February 2022

Research Center Project

Center name:	International Research Center for Neurointelligence
Host institution:	The University of Tokyo
Head of host institution:	Teruo Fujii, President
Center director:	Takao Kurt Hensch, Project Professor, International Research Center for Neurointelligence
Administrative director:	Nobukazu Toge, Project Professor, International Research Center for Neurointelligence

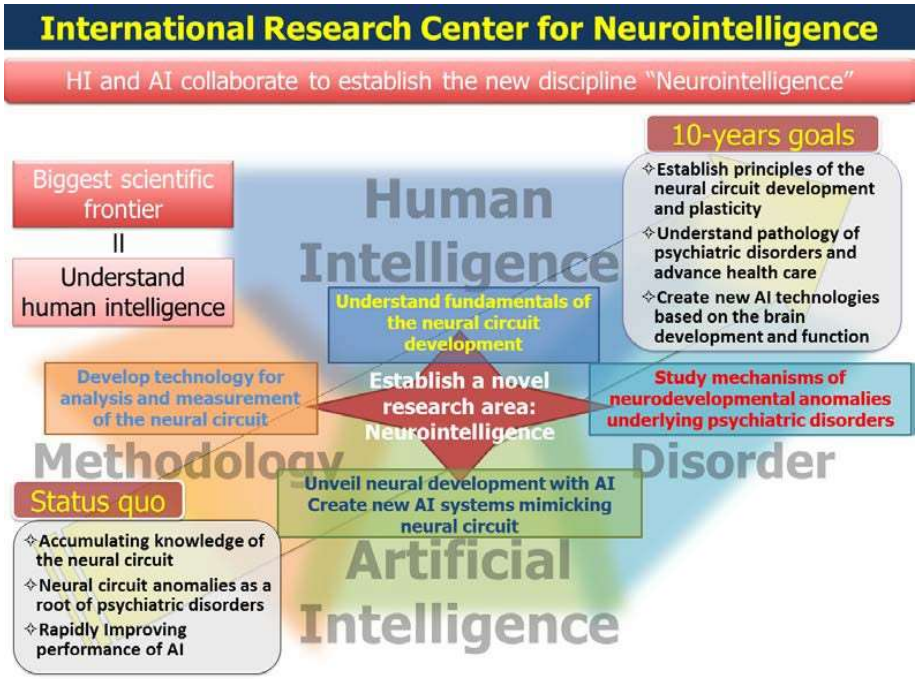
1) Overall Image of Your Center

* 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 giving rise to 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 directed 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 novel 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, 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/psychology.

The backdrop for 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 generalizable 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, consistent with neural circuit dysfunction as their etiological origin. Accordingly, potential elucidation of the biological bases for neuropsychiatric disorderstoward objective diagnosis and treatment has become increasingly realistic. Third, expectations for and concerns about next-generation AI have been exacerbated as several specific functions are already demonstrably better performed by AI.

In this context, IRCN was conceived to elucidate mechanisms of neural circuit development, to clarify the pathology of neuropsychiatric disorders in human patients as well as animal models, and to pioneer new AI systems utilizing the same principles as seen in the 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 at UTokyo Hospital, and world-class researchers in the fields of mathematics and information science. Combining these nine selected researchers with seven newly recruited PIs, led by Takao Hensch, has established a truly global faculty that is highly diverse both in gender and nationality. Furthermore, IRCN hosts a satellite unit at Boston Children's Hospital (Harvard Medical School) and partners with over 20 international institutions, aiming to be one of the world's highest level research organizations. Together, our mission is to create a new discipline, "Neurointelligence" which will help to overcome mental disorders and to promote next- generation AI systems based on principles governing the development and function of integrated brain circuits that give rise to HI.



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)

Target research fields

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 nonlinear dynamics of neural circuits in the brain. To achieve such a complex function, an adequately balanced number of excitatory / inhibitory neurons need 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 during critical periods of postnatal development, producing mature functional neural circuits. In turn, AI has recently achieved sensational success, mostly in the field of deep learning based loosely on the multi-layered neural networks observed in unimodal visual cortex. Yet, AI is still far from achieving the multi-modal integration fundamental to HI. Incorporating neuronal dynamics as well as principles of sequential neuronal circuit development and learning rules are thus expected to contribute toward innovative next-generation AI.

Meanwhile, Japan in particular is rapidly becoming a super-aging society with declining birth rates ahead of other countries. The increasing social burden of mental disorders, like autism and schizophrenia, has become a serious world-wide problem. Pathological study and treatments for such cognitive disorders are thus urgently needed. Improper or excessive circuit connectivity in childhood and adolescence is generally believed to cause cognitive disorders whose underlying genes are often identified at synapses. Advances in medical imaging now permit the visualization of disturbances in psychiatric patients, offering unprecedented opportunities for IRCN as a bridge for translation from bench-to-bedside. By gathering neuroscientists, big data statisticians and psychiatrists, synergistic research into neural circuit development and dysfunction can inspire novel AI to help human activities and substitute for the rapidly shrinking workforce. 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) / MIT Quest for Intelligence & Picower Institute for learning & 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 all three areas of basic neuroscience, psychiatry and computational/information/AI science. Importantly, IRCN includes large clinical centers in Tokyo and Boston (i.e. UTokyo Hospital & 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, eventually establishing Neurointelligence as a new discipline integrating HI and AI.

2)-2 Research objectives

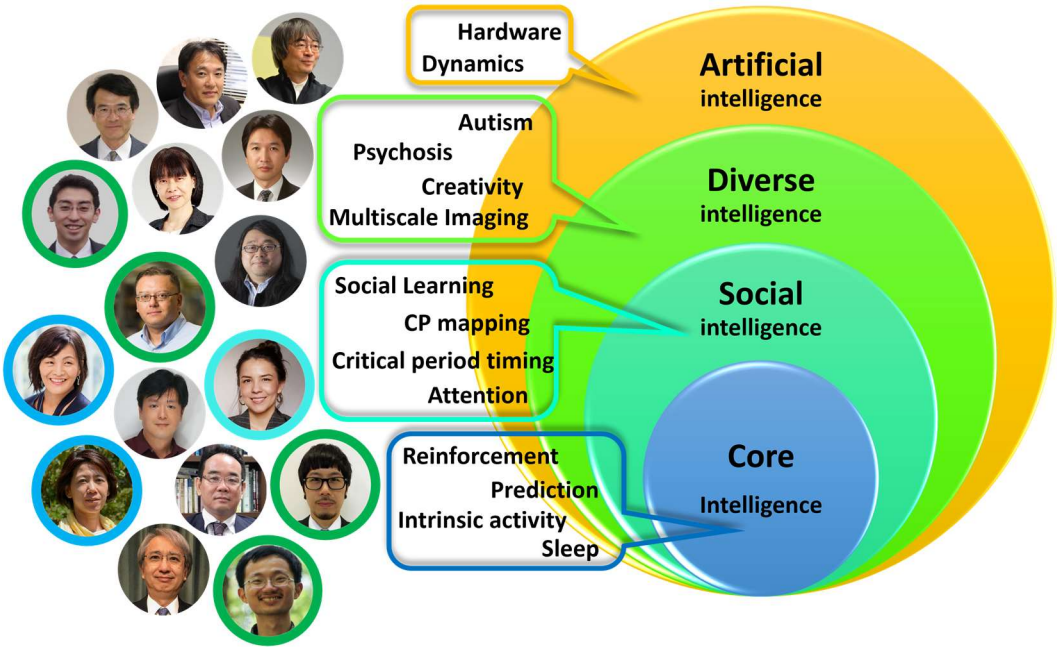
* Describe in a clear and easy-to-understand manner the research objectives that the project seeks to achieve by the end of its grant period (in 5 years). In describing these objectives, the following points should be articulated in an easily understandable manner: The kind of research area(s) you plan 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

How does human intelligence arise? To tackle this overarching question, IRCN seeks: 1) basic understanding of the principles of brain development that underpin the emergence of HI, which in turn will 2) illuminate the etiology and treatment of cognitive disorders, and 3) inspire next-generation AI. The Center has now attained a well-balanced membership across gender, nationality and discipline, including neurobiology, human/clinical neuroscience, and computation, in order to pursue a Team Science approach.

Research plan

We take the view that HI is composed of multiple intelligences – one that is informed by brain evolution. At its "core", each brain must be capable of learning (reinforcement), predicting and intrinsic activity/sleep. Collections of brains can then interact to yield a "social" intelligence that is shaped by attention, critical periods of shared experience and social learning. While aspects of core and social intelligence may be seen across species, further flexibility gives rise to "diverse" intelligence uniquely characteristic of humans, spanning a spectrum from creativity to mental disorders (autism, psychosis). Ultimately, AI inspired by these neurobiological insights will expand the capacity of HI, synergistically shaping our own future world. To answer "how does human intelligence arise", twelve IRCN Team Science projects now span all four intelligences and how they are interrelated:



The IRCN vision of HI arising from nested intelligences has attracted 9 talented PIs from UTokyo and 7 more from outside who have increased the diversity of disciplines, gender, nationality (indicated in colored circles). An additional ~47 international senior Affiliated Faculty (AF) and dozens of IRCN postdoctoral or Associate Research Fellows (ARF) have joined the IRCN mission.

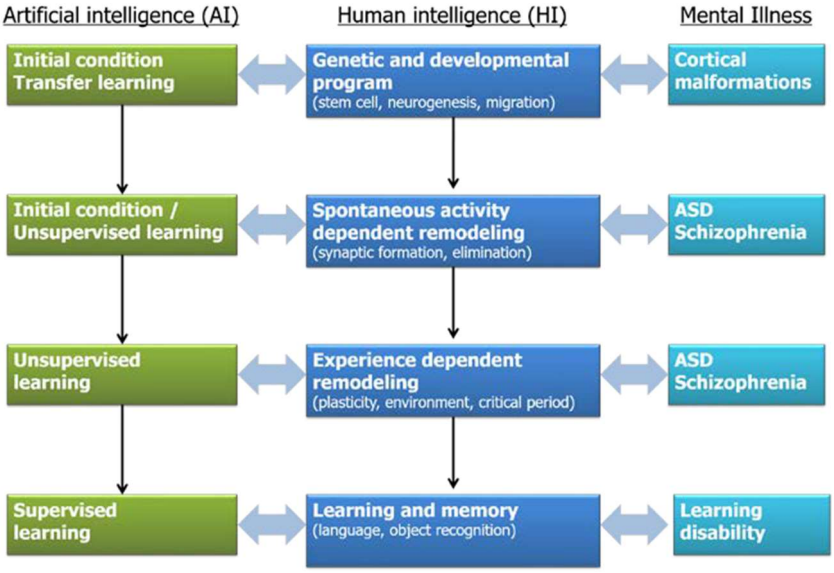
(1) Elucidating fundamental principles and learning rules of neural circuit development

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 priorto 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 will help to unravel neurodevelopmental disorders, as abnormalities in genetic programs of brain development lead to such disorders 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 neuralcircuit remodeling driven by 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, intrinsic activity-dependent remodeling of neural circuits includes the 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 "elimination". Masanobu Kano pursues the principles and cellular mechanisms of synapse elimination in the developing cerebellum. Kazuo Emoto studies molecular and cellular mechanisms underlying neurite shape remodeling of their axonal and dendritic arbors in response to various stimuli in sensory circuits of mice and fruit flies.



B) Next, 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. Hensch discovered that the maturation of inhibitory circuits in the visual cortex is a key determinant of critical period timing, which was extended to the birdsong system with Yoko Yazaki-Sugiyama.

A number of molecules involved in the maturation of these GABAergic circuits accelerate or delay the window of brain plasticity. Beyond this, Hensch identified factors which then actively suppress rewiring, such that their removal would reopen plasticity in adulthood. The concepts of plasticity "triggers" and "brakes" have been found to apply broadly across brain regions, including auditory, insular and prefrontal cortex, and species such as zebra finch with Dr Yoko Yazaki-Sugiyama. Such regions support higher order brain functions beyond vision, including phoneme discrimination, multisensory integration, preference behaviors or attention.

Kenichi Ohki elucidated 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. Sho Tsuji examines the language system in infants, which is fundamental to human communication, and a basis for intelligence and creativity. She pursues how language is acquired over development by 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, and how reinforcement learning is embedded in synapses for the association of sensorimotor and emotion signals. In the actual brain, reward is obtained from sensory input and converted into emotion signals encoded by monoamines (e.g. dopamine, noradrenaline, serotonin) which innervate the brain globally. He will study how monoamines encode distinctaspects 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.

Technology research labs collaborate closely with and assist the aforementioned experimental PIs. Yasushi Okada tackles intracellular imaging technologies, which include a microscope of high spatial andtemporal 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. Shoji Takeuchi has made pioneering and outstanding contributions to development of novel microfabrication technologies. In IRCN, he is developing biohybrid sensors for neuromodulators, a flexible electrode array which will allow persistent stable recordings over weeks and months from multiple neurons in vivo, and chemical sensing robots based on mammalian olfactory receptors.

(2) Revealing the pathophysiology of psychiatric disorders caused by impaired HI

Drs Kiyoto Kasai and Takao Hensch, respectively, aim to elucidate pathophysiology of cognitive disorders originating during two developmental critical periods, infancy and adolescence. Kiyoto 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 brainfunctional connectivity in ASD, and structural abnormalities of subcortical nuclei in schizophrenia. In IRCN, Kiyoto 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 neuro-feedback, which is expected to normalize abnormalcircuit activities by brain-machine interface (BMI) techniques.

Hensch and colleagues at the Boston Children's Hospital satellite pursue novel, circuit-based etiological insights in preclinical models of ASD and psychosis risk. They introduced innovative whole-brain imaging in awake mice using functional ultrasound. To test critical period insights from mouse to man (above), they are studying cognitive development and EEG in a large cohort of infants exposed to neonatal (GABA active) anesthesia or at-risk for autism. Finally, they seek to correct derailed developmental trajectories or reopen brain plasticity later in life to restore aberrant circuit function. Treating the common circuit abnormality rather than heterogeneous gene defects is innovative, based on principles of critical period plasticity and more readily translatable to clinical trials, such as at Boston Children's Hospital.

(3) Creating next-generation AI based on principles of neuronal circuit development

Newly identified principles of development and operation of neural circuits in the actual brain have already started to inspire next-generation AI systems:

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

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. Mingbo Cai hypothesizes that it is because neural circuits in the human brain are optimized through multiple developmental processes (summarized above), such as genetic programming, spontaneous activity-dependent remodeling, and experience-dependent remodeling with the help of emotion systems.

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. He 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, Zenas Chao 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 activities from a large number of neurons

Kazuyuki Aihara 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 forneural network development and function in the brain. By modifying neural network models with normal functions Aihara constructs mathematical models of mental illnesses with Kiyoto Kasai to understand their pathological dynamics, detect pre-disease states, 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 pathological dynamics, 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. Takamitsu Watanabe's energy landscape modeling has identified a reversible rigidity of resting brain states in autistic patients and mouse models. Finally, Yukie Nagai develops algorithms for

robots to simulate and interact with autistic subjects. Based on alterations in predictive coding, this work also helps to reduce the stigma around mental illness by allowing neurotypical subjects to experience the autistic worldview.

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 the principal investigators who are expected to join the center.

Center's research organization

IRCN created a 3-office structure to promote research "Synergy", "Community" and "Sustainability". Led by Deputy Directors (DD), these subgroups meet regularly to create a vibrant and inclusive research ecosystem. Synergy Office, in particular, has set aside seed funding to launch a "Team Science" approach to promote collaborative and inter-disciplinary research and selected twelve themes. These themes and collaborations are fundamentally proposed bottom-up, highlighting the strengths of our PIs. While they span very large conceptual and methodological spaces, the Teams nicely cover the four intelligences constituting HI (see above). Given our limited resources and personnel, Teams are evaluated semi-annually by the Synergy Office which established criteria to narrow down and focus the Center's scope on the most successful fusions.

The Community Office engages Center members in various collective opportunities, such as graduate teaching, outreach planning, and support for international scientists. The Sustainability Office actively seeks funding opportunities to bridge IRCN research disciplines, such as domestic and international grants, potential donors, or corporate sponsors. To brainstorm new areas of fusion research, a weekly Science Salon, featuring one PI, AF or international partner, and Annual Retreat offer regular interactions.

In order to promote collaborative research amongst research units, IRCN established five state-of-the-art core facilities: cellular imaging, fMRI, ES mouse/virus production, data science, and science writing (led by a former Cell Press editor). Core managers (Project Associate Professors) facilitate fee-for-service usage of large-scale advancedequipment by skilled operators and analysis staff. In addition, we secured collaboration space adjacent to these rooms for workshops, receptions and brainstorming. In order to coordinate close cooperation between Team Science and overseas partners, an administration office based on the know-how of our existing sister WPI institute, Kavli IPMU, will support center management.

Plan for achieving the center's final staffing goal

We defined the startup period from FY 2017 to FY 2019 to establish management organization and

PIs, filling laboratories with researchers. Immediately after award decision in October, we followed UTokyo procedures to set up IRCN under the UTokyo Institutes for Advanced Study (UTIAS). An administrative office modeled after the existing WPI institute, Kavli IPMU, was established so as to be immediately responsive to the Director's decisions. Space under one roof was secured for renovation and installation of new laboratories in the first medical building. The desired staffing of 16 PIs and lab members was exceeded by 2020. Core facilities were immediately set up.

Stable operation commenced in FY2020. We will continue new recruitment of Team postdocs, and organize international conferences to increase visibility of IRCN. Joint research and personnel exchanges with satellites and international partners will be actively supported by Director's Globalization Awards. We will also continue to improve the equipment in the core facility. Finally, to create an environment for daily interaction, discovery and more natural idea sharing, UTokyo will establish a location and relocation plan for a modern research building where all members unite.

Role of satellites: In addition to units at UTokyo, IRCN established one satellite at Boston Children's Hospital (Harvard Medical School). The clinical resources there focus on the pathologies of psychiatric disorders or early life stress exposures to develop interventions. 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; Charles Nelson performs behavioral analysis, electrophysiology, and functional imaging of children at-risk for ASD; Charles Berde, Laura Cornelissen and Laurel Gabard-Durnam examine the impact of neonatal anesthesia on cognitive development; Nancy Kopell and colleagues (BU) prepare computational models; and David Hunter and colleagues pilot clinical trials to reopen brain plasticity for recovery from amblyopia in adulthood.

Linkage with other institutions without establishing satellite functions: Numerous MOU partnerships were signed both globally and locally (see map). These include strategic sites that complement the work at IRCN: RIKEN Center for Advanced Intelligence Project (AIP Center), RIKEN Brain Science Institute (BSI) and RIKEN Quantitative Biology Center (QBiC); Swiss NCCR Synapsy bridging psychiatry and neuroscience; OIST; Italian Institute of Technology in the area of computation and robotics; A*Star Singapore and Hong Kong Univ Science & Technology for cohort studies; College de France and Ecole Normale Superieure for cross-cultural infant studies; the Stockholm trio and Max-Planck Institute Florida for cellular imaging. The satellites and partners promote bidirectional exchange of trainees with UTokyo through matching support for travel and staying expenses.

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

	At beginning of project	At end of FY 2021	Final goal (March 31, 2027)
Researchers from within the host institution	12	15	14
Foreign researchers invited from abroad	2	2	1
Researchers invited from other Japanese institutions	0	1	1
Total principal investigators	14	18	16

b) Total members

	At beginning of project		At end of FY 2021		Final goal (March 31, 2027)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	27		123		70	
Overseas researchers	3	11	45	37	23	33
Female researchers	4	15	20	16	14	20
Principal investigators	14		18		16	
Overseas PIs	2	14	4	22	3	19
Female PIs	1	7	4	22	4	25
Other researchers	13		105		54	

		Overseas researchers	1	8	41	39	20	37
		Female researchers	3	23	16	15	10	19
Research support staffs			0		38		20	
Administrative staffs			3		20		10	
Total number of people who form the "core" of the research center			30		181		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 (FY2017-2021).

FY	2017	2018	2019	2020	2021	Total
Secured funding (JPY)	0	12,700,000	59,434,000	257,939,655	353,661,995	683,735,650

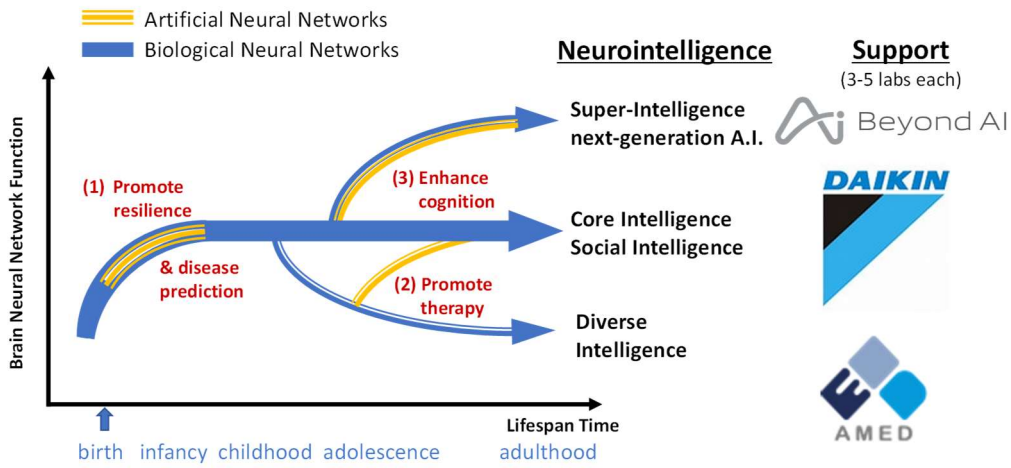
Prospects after establishment of the center

* 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. Be sure that the prospects (FY2022-2026) are realistically based on the past record.

All Japanese PIs hold competitive grants from Grants-in-Aid for Scientific Research, AMED, or JST. Examples include Transformative Research Areas (A) (Kano, K. Kasai, Y. Okada), Scientific Research on innovative Areas (Emoto, K. Kasai), Scientific Research (S) (Gotoh, H. Kasai, Ohki, Aihara, Takeuchi), BrainMapping by Integrated Neurotechnologies for Disease Studies (Ohki, K. Kasai), and Strategic Basic Research Project–CREST (H. Kasai, Y. Nagai), serving as a part of the initial capital of IRCN. The total amount of competitive research funding that is directly accounted by IRCN is approximately 350 million Yen in FY2021 and is in a growing trend. Note that PIs, who are also affiliated with other Faculty within UTokyo or elsewhere, are attaining similar amounts of additional research funds that are separately accounted there.

By taking a brain development perspective, their fusion research has further focused the IRCN roadmap and milestones on three major deliverables: **1) promote resilience & disease prediction** early in life, **2) promote therapeutic strategies to redirect or reopen plasticity** later in life, **3) enhance performance of HI in harmony with novel AI**. These goals have been rewarded with competitive funding in FY2020, including collaborations with UTokyo corporate sponsors like Softbank (BeyondAI) and Daikin, and leadership roles in JST, MEXT, and AMED grants (Gakujyutu Henkaku A, Moonshot), as indicated below.

Now established, our PIs will continue to actively apply for grants, such as Grants-in-Aid for Scientific Research on Innovative Area, JST-CREST, HFSP (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 participating departments for the laboratory space, animal facility,



and common space for equipment. All IRCN members have some share of their labs inside the same Medical building #1 to boost interactions within IRCN.

MOONSHOT RESEARCH & DEVELOPMENT PROGRAM

文部科学省 科学研究費補助金 学術変革領域研究(A)
脳の若返りによる生涯可塑性誘導ーiPlasticity
臨界期生物学

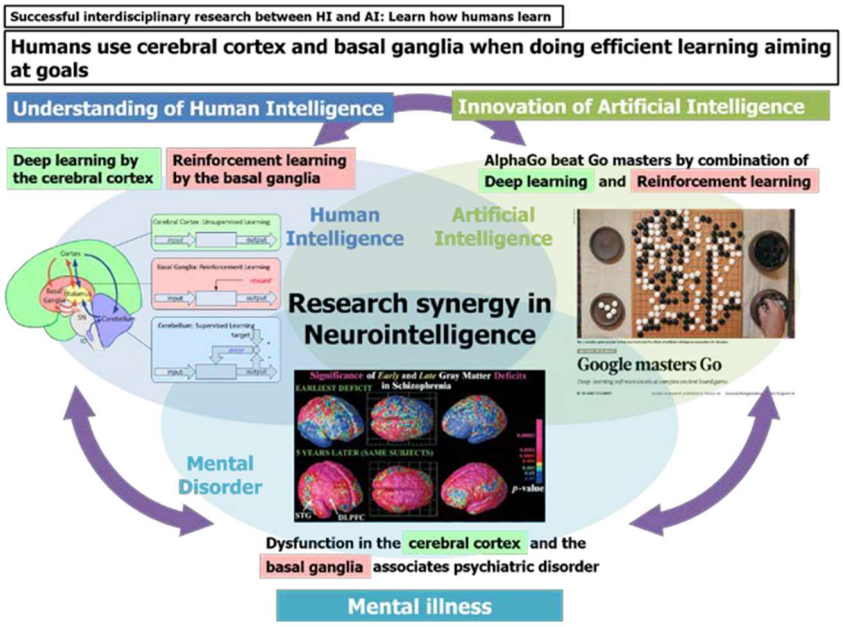
3) Interdisciplinary Research

* 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 created, is an integration of research on neural circuit development, technology development for probing neural circuits, studying psychiatricdisorders, 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 newtherapies of psychiatric disorders based on neural circuit dysfunction.

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 thecortex 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 disordersis considered to exist in thecortex and basal ganglia. We expect that explorations by IRCN of unknown information processing mechanisms, inaddition to the two mentioned above (i.e. cortex–deep learning and basal ganglia–reinforcement learning), willadvance AI studies to the next generation.

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.

Strategy for conducting interdisciplinary research

IRCN takes a **Team Science** approach to research fusion combining sixteen world-class principal investigators (PIs) spanning four domains of research. In the area of **Neurodevelopment**, selected model systems elucidate the fundamental principles of neural circuit development: Yukiko Gotoh (prenatal stem cell fate); Masanobu Kano (synapse elimination in postnatal development); Kazuo Emoto (elimination and remodeling of dendrites); Kenichi Ohki (activity-dependent neural circuit development); Yoko Yazaki-Sugiyama (birdsong learning). In the area of **Human/clinical** research, psychophysical, non-invasive imaging and patient cohort studies establish valuable insight into human brain development and dysfunction: Sho Tsuji (infant language acquisition); Takao Hensch (perinatal critical periods & autism); Kiyoto Kasai (adolescent critical periods & psychosis); Zenas Chao (prediction & creativity). In the area of **Computation**, neuro-inspired mathematical principles focused on brain dynamics will be pursued: Kazuyuki Aihara (dynamical network biomarkers & neuromorphic hardware); Mingbo Cai (prediction); Takamitsu Watanabe (energy landscape modeling & autism); Yukie Nagai (developmental robotics). Novel **Technology** will advance state-of-the-art neural circuit analysis: Haruo Kasai (reinforcement learning & synaptic plasticity); Yasushi Okada (neuronal imaging); Shoji Takeuchi (biohybrid sensors). Multiple teams are formed "bottom-up" by intentionally combining PIs across these four areas, such as Social Learning, Critical Period Timing, Prediction, Reinforcement, Intrinsic Activity, Multiscale imaging, Autism or Psychosis.

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, Director of IRCN,has clear perspectives about the WPI goal and its impact on biology and medicine. His leadership has attracted talented young researchers irrespective of country 2) Outstanding members: We selected the best researchers from a wide range of scientific disciplines both within UTokyo and from 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 between IRCN and satellite/partner 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 acrossmultiple countries will be achieved by a multi-level enterprise by researchers, trainees and administrative staff with the following strategies:

- highest priority on recruitment of young researchers with high international activity and potential.
- IRCN members will be encouraged to do collaborative research overseas each year. This rule has beenin 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.
- provide scientific programs that facilitate active interaction between the core IRCN and satellites.
- research conferences andmeetings conducted in English in principle.
- IRCN will interact with multiple graduate student programs in UTokyo and abroad as a platform for facilitating global leadership of young scientists.
- sponsor large-scale international symposia each year. In addition, frequent workshops, sabbaticals and seminars by top foreign researchers are planned to attract scientists from outside of IRCN.

Strategy for staffing foreign researchers: The Director, supported by EB/SC, will put highest effort toward recruitment of young foreign researchers with high motivation and ability. After recruitment, the outstanding fusion research achievement during their term at IRCN will be encouraged to 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.
- For young PIs, we minimize duties to maximize their research-related activity. Assistant Professors are hired initially for five years then reviewed in the fifth year based on research outcomes. The review will determine whether the appointment (1) ends with 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 to WPI postdocs and PIs from abroad 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 everyyear. 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 international satellites and partners will host symposia abroad in rotation. These meetings not only promote exchange of researchers but also advertise IRCN research abroad.

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 pre-existing system of university administrators in UTokyo supports human resources necessary for IRCN administration. IRCN provides training and full support for successful writing of grant proposals through the postdoctoral advisory committee (I-PAC). 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. The Kavli IPMU under UTIAS provides a model framework for IRCN to have discretion in recruiting researchers and budgetary requests.

Role of the center director: The center Director is given full authority regarding organization and management of the center with ultimate responsibility for all decisions in IRCN:

- Setting both long- / short-term missions and goals of IRCN; proposes plans and timetables that effectively lead to their realization.
- Effective organization of researchers in IRCN, providing ideas, designs and plans to maximize the interactions and effective collaboration of researchers in IRCN.
- Administrative decisions with the support of the Directorate's Office (DO) / EB
- Recruitment of promising young scientists; dissemination of the Center's research outcomes to the scientific community and society.

Professor Takao Hensch, the first IRCN Director, started his career as a researcher at UTokyo after graduating from Harvard. He has lengthy 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 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 UTokyo President's office has created a Taskforce to work closely with Professor Hensch to ensure he is adequately supported as Director.

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 designated 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 three 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.

We enlisted Dr Nobukazu Toge as AD of IRCN. Dr. Toge has been engaged in top-level administration at KEK and was responsible for management of large-scale research funds. He fully understands the WPI mission. He has profound knowledge about research in the United States, and this experience will further help communication with foreign researchers and administrative staff. 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 IRCN secretariat is modeled after that of 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 sectionsof 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.

Decision Making System	
Components	Personnel and Members
Director	Dr. Takao Hensch
Deputy Director (DD)	Drs. Masanobu Kano, Kazuyuki Aihara and Kazuo Emoto
Directorate's Office (DO)	Director, Administrative Director (AD) Special Advisor to the Director (SAD), Executive Director (ED), and General Manager (GM)
Executive Board (EB)	Director, three DDs, SAD and AD
Steering Committee (SC)	Members of the EB and all of PIs
External Advisory Committee (EAC)	Seven internationally recognized scientists

Administrative organization	
Components	Personnel and main roles
Administrative division	General affairs Team: handling personnel and public relation
	Financial planning Team: handling financing, purchasing, and basic infrastructure
	Research support Team: handling competitive research funds, research regulations and compliance
	International relations Team: handling international conferences and workshops, support for staff and visitors from abroad

Center's decision-making system: Managerial authority is concentrated on the Director and AD for flexible daily operation and quick implementation of decisions with support from a competent secretariat (DO). The Director receives advice from the Executive Board (EB), consisting of the Administrative Director (AD), Special Advisor (SAD) and three Deputy Directors (Masanobu Kano, Kazuo Emoto, Kazuyuki Aihara) for smooth advice on hiring new faculty, setting research strategies and swift decision-making. The Steering Committee (SC) is responsible for approval of the Director's decisions and their execution.

The External Advisory Committee (EAC) provides advice to the Director on IRCN activity from a global perspective. 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 fusion Team Science. 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 head of the host institution, President of UTokyo, appoints the Director and approves the PIs. All other personnel matters and 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 pre-existing frameworks. 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 the 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 paysand 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 initiated this process by securing rooms for IRCN in the Faculty of Medicine Building 1. IRCN has built common research space with advanced instruments and core facilities providing cutting-edge instruments, along with fee-for-services provided by skilled operators and data analysis. These common research spaces facilitate collaboration of different Teams. UTokyo will further seek the possibility of constructing a new research building that provides research housing for all IRCN members and central gathering spaces. Access to the building should be convenient for all IRCN members while its location will follow the University's Hongo campus plan.

Environment in which researchers can work comfortably on their research

(1) General support for researchers

- Reduced administrative duties: IRCN decision-making is designed to be simple and effective. All important decisions are made by the Director with SC approval and executed by the DO.
- 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: staff is arranged to support meetings and conferences, such as 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 include 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 Boston satellite is actively 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 driver of University 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 Young Researcher System started in FY2016, to stabilize posts for young faculty members supports 4 PIs. In addition, support systems for female researchers have helped with recruitment into IRCN.
- Priority acceptance to residences has helped recruit excellent researchers.
- 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 "UTokyo Compass", the University is striving 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 "Sustainability Office" gathers information from domestic and foreign funding agencies and foundations to boost IRCN activities. Clinical neuroscience in IRCN will promote collaboration with pharmaceutical companies. Partnerships with Daikin and Softbank are already implemented. Investment and collaboration with venture capital entrepreneurs will be encouraged. Philanthropic funds for trainees will be gathered. Finally, continuous support from the University remains critical to maintain and expand IRCN. In its draft *Fourth Mid-Term Goals and Plans*, the University of Tokyo (UTokyo) is committed to "facilitate the activities by research hubs such as Kavli IPMU, IRCN and Tokyo College. Specifically, these three hubs would invite and accept substantial numbers of researchers from abroad and that IRCN and Tokyo College will be transformed into permanent institutions". For this purpose, particular attention has been and will be paid to "reinforce the organizational structure and operations platform of the University of Tokyo Institutes for Advanced Study (UTIAS) and other centers of excellence."

The *UTokyo Compass,* released in September 2021 to embody the motto of excellence and diversity, specifies to "further strengthen our world-class research facilities as hubs for linking different types of knowledge, promoting research of the highest global standards, and generating new academic knowledge through co-creation across disciplines." as a key action plan. 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 centers, IRCN has discretion in recruiting researchers and budgetary requests to MEXT. IRCN thus acts as an autonomous unit within 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.