Never doubt the ability of a small group of committed individuals to change the world. Indeed, it is the only thing that ever has.”

--- Margaret Mead

Thanks

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