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Perspective

Toward common mechanisms for risk factors in Alzheimer's syndrome

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Abstract The global strategic goal of reducing health care cost, especially the prospects for massive increases due to expanding markets for health care services demanded by aging populations and/or people with a wide range of chronic disorders-disabilities, is a complex and formidable challenge with many facets. Current projections predict marked increases in the demand for health driven by both the exponential climb in the prevalence of chronic disabilities and the increases in the absolute numbers of people in need of some form of health care. Thus, the looming predicament for the economics of health care systems worldwide mandates the formulation of a strategic goal to foster significant expansion of global R&D efforts to discover and develop wide-ranging interventions to delay and/or prevent the onset of chronic disabling conditions. The rationale for adopting such a tactical objective is based on the premise that the costs and prevalence of chronic disabling conditions will be reduced by half even if a modest delay of 5 years in the onset of disability is obtained by a highly focused multinational research initiative. Because of the recent history of many failures in drug trials, the central thesis of this paper is to argue for the exploration-adoption of novel mechanistic ideas, theories, and paradigms for developing wide range and/or types of interventions. Although the primary focus of our discussion has been on biological approaches to therapy, we recognize the importance of emerging knowledge on nonpharmacological interventions and their potential impact in reducing health care costs. Although we may not find a drug to cure or prevent dementia for a long time, research is starting to demonstrate the potential contributes of nonpharmacological interventions toward the economics of health care in terms of rehabilitation, promoting autonomy, and potential to delay institutionalization, thus promoting healthy aging and reductions in the cost of care.

Keywords: Alzheimer's; Dementia; Syndrome; Prevention; Pathogenesis; Risk factors

1. Introduction

The global strategic goal of reducing health care cost, especially the prospects for massive increases due to expanding markets for health care services demanded by aging populations and/or people with a wide range of chronic disorders-disabilities, is a complex and formidable challenge with many facets. Current projections predict marked increases in the demand for health driven by both the exponential climb in the prevalence of chronic disabilities and the increases in the absolute numbers of people in need of some form of health care.

Thus, the looming predicament for the economics of health care systems worldwide mandates the formulation

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of a strategic goal to foster significant expansion of global R&D efforts to discover and develop wide-ranging interventions to delay and/or prevent the onset of chronic disabling conditions. The rationale for adopting such a tactical objective is based on the premise that the costs and prevalence of chronic disabling conditions will be reduced by half even if a modest delay of 5 years in the onset of disability is obtained by a highly focused multinational research initiative [1,2].

Because of the recent history of many failures in drug trials, the central thesis of this paper is to argue for the exploration-adoption of novel mechanistic ideas, theories, and paradigms for developing wide range and/or types of interventions. Although the primary focus of our discussion has been on biological approaches to therapy, we recognize the importance of emerging knowledge on nonpharmacological interventions and their potential impact in reducing health care costs. Although we may not find a drug to cure or prevent dementia for a long time, research is starting to demonstrate the potential contributes of nonpharmacological interventions toward the economics of health care in terms of rehabilitation, promoting autonomy, and potential to delay institutionalization, thus promoting healthy aging and reductions in the cost of care.

An international strategic research-planning workshop (The meeting was convened by the Network Center for Biomedical Research in Neurodegenerative Disease (CIBERNED), CIEN Foundation, and Reina Sofia Foundation, Madrid, Spain.) was organized on September 21–23, 2016 in Malaga, Spain to consider some forward-looking ideas for such an international cooperative research effort. The present paper outlines the challenges and recommendations for future research on a broad spectrum of interventions.

2. Why focus on Alzheimer's disease?

Chronic brain disorders, such as Alzheimer's disease (AD), dementia, and other neurodegenerative disorders, constitute some of the most significant contributors to the quandary of health care systems worldwide. These neurological conditions that lead to prolonged functional impairments (i.e., diminish individuals' capacity to carry out activities of daily living) exemplify a unique class of disabilities because of their profound economic impact and psychosocial ramifications. Progressive functional impairments of cognition, motor skills, and emotion, which are the most common clinical features of these unremitting brain conditions, ultimately lead to total reliance on labor-intense care to sustain life. AD has been proposed as the perfect prototype for this wide range of disorders and a pragmatic starting point (a proxy) for attacking the larger and more complex problem of chronic brain disorders [1,2].

Remarkable advances have been made in recent years in understanding the biological basis of neurodegeneration. Subsequently, it has become increasingly accepted that delaying the onset of disabling symptoms of neurodegenerative conditions is an attainable goal. Hence, developing R&D capacity for innovations that will reduce the prevalence of chronic brain disorders is an urgent need. However, several scientific impediments should be first surmounted. Among these barriers, crucial challenges are (1) changing current paradigms for the development of novel treatments and (2) improving the discovery of more effective therapeutic targets.

In the general arena of stimulating new thinking and fostering new perspectives, the important topics of modifiable risk factors and disease mechanism were the focus of discussion at the Malaga meeting. The present paper outlines the perspectives and recommendations of some key opinion leaders in the field of dementia research participating in the event. Here, we discuss some of the important obstacles to develop effective therapies as well as future direction for research and opportunities for therapy development.

3. New perspectives on risks factors and disease mechanisms

Alzheimer's syndrome is a polygenic and heterogeneous disorder with multiple patterns of expression. The late-onset sporadic form (SAD) is the most prevalent AD type, with the early-onset familial type (FAD) being responsible of only about 1% of the cases. Although both types follow a similar pathological and biochemical course, it is highly debated whether they should be considered as a single pathophysiological entity. Therefore, it would be of the highest importance to have a single general mechanistic hypothesis that could harmonize all biochemical and neuropathological features of both AD types.

In this context, a large part of the deliberations at Malaga were devoted to the pathogenic mechanisms underlying the neurodegenerative process. It has been a quarter of a century since the amyloid cascade hypothesis proposed that the presence of amyloid beta (Aβ) peptide aggregates is the first cause in the development of AD pathogenesis, whereas neurofibrillary pathology and neuronal cell loss are consequences of that primary cause [3]. Although FAD-based genetic evidence has provided strong support to the hypothesis, clinical trials targeting the amyloid pathway on SAD patients have shown disappointingly negative results in recent years, leading to discussions about whether the amyloid cascade hypothesis might not be valid for all SAD cases [4,5].

Discovery of mutations in the *APP*, *PSEN1*, and *PSEN2* genes causing FAD has been instrumental in the current understanding of the biochemical pathways leading to neurodegeneration and dementia. Furthermore, the findings from genome-wide association studies (GWASs) and massive parallel sequencing have come to underscore the multifactorial nature of AD. Notwithstanding, translating genetic findings into functional molecular mechanisms biologically relevant in disease pathogenesis and therapy design still remains a challenge.

On the other hand, several stages during disease progression have been proposed, with Aβ pathology developing early and neurofibrillary pathology and neuronal death taking place later [6]. The first stage would be a clinically silent, symptom-free condition but may be the right moment for Aβ-targeted treatment. Indeed, it has been proposed that at later stages of the disease, once tau pathology has developed, anti-amyloid therapies might not be as effective [7].

With regards to SAD cases, there is growing evidence suggesting that the appearance of pathology is due to the interplay of a combination of factors that include potentially modifiable risk factors based on lifestyle, such as education, socioeconomic position, physical activity, cardiovascular or metabolic profile [8–10], as shown in Table 1. In addition, although some genetic risk factors have been identified [11], aging remains by far the main risk factor for SAD, a risk that could be associated with some specific molecular changes such as for instance calcium homeostasis [12,13], that could affect synaptic function or neuronal health and facilitate the development of the disease.

The relative importance of any one of these factors in increasing the risk or influencing the expression of the disease differs from one individual to another in SAD, whereas for FAD, the presence of a specific mutation results in higher similarities among the patients [11]. Thus, some special features of SAD lead to the recognition of Alzheimer's as a syndrome rather than a disease, collectively characterized by a group of symptoms, often consisting of mixed or overlapping pathologies. Alzheimer's syndrome is heterogeneous with respect to factors such as age of onset of symptoms, patterns or mix of clinical symptoms, neuropathology, biomarkers, response to treatment, risk factors, and genetics. Furthermore, it is now evident that the gradual molecular changes in the brain leading to the syndrome start decades before any symptoms can be detected.

It is important to highlight that cognition is not confined to memory but involves the full range of cognitive functions such as language, perception, creativity, and social activity. Thus, the concept of a cognitive footprint has been recently put forward [9] by which a range of activities throughout the life span will have an effect (either positive or negative) on cognition that could be associated with specific footprints of the disease.

Martin Rossor has been a strong advocate for the value of stratification, namely the effort to explore and classify the different types of dementia as well as the various forms of the concept of AD, such as the differences between SAD, young onset Alzheimer's disease, and autosomal-dominant familial AD. (Presentations at the Malaga meeting can be accessed through the following link: www.youtube.com/watch?v=u2AGVQ-XeDA.) Rossor has also argued for the value of considering cognitive impairment in its totality and to the many different factors, which can contribute to cognitive impairment, many of which alone may not result in severe cognitive impairment or dementia but are likely to influence the phenotypic expression of AD. These factors may influence cognition at different times of the life course but have the potential to impact adversely on the presence of AD late in life. Over the life course, these factors will include epigenetic ones via ancestral environment, pregnancy and perinatal factors, education, poverty, pollution, and the effects of systemic illness and medication among others. All of these factors can influence cognitive capital at both an individual level and group level. Policies and individual actions that enhance cognitive capital, that is, those with positive as opposed to negative cognitive footprints, might be anticipated to mitigate the effects of AD late in life.

Table 1
Risk factors for sporadic Alzheimer's disease

Nonmodifiable factors	Aging
	Genetic factors
Modifiable factors	Life style factors (physical activity, diet, education)
	Cardiovascular profile (stroke, lipid metabolism)
	Metabolic syndrome (diabetes, hypertension, obesity)
	Depression

Thus, there could be modifiable and nonmodifiable risk factors, the first ones mostly related to life style and the second ones to genetic factors. Implementation of an increasing number of case-control studies and the upcoming of large-scale GWASs have brought us a mounting list of genetic risk factors linked to common genetic variants that have been associated with sporadic AD, the ε4 allele of the apolipoprotein E (*APOE*) being the most relevant genetic factor for SAD [14].

Cedazo-Minguez has been gathering evidence that supports his notion that impairment in cholesterol metabolism is important in the mechanisms behind neurodegenerative processes, particularly in AD [15,16]. (Presentations at the Malaga meeting can be accessed through the following link: www.youtube.com/watch?v=u2AGVQ-XeDA.)

The importance of cholesterol metabolism in modulating AD risk and pathogenesis was initially suggested by clinical and epidemiological studies [17,18] and has been confirmed by more recent genetic and basic research studies [15]. As already mentioned, the presence of the *APOE* ε4 allele is the strongest known genetic risk factor for sporadic AD. ApoE is the major transporter of cholesterol in the CNS, and individuals carrying *APOE* ε4 (15–20% of the population) have a higher probability to develop AD and several other neurodegenerative disorders, compared to carriers of other apoE isoforms [15]. Because of the strong association of *APOE* ε4 with AD, extensive efforts have been made to investigate its relation with Aβ pathology (reviewed in [19]). Individuals carrying the *APOE* ε4 allele showed increased plaque deposition. In addition, in animal models of brain Aβ-amyloidosis, the pathology was increased with the insertion of the human apoE4 isoform. Lipid-coupled apoE4 binds Aβ with lower affinity than lipid-coupled apoE3 suggesting that apoE4 lipoproteins are less efficient in mediating Aβ clearance. Moreover, glial cells carrying

apoE3 were shown to degrade Aβ better than cells carrying apoE4 (reviewed in [19]).

As the main role of apoE in the CNS is to carry and deliver cholesterol from glial cells to neurons, it is suggested that a reduced capacity of apoE4 in transporting cholesterol would have consequences for synaptogenesis and repair mechanisms, and thus in disease progression. Indeed, the results from recent GWASs are in agreement with this hypothesis, as other genes related to cholesterol synthesis, transport, uptake, or metabolism (i.e., ABCA7, ABCA1, CLU, CYP46A1) have been found to be associated with AD (Fig. 1). All these evidences imply that manipulation of brain cholesterol metabolism has therapeutic potential for AD. Improving the lack of function of apoE4 in cholesterol transport and neutralizing its negative effects for Aβ pathology are necessary efforts to counteract the role of apoE4 to neurodegenerative processes.

Another aspect of the role of cholesterol in AD pathogenesis is the influence of the peripheral cholesterol on the disease mechanisms. As cholesterol is unable to pass the blood brain barrier (BBB), it remains puzzling to understand its relation to the accumulation of Aβ or hyperphosphorylated tau in the brain. Unlike cholesterol, its side-chain oxidized forms known as oxysterols are able to traverse the BBB from both directions [20]. High levels of circulating cholesterol are associated with increased production of 27-hydroxycholesterol (27OH), a peripherally produced and BBB permeable oxysterol. Thus, hypercholesterolemia is associated with augmented blood-to-brain flux of 27OH [20]. Indeed, increased levels of 27OH were found in brains and cerebrospinal fluid from AD patients [21]. Cedazo-Minguez's group and others have contributed to deciphering the role of 27OH, in relation to neurodegeneration and AD [20], including a plausible link between the increased levels of this oxysterol, hypertension, and AD-related neurodegeneration [22,23]. Furthermore, new functions of 27OH related to memory formation and consolidation were also discovered, and treatment with dietary cholesterol or excessive 27OH was shown to reduce the levels of the "memory protein" activity-regulated cytoskeleton-associated protein (Arc) in vivo and in vitro [24].

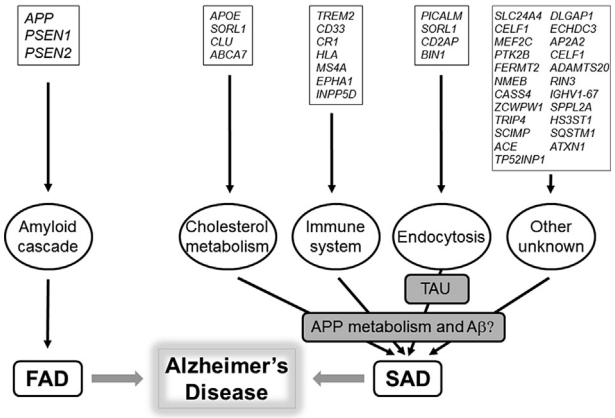

Fig. 1. List of genes involved in familial (mutations) and sporadic (risk factors) Alzheimer's disease [26,43,44]. Abbreviations: FAD, familial Alzheimer's disease; SAD, sporadic Alzheimer's disease.

The molecular mechanisms leading to AD pathology are certainly complex and include dysfunctions in several processes such as oxidative stress, protein misfolding, mitochondrial dysfunction, neuroinflammation, and alterations in signal transduction and neurotransmission [25]. Ongoing studies, using novel transgenic modified mice, are designed to investigate the mechanistic contribution of altered cholesterol metabolism and 27OH on the neuropathological mechanism leading to AD. The preliminary data presented at the meeting reinforced the idea that disruptions in cholesterol homeostasis are active contributors to AD pathogenesis. The notion of a heterogeneous etiology of AD is gaining acceptance in the scientific community, and increasing evidence suggests that alterations in the metabolism of cholesterol could be one of the driving forces toward AD [26]. The identification of patient subtypes, with homogenous etiology and prognosis, will result in more accurate treatments in the future [27]. It is likely that different subtypes, resulting from different causing pathways, should be treated differently. In addition, the identification of novel biomarkers for subtyping AD will open possibilities for precise medicinal interventions. Following this rationale, the classification of individuals with high 27OH and the characterization of the toxic, proneurodegenerative effects of this oxysterol would be important to stop or to reduce the risk for AD in those individuals.

Besides *APOE*, which presents a strong association with the disease, the rest of the gene factors mentioned previously have moderate or low degrees of association [28,29]. These genetic factors related to the risk of appearance of the disease can be linked to a few biochemical pathways such as lipid metabolism [30], immune system, endocytosis [31], or calcium homeostasis [32]. In addition, a specific feature for SAD could be the failure of adult neurogenesis, at the dentate gyrus.

The potential role of deficient adult neurogenesis in memory loss has also been studied by Avila's group using two distinct mouse models overexpressing glycogen synthase kinase (GSK-3β) under two different promoters, one being expressed early and the other one late during the neurogenesis process in the dentate gyrus. The results show that overexpressing GSK-3β at different time points during adult neurogenesis has opposite consequences on memory. An increase in GSK-3β levels at earlier stages facilitates the generation of newborn neurons, whereas at later stages, it leads to an aberrant neuronal morphology and function resulting in impaired neurogenesis. Changes in microglia population were also observed, together with an increase in the level of aging-related proteins such as eotaxin, which could be toxic for neuronal precursor cells [33]. Potential implications for the use of kinase inhibitors were also discussed.

However, all the genetic factors together can only account for a fraction of the AD risk, so that rare variants and epistatic gene interactions should be considered when trying

to capture the full picture of the AD-associated genetic risk. Nevertheless, despite the identification of these genetic loci associated with AD, a large proportion of the genetic component of the disorder remains to be elucidated. Hence, other mechanisms must exist to at least partially explain this missing heritability, such as for instance epistasis, rare variants, or the presence of somatic mutations.

Somatic genomic events, which occur in only one generation or one group of cells and which may affect specific genes, are known to be associated with various disorders, particularly cancer. It has been estimated that approximately 80% of all types of cancers arise from somatic mutations [34,35]. It is a commonly held view that the initial step in many tumors is mediated by DNA damage and mutations, which trigger activation of proto-oncogenes, inactivation of tumor-suppressor genes, and tumor progression and metastasis. Identifying genes that are mutated in cancer has been crucial not only for understanding the pathogenesis but also for designing novel therapeutic agents [36,37].

The so-called somatic mutation theory of aging states that the accumulation of mutations in the somatic cells genetic material as a function of time results in decreased cellular function. Thus, it has been proposed that a combination of lifestyle and genetics may lead to the occurrence of brain somatic mutations that could also play a part in the "dark matter" of AD because a significant proportion of the conceivable genetic defects linked to the development of SAD remains unexplained. This missing defect has been named as the "dark matter" in an effort to explain the missing heritability by means of GWAs analysis using DNA from lymphocytes [38].

Systematic studies searching for somatic brain mutations in SAD or other neurological diseases have not been performed until very recently. Whole-exome sequencing has been used to investigate the presence of single-nucleotide polymorphisms, single-nucleotide variations (SNVs), and mutations specific to brain genomic DNA in SAD, and absent in the blood genome of the same subjects, finding a remarkably unusual number of brain-specific SNVs in SAD patients [39,40]. These variations may arise from somatic mutations that take place during development or during adulthood. Another study showed that the appearance of SNVs is not random throughout the genome but that there are a higher proportion of those variants at specific chromosomes [41,42]. Additional recent studies have reported brain-specific retrotransposon insertions [43,44] and somatic copy number variations in control human neurons [45], which taking all together emphasize the variability in the brain genome, and indicate that genetic mosaicism and brain-specific genetic variations may contribute to the pathogenesis of SAD.

Thus, different triggering events in FAD could result in a different initial development of pathological mechanisms (e.g., mutations in APP or PSEN1 genes could trigger initial steps in the pathological cascade). However, as pathology progresses further, common features might start appearing. Something similar may take place in SAD that could have different initial causes but will end with a common pathological signature.

4. Crucial challenges for disease mechanism–based interventions

Despite remarkable advances in understanding the neurobiology underlying AD, during the last three decades, numerous attempts to develop effective disease-modifying therapies have failed to demonstrate clinical efficacy. The reasons for these successive failures to develop treatment for AD have been the topic of extensive deliberations, where a variety of potential contributors or plausible answers for these disappointing results have been considered. However, these explanations do not adequately account for the poor outcomes of most efficacy trials.

The failures in therapy development have begun to reinforce the growing recognition that there are major gaps in our understanding of the neurodegenerative process in AD. An important contributing factor to this dilemma might be the [nearly] exclusive reliance of current therapy development paradigm on a single [or limited] presumption about pathobiology of the disease. It is now clear that dementia-AD is a complex entity that includes a variable genetic signature potentially accounting for a significant portion of disease risk [46-47]. The failure to account for these complex relationships between the clinical features and the biological phenotypes of the disease may underlie or explain the reason for the failures of clinical studies on treatments.

The prospect of a "complex disease" model for dementia-AD will require re-evaluating current drug development paradigms, which rely on a set or hierarchy of assumptions derived from reductionist approach to explain the underlying biological of neurodegenerative process. This line of reasoning, which infers a single pathogenic pathway to all forms of AD (for instance, late-onset sporadic AD vs. early-onset familial AD), has led to acceptance of a linear or a unitary pathogenic pathway. This potentially erroneous assumption of a single pathogenic pathway, without due consideration for the complex interactions among the multiple molecular mechanisms involved in the path to dementia, may account for the selection or focus on inappropriate therapeutic targets in the failed clinical trials.

Thus, to attain the goal of a quantum shift in prospective paradigms for therapy development, the grand challenge for the field is to reexamine all major ideas-theories on the origins, that is, underling neurobiology, of neurodegeneration and start formulation-adopting alternative or novel models of dementia, based on complexity sciences and systems theory [48].

5. Novel conceptual models of dementia

One example for an alternative conceptual model for dementia could be formulated on the premise of considering AD as a syndrome, rather than a disease. This designation of a syndrome explicitly implies that the disorder consists

of different patterns of behavioral or clinical features and thus argues for the occurrence of several interconnected neural networks. In such a complex model, the discrete neural networks that underlie the various clinical features, for example, depression, agitation, cognitive decline, and so on could overlap and coexist. This scenario will require exploring several therapeutic targets in parallel for improving a series of symptoms beyond cognition, such as depression, agitation, sleep, movement disorder, and so on. This model is based on the premise that the array of clinical features, which characterize the different forms of the disorder, that is, dementia-AD, reflect a systems failure in the various components of a complex neural network. Thus, clinical symptoms of the syndrome would be the result of progressive dysfunctions in various interconnected networks within a system, for instance the cholinergic system [49].

The "systems failure model" does not rely on a unitary mechanism to trigger the neurodegenerative process but rather it requires the dissection of complex interactions among several essential functional elements of a system. Thus, the novel paradigm for therapy development entails the analysis of constitutive components of the system to understand the interactions among major parts of the system to identify strategies (interventions improving or maintaining the overall performance of the system). Such a model, a "system" built on the integration of a hierarchy of function components with increasing levels of complexity, would allow exploration of suitable targets for interventions at various levels of the system such as a cell signaling biochemical pathway, a neuron, a neural circuit or network, a brain structure, or a physiological system. The future challenge for this conceptual framework is to figure out the intricate interactions among various processes needed for sustaining optimal system performance. The development of effective interventions, based on a systems model, will require new research to understand better the interplay within various brain environments, genetic variants, and ensuing phenotypes. We need to account for the evolution and temporality of upstream and downstream pathological alterations to explain heterogeneity of the disorder, that is, the possibility that different individuals experience brain failure for distinct reasons and through different pathways.

Presently, there is no single unifying theory that accounts for all of the well-established facts about the neurobiology of dementia-AD. There is an urgent need to critically reassess all major ideas to develop novel conceptual models of dementia by creating a solid framework for diversifying and refining drug discovery and development undertakings. It is only through such redirection of R&D efforts we can expect to improve the prospects for more effective and safe interventions.

6. Remaining challenges and unanswered questions

To move forward with the long-term global objective of reducing health care costs by developing interventions to delay or prevent the onset of disability, thus enable or prolong independent function of people with chronic disorders, such as dementia-AD, we must address several challenges. Here, we discuss the major obstacles that must be surmounted and the crucial scientific questions that must be tackled.

6.1. What are the obstacles that must be surmounted in the formulation of a prospective comprehensive theory on neurodegenerative disorders, for example, dementia-AD syndrome?

Presently, there is no single unifying theory that accounts for all the well-established facts about the neurobiology of dementia-AD. There is an urgent need to critically reassess all major ideas to develop novel conceptual models of dementia by creating a solid framework for diversifying and refining drug discovery and development. It is only through such redirection of R&D efforts we can expect to improve the prospects for more effective and safe interventions.

6.2. What are the serial [temporal] and causal [mechanistic] links or relationships among the major ideas on putative etiological and risk factors?

Although emerging data are beginning to show potential linkages among some of the major hypotheses on the origins of dementia (e.g., ideas on the role of amyloid, tau, inflammation, calcium, cholinergic, metabolic, etc.), these putative relationships have not been validated. Thus, to untangle the complex interactions among these molecular events, we must develop novel models or modeling systems (e.g., in silico simulations) for systematic explorations and validation of these associations among these biochemical signaling systems or paths.

6.3. What are [if any] the common threads for risk factors in Alzheimer's syndrome?

Presently, the mechanistic relationships among the various risk factors are not known, and the various hypotheses about these common mechanisms have not been validated. This question remains as one of the important challenges for future R&D on preventive therapies.

6.4. What are, if any, the risk factors that can accurately detect the presence of the "disease" or predict with great precision the pending onset of symptoms in asymptomatic individuals, rather than in cohort or populations?

One of the critical challenges for the ongoing research on modifiable and unalterable risk factors is to discover and validate (by longitudinal prospective studies) a risk factor or combination of risk factors that can accurately detect the "disease" in the very early stages; ideally in asymptomatic or preclinical stages. The knowledge and the technology to enable this early

identification of people at risk is an essential prerequisite for the development and testing of prevention therapies.

6.5. What are the challenges associated to the strategies for mitigation and monitoring these risks?

The current ongoing studies, in the EU and US, on various aspects of risk factors are not specifically designed to validate the prognostic potential or predictive precision of any individual or group of biomarkers or risk factors. The particular requirements for such a study, which include very large numbers of well-characterized subject, long duration (several years) longitudinal study design, coordination across multiple sites/countries, high cost, and so on, make the planning, the launch, and execution of such a massive project difficult challenges.

6.6. What are the links among such neurodegenerative diseases as Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, amyotrophic lateral sclerosis, and frontotemporal dementia?

The precise nature of the molecular links among several neurodegenerative disorders is not known; however, there are several speculative ideas that need to be validated by further studies, such as the notion of a "final common path" mediated by gradual-progressive loss of synaptic connectivity [13]. The ongoing efforts to re-evaluate all major theories with an eye toward developing a common framework for comparing major ideas on etiology are intended to establish cross-disease pathways underlying common molecular mechanisms in neurodegenerative disorders [48,50–52].

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