Research Center Project

Center name: International Research Center for Neurointelligence

Host institution: The University of Tokyo

Head of host institution: Makoto Gonokami, President

Prospective center director: Takao Kurt Hensch
Professor of Molecular Cellular Biology at Harvard University
Professor of Neurology at Harvard Medical School

Appendix 1 For the prospective center director, fill in the "biographical sketch of prospective center director."
Appendix 2 Provide a reference (recommendation) for the prospective center director (free format not subject to the 3-page limitation).

Prospective administrative director: Tetsushi Kagawa
Project Professor of Research Enhancement Strategy Office at National Institute for Physiological Sciences

Appendix 3 For the prospective administrative director, fill in the "biographical sketch of the prospective administrative director."

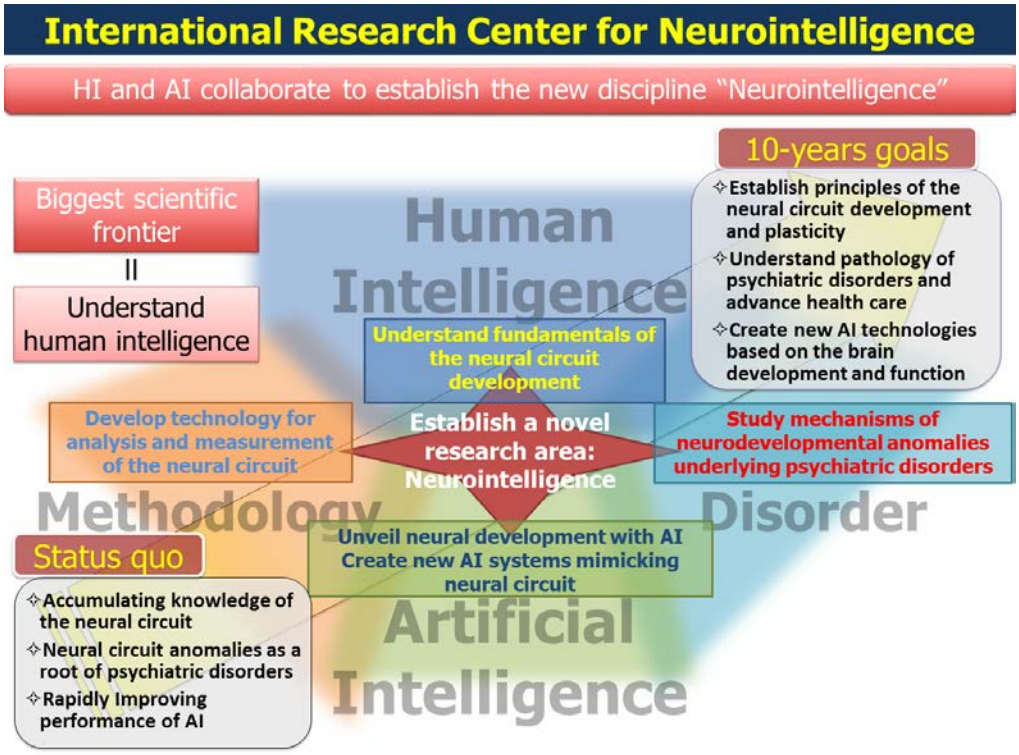
1) Overall Image of Your Center

* Concisely describe your institute's identity and provide its mission statement as a WPI center.

Elucidating brain functions is indispensable for understanding human intelligence (HI). This is a highly complicated and difficult endeavor, but one of the biggest scientific frontiers on par with the origin of the universe. The International Research Center for Neurointelligence (IRCN) aims to elucidate the late fetal and postnatal developmental period in which neurons are differentiated, neural circuits are formed, and shaped by the environment to develop mature brain function. This process follows the principles that the organism has acquired over its long history of evolution, and forms the basis for various high-order functions of the human brain. IRCN to be led by Takao Hensch (Harvard University), a leading researcher of neural circuit development, will tackle the following three issues. First, it will advance understanding of HI by elucidating basic principles of neural circuit development. Second, it will pursue the pathology of neuropsychiatric disorders caused by impairments in the maturation process. Third, it will promote innovation and learning paradigms for next-generation artificial intelligence (AI), based on the newly found developmental principles and multimodal neuronal functions, spanning sensory, motor and emotional systems and enabling human communication unlike currently available AI. To this end, IRCN will establish "Neurointelligence" as a new discipline merging diverse areas such as life science/medicine and mathematics/information science/linguistics.

The background for the proposed IRCN is threefold. First, recent insights into molecular and cellular diversity of the nervous system and advanced technology for neural circuit analysis offer unprecedented tools to elucidate principles governing the development and operation of multimodal information processing in the brain underlying HI. Second, common cognitive disorders, including autism spectrum disorder (ASD) and schizophrenia, are increasingly linked to a number of related genes mostly associated with molecules functioning at synapses, supporting neural circuit dysfunction as their etiological origin. Accordingly, potential elucidation of the biological bases for neuropsychiatric disorders toward an objective diagnosis and treatment has become more and more realistic. Third, expectations for and concerns about next-generation AI have been exacerbated as several unimodal functions are already demonstrably better performed by AI.

Against this backdrop, IRCN was conceived to elucidate mechanisms of neural circuit development, to clarify pathology of neuropsychiatric disorders by research into ASD and schizophrenia in human patients as well as animal models, and to pioneer new AI systems utilizing the same principles as that seen in development and operation of neural circuits in the living brain. The University of Tokyo (UTokyo) is home to many leading neuroscientists, a clinical psychiatry group of the largest scale in Japan based in the University of Tokyo Hospital, and world-class researchers in the fields of mathematics and information science. From them, twelve researchers were chosen as PIs of IRCN to be led by Takao Hensch who has been a leading player in the study of neural circuit development. Arthur Konnerth and Rachel Wong, specialists of similar stature in innovative technologies for large-scale neural circuit analysis and the investigation of neural circuit development, respectively, will also participate as PIs. Furthermore, IRCN will host satellite units both at Harvard University and Max-Planck Florida Institute for Neuroscience, aiming to be one of the world's highest level research organizations. Together, our mission is to clarify principles governing the development and function of integrated multi- modal brain circuits that realize HI, which in turn will promote next-generation AI systems based on these principles and contribute to overcoming mental disorders reflecting a dysfunction of such neural circuit development.



2) Research Activities

2) -1 Research field

* Write in the target research field(s)
* Describe the importance of the target research field(s), including the domestic and international R&D trends in the field(s) and scientific and/or social significance.
* Describe the value of carrying out research in the field(s) as a WPI center (e.g., Japan's advantages, global impact on science and/or society, future prospects)
* If there are other centers either in Japan or overseas advancing research in fields similar to the center's field(s), please list them. (up to 5 organizations)
* Provide a list of 10 English-written papers that are closely related to the center's project and enclose the PDF files of those papers. Label this bundle of documents "Appendix 8."

Target research fields

The target research fields of IRCN are brain sciences, especially developmental neuroscience, neural

information processing, neuronal plasticity, brain imaging, neural networks and psychiatric disorders.

Importance of the research fields and value of carrying out research as a WPI center

Human intelligence (HI) reflects the dynamics of neural circuits in the brain. To achieve such a complex function, an adequately balanced number of neurons needs to be produced and optimally arranged during the fetal period, then their neurites must form proper synaptic connections with appropriate targets, and ultimately be modified to fit the environment in the postnatal developmental period, producing mature functional neural circuits. While AI has recently achieved sensational success, mostly in the field of deep learning, typically based on the multi-layered neural networks observed in the visual cortex. However, AI is still far from achieving multimodal integration fundamental to HI. Further studies of neural circuit development and principles of learning rules are thus expected to contribute toward innovative next-generation AI.

Meanwhile, the increasing social burden of psychiatric disorders, including ASD and schizophrenia, have become a serious world-wide problem, particularly in Japan which is rapidly becoming a super-aging society with reduced birthrate ahead of other countries. Pathological studies and treatments of such disorders are thus urgently needed. Improper or excessive circuit connectivity in childhood and adolescence is generally accepted as a substrate for cognitive disorders whose underlying genes are often identified at synapses. Advances in medical imaging techniques now permit the visualization of disturbances in patients with psychiatric disorders, offering unprecedented opportunities for IRCN as a bridge for translation from bench-to-bedside. By gathering neuroscientists, statisticians and psychiatrists, synergistic research into neural circuit development and dysfunction can foster novel AI. In a super-aging society with reduced birthrates, AI based on deeper knowledge of HI will help human activities and substitute the shrinkage of the working population. Pursuing Neurointelligence as a new discipline by IRCN carries great breakthrough potential not only as a field of scientific inquiry but also for its social impact.

Other centers advancing research in fields similar to the center's field(s)

HHMI Janelia Research Campus (USA) / Allen Institute (USA) / Picower Institute for learning and memory (USA) / Max Planck Institutes (Germany, USA) / RIKEN Brain Science Institute (Japan)

While a number of research institutes for Neuroscience or Brain Science have been established including those above, none feature a close interaction between world-class researchers in basic neuroscience, psychiatry and computational/information/AI science. Importantly, IRCN includes large clinical centers in Tokyo and Boston (i.e., the University of Tokyo Hospital and Boston Children's Hospital, see below) for active translational research, which cannot be achieved by other neuroscience/brain science institutes without clinical branches. In this context, IRCN is a unique avenue to facilitate collaborative study across three disciplines to elucidate fundamental principles of neural circuit development and function as a basis for HI, to advance the understanding of psychiatric disorders as an impairment of HI, and to create next-generation AI based on these principles of development and brain function –

eventually establishing neurointelligence as a new discipline integrating HI and AI.

2)-2 Research objectives

* Describe in a clear and easy-to-understand manner the research objectives that the project seeks to achieve by the end of its grant period (in 10 years). In describing these objectives, the following points should be articulated in an easily understandable manner: The kind of research area(s) you plan to cultivate by, for example, fusing various fields. In that process, what world-level scientific and/or technological issues are you seeking to solve? What will the expected impact of the scientific advances you aim to achieve be on society in the future?
* Describe concretely your research plan to achieve these objectives and any past achievements related to your proposal.

Research objectives

IRCN sets the following research goals: systematically combining basic exploration of neural circuit development, pathological studies of psychiatric disorders, and next-generation AI research; elucidating the formative principles of flexible neural circuits that engenders HI by utilizing the synergy of those insights; promoting development of next-generation AI based on these principles; and overcoming psychiatric disorders by correcting neural circuit maldevelopment.

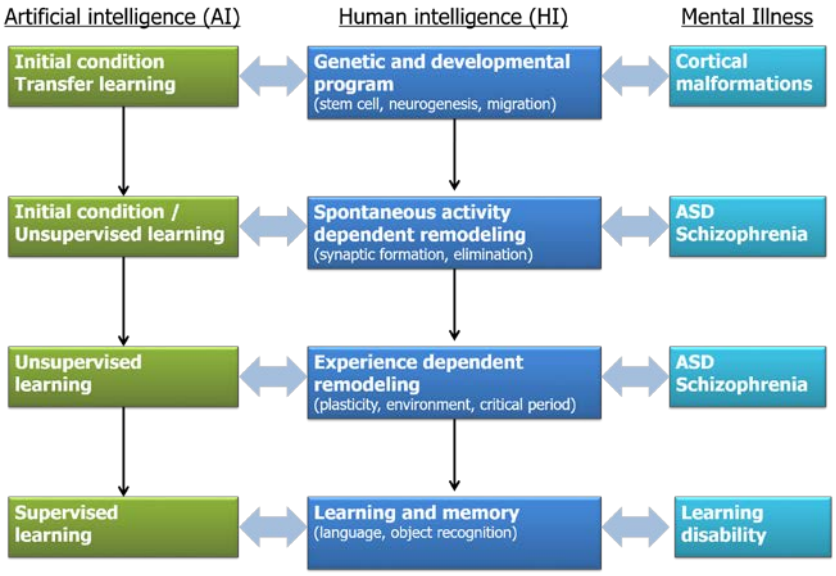
Research plan

Laboratories in IRCN aim to (1) elucidate fundamental principles and learning rules underlying neural circuit development, (2) advance the understanding of pathophysiology of psychiatric disorders caused by impaired HI, and (3) contribute to the development of next-generation AI based on the principles of development and function of multimodal neuronal connections in the brain.

(1) Elucidation of fundamental principles and learning rules underlying neural circuit development

For proper brain function, an adequately balanced number of excitatory and inhibitory neurons should be produced; they must be arranged in appropriate locations in the brain; individual neurons should be connected to appropriate counterparts with an appropriate number of synapses; and neural circuits should be properly wired. Yukiko Gotoh investigates the genetic and epigenetic mechanisms how neural stem cells generate a variety of different cell types including neurons and glia in the brain. Kenichi Ohki investigates the mechanisms by which early neural circuits are formed depending on the ontogeny of neurons. Appropriate formation of neural circuits early in development is prerequisite for learning such that the brain adapts quickly and properly to the external environment and, therefore, constitutes a basis for higher brain functions. When designing AI, it is important to choose the initial conditions prior to learning. If initial conditions are chosen optimally, it may also allow AI to learn quickly without requiring big data, currently a big hurdle. Elucidation of the genetic program of neuronal development, which is optimized through evolution, can therefore contribute to the creation of next-generation AI. Moreover, the study of early circuit formation contributes to the understanding of neurodevelopmental disorders, since abnormalities in genetic programs of brain development lead to brain disorders such as cortical malformations and ASDs.

Next, neural circuits formed earlier in fetal development are modified to adapt to the external environment and then functionally mature into adulthood. This process consists of three stages of neural circuit remodeling based on A) spontaneous neural activity, B) activity evoked by the external environment, and C) convergent external cues and instructive signals for learning and memory throughout life.



A) Spontaneous, internal activity-dependent remodeling of neural circuits includes formation of immature contacts followed by strengthening of a limited subset of early-formed synapses and the massive elimination of redundant ones, a process known as “synaptic pruning” or “synapse elimination”. Masanobu Kano pursues the principles and cellular mechanisms of synapse elimination in the developing cerebellum. To enact changes in connectivity, certain neurons modify the shape of their axonal and dendritic arbors in response to various stimuli. Kazuo Emoto studies molecular and cellular mechanisms underlying neurite remodeling in sensory circuits of mice and fruit flies, both of which are representative models of developmental circuit plasticity. Rachel Wong elucidates principles and mechanisms of synapse assembly in the vertebrate retina in multiple models such as mice and zebrafish. She develops novel live cell imaging approaches to track structural changes in neurons throughout their development, during neuronal degeneration and upon regeneration of circuits in disease models.

B) Following event A), neural circuits undergo a crucial remodeling to optimize their structure and operation to fit the external environment. For example, when input from one eye is deprived during a limited period in postnatal development, known as the “critical period”, the structure and function of neural circuits are reshaped so that input from the deprived eye can no longer excite neurons in the visual cortex. Response preferences of visual cortical neurons to the orientation of objects are also sculpted during a similar critical period depending on the distribution of oriented objects viewed. Takao Hensch discovered that the maturation of inhibitory circuits in the visual cortex is a key determinant of the critical period. A number of molecules involved in the maturation of these GABAergic circuits could accelerate or delay the window of brain plasticity. Moreover, he identified factors which actively suppress rewiring, such that their removal would reopen plasticity in adulthood. These principles of “triggers” and “brakes” on plasticity have been found to apply broadly across brain regions, including auditory, insular and prefrontal cortex. Such regions support higher order brain functions beyond vision, including phoneme discrimination, multisensory integration and preference behaviors or attention.

Kenichi Ohki elucidates learning rules underlying adaptation of visual cortical neurons to the orientation of objects in the external world. This process does not depend on instructive signals and is considered to be a learning process of the statistical distribution of object orientations in the external environment. However, precise learning rules remain unknown and identification of principles of this type of learning is expected to contribute significantly to novel forms of unsupervised learning in AI.

C) Higher brain functions, which constitute important elements for HI beyond development, are ultimately acquired by learning and memory dependent upon the external environment and instructive signals. Kenichi Ohki studies visual object recognition in mice and marmosets. What signals are conveyed in feedforward and feedback pathways between lower and higher visual areas during learning of visual objects may substitute for error backpropagation used in supervised learning in AI currently and will contribute to new algorithms for AI. Kuniyoshi Sakai examines the language system in the brain, which is fundamental to human communication, and a basis for intelligence and creativity. He pursues how language is acquired over development by neural circuits through close and dynamic interaction with the external environment. Finally, Haruo Kasai investigates the causal relationship between synaptic structural plasticity and various forms of learning and memory, which are the major lifelong mechanisms of HI. He also studies how reinforcement learning is embedded in synapses for the association of sensorimotor and emotion signals. In the actual brain, reward signal is obtained from sensorimotor signals, and converted into emotion signals encoded by monoamines (e.g. dopamine, nor-adrenaline, serotonin) which innervate the brain globally. He will study how monoamines encode distinct aspects of emotion other than reward (e.g. motivation, punishment, saliency, novelty, arousal, etc.), and act on discrete subsets of neurons, in a vectorial manner rather than as scalar reward signal.

Laboratories within the Technology Development Unit collaborate closely with and assist the aforementioned eight laboratories of the Development Study Core Unit. Yasushi Okada tackles development and improvement of imaging technologies, which include a microscope of high spatial and temporal resolution and optical bioprobes based on fluorescent organic dyes, fluorescent proteins and/or (bio)luminescent proteins. Haruo Kasai invented a sophisticated method to selectively label synapses that are active during memory acquisition, and then to eliminate the labelled synapses by blue light. Using this technique, he demonstrated that structural plasticity of synapses actually underlies motor memory. He will further improve this technique. Arthur Konnerth is a pioneer who realized *in vivo* imaging of calcium signals from multiple neurons using 2-photon microscopy. He continues to improve the time and spatial resolution of this technique. Shoji Takeuchi has made pioneering and outstanding contributions to development of novel microfabrication technologies. In IRCN, he will develop a flexible electrode array which will allow persistent stable recordings over weeks and months from multiple neurons in vivo. The innovative techniques described above will facilitate the studies of Gotoh, Emoto, Kano, Wang, Ohki, Hensch, Kiyoto Kasai (below), Haruo Kasai, and Konnerth.

(2) <u>Advancing the understanding of pathophysiology of psychiatric disorders caused by impaired HI</u>

In the Neurodevelopmental Disorder Pathology Unit, Kiyoto Kasai and Takao Hensch aim to elucidate pathophysiology of cognitive disorders caused by an impairment of HI. Kasai's laboratory possesses a large-scale MRI database of psychiatric disorders based on collaborations among multiple universities and hospitals across Japan. Utilizing this database, he has succeeded in demonstrating abnormal brain functional connectivity in ASD, and structural abnormalities of subcortical nuclei in schizophrenia. In IRCN, Kasai will combine multi-modal neuroimaging techniques with MRI, including electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (NIRS), and magnetic resonance spectroscopy (MRS) to precisely identify circuit abnormalities in psychiatric disorders. He will then localize the identified circuits onto homologous circuits in non-human primates and rodent models of psychiatric disorders. Through innovative circuit manipulation methods, he will clarify the relationship between neural circuit dysfunction and behavioral abnormalities. Finally, he will use machine learning and AI techniques to develop objective biomarkers for the diagnosis of psychiatric disorders and a new treatment strategy, called neurofeedback, which is expected to normalize abnormal circuit activities by brain-machine interface (BMI) techniques.

Takao Hensch will pursue novel, circuit-based etiological insights using preclinical models of autism and schizophrenia risk. Based on insights from critical period studies (above), he will correct derailed developmental trajectories or reopen brain plasticity later in life to restore aberrant circuit function. Treating the circuit abnormality rather than heterogeneous gene defects based on principles of critical period plasticity is innovative and more readily translatable to clinical trials, as he has started to do at Boston Children's Hospital (see below).

(3) Development of next-generation AI based on new principles of development and operation of neural circuits in the brain

Laboratories in the Mathematical Information Systems Unit will tackle the development of next-generation AI based on the newly identified principles of development and operation of neural circuits in the actual brain in the following three projects:

A) Development and mathematical analysis of novel AI technology based on neural mechanisms in the brain

Deep learning, the mainstream of present AI research, is based on simple multi-layered feedforward neural networks of oversimplified artificial neurons. The cerebral cortex, however, has a complex six-layered structure composed of various types of neurons connected through many synapses including recurrent connectivity and projections from limbic systems carrying emotion signals, as well as more global hierarchical structure with bottom-up and top-down pathways across different cortical areas.

IRCN's research aims at developing novel AI technology based on neural mechanisms in the actual brain and defining its mathematical properties. First, humans learn very quickly without requiring big data, unlike the current deep learning technology. As described in section (1), we hypothesize that it is because neural circuits in the human brain are optimized through multiple developmental processes,

such as genetic programming, spontaneous activity-dependent remodeling, and experience-dependent remodeling with the help of emotion systems. By incorporating such principles, Masashi Sugiyama will construct a novel machine learning framework. Second, GABAergic neurons are not commonly used in the field of deep learning, but they play pivotal roles in the human brain. As described by Hensch, they control the critical period and play roles in information processing, such as surround suppression. Masashi Sugiyama and Kazuyuki Aihara will incorporate GABAergic neurons in network structure and examine how they change the behavior of neural networks. Finally, by incorporating learning rules in feedforward and feedback pathways between lower and higher areas, Masashi Sugiyama will implement novel learning rules to recognize complex time-series data and infer causal relations that current deep learning technology cannot achieve.

B) Computational and mathematical analyses of big neuroinformatics data covering an entire brain and of activities from a large number of neurons

Hiroki Ueda has developed a new experimental method to obtain neural circuit data covering an entire brain and associated neuroinformatics methods to identify multimodality from whole-brain circuit data of individuals. He also creates computational and mathematical methodologies to analyze big neuro-informatics data such as neural circuit data covering an entire brain and neural activity data observed simultaneously from a large number of neurons in the same brain. These include nonlinear data analysis method for spatio-temporal point processes of neuronal spikes generated from many neurons, and integrative and quantitative analysis of real experimental data.

C) Mathematical modeling of psychiatric disorders applied to understanding their pathophysiology

This theoretical research considers mental illnesses as disorders or collapses of normal mechanisms for neural network development and function in the brain. By modifying neural network models with normal functions, Kazuyuki Aihara constructs mathematical models of mental illnesses to understand their pathological dynamics and explore possible circuit-based therapies from a theoretical viewpoint. More specifically, based on the work of Hensch, he will explore how mistiming of excitatory-inhibitory balance results in ASD, while a failure to close critical period plasticity properly might result in psychosis. By analyzing nonlinear spatio-temporal dynamics of neural network models, we explore possibility that mistiming or failure of developmental transitions in such nonlinear dynamics results in abnormal circuit operation.

2)-3 Project management

* Describe the center's research organization (including its research, support and administrative components) and your concept for building and staffing the organization.
* Describe your concrete plan for achieving the center's final staffing goal, including steps and timetables.
* If the center will form linkage with other institutions, domestic and/or foreign, by establishing satellite functions, provide the name(s) of the partner institution(s), and describe their roles, personnel composition and structure, and collaborative framework with the center project (e.g., contracts to be concluded, schemes for resource transfer).
* If the center will form linkage with other institutions, domestic and/or foreign, without establishing satellite functions, provide the names of the partner institutions and describe their roles and linkages within the center project.
* List in Appendix 4 the principal investigators who are expected to join the center. If it there are any changes from the list you submitted for the first screening, please state the changes and give your reasons for them.
* Provide a biographical sketch for each principal investigator using Appendix 5.
* List in the Appendix 6 the personnel making up center, including researchers and other center staffs, satellites, partner institutions.

Use Excel format when preparing the list.

* Regarding the researchers invited from abroad or from other Japanese institutions, attach a letter from each of them indicating their intent to join the center project (free format). Label this bundle of documents "Appendix 7."

Center's research organization

To achieve the goals stated above, fifteen world-class principal investigators (PIs) are recruited from within UTokyo and from research institutes overseas to organize the four research units: Development Study Core Unit, Technology Development Unit, Neurodevelopmental Disorder Pathology Unit and the Mathematical Information Systems Unit. If awarded, our center would realize studies with a new dimension produced by their deep synergy, as it will naturally boost existing individual interactions, due to substantial overlap in research interests, as described below.

- **Development Study Core Unit**: Eight PIs use their individual model systems to pursue the fundamental principles of neural circuit development as well as the neural basis of language, a representative function of HI: Yukiko Gotoh studies regulation of neural stem cell fate; Masanobu Kano, synapse elimination in postnatal development; Kazuo Emoto, elimination and remodeling of dendrites; Rachel Wong, neural circuit formation in the retina; Takao Hensch and Kenichi Ohki, neural circuit development in the cerebral cortex; Haruo Kasai, reinforcement learning for multimodal association; and Kuniyoshi Sakai, cerebral mechanisms of human language information processing.
- **Technology Development Unit**: Yasushi Okada, Haruo Kasai, Arthur Konnerth, and Shoji Takeuchi develop the most advanced neural circuit analysis technologies for probing neural circuit development in cooperation with the Development Study Core Unit. Okada is responsible for establishing and improving imaging technologies including high spatio-temporal resolution microscopy and probes; Kasai for single synapse manipulation technology and enabling measurement of synapse fluctuations; Konnerth and Takeuchi for the simultaneous measurement of the activity of a number of living neurons in the brain of animals.
- **Neurodevelopmental Disorder Pathology Unit**: Kiyoto Kasai aims to elucidate the pathology of ASD and schizophrenia in living humans by structural and functional imaging analyses using MRI. Takao Hensch pursues potential circuit-based treatments for cognitive disorders using model animals of ASD and schizophrenia development and critical period timing manipulation in the mature brain.
- **Mathematical Information Systems Unit**: Hiroki Ueda investigates the regulation and principles hidden beneath complicated biological phenomena using mathematical analysis, and also attempts the comprehensive description and analysis of neural circuits in part or whole brain, using his original brain clarification technique; Kazuyuki Aihara and Masashi Sugiyama seek to create next-generation AI technology based on the regulation of neural circuit development etc. in the actual brain. In addition, Aihara aims at understanding brain pathology by modeling psychiatric disorders according to the regulation of neural circuit development etc.

We expect that interdisciplinary cooperation and the resulting synergy of research units will be effective 1) in revealing principles of neural circuit development and learning rules which enable flexible ways of thinking, a core characteristic of HI, 2) in promoting understanding of dysfunctional conditions due to disturbance of neural circuits, and 3) in paving the way to innovative next-generation AI systems based on these principles of neural circuits in the brain.

In order to promote collaborative research amongst research units, we will set up advanced equipment rooms and core laboratories, and will facilitate fee-for-service usage of large-scale advanced equipment by skilled operators and analysis staff. In addition, we will secure collaboration space adjacent to these rooms. In order to coordinate close cooperation between these research units and overseas satellites, we will establish an administration office based on the know-how of an existing WPI institute, Kavli IPMU, and support center management.

Several PIs have laboratories outside the Hongo Campus. Each of these PIs will host their own research labs within the IRCN, which will include academic staff and researchers based at UTokyo. This will enable the research in these groups to progress smoothly even when the PI is not in Tokyo. Guidance of staff will be provided by these PIs on their regular visits to the IRCN and through day-to-day online communication with the help of data-sharing tools and web-conferencing software. In addition, the PIs will actively catalyze collaborations with other groups within the IRCN, which will contribute to the success of the center. As the IRCN becomes fully established, we expect that research carried out by each PI will have a greater impact on the center as a whole, and that this will automatically result in increased effort ratios.

Plan for achieving the center's final staffing goal

We will define the startup period from FY 2017 to FY 2019 to establish management organization and research units, filling laboratories with researchers. Immediately after award decision in October, we would follow university procedures to set up IRCN under the UTokyo Institutes for Advanced Study

(UTIAS). We will quickly establish an administrative office with reference to the existing WPI institute, Kavli IPMU, so as to be immediately responsive to the Director's decisions. We will secure space planned for installation within the university and proceed with procedures to build it out. We will start hiring young researchers and postdoctoral fellows as the core of each research unit and attain approximate desired staffing within 2019. Shared use facilities, the Life Science Research Equipment Support Room and Imaging Center, equipped with advanced imaging equipment will be set up. Negotiations with foreign organizations scheduled to become satellites will begin in FY 2017 and formally established by written agreement during FY 2018.

Stable operation is slated for FY2020 and beyond. We will continue new recruitment of researchers, and organize international conferences to increase visibility of IRCN. Joint research and personnel exchanges with satellites will be actively run. We will also continue to improve the equipment in the Life Science Research Equipment Support Room and Imaging Center. Finally, to improve the environment for constant interaction, discovery and natural idea sharing, we will consider the location and relocation plan for constructing a new research building where all members can come together.

Role of satellites: In addition to units at UTokyo, IRCN has satellite units in Harvard University and the Max-Planck Florida Institute for Neuroscience. The Harvard satellite unit will include resources of Boston Children's Hospital, and aims to understand pathologies of psychiatric disorders and to develop treatments, mainly collaborating with the Neurodevelopmental Disorder Pathology Unit. In addition to Takao Hensch, Michela Fagiolini heads the mouse Neurodevelopmental Behavioral Core facility where she performs preclinical analysis of Mecp2-deficient models of Rett syndrome, and Charles Nelson performs behavior analysis, electrophysiology, and functional imaging of ASD in children. The second satellite unit at the Max Planck Florida Institute for Neuroscience aims to understand basic principles of neural circuit development, mainly collaborating with the Development Study Core Unit. Ryohei Yasuda studies the mechanism of synapse plasticity and David Fitzpatrick studies neural circuit development in the cortex. The satellites will hold mutual joint retreats every year to promote exchange among researchers.

Linkage with other institutions without establishing satellite functions: Sugiyama in the Mathematical Information Systems Unit is a professor of the Graduate School of Frontier Science and also the director of RIKEN Center for Advanced Intelligence Project (AIP Center). This facilitates collaboration with both the UTokyo AI Center and RIKEN AIP Center. We also seek strategic collaboration with RIKEN Brain Science Institute (BSI) and RIKEN Quantitative Biology Center (QBiC) in future. In addition, we seek possible cooperation with the "Tsukuba-Kashiwa-Hongo Innovation Corridor" that UTokyo is now developing as a site on the Kashiwa campus for collaborative research on multiple topics (innovative materials, AI, analytical and measurement technologies) with a variety of counterparts (National Research and Development Agencies, including the National Institute of Advanced Industrial Science and Technology (AIST) and the National Institute for Materials Science (NIMS), National Cancer

Center Japan, and businesses including ventures originated in the University).

a) Principal investigators (full professors, associate professors or other researchers of comparable standing)

* Paste on table a) of Appendix 6

(persons)

	At beginning of project	At end of FY 2017	Final goal (Date: March, 2022)
Researches from within the host institution	12	12	11
Foreign researchers invited from abroad	3	3	4
Researchers invited from other Japanese institutions	0	0	2
Total principal investigators	15	15	17

b) Total members

* Paste on table b) of Appendix 6

	At beginning of project		At end of FY2017		Final goal (Date: March, 2022)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	20		35		70	
Overseas researchers	3	15	8	22.9	19	27.1
Female researchers	2	10	6	17.1	17	24.3
Principal investigators	15		15		17	
Overseas PIs	3	20.0	3	20.0	4	23.5
Female PIs	1	6.7	1	6.7	2	11.8
Other researchers	5		20		53	
Overseas researchers	0	0	5	25	15	28.3
Female researchers	1	20	5	25	15	28.3
Research support staffs	5		10		20	
Administrative staffs	3		5		10	
Total number of people who form the "core" of the research center	28		50		100	

2)-4 Securing research funding

Past record

* Give the total amount of research funding (e.g., competitive funding) secured by the principal investigators who will join the center project. Itemize by fiscal year (FY2012-2016).

FY	2012	2013	2014	2015	2016	Total
Secured funding (JPY)	1,910,515,785	2,530,767,010	1,944,229,204	2,069,391,913	3,348,099,264	11,803,003,176

Prospects after establishment of the center

* Based on the past record, describe the concrete prospects for securing resources that match or exceed the WPI project grant.
* Calculate the total amount of research funding (e.g. competitive funding) based on the percentage of time that the researchers will devote to research activities at the center vis-à-vis the total time they spend on research activities ("Effort" in Appendix 5). Be sure that the prospects (FY2017-2021) are realistically based on the past record.

All the prospective Japanese PIs hold competitive grants from Grants-in-Aid for Scientific Research, AMED, or JST. Examples include Specially Promoted Research (Kano), Scientific Research on innovative Areas (Emoto, K. Kasai), Scientific Research (S) (Gotoh, H. Kasai, Ueda, Ohki, Aihara, Takeuchi), Brain Mapping by Integrated Neurotechnologies for Disease Studies (Ohki, Ueda, K. Kasai), and Strategic Basic Research Project–CREST (H. Kasai), serving as a part of the initial capital of IRCN. The total amount of competitive research funding based on the percentage of time that the researchers will devote to research activities at the center is 1.4 to 2.6 billion yen (mean 1.8 billion, median 1.6 billion) per year.

After IRCN is established, the PIs will actively apply for grants, such as Grants-in-Aid for Scientific Research on Innovative Areas, JST-CREST, the Human Frontier Science Program, both as individuals and as IRCN-based groups. As calculated above, we expect to obtain at least 1.4 billion yen per year, which exceeds the WPI project grant. We expect full support from the Graduate School of Medicine and other faculties for the laboratory space, animal facility, and common space for equipment. In the long run, all IRCN members will have their laboratories in the same building to accelerate interaction within IRCN.

3) Interdisciplinary Research

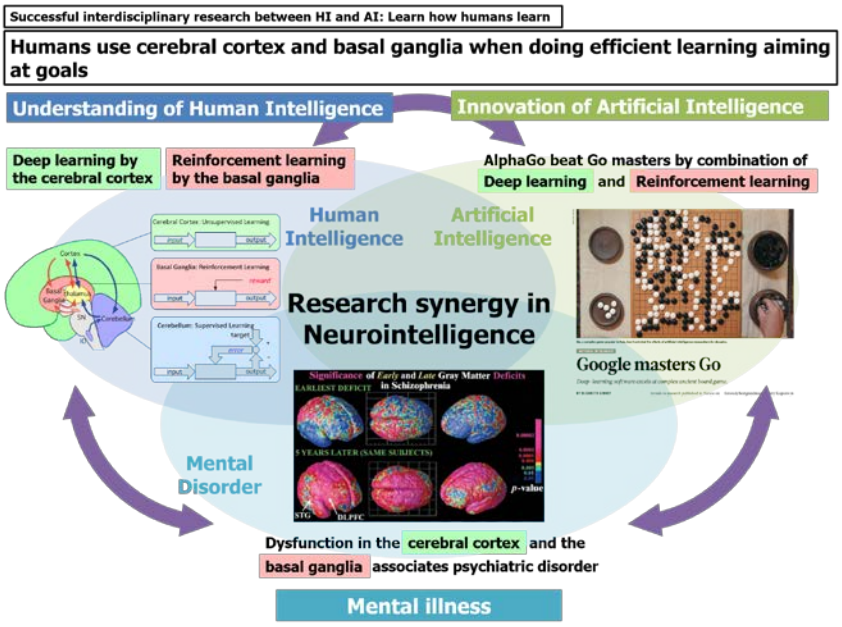
* Describe why interdisciplinary research is necessary and important in the target field(s) and what new field(s) can be expected to be created by way of this project. Describe your concrete strategy for advancing such interdisciplinary research.

The need and significance of interdisciplinary research

Interdisciplinary cooperation between life science, medicine, linguistics, mathematics, and information science is a prerequisite for understanding highly complex brain functions and elucidating the pathology of brain diseases. Neurointelligence, a new discipline that IRCN proposes, is an integration of research on neural circuit development, technology development for probing neural circuits, studying psychiatric disorders, and AI research. The synergy of these fields will elucidate principles of flexible neural circuit development to realize HI, promote development of next-generation AI, and contribute proposed new therapies of psychiatric disorders based on neural circuit dysfunction.

To our knowledge, there are few interdisciplinary research centers designed to promote such collaboration between world-renowned basic neuroscientists, physicians, and AI researchers with a long-term goal of better understanding HI and creating new AI principles. Thus, IRCN will become a highly competitive research center with unique scientific mission and profound social impact.

Studies on the learning process, the basis for HI, is an example of successful inter- disciplinary research, which revealed that effective human goal-directed learning is based on deep learning by the cortex and reinforcement learning by the basal ganglia. The “Alpha Go” system that defeated professional Go players, utilizes these two learning processes. The core dysfunction underlying psychiatric disorders is considered to exist in the cortex and basal ganglia. We expect that explorations by IRCN of unknown information processing mechanisms, in addition to the two mentioned above (i.e. cortex–deep learning and basal ganglia–reinforcement learning), will advance AI studies to the next generation.



Strategy for conducting interdisciplinary research

The world-class PIs in IRCN will organize four research units: Development Study Core Unit, Technology Development Unit, Neurodevelopmental Disorder Pathology Unit, and Mathematical Information Systems Unit. The units with distinct disciplines are expected to maintain close mutual relationships, as specified below.

(i) Technology Development Unit develops state-of-the-art advanced techniques of neural circuit analysis and measurement, including fluorescent and (bio) luminescent probes, manipulation of single synapse, and simultaneous measurement of the activity of a number of neurons, to support neural circuit studies in the Development Study Core Unit.

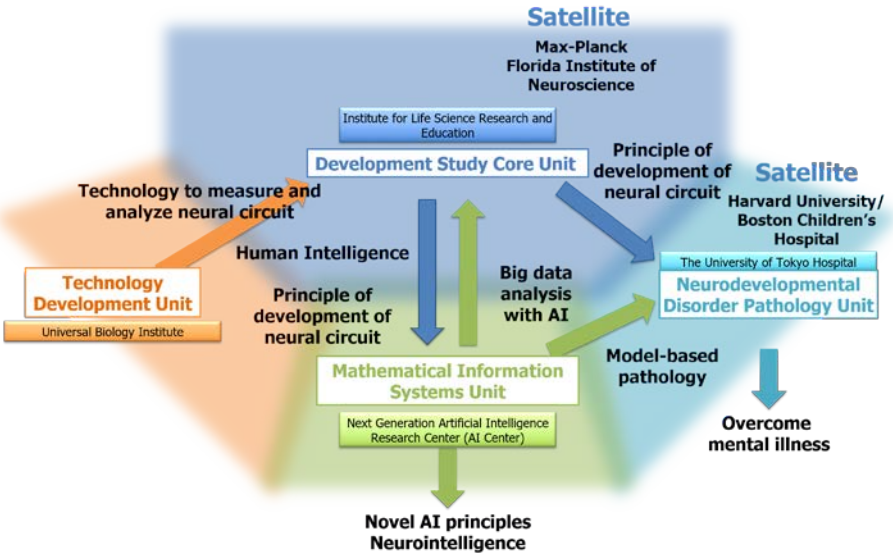
(ii) Development Study Core Unit pursues the development of neural circuits and study of learning rules in cooperation with the Technology Development Unit, which serves as a basis for exploration of novel AI models in cooperation with the Mathematical Information Systems Unit. Furthermore, the unit cooperates with the Neurodevelopmental Disorder Pathology Unit to elucidate psychiatric disorder pathologies.

(iii) Mathematical Information Systems Unit creates next-generation AI based on the regulation of neural circuit development etc. in the brain in cooperation with the Development Study Core Unit, and systematically analyzes a large amount of data obtained by the Core Units, utilizing methods based on mathematical science and AI. Moreover, this unit works together with the Neurodevelopmental Disorder Pathology Unit to better understand psychiatric disorders by models incorporating new rules of neural

circuit development etc.

(iv) Neurodevelopmental Disorder Pathology Unit will clarify the etiology of developmental disorders and ASD by analyzing the neural circuit of animal disease models in cooperation with the Development Study Core Unit. This unit also collaborates with the Mathematical Information Systems Unit and aims at understanding psychiatric disorders by modeling based on rules of neural circuit development etc. Furthermore, it will perform quantitative analysis of images and physiological data from psychiatric patients aiming at establishing objective criteria for diagnosis.

Cross-disciplinary communication among researchers will be encouraged by frequent joint meetings designed for exchange of ideas and information on research subjects, techniques and resources. This will be further supplemented by yearly retreats and international symposia.



4) International Research Environment

4)-1 System for advancing international research

* Describe your concrete plan for building an international research center including the makeup of its foreign researchers, establishment of oversea satellites, and provision of researcher exchanges. Please include a timetable for this plan.

* Describe concretely your strategy for staffing foreign researchers (e.g., postdoc positions) through open international solicitations. Describe the procedures you will use to do so.

Successful establishment of an international research center will depend on many factors, but the following three points are critical. 1. Strong leadership: Dr. Takao Hensch, prospective Director of IRCN, has clear perspectives about the WPI goal and its impact on biology and medicine. His leadership will attract talented young researchers irrespective of country 2. Outstanding members: We select the best researchers from a wide range of scientific disciplines both from UTokyo and outside institutions to assemble IRCN. Top-level researchers further enhance international visibility of IRCN. 3. Rich academic environment: The center will fully utilize the rich educational and administrative resources of UTokyo. Active flow of researchers through IRCN and satellite institutes will accelerate the international collaborative activity. Hensch has many years of experience with student exchange into Japan.

Plan for building an international research center: Recognition of IRCN as a research hub across multiple countries will be achieved by a multi-level enterprise by researchers, students and administrative staff with the following strategies:

- Scientific Board (SB) and Scientific Advisory Committee (SAC) selected from among SB members

put highest priority on recruitment of young researchers with high international activity and potential.

- IRCN members are encouraged to do collaborative research overseas each year. This rule has been in operation in Kavli IPMU and is effective in networking with foreign researchers and research institutes, as well as providing young researchers with opportunities for career advancement.
- SB and SAC provide scientific programs that facilitate active interaction between the core IRCN and satellite units, located at Harvard University and the Max-Planck Florida Institute of Neuroscience.
- In order to facilitate interactions between foreign and Japanese members, research conferences and meetings are conducted in English in principle.
- IRCN will interact with multiple graduate student programs in UTokyo and Harvard University and serve as a platform of facilitating global leadership of young scientists.
- IRCN sponsors a large-scale international symposium every year. In addition, frequent meetings and seminars by top foreign researchers are planned to attract scientists outside of IRCN.

Strategy for staffing foreign researchers: The Director, supported by SAC and SB, will put highest effort on recruitment of young foreign researchers with high motivation and ability. After recruitment, the Director will help the recruited scientists realize outstanding achievement during their term at IRCN and become a strong candidate for faculty or post-doctoral positions at other globally leading research institutions.

- Attractive job conditions are offered for foreign researchers with an annual salary system based on their competence and performance.
- Job advertisement is made by wide announcement in media including first-rate scientific journals. Applications will be received online. The hiring cycle will be made to fit overseas standards.
- Scientists with special knowledge and technology are invited to stay for several months to perform joint research and seminars, which may provide opportunities for their future relocation to IRCN.
- The positions of Assistant Professors will be intended as tenure-track. For young faculty members, we minimize duties to maximize their research-related activities. Assistant Professors are hired initially for five years, and reviewed in the fifth year with their research outcomes. The review will determine whether the appointment (1) ends at the end of the fifth year, (2) is extended for three more years, or (3) is promoted to Associate Professorship with tenure.

４) -2 Establishment of international research environment

* Describe your concrete strategy for establishing an international research environment and administration system, and the support system to be provided for researchers from overseas.
* Describe your strategy, procedure and timing for periodically holding international research conferences or symposiums (at least once a year).
* Describe your measures to ensure that top-caliber researchers from around the world can work comfortably in carrying out their research within a competitive international environment.

Strategy for establishing an international research environment and administration system, and the support system for researchers from overseas: We will support foreign scientists to adapt to the Japanese grant system, while lowering hurdles associated with daily life.

- Startup funds are provided for starting the work as soon as possible after arrival.
- Information for grant writing and management of accepted grants will be provided to encourage foreign scientists to apply for grants from the government of Japan.

- A multilingual secretariat provides foreign researchers with various services according to the model of Kavli IPMU. Examples include a website for information on daily life, accompanying researchers to city offices, banks, real estate agents, etc., orientation services, Japanese language classes, online safety education, and a 24-hour emergency medical service, including that for pregnant women.
- Priority acceptance to the residences around the campus may be considered.

International research conferences: IRCN will sponsor a large-scale international symposium every year. Director Hensch is well known in the international neuroscience community and his experience, visibility and esteem will entice participation of top foreign scientists at our international conferences. The kickoff symposium in the first year will be of utmost importance to set the framework of IRCN activity. Our satellites will host international symposia abroad in rotation. These meetings promote exchange of researchers among the core IRCN, its satellites and other institutes.

Measures to ensure that top-caliber researchers from around the world can work comfortably in carrying out their research: IRCN's administrative staff help researchers to prepare application forms for research grants. The preexisting system of university research administrators (URAs) in UTokyo supports human resources necessary for IRCN administration. IRCN provides training and full support for successful writing of grant proposals. This encourages researchers to secure the research funding without barriers. Administrative staff also supports grant management and report preparation. Support for insuring and locating housing, daycare, and spousal employment will be prepared.

5) Center Management

5) -1 Operational management

* Describe the role of the center director.
* Describe the role of the administrative director.
* Concretely describe your concept for establishing an administrative organization.
* Concretely describe the center's decision-making system.
* Concretely describe how authority is allocated between the center director and the host institution.
* Concretely describe how the center will adopt a rigorous system for evaluating research and will introduce a system for merit-based compensation (e.g. annual salary scheme). Please describe your procedures and timing for operationalizing these systems.

IRCN will be the third entity operating as the UTokyo Institute for Advanced Study (UTIAS). UTIAS is an independent research organization, acting as an autonomous unit in the University and regarded as a test case in the reform of Japanese universities. Two are already established at UTokyo, the Kavli IPMU and Integrated Research System for Sustainability Science (IR3S), providing a framework for IRCN to have discretion in independence of recruiting researchers and budgetary requests.

Role of the center director: The center director is given all authority regarding organization and management of the center. The center director has ultimate responsibility for all decisions in the IRCN. The major roles are as follows:

- Setting missions and goals of IRCN: The Director sets both long- and short-term mission and goals of IRCN and proposes plans and timetables that effectively lead to their realization.
- Effective organization of researchers in IRCN: The Director provides ideas, designs and plans that maximize the interactions and effective collaboration of researchers in IRCN.
- Administrative decisions: To reduce the burden of the Director, IRCN will recruit a strong

Administrative Director, who has broad knowledge in both neuroscience and research administration.

- Recruiting scientists: The Director actively acts on the recruitment of promising young researchers and dissemination of the Center's research outcomes to the scientific community and society.

Professor Takao Hensch, nominated as first director of IRCN, started his career as a researcher at UTokyo after graduating from Harvard. He has experience running a laboratory and CREST Group in Japan and is well acquainted with the management of institutes like RIKEN. His excellent achievements, broad perspectives and outstanding communication skills will attract top-quality researchers from around the world and organize them as effective research teams. He is the best candidate for director. He will spend time at UTokyo on a regular basis to oversee management of the entire center and lead the Harvard Medical School (Boston Children's Hospital) satellite. The president's office will work closely with Professor Hensch to ensure his full function as the IRCN Director. In particular, the office will be responsible for increasing his physical presence at UTokyo to an adequate level, a minimum of 50% of his total working hours, as soon as practicable. The office will immediately initiate negotiations with Boston Children's Hospital at Harvard Medical School to reach a memorandum of understanding (MOU) with UTokyo.

Role of the administrative director (AD): The AD cooperates with the Director and provides administrative services necessary for the execution of IRCN activities. The AD executes plans designed by the Director and orders other administrative staff for regular administrative duties and special events. The AD coordinates activities of IRCN and other organizations both inside and outside of UTokyo, with emphasis on linking educational programs for graduate students. The AD and two deputy Directors help the Director communicate with other IRCN members while the Director is occupied with outside tasks, such as visits to satellites and international outreach activities.

We nominate Tetsushi Kagawa as AD of IRCN. Dr. Kagawa has been engaged in top-level neuroscience and fully understands the mission of the center. He has profound knowledge about research in the United States. His personal networks will help recruit talented foreign postdoctoral fellows. His experience in the United States will also help communication with foreign researchers and administrative staff. Currently he is engaged in administrative work at AMED, a Japanese funding agency for medical research, and responsible for management of large-scale research funds. He is well acquainted with the system of research funding in Japan and his support will be valuable for foreign researchers to apply for domestic research funds.

Concept for establishing an administrative organization: The secretariat of IRCN is modeled after that of the Kavli IPMU. The staff is strategically recruited utilizing systems such as post reallocation at the discretion of the President, or employment with annual salary and unlimited term. Four sections of the administrative division are shown in the table below. Staff with special backgrounds, such as bilinguals and specialists of institutional research, will be placed in related sections.

Center's decision-making system: Managerial authority is concentrated on the Director and AD for flexible decision making and, with support by the competent secretariat, for quick implementation of the decision. The Director receives advice from the organizations shown in the table. The Executive Board (EB), consisting of the Administrative Director (AD) and two deputy Directors, strongly supports the Director for smooth operation and swift decision making. The Steering Committee (SC) serves as personnel committee for faculty. The SB is responsible for approval of the Director's decisions and their execution.

Decision Making System	
Components	Personnell and Members
Director	Dr. Takao Hensch
Deputy Director	Drs. Masanobu Kano and Kazuo Emoto
Executive Board (EB)	two Deputy Directors and AD
Steering Committee (SC)	members of the EB and a couple of Pis
Scientific Board (SB)	all Pis
Scientific Advisory Committee (SAC)	two Deputy Directors and several Pis
External Advisory Committee (EAC)	seven internationally recognized scientists
Office for Research Strategies (ORS)	two Deputy Directors and URAs

Administrative organization	
Components	Personnell and main roles
Administrative division	general affairs section: handling personnel and public relation
	accounting section: handling financing, purchasing, and managing external funds
	international relations section: handling international conferences and workshops, support for staff and visitors from abroad
	evaluation and analysis section: providing data necessary for management decisions, collects survey indicators and prepares various reports

The Scientific Advisory Committee (SAC) advises the Director on hiring new faculty and setting research strategies. The External Advisory Committee (EAC) provides advice to the University President on IRCN activity. The Office for Research Strategies (ORS) analyzes research activities and future direction and reports to the Director. The PIs have a large autonomy in the research they conduct. Their research is funded through competitive grants, but they can propose hiring of postdocs and senior scientists to the Director in order to carry out their research. The Director's approval on the proposed appointments will reflect the scientific vision and priorities set by the Director.

Authority allocation between the center director and the host institution: The president of UTokyo, the head of the host institution, will appoint the Director and approve the principal investigators. Other personnel and the operation of IRCN, including recruitment of researchers, management, and financial planning is done by the Director.

Research evaluation system linked with a system for merit-based compensation: By placing IRCN within UTokyo Institutes of Advanced Study (UTIAS), its administration is less restricted by the pre-existing framework. IRCN is given a status of "special district" within the University. In this scheme, it is possible to implement top-down management, flexible hiring system and merit-based salary system. Kavli IPMU, the first institute of UTIAS, has been successful in recruiting talented early-career scientists by implementing an accurate and transparent evaluation system linked to annual salary system. Stimulated by the success of these new approaches taken by the Kavli IPMU, UTokyo has intensified the system reforms including merit-based salary scale, cross appointment, tenured position with non-traditional external funding, nenpo system (no traditional bonus / retirement benefit) with higher pays and mobility, and flexible management of positions.

5) -2 Research environment

* Concretely describe how equipment and facilities, including laboratory space, will be provided in a manner appropriate for a top world-level research center. Include your procedure and timing.
* Concretely describe how the center will provide an environment in which researchers can work comfortably on their research by being exempted from duties other than research and related educational activities, and how they will be provided adequate staff support to handle paperwork and other administrative functions. Include your procedure and timing.
* Concretely describe how the center will arrange for its researchers to participate in the education of graduate students.

Equipment and facilities: IRCN will extensively rearrange pre-existing research spaces, equipment, and related resources. We initiate this process by securing space for IRCN in the Faculty of Medicine Building 1. IRCN will build common research space with advanced instruments and a core laboratory providing cutting-edge instruments, along with fee-for-services provided by skilled operators and data analysts. These common research spaces will facilitate collaboration of different units. IRCN will further seek the possibility of constructing a new research building that provides research housing for all IRCN members. Access to the building should be convenient for all IRCN members while the location should follow the University's campus plan.

Environment in which researchers can work comfortably on their research

(1) General support for researchers

- Reduction of administrative duties: Decision making in IRCN is designed to be simple and effective. All important decisions are made by the Director with SB approval and executed by the AD / EB.
- Support for institutional research: Administrative staff collects and analyzes data related to the institution and affiliated researchers and provides useful information to IRCN members.
- Support for specific events: We arrange the staff to support meetings and conferences, including guest invitations, logistics, arrangement of trips and accommodations, advertisements, etc.

(2) Specific support for foreign scientists

IRCN will support international researchers to ensure a smooth start to their research in Japan. Examples are support for Certificate of Eligibility and Visa, orientation about daily life in Japan, support for residence registration, housing, bank account, childcare, healthcare and spousal employment. In addition, the University will make special efforts to provide housing for Center researchers.

Participation of researchers in the education of graduate students: Education of graduate students is an indispensable aspect of the Center. Starting with director Hensch at Harvard, our faculty members are all part of pre-existing graduate schools. UTokyo reinforces education at the graduate level to produce qualified professionals through initiatives including the establishment of World-leading Innovative Graduate Study (WINGS), a novel framework of the graduate course of international excellence. Within this framework, we will extend the education of graduate students under IRCN's outstanding international research environment both at UTokyo and abroad. Through the Reischauer Institute at Harvard, bidirectional student exchange with the satellite will be encouraged and supported.

5) -3 Establishing the center in sync with organizational restructuring

* Concretely describe the host institution's organizational reform that will be synchronized with the establishment of the center.
* Describe measures that will be taken by the host institution to sustain the center's operation after the WPI funding ends. Also describe how the host institution will promote the centers autonomy after WPI funding ends and how it will over the mid-to-long term restructure its existing organization in ways that give the center a permanent place within its organization.

Reform of host institution synchronized with the establishment of the center: IRCN, along with Kavli IPMU, will continue to act as a core originator in the University's reform. Establishment of IRCN will synchronize with the following reform of the host institution.

- New employment systems for faculty level staff are in progress, including the Excellent Researchers System started in FY2016, to stabilize posts for young faculty members. In addition, support systems for female researchers will also help with recruitment into IRCN.
- Priority acceptance to residences (under construction) will help recruit excellent researchers.
- Establishment of certification and employment system for URAs will help IRCN management.
- New administration staff system of UTokyo will promote service-oriented attitude at IRCN.
- Initiatives including the establishment of WINGS will enable education of graduate students under IRCN's outstanding international research environment.

According to "University of Tokyo: Vision 2020", the University is trying to attain financial independence with efficient management and resource expansion by utilization of land assets, promoting industry-university cooperation, etc. Secured budgets are to be used for the promotion of excellent research and are necessary for strategic investment in IRCN.

Sustainable operation of the center after the WPI funding ends: The ORS gathers information from domestic and foreign funding agencies and foundations to boost IRCN activities. Clinical neuro-science in IRCN will promote collaboration with pharmaceutical companies. Continuous support of the University is also critical to maintain and expand IRCN. In "The University of Tokyo: Vision 2020" published in October 2015, President Gonokami sets "expansion and establishment of internationally renowned bases for research" as one of the important action plans. This is expected to materialize one of the basic principles, "synergy between excellence and diversity". The third mid-term objectives/plans of the University state that the University will form "research centers that can contribute in solving issues in both academic and social domains, with pioneering, prompt, agile, and practical approaches". This plan also states that "research centers objectively recognized by their excellence, such as UTIAS, are prioritized for support from the University." Hence, the President of UTokyo strongly supports the center and regards IRCN as one of the most important units in the University and will provide full-fledged support. Organizational structure of UTIAS enables IRCN to give a status of "special district" within the University. Like the other two UTIAS, IRCN has discretion in recruiting researchers and budgetary requests to MEXT. IRCN thus acts as an autonomous unit in the University and pioneers the University's organization reform. In addition to the University's special consideration of operation costs, human resources and space for IRCN, the University's reform including personnel, employment and education as described above will assure the sustainability of IRCN.