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GREETINGS

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Ageing and neurodegeneration are challenges for both research and society. Due to demographic developments, the proportion of elderly people in the population is growing in Japan as well as in Germany. As a result, an increasing number of people is affected by neurodegenerative diseases.

What are the challenges currently facing researchers in Japan and Germany? What are the social, ethical, and economic implications of this trend, and what can societies do in response? The German-Japanese symposium co-organized by the German Research and Innovation Forum Tokyo (Deutsches Wissenschafts- und Innovationshaus Tokyo – DWIH Tokyo) and the German Center for Neurodegenerative Diseases (Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. – DZNE) in Osaka in December 2011, provided a platform for high-level exchange on these compelling issues.

Around 100 experts from research and industry debated in Osaka why ageing is a main risk factor for neurodegenerative diseases such as Alzheimer's or Parkinson's, how new therapies and more effective preventative measures can be designed and how German and Japanese researchers can jointly push forward in these fields.

We are pleased to present to you a summary of the symposium's proceedings, which will contribute to making its outcomes known to the wider scientific community.

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Challenges and Opportunities in Neurodegenerative Disease Research

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Perhaps no biomedical field better exemplifies the urgency, excitement and challenge of translational research than the field of neurodegenerative diseases. Despite important breakthroughs in our understanding of the pathogenetic mechanisms underlying these conditions, and major investments in clinical trials of promising pharmaceuticals, our previous attempts to bring disease-modifying treatments “from the bench to the bedside” have been disappointing. This brief review outlines areas of recent progress and current knowledge gaps in the two most prevalent neurodegenerative disorders, Alzheimer’s and Parkinson’s diseases (AD & PD), complementing the individual presentations given at the German-Japanese Symposium on Ageing and Neurodegeneration.

General Considerations

There is no doubt that effective interventions against neurodegenerative disorders are urgently needed. The personal suffering associated with the progressive loss of cognitive, emotional and/or motor function is enormous. The societal burden is also substantial, and projections of future disease prevalence and costs in an increasingly aged population are truly staggering. A recent European Brain Council study of the size and burden of brain disorders in Europe estimated that 6.34 million people have been diagnosed with dementia (including AD) and 1.2 million have PD; the total costs for these two disorders in 2010 were calculated to be 105 billion € and 14 billion €, respectively^[1]. The number of individuals with PD in the world’s most populous nations will double by 2030^[2], and the Alzheimer’s Association reports an expected five-fold increase in care costs for AD in the USA from USD 172 billion to USD 1 trillion by 2050. Although our goal is ultimately to prevent or cure these diseases completely, even partially effective interventions would render substantial benefits. For example, it has been estimated that the introduction of a means to simply delay AD onset by five years would reduce care costs by 40%^[3].

It is also clear that advances in the laboratory have led to dramatic recent progress in our understanding of how neurodegenerative diseases develop. We now know much more about how genetic factors influence disease risk, thanks to genome-wide association studies in humans and new transgenic laboratory animal models. Genetic mutations are the predominant cause of neurodegenerative disease in only a small subset of cases (e.g. certain mutations in presenilin or amyloid precursor protein are sufficient to cause early onset AD). Far more disease is caused by complex interactions between genetic constitution and non-genetic factors (including co-existing health conditions, nutritional status and environmental exposures such as tobacco smoke). The discovery of both dominant

and non-dominant genetic changes associated with human disease has given us important clues about disease mechanisms, while experimental animal models provide the opportunity to test these pathways and identify non-genetic risk (or protective) factors.

Extensive research in humans and animal models has demonstrated a feature shared by many neurodegenerative disorders (including AD, PD, amyotrophic lateral sclerosis, frontotemporal dementia and Huntington's disease): the accumulation of misfolded endogenous proteins seems to play a key role in synaptic dysfunction and neuronal cell death ^[4]. Some of these proteins are also capable of acting as "seeds" for aggregation and spreading of disease in the nervous system ^[5]. Increased formation or decreased clearance of these abnormal proteins may explain why ageing is a major risk factor for many of these diseases ^[6]. This recognition of misfolded and aggregating proteins has created a whole new strategy for new therapies (e.g. immunotherapy against α -amyloid). The availability of rapid and sophisticated screening systems also now enables scientists to test large numbers of candidate drugs that might bear the promise of halting or even reversing the progression of neuropathology.

The enthusiasm generated by these advances in knowledge and technology has been dampened significantly by the failure of clinical trials to demonstrate convincing efficacy and acceptable safety outcomes in humans. This low yield, together with the hefty cost of running large, long duration trials have become a disincentive to investment by the pharmaceutical industry. The reasons for the persistent lack of success in "translating" promising laboratory findings into real patient benefit have stimulated much discussion ^[7]. One priority identified is the need for better biomarkers. There is general consensus that validation of biomarkers (for example, changes in cerebrospinal fluid chemistry, or new brain imaging modalities) will provide a more sensitive and rapid way to monitor disease progression and response to intervention. Furthermore, certain biomarker patterns may help identify the patient subgroups most likely to benefit from specific interventions. These general themes will now be discussed in the context of Parkinson's and Alzheimer's diseases.

Parkinson's Disease

Two major discoveries have driven PD research in new directions over the past decade, and have in fact established a new paradigm of the disease itself. The first of these turning points was discovery of the importance of α -synuclein in this disease. This started with the 1997 report of autosomal dominant parkinsonism arising from a single point

mutation in the gene for α -synuclein ^[8], followed quickly by the demonstration that α -synuclein represents a major component of Lewy bodies and Lewy neurites (the intraneuronal inclusion bodies described by pathologist Friedrich Heinrich Lewy decades ago), in sporadic, “idiopathic” PD ^[9]. Further evidence of the importance of this protein in disease pathogenesis was found in rare genetic cases of parkinsonism associated with multiplication mutations of the α -synuclein gene; in these cases, just the increased expression of normal, non-mutated α -synuclein has a toxic effect ^[10]. These findings have spurred new lines of research aimed at answering a broad spectrum of intriguing questions, including:

- What is the normal function of α -synuclein?
- How do genetic and environmental factors affect the levels, post-translational modification and degradation of α -synuclein?
- Under what circumstances is α -synuclein toxic to neurons, and by what mechanism?
- Are certain α -synuclein species a viable biomarker of disease status?
- Is this protein a promising target for pharmacologic intervention?

Genome-wide association studies have also identified other proteins and pathways that likely play a role in the pathogenesis of PD, such those involved in inflammation, oxidative stress and glucocerebroside metabolism ^[11]. How these other pathways are connected to α -synuclein and neuronal death is an active area of investigation.

A second key discovery has emerged from the systematic analysis of the distribution of α -synuclein inclusions in brains of persons who died with PD. In fact, these inclusions seem to spread in a pattern that matches the general progression of the classic clinical PD manifestations, from motor signs to the later onset dementia that occurs in most cases of advanced disease ^[12]. There is interesting evidence that α -synuclein may in fact spread from cell to cell, via a process of seeding and propagation of aberrantly folded protein ^[13]. A fascinating recent finding is that abnormal α -synuclein aggregates can also be observed in the peripheral nervous system, such as the intestinal plexi, even in individuals with limited brain pathology ^[14]. This finding correlates well with recently emerging recognition that the traditional diagnostic features of PD (tremor, bradykinesia, rigidity, postural instability) focus on the consequences of nigrostriatal degeneration, and fail to encompass the multi-neurotransmitter, systemic nature of the disease process. In fact, PD patients quite commonly suffer from a variety symptoms reflective of disturbances of sleep and autonomic nervous function ^[15] that are often present early in the disease course. The new paradigm of PD as a “whole body” disease, perhaps even one that starts outside the

central nervous system and could be diagnosed in a premotor phase, offers exciting prospects for understanding the root causes of disease.

New approaches to preventing, recognizing and treating PD are sorely needed. Current diagnosis, and distinction of PD from other forms of parkinsonism, is based on motoric (movement) signs and symptoms and can be challenging even for movement disorder specialists ^[16]. The pharmacologic cornerstone of PD treatment remains dopamine replacement therapy, which does offer symptomatic relief of motor dysfunction but over time is associated with disabling adverse effects, including dyskinesias ^[17]. Deep brain stimulation can also offer substantial relief from motor symptoms and reduce the need for dopaminergic therapy. However, neither of these treatments provides a neuroprotective benefit that delays worsening motor impairments and prevents further disabling manifestations such as falling and dementia. Cell replacement therapy has met with variable success, and unfortunately the transplanted cells also seem to acquire synucleinopathic changes over time ^[18].

The lack of disease-modifying therapy represents the most significant unmet need in the care of PD patients ^[19]. A number of clinical trials, designed to test agents with sound biologic rationale for neuroprotection (e.g. monoamine oxidase inhibitors and antioxidants), have been unsuccessful and difficult to interpret. Another, much debated example has been glial-derived neurotrophic factor, which despite promising results in both rodent and primate models has yielded inconclusive results in human trials ^[20]. It is not clear that the agents being tested are truly ineffective. Rather, fundamental questions concerning the trial designs have been raised, including:

- Are the interventions being tested in patients with too-advanced disease? How can earlier stage disease cases be identified, when traditional diagnostic methods are imprecise?
- How can disease-modifying benefit be clearly distinguished from symptomatic benefit, or even placebo effect?

This latter issue has led to the development of novel trial designs, such as the delayed start model used in the ADAGIO trial of rasagiline ^[21]. Interestingly, in this trial a dose of 1 mg/day met the endpoints consistent with a disease-modifying effect, over a 72 week-long trial period, but 2 mg/day did not. One explanation for this finding is that the UPDRS rating scale as outcome measure is in fact not ideal for the measurement of progression in early disease ^[19]. Having access to more refined and sensitive markers of disease status and change would certainly boost the power of prevention and treatment trials, and a variety of promising new biomarkers is under current investigation ^[22].

A similar contrast between research progress and translational challenge is apparent in the AD field. The discovery of the genetic underpinnings of early onset, autosomal dominant AD (mutations or duplications in amyloid precursor protein genes, or mutations in the presenilin genes encoding part of the γ -secretase complex) and genetic risk profiles associated with ApoE and Down's syndrome have catalyzed research into the mechanisms of sporadic disease ^[23]. The major protein components of the hallmark neuropathological findings in AD brains were identified in the mid-1980's: β -amyloid ($A\beta$) in extracellular plaques/vascular deposits and tau in intracellular neurofibrillary tangles. The normal role of these proteins in neuronal physiology is still being defined. Transgenic animal models of cerebral amyloidosis and tau pathology have been generated to explore how $A\beta$ and tau are involved in neurotoxicity, and to search for candidate therapeutic agents aimed at these targets.

Genetically modified mouse models have provided striking evidence that misfolded amyloid protein can spread into the central nervous system even if injected peripherally ^[24]. (This has led to AD been called a "prion-like" disease, however evidence of prion-like infectivity that permits transmission between animals or humans lacking). Tau aggregates spread along neuronal tracts in a manner that closely resembles the spatial and temporal progression of AD in human brain ^[25]. However, although amyloid and tau pathology can be produced in these models, neuronal loss is often fairly limited and behavioral deficits do not correlate consistently with the status of plaques and tangles ^[26]. There may even be significant differences in plaque chemistry between species, since plaques in the mouse model are not well labeled by the PET imaging ligand PIB used in humans ^[27]. Just as for PD, there are open questions about how predictive these animal models are for sporadic human AD, in which the gradual neurodegenerative process is likely perpetuated by a complex interaction of genetic and environmental factors, influenced by co-existing health conditions such as vascular disease, metabolic syndrome and ageing/frailty ^[28]. More research is needed to confirm key aspects of the amyloid hypothesis of disease, including identification of neurotoxic $A\beta$ species, and how $A\beta$ is linked to tau in the neurodegenerative process.

Despite the many unknowns about amyloid's role in AD, drug trials have mostly aimed at reducing $A\beta$ production or increasing its clearance. Neuroprotective treatment is urgently needed; the currently available therapy (based on inhibition of acetylcholinesterase or antagonism of NMDA receptors) can offer only modest benefit with regard to cognition and function ^[29], but does not slow cell death and brain atrophy. Unfortunately, despite mas-

sive investment in clinical trials during the past decade, drugs that seemed highly promising in preclinical testing have failed, either because disease-modifying efficacy could not be demonstrated, or due to the emergence of unanticipated adverse effects such as skin cancer (with semagacetat, a γ -secretase inhibitor), meningoencephalitis and vasogenic brain edema (noted with active and passive immunization, respectively) ^{[30], [31]}. The results of several ongoing passive immunization clinical trials that include standard clinical endpoints plus some biomarker outcomes will become available in 2012. Drugs that target pathways other than amyloid (such as intracellular tau aggregation) are also being evaluated.

The dearth of clinical trial success has discouraged large-scale industry investments in clinical dementia research, and has prompted a spirited debate about the reasons for failure and how to address them. Questions that persist include:

- How well do current animal models correlate with sporadic human AD processes – are the key pathogenetic mechanisms known, and are relevant drug targets engaged at effective dose levels?
- Was the power of the studies limited by underlying disease heterogeneity among enrolled subjects and/or lack of stratification in study analysis?
- Did these trials enroll participants with too-advanced, irreversible disease?
- Are better outcome measures available that enable more precise measurement of disease progression (or prevention of progression), over a shorter trial period?

Although the clinical intervention trials have not yet proven successful, a large amount of new biomarker evidence arriving from cross-sectional and longitudinal studies is now defining the mechanistic and temporal continuum of AD progression. It has become clear that A β accumulation in the brain begins at least ten years before the appearance of dementia symptoms; even as this “preclinical” stage evolves, biochemical markers (e.g. CSF A β -42 levels), brain images (radioligand binding of A β , diffusion tensor imaging) and sensitive neuropsychological tests show the development of altered brain physiology and network dysfunction. Increasing synaptic loss and neuronal injury are accompanied by increased cerebrospinal fluid tau and phosphorylated tau levels as well as structural (regional volumetric loss) and functional (hypometabolism) brain imaging patterns ^[32]. Further research is needed to clarify the interactions between the initiating disease pathways and subsequent adaptive or maladaptive response mechanisms. For example, amyloid accumulation is a common feature of the aged human brain, but not consistently associated with progressive cognitive decline ^[33]. It is possible that events downstream of initial

amyloid toxicity are involved in the transition from synaptic dysfunction to increasingly irreversible changes in plasticity and structure, such as epigenetic blockade^[34].

While the performance characteristics of new biomarkers are not yet fully characterized (especially in healthy ageing populations), these studies have provided a basis for defining the symptomatic prodementia phase of AD in a systematic manner^{[35],[36]}. These new constructs of mild cognitive impairment (MCI), and even earlier “pre-MCI amyloid accumulation”, will facilitate the identification of cohorts in which interventions can be tested at an earlier disease stage, presumably when disease modification is more readily achieved. Improved understanding of how AD pathology starts, and the factors that drive disease progression and compensatory mechanisms, will also serve the testing of effective non-pharmacologic interventions. In fact, there is emerging evidence that physical activity and specific cognitive training and exercise can yield objective and potentially neuroprotective benefits^{[37],[38]}.

Improving Translation

There is strong general agreement about the priorities for the next phase of neurodegenerative disease research and translation. First, improved *in vivo* and *in vitro* preclinical models must be developed, particularly models that can be used to assess more complex, “multiple-hit” hypotheses of pathogenesis. Such tools could also be employed to discover new biomarker profiles, explore mechanisms of neuroprotection and identify pharmacologic agents with higher probability of efficacy. New technologies in genetic/epigenetic manipulation and RNA interference are highly promising, as is the use of induced pluripotent stem cells derived from patient fibroblasts^[39], a technique that produces a “human disease in a test tube” model amenable to screening new drug candidates.

A second research priority is clearly the validation of biomarkers. Validation of markers in longitudinal cohort studies can help us distinguish healthy ageing mechanisms from those that drive disease initiation and progression. Biomarkers can improve our ability to diagnosis earliest stages of disease with accuracy and improve clinical study quality by refining patient selection criteria and analytic power. They can enable us to design shorter, proof-of-concept clinical trials to demonstrate drug-target engagement and physiologic effect. Finding and validating “ideal” biomarker profiles is a daunting and expensive undertaking that requires the concerted efforts of all stakeholders. A number of exciting academic-industry consortia, endorsed by patients and advocacy groups, have been established to create standardized methods and share data, such as the Alzheimer’s Disease Neuroimaging

Initiative ^[40] and the Parkinson Progression Marker Initiative ^[41]. An EU Joint Programme – Neurodegenerative Disease Research has also been launched, with biomarker studies a primary focus of its first funding call ^[42].

Finally, it is important to note that effective translation is not limited to the “bench to bedside” flow of information. In fact, findings in clinical and epidemiologic studies constitute the “bedside to bench” half of the feedback loop, ensuring integration of the “human model” results into laboratory study design. Nor should translational research be limited to drug discovery and secondary prevention therapies. Application of evidence-based primary prevention strategies could have a profound impact on disease prevalence and socioeconomic burden ^[43]. And, for patients with advancing disease, there is much to be learned about how to preserve autonomy and quality of life in both home and institutional care settings. Neurodegenerative disease research and care can pose important ethical questions that must be considered in a culturally sensitive way. Research institutions and collaborative networks that embrace a multi-disciplinary approach to the challenge of neurodegenerative disease will be best poised for true translational success.

Ageing without Alzheimer's Disease: The Challenge of the Next Four Decades

Konrad Beyreuther

Life expectancy around the world has increased steadily for nearly 200 years. Improvements in sanitation, housing and education caused a steady decline in early and mid-life mortality, which was mainly due to infections. This trend continued with the development of vaccines and the antibiotics causing a decline in late-life mortality. Why life expectancy continues to rise and where and when this process might end remains obscure. This is something we need urgently to discover because if this trend continues Alzheimer's disease (AD) becomes a major health problem in the next four decades. Given the predicted increase of ten years in life expectancy by 2050, there will be at least a triplication in the number of patients with AD worldwide from 35.6 to 115.4 million. The estimated worldwide annual cost of care for patients with AD and other dementias will increase from estimated US \$ 604 billion in 2010 to 1.8 billion in 2050. We need to be prepared to effectively treat patients with AD and to postpone the onset of symptoms in individuals at risk in order to prevent the vast increases in AD patients. The challenge for treatment is to compensate for the neuronal loss. The challenge for prevention is to postpone the onset of AD by ten to eleven years, because after age 60 the prevalence of AD doubles roughly every five and a half year of age.

How can this be achieved? Looking ahead, it seems unlikely that the ageing process itself will be abolished any time soon. Given that ageing is driven by random damage of molecules, cells and organs, there must be a considerable overlap between the underlying causative pathways of age-related chronic diseases such as AD, cardiovascular disease, cancer and diabetes. As revealed by demography, this seems to be the case and changes in lifestyle seem to slow down the rate at which age-associated damages accumulate and diseases progress.

With regard to AD, it has recently been suggested that up to half of all cases worldwide are potentially attributable to seven risk factors. All of these can be influenced by lifestyle. What causes the other half of AD cases remains obscure. However, as suggested by genetics and epidemiology, brain cholesterol homeostasis and inflammation may be among the other key players. Appropriate approaches to unravel these and other unknown links between ageing and AD requires the study of interactions between all components of the human biological system. Only by systematically probing the complex mechanisms underlying ageing and most if not all of its associated diseases can we transform our dramatic past success in postponing death into a future without symptomat-

ic AD. In this context, it needs to be emphasized that worldwide scientific collaboration is an important factor because collaboration, an important indicator of competitiveness, enhances the quality of research, improves its efficiency and effectiveness, and is increasingly necessary as the scale of both budgets and research challenges grow.

Exploration into the Molecular Mechanisms Underlying Parkinson's Disease Using Medaka Fish Models

Ryosuke Takahashi^[44]

Parkinson's disease (PD) is the second most common neurodegenerative disease among elderly people. The major clinical features of PD are motor disturbances such as tremor, rigidity and akinesia that are caused by selective dopaminergic cell loss in the substantia nigra in the midbrain. Regarding the etiopathogenesis, exposure to toxins and genetics are thought to constitute the main determinants in the onset of PD. Although model animals including mice, *Drosophila* and nematodes have been used to recapitulate the clinical and pathological features of PD through exposure to neurotoxins or gene manipulation, highly successful models are yet to be obtained.

The medaka fish, *Oryzias latipes*, is an emerging vertebrate model with several unique advantages. The genome size of medaka is relatively small, i.e., around 800Mb, and genome sequencing has been completed. Moreover, genetic engineering methodologies such as mutagenesis and transgenic techniques have already been established. Furthermore, they are easy to maintain at low costs. Recently, we have established neurotoxin and gene mutagenesis-based models of PD in medaka fish.

Treatment of medaka at the larval stage with 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP), a classical dopaminergic neurotoxin, decreased the number of dopaminergic cells in the diencephalon and reduced spontaneous movement, which is reminiscent of human PD patients and other MPTP-induced animal PD models. Among TH(+) neurons in the medaka brain, only a specific cluster in the paraventricular area of the middle diencephalon corresponding to the substantia nigra of mammals was vulnerable to MPTP toxicity. Taking advantage of the ease of accessibility of the cerebrospinal fluid (CSF) in fish, we injected proteasome inhibitors, lysosome inhibitors and endoplasmic reticulum (ER) stress inducers into the CSF space of medaka. In all these cases, selective dopaminergic and noradrenergic cell loss was observed. Furthermore, treated fish exhibited reduced spontaneous movement. Treatment with these compounds also

induced the formation of inclusion bodies resembling Lewy bodies, which are characteristic of PD. These results suggest that disturbances of proteolytic systems and ER stress may contribute to the pathogenesis of PD.

Study of the genes responsible for familial PD have significantly contributed to the understanding of the molecular pathogenetic mechanisms underlying PD. Recently, we have succeeded in establishing models of an autosomal recessive form of PD termed PARK 6 in medaka by screening of TILLING library. *PINK 1*, the gene responsible for PARK 6, encodes a putative protein kinase localized in the mitochondria. *PINK 1* null mutant medaka did not display neurodegenerative phenotype. However, they showed a significant decrease in spontaneous movement during the late stages of life as well as downregulation of dopamine metabolism. We have also established medaka models for PARK 9, another autosomal recessive familial PD. PARK 9 model displayed dopaminergic neuronal degeneration with functional and morphological lysosomal abnormalities. These data suggest that PARK 9 may be caused by lysosomal dysfunction. The medaka fish model provides excellent opportunities to dissect the molecular mechanisms underlying PD.

Ageing and Neurodegeneration: What's Next?

Pierluigi Nicotera

The ageing demographic of society poses an enormous challenge to both industrialized and non-industrialized countries. While it is clear that ageing represents a major common risk factor for many diseases, including AD and PD, the underlying biologic mechanisms remain to be defined. For example, caloric restriction is well known to delay ageing by years in non-human primates. The mechanisms by which nutrient status can affect lifespan so dramatically has been investigated in animal models such as *Caenorhabditis elegans*. In this worm model, DZNE scientists have demonstrated that longevity is modulated by WAH-1 (AIF homologue) signaling pathways that link oxidative stress, mitochondrial activity and autophagy. From a mechanistic standpoint these ageing investigations seem to be directly relevant to similar findings in models of neurodegenerative disease. However, although relatively simple animal models serve the purpose of defining mechanistic pathways and potential therapeutic targets, they will not suffice to answer the more complex question of how to extend the length of healthy, high-quality life for elderly people.

Another missing piece of the puzzle is elucidation of the biologic underpinnings of cognitive reserve, or the resilience of brain in maintaining cognitive function despite progressive damage. This may be achieved through recruitment of alternative networks and thus research into synaptic plasticity is of key importance. Recent data obtained from transgenic animal studies in our laboratories have provided insights into the dynamics of dendritic spine morphology and synaptic connectivity, regulated by non-coding microRNAs such as mir29. There is also accelerating interest in the role of inflammation and immunity (both innate and acquired) in neurodegeneration. We must press forward with fundamental research on multiple fronts, even as we apply early findings to translational initiatives such as new target screening technologies and biomarker discovery. Finally, it has become increasingly clear that innovative models of cooperation between academia, industry and governmental agencies are needed to make efficient headway against the challenge of neurodegenerative disease. The traditional clinical trial model (large, long-term studies, relatively insensitive endpoints) has not yielded effective treatments for neurodegenerative disease. Validation and regulatory acceptance of biomarkers correlated with disease pathogenesis and progression will enable a much more efficient process of small proof-of-principle trials of promising drug candidates. One new model of cooperation is being developed in Germany, where the German government is establishing national health centers, including the DZNE which is specifically focused on neurodegenerative disease research. Founded in 2009, the DZNE now employs over 400 scientists, working across the entire spectrum of translational investigation. The interaction of fundamental, clinical, population and health care system research disciplines offers exciting opportunities for new insights and approaches. A program of active collaboration national (industry, insurance, academic and governmental) and international partners has been launched. The DZNE would welcome the opportunity to extend its research network to Japanese partners in the near future.

Molecular Mechanisms Underlying Initiation of Development of Alzheimer Disease and Therapeutic Strategy

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Katsuhiko Yanagisawa

A great deal of effort has been made to develop strategies to prevent and treat Alzheimer disease (AD); however, there is still no cure for the disease. Although the development of symptomatic treatments has been partly successful, development of disease-modifying drugs has not succeeded yet. It is likely that the clarification of early and specific molecular event(s) in AD is a prerequisite for the development of bona fide drugs that suppress the emergence and progression of the disease. Several fundamental questions about the amyloid cascade hypothesis, which is widely accepted and supports anti-amyloid therapies, have not been satisfactorily answered. For example, it remains to be clarified why and how A β assembles and deposits in the brain only in region-specific and age-dependent manners.

To elucidate these issues, we previously examined human brains with or without AD pathology and identified a unique A β species, which was characterized by its tight binding to a ganglioside (GM1), specifically in membrane fractions prepared from human brains in the early stage of AD. On the basis of the molecular characteristics of the ganglioside-bound A β (GA β), including its high potency to facilitate assembly of soluble A β and its altered immunoreactivity, we hypothesized that A β adopts an altered conformation through its binding to ganglioside, and then induces A β assembly into amyloid fibrils by acting as a seed. To date, various *in vitro* and *in vivo* studies on GA β have been performed and have revealed how A β preferably binds to gangliosides, i.e., what are the favorable physicochemical and neurobiological conditions for GA β generation, and what is the pathological significance of GA β -dependent A β assembly in the development of AD. Notably, GA β is favorably generated in unique ganglioside-clustered, raft-like membrane microdomains. The membrane microdomains, which are responsible for GA β generation, were characterized using synaptosomes and non-synaptosomes prepared from mice of different ages. Interestingly, the membrane microdomains with a high potency to induce A β fibril formation through GA β generation predominantly appeared in an age-dependent manner specifically in synaptosomes but not in non-synaptosomes. Furthermore, high-density ganglioside clusters, which were specifically recognized by a novel peptide p3, were detected specifically in synaptosomes prepared from the aged mouse brains. Currently, it remains to be clarified how the ganglioside clustering is induced in the brains that are prone to harbor A β deposits; however, it has been suggested that lipid molecules other than gangliosides in the raft-like, membrane microdomains, such as cholesterol and sphingomyelin, are involved in the process.

The GA β hypothesis may also explain why A β deposition occurs only in a region-specific manner. In regard to this issue, we previously focused on hereditary variant-type A β s because these A β s deposit in the brain strictly in a region-specific manner as follows. The Arctic-type A β exclusively deposits in the brain parenchyma whereas the Dutch-type A β predominantly deposits in blood vessel walls. On the basis of the assumption that GA β plays a crucial role in the initiation of A β assembly, we examined the possibility that local gangliosides are responsible for the regional specificity of A β deposition by incubating the variant-type A β s in the presence of various ganglioside species. Interestingly, the A β s preferentially and significantly assembled into fibrils in the presence of particular gangliosides: the Arctic- and Dutch-type A β s require GM1 and GM3/GM2 gangliosides, respectively, for their assembly. Furthermore, GM1 and GM3/GM2 gangliosides were selectively expressed on the surface of presynaptic neuronal membranes and vascular smooth muscle cells where A β deposition starts to form amyloid in the brain parenchyma and blood vessel walls, respectively.

To apply our findings on GA β to the development of disease-modifying drugs for AD, we have performed molecular dynamics of the interaction between A β and the sugar chain of gangliosides. On the basis of the successfully defined GA β structure, screening in silico from chemical libraries to obtain candidate compounds is now in progress.

Therapeutic Strategies for Treatment of Alzheimer's Disease: Challenges from a Drug Discovery Perspective

Bernd Sommer

Alzheimer's disease is characterized by progressive memory loss, a decline of perceptual and intellectual abilities and the ultimate loss of personality. A definite diagnosis is only possible post mortem. It is the most abundant form of dementia and patient numbers are expected to increase two- to three-fold by the year 2050. Currently available therapies show only limited efficacy in improving daily living performance. Therefore new medications which improve functional performance and slow down disease progression are urgently needed.

The discovery efforts towards new treatment approaches have been guided by neuroanatomical mapping of affected memory domains, an increase in mechanistic understanding of processes underlying synaptic transmission and plasticity as well as findings from pathology and genetic analysis of the disease. New avenues pursued to improve synap-

tic function of demented patients focus on targets along the glutamatergic transmission path, a system shown to be significantly impaired in Alzheimer's disease. Numerous drug candidates acting along this pathway have been identified, which increase synaptic strength and improve memory function in preclinical models, however clinical proof of concept for these new mechanisms of action is still elusive.

The amyloid β cascade hypothesis as the dominant concept for new disease-modifying approaches emerged about two decades ago and has been continuously supported by strong evidence from disease pathology, human genetics and preclinical models. A plethora of approaches targeting brain amyloid β by reduction, clearance or inhibition of its production is being pursued by pharmaceutical industry with the most advanced projects being in late stage clinical development. Nevertheless also for these projects a clinical proof of concept has not been obtained to date.

Therefore, from a patient's perspective, the history of drug development in Alzheimer's disease must appear sobering. In the past 20 years more than 50 compounds entered clinical phase 2 or later, yet only five drugs are approved for the treatment of Alzheimer's disease and none of the clinical candidates in phase 3 has delivered a proof of concept. This lack of clinical proof of efficacy mirrors a general trend in pharmaceutical drug development namely the increasing number of project terminations in late stage development, indicating an insufficient predictivity of preclinical results for clinical outcome. Consequently, major efforts are required to identify and improve translational approaches and methodology which can bridge the gap from bench to bedside.

Such efforts must include the identification and validation of suitable biomarkers to enable a more precise demonstration of drug engagement with the target and better guidance for clinical dose selection to aid better patient stratification or to measure disease progression. Furthermore the revision of clinical assessment tools and the alignment with preclinical readouts may provide a basis for better predictability of new drug concepts. In fact, new imaging technologies such as structural MRI or PET with amyloid specific tracers as well as biochemical markers such as the amyloid β peptide and the tau protein or phospho-tau are being qualified as biomarkers, and offer already a promising basis for better prediction of drug efficacy at earlier time points. Similarly, neuropsychological tests based on non-verbal performance (such as CANTAB) are being employed in analogous set-ups for clinical trials and preclinical tests with the aim to improve predictability.

These biomarker studies have already provided evidence that relevant pathological changes start much earlier than Alzheimer's disease is currently diagnosed with regulatory accepted outcome measures. This imposes a high failure risk on new treatment ap-

proaches in clinical trial designs beyond a point of no return and urgently asks for a revision of disease taxonomy and regulatory adaptation.

Authorities are now beginning to recognize this challenge and revise their guidelines. Recommendations for criteria to define earlier stages of disease definition are being elaborated. Nevertheless, it will require large continuing efforts across disciplines and boundaries with intense dialogues between preclinical and clinical researchers and regulatory authorities to overcome these challenges for the benefit of future patients.

Cognitive Ageing versus Dementia: When to Relax, When to Worry?

Gereon Fink

The steady increase in life expectancy and associated predicted rise in dementia prevalence pose substantial socioeconomic challenges. The increase in life expectancy currently averages 12 months every five years and shows no sign of abating. For example, the number of Europeans aged 65 and over is expected to increase by 45% between 2008 and 2030, and will be over 30% of the population by 2060. Unfortunately, the risk of developing dementia also doubles with increasing age: while those ranging from 65 to 69 years suffer a 2% risk of developing dementia, those aged 90 -95 years have a 35% risk. Furthermore, as long as the key neurodegenerative processes remain to be further elucidated in order to develop novel causal treatment strategies, an as early as possible diagnosis of subjects at risk is important. The latter necessitates that normal ageing associated cognitive decline can be differentiated from mild cognitive impairment (MCI) associated with an increased risk of conversion into dementia. Likewise, a better definition of subjects at risk may help to allocate available symptomatic treatment to those who benefit most. In fact, major reasons for the failure of clinical trials include too-late intervention and non-specific subject selection criteria.

Increasing chronological age is associated with brain frailty, reflected in increases in error rates and test completion time in neuropsychological assessments. Stress and ApoE ϵ 4 status also have negative impacts on memory retrieval ability in older persons. "Mild cognitive impairment" exists when significant impairment of episodic memory is present (without altered activities of daily living or other cognitive impairment). This diagnosis is significant because 75% of MCI patients will progress to dementia over a five-year period (although, importantly, 25% will not). To date no single biomarker (including structural and functional MRI and PET imaging, cerebrospinal fluid analysis) has been doc-

umented to be sufficiently sensitive and specific to identify the earliest MCI stages that will evolve into dementia, but combinations of such markers may do so. Recent studies suggest that some interventions might delay the progression of early cognitive dysfunction (e.g. donepezil in ApoE ϵ 4 carriers, exercise), and should be investigated further utilizing carefully selected and phenotyped subject populations. The emerging data allow further insights into the neurobiology of normal ageing and the neural pathomechanisms underlying mild cognitive impairment.

The Challenges in Genomics: Exploration into Better Understanding the Molecular Basis of Neurodegeneration

Shoji Tsuji

During the past three decades, we have witnessed remarkable advances in our understanding of the molecular basis of hereditary neurodegenerative diseases, which have been accomplished by “positional cloning” strategies started in early 1980s. The discoveries of the causative genes for hereditary neurodegenerative diseases accelerated not only the studies on the molecular mechanisms of diseases, but also the studies for development of disease-modifying therapies based on the molecular mechanisms of diseases.

To elucidate the molecular basis for sporadic diseases, genome-wide association studies (GWAS) based on the “common disease-common variants hypothesis” have been undertaken to identify the disease-relevant alleles. Although GWAS has successfully revealed numerous disease-susceptibility genes for neurodegenerative diseases, odds ratios associated with risk alleles are generally low and account for only a small proportion of estimated heritability. In contrast to these observations, substantially high λ s, an estimation of recurrent risks for siblings of affected individuals, have been demonstrated in sporadic neurodegenerative diseases, including Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis.

We have recently learned that the effect size of the disease-relevant alleles that are identified by comprehensive resequencing of GBA of large data sets of cases of Parkinson disease and controls are substantially larger than those identified by GWAS^{[45], [46]}. These findings strongly argue for the role of the “common disease-multiple rare variants hypothesis” in identifying disease-susceptibility genes for sporadic neurodegenerative diseases. To identify disease-relevant alleles based on the “common disease-multiple rare variants hypothesis”, however, comprehensive genome sequencing is required^[47].

Given the rapidly improving technologies of next generation sequencing (NGS), it has become possible to apply comprehensive genome sequencing to identify disease-relevant alleles with large effect sizes. To accomplish this aim, we have very recently established Medical Genome Center as a core facility at the University of Tokyo Hospital. This center is being designed to produce 1,500Gb in two weeks. In a single personal genome, there are more than 3,000,000 variations. Thus, “genome informatics” is becoming a challenging field in the personal genome analysis. In our Medical Genome Center, a strong interdisciplinary research team consisting of specialist in neurology, clinical genetics and genome informatics has been organized. We are currently applying the comprehensive resequencing of human genome to elucidate the disease-relevant alleles to elucidate the molecular basis of sporadic neurodegenerative diseases based on “common disease-multiple rare variants hypothesis”. We are also planning to apply these technologies for the clinical practice in the near future.

A New Culture of Responsibility: Science, Ethics and the Challenges of Neurodegenerative Disease

Dieter Sturma

The diagnosis and treatment of neurodegenerative diseases, particularly those causing psychiatric disorders and dementia, pose severe challenges across a wide spectrum of issues, including medical, research, economic, political, ethical, moral and legal problems. These issues should be considered in the context of the life of persons over time, within which certain groups such as the very young and persons with cognitive impairment (in the case of dementia, “disappearing subjects”) are – at least in the realm of political decisions – underprivileged compared with active, autonomous adults. Alzheimer’s and other dementing diseases present particularly complex decision scenarios: If disease risk can be demonstrated with new biomarkers decades before symptom onset, and with little preventive therapy to offer, how should that risk be communicated to individuals? As cognitive impairment appears and progresses, how are informed decisions made about participating in research or receiving care? What are the key determinants of quality of life for a person with advanced dementia—lacking understandable linguistic expression and a sense of self over time?

Adherence to a framework of bioethical principles – such as autonomy, beneficence, non-maleficence, and justice – and the use of bioethical methods allow for a recognition of

different hierarchies of values and grounds for reasonable disagreement, beyond dogmatism and fundamentalism. In accordance with these principles a standard of living adequate for the health and well-being is considered a human right, which covers medical care and necessary social services for persons of old age. The bioethical principles set clear limits to a priority of cost-benefit-considerations in the field of medical research, therapy and care. The bioethical principles do not guarantee the right to all forms of medical treatment. In a health system burden and benefit have to be in balance. No generation or social group can be expected to bear a disproportionate burden. The determination of what can count as a disproportionate burden varies depending on the socio-economic context. For instance, the increase of social contributions and health expenses needs to be put in context with the general improvement in living standards and the constantly rising level of medical care.

A new culture of responsibility needs to be established when it comes to dealing with neurodegenerative diseases. This culture should be able to increase ethical sensitivity in everyday life, to revise our conventional notions of personal identity and to set responsibility, autonomy, paternalism, and care in a reasonable relation to each other. Finally, we need to inquire more deeply into the difference between normal ageing and pathological decay. There is already a culture of responsibility for early stages of human life, which is established both, ethically and legally. Corresponding regulations for later stages of life can be found in legislation, but are missing in the social realm. Objectives of the new culture of responsibility should include: a) a new understanding of the life of persons over time, b) an extended responsibility for the entire life (in the first and third person perspective), c) the recognition of different life plans in later stages, d) the formation of a profound intergenerational and intragenerational balance, e) new guidelines for research ethics in the event of declining cognitive capabilities of probands and patients, and f) an improvement of medical research and care for the late stages of the life of persons.

The DWIH Tokyo and the DZNE welcomed approximately 100 participants from academia as well as health care and industry organisations to the German-Japanese Symposium on Ageing and Neurodegeneration.

The two countries share many pertinent similarities which make collaboration in the area of neurodegenerative disease compelling: international leadership in science and technology, excellent health care systems and the challenge of an ageing population susceptible to dementia and other chronic neurologic disorders. The symposium was an opportunity to find new approaches and collaborations for translational research linking academic and industry partners. The two major themes covered by the symposium were recent research advances and directions, and social and ethical dimensions of ageing and neurodegeneration.

The productive and stimulating discussion focused on challenges and new ways to facilitate collaboration between Germany and Japan, across academia, industry, and regulatory parties.

Recent Research Advances and Directions in Germany and Japan

- It was suggested that in addition to new drug targets, the repositioning of drugs developed for other purposes might prove valuable. Examples cited include an anti-epileptic agent with efficacy in PD and an anti-diabetic drug with potential neuroprotective effects. The interest in utilizing high-throughput screening as a means to identify promising drug candidates was expressed, although the compound libraries needed for such investigations are extremely expensive.
- It was agreed that the repositioning of drugs was one approach that might help identify novel targets. At the same time, it was not expected that this would make a major impact. A more viable approach would be to identify a pharmacologic agent's efficacy at an earlier disease stage.
- Participants commented on the current situation of having insufficient data to guide therapeutic trials, and advocated for academia and industry to identify common interests for collaborative work. It was noted that specific collaborative projects involving industry (including small biotechnology firms) and academia could be a mutually beneficial discovery avenue.
- Furthermore, it was stated that multi-disciplinary research was needed to overcome the complexity of overlapping risk factors and gene-environment interactions. Research into health care approaches was also seen as important, but quite challenging given the differ-

ences even between European countries with regard to care models and health data portability. The importance of non-competitive consortia in genetics research, and of studying non-coding DNA regions as well as coding variants was emphasized.

- There was general agreement about the need for clear rationale behind the selection of specific in vitro or in vivo models for specific studies (cell death, cortical function, etc.), whether studying basic pathogenetic mechanisms or screening new drugs.
- It was specified that the highest priority is to cut down the time and cost of clinical trials, by designing smaller proof-of-principle studies with better biomarkers. Also, a systems biology approach was needed to avoid over-emphasis on a multitude of individual drug targets.
- The bioethical difficulties posed by very early disease diagnosis were especially noted. At the same time, participants were optimistic that development of the personal genome approach would lend insight into causes and optimised treatment.

Perspectives for Collaboration

- It was noted that German-Japanese collaborations in the area of genetics research could provide opportunities to address the challenge of evaluating the clinical significance of sequence variations, by performing collaborative studies or networking large databases. Fear of discrimination was seen as one obstacle to enrolling subjects in genetics studies in Japan. In Germany, on the other hand, there was general willingness to participate if it is clear how the genetic information is used.
- It was noted that a German-Japanese collaboration in the area of dementia research would be very rewarding, given for example the differences between the two societies with regard to the concepts of dignity and the place of aged and disabled people in society. It was further specified that one fruitful area of collaboration could be in mixed AD-vascular dementia, the prevalence of which is high in Japan.
- In discussion with the audience it was acknowledged that although clinical trials and high-throughput screening could be done more quickly in other countries, Germany and Japan could combine their strengths in careful research design and implementation (e.g. precise patient stratification) as well as cutting-edge technology. Government funding should be encouraged in particular areas such as new clinical/biological endpoints and systems neurology.

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German Research and Innovation Forum Tokyo

The German Research and Innovation Forum Tokyo (DWIH Tokyo) acts as an umbrella for German scientific and research interests in Japan. Its aim is to present German research organisations and innovative companies in a concerted effort, thereby strengthening scientific and economic cooperation with Japanese partners.

The DWIH Tokyo is thus the central point of contact for Japanese and German research organisations, universities, and businesses or the interested public in general. At the same time it supports and supplements the activities of the participating German organisations by providing information via its website, a comprehensive, subject-specific calendar of events and a number of jointly organised events.

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German Center for Neurodegenerative Diseases (DZNE)

The DZNE was founded by the German government in 2009 as the first of six health research centers focusing on the most challenging major diseases. DZNE is a multi-campus biomedical research center with the mission of discovering the causes of neurodegenerative diseases (including Alzheimer's disease (AD) and other dementias, Parkinson's disease (PD), amyotrophic lateral sclerosis and rare disorders), and developing effective preventive and therapeutic interventions against them. Within just a few years the DZNE has grown to nine centers (Berlin, Bonn, Dresden, Göttingen, Magdeburg, Munich, Rostock/Greifswald, Tübingen, Witten) and over 500 members of staff. DZNE scientists are engaged in research investigations spanning a broad range of themes, including laboratory science, population studies, clinical science and health care systems research. This multidisciplinary approach coupled with an active program of collaboration with industry and international partners is structured to create the synergy needed to develop new and truly effective preventive and therapeutic strategies.

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