Published in final edited form as:

Lancet Neurol. 2013 January ; 12(1): 4–6. doi:10.1016/S1474-4422(12)70284-3.

2012: the year in dementia

Sam Gandy and

Icahn School of Medicine at Mount Sinai and James J Peters VA Medical Center, New York, NY 10029, USA

Steven T DeKosky

University of Virginia, Charlottesville, VA 22908, USA

Sam Gandy: samuel.gandy@mssm.edu; Steven T DeKosky: dekosky@virginia.edu

In Alzheimer's disease research, 2012 has been quite a rollercoaster year. Two genetic discoveries, both made by deCODE in Iceland, were exciting and reassuring. Most striking was the report of a mutation in the amyloid precursor protein (APP), A673T, a missense mutation that rendered APP a much less avid substrate for β -secretase.¹ As a result, all cells in individuals with that mutation produced 25–50% less amyloid- β peptide than did those in individuals without the mutation. The mutation caused no observable harmful effects; on the contrary, the APP A673T mutation conferred protection from Alzheimer's disease. Notably, 25 individuals homozygous for apolipoprotein E ϵ 4 (*APOE* ϵ 4) were protected from Alzheimer's disease, in that despite the significant risk of Alzheimer's disease conferred by *APOE* ϵ 4 homozygosity, they did not develop dementia.

The most obvious outcome of the A673T APP finding is that the amyloid hypothesis of Alzheimer's disease was strengthened substantially. These results also have therapeutic implications. The health of carriers of the A673T APP mutation tells us that chronic modest reduction of amyloid- β concentration has no significant observable effect on human development or health. These findings also provide an estimate of the reduction in amyloid- β concentration we should target to have a meaningful effect on Alzheimer's disease. Finally, whereas *APOE* ϵ 4 homozygosity is the strongest genetic predisposition to Alzheimer's disease, the effect of ϵ 4 is trumped by the low concentration of amyloid- β in these patients (greatly reducing Alzheimer's disease incidence), suggesting that whatever other effects *APOE* ϵ 4 has on the development of Alzheimer's disease, its effect on amyloid is most significant.

The A673T APP narrative complements data from the Dominantly Inherited Alzheimer Network (DIAN) showing that amyloid metabolic changes begin 15–25 years before the onset of symptoms.² Taken together, the A673T and DIAN studies form strong support for therapeutic interventions that decrease amyloid- β concentration as early as possible before the onset of symptoms. Of course, the toxicity profile of the intervention and cost will mitigate early prophylaxis to some extent. In DIAN, all participants had completely penetrant mutations, and thus were destined to develop Alzheimer's disease, so the benefit-to-risk ratio is much different than it would be in the common forms of late-onset Alzheimer's disease. A second effort, known as the Alzheimer Prevention Initiative,³ also began this year and is directed at autosomal dominant Alzheimer's disease in a large cohort

in Colombia; the initial therapy for genetically proven individuals was announced recently as the amyloid monoclonal antibody crenezumab.

Two major clinical trial disappointments were reported in 2012: neither bapineuzumab⁴ nor solanezumab⁵ showed any measurable or meaningful clinical benefit. Bapineuzumab reduced plaque burden and CSF tau levels⁴ but the primary study outcomes were not achieved. Whereas neither of the two individual trials of solanezumab slowed disease progress significantly, when the two parallel cohorts were pooled and analysed, a significant benefit was noted on neuropsychological testing in patients with the mildest disease. The fact that the medication showed the most promising effects in patients with the mildest disease symptoms lends support to the increased emphasis on interventions aimed at early, even presymptomatic, disease.

The importance of traumatic brain injury and the risk for chronic traumatic encephalopathy continued to gain traction in 2012 after the report⁶ of the first patient with chronic traumatic encephalopathy apparently attributable to blast exposure from improvised explosive devices in Operation Iraqi Freedom/Operation Enduring Freedom, or in Afghanistan. The US Department of Defense committed US\$100 million to research in traumatic brain injury or chronic traumatic encephalopathy and the National Football League committed \$30 million to subsidise a National Institute of Neurological Disorders and Stroke (NINDS) effort on these disorders. Important starting points include epidemiology and genetics; first, to obtain the best possible estimate of the frequency of chronic traumatic encephalopathy that is attributable to blast exposures or to athletic injuries; and second, to determine whether genetic testing of adolescents provides useful estimation of who is at the greatest risk for chronic traumatic encephalopathy.⁷

In late 2012, a molecule involved in microglial activity and inflammation, triggering receptor expressed on myeloid cells 2 (TREM2), was linked to common forms of late-onset Alzheimer's disease.⁸ Initial experiments showed that TREM2 is involved in microglial phagocytosis of amyloid- β , and that the clinical mutation impairs its phagocytic action. Other data showed that interleukins 12 and 23 had key roles in the pathogenesis of Alzheimer's disease.⁹ These findings and the demonstration that ablation of their signalling reduced amyloid deposition and slowed behavioural changes in transgenic mice are certain to stimulate renewed investigation of the potential role for anti-inflammatory drugs in modulating the progression of Alzheimer's disease. This investigation is now armed with newly increased specificity toward target molecules of the inflammatory cascade that have crucial roles in the pathogenesis of Alzheimer's disease. The shift of emphasis toward the use of amyloid- β -lowering drugs for prophylaxis might also apply to immunomodulatory or anti-inflammatory interventions.

Removal of amyloid deposition with such treatment might produce the desired effect of reversing the disease process. This treatment might work but might need to be taken for a longer time (eg, 2–3 years to remove all the plaque) than people with symptomatic disease would tolerate; more rapidly acting medications are needed in symptomatic disease. To prevent disease, however, such treatments could be given to patients who were not destined to develop symptoms for a decade or more. Proving efficacy in this situation will initially

require demonstration of altered trajectories of key biomarkers. Long-term follow-up will be needed to prove successful prevention or delay of onset of clinical disease.

The concept of trans-synaptic spread of the aggregated protein pathology of Alzheimer's disease matured in 2012 with the discovery that pathological changes in tau^{10,11} and synuclein¹² can be propagated through the brain in this fashion. The synuclein finding was especially important because the host into which the aggregated inoculum was injected expressed wild-type synuclein deposits. The aggregated synuclein injection induced Lewy-body-like pathological changes throughout the brain and selective demise of dopaminergic neurons. The next challenge is to elucidate the intercellular and intracellular underpinnings of this so-called infectious (some say prion-like) propagation phenomenon, and to develop interventions that would limit the spread of pathological changes and subsequent symptom expression.

In summary, 2012 was marked by further expansion of intervention research into prophylaxis of Alzheimer's disease with anti-amyloid strategies, and by the initiation of two landmark prevention trials in autosomal dominant Alzheimer's disease. Pathogenesis research was galvanised this year by the discovery of surprising mechanisms of protection and of propagation. Chronic sequelae of traumatic brain injury, the most robust environmental risk for Alzheimer's disease, are being pursued across the lifespan to determine just how serious the risk is on a quantitative basis, and whether predisposing genetic factors can be identified and used to predict and counsel those at greatest risk.

Acknowledgments

SG has received support of the Cure Alzheimer's Fund, National Institute of Neurological Diseases and Stroke, VA MERIT Review, and research grants from Amicus Therapeutics and Baxter Pharmaceuticals. SG is also supported by National Institute on Aging grant. Within the past 5 years, SG has served on the Scientific Advisory Board of Diagenic Inc, and on the Safety Monitoring Boards for the Pfizer-J&J Alzheimer Immunotherapy Alliance and for Balance Therapeutics. STDeK declares the consultation for or research support from NIA, Elan, Novartis, Janssen, Pfizer, Baxter, Myriad, Neurochem, Genzyme, Helicon Therapeutics, Siemens, and GlaxoSmithKline in the past 5 years. STDeK is also supported by NIA grants at the University of Pittsburgh, and chairs the Safety Monitoring Board for the CREST-E study of creatine in Huntington's Disease for the National Center for Complementary and Alternative Medicine (NCCAM). He also serves on the Scientific Advisory Council for NCCAM.

References

1. Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. *Nature*. 2012; 488:96–99. [PubMed: 22801501]
2. Bateman RJ, Xiong C, Benzinger TL, et al. Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012; 367:795–804. [PubMed: 22784036]
3. Reiman EM, Quiroz YT, Fleisher AS, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study. *Lancet Neurol*. 2012; 11:1048–56. [PubMed: 23137948]
4. Blennow K, Zetterberg H, Rinne JO, et al. AAB-001 201/202 Investigators. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. *Arch Neurol*. 2012; 69:1002–10. [PubMed: 22473769]
5. Farlow M, Arnold SE, van Dyck CH, et al. Safety and biomarker effects of solanezumab in patients with Alzheimer's disease. *Alzheimers Dement*. 2012; 8:261–71. [PubMed: 22672770]

6. Omalu B, Hammers JL, Bailes J, et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurg Focus*. 2011; 31:E3. [PubMed: 22044102]
7. Gandy S, Dekosky ST. *APOE ε4* status and traumatic brain injury on the gridiron or the battlefield. *Sci Transl Med*. 2012; 4:134ed4.
8. Jonsson T, Stefansson H, S S Ph D, et al. Variant of TREM2 Associated with the Risk of Alzheimer's Disease. *N Engl J Med*. 2012 published online Nov 14. 10.1056/NEJMoa1211103
9. vom Berg J, Prokop S, Miller KR, et al. Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. *Nature Med*. 2012 published online Nov 25. 10.1038/nm.2965
10. de Calignon A, Polydoro M, Suárez-Calvet M, et al. Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron*. 2012; 73:685–97. [PubMed: 22365544]
11. Liu L, Drouet V, Wu JW, et al. Trans-synaptic spread of tau pathology *in vivo*. *PLoS One*. 2012; 7:e31302. [PubMed: 22312444]
12. Luk KC, Kehm VM, Zhang B, O'Brien P, Trojanowski JQ, Lee VM. Intracerebral inoculation of pathological α -synuclein initiates a rapidly progressive neurodegenerative α -synucleinopathy in mice. *J Exp Med*. 2012; 209:975–86. [PubMed: 22508839]

Biography