Forum
Amyloid in Alzheimer’s Disease: Guilty Beyond Reasonable Doubt?
Christian Behl1,∗

Recently failed antiamyloidogenic trials call for an objective reassessment of the dominating amyloid cascade hypothesis of Alzheimer’s disease (AD). Ongoing efforts focusing on amyloid β protein (Aβ), its deposition, and its removal need to be complemented by more intensive research in new directions. Those may either integrate amyloid pathology or will propose pathogenetic routes independent of Aβ in the search for the causes of AD.

Introduction
Epistemology teaches us that we always need to challenge scientific findings and to disbelieve and active dispute drive scientific progress. The amyloid cascade hypothesis of AD, which holds the deposition of Aβ as the key event in AD pathology, just turned 25 years old. Although the amyloid hypothesis is built on solid experimental grounds, it is awaiting final proof-of-concept confirmation in humans. Driven by recent failures of anti-amyloidogenic therapy approaches in clinical studies, and based on more recent findings, this Forum article aims to stress a moment of rethinking on AD.

AD is the primary form of dementia, and aging is the key risk factor for the majority of all AD cases (sporadic AD). Dementia starting before the age of 65 years based on gene mutations [in the genes for amyloid precursor protein (APP), and presenilin (PS)1 and PS2] represents only 1–5% of AD cases, but most of the molecular AD research in cells and mice has used these mutations in the search for the cause of AD. Together, these findings on various heritable/genetic forms (fully penetrant mutations) of AD linked to Aβ deposition have formed the basis of the so-called amyloid cascade hypothesis [1]. While many improvements in the care and support of AD patients have been introduced, no treatment is available that can stop or reverse AD [2]. Initially, research studies focusing on Aβ and a second AD hallmark protein, tau (Box 1), were considered competing research directions (‘Baptists’ and ‘Tausists’). Today, tau is integrated into the amyloid cascade hypothesis and is also therapeutically targeted.

Antiamyloidogenic Therapies and Failed Clinical Trials
Genetics, biochemistry, an army of mouse models, observations in postmortem human brains, and clinical findings provide strong arguments for the amyloid cascade hypothesis, no doubt. But an unbiased discussion may also uncover weak points of this view [3]. Transgenic APP and PS mice are ideal to study the biochemistry of APP processing and deposition but are not adequately modeling human AD. Moreover, it is appropriate to study a complex and genetically diverse human disorder taking decades to develop in inbred mouse strains living under fully controlled conditions only for 2 years? Furthermore, is a highly personalized disease such as AD explainable by just one key pathway? We should remember Karl Popper’s advice in Objective Knowledge: An Evolutionary Approach: ‘Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.’

From early on, the amyloid cascade hypothesis faced criticism primarily based on a poor correlation between the actual amyloid depositions in the human brain and several parameters of AD pathology at the electron microscopy (EM) level [4,5]. However, the beauty of the amyloid cascade hypothesis lies in its simplicity and linearity displaying defined targets all linked to Aβ (generation/processing, aggregation, removal of Aβ in soluble and aggregated forms). Consequently, as AD therapy that ultimately improves memory, antiamyloidogenic approaches aim to prevent generation and deposition of Aβ or to enhance its clearance; no clinical trial so far has led to improved memory. Last year, solanezumab, an antibody designed to clean up Aβ from blood and cerebrospinal fluid, failed in a large clinical AD trial, as did bapineuzumab, another passive immunotherapy. Earlier this year, yet another potential AD drug, this time the beta-secretase inhibitor verubecestat, failed in a clinical trial. One ongoing promising immunotherapy candidate is aducanumab, a high-affinity human IgG1 monoclonal antibody against aggregated forms of Aβ. This antibody approach cleverly takes aging as an AD risk factor into account since this antibody was obtained from aged healthy donors resisting AD based on – according to the hypothesis behind it – their immune system (reverse translational medicine approach). Aducanumab is currently in a phase III clinical trial running until 2022 in 150 AD centers worldwide. A positive outcome that shows slowing cognitive decline would be good, indeed, and in the view of the investigators in this study, would also provide compelling support for the amyloid hypothesis [6].

Experimental failure is at the heart of science and, in particular regarding this devastating disease, we have the obligation to try and try again. At the same time, it is also obligatory to open the mind for alternative approaches and have the courage to leave worn-out paths. There is still a huge gap between the fast progression in understanding the details of Aβ biochemistry and the clinical reality since ‘…what triggers the characteristic pathology of AD and which mechanisms
drive the progression of the disease remain unknown.‘ [2]. But what can be offered instead? The slowly beginning consideration of widening AD research beyond the amyloid cascade hypothesis is finally indeed good news. Some alternatives present pathways completely independent of a causal role of Aβ, while others integrate the deposition of Aβ into the overall hypothesis.

**Thinking Outside the Box**

Interestingly, as neurons age, a switch occurs in the protein degradation pathways, from proteasome to autophagy [7]. A strong involvement of autophagy in AD pathogenesis was demonstrated >10 years ago and was subsequently introduced as an Aβ-independent AD pathomechanism [8]; a recent EM study on AD brains confirmed this view [9]. Moreover, in both normal aging and AD oxidative stress, brain metabolism deficiencies and mitochondrial dysfunction occur, arguing for a prominent role of altered neuronal bioenergetics and redox homeostasis in AD pathogenesis. Early data but also more recent findings strongly support a key function of neuroinflammation (now frequently referred to as the third neuropsychopathological correlate of AD), vascular dysfunction, overall disturbed neuronal calcium homeostasis, and failure of cell cycle control (cell cycle re-entry hypothesis). Genome-wide association studies have identified additional AD risk genes that include genes involved in cholesterol metabolism, in the innate immune system, and in endosomal recycling and vesicle trafficking. Importantly, such genes that increase the AD risk need to be distinguished from the AD mutations definitively leading to familial/genetic early-onset AD.

**Risk Factor Genes Point to New Directions**

Rare missense variants in TREM2 (triggering receptor expressed on myeloid cells-2) were associated with an approximately 2–4-fold increased risk of developing AD [10,11] and other neurodegenerative disorders such as Parkinson’s disease, amyotrophic lateral sclerosis, and frontotemporal dementia (FTD). In the brain, TREM2 is highly expressed in microglia – the resident immune cell type in the brain – and strikingly, there is a strong decrease in microglia surrounding Aβ plaques in TREM2-deficient mice [12]. TREM2 as an AD risk factor points to so far somewhat underevaluated directions, namely AD-linked changes in the metabolism of lipids and glucose. Interestingly, apolipoprotein E (APOE4), known as the strongest genetic risk factor for sporadic AD, is a ligand for TREM2, and TREM2 itself binds anionic lipids and lipoproteins, suggesting that the lipid-sensing function of microglia in the brain might be disease-relevant as well. Excitingly, Alois Alzheimer already described the accumulation of lipids in the dementia brain (Box 1). Moreover, an FTD-like syndrome-associated TREM2 loss of function mutant leading to reduced microglial activity was shown to cause reduced cerebral blood flow (hypoperfusion) and brain-wide metabolic alterations, suggesting a link between microglia and brain glucose metabolism [13]. This is consistent with (i) reduced glucose utilization that is seen in AD decades before cognitive changes; (ii) glucose being the key energy substrate for neurons; and (iii) neurons having high energy demand, underlying a possible pathogenic role for TREM2 in neurodegeneration.

One might hypothesize that TREM2 dysfunction induces early Aβ-independent alterations in glucose and energy metabolism that are the primary cause of neuronal dysfunction and subsequent demise. This in turn may enhance generation of Aβ as a stress response which then may induce secondary inflammatory consequences. So the primary therapeutic goal could be the support and maintenance of the metabolic status to assure neuronal function and resilience against further insults. TREM2 dysfunction might also be the link to the disturbed autophagy-lysosomal degradation observed in sporadic AD [14].

**Finally: Is It Alzheimer’s disease or Alzheimer’s diseases?**

The genetic (strictly inherited) AD forms certainly comprise a small separate group, and for familial AD, Aβ is likely the disease cause and removal of Aβ (at the right time) represents an adequate therapeutic approach. However, the overall genetic heterogeneity, stringent association with age, individual patient history, lifestyle and genetic risk factors argue in favor of the existence of various subgroups of sporadic AD. Based on the individual background we would face etiologically different forms of AD (Alzheimer-type disorders), with different early disease-initiating events consequently calling for individual forms of therapy.

Here, I plead for more objectivity in the scientific discussion, not to eliminate amyloid from our thinking, but to allow also novel amyloid-independent pathways to be put on the research agenda. In fact, it is well possible that Aβ deposition and tau pathology come late during the disease and various (age-related) early changes initiate the disease that ultimately precipitates Aβ and tau pathology. We should not forget that Aβ alone appears to be insufficient for the development of AD, and changes in tau are not specific for AD and are seen also in other neurodegenerative

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**Box 1. Alzheimer’s Consequential Look at the Dementia Brain**

In 1907, Alois Alzheimer described in clinical terms the condition of a dementia patient, who was subsequently acknowledged as the first case of AD. By looking at the postmortem brain tissue he found an atrophic brain and vascular tissue with arteriosclerosis. At the microscopic cellular level, Alzheimer discovered changes in so-called neurofibrils – today known as intracellular neurofibrillary tangle strands – and the deposition of a special substance in the cortex, later designated (senile) plaques containing Aβ. In addition, he reported on many glial fibers and that many glial cells show adipose saccules (lipid-containing compartments) as additional histopathological hallmark.
disorders as well as in nondemented elderly individuals. If we are lucky and it turns out that Aβ is also responsible for sporadic AD, based on the huge mountain of Aβ data that we have on hand, we will soon have specifically designed antiamyloidogenic treatment options. But what if this is not the case? To address this scenario, we have to further strengthen research into other potential Aβ-independent pathogenetic routes.

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1Institute of Pathobiocchemistry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

*Correspondence: cbehl@uni-mainz.de (C. Behl), http://dx.doi.org/10.1016/j.tips.2017.07.002

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