CLINICAL IMPLICATIONS OF BASIC RESEARCH

Preclinical Success against Alzheimer's Disease with an Old Drug

Frank M. LaFerla, Ph.D.

Alzheimer's disease is a chronic and devastating neurodegenerative disorder that impairs the patient's memory, destroys the ability to reason and make rational judgments, and leads to myriad behavioral and psychiatric symptoms. With a new case of Alzheimer's disease now developing every 68 seconds in the United States, estimates indicate that the prevalence may nearly triple by midcentury, from 5.4 million to at least 13.5 million patients. If these estimates are accurate, Alzheimer's disease will pose an unprecedented medical, social, and economic burden on our society.

After decades of research into the molecular and genetic mechanisms underlying this insidious disease, it is disappointing that no disease-modifying therapies have yet been introduced into clinical practice. The impending tsunami of new cases and the time required for introducing a drug to the market increase the urgency of identifying new therapeutic targets and strategies. In a recent study, Cramer et al.[1] report that the drug bexarotene (Targretin), already approved by the Food and Drug Administration for the treatment of cutaneous T-cell lymphoma, shows promising efficacy in preclinical models of Alzheimer's disease.

The hallmark neuropathologic lesions of Alzheimer's disease are neuritic plaques and neurofibrillary tangles.[2] Neuritic plaques consist of a small, aggregation-prone peptide, β-amyloid (Aβ), which is generated by proteolytic cleavage of the transmembrane amyloid precursor protein (Fig. 1). The vast majority of such cases occur sporadically, unlike early-onset, autosomal dominant familial Alzheimer's disease, which is caused by mutations in one of three genes (encoding amyloid precursor protein, presenilin 1, or presenilin 2) and is thought to be caused by increased production or aggregation of Aβ. Sporadic cases are thought to result from a failure in Aβ clearance mechanisms, and the major risk factor for such cases is a polymorphism affecting apolipoprotein E (APOE), a cholesterol transport protein that promotes the proteolytic degradation of Aβ.[3]

The gene encoding APOE is polymorphic, with the occurrence of three allelic variants in the human population, *APOE2*, *APOE3*, and *APOE4*. The most common allele in the general population is *APOE3*, although the *APOE4* allele is significantly overrepresented in patients with Alzheimer's disease; it occurs in 40 to 65% of all affected persons. Although carrying the *APOE4* allele is neither necessary nor sufficient for disease, the presence of such an allele significantly increases risk. In contrast, *APOE2* is neuroprotective, and carriers have a reduced probability of disease. The mechanism by which APOE4 accelerates the disease is unknown, although both toxic gain-of-function and loss-of-function effects (which might compromise the ability of APOE to clear Aβ) are plausible. Expression of *APOE* is regulated through the action of the nuclear receptors peroxisome-proliferator–activated receptor γ (PPAR-γ) and liver X receptor in conjunction with retinoid X receptor, representing a target of opportunity to modulate its levels pharmacologically (Fig. 1).

Cramer and colleagues hypothesized that bexarotene, an agonist of retinoid X receptor, might improve the degenerative phenotype in Alzheimer's transgenic mice by enhancing apoE levels, thereby reducing the amount of Aβ in the brain.[1] This is exactly what happened in transgenic mice, although the rapidity of the clearance was astonishing, with areas of Aβ plaques reduced by more than 50% within 72 hours. Treatment also reversed the cognitive, social, and olfactory deficits. Importantly, bexarotene reduced Aβ levels in an apoE-dependent manner (i.e., it had no effect in apoE-null mice). The authors found that the drug converts microglia into their alternative activation state and thereby promotes Aβ phagocytosis.

Rarely is science straightforward. Bexarotene rapidly reduced plaques by as much as 75% after

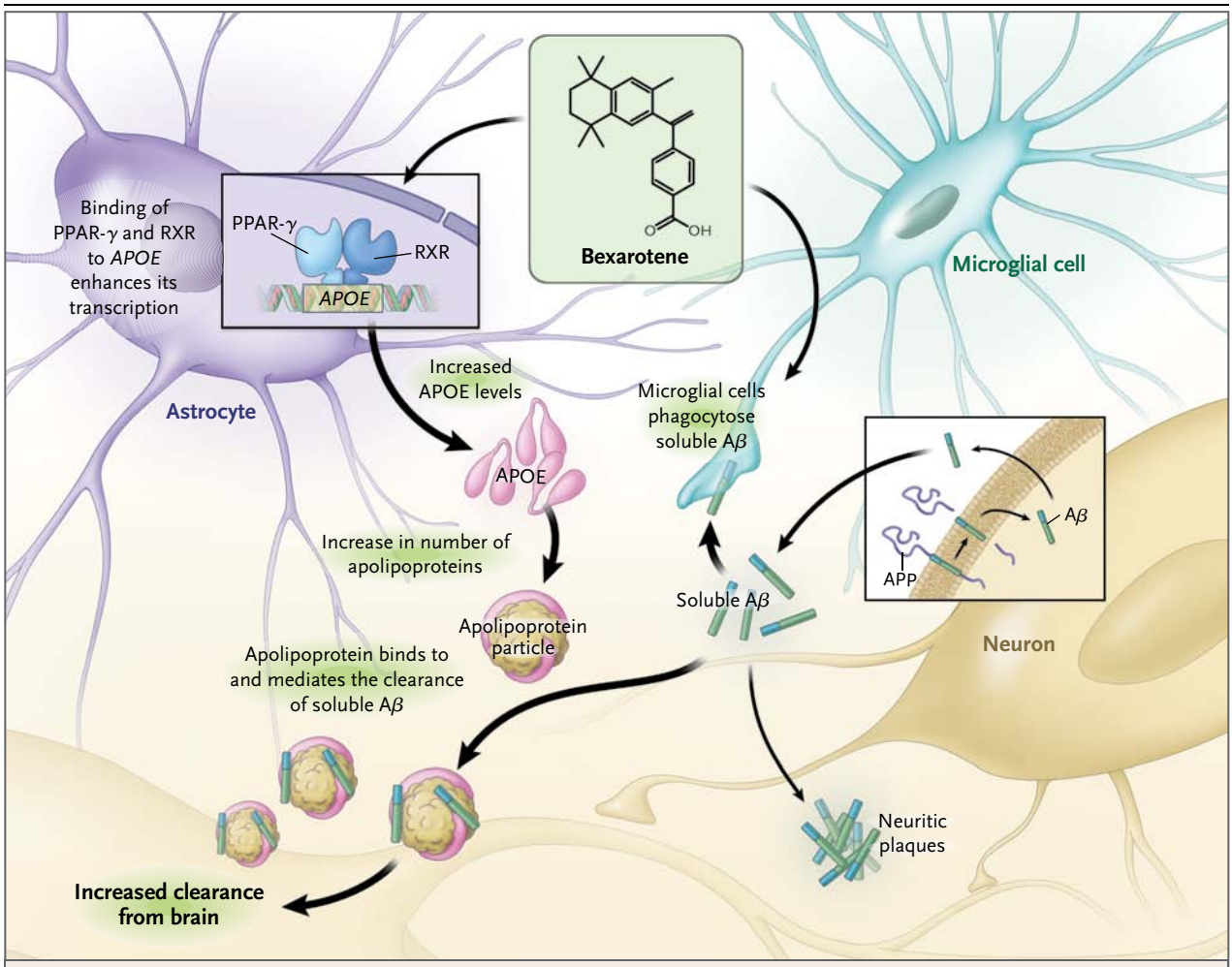

Figure 1. A Molecular Model of β-Amyloid Clearance and Cognition.

Neurons are thought to be the main cellular source that releases the aggregation-prone β-amyloid (Aβ) peptide, which can then form neuritic plaques, a hallmark pathologic feature of Alzheimer's disease. Apolipoprotein E (APOE) is released mainly from astrocytes and microglia, although a small amount may also come from neurons. APOE associates with lipoproteins to form APOE-associated lipoprotein particles, which can bind to soluble Aβ, promoting its clearance from the brain. Cramer et al.[1] have recently reported that bexarotene, a nuclear receptor agonist, increases APOE expression, which stimulates the clearance of Aβ and improves the cognitive deficits in a murine model of Alzheimer's disease. PPAR-γ denotes peroxisome-proliferator–activated receptor γ, and RXR retinoid X receptor.

14 days in the transgenic mice, but treatment over the course of 3 months was accompanied by a reversion of plaque burden to the point at which it was equivalent to that in control mice. The clinical implications of this observation are not yet clear; it may indicate that the treatment regimen or interval of administration needs to be carefully considered.

Despite the encouraging results, one cannot help but feel that the field has been down this road before, as successes in preclinical models have thus far not translated well into the clinic. Why have so many therapies and interventions for Alzheimer's disease been successful in preclinical models but universally failed when evaluated in clinical trials in humans? The answer to this question is multifactorial, but the most parsimonious explanation is that the majority of compounds are evaluated in models that harbor only amyloid pathology and notably lack other critical pathological features, such as neurofibrillary tangles and substantial neuronal death. Another likely reason is that a disorder as complex as Alzheimer's disease will require multiple ther-

apeutic interventions. As pointed out by Lowenthal et al.[4] in this issue of the *Journal*, only a well-designed and carefully executed clinical trial will reveal whether this class of drug lives up to its promise. Until such trials are performed, it would be a mistake to offer this treatment to Alzheimer's patients.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Institute for Memory Impairments and Neurological Disorders, University of California, Irvine.

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