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Catalytic antibody (catabody) platform for age-associated amyloid disease: From Heisenberg's uncertainty principle to the verge of medical interventions

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ABSTRACT

Quantum mechanics-based design of useful catalytic antibodies (catabodies) failed because of the uncertain structure of the dynamic catalyst-substrate complex. The Catabody Platform emerged from discovery of beneficial germline gene catabodies that hydrolyzed self-proteins by transient covalent pairing of the strong catabody nucleophile with a weak target protein electrophile. Catabodies have evolved by Darwinian natural selection for protection against misfolded self-proteins that threatened survival by causing amyloid disease. Ancient antibody scaffolds upregulate the catalytic activity of the antibody variable (V) domains. Healthy humans universally produce beneficial catabodies specific for at least 3 misfolded self-proteins, transthyretin, amyloid β peptide and tau protein. Catabody are superior to ordinary antibodies because of catalyst reuse for thousands of target destruction cycles with little or no risk of causing inflammation, a must for non-toxic removal of abundant targets such as amyloids. Library mining with electrophilic target analogs (ETAs) isolates therapy-grade catabodies (fast, specific). *Ex vivo*- and *in vivo*-verified catabodies specific for the misfolded protein are available to dissolve brain, cardiac and vertebral amyloids. Immunization with ETAs overcomes important ordinary vaccine limitations (no catabody induction, poor immunogenicity of key target epitopes). We conceive electrophilic longevity vaccines that can induce catabody synthesis for long-lasting protection against amyloid disease.

1. Emergence of the catabody concept as an anti-aging defense

The quest for developing specific catalytic antibodies (catabodies) that accelerate chemical reactions as a medical targeting principle dates back to the transition state theory of Linus Pauling (Pauling, 1946). Quantum mechanics-based design of medically useful catabodies that hydrolyze peptide bonds, however, failed because of the Heisenberg's uncertainty principle (Pollack et al., 1989; Tramontano et al., 1986). There was ambiguity about the dynamic electronic structure of the catalyst-substrate complexes en route to product formation, including the high energy non-covalently bonded transition state and the somewhat more discrete intermediates with covalently bonded character. The hurdle is not limited to accurate structural mimicry of the substrate transition state for use as a catabody-inducing immunogen. Lessons from enzymes, the classical biological catalysts, indicate that rigid catalyst shape complementarity with a single state of the substrate is insufficient. Rather, catalysts must adapt their active site conformation to accommodate the transient electronic structures of multiple substrate states for efficiently completing the catalytic cycle and initiating additional reaction cycles.

We discovered human autoantibodies that catalyze the hydrolysis of peptide bonds in the self-antigen vasoactive intestinal peptide (Paul et al., 1989). Far from an abstruse rarity, increased production of catabodies directed to self-antigens is now viewed as a contributory factor in the pathogenesis of autoimmune disease (Nevinsky and Buneva, 2010; Paul et al., 2012). The prevalence of autoimmune disease increases with advancing age. Specific inhibitors of harmful catabodies to self-antigens were suggested as a potential therapy (Nishiyama et al., 2004; Planque et al., 2008). The autoimmune disease findings were the proverbial tip of the iceberg. Increasing evidence suggests the existence of beneficial catabodies as a universal first-line defense system that evolved by Darwinian evolution for protection against misfolded self-

Abbreviations: Aβ, amyloid β; BCR, B cell receptor; C, constant; CAA, cerebral amyloid angiopathy; catabody, catalytic antibody; D, diversity; ETA, electrophilic target analog; E-vaccine, electrophilic vaccine; FR, framework region; HIV, human immunodeficiency virus; IVIG, intravenous immunoglobulin; J, Joining; mis, misfolded; MRI, magnetic resonance imaging; RNAi, RNA interference; TTR, transthyretin; V, variable

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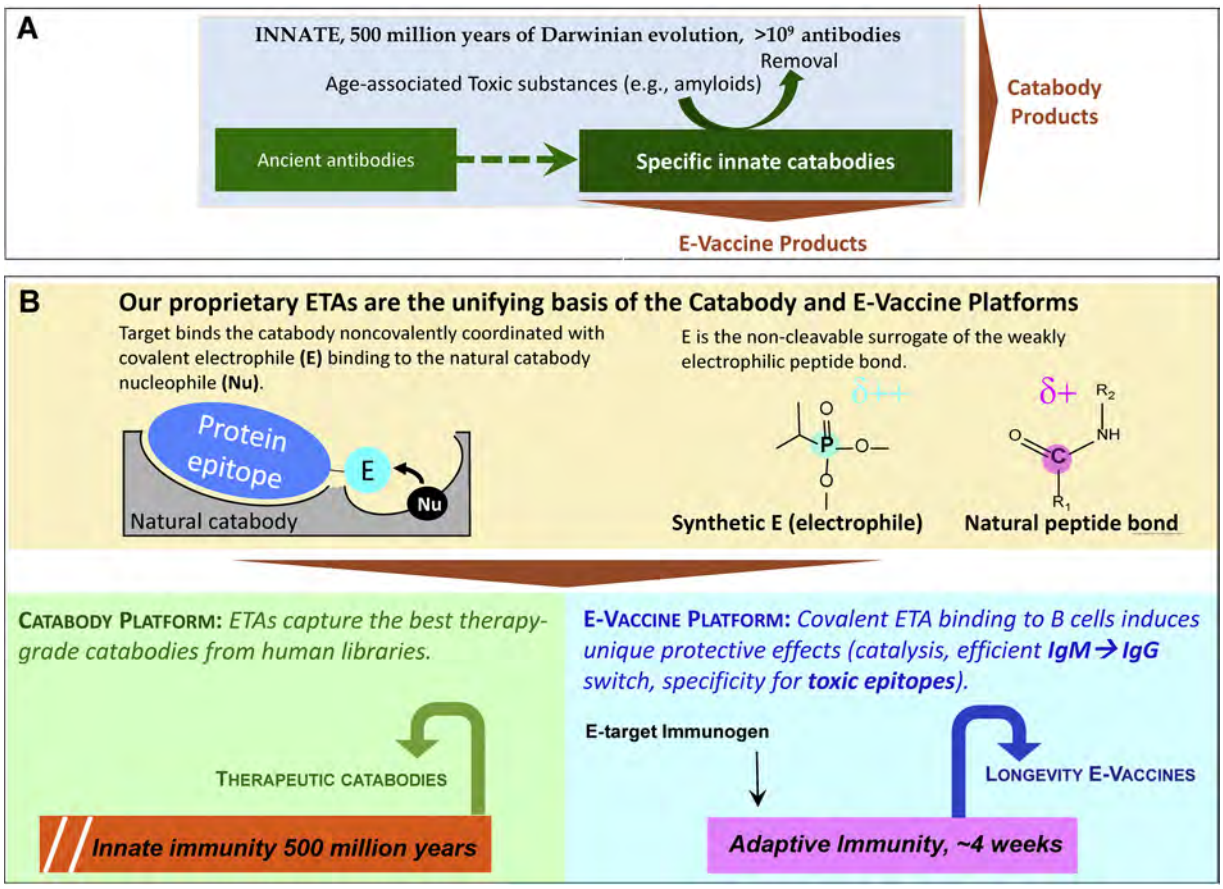

Fig. 1. Birth of the nature-made catalytic antibody (Catabody) and electrophilic vaccine (E-vaccine) platforms. ***A.*** The Catabody Platform technology is based on discovery of constitutive (or innate germline-encoded) catabodies that clear at least two classes of toxic substances, pathogenic misfolded aggregates of self-proteins and microbial superantigens. Therapeutic catabody drugs can be isolated from the innate catabody repertoire. E-vaccines amplify and improve the innate catabody repertoire for potential prophylactic and therapeutic use. ***B.*** ETAs are the unifying basis of the two platforms. The strongly electrophilic phosphonate group inserted into the ETA binds covalently to the catabody nucleophilic site in coordination with epitope binding to the noncovalent catabody site (blue), capturing the rare catabodies with greatest catalytic rate and specificity from human antibody libraries. ETAs used as immunogens to amplify and improve the natural catalytic antibody repertoire by adaptive mechanisms are designated E-vaccines (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

proteins responsible for causing age-associated amyloid disease (Fig. 1A). Development of the foregoing concept occurred in two distinct stages. Constitutively produced, germline gene-encoded catabodies affording low affinity and promiscuous hydrolysis of peptide bonds were identified as ubiquitous components of the blood in healthy humans (Kalaga et al., 1995; Planque et al., 2004). Next, smaller subsets of catabodies that were still ubiquitously-distributed in healthy humans were found to specifically catalyze the breakdown of self-proteins that misfold into amyloid structures (Planque et al., 2014b; Taguchi et al., 2008a).

The misfolded self-protein directed catabodies are the basis of our anti-aging Catabody Platform. Basic science building blocks of the platform were: ***(a)*** Deciphering the catabody specificities and chemical mechanisms (Gao et al., 1995; Hifumi et al., 2012; Lacroix-Desmazes et al., 2006; Paul et al., 2012; Polosukhina et al., 2004); ***(b)*** Defining the immune ontogeny of the catalytic site and antibody scaffold effects (Gololobov et al., 1999; Kamalanathan et al., 2010; Le Minoux et al., 2012; Paul et al., 2004; Planque et al., 2004; Sapparapu et al., 2012); and ***(c)*** Development of electrophilic target proteins analogs (ETAs) used to isolate therapy-grade catabodies (Planque et al., 2015; Taguchi et al., 2008b) and induce their synthesis for prophylactic and therapeutic vaccination (Durova et al., 2009; Gunter et al., 2018; Nishiyama et al., 2009; Paul et al., 2003; Planque et al., 2014a; Reshetnyak et al., 2007). We suggest that the field has moved from its erstwhile 'science fiction' status to an enabling technology suitable for medical needs that are not met by traditional means.

2. Constitutive antibody repertoires as anti-aging catabody sources

Thirty seven self-proteins misfold into particulate and soluble aggregates (Chiti and Dobson, 2017). The misfolded soluble oligomers serve as precursors for the higher order particulate aggregates, appearing in test tube solutions of purified amyloidogenic proteins within minutes to days. The misfolding process is accelerated by age-associated metabolic disturbances, for example, increased generation of advanced glycation and lipid peroxidation end products (Butterfield et al., 2010; Srikanth et al., 2011). Misfolded self-protein aggregates are a significant cause of aging, exemplified by appearance of lumbar spinal stenosis and carpal tunnel syndrome due to misfolded transthyretin (misTTR) in 40–50 % of humans > 50 years age and cardiac myopathy at a later age (Aus dem Siepen et al., 2019; Sekijima et al., 2011; Westermark et al., 2014; Yanagisawa et al., 2014). About 15–20 % of humans show at least mild cognitive impairment due to Alzheimer disease, thought to be triggered by misfolded amyloid β (Aβ) aggregates starting around age 65 years (Alzheimer's Association, June 10, 2019).

Our studies suggest that specific, constitutively produced catabodies are the primary proteostatic mediators in the blood of humans that destroy the disease-causing misfolded self-protein aggregates (Planque et al., 2014b; Taguchi et al., 2008a). In contrast, text-book portrayals of

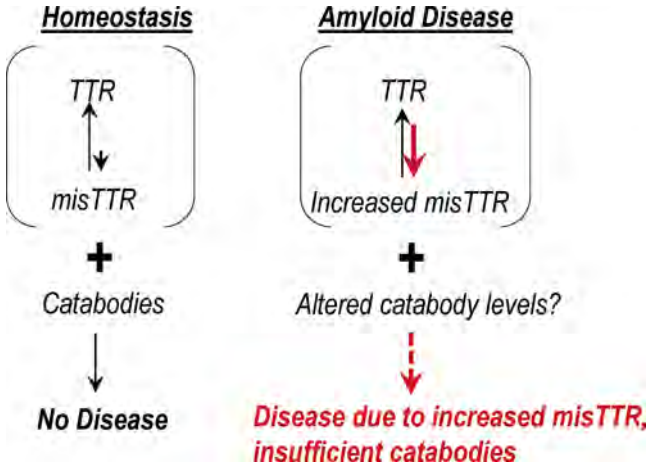

Fig. 2. Catabody defense against TTR amyloid disease. misTTR amyloid is deposited when its formation rate (red arrow) exceeds its removal rate by catabodies. misTTR formation can increase by these mechanisms: *(a)* Generation of oxidized misTTR with enhanced amyloid-forming tendency in circumstances inducing the "carbonyl stress state", e.g., inflammation(Zhao et al., 2013); and *(b)* Metal ions that accelerate misfolding (Castro-Rodrigues et al., 2011). Changes in the catabody concentrations could also contribute to disease, for example, due to age-as sociated weakening of the immune system (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.).

humoral immunity focus on IgG class antibodies that mature within days to weeks following stimulation with the foreign (non-self) antigens. The variable (V) domains of ordinary antibodies acquire their functional properties (high affinity, specific target epitope binding) only after their somatic affinity maturation driven by an immunogen expressing the target epitope. A subset of germline V gene-encoded catabodies produced by B lymphocytes *without* prior treatment with the immunogen expressed robust proteolytic activity, justifying description of such catabodies as 'constitutive' or 'natural' (Gololobov et al., 1999; Kamalanathan et al., 2010; Le Minoux et al., 2012). The IgM→IgG class switching maturational step suppresses the catalytic function of antibodies. In this step, the constant (C) domains of highly catalytic IgMs, the first antibody class produced by lymphocytes, are replaced by the IgG C domains that downregulate the activity of the remote catalytic site located in the V domains (Sapparapu et al., 2012).

The observed catabody properties display clear departures from classical immunology rules. Our perspective of constitutive catabodies specific for the disease-causing misfolded self-proteins is conditioned by the organismal survival requirements during Darwinian evolution. Natural selection pressures have shaped the Darwinian evolution of the large germline V domain repertoire ($> 10^9$ domains with differing sequence) produced by immunogen-independent recombination of the V genes with the diversity (D) and joining (J) genes (which precedes the immunogen-driven somatic V domain affinity maturational step). This process had already evolved about 500 million years ago at the start of the phanerozoic era in the earliest extant organisms with a discernible antibody-based immune system (jawed fish). *Nota bene*, as the problem of self-protein misfolding is an intrinsic organismal weakness that is even more ancient than the threat of extinction due to the external (non-self) microbes, eliminating amyloid disease at an early age can safely be assumed to serve as a strong selective pressure for evolving a constitutive immune defense against the misfolded self-proteins, *i.e.*, the specific germline gene-encoded catabodies. Note also the radically different functional outcomes in catabody targeting of the misfolded self-protein aggregates *versus* their properly-folded counterparts – immune tolerance to the properly-folded self-protein conformation is essential for homeostasis, whereas evolving catabodies specific for the misfolded conformation serves is a survival mechanism. The blood-borne IgM catabodies displayed exquisite specificity for misTTR with no evidence of reactivity towards properly-folded TTR, assuring that the catabodies can selectively destroy the pathogenic target responsible for disease without interfering in the important physiological functions of TTR (Planque et al., 2014b). From these considerations, we suggest that catabodies specific for misfolded self-proteins evolved early in phylogeny as a first-line immune defense against age-associated amyloid disease.

Precedents for the observed properties of catabodies to misfolded proteins are available. Therapeutic IVIG formulations (intravenously administered IgG pooled from disease-free humans) contain antibodies that bind Aβ and misfolded tau, polypeptides fundamental to the pathogenesis of brain degeneration in Alzheimer disease (Klaver et al., 2010; Smith et al., 2014). Extensive evidence indicates that humans produce germline catabodies and ordinary antibodies specific for the 'superantigenic' epitopes that microbes use to evade an immunogen-induced protective immune response (Berberian et al., 1993; Neshat et al., 2000; Paul et al., 2004, 2012; Silverman et al., 2000). We documented the cross-reactivity of some but not all monoclonal catabodies to misTTR aggregates with microbial superantigens, suggesting the potential of a common evolutionary origin of catabodies to these protein classes (Planque et al., 2014b).

Thus, the constitutive (preimmune) antibody V domain repertoire is available as a rich source of specific catabodies for targeted destruction of misfolded proteins that cause amyloid disease. The small, highly catalytic and highly specific catabody subset is of greatest interest both as a natural defense against amyloid disease and as a source of potential immunotherapy agents. We suggest that amyloid disease occurs when the catabody clearance capacity is overwhelmed by increasing age-associated accumulation of the misfolded self-protein aggregates (Fig. 2). Further, the health and regulatory environment of B lymphocytes could result in up-regulation or down-regulation of the catabody concentration. Preliminary findings suggest decreased blood concentrations of catabodies to misTTR in aged patients with TTR amyloid disease, and we documented increased blood concentrations of catabodies to Aβ in patients with Alzheimer disease (Taguchi et al., 2008a).

3. Benefits, enablement and scope of catabody anti-aging platform

Catabodies outperformed ordinary antibodies in two significant aspects. By definition, a catalyst is re-used again and again to inactivate and destroy large quantities of the harmful target (Fig. 3). First, we proved in side-by-side tests that a small catabody amount permanently removes the target with efficacy far superior to an ordinary antibody (which can only bind reversibly to the target on a 1:1 basis) (Table 1). Human IgM catabodies selectively destroyed misfolded but not normally folded TTR into non-aggregable fragments without potential for initiating or sustaining systemic amyloid disease (Fig. 4). Likewise, human catabody fragments digested Aβ into non-toxic and non-aggregable fragments without potential for initiating or sustaining Alzheimer's disease (Planque et al., 2015; Taguchi et al., 2008b). Second, while ordinary antibodies form stable immune complexes that inevitably induce inflammation, the catabody-substrate complexes are too transient to activate inflammatory cells, as observed for catabody studies of brain Aβ targeting in mouse models (Kou et al., 2015; Planque et al., 2015). Catabodies are particularly valuable if large amounts of the target are to be removed, as is required for effectively treating amyloid diseases. In such diseases, the inflammatory damage induced by an ordinary antibody will be so great that the favorable amyloid removal effect is essentially canceled out.

Selection of large human antibody libraries with the mechanism-based target protein analogs is a key step in isolating the best catabodies suitable for development as therapeutic reagents. We found that catabodies utilize the split active site model to accomplish specific catalysis. Catabody specificity derives from binding of individual target proteins at a noncovalent subsite, followed by peptide bond hydrolysis

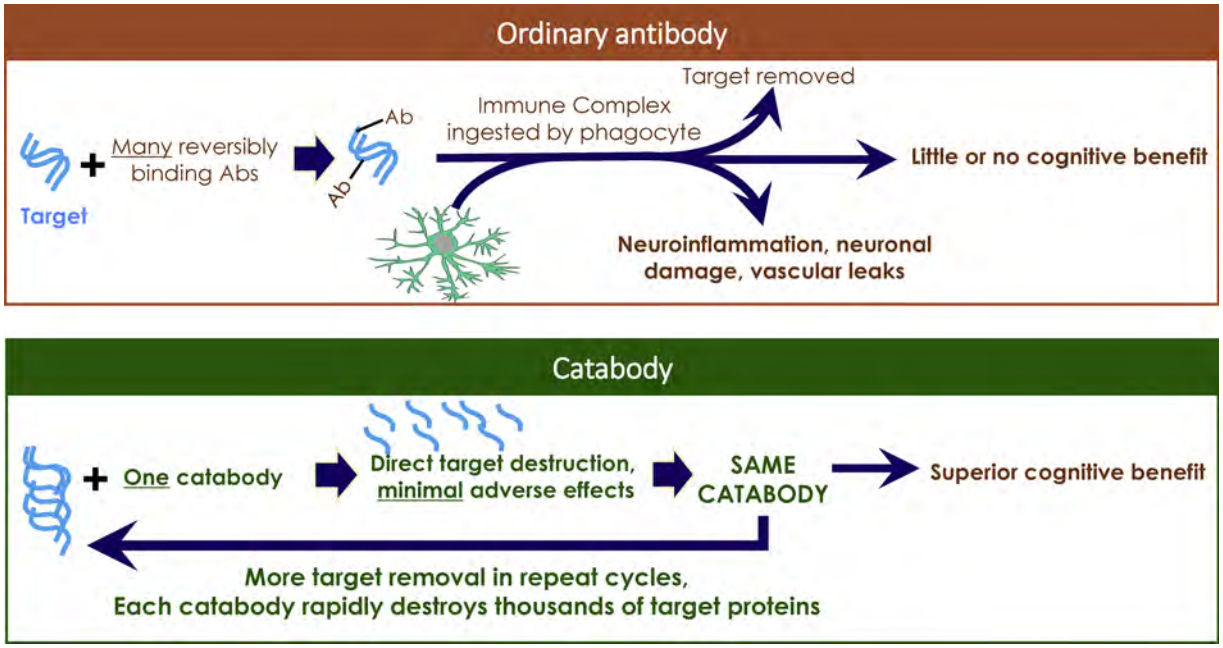

Fig. 3. Catabodies outperform ordinary antibodies. Ordinary antibodies only bind the target amyloid. They depend on inflammatory cells for removing the antibody-target immune complex, which inevitably activate neuroinflammatory and blood vessel leakage processes that impair tissue function even if the objective of tissue amyloid removal is successful. The example of catabody effects in the brain is shown. In contrast, catabodies bind only very transiently to the target amyloid, quickly moving to direct amyloid destruction without dependence on inflammatory cells. Moreover, catabodies are reused for multiple reaction cycles, whereas ordinary antibodies work on a 1:1 basis only for a single reaction cycle.

Table 1
Efficacious dissolution of misfolded TTR amyloid aggregates by Cardizyme. Cardizyme was isolated from the B cell repertoire of a healthy human by selection with an E-misfolded TTR ETA as in (Planque et al., 2014b) and preparation of a cell secreting this catabody. Hydrolysis of misfolded TTR by Cardizyme resulted in potent dissolution of the amyloid. Misfolded amyloid preparation, Cardizyme selection method and assays of misfolded TTR hydrolysis and dissolution are described in ref Planque et al., 2014b.

Antibody	80 % misTTR dissolving concentration
Ordinary antibody	No dissolution at 2000 μg/ml
Catabody	0.210 μg/ml

at a spatially neighboring catalytic subsite (Gao et al., 1995; Paul, 1996). A strong nucleophile in the catabody subsite pairs covalently with the weakly electrophilic peptide bond in the target protein. The reaction proceeds to completion by water attack on the covalent catabody-target intermediate. Based on this reaction mechanism, we synthesized non-hydrolyzable protein analogs containing the phosphonate electrophilic group in proximity of the target epitope (ETA) (see schematic structure in Fig. 1B). From the reaction energetics perspective, an ETA mimics the high-energy covalent intermediate of the target misfolded protein complexed to the nucleophilic catabody site (Fig. 5). ETAs capture catabodies that form specific covalent intermediates with their target. The intermediate is less evanescent than its precursor noncovalent target-catalyst transition state, thus bypassing at least some of the uncertainty imposed by the Heisenberg principle. The ETAs were enabling, in that they allowed isolation of cell lines producing therapy-grade catabodies to diverse targets from libraries of human antibody-producing B cells and phage-displayed antibody fragments (rapid catalytic rate, no off-target reactivity).

Many things go wrong in human aging, and if humans live long enough something or the other invariably goes wrong. The phenomenon of constitutive catabodies is not limited to the misTTR and Aβ disease-causing self-proteins. We identified catabodies to additional amyloid-forming proteins (misfolded tau, immunoglobulin light

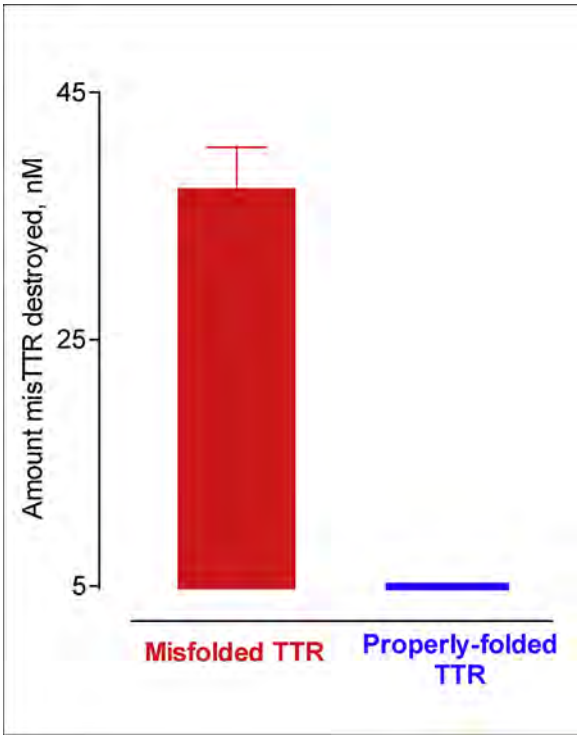

Fig. 4. Catabody destruction of misfolded self-protein aggregates. Example data of selective catalytic destruction of misfolded TTR aggregates (misTTR) but not properly folded TTR by IgMs purified from the blood of healthy humans. Data are from Planque et al., 2014b.

chains). Indeed, the value of the Catabody Platform likely extends to virtually any of the innumerable proteins that contribute directly or indirectly in disease and damage to various organ systems in aging, including the protein targets involved in increased susceptibility of

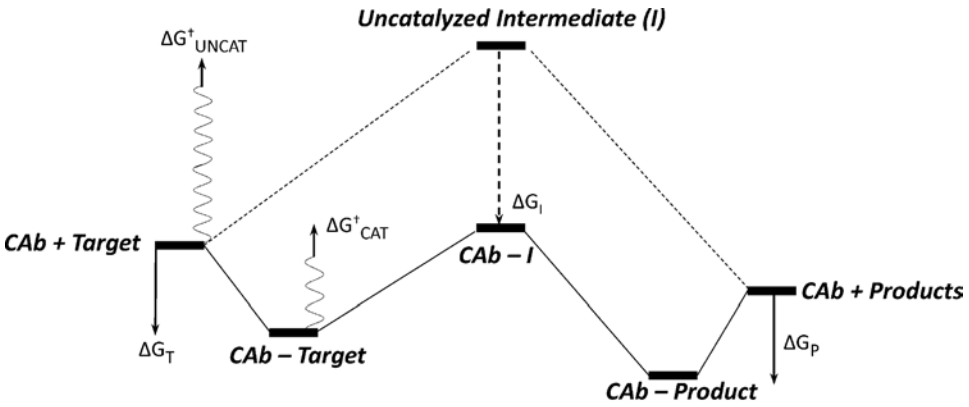

Fig. 5. Free energy of catalytic peptide bond hydrolysis. A nucleophilic catabody (CAb) reacts transiently by covalent means with the weakly electrophilic peptide bonds in the targeted antigen, which stabilizes the intermediate of peptide bond hydrolysis reaction. Catalysis occurs only if $\Delta G^{\dagger}_{CAT}$ is lower than $\Delta G^{\dagger}_{UNCAT}$ (these terms represent, respectively, the free energy input for generating the reaction intermediate with or without catabody). Note that ΔG_T, the stabilization energy obtained from noncovalent catabody target binding, is smaller than ΔG_I, the stabilization energy from reaction intermediate binding.

- Catalysis occurs because $\Delta G_{CAT} < \Delta G_{UNCAT}$
- $\Delta G_T < \Delta G_I$

humans to microbial infections and autoimmune, neurological, cardiovascular and neoplastic disease. Specific catabodies can be generated on-demand either from the constitutive or immunogen-induced antibody repertoires. The current monoclonal antibody market is mostly devoted to suppressing self-proteins for achieving disease control. We and others documented increased catabodies to numerous self-proteins in autoimmune disease (Bangale et al., 2003; Saveliev et al., 2003; Shuster et al., 1992; Wootla et al., 2011). Our antibody fragment library from patients with autoimmune disease is an important source of novel catabodies to disease-associated self-proteins, for example, the epidermal growth factor receptor for tumor targeting, the enzyme PCSK9 for reducing serum cholesterol, immunoglobulin E for allergy control, and TNFα and other cytokines/chemokines for treating diseases such as rheumatoid arthritis and psoriasis. We think catabodies hold potential to capture a significant portion of the still-expanding therapeutic antibody market.

4. Lead anti-aging catabodies

We describe support for developing two preclinical stage catabodies. Catabody Cardizyme is intended to treat systemic age-associated amyloid disease caused by misTTR. Partially effective competing drugs are beginning to emerge for this disease. Catabody Alzyme alone or in combination with catabody Tauzyme is intended for treatment of Alzheimer disease. The potential medical significance and market size is enormous. The catabodies rely on uniquely favorable mechanisms and proof-of-concept for their efficacy and safety has been generated. We suggest that the risk *versus* reward ratio for the Cardizyme and Alzme/Tauzyme lead products is favorable.

4.1. Cardizyme for systemic amyloid disease

Cardizyme targets the toxic oligomers and higher order amyloid aggregates of misTTR, the singular cause of TTR amyloid disease. The Cardizyme drug development path is comparatively short and uncomplicated. TTR amyloid disease is a substantial and increasing cause of morbidity and mortality as human age beyond the fifth decade. The age-associated disease market for Cardizyme world-wide is large, and 3–4 % of African-Americans are at risk for the familial form amyloid disease because of a mutation in the TTR gene (Buxbaum and Ruberg, 2017). Clinical trial data obtained mostly from patients with the familial amyloid disease suggest that the competing drugs under development have limited efficacy. Further, the drug mechanism leaves open the risk of significant side effects due to drug interference with the physiological functions of properly folded TTR (Tafamidis, a stabilizer of the TTR tetramer; Patisiran/Inotersen, RNAi drugs that silence the TTR gene). Properly folded TTR is the carrier for thyroid hormones, retinol and retinol binding protein in blood. Long-term TTR suppression may be associated with negative effects on visual acuity and lipid metabolism. These drugs may reach the market for age-associated TTR amyloid disease ahead of Cardizyme (Adams et al., 2017; Maurer et al., 2018; Minamisawa et al., 2019), but an unmet medical need for treating the disease more effectively will remain. Their clinical trials were focused on the cardiac myopathy and polyneuropathy disease manifestations. Several recent publications indicate that age-associated accumulation of TTR amyloid causes musculoskeletal disease as early as middle age: lumbar spinal stenosis, carpal tunnel syndrome and osteoarthritis (Aus dem Siepen et al., 2019; Matsuzaki et al., 2017).

Cardizyme is an IgM class catabody isolated using a mechanism-based misTTR ETA that selects B cells from healthy humans producing rapid and specific catabodies. The ETA selection method for Cardizyme source lymphocytes was validated (Planque et al., 2014b). *Ex vivo* efficacy studies indicated complete amyloid removal from the lumbar vertebral tissue of a patient with spinal stenosis (Fig. 6**A,B**). Small Cardizyme amounts rapidly destroyed and dissolved misTTR aggregates into harmless smaller fragments. There was no reactivity with properly folded TTR or irrelevant proteins. Cardizyme is the only drug capable of directly and selectively destroying the misTTR aggregates. Other drugs under development do not target the preformed misTTR that causes disease. For example, competing RNAi drugs inhibit overall TTR synthesis, which also suppresses the physiological TTR functions. Further, non-inflammatory destruction of misTTR is an important Cardizyme feature. Ordinary antibodies require macrophages to accomplish amyloid removal, which activates inflammatory processes that damage the amyloid-laden tissue.

4.2. Alzyme/Tauzyme for Alzheimer disease

Alzyme, a single chain dimer composed of two antibody light chain V domains, is a nanocatabody fragment specific for Aβ (Taguchi et al., 2008b). Alzyme is a stand-alone product in its own right. It exemplifies the power of the Catabody Platform to obtain rapid and specific catabodies in alternative molecular formats suitable for different diseases. It also provided proof that the observed *ex vivo* amyloid dissolution activity of catabodies translates to amyloid clearance *in vivo*. Removal of brain Aβ deposits by low-dose, brief intravenous Alzyme treatment was

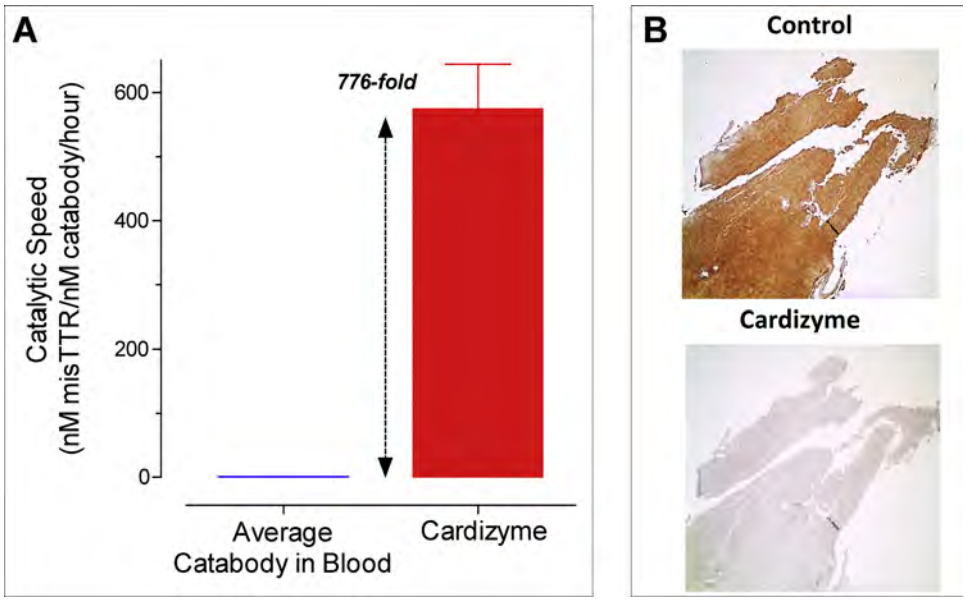

Fig. 6. Selection of lead catabody that dissolves human misfolded TTR (misTTR) vertebral amyloid deposits *ex vivo*. ***A.*** Compared to the average catalytic misTTR destruction of IgMs in the blood of healthy humans, the lead IgM catabody (Cardizyme) selected by human B lymphocyte binding to an E-misTTR ETA displayed about 780-fold faster destruction rate. Methods for selecting Cardizyme and measuring catalytic misTTR destruction are described in Planque et al., 2014b. ***B.*** Sections of lumbar vertebral ligamentum flavum from a patient with spinal stenosis were treated with 100 nM Cardizyme (bottom) or an equivalent noncatalytic antibody concentration (top). misTTR amyloid deposits were visualized by staining with a monoclonal misTTR-binding IgG (brown deposits). Near-complete misTTR removal from the diseased tissue is evident. The dissolution of misTTR deposits occurred without provision of inflammatory cells required by ordinary antibodies.

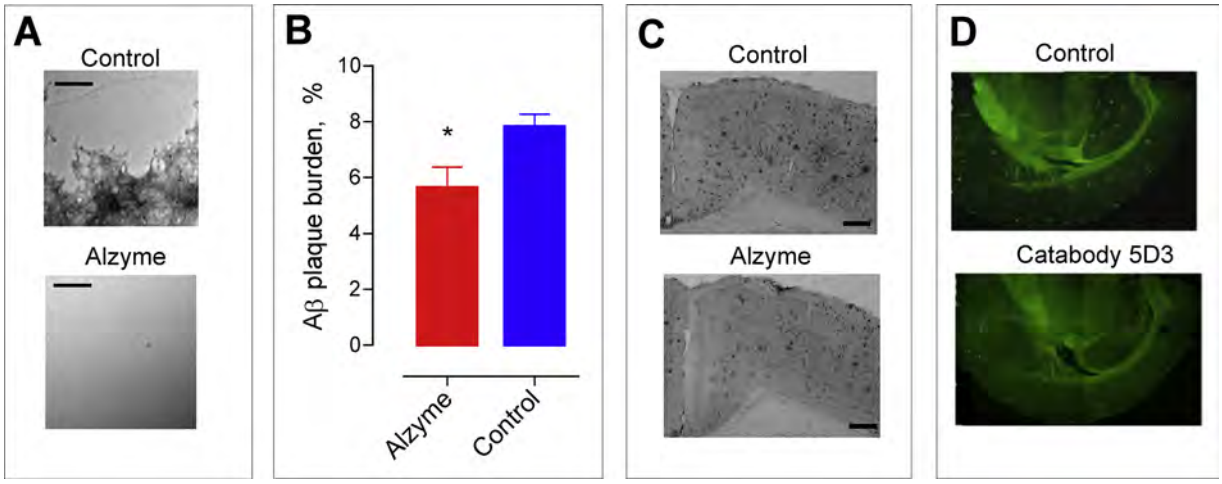

Fig. 7. Alzyme destroys and removes Aβ aggregates in mouse Alzheimer models. Panels A, B and C are from Planque et al., 2015. Panel D is from Kou et al., 2015. **A** Transmission electron micrographs of preformed Aβ42 fibrils treated with Alzyme or a control antibody construct with the same molecular structure (single chain heterodimer light chain variable domains). Scale bar, 200 nm. The dense Aβ plaques visible after control antibody treatment (*top*) has been dissolved by Alzyme (*bottom*). **B** A brief (10 days), low dose (100 μg) intravenous treatment of transgenic mice overexpressing human Aβ (Tg-SWDI strain) reduced the amyloid plaque burden in the brain neocortex compared with mice treated equivalently with the control antibody construct. *, $p < 0.05$. **C** Bottom and top images, respectively, representative Aβ plaque burden in neocortex sections from Alzyme and control antibody construct mice reported in Panel B Scale bar, 0.25 mm. **D** Bottom and top images, respectively, representative Aβ plaque burden in neocortex sections 5 months after catabody 5D3 gene transfer or control vehicle transfer into the brain of transgenic mice (strain TgAPPswe/PS1dE9). A decrease in plaque was evident ($p < 0.05$). Catabody 5D3 is a single light chain V domain with catalytic properties similar to Alzyme as described in (Taguchi et al., 2008b).

documented in a mouse model of Alzheimer disease (Fig. 7) (Planque et al., 2015). Alzyme gene transfer in a second mouse model had the same effect (Kou et al., 2015).

Numerous trials of ordinary antibodies that bind Aβ for treating Alzheimer patients have failed (Biogen, March 21, 2019; Panza et al., 2019). After completing the futility analysis of one such trial, Biogen announced that additional high dose and very prolonged antibody treatment data showed a significant reduction in the rate of cognitive decline (Biogen, October 22, 2019). Taken together, the trials have revealed intrinsic efficacy and safety limitations of ordinary antibodies to Aβ. Nonetheless, the failed antibodies do nothing to downgrade the amyloid hypothesis *per se*. That hypothesis only states that Aβ overproduction *initiates* Alzheimer disease, not that it is the sole cause of brain damage. Importantly, ordinary antibodies have failed at least in part because they themselves induce pathogenic neuroinflammation that nullifies the benefit of Aβ removal (Panza et al., 2019; Weekman et al., 2016). In our view, the antibody trials have yielded clues about next generation drugs needed for an effective Alzheimer therapy. The catabody solution is promising. Our future research and development plans take into account the following central events in Alzheimer pathogenesis: ***(a)*** The Aβ polypeptide misfolds into toxic oligomers and particulate aggregates that damage neurons and the brain architecture directly (Haass and Selkoe, 2007), ***(b)*** Aβ overproduction triggers intracellular accumulation of misfolded tau (misTau) oligomers and particulate amyloid (the tangles). Neuron-to-neuron spread of taupathy occurs by misTau release into the interstitial fluid followed by misTau re-uptake by adjacent neurons, acting as a seed for accelerated intracellular misTau aggregation (Goedert and Spillantini, 2017), and ***(c)*** The Aβ aggregates activate inflammatory cells (mostly microglia, the brain's resident macrophages), stimulating release of proinflammatory

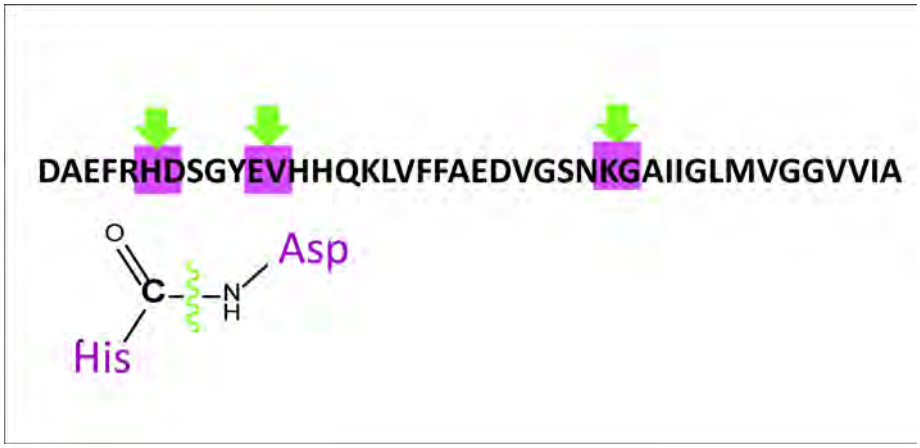

Fig. 8. Aβ hydrolyzing catabody induced by an E-Aβ immunogen. One letter amino acid sequence of amyloid β peptide 1–40 (Aβ) showing scissile bonds (magenta boxes) hydrolyzed by murine monoclonal IgG 6H3 that was induced by immunization with the E-Aβ analog. The amide linkage structure of an example scissile bond is included (bottom). The scissile bonds were deduced by reversed phase high performance liquid chromatographic separation of the catabody-generated Aβ fragments followed mass spectroscopy as in Taguchi et al., 2008a. The E-Aβ structure can be found in Taguchi et al., 2008b.

mediators that are themselves neurotoxic and are also involved in causing vascular leaks (Attems et al., 2011; Sondag et al., 2009).

We agree with the growing consensus that effective treatment of Alzheimer disease may require not only Aβ removal, but also control over targets that cause downstream brain damage. We think Aβ-binding antibodies that rely on inflammatory cells to remove Aβ-containing immune complexes are intrinsically unsuitable for Alzheimer therapy, because they inevitably cause neuroinflammation (Adolfsson et al., 2012; Morkuniene et al., 2013; Weekman et al., 2016). Once triggered, brain inflammation is an independent cause of diminished cognition (Kumar, 2018; Ownby, 2010), no matter the amyloid status of the brain.

The foregoing perspective is supported by findings that the level of Aβ-containing immune complexes formed by Aβ-binding autoantibodies in patients with Alzheimer disease is negatively correlated with cognitive performance (Maftei et al., 2013). The authors concluded that production of autoantibodies is a pathogenic factor in the disease. Most patients with Alzheimer disease develop cerebral amyloid angiopathy (CAA). The relationship between Aβ-binding autoantibodies and CAA is striking – increased autoantibody levels were correlated with appearance of CAA, and decreased autoantibody levels with remission (Piazza et al., 2013). It is difficult to conceive a solution for the inflammatory and vascular damage induced by an ordinary antibody that is intended as a disease therapy, as the Fc receptor-dependent ingestion of the Aβ-antibody immune complex is the primary Aβ removal mechanism. Alzyme directly destroys Aβ without dependence on inflammatory cells. We documented removal of brain Aβ free of neuroinflammation or blood vessel damage *in vivo* (Kou et al., 2015; Planque et al., 2015).

The second important feature of our suggested solution for Alzheimer disease is combining Alzyme with a Tauzyme catabody that selectively destroys the misTau protein. Several companies have initiated clinical trials of tau-binding antibodies for the disease. We think tau-binding antibodies may encounter the same neuroinflammation problem seen with Aβ-binding antibodies. We identified human catabodies that selectively destroy misTau aggregates (Paul et al., 2018). We have in hand prototype Tauzyme candidates for further tests.

5. Longevity vaccines?

Irreversible tissue damage due to dysfunctional aging processes cannot be readily repaired, for example, the damage to heart wall regions that control electromechanical activity caused by misTTR in systemic amyloid disease or to brain regions that integrate cognitive processes caused by Aβ and misTau. We subscribe to the view that preventing age-associated dysfunctional processes before they have caused substantial damage is the preferred medical strategy for prolonging healthy lives. Since the first cowpox vaccine of Edward Jenner in 1796, prophylactic vaccines against infectious microbes have improved public health enormously. We suggest that lessons from our electrophilic vaccine (E-Vaccine) approach for microbes are valuable in developing safe and efficacious anti-amyloid longevity vaccines.

The central requirements for such longevity vaccines is inducing long-lasting synthesis of catabodies with epitope specificity suitable for destroying the disease-causing misfolded self-proteins without interfering in the physiological functions of the properly folded conformations of these proteins. Constitutive catabodies directed to misTTR already meet this requirement (Planque et al., 2014b) by virtue of specificity for the 'amyloid epitope' found on misTTR but not properly folded TTR (unpublished observations). We also documented the analogous amyloid epitope of Aβ recognized by constitutive catabodies (Planque et al., 2015). Both the epitope amino acid sequence and acquisition of increased β sheet structure govern constitutive catabody recognition of such amyloid epitopes. As the preimmune catabody repertoire has already developed the desired epitope specificity by Darwinian evolution, the task of specific vaccination against the misfolded self-protein conformations reduces to an immunization procedure that successfully induces the synthesis of catabodies with the pre-existing specificity features.

Our E-Vaccine Platform relies on immunization with chemically engineered analogs of the target protein (the ETAs). Fig. 8 is an example monoclonal IgG induced by immunization with an Aβ ETA that catalyzes the breakdown of Aβ. The E-Vaccine Platform was shown previously to recruit the catabody germline genes with pre-existing specificity directed to a superantigenic HIV-1 coat protein epitope for inducing sustained catabody synthesis (Planque et al., 2012). The immune stimulatory principle is novel – covalent ETA binding to the nucleophilic subsite of a catabody expressed as a B cell receptor (BCR), coordinated with epitope binding at the noncovalent catabody site (Nishiyama et al., 2009; Paul et al., 2004; Planque et al., 2003, 2014b). Catalytic BCRs hydrolyzes the protein substrate, but the ETA is non-hydrolyzable, thus sustaining the BCR-stimulated cellular signaling. The ETA drives B cell clonal proliferation and affinity maturation, resulting in amplified synthesis of the germline catabody BCRs specific for the ETA. Catalytic rate and target specificity improvements occur by the same mechanism underlying immunogen-induced affinity maturation of ordinary antibodies (Nishiyama et al., 2009; Paul et al., 2003) – random V domain somatic hypermutation and ETA-driven selection of mutant catabodies. Our ETA immunogen studies also invented *irreversible antibodies*, molecular cousins of the catabodies that possess a very strong nucleophile but do not support water attack on the covalent intermediate (Nishiyama et al., 2006, 2007b). Irreversible antibodies can be thought of as 'forever' antibodies with infinite affinity. Unlike ordinary antibodies, they bind the target and never release it.

If a pre-existing germline catabody can protect against amyloid disease, amplified synthesis of that catabody by E-vaccination will

Table 2
Increased neutralization efficacy of irreversible antibodies induced by immunization of mice with an E-peptide immunogen of the gp120 protein compared to the reversibly-binding antibodies induced by the non-electrophilic counterpart of the same immunogen (HIV subtype B coreceptor CXCR4 strain MN). A 71-fold efficacy increase is evident, computed from the decreased concentration requirement to achieve 80 % neutralization. Data from Nishiyama et al., 2007b.

Antibody	80 % HIV neutralizing concentration, μg/mL
Reversibly-binding ordinary antibodies	357
Irreversible antibodies	5

strengthen the protection (Planque et al., 2012). Like catabodies, irreversible antibodies inactivate the target permanently with potency superior to an ordinary dissociable antibody (Table 2) (Nishiyama et al., 2007a). Ordinary vaccines bind B cells exclusively by noncovalent means, and there is no selective pressure driving production of the catabody or irreversible antibody subsets. Thus, E-vaccines should afford greater disease protection compared to ordinary vaccines.

E-vaccines also display other mechanistically important benefits owing to their unique ability to stimulate B cells covalently. They accelerate the IgM→IgG class switch step in the B cell clonal differentiation pathway. Further, E-vaccines can induce robust and mature catabody responses to protein epitopes that generally induce poor ordinary antibody response to themselves. For example, microbial superantigenic epitopes such as the one targeted by our HIV E-vaccine suppress production of protective antibodies against itself due to defective IgM→IgG class switching. The HIV E-vaccine corrected the defect (Fig. 9) (Planque et al., 2014a). Covalent BCR binding to an E-vaccine releases a very large amount of binding energy compared to the far smaller amount of binding energy generated by noncovalent BCR binding to an ordinary vaccine. Ligand-BCR binding energy is a central event in regulating the differentiation and survival of a B cell leading to antibody production or lack thereof (e.g. it is well-known that the outcome from a high affinity, more energetic binding is distinct from low affinity, less energetic ligand-BCR binding). The binding energy is transduced in a defined BCR conformational change(s) needed to trigger discrete stimulatory or inhibitory intracellular pathways that regulate the antigen- or superantigen-induced adaptive phase of the immune response.

The evolutionary nexus between constitutive catabodies to the amyloid epitope and microbial superantigens based on cross-reactivity data was noted in Section 2. Another common feature is that the constitutive catabodies use their V domain framework regions (FRs) for specific recognition of both the amyloid epitope and microbial superantigens (Neshat et al., 2000; Planque et al., 2015). Physiological epitope interactions at antibody FRs were suggested by several investigators to induce immunosuppression against microbial superantigens or tolerance against self-antigens (Chiorazzi and Efremov, 2013; Silverman et al., 2000). E-vaccines provide a means for the first time to generate protective catabody responses to such epitopes. As a result, E-vaccines can be developed to target diseases that are resistant to ordinary vaccines (Fig. 10).

6. Future Directions

Our vision is to bypass the mechanism-based limitations of ordinary antibodies and vaccines for fulfilling important unmet medical needs: *(a)* Intrinsic inability of ordinary antibodies to bind the target with stoichiometry greater than 1:1; *(b)* The inevitable activation of inflammatory pathways upon antibody-target binding that not only cause unacceptable side effects but also reduce efficacy through functional antagonism pathways, as seen in numerous failed trials of antibodies in patients with Alzheimer disease; and *(c)* Failure of ordinary vaccines to induce protective immunity to certain protein epitopes because of immune check-point suppressor mechanisms.

The lead products generated from our Catabody Platform have not shown these limitations. Success in early stage human trials of any one lead catabody will make the entire underlying technology more attractive, thus encouraging development of additional catabodies and E-vaccines for new disease targets. For instance, TTR amyloid disease and Alzheimer disease are but 2 of 56 amyloid diseases caused by misfolded

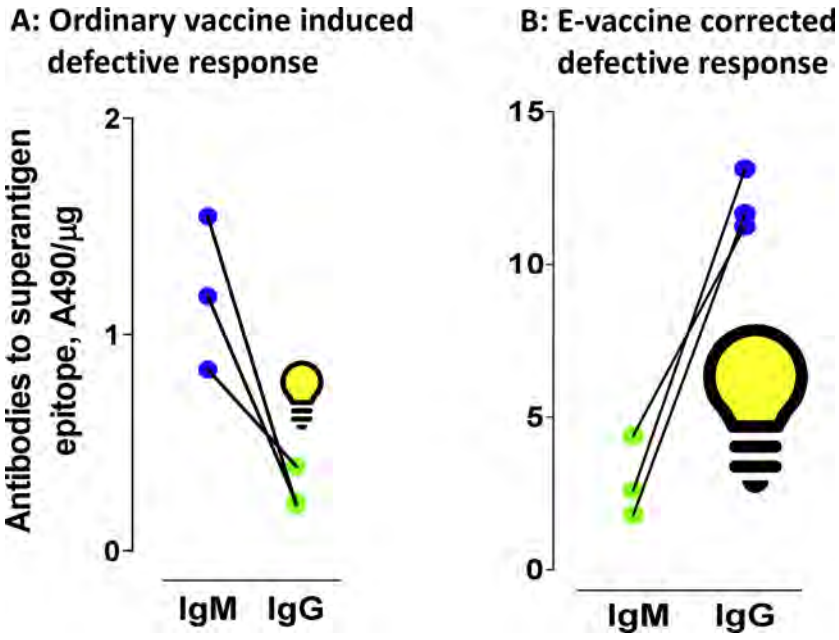

Fig. 9. Defective IgM→IgG maturation of the antibody response to a superantigenic HIV gp120 epitope induced by ordinary vaccination and correction of the defect by the HIV E-vaccine candidate. Each point represents a mouse. Data from Planque et al., 2014a. ***A.*** The antibody response directed against the gp120 superantigen epitope in mice immunized with an ordinary vaccine candidate (control HIV coat protein gp120 devoid of inserted electrophilic groups) did not switch efficiently to mature IgGs customarily produced to conventional protein epitopes. HIV-infected humans also show a similar IgM→IgG maturational defect. ***B.*** The E-vaccine candidate (an electrophilic gp120 analog) corrected the defective production of mature IgGs in side-by-side tests. The large light bulb signifies our conception of high energy covalent E-vaccine binding to B cells as the basis for the corrected maturational defect.

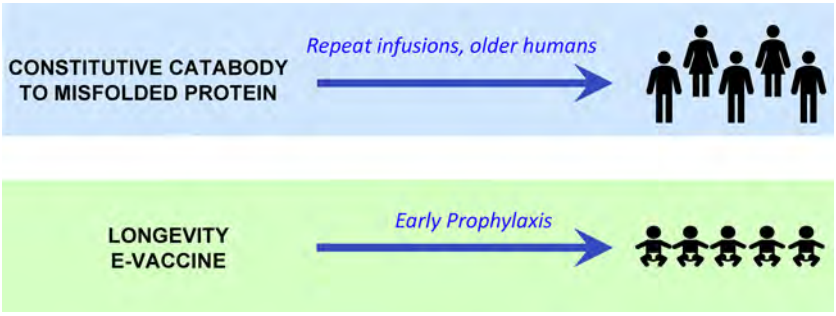

Fig. 10. Longevity E-vaccine? Selective destruction of misfolded but not properly folded TTR by monoclonal constitutive catabodies from healthy humans meets the requirement for a therapeutic reagent that does not interfere with the physiological TTR functions (Top). The E-vaccine technology provides a strong basis for developing a safe prophylactic candidate vaccine that induces catabodies and memory B cells with misTTR specificity properties similar to the constitutive catabodies.

proteins (Chiti and Dobson, 2017). Our findings suggest that destruction of misfolded proteins by catabodies extends beyond the targets described in this article. The Catabody Platform is enabled to utilize both innate Darwinian immunity and immunogen-induced acquired immunity for generating catabodies to virtually any target protein. Examples of novel catabodies that may help improve efficacy over current immunotherapy approaches are catabodies to cancer-associated proteins for tumor targeting, enzymes that regulate lipid levels, blood coagulation factors, and cytokines/chemokines involved in autoimmune disease.

Success in arresting brain degeneration in Alzheimer patients in our view requires eliminating multiple pathogenic processes underlying the disease. Ordinary antibody therapy exacerbates the pre-existing neuroinflammation in the Alzheimer brain. Catabody catalyzed amyloid removal appears free of the neuroinflammatory effect of ordinary antibodies. Only about 3–5 % of the intravenously injected catabodies cross the blood-brain barrier in mouse models (Planque et al., 2015). This provides for the first time the opportunity to increase efficacy through enhanced catabody delivery to the brain by incorporating brain penetrating tags without fear of inflammatory brain damage. Misfolded aggregates of both Aβ and tau are involved in neurodegeneration, requiring combined Alzyme/Tauzyme tests. The Tauzyme catabody may also be developed as a monotherapy for taupathy-dominant diseases such as frontotemporal dementia in the future.

Vaccines enable low-cost prophylaxis against disease accessible to economically disadvantaged human communities. An exciting R&D direction is the development of prophylactic longevity vaccines. Our HIV E-vaccine the only documented vaccine candidate for an infectious disease that has remained intractable to ordinary vaccines despite massive investments (Planque et al., 2014a). It provides inspiration to test longevity E-vaccines for preventing age-associated amyloid diseases based on the shared evolutionary origin of constitutive catabodies to misfolded self-proteins and microbial superantigens. The main challenge is limiting the reactivity of vaccine-induced catabodies to only the disease-causing misfolded self-protein. We think the challenge can be met by 'amyloid epitope'-based E-vaccines that amplify and improve the starting catabody specificity for misfolded self protein targets generously made available by millions of years of Darwinian evolution.

In summary, the prevalence of most diseases increases in aged humans, and solving the aging problem requires novel solutions. Ordinary antibodies and vaccines have clear limitations that are rectified by catabodies and E-vaccines. We view further preclinical and clinical development of the lead amyloid-directed catabodies as the most expedient path to medical validation of the Catabody Platform. E-vaccines have the potential of broad utility against microbial infections that are intractable to ordinary vaccines and are responsible for disproportionately increased mortality in aged humans, *e.g.*, influenza virus and drug-resistant *Staphylococcus aureus*. We are taking a calibrated approach to the notion of longevity E-vaccines against misfolded self-proteins. It will be rewarding to eliminate a substantial contributor to the aging problem, amyloid disease. Cautious extensions of lessons from previous anti-microbial vaccines are necessary. We must assure that early-age longevity vaccination does not risk disrupting the youthful homeostatic processes.

The authors hold an equity stake in Covalent Bioscience Inc. Most scientific results generated by the authors reported in this review are from projects conducted at academic institutions (University of Texas Houston Medical School, University of Nebraska Medical Center). The authors have now elected to conduct their research full-time in behalf of Covalent Bioscience as their inventions are close to the commercialization phase.

Declaration of Competing Interest

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