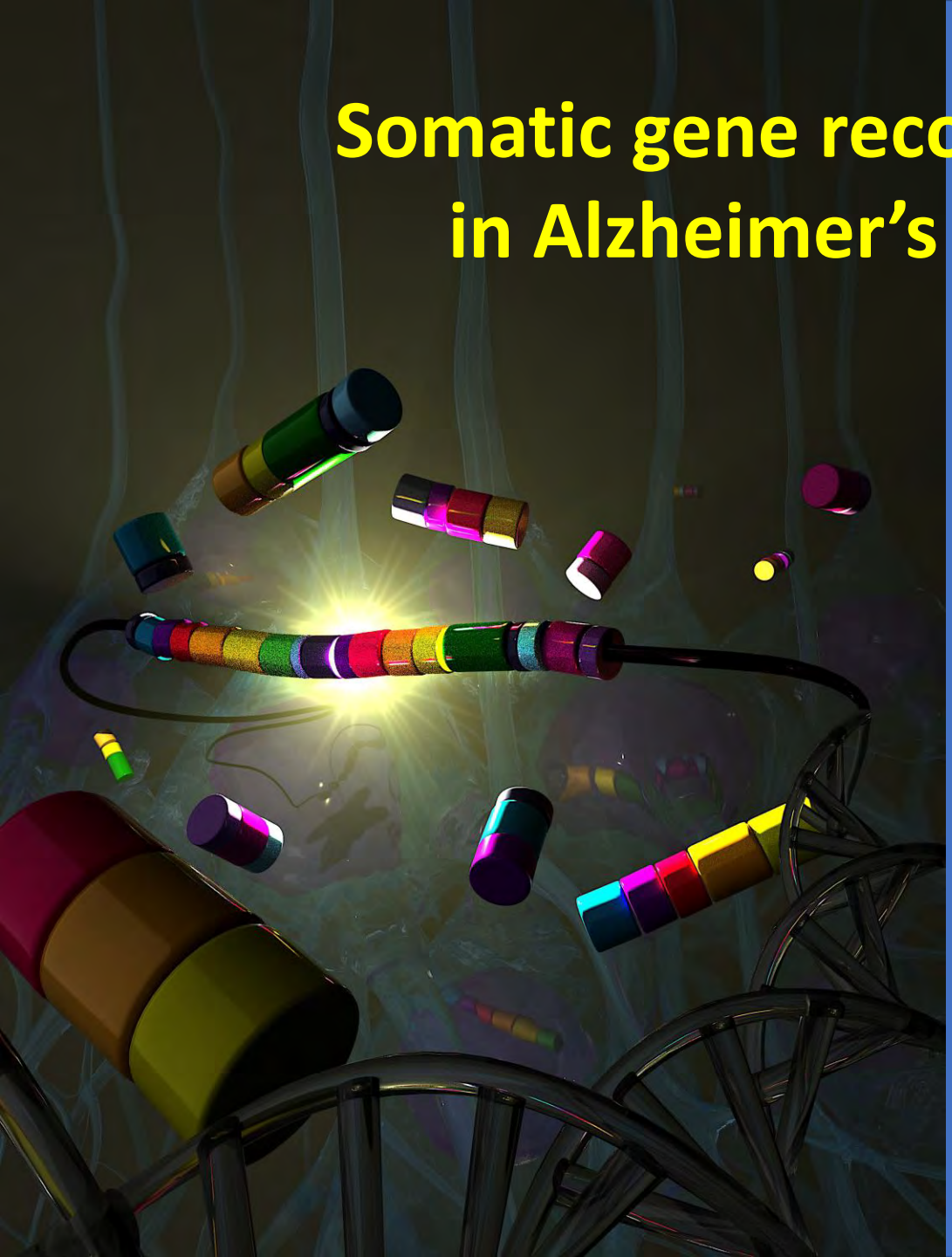
Somatic gene recombination in Alzheimer's disease



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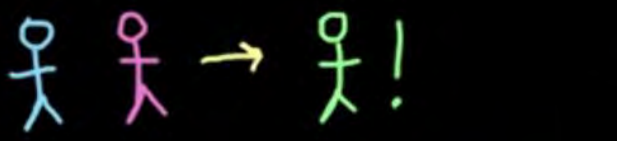
Fundamentals of Life: Current Views of Molecular biology and Neurobiology

1. We have two copies of each gene, one from mom, one from dad
2. ”Central Dogma” of Molecular Biology: DNA to RNA to Protein
3. All cells have the same DNA (same genome)

Central Dogma



James Watson

Francis Crick

DNA

RNA

PROTEIN

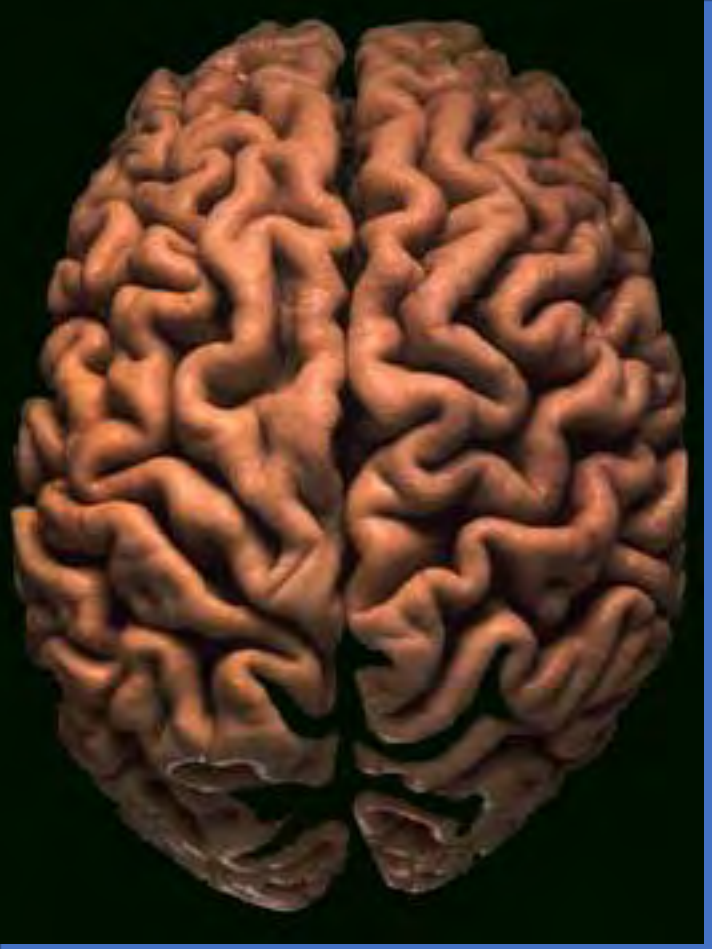
replication

transcription

translation

nucleic acids

amino acids



Alzheimer's disease is the most common cause of dementia, with great societal and economic costs ($280B/y).

We still do not understand the most common forms of the disease that constitute ~99% of cases: **Sporadic Alzheimer's disease** (**SAD**).

NO disease-modifying therapies exist, despite many **FAILED** clinical trials.

The Amyloid Precursor Protein "*APP*" gene is pathogenic if mutated or present as 3 copies (Down syndrome (Trisomy 21) or rare FAD *APP* CNVs). APP is cleaved to produce amyloid beta peptide (Aβ). **APP gene copies are thought to be constant (2 copies) in SAD.**

ARTICLE

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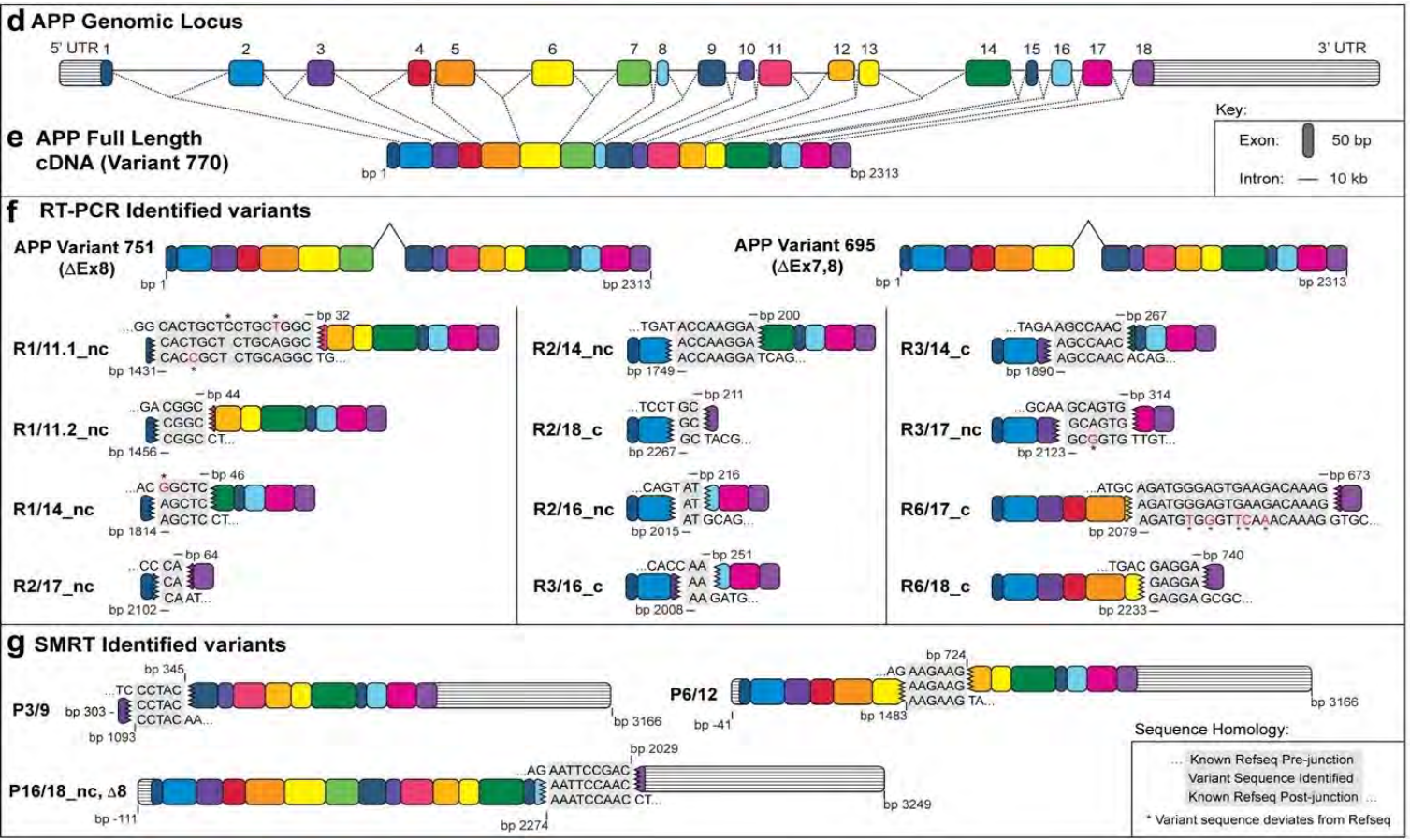
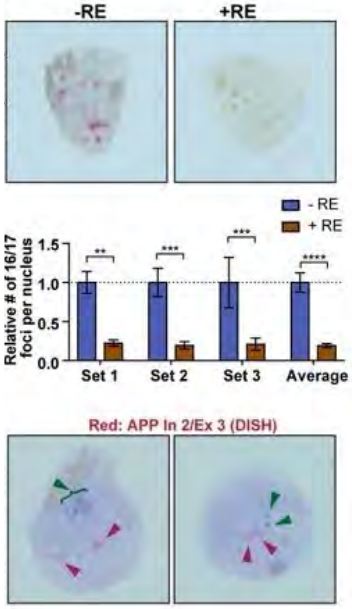
Somatic *APP* gene recombination in Alzheimer's disease and normal neurons

Ming-Hsiang Lee[1], Benjamin Siddoway[1,3], Gwendolyn E. Kaeser[1,2,3], Igor Segota[1,3], Richard Rivera[1], William J. Romanow[1], Christine S. Liu[1,2], Chris Park[1,2], Grace Kennedy[1], Tao Long[1] & Jerold Chun[1]*



"gencDNAs"

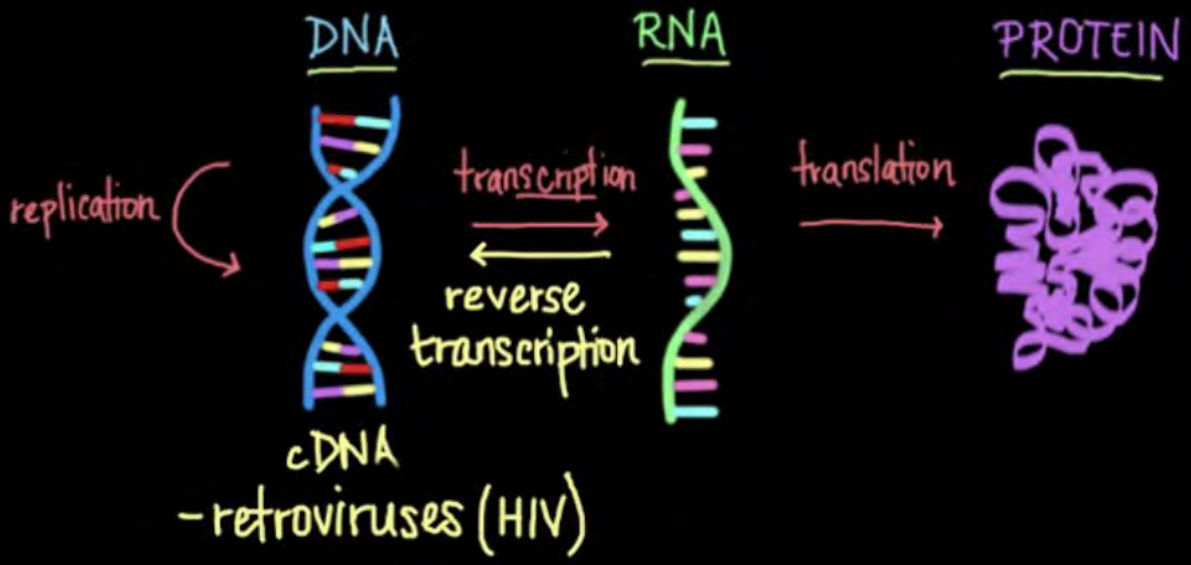


Nature *563*, 639-645 (2018)

Central Dogma revisited...

David Baltimore

Howard Temin



gencDNAs

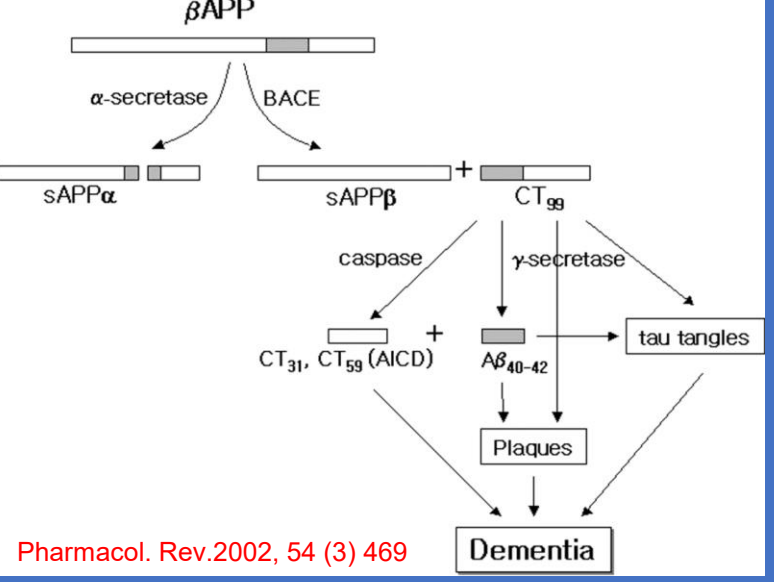
Involving normal and modified cellular genes

khanacademy.org

Fundamentals of Life: Current Views of Molecular biology and Neurobiology

1. We have two copies of each gene, one from mom, one from dad
2. ”Central Dogma” of Molecular Biology: DNA to RNA to Protein
3. All cells have the same DNA (same genome)

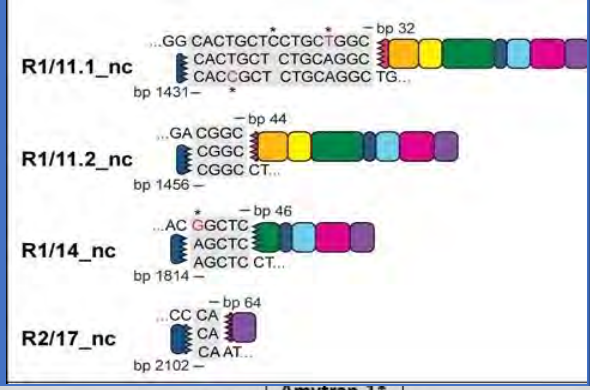
NOT TRUE IN ALZHEIMER’S!

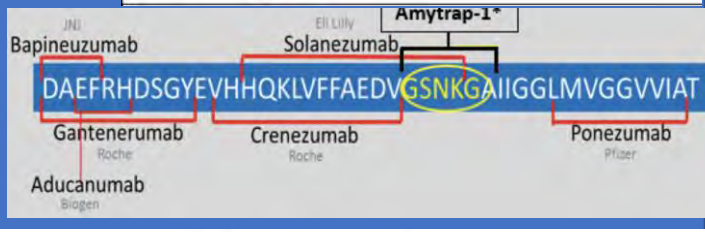


Pharmacol. Rev.2002, 54 (3) 469

Aβ therapeutic failures explained by inadequate target engagement:

Can't capture diversity, don't need secretases





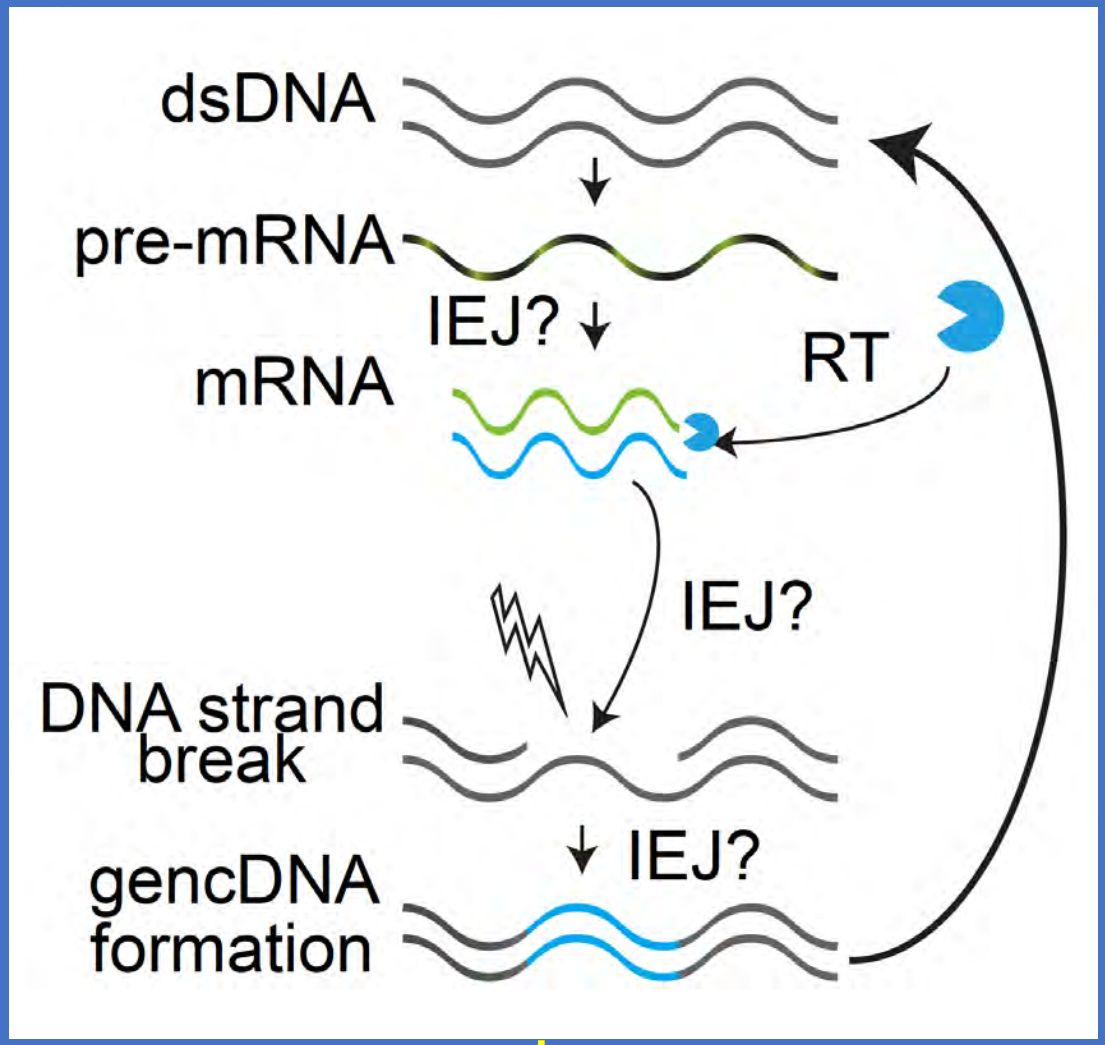
Clinical candidate	Mouse antibody analog	Clinical stage	Aβ sel ectivity (Monomer, Aggregate)	Epitope (residues)	Structure	Ref.
aducanumab	^{ch}aducanumab	Ph3	A≫M	3–7	yes	[8] and this work
gantenerumab	^{ch}gantenerumab	Ph3	A>M	3–11, 18–27	yes	[9,10]
BAN2401	mAb158	Ph2	A≫M	1–16	no	[11,12]
NA	PFA1	NA	A>M	2–7	yes	[13]
bapineuzumab	3D6	discontinued	A, M	1–5	yes	[8,14,15,54]
crenezumab	MABT5102A	Ph3	A, M	13–24	yes	[16,17]
solanezumab	m266	Ph3, partially halted	M≫A	16–26	yes	[15,18]
ponezumab	2H6	discontinued	M≫A	30–40	yes	[19]

Table 1. Properties of selected anti-Aβ antibodies.

Scientific Reports (2018) 8:6412

Alzheimer's disease: *APP* Somatic Gene Recombination

Gone Wild…



APP gencDNAs require Reverse Transcriptase (RT) activity; SNVs produced by sloppy RT

There is a disease that is being treated with RT inhibitors: HIV is treated with "cART" (combination anti-retroviral therapy that includes RT inhibitors)

Prevalence of Alzheimer's and Other Dementias in the United States

An estimated 5.7 million Americans of all ages are living with Alzheimer's dementia in 2018. This number includes an estimated 5.5 million people age 65 and older[A1,30] and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's, though there is greater uncertainty about the younger-onset estimate.[147]

- One in 10 people (10 percent) age 65 and older has Alzheimer's dementia.[A2,30,145]
- The percentage of people with Alzheimer's dementia increases with age: 3 percent of people age 65-74, 17 percent of people age 75-84, and 32 percent of people age 85 and older have Alzheimer's dementia.[30]
- Of people who have Alzheimer's dementia, 81 percent are age 75 or older (Figure 1).[A3,30]

From the CDC and Alzheimer's Association, Facts and Figures 2018

>100,000 HIV+ patients on RTis

3% = **3,000**
10% = **10,000**
17% = **17,000**

THOUSANDS of AD cases should exist in aged, HIV+ patients
(so how many have been reported in the peer-reviewed literature?)

One Case

First reported in 2016

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 4 (2016) 1-5

Alzheimer's & Dementia

Diagnostic Assessment & Prognosis

An individual with human immunodeficiency virus, dementia, and central nervous system amyloid deposition

Interpretation: We report the first HIV+ individual with a positive amyloid positron emission tomography (PET) scan.

Abstract

Human immunodeficiency virus (HIV)–associated neurocognitive disorder (HAND) is found in 30%–50% of individuals with HIV infection. To date, no HIV+ individual has been reported to have a positive amyloid PET scan. We report a 71-year-old HIV+ individual with HAND. Clinical and neuropsychologic evaluations confirmed a progressive mild dementia. A routine brain MRI was normal for age. [18F]Fluorodeoxyglucose–PET revealed mild hypermetabolism in bilateral basal ganglia and hypometabolism of bilateral parietal cortex including the posterior cingulate/precuneus. Resting state functional MRI revealed altered connectivity as found with individuals with mild AD. CSF examination revealed a low Aβ42/tau index but a low phospho-tau. An amyloid PET/CT with [18F]florbetaben revealed pronounced cortical radiotracer deposition. This case report suggests that progressive dementia in older HIV+ individuals may be due to HAND, AD, or both. HIV infection does not preclude CNS Aβ/amyloid deposition. Amyloid PET imaging may be of value in distinguishing HAND from AD pathologies.

1) There are NO approved disease-modifying therapies for AD. **All current AD patients will be gone or irreversibly diseased by the time current clinical trial agents are approved and have long-term safety.**

2) Reverse transcriptase inhibitors (RTis) are FDA approved for HIV and hepatitis B and have been in humans for decades with proven, real-world safety. **No AD investigational agent will have this level of safety in our lifetimes**.

3) The United States has two compassionate use pathways for NON-approved experimental agents:

FDA Expanded Access (**EA**) Program
SB 204 Right-to-Try Law (**RTT**) (30 May 2018)

4) However, RTis actually supersede both EA and RTT since they are **already FDA-approved** and can be prescribed **off-label** in the United States.

5) RTis can therefore be prescribed for AD patients **NOW**, albeit with caveats. Controlled clinical trials should absolutely be pursued.