

Interview with Takeshi Iwatsubo, Professor of the Department of Neuropathology, Graduate School of Medicine, The University of Tokyo

Very Early Treatment of Alzheimer's Disease & Impact of Public-Private Partnership

By Japan SPOTLIGHT

Aging in Japan is proceeding more rapidly than in any other country. It is thus very urgent for the Japanese medical profession to develop a cure for Alzheimer's disease, which becomes more widespread as the population ages. Dr. Takeshi Iwatsubo, one of the most distinguished experts in this domain in Japan, talked to *Japan SPOTLIGHT* about the latest developments in Japanese medical science for the treatment of Alzheimer's disease and how the nation and society can promote them.

(Interviewed on Jan. 31, 2017)

JS: Could you tell us briefly what you have been researching as a medical doctor?

Iwatsubo: I was originally a medical doctor of neurology and working on patients. My expertise is in the diseases caused by the aging of the nervous system, and I am now working on neuropathology and doing some experimental studies on the mechanism of Alzheimer's disease and its remedies.

Alzheimer's disease is a dementia caused by atrophy of the cerebral cortex. In the brain, with such contraction, a number of neurons are lost and two kinds of abnormal proteins get deposited. These abnormal proteins have been a big mystery for a long time and at the same time a big clue to curing the disease. We have been studying what kind of abnormal proteins are kept there and how they are accumulated and how they turn into this disease. To make a long story short, we have found that one of those proteins forms amyloid deposits called senile plaques and that this may be deeply related to the cause of Alzheimer's disease. Today, medical researchers and pharmaceutical companies are working on how to prevent this amyloid. We also discovered that this senile plaque consists of around 40 amino acids and is created by a short scrap of protein of which the longer original protein has been cut twice by two enzymes named secretases that gather in the brain. Therefore, we are now working on research to analyze the function of secretases and invent a medicine to prevent it or discover a therapy to eliminate the senile plaque by using antibodies to amyloid.



Takeshi Iwatsubo, Professor of the Department of Neuropathology, Graduate School of Medicine, The University of Tokyo

Therapy for Alzheimer's in an Aging Society

JS: It is often said by journalists that we are now within reach of realizing a society where people can continue to work in good health until the age of 90, thanks to the remarkable progress of medical science. Of course, we would need to reform our social systems, in particular our work systems, and change our mindset to achieve it. But if we can manage to do it, we could reduce our medical costs and also mitigate the labor force shortage. Do you think such an idealistic society could be realized soon?

Iwatsubo: I can show you interesting data in the [Table](#) describing the social and economic cost of Alzheimer's disease in the

United States, United Kingdom and Japan. In Japan, we can calculate the number of patients with dementia at around 4.6 million, of whom 60% are suffering from Alzheimer's disease.

The economic loss possibly caused by Alzheimer's disease in Japan made public in 2015 amounted to 14.5 trillion yen for the year 2014. It consisted of 1.9 trillion yen in medical expenditure narrowly defined, 6.4 trillion yen in expenditure on public caregiving, and 6.2 trillion yen in informal care cost which is the sum of the costs of a patient's family labor provided free of charge and loss of working opportunity for a patient. This figure will constantly increase from now on in light of the spread of Alzheimer's disease. Thus, we definitely need to make our

best efforts to reduce the number of new dementia patients or retard the progress of the disease at the very early stage.

Meanwhile, we see so many aged people today in good health, and this is certainly a reality. The Japan Gerontological Society recently announced their proposal that we should redefine “aged people” from those over 65 to those over 70 or 75. As this episode tells us, we see our enthusiasm rising today to let aged people in good health and still full of vitality continue to work and be active and even take care of other aged people not in good health, and above all to make our aging society more resilient by institutional reforms, whether or not an idealistic society can be fully realized.

JS: I think the percentage of patients suffering from dementia in Japan seems to be higher than in the US or UK, is that right?

Iwatsubo: We cannot say so immediately, since research methodologies differ among the nations. However, as the percentage of aged people to the total population in Japan is higher than any other country, we would have a slightly larger number of patients suffering from dementia than other countries. But my guess is China should have the largest number of patients suffering from dementia. Though it is not clear in their official statistics, I guess so given its huge population and its population structure by age.

JS: So dementia is truly a worldwide phenomenon to be tackled internationally, I suppose.

Iwatsubo: Yes, exactly. It is a big issue not only among developed nations but also among emerging nations with big populations such as China and India. Any country in the world probably faces this issue.

JS: Thinking about how long one can be in good health, would it be possible for a human being to live biologically until 120 years old? If not, could medical experts predict our life expectancy in the future? This question is important in drawing up a blueprint for an aging society, in particular devising an institutional framework to enable all people living in an aging society to be happy.

Iwatsubo: I am not quite sure how long we can live exactly. But it is certainly true that we see an increasing number of people living in good health over the age of 90 or 100. But the primary factor provoking Alzheimer’s disease is aging, and so as the number of aged people increases we would have a high risk of an increase in the number of patients suffering from Alzheimer’s disease.

We recently discovered an inspection method named PET (positron emission tomography) scan to detect brain amyloid (we call it amyloid beta) that accumulates in the brain, a cause of Alzheimer’s. There is a

TABLE

Number of patients with dementia & the economic loss caused by the disease

	US	UK	World	Japan
Population (number of patients)	316 million (AD 5.2 million)	64 million (Dementia: 815,000)	7 billion (Dementia > 35 million)	127 million (Dementia: 4.6 million)
Total cost	\$214 billion	\$17.3 billion (26.3 billion pounds)	\$604 billion	\$120 billion (14.5 trillion yen)
Contents	Direct \$150 billion (Medicare \$113 billion, Medicaid \$37 billion) Indirect \$64 billion	Medical expenditure 4.3 billion pounds Public caregiving expenditure 10.3 billion pounds Household caregiving expenditure 11.6 billion pounds	Direct \$352 billion (including medical \$96.4 billion) Indirect \$252 billion	Medical expenditure \$16 billion (1.9 trillion yen) Public caregiving expenditure \$55 billion (6.4 trillion yen) Informal care cost \$53 billion (6.2 trillion yen)
Sources	Facts and Figures 2014; Alzheimer’s Association US	Dementia UK: Second edition (2014); Alzheimer’s society UK	World Alzheimer Report 2010: The Global Economic Impact of Dementia; (Alzheimer’s Disease International)	Ministry of Health, Labour and Welfare (Released on May, 2015)

\$1 = 0.68 pounds = 116.38 yen

certain period during which we would not be able to find this symptom of dementia before the accumulation persists for 10 or more years, and then memory symptoms will emerge. Generally speaking, we see such an accumulation of this amyloid among 10% of people in their 60s, 30% in their 70s, and 50% in those over 80.

JS: So we may as well think about preventing this disease in our daily life without going to a doctor. For example, would doing physical exercise or being more careful in our eating habits be effective in disease prevention?

Iwatsubo: According to an epidemiologic study, lifestyle-related diseases, or in broader sense metabolic syndrome or diabetes, the core disease of metabolic syndrome, would increase the risk of dementia. This is drawing much attention today, so it is good to bring lifestyle diseases under control by diet and aerobic exercises, which can be expected to prevent dementia to a certain extent. To prevent all diseases, we often say that we should not eat too much and take appropriate physical exercise. This is effective for dementia as well. As for meals, Mediterranean cuisine with fewer lipids would be better for preventing dementia than other Western-style cuisines with more lipids from cooking meat. However, Alzheimer disease emerges with rapid speed of expansion and intensity and it would be difficult to control it only by such prevention efforts in daily life.

JS: Would using our brains more lead to prevention of dementia? As we get older and have less to do after retirement, we might become depressed and use our brains much less than before. Would this lead to further deterioration of our brain functions?

Iwatsubo: We do not know yet if we can prevent the process of Alzheimer's disease by using the brain. On the other hand, as the human brain has an extremely large capacity, even if some neurons were lost with the progress of aging or through Alzheimer's disease, the remaining neurons or neural circuit could work as a substitute. In this light, I believe that how we can activate the remaining neurons in our daily life or intellectual activity would be a key to controlling symptoms. Yes, it would certainly be crucial to the health of aged people to maintain a high level of brain activity by socializing with others or doing sports or being engaged in an intellectual activity. However, even with such activities to avoid solitude among the elderly, Alzheimer's disease could occasionally invade a brain and stop these people from enjoying those activities. We will certainly need to pursue a more in-depth approach to this disease.

Most Advanced Therapies for Alzheimer's

JS: Could you tell us about the most advanced therapies for Alzheimer's disease? And how do you assess the capacity of Japanese medical science in this domain in comparison to global standards?

Iwatsubo: Basic research on Alzheimer's disease in Japan was started as early as in many countries, and our study on how amyloid is gathering in the brain has been done in parallel with other developed nations' research on it. However, on clinical research including research on remedies, the US has a longer history than Japan.

At this moment, there are four medicines for Alzheimer's disease officially authorized to be used and all of them are medicines for symptomatic treatment. The most well-known one is "Aricept" produced at the end of the 1990s by Eisai, a Japanese pharmaceutical company. In Alzheimer's disease, a neuron releasing acetylcholine, one of the substances working on neurotransmission in the brain, is reduced and does not work well. Acetylcholine is expected to activate neurons in the cerebral cortices which would be lost with Alzheimer's disease. A symptomatic treatment, in this light, is to supplement acetylcholine and try to keep this neuron receiving it as vital as ever. Aricept prevents acetylcholine from breaking down by blocking a breakdown enzyme in acetylcholine.

There is another similar medicine called "Galantamine" (brand name: Reminyl) produced by Johnson & Johnson. The *Chart* shows the effect of Galantamine. The time lapse is on the horizontal axis and cognitive function on the vertical axis, showing that cognitive function worsens as the data move downward. With Galantamine supplementing acetylcholine, cognitive functions would improve a little and the level of improvement would be maintained for about a year, but after functions slowly worsen again.

What I would like you to learn from this *Chart* is that there is no difference between the group with Galantamine and the group without it regarding the speed of the worsening of cognitive functions, represented by the slope. This means that we supplement the necessary substance running short but we cannot change the speed of a neuron being lost.

Hereafter, I believe that we should be able to make this *Chart* slope more gentle and retard the progress of the disease, even though we

cannot stop it completely, if we manage to find a theory for Alzheimer's disease and discover a remedy to prevent the production of amyloid beta or eliminate it by using antibodies. This is what is called fundamental therapy or disease-modifying therapy. As of now, we have not been able to find any medicine with a definite effect on the disease, but our R&D efforts are proceeding on this point.

JS: Younger people could also suffer from Alzheimer's disease. Would there be different therapies for aged people and for younger people?

Iwatsubo: There would not be any difference. Whether a patient is old or young, the factor of aging matters for both. The basic story is the same: amyloid beta gathers in the brain and causes Alzheimer's disease, and then tau proteins gather inside a neuron and kill it and cause dementia symptoms. These two processes go together and make Alzheimer's disease progress. The medicines for its treatment may be basically similar, though in the case of young patients the progress of the disease is more rapid and its symptoms are much worse.

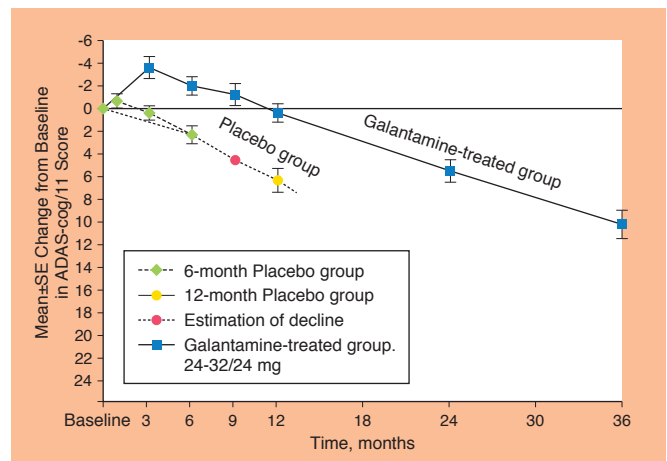
JS: A possible vaccine against Alzheimer's disease is drawing a lot of attention today. How would it work as a therapy?

Iwatsubo: Immune therapy for Alzheimer's disease is to provide a patient with a specific antibody to amyloid beta. An antibody therapy to prevent amyloid beta from gathering or eliminate it in the brain has been developed and large-scale clinical trials have been done by pharmaceutical companies to put this into practice.

At the beginning of the 21st century, a clinical trial for a remedy using a vaccine against amyloid beta was carried out. But after having found that human antibodies would work safely and better, we are shifting our research from vaccine therapy to antibody therapy. In

CHART

Medical effects of Galantamine



Source: Adopted and modified from Raskind et al. *The Cognitive Benefits of Galantamine Are Sustained for at Least 36 Months: A Long-term Extension Trial*, *Arch Neurol.* 61:252-256, 2004

December 2016, in San Diego, Eli Lilly and Co. announced the outcome of a clinical trial at an international conference on Clinical Trials on Alzheimer's Disease. This trial was a large-scale one covering 2,000 people in the mild stage of Alzheimer's dementia. The therapy was successful in having a certain effect upon the disease, but unfortunately the size of effect was not large enough, and then Eli Lilly announced it would give up the clinical trials thereafter.

Alzheimer's disease has a very long time span for progress. Their clinical trial targeted patients at an early stage of the symptomatic disease. Even before that stage, there is a stage of mild cognitive impairment where forgetfulness has clearly reached a pathologic level but is not yet judged as dementia because no other impairment in daily life is observed. Even at this early stage, there is an abnormal change under progress in the brain. Thanks to PET scan, we can recognize amyloid beta gathering even at the stage called preclinical Alzheimer's disease prior to mild cognitive impairment where any memory problem has not yet emerged. Our most recent research is to try to prove that antibody therapy for those people at such a very early stage of the disease could lower the speed of the disease's progress significantly.

In the US, they started a clinical trial for an antibody called solanezumab to be used for patients at the preclinical stage, two stages earlier than that of the failed clinical trial. This is called Anti-Amyloid treatment in Asymptomatic Alzheimer's Disease (A4). This very large-scale clinical trial was initiated by Harvard University a few years ago and joined by pharmaceutical companies like Eli Lilly organized as a PPP (Public-Private Partnership). The University of Tokyo Hospital also joined this experiment in September 2016. We call this pre-emptive therapy or very early treatment, since it is a treatment to deal with the disease at a very early stage where no clinical symptoms are manifested.

JS: If it is crucial for a therapy's success to discover the disease at an early stage, regular medical checks for the whole nation would be necessary. That would be very expensive.

Iwatsubo: Yes. Amyloid PET scan is the inspection method used in current research or clinical trials, but it is not officially approved by the authorities yet. There are two obstacles to this inspection method being used broadly. The first is its high price. It costs several hundred thousand yen for each scan. The second is that we do not have any effective medicines yet to cure Alzheimer's disease even though we can detect the risk of it through the scan. This raises an ethical question if you cannot cure a disease even though you find the risk of it in a medical check. So we need to develop a simpler method for inspection while pursuing studies on therapies.

Role of Ventures in Containing Alzheimer's

JS: PPPs could be very important in that case to deal with costs. Ventures could also be expected to play a role in such partnerships. What do you think about the role of ventures in this area in Japan?

Iwatsubo: I would like to mention one example in the US. There are now two PET drugs for the diagnosis of Alzheimer's approved by the authorities and on a waiting list of insurance companies' approval for reimbursement. One is developed by a venture company, Avid Radiopharmaceuticals acquired by Eli Lilly, and the other developed by General Electric. In both cases, the key to their success was open innovation. Large pharmaceutical companies in general would hesitate to publish the data of clinical trials, since they would not want to see undesirable data made public. By contrast, venture businesses would be very active in publishing their data on clinical studies, since they want the US ADNI (Alzheimer's Disease Neuroimaging Initiative), a group of medical researchers working on Alzheimer's disease, to use their developed medicines in clinical studies as much as possible. As one of them was used in a number of academic studies and then by mega-pharmaceutical companies as well, the medicine became a *de facto* standard and the venture that developed it was finally acquired by Eli Lilly, a mega-pharmaceutical company. This is certainly one way for a venture to achieve business success.

In Japan, we at J-ADNI also founded a consortium in collaboration with the New Energy and Industrial Technology Development Organization (NEDO), a Japanese public organization. It was joined by most Japanese pharmaceutical companies and imaging diagnosis companies, together with academia in Alzheimer's clinical medicine. Among those companies, MICRON Inc. (Molecular Imaging CRO Network), the first Japanese contract research organization to support clinical trials with its expertise in imaging diagnosis, has been working on standardizing amyloid PET scan and promoting it. This company achieved a big business success by participating in this project. It was successful in raising its market share and is now playing a key role in a clinical experiment on a fundamental therapy.

JS: PPP or open innovation seem to be the key to success in containing the enormous costs of dealing with Alzheimer's disease, don't they?

Iwatsubo: Yes. That is exactly what the US is doing now and they initiated this process as a pioneer. In Japan as well we have started talking about creating a new platform on dementia based on PPP. As I told you, the battle against dementia must be considered from the long-term perspective, and so the Ministry of Health, Labour and Welfare founded a research team headed by a well-known nephrologist, Dr. Kiyoshi Kurokawa, emeritus professor of the University of Tokyo's Graduate School of Medicine, and we have started talking about how PPP should work in our project. Given that prevention of Alzheimer's disease will be vital to the success of our business community as well, we would encourage our business leaders to be actively engaged in our project as a part of our PPP. **JS**

Written with the cooperation of Naoko Sakai who is a freelance writer.