Such complexity may account for the serial failure of antibodies directed against amyloid-β—namely, Pfizer's bapineuzumab and ponezumab and Eli Lilly's solanezumab (*Nat. Biotechnol.* **36**, 483–484, 2018). Other amyloid-β-directed antibodies still in clinical development include Biogen's aducanumab, Roche's crenezumab and AstraZeneca's MEDI1814. Roche's gantenerumab failed a phase 3 trial, but the program has been reanimated after the company re-evaluated the results using a different subindication. The plethora of amyloid variants suggested by the new research could also render β-secretase inhibitors ineffective.

Chun is keen to point out, however, that these new findings may challenge amyloid-β as a drug target but do not unravel the amyloid cascade hypothesis of Alzheimer's disease. "We still maintain a role for the amyloid precursor protein," he says. Indeed, he says, there was "a huge change in both the number and forms" of the genomic *APP* variants seen in the brains from patients with sporadic Alzheimer's disease and those from age-matched unaffected controls.

For instance, in small brain samples of about 50 cells, the scientists detected three to five times more *APP* variants in affected individuals than in healthy controls. Furthermore, among the APP variants identified in neurons from patients with sporadic Alzheimer's disease were 11 somatically derived single nucleotide variants that had previously been published as pathological mutations. None of those 11 variants was found in unaffected brains.

The Sanford Burnham Prebys researchers have proposed that the *APP* variants arise from a 'retro-insertion' of RNA into the APP gene that gives rise to thousands of brain-specific genomic variants. The three-step process involves transcription, copying of major mRNA splice variants and other species by reverse transcriptase, and reinsertion of the cDNA through strand breaks in DNA. Subsequent cycles of expression of the inserted *APP* variants could further extend the range of variants generated.

That somatic recombination takes place in brain cells intrigues Jeong Ho Lee, an associate professor at KAIST (the Korea Advanced Institute of Science and Technology) and chief technology officer at SoVarGen in Daejeon, Korea. His group's work in epilepsy also identified somatic genetic mosaicism resulting from somatic recombination taking place in neuronal cells. Lee's group identified a number of somatic point mutations in the mTOR protein kinase, a result that singled out mTOR as a treatment target for intractable epilepsy. The presence of those mutations is now being incorporated into the diagnostic criteria for the disease, he says.

"In epilepsy, causality between somatic mutation and disease has been proved," says Lee. For sporadic Alzheimer's disease, in contrast, "there is now a very good hypothesis for the variation in *APP* and this is a big step towards identifying a disease etiology that hadn't been considered before." However, linking the genomic *APP* variants to the emergence of disease would, he says, require data to connect the somatic recombination to disease pathology and outcomes.

The immediate impact of Sanford Burnham Prebys work on clinical investigations may be small, however. "My main hope is that this aids better understanding of the underlying biology of dementia," says the Dementia Discovery Fund's Maruyama. "I don't believe that this intriguing result will deflect the course of anti-amyloid trials already in progress, but it would be wise for investigators initiating future anti-amyloid therapies to assess their impact across a range of mosaic-driven recombinant amyloid." ❐

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Digital inhaler for asthma gets FDA nod

An inhaler with a sensor gained US Food and Drug administration go-ahead in December to treat asthma and chronic obstructive pulmonary disease (COPD). The ProAir Digihaler from Teva, based in Petah Tikva, Israel, is an inhaler containing the short-acting bronchodilator albuterol, with built-in sensors to detect when the inhaler is used and to measure inspiratory flow. The data are transmitted wirelessly to a companion mobile app, which enables patients to review and share the information with their healthcare professionals if they choose. Although effective therapies for asthma are widely available, many patients have disease that is poorly controlled. A smart inhaler-and-app combination could help track their inhaler usage, remind them to take their medication and gather data to help manage their condition, and may improve compliance (*Nat. Biotechnol.* **34**, 239–246, 2016). Several other smart inhalers for asthma and COPD are on the market, such as Hailie (from Adherium), Propeller (Propeller Health) and Herotracker (Cohero Health), but Teva's is the first with built-in sensors. Competitors' add-on sensors, however, are compatible with most inhalers. The added medical value of Teva's product is unclear, but the fact that the technology, product and software all belong to the same company might offer Teva a competitive advantage. Teva plans a US-wide launch of ProAir Digihaler for 2020, following a small number of programs to gather real-world experience this year.

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PODCAST

First Rounders: Chad Womack

Chad Womack is director of STEM initiatives at the UNCF. The episode covers Womack's path to HIV research, his experience founding a biotech just before the Great Recession, and what the election of Barack Obama meant to African Americans. Image credit: Chad Womack.
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