Feature 2016 Nobel Prize Winner and Japan's Efforts to Promote Academic and Basic Research

Tokyo Institute of Technology Honorary Professor Yoshinori Ohsumi won the Nobel Prize in Physiology or Medicine on October 3, 2016 for discovering mechanisms called "autophagy" or "self-eating" which enable cells to internally degrade and recycle proteins. This news excited many people across Japan.

Professor Ohsumi's award extended Japan's Nobel Prize winning streak to three years; more great news for the nation.

This feature summarizes Professor Ohsumi's prize-winning research and presents current discussions his award has stimulated on the promotion of academic and basic research.

1 Summary of Professor Ohsumi's Prize-Winning Research

Tokyo Institute of Technology Honorary Professor Yoshinori Ohsumi won the Nobel Prize in Physiology or Medicine in 2016. He is the fourth Japanese winner in this category and the first solo Japanese winner from any of the natural sciences in the 29 years since Professor Susumu Tonegawa's award in 1987. Ohsumi's major accomplishment is the discovery of a key molecular process in cellular degradation mechanisms called autophagy. Although autophagy has been known to science for at least half a century, research in the area had not made progress for many years. The Karolinska Institute, which awards the Nobel Prize in Physiology or Medicine, praised Ohsumi's achievement, stating, "Ohsumi's discoveries have led to a new paradigm in our understanding of how cells recycle their contents."

Professor Ohsumi at the Nobel Prize ceremony
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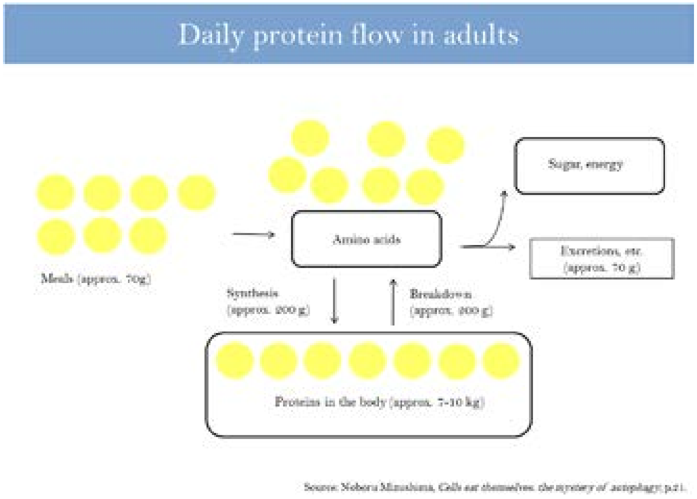
(1) Professor Ohsumi's research accomplishments: from yeast to mammals
His efforts developed into an important research field.

Amino acids are indispensable to the processes that sustain the lives of organisms. Digested proteins break down into amino acids. A human adult presumably synthesizes 200-300 g of proteins daily, including approximately 60-80 g of protein intake from meals. How does the body acquire proteins other than via meals? Autophagy is the key to answering this question. Intracellular proteins are broken down into amino acids by means of autophagy and are then used to resynthesize proteins, generate energy or for other purposes.



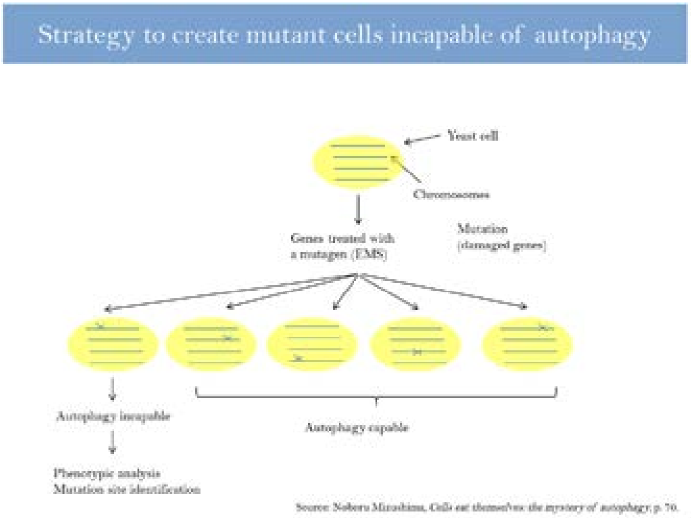
Daily protein flow in adults
Source: Prepared by MEXT based on the book titled *Cells eat themselves: the mystery of autophagy* by Noboru Mizushima.

Humans are said to be capable of surviving only on water for at least a week when, for example, lost in the mountains. Autophagy makes this possible by enabling us to break down proteins in our cells and tissues into necessary amino acids. We will explain below how the mechanisms of autophagy were discovered by outlining Professor Ohsumi's achievements.

Professor Ohsumi earned his doctorate in science from the University of Tokyo in 1974 and went to work at the Rockefeller University in the United States as a postdoctoral fellow. During his time there, Ohsumi was inspired by the research of Leland Hartwell (a biologist and winner of a Nobel Prize in Physiology or Medicine) on the proliferation of budding yeast cells and began researching yeast himself. He then carried out independent research on substance transport by yeast vacuoles at the Department of Botany, School of Science, University of Tokyo under the supervision of School of Science Professor Yasuhiro Anraku (currently a University of Tokyo Professor Emeritus). When Ohsumi became an associate professor at the University of Tokyo's College of Arts and Sciences in 1988, he launched his own lab and began to focus his research on identifying degradation mechanisms within yeast vacuoles.

In plant cells, vacuoles make up a large proportion of cellular volume. They were viewed merely as inactive cellular organelles used for waste storage as recently as the 1980s. When yeast cells are starved of nutrients, they undergo intracellular transformation and form spores to survive. Ohsumi observed starving yeast cells whose vacuoles lacked degrading enzymes under an optical microscope and found many tiny particles moving vigorously within the vacuoles. Subsequent detailed electron microscopic observation revealed this process to be autophagy in action: vacuoles engulfing proteins and other substances and breaking them down.

Professor Ohsumi then conducted experiments in which he artificially created yeast cells incapable of autophagy even under nutrient-deficient conditions by randomly damaging their genes. As described above, when autophagy occurs, tiny particles move vigorously within vacuoles. Professor Ohsumi's research group observed the movement of individual particles in the vacuoles of starving yeast under an optical microscope. After examining some 2,000 mutant cells, the group succeeded in finding one cell incapable of autophagy. The group then identified the mutation sites, thereby determining which genes are vital to autophagy.



Strategy to create mutant cells incapable of autophagy
Source: Prepared by MEXT based on the book titled *Cells eat themselves: the mystery of autophagy* by Noboru Mizushima.

Professor Ohsumi's team ultimately discovered 14 of 18 genes involved in autophagy using this technique. These results were published in FEBS Letters in 1993.

The discovery of genes linked to autophagy and the proteins synthesized by these genes prompted a rapid popularization of autophagy research. Professor Ohsumi relocated to the National Institute for Basic Biology in Okazaki City, Aichi Prefecture in 1996. He then invited Kansai Medical University Research Assistant Tamotsu Yoshimori (currently an Osaka University Distinguished Professor)—an animal cell expert—to his lab and appointed Yoshimori as an assistant professor. The following year, Noboru Mizushima (currently a University of Tokyo Professor)—who had training in internal medicine—also joined the lab. Through Professor Ohsumi's collaborative research with Yoshimori and Mizushima, he was able for the first time to confirm the existence of autophagy genes in mammals. Professor Ohsumi was repeatedly feted for his accomplishments between 2005 and 2012, winning the Fujiwara Award, the Japan Academy Prize, the Asahi Prize and the Kyoto Prize.

As clinical applications for autophagy research became a real possibility, the number of articles published on autophagy research worldwide dramatically increased from a handful each year in the 1990s to several thousand papers annually in recent years. Thus, autophagy has grown into a globally significant research subject.

(2) Key to Professor Ohsumi's success: Keep asking questions.

Although the concept of autophagy had been hypothesized long ago, research and understanding of autophagy mechanisms stagnated for many years due to some restrictions, such as the necessity of using an electron microscope to observe autophagy. How was Professor Ohsumi able to pioneer this area of study?

When he was a researcher at the Rockefeller University, he performed experiments in which he isolated nuclei from yeast cells. The contents of centrifuge tubes were discarded after each experiment. He became aware that the concentrated top layers of the contents of the centrifuge tubes consisted of vacuoles, and wondered what important roles they might play.

When Professor Ohsumi was an assistant professor at the University of Tokyo's College of Arts and Sciences, he focused his research on vacuoles rich in degrading enzymes because they were the only cellular organelles he was able to see under an optical microscope. He hypothesized that any vacuolar degradation activities in yeast cells would increase when the cells were starved and decided to observe this process using an optical microscope. He starved yeast cells that lacked degrading enzymes and observed them. When vesicles containing proteins and other substances fuse into vacuoles, the vacuoles normally break down the vesicular contents. However, using yeast cells with vacuoles lacking degrading enzymes enabled Professor Ohsumi to observe vesicular contents accumulating within vacuoles without breaking down during the autophagy processes. This was the world's first optical microscopic observation of this phenomenon.

Based on Professor Ohsumi's guiding principle that phenomena of interest should be observed in situ, researchers at the Ohsumi Laboratory today still initiate their studies with optical microscopic observations. This guiding principle led to the successful observation of autophagy processes and the subsequent popularization of autophagy research.

After Professor Ohsumi moved to the National Institute for Basic Biology in Okazaki City, Aichi Prefecture in 1996, he invited Tamotsu Yoshimori to join his lab upon Yoshimori's return from Germany. Through the addition of Yoshimori, Ohsumi intended to expand his research targets from yeast—his specialty—to higher animals and plants. As he hoped, his lab ultimately succeeded in identifying the molecular mechanisms of autophagy in higher animals and plants in addition to yeast.

Although autophagy research has been applied even in clinical medicine in recent years, Professor Ohsumi's true interest remains a deeper understanding of autophagy mechanisms.

Concurrent with his joint research with Yoshimori, Professor Ohsumi has also been engaged in long-term joint research to identify autophagy mechanisms in greater detail under the slogan, "Let's identify all structures involved in autophagy." Ohsumi has been conducting this project in collaboration with structural biologists, including the late Hokkaido University Professor Fuyuhiko Inagaki.

Efforts to understand the ubiquity of autophagy across all types of organisms and the structures of proteins involved in autophagy have been driven purely by the intellectual desire to "understand the underlying mechanisms of autophagy."

Professor Ohsumi collaborates with other researchers across a variety of disciplines to satisfy his intellectual curiosity rather than restricting his efforts to his own area of expertise. It can be said that this interdisciplinary approach resulted in the current popularity of autophagy research.

Professor Ohsumi once stated in an interview that, "I encourage people pursuing science as a profession to try something novel and of heartfelt interest. If the subjects of your research are attractive and interesting to you, you should be able to overcome any difficulties you may encounter." He also encouraged young researchers to pursue their own research interests during the news conference at the Karolinska Institute in Stockholm after the Nobel Prize reception, saying, "So I have to keep asking questions to yeast."

The intellectual curiosity to answer questions motivates people interested in pursuing careers in research and is the driving force for researchers as they search for new ideas. A case can be made that Professor Ohsumi's scientific curiosity was a crucial contributor to the current popularity of autophagy research.

(3) Future prospects of autophagy research

One function of autophagy is recycling; it enables the degradation of cellular components to contribute necessary amino acids. Another function of autophagy is cleaning; it enables breakdown of damaged and deformed protein masses. This can be considered to be a type of biological defense mechanism.

Because of these benefits of autophagy, understanding autophagy mechanisms could lead to the development of medical and health-related techniques. For example, knowledge of autophagy mechanisms may be applicable in maintaining cell balance by breaking down unnecessary intracellular proteins, thereby delaying aging, and in treating cancer by blocking autophagy in cancer cells.

Indeed, neurodegenerative diseases caused by autophagy dysfunction were reported in 2006. Additional reports have since been produced, such as studies on links between autophagy and diseases caused by the accumulation of abnormal intracellular proteins, and clinical trials involving the blocking of autophagy functions in cancer cells.

This succession of findings has revealed that autophagy is not only an adaptive strategy for starvation but also involved in various physiological functions.

Meanwhile, many aspects of autophagy mechanisms are still unknown. For example, vesicular membranes—which separate cellular components from proteins to be broken down—are formed at the initiation of autophagy processes. The mechanism of membrane formation is still unknown.

Progress has been made in autophagy research mainly as a result of years of interdisciplinary collaborative research efforts driven by pure intellectual curiosity: the desire to understand amazing biological mechanisms at the molecular level. An interdisciplinary approach will continue to be important for the further advancement of autophagy research, including clinical studies for treating cancer and delaying aging.

2 Research and Development Environment That Facilitated Groundbreaking Academic and Basic Research

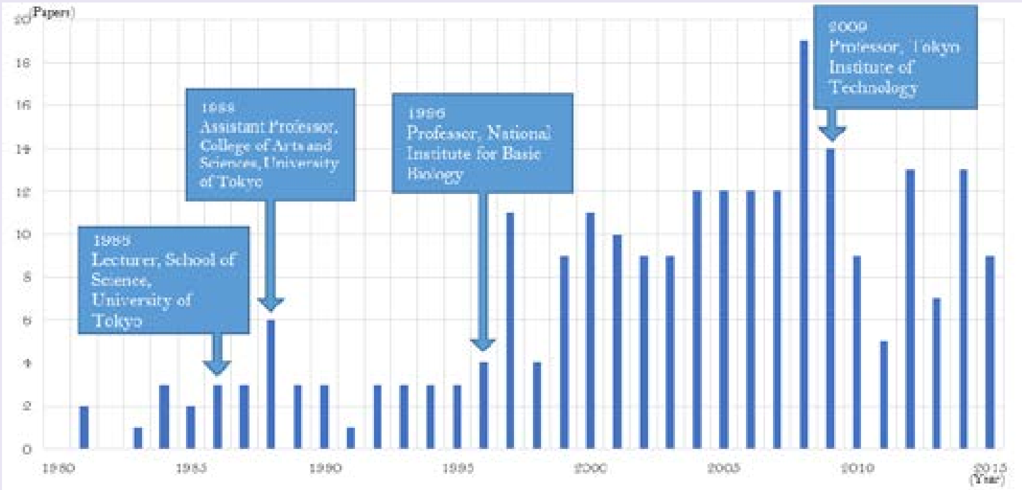
While all Nobel Prize winning, groundbreaking scientific discoveries result from the tireless efforts of the winning researchers, it is also vital for researchers to have access to ideal research-conducive environments capable of bringing out the best in them.

The following is a broad outline of Professor Ohsumi's research activities at the various research organizations with which he has been affiliated, with a special focus on changes in the number of research papers he has published and in the degree of support his research has received from the Grants-in-Aid for Scientific Research (KAKENHI). Based on this information, we discuss how the acquisition of competitive funding and the research environments available at different research organizations affected Professor Ohsumi's research activities. We then suggest research funding systems and research environments necessary to support researchers in Japan.

(1) Changes in the number of Professor Ohsumi's papers and in the number of papers on autophagy

The number of research papers published annually by Professor Ohsumi began to greatly increase with his 1996 appointment to the National Institute for Basic Biology (Figure 1).

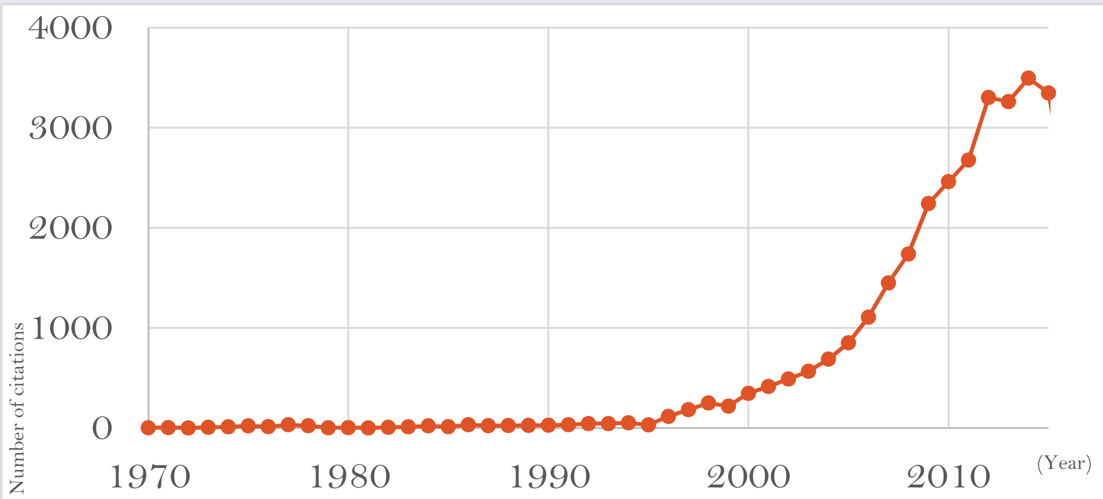
■ Figure 1. Yearly change in the number of research papers published by Professor Ohsumi (1980–2015)



Source: Prepared by MEXT based on the article, "Scientific background of breakthrough research: an analysis for autophagy research" (SciREX-WP-2017-#05) authored by Yasushi Hara and Shinichi Akaike.

In addition, the number of annual citations of Professor Ohsumi's papers began to rapidly increase in 2000 (Figure 2).

■ Figure 2. Cumulative number of citations of Professor Ohsumi's papers

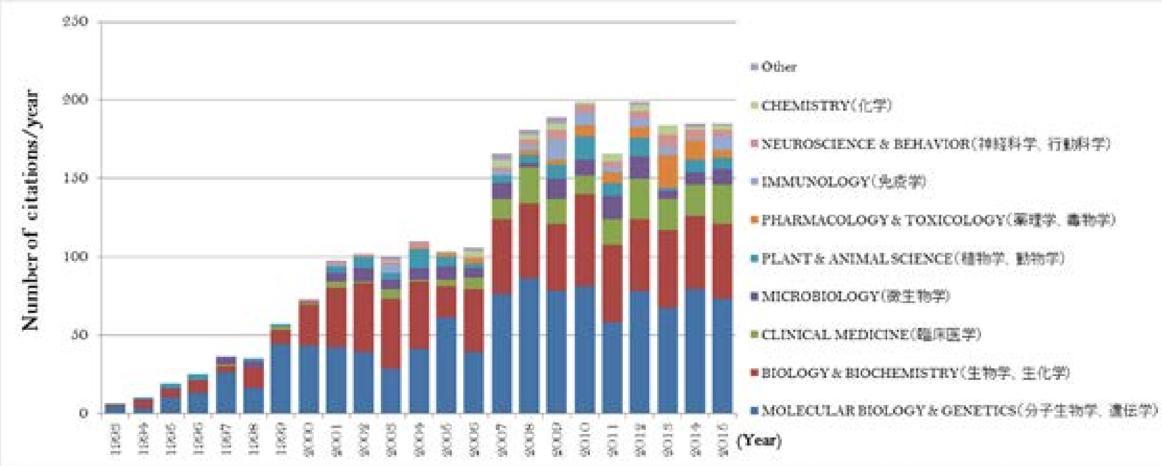


Note: The graph represents cumulative values. For example, the value for 2010 indicates the total number of times the papers published between 1970 and 2010 were cited.

Source: Prepared by MEXT based on the article, "Scientific background of breakthrough research: an analysis for autophagy research" (SciREX-WP-2017-#05) authored by Yasushi Hara and Shinichi Akaike.

Focusing on the four key Professor Ohsumi publications which led to his Nobel Prize, the number of times these four papers were cited began to increase greatly in 2007 (Figure 3). Although it was uncommon for these papers to be cited in research on clinical medicine and pharmacology and toxicology before 2007, citation of them jumped thereafter.

Figure 3. Number of annual citations of Professor Ohsumi's key publications

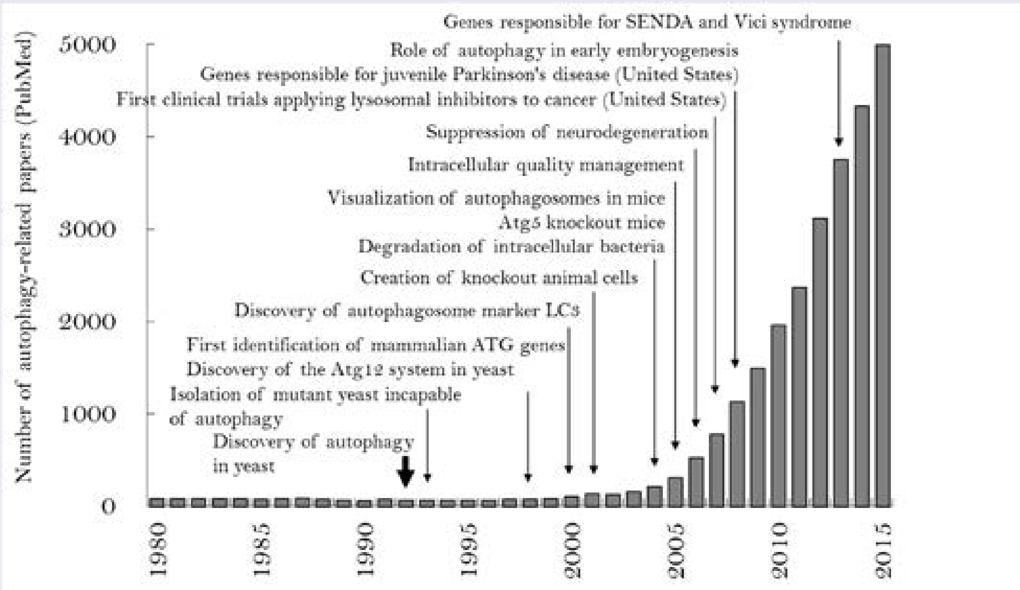


Note: The key publications were identified from the references section on the "Scientific Background" page of the Nobel Foundation website.

Source: Prepared based on the summation and analysis of Thomson Reuters' Web of Science XML raw data (SCIE as of the end of 2015) performed by the National Institute of Science and Technology Policy. Research articles and reviews were the subjects of the analysis.

Moreover, the number of research papers that use "autophagy" as a keyword began to increase dramatically starting around 2006 (Figure 4).

Figure 4. Change in the number of research papers that use "autophagy" as a keyword

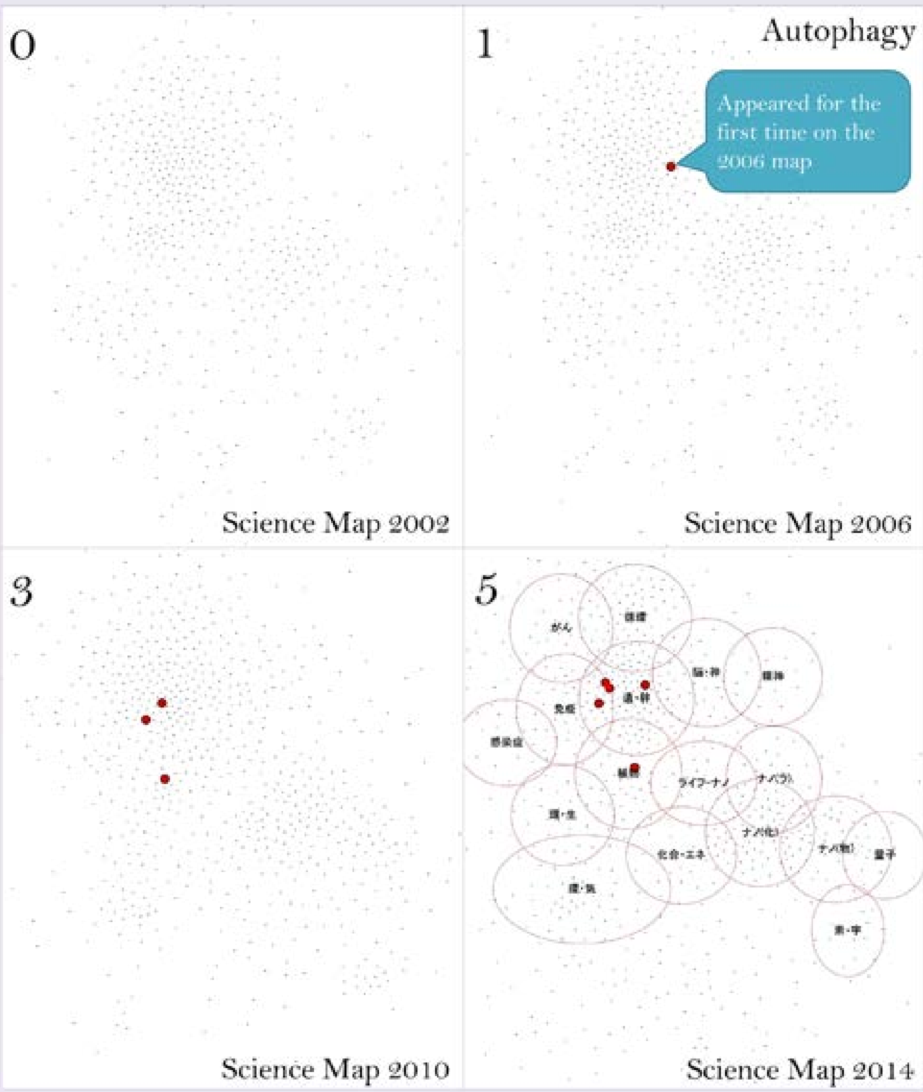


Source: University of Tokyo Professor Noboru Mizushima

In around 2006, autophagy was discovered to play a vital role in the suppression of neurodegeneration, and autophagy research involving clinical trials on Parkinson's disease made progress. These discoveries and research advancements presumably contributed to popularizing autophagy research as indicated by the increased citation of autophagy-related papers during this period.

We also analyzed changes in the popularization of autophagy research using the "Science Maps" created by the MEXT National Institute of Science and Technology Policy (NISTEP). The Science Maps—which are constructed based on research paper database analysis—can be used to visualize research areas that are drawing international attention. We searched the titles of core papers (the most frequently cited 1% of articles within their respective research areas) containing the word "autophagy." Autophagy-related papers appeared for the first time on the Science Map 2006. This further confirms that the popularity of autophagy research rapidly increased around 2006 when research began on the link between autophagy and Parkinson's disease. According to the Science Map 2014—the most recent such map as of April 2017—autophagy-related papers were published on research in botany, immunology, gene expression regulation and stem cells (Figure 5).

■Figure 5. Changes in the research areas in which autophagy-related core papers (i.e., core papers with titles containing the word "autophagy") were published



Source: NISTEP summarized, analyzed and visualized data (Science Map Visualizer) using Thomson Reuters' Essential Science Indicators (NISTEP ver.) and Web of Science XML raw data (SCIE as of the end of 2015).

We then studied temporal changes in the frequency of the appearance of specific terms in the titles of core papers in each research area starting with the Science Map 2002. We found that the number of core paper titles containing the term "autophagy" was virtually the same as those containing the term "iPS cells" on the Science Map 2014, indicating a rapid increase in the popularity of autophagy research (Figure 6).

■Figure 6. Comparison of the number of core paper titles containing the terms "autophagy" and "stem cell" detected in the Science Maps 2002 to 2014

Word (in Japanese)	Word (in English)	SM2002	SM2004	SM2006	SM2008	SM2010	SM2012	SM2014	Total	Mean point in time of detection
オートファジー	autophagy			20	61	62	64	40	247	2010.3
Byword (in Japanese)	Byword (in English)	SM2002	SM2004	SM2006	SM2008	SM2010	SM2012	SM2014	Total	Mean point in time of detection
神経幹細胞	neural_stem	11	5	4	4	6	6	6	42	2007.5
胚性幹細胞	embryonic_stem	19	31	63	56	50	26	17	262	2007.8
幹細胞移植	stem-cell_transplantation	5	9	4	7	4	8	7	44	2008.2
造血幹細胞	hematopoietic_stem	13	17	18	23	15	21	17	124	2008.3
幹細胞	stem_cell	92	119	157	203	222	199	138	1,130	2008.6
心筋幹細胞	cardiac_stem		2	3	7	4	4	2	22	2009.0
間葉系幹細胞	mesenchymal_stem	3	4	18	30	23	15	15	108	2009.2
幹細胞誘導	stem_cell-derived	1	1	3	3	9	2	3	22	2009.3
幹細胞/前駆細胞	stem_progenitor	1	2	3	9	7	8	4	34	2009.5
がん幹細胞	cancer_stem		2	3	15	24	13	1	58	2009.6
人工多能性幹細胞	pluripotent_stem	1			14	52	61	37	165	2011.4

Source: NISTEP summarized and analyzed data using Thomson Reuters' Essential Science Indicators (NISTEP ver.) and Web of Science XML raw data (SCIE as of the end of 2015).

(2) Professor Ohsumi expands his network of research collaborators

We compared the number of research papers published by Professor Ohsumi during the five year periods before and after 1996—the year he moved to the National Institute for Basic Biology and began publishing many more papers. We also compared the number of researchers who co-authored papers with Professor Ohsumi during these two periods and the number of citations of papers published by Professor Ohsumi during these two periods (as of March 2017). The number of co-authors approximately quadrupled from the first to the second periods (Table 7), indicating a connection between increased research collaboration and an increased number of papers published.

■Table 7. Comparison of the number of papers published by Professor Ohsumi and the number of researchers who co-authored papers with him during the five year periods before and after he was appointed at the National Institute for Basic Biology. The number of citations of papers he published between 1991 and 1995 and between 1996 and 2000 were also compared.

Time period (affiliated organization)	No. of papers published	No. of co-authors	No. of times cited
1991-1995 (University of Tokyo)	11	20	2217
1996-2000 (National Institute for Basic Biology)	41	82	10925

Note: The "number of times cited" refers to the cumulative number of citations as of March 2017.
Source: Prepared by MEXT based on the article, "Scientific background of breakthrough research: an analysis for autophagy research" (SciREX-WP-2017-#05) authored by Yasushi Hara and Shinichi Akaike.

We then counted the number of research papers published by Professor Ohsumi in different research areas (which correspond to the scientific journal categories adopted in the research paper databases we analyzed) during various years (Table 8).

While Professor Ohsumi's papers were limited to three research areas in the 1970s, they were found in 13 research areas by 2010-2017, indicating Ohsumi's involvement in an expanding range of research areas over the years.

■Table 8. Number of research papers published by Professor Ohsumi in different research areas over time

Research area	'70-	'80-	'90-	'95-	'00-	'05-	'10-
農業、生物化学 (Agricultural and Biological Sciences)	0	0	0	3	6	6	5
生化学、遺伝学、分子生物学 (Biochemistry, Genetics and Molecular Biology)	2	15	10	25	41	53	43
化学工学 (Chemical Engineering)	0	0	1	0	2	0	0
化学 (Chemistry)	0	0	0	0	1	1	3
意思決定科学 (Decision Sciences)	0	0	1	0	0	0	0
免疫学、微生物学 (Immunology and Microbiology)	1	6	1	0	3	1	0
数学 (Mathematics)	0	0	1	0	0	0	0
薬学 (Medicine)	0	2	3	2	3	7	9
学際領域 (Multidisciplinary)	1	0	0	1	2	0	0
神経科学 (Neuroscience)	0	0	0	0	0	1	0
薬理学、毒物学、薬学 (Pharmacology, Toxicology and Pharmaceutics)	0	0	0	0	0	0	1
物理学、天文学 (Physics and Astronomy)	0	0	0	0	1	8	1
未定義 (Undefined)	0	0	0	2	0	4	0
Number of papers published (in each time period)	3	23	12	30	49	63	43
Number of papers published (cumulative)	3	26	38	68	117	180	223
Number of research areas involved (in each time	3	3	6	5	8	8	6
Number of research areas involved (cumulative)	3	4	7	9	11	12	13

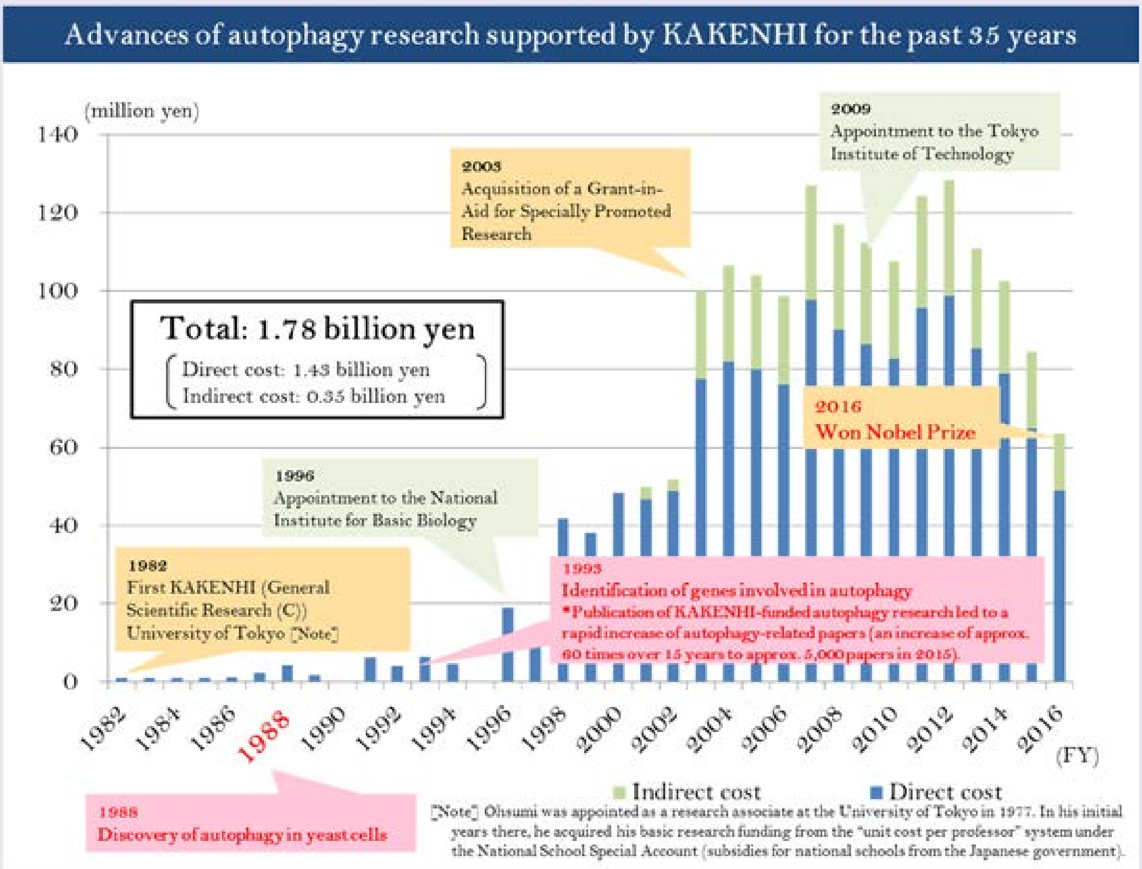
Note: Research areas mentioned here correspond to Scopus classifications. The sum of the number of papers across the various research areas do not always match the total number of papers published by Professor Ohsumi because some journals are classified into two or more research areas.

Source: Prepared by MEXT based on the article, "Scientific background of breakthrough research: an analysis for autophagy research" (SciREX-WP-2017-#05) authored by Yasushi Hara and Shinichi Akaike.

(3) Contribution of the Grants-in-Aid for Scientific Research (KAKENHI)

In the July 2015 issue of the KAKENHI Essay Series (also included in KAKENHI NEWS, FY2016 Vol. 1) published by the Japan Society for the Promotion of Science, Professor Ohsumi expressed his gratitude for the support he received from the Grants-in-Aid for Scientific Research (KAKENHI) as follows: "My research has been funded almost entirely by KAKENHI. In recent years in particular, I have been able to make progress in my research with support from KAKENHI for my project in the Specially Promoted Research category, and I am sincerely grateful for that." Indeed, looking through the list of the KAKENHI support provided to Professor Ohsumi, he has continued to receive the support almost without a break since 1982 when he was in the initial stage of his career as a researcher at the University of Tokyo (grants totaling approx. 1.8 billion yen awarded for 28 research projects from 1982 to 2016) (Figure 9). Since his autophagy research conducted in that initial stage led to his later winning the Nobel Prize, the KAKENHI played an extremely important role in finding academic value in his research and providing support.

■Figure 9. Change in the amount of KAKENHI provided to Professor Ohsumi



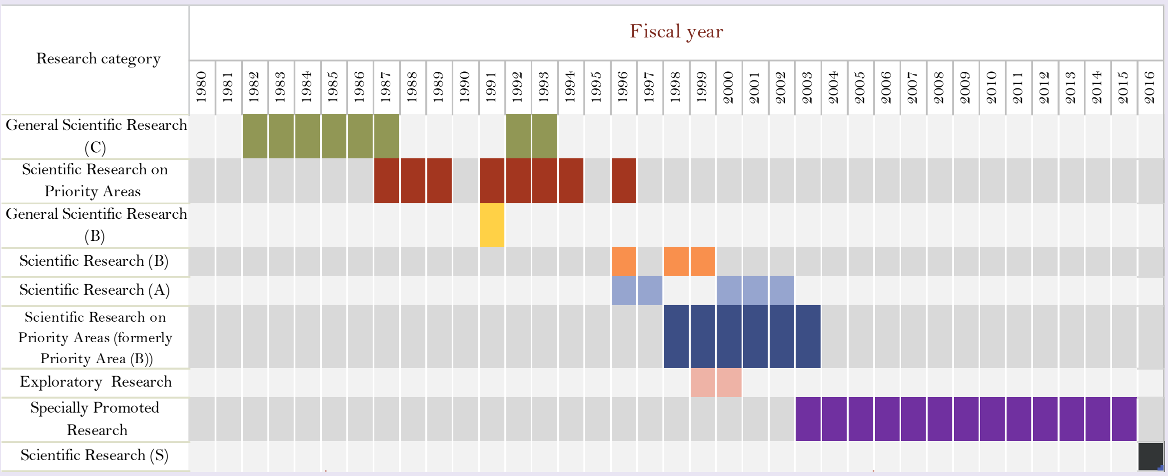
Source: MEXT

The types of KAKENHI Professor Ohsumi acquired shifted over time—he was initially mainly awarded a Grant-in-Aid for General Scientific Research (C) (up to 3 million yen) but eventually granted larger funds, such as a Grant-in-Aid for Specifically Promoted Research (about 500 million yen) and a Grant-in-Aid for Scientific Research (S) (50 to 200 million yen). His main research focuses also changed gradually over time from yeast in early years to physiological mechanisms in yeast and then to a wider ranges of subjects (Figure 10 and Table 11).

Thus, the types of KAKENHI Professor Ohsumi acquired changed as his research areas changed. This relationship suggests that research categories for the KAKENHI have been properly formulated and that properly categorized funding levels in accordance with research progress stages are important.

In addition, while Professor Ohsumi was conducting research at the University of Tokyo, the research had been funded not only by the abovementioned KAKENHI, but also by other funds including the "unit cost per professor" under the National School Special Account. This suggests the importance of the basic research funds provided by the government in supporting scientific research based on free thinking by researchers.

■Figure 10. Change in research categories of KAKENHI provided to Professor Ohsumi



Source: MEXT

■Table 11. List of titles of Professor Ohsumi's research projects funded by KAKENHI

Research period (FY)	Research category	Research project title
1982–1983	General Scientific Research (C)	Physiological and biochemical studies on yeast vacuoles
1984–1985	General Scientific Research (C)	Analysis of H^+-ATPase capable of binding to yeast vacuolar membranes and vacuolar membrane transport system
1986–1987	General Scientific Research (C)	Apical cellular growth inducing mechanism: conjugation tubes formation induced by sex pheromones
1987	Scientific Research on Priority Areas	Yeast cell replication using Ca^{2+}
1988	Scientific Research on Priority Areas	Yeast cell replication control mechanism usingCa ├D12 ├D1+┤ D1
1988	Scientific Research on Priority Areas	Analysis of Ca^{2+} mobilization using the yeast pheromone, α-factor
1989	Scientific Research on Priority Areas	Analysis of Ca^{2+} mobilization using the yeast pheromone, α-factor
1991	General Scientific Research (B)	Analysis of inducing mechanism and physiological role of autophagy in yeast and plant cell
1991	Scientific Research on Priority Areas	Analysis of localized growth mechanism of cell surface
1991	Scientific Research on Priority Areas	Molecular biological studies on the formation of autophagosomes and their specific fusion processes

Research period (FY)	Research category	Research project title
1992	Scientific Research on Priority Areas	Molecular biological studies on the formation of autophagosomes and their specific fusion processes*
1992	General Scientific Research (C)	Analysis of genes involved in autophagy of yeast*
1993	Scientific Research on Priority Areas	Molecular biological analysis of gene clusters involved in autophagy*
1993	Scientific Research on Priority Areas	Autophagy signaling system induced by nutrient starvation stress and its physiological role*
1993	General Scientific Research (C)	Quantification of intravacuolar proteolysis and the analysis of its physiological role*
1994	Scientific Research on Priority Areas	Molecular biological analysis of gene clusters involved in autophagy
1994	Scientific Research on Priority Areas	Autophagy signaling system induced by starvation stress and its physiological role
1996	Scientific Research (B)	Genetic and biochemical study of the process of transition to resting phase using yeast
1996	Scientific Research (B)	Molecular biological analysis of genes required in yeast autophagy
1996–1997	Scientific Research (A)	Molecular mechanism of dynamics of vacuolar system in plant cell
1998–1999	Scientific Research (B)	Molecular cell biological studies of autophagy*
1998–2003	Scientific Research on Priority Areas (formerly Priority Area (B))	Understanding of vacuolar functions as related to survival strategies in plants*
1999–2000	Exploratory Research	Search for new protein binding systems in yeast
2000–2002	Scientific Research (A)	Molecular mechanism and function of ubiquitin-like system in autophagy*
2003–2006	Specially Promoted Research	Molecular mechanism of membrane dynamics during autophagy
2007–2010	Specially Promoted Research	Molecular mechanism and diversity of autophagy
2011–2015	Specially Promoted Research	Identification of the molecular mechanism of autophagy and its integration into cell physiology
2016–2020	Scientific Research (S)	Molecular mechanism and physiological understanding of Autophagy

Note: Asterisks indicate research projects conducted by Professor Ohsumi which led to the production of the key papers listed in the references section on the "Scientific Background" page of the Nobel Foundation website.
Source: MEXT

(4) Contribution of young researchers to Professor Ohsumi's research

According to a Nobel Foundation press release, Professor Ohsumi won the Nobel Prize on the basis of four papers he published. He wrote two of the four papers while he was an assistant professor at the University of Tokyo's College of Arts and Sciences. One of the two papers was coauthored with Miki Tsukada, a graduate student at the Ohsumi Lab at that time. After studying biology at Saitama University, Tsukada began her master's program at the University of Tokyo in April 1991. Professor Ohsumi assigned Tsukada to search for yeast cells incapable of autophagy at his lab. Tsukada diligently observed several thousand yeast cells under a microscope for over a year. The results produced from Tsukada's effort led to Ohsumi's Nobel Prize. In addition, Ohsumi's co-authorship with Tsukada also indicates that Tsukada was a great contributor to Ohsumi's research effort. Professor Ohsumi coauthored three other key papers with Takeshi Noda, who was also a graduate student at the University of Tokyo's College of Arts and Sciences and affiliated with the Ohsumi Lab around the same time as Tsukada. Noda later became Professor Ohsumi's research assistant after Ohsumi's relocation to the National Institute for Basic Biology. Thus, Professor Ohsumi's research collaboration with others—including graduate students at the University of Tokyo's College of Arts and Sciences—made a significant contribution to Professor Ohsumi's research career.

Noda organized the production of a collection of essays entitled "Ohsumi Laboratory in Komaba," in which people associated with Professor Ohsumi wrote their personal memories with him in commemoration of his Nobel Prize win. The essays were completed in December 2016. The essays indicate that when Ohsumi had his lab on the Komaba Campus of the University of Tokyo, professors, assistant professors and research associates on the campus had their own labs to conduct their own independent research. At the same time, they worked collaboratively across their labs by sharing their resources, such as equipment and reagents. Thus, researchers at various laboratories freely engaged in interdisciplinary interactions and discussions which involved university staff members, graduate students and undergraduate students.

Professor Ohsumi was not constantly publishing his research results from the beginning. In fact, it took him four years to publish a paper on autophagy (1992) since he first observed it under an optical microscope in 1988. During these four years, reviewers of Professor Ohsumi' paper recommended that he conduct additional experiments and incorporate new findings from the experiments into his paper.

Professor Ohsumi's relocation to the National Institute for Basic Biology was a major turning point for him. He began to conduct joint research there with Tamotsu Yoshimori—an animal cell researcher—and Noboru Mizushima, who had switched his career from clinical medicine to research. Ohsumi's research efforts during his time at the University of Tokyo led to major scientific findings through these collaborations. Ohsumi coauthored two of the four key papers with Mizushima (Mizushima served as a first author for one of the papers) and coauthored one paper with Yoshimori.

Thus, Professor Ohsumi's Nobel Prize win is attributed in part to the contribution of young researchers at the two research institutions he was affiliated with and his perseverance to move through difficult times.

3 Efforts of the Government to Strengthen Japan's Basic Science Capability

Basic science potentially facilitates the creation and accumulation of new knowledge and continuous innovation leading to social and economic development. Therefore, promoting basic science is extremely important.

Although the winning of a Nobel Prize in Physiology or Medicine by Professor Ohsumi has raised renewed public interest in basic science, many issues also have been brought up as to Japan's capability to continuously produce high-quality research results in academic and basic research.

To address these issues, a "Task Force to Strengthen Basic Science Capability" (hereinafter referred to as the "Task Force") was established at MEXT in November 2016. The Task Force sorted out real issues researchers are facing and discussed concrete measures to promote academic and basic research and strengthen support to young researchers. We describe below the results of the studies conducted by the Task Force and the efforts of the government.

(1) Japan's dwindling basic science capability: three critical issues

Groundbreaking scientific discoveries can be achieved by researchers' tireless efforts, creativity and novel ideas. Therefore, it is vital for researchers to have access to ideal research environments capable of bringing out the best in them. Is Japan capable of continuously producing Nobel-Prize-class, internationally outstanding researchers? Answering this question requires grasping Japan's current situation in science and technology research and identifying issues in this area. In recent years, the number of research papers published by Japanese researchers has been growing at a sluggish pace, and Japan's percentage and ranking in this category have dropped dramatically. For example, we analyzed the top 10% papers (in terms of the number of times they were cited) produced by different countries and compared recent national rankings with those 10 years earlier. Japan's ranking dropped from the fourth between 2002 and 2004 to 10th between 2012 and 2014 (Figure 12). In addition, the number of research papers published by Japanese in disciplines which had been Japan's strength by tradition—such as physics, material science and chemistry—is declining. Japan also has been behind in research in newly emerged disciplinary areas. Moreover, Japan's involvement in international co-authorship is relatively low compared to other countries in terms of the number of publications and the ratio of international co-authorship to domestic co-authorship (Figure 13). Thus, Japan's presence in scientific research is rapidly shrinking.

■Figure 12. National percentages of frequently cited research papers produced by leading countries

2002-2004 (PY) (average)			
Number of adjusted top 10% papers (integer counting method)			
Country	No. of papers	Percentage	World ranking
U.S.A.	36,075	47.4	1
UK	8,957	11.1	2
Germany	8,068	10.0	3
Japan	5,750	7.2	4
France	5,521	6.9	5
Canada	4,447	5.5	6
Italy	3,740	4.7	7
China	3,720	4.6	8

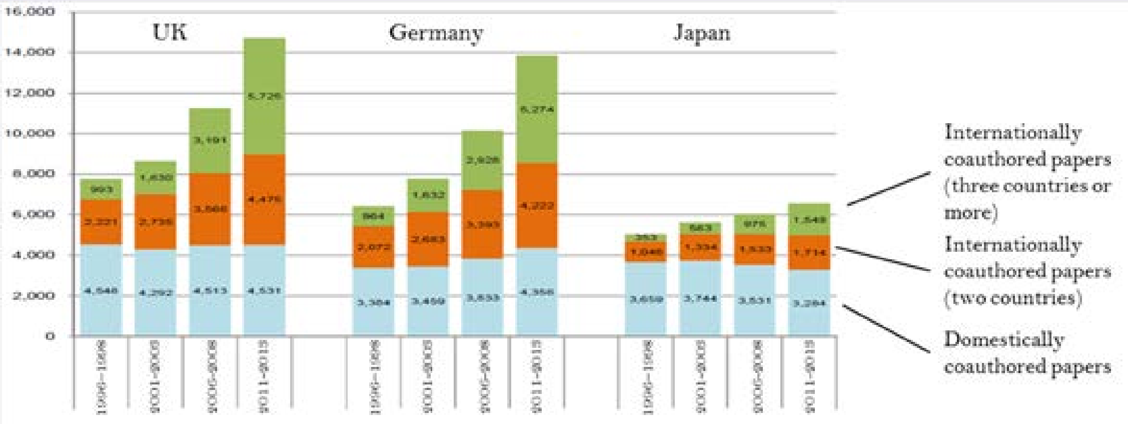
4th

2012-2014 (PY) (average)			
Number of adjusted top 10% papers (integer counting method)			
Country	No. of papers	Percentage	World ranking
U.S.A.	51,837	39.5	1
China	22,817	17.4	2
UK	15,537	11.8	3
Germany	14,343	10.9	4
France	9,428	7.2	5
Canada	8,160	6.2	6
Italy	8,049	6.1	7
Australia	7,074	5.4	8
Spain	6,775	5.2	
Japan	6,524	5.0	10

10th

Source: RM 251 "Japanese science and technology indicators 2016" (August 2016), NISTEP

■Figure 13. Comparison of the number of adjusted top 10% papers produced and the form of co-authorship among the three countries



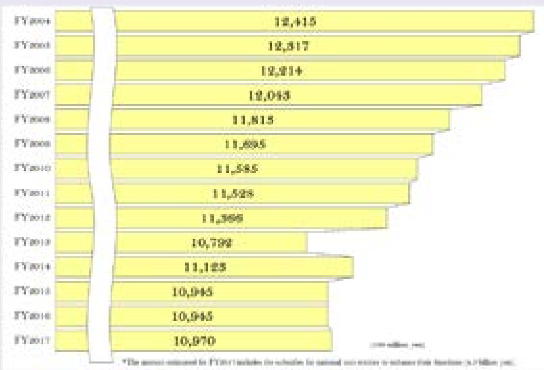
Source: RM 239 "Benchmarking scientific research 2015" (August 2015), NISTEP

Although the causes of and the circumstances related to Japan's weakening basic science capability are complex, the Task Force raised the following three critical issues contributing to this problem.

① Difficulty in performing challenging and long-term research (decreased research funding and time available for research)

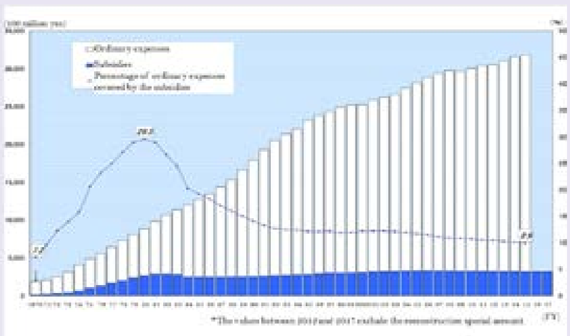
Japanese universities had offered long-term, diverse educational and research activities using basic research funds, such as government subsidies for national universities. They also had been able to innovate and enhance educational and research activities and establish centers for these activities by acquiring competitive funds and using other sources. However, the amount of basic research funds for universities has been decreasing (Figures 14 and 15). In addition, survey results indicate that the amount of funding for independent research is decreasing (Figure 16). Reduced funding amounts have intensified competitions to acquire funding.

■Figure 14. Change in the amount of government subsidies for national universities



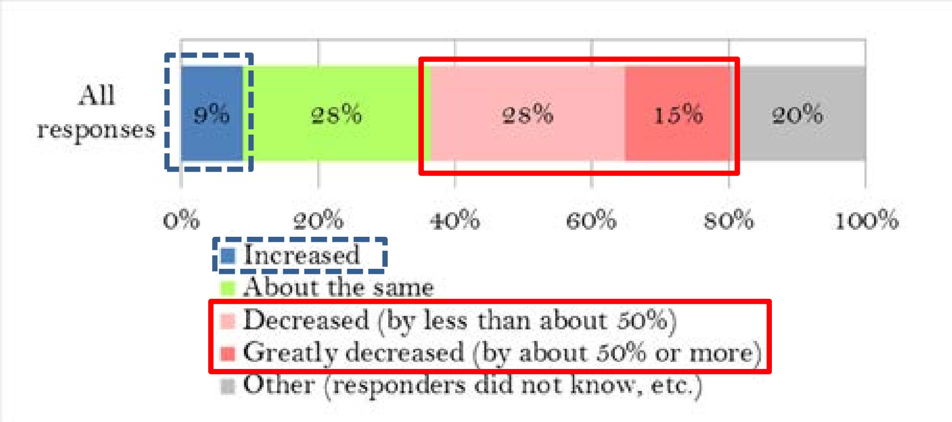
Source: MEXT

■Figure 15. Change in the amount of ordinary expenses in private universities and subsidies provided to cover these expenses



Source: MEXT

■Figure 16. Change in the amount of funding for independent research (compared to 10 years ago)

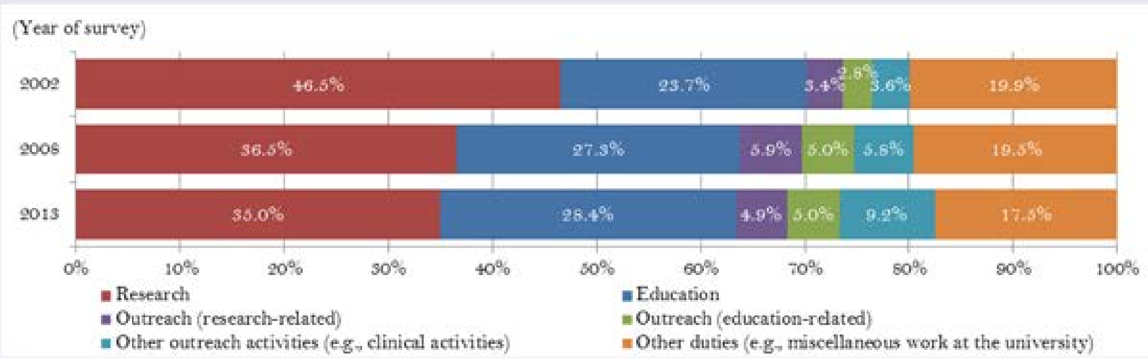


Source: "Results of questionnaires on independent research expenses (summary)" (August 2016), MEXT

Although these types of research funding are becoming inadequate, it is still important to bring about innovation using outstanding research results. Therefore, research support should be provided seamlessly through the following funding sources: basic research funds, KAKENHI, Strategic Basic Research Programs and competitive funds for applied research and development.

In addition to decreased funding, time available for research—another constraint for researchers—has also decreased drastically (Figure 17). Moreover, the burden imposed on researchers is increasing due to such problems as inadequate quality and quantity of research assistants and technical staff, and improper role sharing between researchers and administrative offices in managing research. Researchers' increased dependency on competitive funding is further aggravating these problems.

■Figure 17. Percentage of time allocated to various activities by university faculty members



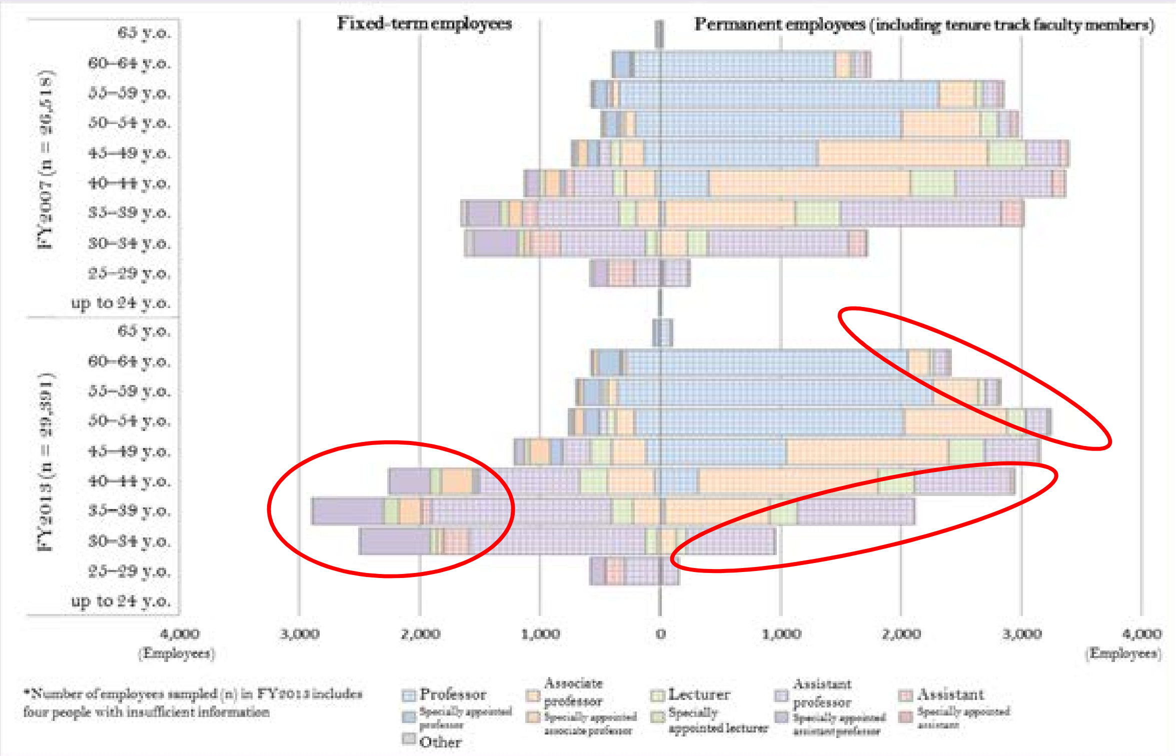
Source: RM 236 "Changes in the ratio of time spent on work activities by university & college faculty members: a comparison of results of the "Survey of full-time equivalency data at universities and colleges" of 2002, 2008 and 2013" (April 2015), NISTEP

② Crisis faced by researchers of the next generation (Deteriorating research environment and employment conditions for young researchers)

Decreased basic research funds for universities have strained the labor budget of full-time faculty members and decreased the number of new faculty members to whom stable employment can be offered.

In addition, increased dependency on competitive research funds has increased the number of unstable, fixed-term employment positions (Figure 18). These unstable employment conditions and economic situations are making it difficult for young researchers to fully engage in truly creative research as they are rushed to produce results and gain experience during their limited appointment periods.

■Figure 18. Change in the employment structure in different age groups across 11 research universities

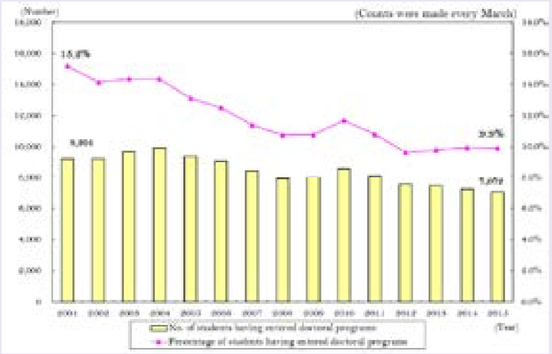


Source: RM 241 "The employment status of instructional staff members at 11 research universities (RU11)" (September 2015), NISTEP

The worsening employment conditions and research environment makes research careers unattractive to currently appointed young researchers and discourage youths with aspiration to become a researcher. Japan has a lower number of doctoral graduates (adjusted to the national population) compared to other developed countries. Uncertainty associated with research careers and the financial burden of attending graduate school appear to be responsible for the decrease in the number of master's graduates pursuing a doctoral degree (Figure 19). In attitude surveys conducted with master's students in science and engineering, they were asked for conditions important in deciding whether to pursue doctoral degree. More students answered that employment conditions after completing their doctoral programs are important than students answering that a high-quality research environment and acquisition of skills are important. These results appear to represent serious economic and employment concerns of master's students upon completing doctoral programs (Figure 20).

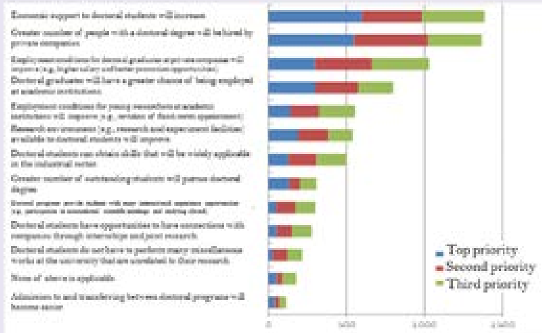
Persistence of these issues may cause deterioration in research communities in Japan: both in quality and quantity, and cause Japan to fall further behind in scientific research.

■Figure 19. Change in the number and percentage of master's graduates who have entered doctoral programs



Source: "FY2016 basic school survey" (December 2016), MEXT

■Figure 20. Conditions important for master's graduates in deciding whether to pursue doctoral degree

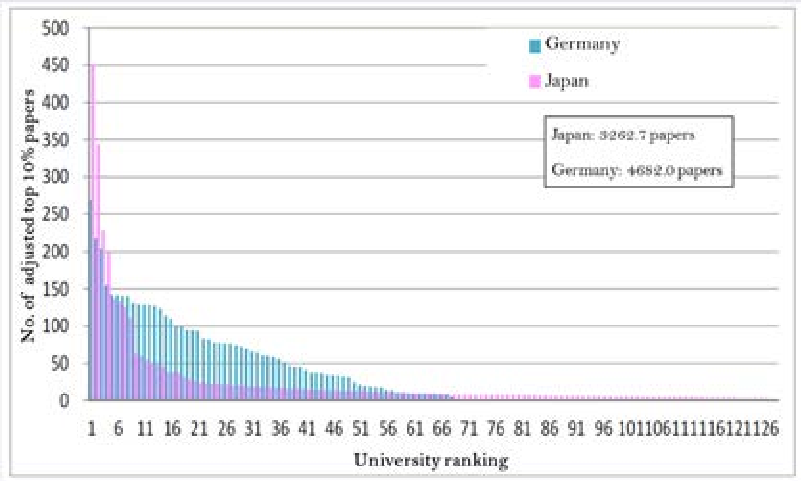


Source: RM 165 "Attitude survey on the career choices of students in master's courses of science and engineering in Japan" (March 2009), NISTEP

③ Difficulty in integrating knowledge (deterioration of research centers enabling knowledge integration)

While the quality and quantity of research papers produced in Japan are generally falling behind other leading countries, Japan's top-level research centers are continuing to produce high-quality papers frequently. However, the impact of these high-quality papers on other research centers across Japan has been limited. For example, the number of adjusted top 10% papers produced by universities was compared between Germany and Japan. While high-ranked universities in Japan produced a greater number of top 10% papers than high-ranked universities in Germany, the results were vice versa when middle-ranked universities were compared. Thus, the comparison with German universities revealed that high-quality papers produced by Japanese universities have been largely attributed to the contribution of high-ranked universities (Figure 21). To improve this situation, it is desirable to establish a variety of "knowledge integration" venues at appropriate organizations compatible with different research types and stages. These venues should offer research environments equipped with adequate hardware resources (e.g., facilities and equipment) and software resources (e.g., research

■Figure 21. Comparison of the number of adjusted top 10% papers produced at ranked universities between Japan and Germany



Source: RM 233 "Quantitative and comparative analysis on national university systems in Japan and Germany based on scientific publications: institutional level and researcher level approaches" (December 2014), NISTEP assistants) and opportunities for researchers in Japan and overseas to engage in friendly competition. The effort to create versatile research centers that meet these conditions need to be expedited.

(2) The government's effort to strengthen Japan's basic science capability

In response to these three issues mentioned in (1), the Task Force formulated national policies to promote basic science which potentially facilitates the creation and accumulation of new knowledge and continuous innovation leading to social and economic development. We present these policies below.

① Measures to address the difficulty in performing challenging and long-term research

Research funding system should be enhanced to facilitate stable funding acquisition by researchers. Support should be strengthened for researchers—including young ones—to engage in international, interdisciplinary, bold and challenging independent research. In addition, adequate basic funds, including basic research funds, should be provided to support basic research, and the number of researchers supported by competitive research funds, including KAKENHI, should be increased.

Specifically, the Task Force proposed that 1) the KAKENHI program increase the proportion of new research proposals to be accepted to 30%, 2) the KAKENHI program establish the "challenging research" category to encourage research based on innovative ideas and 3) assist young researchers to become independent by implementing the KAKENHI program's young researcher support plans. These initiatives intend to reform the KAKENHI program to achieve "intellectual breakthrough" and encourage researchers to collaborate with the industrial sector from the initial research stage—determining research themes—thereby encouraging private sector investment. These strategic approaches seek to promote innovative basic research.

② Measures to address the crisis faced by researchers of the next generation

It is important to provide a research environment conducive to young researchers. The Task Force proposed initiatives to encourage outstanding students to pursue doctoral degrees and careers in research and create stable environments that will allow young researchers to carry out research independently.

Specific measures include 1) revising application eligibility for JSPS Research Fellowship for Young Scientists, 2) improving systems that offer researchers with diverse opportunities such as joint research and internship, and 3) assisting doctoral graduates to obtain research funding from and pursue careers in the industrial sector. In addition, efforts to improve human resources systems include 1) enhancing the Leading Initiative for Excellent Young Researchers (LEADER), 2) creating stable environments that will enable outstanding young researchers considering career in the industrial sector to carry out research independently by allowing them to be cross-appointed between universities and companies, 3) discussing measures to develop and assist diverse human resources through collaboration between the Council for Science and Technology (CST) and the Central Council for Education (CSTP) and 4) formulating Comprehensive Plan to Develop Human Resources in Research (tentative).

③ Measures to address the difficulty in integrating knowledge

The Task Force proposed to 1) develop a research environment attractive and open to the world by supporting the establishment of globally competitive research centers through the World Premier

International Research Center Initiative (WPI) and 2) improve facilities supporting research information infrastructure and appropriate research environments and foundations.

Specific measures will 1) enhance WPI centers—which attract world-class researchers—by strengthening their basic science capability, and then use the appeal of WPI centers to entice large amounts of investment from the industrial sector, 2) strategically support the establishment of globally competitive research centers, which will strengthen specific research areas and facilitate the training of researchers of the next-generation, 3) enhance the information network compatible with big data which is now being used more extensively, 4) enhance research information infrastructure by improving computing infrastructure to meet diverse needs of users, 5) strengthen the functional capability of national university facilities to flexibly accommodate diverse research activities by renovating aged facilities, such as open laboratories, and 6) enhance research environments of private universities.

The Task Force also noted the necessity of establishing a "Working Group to Enhance Basic Capability to Innovate Science and Technology" under the Expert Panel on STI Policy Promotion, Council for Science, Technology and Innovation (CSTI), Cabinet Office (CAO). The working group will 1) hold expert discussion on important subjects related to university reform, 2) identify a variety of funding sources for universities and national research institutes, 3) determine ways in which these organizations can use research funds effectively and efficiently, 4) promote universities' human resources development functions to train workforce for the industrial sector and 5) promote the creation of startups by universities and national research institutes and their activities.

(Conclusion)

Producing results in basic science research is important as such results lead to increased activities in applied research and practical application of research results, social and economic development and creation of new knowledge.

In order for Japan to become a world leader in producing outstanding research results, it is necessary to support Japanese researchers—including young ones—to fulfill their potential by enhancing research environments, reforming human resources systems and improving research funding systems. Active utilization of useful knowledge produced through these efforts is expected to increase research collaboration between universities and bring about social and economic development to Japan. Therefore, it is important for knowledge created by universities and national research institutes to be shared and used by many people, including the industrial sector, by putting in place the mechanisms to facilitate the process.

It is vital that the importance of basic science—as instrument to search for truth—will be understood extensively by Japanese people and accepted culturally. It is also important to raise awareness that results produced by basic science research will enrich the lives of Japanese people.

To increase Japan's basic research capability under the current severe financial situation, it is essential to raise awareness of the Japanese people about the connection between science and their daily lives. It is also critical to gain the support of Japanese people in strengthening basic science.

Japanese scientists have won the second highest number of Nobel Prizes in natural sciences during the 21st century. This fact may imply that Japanese scientists have been highly regarded globally for their creative approaches to the pursuit of truth and contribution to the world. Japan should be very proud of these accomplishments. In addition, many Japanese researchers have made significant achievements in fields that are not the subjects of Nobel Prizes. The Science and Technology Basic Plan notes the necessity of Japan making progress in research in various humanity, social science and natural science fields in order to address ethical, legal and social issues in implementing new scientific and technological findings in society. The number of Japanese people with master's or doctoral degrees in humanities and social sciences is only at an intermediate level compared to other developed countries (the comparison was adjusted to national population sizes (i.e., the number of such people per million people)). Therefore, Japan must pay attention to the fact that vigorous efforts across humanities, social sciences and natural sciences are becoming increasingly important for the development of new social systems.