The International Symposium on
Development and Plasticity of Neural Systems

March 14-17, 2022

Institute for the Advanced Study of Human Biology
ASHBi
Kyoto University

For speakers in Japan & Asia

The International Symposium on Development and Plasticity of Neural Systems

* The time shown below is **JST/Japan Standard Time**

Monday, 14 March (Day 1)

Invited Speakers (S-1 ~ S-39)
Talk time
International: 30-min/person
Japanese and Japanese resident: 20-min/person

Short oral talk (P-1 ~ P-15)
Talk time**: 10-min/person**

Break: 20-min

Tuesday, 15 March (Day 2)

Session 2 (Chair: **Yoko Yazaki-Sugiyama**)

9:00	**S-7 Zhigang He** (Harvard Medical School)
9:30	**S-8 Yutaka Yoshida** (Burke Neurological Institute/Weill Cornell Medicine/OIST)
9:50	**S-9 Tadashi Isa** (Kyoto University)
10:10	Break
10:30	**S-10 Hideyuki Okano** (RIKEN CBS/Keio University)
10:50	**S-11 Mark H. Tuszynski** (University of California, San Diego)
11:20	**S-12 Jun Takahashi** (Kyoto University)
11:40	P-1 **Yuki Fujita**
	P-2 **Miaoxing Wang**
12:10	P-3 **Yusuke Kishi**

Wednesday, 16 March (Day 3)

Session 4 (Chair: **Ryoichiro Kageyama**)

9:00	**S-19 Hongjun Song** (University of Pennsylvania)
9:30	**S-20 Yukiko Gotoh** (The University of Tokyo)
9:50	**S-21 Freda Miller** (University of British Columbia)
10:20	Break
10:40	**S-22 Kazunobu Sawamoto** (Nagoya City University/National Institute for Physiological Sciences)
11:00	**S-23 Arnold Kriegstein** (University of California, San Francisco)
11:30	P-7 **Tadao Usui**
	P-8 **Haruka Sato**
12:00	P-9 **Ayano Kawaguchi**

Thursday, 17 March (Day 4)

Session 6 (Chair: **Tadashi Isa**)

9:00	**S-30 Masanori Murayama** (RIKEN CBS)
9:20	**S-31 Karl Deisseroth** (Stanford University)
9:50	**S-32 Haruhiko Bito** (The University of Tokyo)
10:10	Break
10:30	**S-33 Hitoshi Okamoto** (RIKEN CBS)
10:50	**S-34 Yoko Yazaki-Sugiyama** (OIST/The University of Tokyo)
11:10	**S-35 Takeshi Imai** (Kyushu University)
11:30	P-13 **Kosuke Hamaguchi**
	P-14 **Rikako Kato**
12:00	P-15 **Pin-Wu Liu**

Session 1
Part1 (Chair: Tadashi Isa)
Part2 (Chair: Yasunori Hayashi)

17:00	Opening: **Tadashi Isa**
17:10	**S-1 Yasunori Hayashi** (Kyoto University)
17:30	**S-2 Mu-ming Poo** (Institute of Neuroscience, Chinese Academy of Sciences)
18:00	**S-3 Haruo Kasai** (The University of Tokyo)
18:20	Break
18:40	**S-4 Michisuke Yuzaki** (Keio University)
19:00	**S-5 Ole Kiehn** (University of Copenhagen/ Karolinska Institute)
19:30	**S-6 Martin E. Schwab** (University of Zurich)
20:00	Networking
21:00	

Session 3 (Chair: **Mototsugu Eiraku**)

17:00	**S-13 Adrian W Moore** (RIKEN CBS)
17:20	**S-14 Mineko Kengaku** (Kyoto University)
17:40	**S-15 Victor Borrell** (Institute of Neuroscience, CSIC-UMH)
18:10	Break
18:30	**S-16 Carina Hanashima** (Waseda University)
18:50	**S-17 Chiaki Ohtaka-Maruyama** (TMIMS)
19:10	**S-18 Jonas Frisén** (Karolinska Institute)
19:40	P-4 **Yoshitaka Kameo**
	P-5 **Tomoki Matsuda**
	P-6 **Masafumi Inaba**
20:10	Networking
20:40	

Session 5 (Chair: **Kazunori Nakajima**)

17:00	**S-24 Itaru Imayoshi** (Kyoto University)
17:20	**S-25 Fumio Matsuzaki** (RIKEN BDR)
17:40	**S-26 Jürgen A Knoblich** (IMBA/Medical University of Vienna)
18:10	Break
18:30	**S-27 Pierre Vanderhaeghen** (VIB-KU Leuven)
19:00	**S-28 J. Gray Camp** (Roche Institute for Translational Bioengineering)
19:30	**S-29 Mototsugu Eiraku** (Kyoto University)
19:50	P-10 **Goichi Miyoshi**
	P-11 **Sara Morson**
	P-12 **Masaaki Ogawa**
20:20	Networking
20:50	

Session 7 (Chair: **Yukiko Gotoh**)

17:00	**S-36 Kazunori Nakajima** (Keio Univeristy)
17:20	**S-37 Sebastian Jessberger** (University of Zurich)
17:50	**S-38 Magdalena Götz** (University of Munich)
18:20	**S-39 Ryoichiro Kageyama** (RIKEN CBS/Kyoto University)
18:40	Closing: **Magdalena Götz**

For speakers in Europe

The International Symposium on Development and Plasticity of Neural Systems

* The time shown below is **CET/Central European Time**

Monday, 14 March (Day 1)

Invited Speakers (S-1 ~ S-39)
Talk time
International: 30-min/person
Japanese and Japanese resident: 20-min/person

Short oral talk (P-1 ~ P-15)
Talk time**: 10-min/person**

Break: 20-min

Tuesday, 15 March (Day 2)

Session 2 (Chair: **Yoko Yazaki-Sugiyama**)

1:00	**S-7 Zhigang He** (Harvard Medical School)
1:30	**S-8 Yutaka Yoshida** (Burke Neurological Institute/Weill Cornell Medicine/OIST)
1:50	**S-9 Tadashi Isa** (Kyoto University)
2:10	Break
2:30	**S-10 Hideyuki Okano** (RIKEN CBS/Keio University)
2:50	**S-11 Mark H. Tuszynski** (University of California, San Diego)
3:20	**S-12 Jun Takahashi** (Kyoto University)
3:40	P-1 **Yuki Fujita**
	P-2 **Miaoxing Wang**
4:10	P-3 **Yusuke Kishi**

Wednesday, 16 March (Day 3)

Session 4 (Chair: **Ryoichiro Kageyama**)

1:00	**S-19 Hongjun Song** (University of Pennsylvania)
1:30	**S-20 Yukiko Gotoh** (The University of Tokyo)
1:50	**S-21 Freda Miller** (University of British Columbia)
2:20	Break
2:40	**S-22 Kazunobu Sawamoto** (Nagoya City University/National Institute for Physiological Sciences)
3:00	**S-23 Arnold Kriegstein** (University of California, San Francisco)
3:30	P-7 **Tadao Usui**
	P-8 **Haruka Sato**
4:00	P-9 **Ayano Kawaguchi**

Thursday, 17 March (Day 4)

Session 6 (Chair: **Tadashi Isa**)

1:00	**S-30 Masanori Murayama** (RIKEN CBS)
1:20	**S-31 Karl Deisseroth** (Stanford University)
1:50	**S-32 Haruhiko Bito** (The University of Tokyo)
2:10	Break
2:30	**S-33 Hitoshi Okamoto** (RIKEN CBS)
2:50	**S-34 Yoko Yazaki-Sugiyama** (OIST/The University of Tokyo)
3:10	**S-35 Takeshi Imai** (Kyushu University)
3:30	P-13 **Kosuke Hamaguchi**
	P-14 **Rikako Kato**
4:00	P-15 **Pin-Wu Liu**

Session 1 Part1 (Chair: Tadashi Isa) / Part2 (Chair: Yasunori Hayashi)

9:00	Opening: **Tadashi Isa**
9:10	**S-1 Yasunori Hayashi** (Kyoto University)
9:30	**S-2 Mu-ming Poo** (Institute of Neuroscience, Chinese Academy of Sciences)
10:00	**S-3 Haruo Kasai** (The University of Tokyo)
10:20	Break
10:40	**S-4 Michisuke Yuzaki** (Keio University)
11:00	**S-5 Ole Kiehn** (University of Copenhagen/ Karolinska Institute)
11:30	**S-6 Martin E. Schwab** (University of Zurich)
12:00	Networking
13:00	

Session 3 (Chair: **Mototsugu Eiraku**)

9:00	**S-13 Adrian W Moore** (RIKEN CBS)
9:20	**S-14 Mineko Kengaku** (Kyoto University)
9:40	**S-15 Victor Borrell** (Institute of Neuroscience, CSIC-UMH)
10:10	Break
10:30	**S-16 Carina Hanashima** (Waseda University)
10:50	**S-17 Chiaki Ohtaka-Maruyama** (TMIMS)
11:10	**S-18 Jonas Frisén** (Karolinska Institute)
11:40	P-4 **Yoshitaka Kameo**
	P-5 **Tomoki Matsuda**
	P-6 **Masafumi Inaba**
12:10	Networking
12:40	

Session 5 (Chair: **Kazunori Nakajima**)

9:00	**S-24 Itaru Imayoshi** (Kyoto University)
9:20	**S-25 Fumio Matsuzaki** (RIKEN BDR)
9:40	**S-26 Jürgen A Knoblich** (IMBA/Medical University of Vienna)
10:10	Break
10:30	**S-27 Pierre Vanderhaeghen** (VIB-KU Leuven)
11:00	**S-28 J. Gray Camp** (Roche Institute for Translational Bioengineering)
11:30	**S-29 Mototsugu Eiraku** (Kyoto University)
11:50	P-10 **Goichi Miyoshi**
	P-11 **Sara Morson**
	P-12 **Masaaki Ogawa**
12:20	Networking
12:50	

Session 7 (Chair: **Yukiko Gotoh**)

9:00	**S-36 Kazunori Nakajima** (Keio Univeristy)
9:20	**S-37 Sebastian Jessberger** (University of Zurich)
9:50	**S-38 Magdalena Götz** (University of Munich)
10:20	**S-39 Ryoichiro Kageyama** (RIKEN CBS/Kyoto University)
10:40	Closing: **Magdalena Götz**

For speakers in US East

The International Symposium on Development and Plasticity of Neural Systems

* The time shown below is **EDT /Eastern Daylight Time (US East)**

Monday, 14 March

	4:00	Opening: **Tadashi Isa**
Session 1 Part1 (Chair: Tadashi Isa)	4:10	**S-1 Yasunori Hayashi** (Kyoto University)
	4:30	**S-2 Mu-ming Poo** (Institute of Neuroscience, Chinese Academy of Sciences)
	5:00	**S-3 Haruo Kasai** (The University of Tokyo)
	5:20	Break
Part2 (Chair: Yasunori Hayashi)	5:40	**S-4 Michisuke Yuzaki** (Keio University)
	6:00	**S-5 Ole Kiehn** (University of Copenhagen/ Karolinska Institute)
	6:30	**S-6 Martin E. Schwab** (University of Zurich)
	7:00	Networking
	8:00	

Tuesday, 15 March

Session 3 (Chair: Mototsugu Eiraku)	4:00	**S-13 Adrian W Moore** (RIKEN CBS)
	4:20	**S-14 Mineko Kengaku** (Kyoto University)
	4:40	**S-15 Victor Borrell** (Institute of Neuroscience, CSIC-UMH)
	5:10	Break
	5:30	**S-16 Carina Hanashima** (Waseda University)
	5:50	**S-17 Chiaki Ohtaka-Maruyama** (TMIMS)
	6:10	**S-18 Jonas Frisén** (Karolinska Institute)
	6:40	P-4 **Yoshitaka Kameo** P-5 **Tomoki Matsuda** P-6 **Masafumi Inaba**
	7:10	Networking
	7:40	

Wednesday, 16 March

Session 5 (Chair: Kazunori Nakajima)	4:00	**S-24 Itaru Imayoshi** (Kyoto University)
	4:20	**S-25 Fumio Matsuzaki** (RIKEN BDR)
	4:40	**S-26 Jürgen A Knoblich** (IMBA/Medical University of Vienna)
	5:10	Break
	5:30	**S-27 Pierre Vanderhaeghen** (VIB-KU Leuven)
	6:00	**S-28 J. Gray Camp** (Roche Institute for Translational Bioengineering)
	6:30	**S-29 Mototsugu Eiraku** (Kyoto University)
	6:50	P-10 **Goichi Miyoshi** P-11 **Sara Morson** P-12 **Masaaki Ogawa**
	7:20	Networking
	7:50	

Thursday, 17 March

Session 7 (Chair: Yukiko Gotoh)	4:00	**S-36 Kazunori Nakajima** (Keio Univeristy)
	4:20	**S-37 Sebastian Jessberger** (University of Zurich)
	4:50	**S-38 Magdalena Götz** (University of Munich)
	5:20	**S-39 Ryoichiro Kageyama** (RIKEN CBS/Kyoto University)
	5:40	Closing: **Magdalena Götz**

Session 2 (Chair: Yoko Yazaki-Sugiyama)	20:00	**S-7 Zhigang He** (Harvard Medical School)
	20:30	**S-8 Yutaka Yoshida** (Burke Neurological Institute/Weill Cornell Medicine/OIST)
	20:50	**S-9 Tadashi Isa** (Kyoto University)
	21:10	Break
	21:30	**S-10 Hideyuki Okano** (RIKEN CBS/Keio University)
	21:50	**S-11 Mark H. Tuszynski** (University of California, San Diego)
	22:20	**S-12 Jun Takahashi** (Kyoto University)
	22:40	P-1 **Yuki Fujita** P-2 **Miaoxing Wang**
	23:10	P-3 **Yusuke Kishi**

Session 4 (Chair: Ryoichiro Kageyama)	20:00	**S-19 Hongjun Song** (University of Pennsylvania)
	20:30	**S-20 Yukiko Gotoh** (The University of Tokyo)
	20:50	**S-21 Freda Miller** (University of British Columbia)
	21:20	Break
	21:40	**S-22 Kazunobu Sawamoto** (Nagoya City University/National Institute for Physiological Sciences)
	22:00	**S-23 Arnold Kriegstein** (University of California, San Francisco)
	22:30	P-7 **Tadao Usui** P-8 **Haruka Sato**
	23:00	P-9 **Ayano Kawaguchi**

Session 6 (Chair: Tadashi Isa)	20:00	**S-30 Masanori Murayama** (RIKEN CBS)
	20:20	**S-31 Karl Deisseroth** (Stanford University)
	20:50	**S-32 Haruhiko Bito** (The University of Tokyo)
	21:10	Break
	21:30	**S-33 Hitoshi Okamoto** (RIKEN CBS)
	21:50	**S-34 Yoko Yazaki-Sugiyama** (OIST/The University of Tokyo)
	22:10	**S-35 Takeshi Imai** (Kyushu University)
	22:30	P-13 **Kosuke Hamaguchi** P-14 **Rikako Kato**
	23:00	P-15 **Pin-Wu Liu**

Invited Speakers (S-1 ~ S-39)
Talk time
International: 30-min/person
Japanese and Japanese resident: 20-min/person

Short oral talk (P-1 ~ P-15)
Talk time**: 10-min/person**

Break: 20-min

For speakers in US West

The International Symposium on Development and Plasticity of Neural Systems

* The time shown below is **PDT Pacific Daylight Time (US West)**

Monday, 14 March

	1:00	Opening: **Tadashi Isa**
Session 1 Part1 (Chair: Tadashi Isa) Part2 (Chair: Yasunori Hayashi)	1:10	**S-1 Yasunori Hayashi** (Kyoto University)
	1:30	**S-2 Mu-ming Poo** (Institute of Neuroscience, Chinese Academy of Sciences)
	2:00	**S-3 Haruo Kasai** (The University of Tokyo)
	2:20	Break
	2:40	**S-4 Michisuke Yuzaki** (Keio University)
	3:00	**S-5 Ole Kiehn** (University of Copenhagen/ Karolinska Institute)
	3:30	**S-6 Martin E. Schwab** (University of Zurich)
	4:00	Networking
	5:00	

Tuesday, 15 March

Session 3 (Chair: Mototsugu Eiraku)	1:00	**S-13 Adrian W Moore** (RIKEN CBS)
	1:20	**S-14 Mineko Kengaku** (Kyoto University)
	1:40	**S-15 Victor Borrell** (Institute of Neuroscience, CSIC-UMH)
	2:10	Break
	2:30	**S-16 Carina Hanashima** (Waseda University)
	2:50	**S-17 Chiaki Ohtaka-Maruyama** (TMIMS)
	3:10	**S-18 Jonas Frisén** (Karolinska Institute)
	3:40	P-4 **Yoshitaka Kameo** P-5 **Tomoki Matsuda** P-6 **Masafumi Inaba**
	4:10	Networking
	4:40	

Wednesday, 16 March

Session 5 (Chair: Kazunori Nakajima)	1:00	**S-24 Itaru Imayoshi** (Kyoto University)
	1:20	**S-25 Fumio Matsuzaki** (RIKEN BDR)
	1:40	**S-26 Jürgen A Knoblich** (IMBA/Medical University of Vienna)
	2:10	Break
	2:30	**S-27 Pierre Vanderhaeghen** (VIB-KU Leuven)
	3:00	**S-28 J. Gray Camp** (Roche Institute for Translational Bioengineering)
	3:30	**S-29 Mototsugu Eiraku** (Kyoto University)
	3:50	P-10 **Goichi Miyoshi** P-11 **Sara Morson** P-12 **Masaaki Ogawa**
	4:20	Networking
	4:50	

Thursday, 17 March

Session 7 (Chair: Yukiko Gotoh)	1:00	**S-36 Kazunori Nakajima** (Keio Univeristy)
	1:20	**S-37 Sebastian Jessberger** (University of Zurich)
	1:50	**S-38 Magdalena Götz** (University of Munich)
	2:20	**S-39 Ryoichiro Kageyama** (RIKEN CBS/Kyoto University)
	2:40	Closing: **Magdalena Götz**

Session 2 (Chair: Yoko Yazaki-Sugiyama)	17:00	**S-7 Zhigang He** (Harvard Medical School)
	17:30	**S-8 Yutaka Yoshida** (Burke Neurological Institute/Weill Cornell Medicine/OIST)
	17:50	**S-9 Tadashi Isa** (Kyoto University)
	18:10	Break
	18:30	**S-10 Hideyuki Okano** (RIKEN CBS/Keio University)
	18:50	**S-11 Mark H. Tuszynski** (University of California, San Diego)
	19:20	**S-12 Jun Takahashi** (Kyoto University)
	19:40	P-1 **Yuki Fujita** P-2 **Miaoxing Wang**
	20:10	P-3 **Yusuke Kishi**

Session 4 (Chair: Ryoichiro Kageyama)	17:00	**S-19 Hongjun Song** (University of Pennsylvania)
	17:30	**S-20 Yukiko Gotoh** (The University of Tokyo)
	17:50	**S-21 Freda Miller** (University of British Columbia)
	18:20	Break
	18:40	**S-22 Kazunobu Sawamoto** (Nagoya City University/National Institute for Physiological Sciences)
	19:00	**S-23 Arnold Kriegstein** (University of California, San Francisco)
	19:30	P-7 **Tadao Usui** P-8 **Haruka Sato**
	20:00	P-9 **Ayano Kawaguchi**

Session 6 (Chair: Tadashi Isa)	17:00	**S-30 Masanori Murayama** (RIKEN CBS)
	17:20	**S-31 Karl Deisseroth** (Stanford University)
	17:50	**S-32 Haruhiko Bito** (The University of Tokyo)
	18:10	Break
	18:30	**S-33 Hitoshi Okamoto** (RIKEN CBS)
	18:50	**S-34 Yoko Yazaki-Sugiyama** (OIST/The University of Tokyo)
	19:10	**S-35 Takeshi Imai** (Kyushu University)
	19:30	P-13 **Kosuke Hamaguchi** P-14 **Rikako Kato**
	20:00	P-15 **Pin-Wu Liu**

Invited Speakers (S-1 ~ S-39)
Talk time
International: 30-min/person
Japanese and Japanese resident: 20-min/person

Short oral talk (P-1 ~ P-15)
Talk time**: 10-min/person**

Break: 20-min

Monday, March 14 (Day 1)

Opening Remarks

17:00-17:10 Tadashi Isa

Chair: **Tadashi Isa**

17:10-17:30 **S-1** **Synaptic plasticity during sleep is required for memory**
Yasunori Hayashi (Kyoto University)

17:30-18:00 **S-2** **Dynamics and stability of synaptic connections in adult mice and monkey brain**
Mu-ming Poo (Institute of Neuroscience, Chinese Academy of Sciences)

18:00-18:20 **S-3** **The force of dendritic-spine enlargement facilitating presynaptic exocytosis**
Haruo Kasai (The University of Tokyo)

18:20-18:40 Break

Chair: **Yasunori Hayashi**

18:40-19:00 **S-4** **Bridge over Troubled Synapses with Extracellular Scaffolding Proteins**
Michisuke Yuzaki (Keio University)

19:00-19:30 **S-5** **Brainstem circuits controlling arrest of movements**
Ole Kiehn (University of Copenhagen/Karolinska Institute)

19:30-20:00 **S-6** **From the bench to clinical trials for regeneration enhancing Nogo-A antibodies for spinal cord injury**
Martin E. Schwab (University of Zurich)

20:00-21:00 Networking

Tuesday, March 15 (Day 2 - Morning)

Chair: **Yoko Yazaki-Sugiyama**

9:00-9:30 **S-7** **How do injured CNS neurons respond to axonal insults?**

Zhigang He (Harvard Medical School)

9:30-9:50 **S-8** **Monosynaptic connections between corticospinal neurons and motor neurons underlying manual dexterity in wild-type and ALS model mice**

Yutaka Yoshida (Burke Neurological Institute/Weill Cornell Medicine, Okinawa Institute of Science and Technology graduate University)

9:50-10:10 **S-9** **How the brain works for recovery from spinal cord injury**

Tadashi Isa (Kyoto University)

10:10-10:30 Break

10:30-10:50 **S-10** **Disease Modeling using Marmosets with Germ Line Modification and In Vivo Genome Editing**

Hideyuki Okano (RIKEN CBS/Keio University)

10:50-11:20 **S-11** **Rhesus Macaque vs Rat Divergence in the Corticospinal Projectome**

Mark H. Tuszynski (University of California, San Diego)

11:20-11:40 **S-12** **iPS cell-based therapy for Parkinson's disease**

Jun Takahashi (Kyoto University)

11:40-12:10 **Short Oral Talks (P-1 ~ P-3)**

11:40-11:50 **P-1** Yuki Fujita (University of Pennsylvania)
11:50-12:00 **P-2** Miaoxing Wang (Kanazawa University)
12:00-12:10 **P-3** Yusuke Kishi (The University of Tokyo)

Tuesday, March 15 (Day 2 - Evening)

Chair: **Mototsugu Eiraku**

17:00-17:20 **S-13** **Genetic strategies to create stereotyped arbor wiring**

Adrian W Moore (RIKEN CBS)

17:20-17:40 **S-14** **Cytoskeletal forces driving neuronal migration in 3D brain tissues**

Mineko Kengaku (Kyoto University)

17:40-18:10 **S-15** **New (and small) regulators of cerebral cortex size and folding during evolution**

Victor Borrell (Institute of Neuroscience Alicante)

18:10-18:30 Break

18:30-18:50 **S-16** **Mechanisms of neuronal subtype transition and integration in the cerebral cortex**

Carina Hanashima (Waseda University)

18:50-19:10 **S-17** **Characteristics of subplate neuron molecular expression elucidated by single-cell and spatial transcriptome analysis**

Chiaki Ohtaka-Maruyama (Tokyo Metropolitan Institute of Medical Science)

19:10-19:40 **S-18** **Neurogenesis in the adult human hippocampus**

Jonas Frisén (Karolinska Institute)

19:40–20:10 **Short Oral Talks (P-4 ~ P-6)**

19:40-19:50 **P-4** Yoshitaka Kameo (Kyoto University)
19:50-20:00 **P-5** Tomoki Matsuda (SANKEN, Osaka University)
20:00-20:10 **P-6** Masafumi Inaba (Kyoto University)

20:10-20:40 Networking

Wednesday, March 16 (Day 3 - Morning)

Chair: **Ryoichiro Kageyama**

9:00-9:30 **S-19** **Neurogenesis in the dentate gyrus of the hippocampus as a continuous evelopmental process across the lifespan**

Hongjun Song (University of Pennsylvania)

9:30-9:50 **S-20** **Cell cycle arrest determines adult neural stem cell ontogeny**

Yukiko Gotoh (The University of Tokyo)

9:50-10:20 **S-21** **Defining mammalian neural stem cell transitions and niches from embryogenesis to adulthood**

Freda Miller (University of British Columbia)

10:20-10:40 Break

10:40-11:00 **S-22** **Postnatal neuronal migration in health and disease**

Kazunobu Sawamoto (Nagoya City University/National Institute for Physiological Sciences)

11:00-11:30 **S-23** **Genomic Insights into Early Human Brain Development, Evolution, and Disease**

Arnold Kriegstein (University of California, San Francisco)

11:30–12:00 **Short Oral Talks (P-7 ~ P-9)**

11:30-11:40 **P-7** Tadao Usui (Kyoto University)
11:40-11:50 **P-8** Haruka Sato (Kumamoto University)
11:50-12:00 **P-9** Ayano Kawaguchi (Nagoya University)

Wednesday, March 16 (Day 3 - Evening)

Chair: **Kazunori Nakajima**

17:00-17:20 **S-24** **Analysis of neural stem cell regulatory mechanisms using optogenetics**

Itaru Imayoshi (Kyoto University)

17:20-17:40 **S-25** **Exploring the relationship of progenitor subtypes in and between gyrencephalic species at the single cell level**

Fumio Matsuzaki (RIKEN BDR)

17:40-18:10 **S-26** **A cerebral organoid model for Tuberous sclerosis identifies human-specific aspects of brain**

Jürgen A Knoblich (IMBA/Medical University of Vienna)

18:10-18:30 Break

18:30-19:00 **S-27** **Human-specific temporal mechanisms of brain development**

Pierre Vanderhaeghen (VIB-KU Leuven)

19:00-19:30 **S-28** **Lineage recording in human cerebral organoids**

J. Gray Camp (Roche Institute for Translational Bioengineering)

19:30-19:50 **S-29** **Neural Development in Stem Cell Culture**

Mototsugu Eiraku (Kyoto University)

19:50–20:20 **Short Oral Talks (P-10 ~ P-12)**

19:50-20:00 **P-10** Goichi Miyoshi (Gunma University)
20:00-20:10 **P-11** Sarah Morson (Okinawa Institute of Science and Technology Graduate University)
20:10-20:20 **P-12** Masaaki Ogawa (Kyoto University)

20:20-20:50 Networking

Thursday, March 17 (Day 4 - Morning)

Chair**: Tadashi Isa**

9:00-9:20 **S-30** **Emotional arousal enhances perceptual memory through amygdalo-cortical input during NREM sleep**

Masanori Murayama (RIKEN CBS)

9:20-9:50 **S-31** **TBA**

Karl Deisseroth (Stanford University)

9:50-10:10 **S-32** **TBA**

Haruhiko Bito (The Univresity of Tokyo)

10:10-10:30 Break

10:30-10:50 **S-33** **Discovery of neurons monitoring whether the prediction comes true in the brain of zebrafish escaping in the virtual reality space**

Hitoshi Okamoto (RIKEN CBS)

10:50-11:10 **S-34** **Variable axon connectivity of song memory ensembles in developmental zebra finch song learning**

Yoko Yazaki-Sugiyama (OIST/The University of Tokyo)

11:10-11:30 **S-35** **Lateral inhibition signals for synaptic competitions**

Takeshi Imai (Kyushu University)

11:30–12:00 **Short Oral Talks (P-13 ~ P-15)**

11:30-11:40 **P-13** Kosuke Hamaguchi (Kyoto University)
11:40-11:50 **P-14** Rikako Kato (Kyoto University)
11:50-12:00 **P-15** Pin-Wu Liu (Nagoya University)

Thursday, March 17 (Day 4 - Evening)

Chair: **Yukiko Gotoh**

17:00-17:20 **S-36** **Control of astrocyte dispersion in the developing cerebral cortex**

Kazunori Nakajima (Keio Univeristy)

17:20-17:50 **S-37** **Molecular and functional heterogeneity of neural stem cells**

Sebastian Jessberger (University of Zurich)

17:50-18:20 **S-38** **Novel mechanisms of neurogenesis – the centrosome as a dynamic RNA processing hub in neurogenesis**

Magdalena Götz (University of Munich)

18:20-18:40 **S-39** **Functional rejuvenation of aged neural stem cells by Plagl2 and anti-Dyrk1a activity**

Ryoichiro Kageyama (RIKEN CBS/Kyoto University)

Closing Remarks

18:40-18:50 Magdalena Götz

Short Oral Talks

P-1 **Spatial genome organization during neurogenesis**
Yuki Fujita (University of Pennsylvania)

P-2 **Intracellular trafficking of Notch orchestrates temporal dynamics of Notch activity in the fly brain**
Miaoxing Wang (Kanazawa University)

P-3 **The role of PcG in regionalization of the mouse telencephalon**
Yusuke Kishi (The University of Tokyo)

P-4 **Mechanical modeling of brain morphogenesis caused by multicellular dynamics**
Yoshitaka Kameo (Kyoto University)

P-5 **Development of fluorescent indicators for visualization of N-cadherin interaction across cells**
Tomoki Matsuda (SANKEN, Osaka University)

P-6 **Contractile oscillators regulate the spatial patterning of gut motility**
Masafumi Inaba (Kyoto University)

P-7 **Elucidation of the internal state-dependent modulation of the nociceptive escape behavior**
Tadao Usui (Kyoto University)

P-8 **Thalamocortical axons control the cytoarchitecture of neocortical layers by area-specific supply of VGF**
Haruka Sato (Kumamoto University)

P-9 **Neuronal delamination and outer radial glia generation in neocortical development**
Ayano Kawaguchi (Nagoya University)

P-10 **A FOXG1-dependent critical period for autism-associated GABAergic circuits**
Goichi Miyoshi (Gunma University)

P-11 **Parallel anatomical connections for song memories between two regions of the zebra finch higher auditory cortex**
Sarah Morson (Okinawa Institute of Science and Technology Graduate University)

P-12 **The neural basis for overcoming failure: a dopamine circuit facilitates switching toward new goals**
Masaaki Ogawa (Kyoto University)

P-13 **From Retrospective to Prospective: Integrated Value Representation in Frontal Cortex for Predictive Choice Behavior**
Kosuke Hamaguchi (Kyoto University)

P-14 **Visual instrumental learning without primary visual cortex**
Rikako Kato (Kyoto University)

P-15 **Regulation of synaptic nanodomain and nanocolumn by liquid–liquid phase separation**
Pin-Wu Liu (Nagoya University)

S-1

Synaptic plasticity during sleep is required for memory

Yasunori Hayashi

Kyoto University Graduate School of Medicine

Memories are initially formed in the hippocampus but subsequently transferred to the rest of brain for a long-term storage. This phenomenon is called "memory consolidation," but the cellular mechanism responsible for it has not been fully elucidated. Long-term potentiation (LTP) of synaptic transmission, which increases the efficiency of the transmission of neural activity between cells for long-term, is known as a cellular phenomenon of memory. If we can determine when and where LTP occurs, we can dissect out the cellular process responsible for the memory consolidation. We first developed a technique to detect when and where LTP is occurring. We employed SuperNova, a fluorescent protein derived from sea anemones to accomplish this. Upon illumination, SuperNova releases reactive oxygen species (ROS), which then inactivates the surrounding proteins. We connected SuperNova with cofilin, an actin binding protein specifically accumulates at the synapse after LTP induction. Illumination of cofilin-SuperNova caused an erasure of LTP only within 20 min after the induction. We found light irradiation into the hippocampus immediately after learning or during sleep after learning leads to erasure of the memories in both cases. This indicates that two waves of LTP occurred in the hippocampus immediately after learning and during sleep afterwards, and that these stepwise LTP events shape memories in the hippocampus. To further understand the time window in which memories are transferred to the cortex, we examined the time window of LTP in the anterior cingulate cortex, a cortical region implicated in the recall of old memory and found that LTP was induced in the anterior cingulate cortex during sleep the day after learning but not on the same day. This technology has the potential to elucidate many brain functions involved in memory at the cellular level.

S-2

Dynamics and stability of synaptic connections in adult mice and monkey brain

Mu-ming Poo. Yang Yang, and Min Chen

Institute of Neuroscience, Chinese Academy of Sciences
Shanghai Center for Brain Research Brain-inspired Technology.

Formation and elimination of synapses reflects structural plasticity of neuronal connectivity. We have performed *in vivo* high-resolution two-photon imaging to examine the dynamic turnover of synaptic structures (dendritic spines and presynaptic boutons) in the primary auditory cortex (A1) of adult mice and the prefrontal cortex (PFC) of adult macaque monkeys. In mice A1, we found that the rate of turnover of synaptic structures was relatively low (5-10% over two days). By dual-color labeling of both axon projections from lateral amygdala and A1 layer 5 pyramidal neurons, we found surprisingly that essentially all new synapses formed either spontaneously or induced by auditory fear conditioning involved additions of a presynaptic bouton or a postsynaptic spine to a pre-existing synapse. This indicates that structural modification of adult mouse brain involves changing the strength of existing connections, rather than *de novo* formation of new connections. At the dendrites of layer 5 pyramidal neurons of PFC in four macaque monkeys of different ages, we found that spines were in general highly stable, with a much lower rate of formation and elimination of synapses than those found in the mouse brain. By following the same spines at weekly intervals over months, we found that newly formed spines in the monkey PFC were more susceptible to elimination, with only 40% surviving long term. Enabled by high-resolution imaging of a large number of spines in the macaque PFC, we performed in-depth analysis of spatial distribution of spines on individual dendrites, and found that the distances between adjacent spines conform to Weibull distribution, and spine formation and elimination was more likely to occur in low- and high-density regions, respectively, implicating cellular mechanisms restricting the sites of spine turnover. These results provide new insights into long-term synaptic dynamics and stability of synaptic structures in the adult brain.

S-3

The force of dendritic-spine enlargement facilitating presynaptic exocytosis

Haruo Kasai

Laboratory of Structural Physiology, Faculty of Medicine and IRCN, The University of Tokyo

The majority of excitatory glutamatergic synapses are made on dendritic spines which enlarge during learning. Since dendritic spines and the presynaptic terminals are tightly connected with the synaptic cleft, the enlargement may have mechanical effects on presynaptic functions. We found that the fine and transient pushing of the boutons by a glass pipette markedly promoted an evoked neurotransmitter release and the assembly of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins, whose Förster resonance transfer (FRET) was measured with fluorescence lifetime imaging (FLIM) in rat slice culture preparations. Surprisingly, both effects persisted over 20 min. The increased presynaptic FRET was independent of cytosolic calcium (Ca^{2+}), but dependent on the assembly of SNARE proteins and actin polymerisation in the boutons. Importantly, a low hypertonic sucrose solution (20 mM, 0.5 kg/cm^2) caused facilitatory effects on both the FRET and evoked release without inducing spontaneous release, making a striking contrast with a high hypertonic sucrose solution (300 mM) which induced exocytosis by itself. Finally, the spine enlargement, induced by the two-photon glutamate uncaging, enhanced evoked release and FRET only when the spines pushed the boutons by their elongation. Thus, we have found a mechano-sensory and transduction mechanism in the presynaptic boutons.

S-4

Bridge over Troubled Synapses with Extracellular Scaffolding Proteins

Michisuke Yuzaki

Dean, Keio University Graduate School of Medicine
Professor, Department of Neurophysiology

Abnormal synaptic connections are believed to contribute to various neuropsychiatric, neurodevelopmental and neurological disorders, such as schizophrenia, autism spectrum disorders and Alzheimer's diseases. Thus, it is crucial to clarify the mechanisms by which synapses are formed, maintained, and modified throughout life. Synaptic organizers, which mediate these processes, are classified into secreted factors, such as Wnt and FGF, and cell adhesion molecules, such as neurexins and neuroligins. Recently, a new class of synaptic organizers, secreted extracellular scaffolding proteins (ESPs), such as C1q family proteins, LGI1, neuronal pentraxins and glial thrombospondins, have been discovered (Yuzaki M. Annu Rev Physiol 80:243-262, 2018). They serve as a scaffold for pre- and postsynaptic membrane proteins at the synaptic extracellular matrix. For example, Cbln1, a prototype of the C1q family, is unique in that it is secreted from presynaptic neurons in an activity-dependent manner (Ibata K et al., Neuron 102:1184-1198, 2019), and rapidly induces synapse formation in the adult brain (Matsuda K et al., Science 328: 363-368, 2010; Elegheert J et al., Science 353:295-299, 2016). In contrast, Cbln2, a subfamily member of Cbln1, is reported to be secreted from dendrites of pyramidal neurons in the hippocampus and controls glutamate receptor activity without affecting synapse numbers (Dai et al., Nature 595:261-265, 2021). Furthermore, Cbln4 is reported to regulate inhibitory synapse formation between somatostatin-positive interneurons and pyramidal neurons in the cortex (Favuzzi E et al, Science 363:413-417, 2019; Fossati M et al., Neuron 104:1081-1094, 2019). In this talk, I would like to summarize what is known so far about the C1q family and discuss how we could develop new therapeutic reagents against neuropsychiatric and neurological disorders based on the known structures of known ESPs.

S-5

Brainstem circuits controlling arrest of movements

Ole Kiehn

Department of Neuroscience, University of Copenhagen, Denmark
Department of Neuroscience Karolinska Institute, Stockholm, Sweden

Arrest of ongoing movement is an integral part of executing motor programs. For intended or goal-directed movements, the arrest happens when a goal is reached e.g. reaching and grasping an object or stopping locomotion once the desired location is reached. In other cases the movement arrest is sudden as a reaction to changes in the environment. This talk will focus on work that has identified neuronal brainstem circuits that bridge with executive motor circuits to implement motor arrests. It will describe brainstem circuits in the medulla in mice that implement intended stop of locomotion and also implement left-right directionality of the movement. The lecture will also report the discovery of a distinct excitatory neuron population in the pedunculopontine (PPN) midbrain nuclei that induce global motor arrest with a phenotypical 'pause and play' motor pattern accompanied by bradycardia and slow respiratory frequency that is different from fear-induced freezing. The PPN 'pause and play' circuit may be recruited in an arousal state needed to focus on environmental cues. Our studies ascribe behavioral relevant motor arrests to distinct groups of excitatory brainstem command pathways.

This work was supported by The Novo Nordisk Foundation, European Research Council, and The Lundbeck Foundation.

S-6

From the bench to clinical trials for regeneration enhancing Nogo-A antibodies for spinal cord injury

Martin E. Schwab

Institute for Regenerative Medicine IREM
University of Zurich, Zurich, Switzerland,
NovaGo Therapeutics Inc., Schlieren, Switzerland

Following injury of the mammalian brain or spinal cord, lesioned nerve fibers can spontaneously grow and form new connections. This new 'hardware' can be fine tuned by intensive use and training during rehabilitation. The regrowing fibers are spatially restricted, however, to often less than a mm. Specific neurite growth inhibitory factors were found to restrict plastic and regenerative nerve fiber growth in the adult CNS. The membrane protein Nogo-A is a well characterized, potent neurite growth inhibitor in the CNS. Nogo-A activates an intracellular signalling cascade via multisubunit receptor complexes. Function blocking antibodies against Nogo-A have been applied to rats and macaque monkeys with spinal cord or cortical stroke lesions. In the spinal cord, injured fibers showed enhanced regenerative sprouting as well as long-distance regeneration. Spared fiber tracts showed enhanced compensatory sprouting. In animals with cortical strokes, intact-side corticobulbar or corticospinal fibers crossed the midline, supplying functional innervation to the denervated brain stem and spinal cord under the influence of anti-Nogo-A antibodies. Functional recovery was improved, including bladder functions. - Different antibodies against human Nogo-A were produced, optimized and manufactured under GMP conditions. Their safety and tolerability after intrathecal infusion was tested in non-human primates. A Phase 1 clinical trial showed that repeated injection over 30 days is well tolerated and safe in acute tetra- and paraplegic patients (Kucher et al., 2028). In a placebo controlled, randomized Phase 2 trial, >96 severe, acute tetraplegic patients have been treated up to now in a multinational European clinical trial network (NISCI). Arm – hand function (upper limb motor score), lower limb function, bladder and autonomic functions, pain and quality of life scores are being evaluated over 6 mts. The trial will reach its projected number of patients in Q2/3-2022, and results will be available from Q2-2023 on.

S-7

How do injured CNS neurons respond to axonal insults?

Zhigang He

Boston Children's Hospital, Harvard Medical School

In adult CNS, an axonal damage often triggers retrograde neuronal death and regenerative failure. This contributes to permanent functional deficits after CNS injury and to neurodegeneration in diseases such as glaucoma. Thus, there is a pressing need to understand how neurons respond to injury. In adult mice, optic nerve crush (ONC) injury, which severs all axons of retinal ganglion cells (RGCs), results in massive death of axotomized RGCs and regenerative failure of survivors. With this model, our previous studies identified several critical regulators of neuronal injury responses, such as PTEN/mTOR and/or SOCS3/STAT. However, major challenges remain. First, because some of these interventions have the risk of promoting tumor growth, it is critical to identify alternative and safe pro-regenerative strategies. Second, while the pro-survival and pro-regeneration effects of these available interventions are still partial, it is desirable to identify new molecular targets. My talk will cover our recent progresses in these fronts. In the first part, I will present our results from single cell RNA-seq analysis of RGCs with three interventions (deletion of Pten, deletion of Socs3, and overexpression of CNTF), in collaboration with Josh Sanes's group. Our studies define the injury responses of 46 RGC types with these interventions in both transcriptional and cellular terms. We also discovered several neuropeptides as potential pro-regeneration treatments. In the second part, I will discuss the results from two non-biased genomic studies, in vivo CRISPR screen of transcription factors and ATAC-seq/RNAseq, in collaboration with Dan Geschwind and Josh Sanes. Remarkably, these independent analyses converged on a set of ATF/CEBP transcription factors as critical regulators of survival. These TFs contribute to two degeneration transcriptional programs: ATF3/CHOP preferentially regulate pathways activated by cytokines and innate immunity, whereas ATF4/C/EBPγ regulate pathways engaged by intrinsic neuronal stressors. Thus, our results reveal core transcription programs that transform an initial axonal insult into a degenerative result and suggest novel strategies for treating neurodegenerative diseases.

S-8

Monosynaptic connections between corticospinal neurons and motor neurons underlying manual dexterity in wild-type and ALS model mice.

Yutaka Yoshida

Burke Neurological Institute / Weill Cornell Medicine
Okinawa Institute of Science and Technology graduate University

Corticospinal neurons located in layer V of the sensorimotor cortex are the essential conveyers of motor instructions controlling skilled movements. Corticospinal neurons form monosynaptic connections with motor neurons (which are called corticomotoneuronal (CM) connections) only in primates, which play a role in independent finger movements. In contrast, corticospinal neurons are thought to form only disynaptic connections with motor neurons through spinal interneurons in non-primate mammals. However, we previously showed that CM connections are formed in early postnatal mice that are eliminated by Sema6D-PlexA1 signaling during development. Adult *PlexA1* mutant mice with CM connections exhibit superior dexterity in forearm skilled movements over their littermate controls. This suggests that *PlexA1* mutant mice may provide a better mouse model to study human motor disorders compared to wild-type mice.
The amyotrophic lateral sclerosis (ALS) is a genetically complex disease with causal mutations in over 30 ALS-related genes. In patients with ALS, early symptomatic hallmarks include deficits in fine hand movements. Indeed, CM connections have been suggested to be disrupted in early stages of ALS patients. However, since wild-type mice do not have CM connections, it is not possible to study CM connections using wild-type mice. Therefore, we crossed ALS mouse model (SOD1 mice) with *PlexA1* mutant mice with CM connections. We found that CM connections may be disrupted at early symptomatic timepoints in these mice, whereas disynaptic corticospinal connections are preserved. We are currently investigating the mechanisms underlying disruption of CM connections in these mice.

S-9

How the brain works for recovery from spinal cord injury

Tadashi Isa

Department of Neuroscience, Graduate School of Medicine, Kyoto University
Institute for the Advanced Study of Human Biology (WPI-ASHBi), Kyoto University

Spinal cord injury causes a devastating loss of sensory, motor and autonomic functions to the patients and therapeutic strategies to improve these functions for enhancing their quality of life is an urgent demand. In many cases, the injuries are partial, therefore promoting the functions of the remaining part of the fiber tracts is considered to be the key for recovery. We have been working on the recovery of reaching and grasping movements of the forearm in the macaque model of the partial spinal cord injury. In case the injury is confined to the lateral funiculus which transected the lateral corticospinal tract, the monkeys can recovery the ability of precision grip in several weeks through training. In this case, the spinal cord interneurons bridge the injury and work for the recovery. In addition, very dynamic change in the circuit operation occurs at the cortical level. In addition to the contralesional motor cortex, ipsilateral primary motor cortex (M1) is activated during the early stage (~1 month after injury) by the contralesional M1 via the corpus callosum and contribute to the recovery. In the later stage (3-4 months after injury), the bilateral premotor cortices (PM) contribute to the recovery. Furthermore, the mesolimbic system including the nucleus accumbens facilitates the motor cortex and promotes recovery. In contrast, in case of the subhemisection (larger lesion), usually the recovery of hand movements is slow and very limited even at 6 months after injury. However, through intensive training and weekly extensive electrical stimulation of bilateral PM and M1, the precision grip never recovered but coarse grip considerably recovered in several weeks after injury. In this case, the bilateral PM and M1 are highly disinhibited and interacted with each other, and the corticospinal tract from the contralesional M1 exhibited a massive re-routing; 20-30% of the corticofugal fibers became uncrossed, descended in the contralesional side, crossed the midline caudal to the lesion and reached the gray matter including the motor nuclei of the affected hand/arm muscles, amazing plasticity in the adult brain. These basic

animal experimental studies gave us several conceptual updates for development of the future therapeutic strategies.

References

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S-10

Disease Modeling using Marmosets with Germ Line Modification and In Vivo Genome Editing

Hideyuki Okano

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The common marmoset (*Callithrix jacchus*) is a small New World primate that has been extensively used as biomedical research models. There is also an increasing interest in common marmoset in Brain Science and as appropriate models for major human brain disorders (Okano, Annu Rev Neurosci, 2021; Okano et al., Neuron, 2016; Grillner et al., Nat Neurosci, 2016).

We have been working with a number of collaborators to build a platform for marmoset brain science research. In 2009, we succeeded in generating the world's first genetically modified (GM) marmoset with germline transmission by lentiviral mediated transgenesis (Sasaki et al., Nature, 2009), and in 2015, we succeeded in determining the detailed sequence of the entire marmoset genome using next-generation sequencing (Sato et al., Sci Rep, 2015). On this basis, we successfully created individual genome-edited marmosets (GM) using lentiviral mediated transgenesis (Sasaki et al., Nature, 2009), and in 2015, we successfully sequenced the entire genome of a marmoset using a next-generation sequencer (Sato et al., Sci Rep, 2015). In 2015, we successfully sequenced the entire genome of the marmoset using next-generation sequencing (Sato et al., Sci Rep, 2015), and on this basis, we successfully created genome-edited marmosets (Sato et al., Cell Stem Cell, 2016).
In the present talk, I wish to mention our recent data of generation of transgenic marmoset models of neurodegenerative diseases, including Parkinson disease (PD) which overexpressed the mutant form of □-synuclein suing lentiviral vector. The PD model marmoset showed stage-dependent progression of the disease, such as sleeping disturbance followed by motor deficit. In addition, I will mention a model marmoset of a neurodevelopmental disorder, the Rett syndrome, obtained by genome editing of *MECP2* gene. Abnormalities in brain structure and function in these marmoset models may accelerate discovery of disease biomarkers and mechanisms toward translation (Okano et al., Neuron, 2016).

S-11

Rhesus Macaque vs Rat Divergence in the Corticospinal Projectome

Mark H. Tuszynski

University of California, San Diego

We used viral intersectional tools to map the projectome of corticospinal neurons associated with fine distal forelimb control in Fischer 344 rats and rhesus macaques. In rats, we found an extraordinarily diverse set of collateral projections from corticospinal neurons to 23 different brain and spinal regions. Remarkably, the vast weighting of this "motor" projection was to *sensory* systems in both the brain and spinal cord, confirmed by optogenetic and trans-synaptic viral intersectional tools. In contrast, rhesus macaques exhibited far heavier and narrower weighting of corticospinal outputs toward spinal and brainstem *motor* systems. Thus, corticospinal systems in macaques primarily constitute a final output system for fine motor control, whereas this projection in rats exerts a multi-modal integrative role that accesses far broader CNS regions. Unique structural-functional correlations can be achieved by mapping and quantifying a single neuronal system's *total* axonal output and its relative weighting across CNS targets.

S-12

iPS cell-based therapy for Parkinson’s disease

Jun Takahashi

Kyoto University, Center for iPS Cell Research and Application, Kyoto, Japan

Human induced pluripotent stem cells (iPSCs) can provide a promising source of midbrain dopaminergic (DA) neurons for cell replacement therapy for Parkinson's disease (PD). Towards clinical application of iPSCs, we have developed a method for 1) scalable DA neuron induction on human laminin fragments and 2) sorting DA progenitor cells using a floor plate marker, CORIN. The grafted CORIN+ cells survived well and functioned as midbrain DA neurons in the 6-OHDA-lesioned rats, and showed the minimal risk of tumor formation. In addition, we performed a preclinical study using primate PD models. Regarding efficacy, human iPSC-derived DA progenitor cells survived and functioned as midbrain DA neurons in MPTP-treated monkeys. Furthermore, regarding safety, cells sorted by CORIN did not form any tumors in the brains for at least two years. Based on these results, we have started a clinical trial to treat PD patients at Kyoto University Hospital in Kyoto, Japan, in 2018. The trial evaluates the safety and efficacy of transplanting human iPS cell-derived DA progenitors into PD patients' putamen. We implant approximately 5 million cells into every seven patients and observe for two years. The trial is now ongoing without any trouble.

S-13

Genetic strategies to create stereotyped arbor wiring

Adrian W Moore

RIKEN Center for Brain Science, Wako, Japan

Neurons have stereotyped dendrite and axon arbors. These scaffold synaptic connectivity, and control computation of information by the cell. From vertebrates to invertebrates, dendrite arbor wiring patterns are genetically programmed; our laboratory asks how these programs are decoded. We approach this by examining arbor differentiation as a sequential and changing process, in which different sequences or durations of cell behaviors create specialized wiring pattern outcomes. To reveal the molecular control processes, we integrate *in vivo* high spatiotemporal resolution time-lapse imaging and quantitation of arbor differentiation, with state-of-the-art transcriptomics. Our recent studies using *Drosophila* peripheral sensory neurons as an experimental system, have led to a new model for stereotyped arbor specification; transcription factors encode the growth and branching dynamics of arbor differentiation by setting the identity, spatial organization, and amplitude of microtubule generation events in the neuron.

S-14

Cytoskeletal forces driving neuronal migration in 3D brain tissues

Mineko Kengaku

Kyoto University Institute for Advanced Study, Institute for Integrated Cell-Material Sciences (KUIAS-iCeMS)
Kyoto, Japan

After the last cell division in the germinal zone, newborn neurons migrate from the birthplace to the specific layer in the cortex where they are integrated in functional neural circuits. Delivery of the nucleus which is the largest and stiffest cargo presents the biggest physical challenge for migrating neurons to pass through the crowded neural tissue. It has been shown that the nuclear delivery is orchestrated by the pulling force of cytoplasmic dynein, the minus-end directed microtubule motor, and the contractile force of actomyosin. However, the mechanisms of how cytoskeletal forces are coordinated and converted to actual nuclear behaviors remain unclear.
By using high-resolution live imaging, we attempt to visualize the microtubule- and actin-dependent force in migrating cerebellar granule cells. Unlike the prevailing view that dynein is the predominant microtubule motor driving nuclear migration, we demonstrated that an opposing force by kinesin (KIF5) is also required for normal neuronal migration. Dynein and kinesin dynamically dock to small points of the nuclear envelope and drive complex nuclear dynamics including pinching, rotation and translocation and thereby enable nuclear migration in narrow interstitial spaces. In contrast to the steering forces of the microtubule motors, actomyosin instead exerts strong contractile force in the front and rear of the nucleus. We have found that neurons sense the space confinement via a mechanosensor Piezo1and switch the force generation mechanism by recruiting distinct actomyosin networks. Thus, neurons are equipped with multiple cytoskeletal engines and migrate through diverse extracellular environment by switching the migration modes.

S-15

New (and small) regulators of cerebral cortex size and folding during evolution

Victor Borrell

Institute of Neuroscience, CSIC-UMH, San Juan de Alicante, Spain

The evolutionary expansion and folding of the mammalian cerebral cortex resulted from the amplification of neural stem and progenitor cells during embryonic development. This was secondarily reversed in some lineages like rodents, leading to smaller brains with a smooth cortex. The genetic bases of these complex evolutionary dynamics remain unclear. While brain expansion in the recent human lineage is in part explained by the emergence of few new genes, mounting evidence points at the differential regulation of conserved genetic mechanisms as being central in the evolution of neurogenesis and brain size across vertebrates. I will discuss our findings in mouse showing the central role of microRNAs in the regulation of gene expression in the early embryonic cerebral cortex, with a critical impact on progenitor cell amplification and neurogenesis, and the consequences of their deregulation in pediatric brain cancer. Our recent work further shows that the small non-coding RNA *MIR3607* has a positive influence on cortical progenitor cell amplification, by dramatically activating itself beta-Catenin signaling via blockade of APC expression. Importantly, *MIR3607* is expressed at high levels in germinal layers of the embryonic cortex of primates and carnivores, where it promotes progenitor amplification, but was secondarily lost in the rodent lineage, leading to smaller progenitor pools and, consequently, to the reduction in size and folding of their cortex. Finally, I will present our latest findings on the epigenetic regulation of cortex folding in ferret, where we identify well-known transcription factors as unsuspected key players in this process. Our results show the central importance of mechanisms of gene expression regulation in the evolution of embryonic cortical development, and its consequences on cortex size and folding.

S-16

Mechanisms of neuronal subtype transition and integration in the cerebral cortex

Carina Hanashima

Department of Biology, Waseda University
Center for Advanced Biomedical Sciences

The functional integrity of the brain system relies on the precisely coordinated production of diverse neurons and their placement along the three-dimensional axis. Specifically in the cerebral cortex, progenitor cells produce distinct neuronal subtypes in a stereotypical order and establish a six-layer structure, which are further modified into functional areas. A prevailing view concerning the neurogenesis of the neocortex is that neural stem cells undergo successive rounds of asymmetric cell divisions to produce the principal layer subtypes: preplate, deep-layer, and upper-layer neurons, through a progressive restriction in cell competence. Consistent with this view, we previously showed that transcriptional regulatory network plays a central role in establishing early cell identity and switching neurogenesis. However, recent studies have also indicated that the specification and integration of neocortical neurons relies on communication between distinct cell types, in addition to intrinsic transcriptional regulation. I will present our findings on the mechanisms by which neocortical subtype identities establish in the neocortex, by manipulating gene expression and number of neurogenesis in the developing mouse cortex. Our results indicate that neocortical progenitors integrate both intrinsic and extrinsic cues to generate distinct layer neurons, a system which ultimately balances the production of neocortical subtypes during development and possibly evolution.

S-17

Characteristics of subplate neuron molecular expression elucidated by single-cell and spatial transcriptome analysis

Chiaki Ohtaka-Maruyama

Developmental Neuroscience Project, Tokyo Metropolitan Institute of Medical Science (TMIMS), Tokyo, Japan

In the mammalian neocortex, a large number of neurons are precisely arranged in an ordered 6-layered structure inside out. This structure is formed by the sequential generation of neurons and their migration toward the brain surface, radial neuronal migration. We previously reported that subplate neurons (SpNs), which are one of the first-born and mature types of neurons in the developing neocortex, play an essential role in regulating radial migration. We revealed that SpNs exhibit spontaneous calcium oscillations at E15 and actively extend processes to contact newly born multipolar migrating neurons (MpNs) via synaptic structure. SpNs play a critical role in establishing the first neural circuit between the thalamus and cortex in the mid-embryonic and perinatal stages during neocortical development, suggesting their necessity in the period of cortical formation. Although most SpNs die postnatally, the remaining fraction of SpNs located in layer 6b in adult mammals may continue to fire spontaneously and play a role in brain activity during sleep. To elucidate the function of SpNs in more detail, we are now characterizing their subpopulations using a SpN-specific transgenic mouse line (Lpar1-EGFP) or Cre-ERT2 mouse line (D1B-Cre). Single-cell analysis and Visium spatial transcriptome analysis revealed novel molecular markers of SpNs in the embryonic stage. The result supported the idea that SpNs consist of heterogeneous cell populations and that each subpopulation has distinct roles in the formation and function of the neocortex.

S-18

Neurogenesis in the adult human hippocampus

Jonas Frisén

Department of Cell and Molecular Biology, Karolinska Institute, Sweden

Neurogenesis in the adult hippocampus has been described in many mammals, but is challenging to study in humans. The generation of new neurons in adult humans has been demonstrated by BrdU labelling and ^{14}C retrospective birth dating. In mice, the new neurons are generated by neural stem cells, via intermediate progenitor cells. Several studies have demonstrated the presence of neural progenitor cells in the adult human dentate gyrus as well as changes in their numbers over the lifespan as well as in pathological conditions. However, a few recent studies have failed to find progenitor cells in the adult human hippocampus either by immunohistochemistry or snRNA-seq, prompting them to suggest that neurogenesis is absent in adult humans, fueling a new wave of controversy in this research field.
We have analyzed the human hippocampus by large scale snRNA-seq in 26 subjects 0-78 years old and identified a neurogenic cell trajectory from stem cell to immature neuron present from birth to high age. We distinguish different cell stages, their markers and gene regulatory networks and explain why others have failed to detect these cells. The number of cells of all stages of neurogenesis is highest in early childhood and is maintained at lower levels throughout adulthood into high age, underlying adult neurogenesis. The identification and molecular characterization of the cells underlying hippocampal neurogenesis through the human lifespan will aid studies on the regulation and role of this process in health and disease.

S-19

Neurogenesis in the dentate gyrus of the hippocampus as a continuous developmental process across the lifespan

Hongjun Song

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Immature dentate granule cells arising from adult hippocampal neurogenesis contribute to plasticity and unique brain functions in rodents and they are dysregulated in many human neurological disorders. Using genetic clonal lineage-tracing, we identified a pool of neural stem cells that exhibit similar molecular and epigenetic characteristics and continuously generate dentate granule neurons throughout life in the mouse hippocampus. Single-cell RNA-seq analysis further reveals a transition from active to quiescent neural stem cell state during the early postnatal stage followed by a continuous maturation process. Rather than categorize hippocampal neurogenesis into two stages of “embryonic neurogenesis” vs. “adult neurogenesis”, we propose a continuous model of neurogenesis suggesting that dentate gyrus development is a life-long process. We further provide evidence for the present of immature dentate granule neurons and identify their molecular characteristics in the human hippocampus across the lifespan.

S-20

Cell cycle arrest determines adult neural stem cell ontogeny

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Quiescent neural stem cells (NSCs) in the adult mouse brain are the source of neurogenesis that regulates innate and adaptive behaviors. Adult NSCs in the subventricular zone are derived from a subpopulation of embryonic neural stem-progenitor cells (NPCs) that is characterized by a slower cell cycle relative to the more abundant rapid cycling NPCs that build the brain. Yet, how slow cell cycle can cause the establishment of adult NSCs remains largely unknown. Here, we demonstrate that Notch and an effector Hey1 form a transcriptional module that is upregulated by cell cycle arrest in slowly-dividing NPCs. In contrast to the oscillatory expression of the Notch effectors Hes1 and Hes5 in fast cycling progenitors, Hey1 displays a non-oscillatory stationary expression pattern and contributes to the long-term maintenance of NSCs. These findings reveal a novel division of labor in Notch effectors where cell cycle rate biases effector selection and cell fate.

S-21

Defining mammalian neural stem cell transitions and niches from embryogenesis to adulthood

Freda Miller

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This lecture will describe our recent work focusing on mammalian forebrain neural stem cells to address two key questions in the field of neural stem cell biology. First, how is the mammalian pool of adult dormant neural stem cells generated developmentally and second, how does the neural stem cell niche evolve over developmental time and following injury? The lecture will also discuss potential insights this work provides into the reactivation of adult neural stem cells following demyelinating injuries.

S-22

Postnatal neuronal migration in health and disease

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New neurons are continuously generated from neural stem cells in the ventricular-subventricular zone (V-SVZ) of the walls of the lateral ventricles in the postnatal mammalian brain. These new neurons migrate toward their destinations, where they are differentiated into mature neurons involved in the maintenance and plasticity of brain tissues. After brain injuries, new neurons migrate toward the injured area for regeneration. However, they generally terminate the migration before reaching the lesion site unless their intrinsic capacity is modified or the environment is improved. It is important to understand which factors impede neuronal migration for functional recovery of the brain. Neuronal migration is restricted by the meshwork of activated astrocytes in and around the lesion. To move toward the lesion, new neurons form chain-like aggregates and migrate along blood vessels, which increases their migration efficiency. Radial glia are polarized embryonic neural stem cells, which guide newly generated neurons by providing their fibers as a migratory scaffold. Radial glial fibers are maintained for an extended period in the injured neonatal mouse brain and provide a scaffold on which V-SVZ-derived new neurons migrate toward the injured cerebral cortex. New neuron migration toward the lesion can be promoted by clearing the path of astrocytic processes, and by inserting artificial scaffolds that mimic the endogenous scaffolds. These findings suggest that strategies designed to help migrating neurons reach the lesion may improve stem/progenitor cell-based therapies for brain injury. This talk will highlight similarities and differences in the mechanisms of postnatal neuronal migration under physiological and pathological conditions to provide novel insights into endogenous neuronal regeneration.

S-23

Genomic Insights into Early Human Brain Development, Evolution, and Disease

Arnold Kriegstein

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The human cerebral cortex is more than three times expanded compared to our closest non-human primate relatives. The cortex emerges from an initially pseudostratified neuroepithelium that gives rise to radial glia, the neural stem cells of the cortex. A number of subtypes of radial glia have been identified, and single cell RNA sequencing (scRNAseq) has contributed to a novel model of primate corticogenesis, highlighted human-specific features of cortical development, suggested a relationship between oRG cells and brain tumors, and provided a benchmark for *in vitro* organoid models of brain development and disease. We have begun to characterize the molecular populations of cellular subtypes that exist at the onset of neurogenesis. Our single-cell transcriptomic and *in-situ* data suggest that early cortical areal patterning is strongly defined by the mutual exclusion of strong frontal or occipital gene expression signatures, with the specification of areas between these two poles arising from the resulting gradients at later developmental timepoints. Thus, we find evidence supporting the existence of a cortical protomap at the extremities, but also support for the protocortex hypothesis to refine spatial identity between the poles. Using velocity analysis, we find that major signaling pathways including Notch, Wnt, and mTOR drive the specification and maintenance of neuroepithelial stem cells and radial glia. Comparison of these progenitor populations to organoid systems highlights important differences and suggests that manipulation of these signaling pathways may improve in vitro models of early progenitor populations. Overall, we provide a comprehensive molecular and spatial atlas of early stages of human brain and cortical development at the onset of neurogenesis.

S-24

Analysis of neural stem cell regulatory mechanisms using optogenetics

Itaru Imayoshi

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The mammalian brain consists of a complex ensemble of neurons and glial cells. Their production during development and remodeling is tightly controlled by various regulatory mechanisms in neural stem cells. Among such regulations, basic helix-loop-helix (bHLH) factors have key functions in the self-renewal, multipotency, and fate determination of neural stem cells. Here, we highlight the importance of the expression dynamics of bHLH factors in these processes. We propose the multipotent state correlates with oscillatory expression of several bHLH factors, whereas the differentiated state correlates with sustained expression of a single bHLH factor. We also developed new optogenetic methods that can manipulate gene expressions in neural stem cells by light. We used this technology to manipulate the growth and fate-determination of neural stem cells. We are also analyzing dynamic changes in downstream gene expressions and cellular states caused by systematic light-induced manipulations of bHLH transcription factors.

S-25

Exploring the relationship of progenitor subtypes in and between gyrencephalic species at the single cell level

Fumio Matsuzaki

RIKEN Center for Biosystems Dynamics Research

The expansion of the mammalian brain during evolution are thought to largely depend on the emergence of a new germinal layer (the outer subventricular zone: OSVZ) and great heterogeneity of progenitor cell types. As distinct subtypes of neural progenitors may generate different populations of progenies, it is crucial to characterize the spatial and temporal pattern of individual progenitor types and their terminal fates.

in vivo genetic manipulation and single-cell transcriptome (scTCM) analyses are two powerful approaches to understand molecular and cellular properties of particular cells. scTCM of the human brain has been extensively performed, revealing transcriptional signatures of diverse progenitor populations. However, *in vivo* mechanisms underlying the development of human radial glial (RG) cells remained less explored due to a limited experimental access. Studies using brain organoids turned out to face problems to recapitulate molecular properties of cell-types in human brain development.

Under this situation, a valuable animal model to overcome difficulties in studying the human brain is the ferret (*Mustela putorius furo*), a carnivore with gyrencephalic features such as the OSVZ, forming a complex and folded brain, and also available for *in utero* electroporation (Kawasaki et al., 2012) and *de novo* genome-editing (Tsunekawa et al., 2016). Yet, the temporal pattern of molecular signatures of ferret progenitors remained largely unexplored at a high resolution. We investigated progenitor subtypes in the ferret by scTCM along the developmental course, and compared them with human information to reveal common and species-specific cell-types during the development of the complex brain. We also manipulated progenitors in ferrets by several approaches to understand subtype relationships and fates of neural progenitors.

S-26

A cerebral organoid model for Tuberous sclerosis identifies human-specific aspects of brain development

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The human brain is unique in size and complexity, but also the source of some of the most devastating human diseases. Cerebral organoids derived from patients suffering from neurodevelopmental disease can recapitulate the developmental defects leading to those diseases and allow us to disentangle the mechanistic complexity of disorders like Epilepsy and Autism. We were able to recapitulate the histological characteristics of Tuberous sclerosis, a severe form of epilepsy caused by genetic upregulation of mTOR signaling. We show that different culture conditions can be used to recapitulate either tumor formation or generation of giant neurons, both features that are diagnostic of TSC patient brains. Unlike all mouse models, organoid models display those features even in heterozygous patients without the need for loss of heterozygosity. Using single cell transcriptomics, we identify the CLIP cells (caudal late interneuron progenitors), a previously unknown human specific progenitor cell located in the caudal ganglionic eminences. Our data suggest that CLIP cells are responsible for the massive postnatal migration of interneurons into the prefrontal cortex that is seen in humans but not in rodents, adding functional relevance to this recently discovered phenomenon. Our results indicate that organoid models can fundamentally change widely accepted human disease concepts and lead to fundamental insights into the human-specific aspects of brain development.

S-27

Human-specific temporal mechanisms of brain development.

Pierre Vanderhaeghen

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The human brain, in particular the cerebral cortex, has undergone rapid expansion and increased complexity during recent evolution.
One striking feature of human corticogenesis is that it is highly protracted in time, from prenatal stages of neurogenesis (taking months instead of days in the mouse), to postnatal stages of neuronal maturation and circuit formation (taking years instead of weeks in the mouse). This prolonged development is thought to contribute in an important fashion to increased cortical size, but also enhanced circuit complexity and plasticity. In vitro and xenotransplantation models indicate that the developmental timing of corticogenesis is largely intrinsic to cortical progenitors and neurons. The underlying mechanisms include human-specific molecular and cellular properties, which may underlie human sensitivity to certain brain diseases.

S-28

Lineage recording in human cerebral organoids

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Induced pluripotent stem cell (iPSC)-derived organoids provide models to study human organ development. Single-cell transcriptomics enable highly resolved descriptions of cell states within these systems; however, approaches are needed to directly measure lineage relationships. Here we establish iTracer, a lineage recorder that combines reporter barcodes with inducible CRISPR–Cas9 scarring and is compatible with single-cell and spatial transcriptomics. We apply iTracer to explore clonality and lineage dynamics during cerebral organoid development and identify a time window of fate restriction as well as variation in neurogenic dynamics between progenitor neuron families. We also establish long-term four-dimensional light-sheet microscopy for spatial lineage recording in cerebral organoids and confirm regional clonality in the developing neuroepithelium. We incorporate gene perturbation (iTracer-perturb) and assess the effect of mosaic TSC2 mutations on cerebral organoid development. Our data shed light on how lineages and fates are established during cerebral organoid formation. More broadly, our techniques can be adapted in any iPSC-derived culture system to dissect lineage alterations during normal or perturbed development.

S-29

Neural Development in Stem Cell Culture

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Pluripotent stem cells (such as ES cells and iPS cells) can, in principle, differentiate into all cell types that make up our body. In a last decade, a technology that induces the differentiation of pluripotent stem cells into desired cell types by mimicking the environment of the developing organ in a culture dish has greatly developed. We have developed a method to induce various neural regions such as cerebral cortical tissue and retinal tissue from pluripotent stem cells (cerebral organoids and retinal organoids), and have studied the molecular basis of self-organization in the pattern formation and morphogenesis. In this talk, I will introduce a new means to form a tissue with the function as a circadian clock center, capable of sustaining stable gene expression oscillations in a 24-hour cycle for more than 20 days from pluripotent stem cells. In addition, I will talk about induction of human olfactory sensory epithelium organoids and its application to elucidate the mechanism of olfactory abnormality caused by SARS-CoV2 infection.

S-30

Emotional arousal enhances perceptual memory through amygdalo-cortical input during NREM sleep

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Emotional arousal is thought to enhance memory consolidation through projections from the basolateral amygdala (BLA) to sub-/cortical regions. However, it is still unclear where and how the BLA interacts to enhance memory consolidation. Furthermore, even the question of whether rapid-eye-movement (REM) or non-REM (NREM) sleep state is essential for enhancing memory consolidation by emotional arousal has not been settled. Using electrophysiological recordings and manipulating a BLA-cortical circuit during a perceptual-emotional associative learning task, we report that BLA neurons store emotional memory and enhance perceptual memory through BLA inputs to the cortex during NREM sleep. In the associative learning task, male mice learned the floor texture paired with a female in a cup on the floor. Male mice that had associated the floor texture with the female showed a more extended retention period of the floor texture memory than mice that had not met the female. We previously reported that inputs from the secondary motor cortex (M2) to the primary somatosensory cortex (S1) play crucial roles in texture memory consolidation. Based on the results, anatomical studies indicated a strong projection from the BLA to the M2 but weak to the S1. Immunohistological analysis of activity-dependent early gene expression revealed that the female presentation to male mice during the task activates BLA neurons. Chemogenetic inactivation of M2-projecting BLA neurons during the post-learning period impaired female memory consolidation. Interestingly, the inactivation of this circuit did not impair texture memory but did suppress the texture memory enhancement. Furthermore, simultaneous extracellular recording from the BLA, the M2, and the S1 revealed that the female presentation enhanced reactivations of the inter-regional cell-ensembles during NREM but not during REM sleep. Finally, optogenetic inactivation of BLA inputs at the M2 during NREM sleep suppressed the texture memory enhancement but not the female memory. A similar circuit manipulation during REM sleep did not impair any behavioral parameters in our observations. These results demonstrate that BLA-M2 inputs during NREM sleep have a causal role in enhancing perceptual memory consolidation by emotional arousal.

S-31 TBC

Talk Title

Speaker name

Affiliation(s)

S-32 TBC

Talk Title

Speaker name

Affiliation(s)

S-33

Discovery of neurons monitoring whether the prediction comes true in the brain of zebrafish escaping in the virtual reality space

Hitoshi Okamoto

RIKEN Center for Brain Science

Based on the recent finding that the brain of adult zebrafish, a small tropical fish, is small and relatively simple, but shares the most basic structure with that of the mammalian brain, we have devised a new virtual reality setup specifically for adult zebrafish and studied the time-lapse change of neuronal activity in the brain of zebrafish swimming in this device as they learn to avoid danger. As a result, we found in the part of the zebrafish brain that corresponds to the cerebral cortex of mammals that repeated avoidance training produces a cluster of neurons whose activity represent the prediction error between the training-informed prediction of the optimal future situation and the actual view, and that the fish behaves in a way that minimizes the activity of this cluster of neurons, resulting in the most efficient escape behavior. In this meeting, I would like to report our recent advance in the study of how such prediction and prediction error is generated by training, and how it is implemented for the improvement of behaviors by observing neural activities of the deeper parts of the telencephalon.

S-34

Variable axon connectivity of song memory ensembles in developmental zebra finch song learning

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WPI-IRCN, the University of Tokyo

Songbirds learn to sing as humans learn to speak during development. They first listen and memorize their tutors' vocalization in the auditory learning period, and then in the following sensorimotor learning period, they practice their motor skills (vocalization) based on tutor vocal memories. Recently we reported that the tutor song memory ensemble stored in the caudomedial nidopallium (NCM), analogous to mammalian higher auditory cortex in zebra finches. However, the brain developmental principles governing this time-sensitive sensorimotor learning are poorly understood. Here we performed a zebra finch whole brain connectome mapping across the developmental song learning period by the combination of whole brain tissue clearing and viral labeling of axonal projections from a cluster of NCM neurons activated by tutor song exposure. We found previously unreported axonal projections to HVC AIV, Area X and HVC-Shelf in juveniles in the sensorimotor learning period. In contrast in the adult when their songs became stereotyped, we observed a selective axonal disconnection between NCM and HVC, the pre-motor song output area. Viral ablation of the NCM neuronal memory ensemble in juveniles prevented song learning. Conversely, when juvenile birds learned two songs sequentially, from the first tutor of a different species and then from a second one of their own species, memory ensembles of both tutors and their NCM-HVC connections remained in the adults. The findings show that the NCM memory ensemble makes a transient connection to HVC for juvenile song learning and while a permanent adult connection is required to encode two songs. These results demonstrate dynamic interarea neuronal connectivity for two step, sensory and sensorimotor, acquisition of individually unique songs in zebra finches. Extensive experiences in juvenile period might increase a capacity of neuronal circuits in the adults that may have implications for neural mechanisms of human second language learning.

S-35

Lateral inhibition signals for synaptic competitions

Takeshi Imai

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In developing brains, neurons initially form excessive connections and then remodel them to form precise neuronal circuitry. Inter-and intra-neuronal synaptic competitions have been postulated, but their nature has remained elusive. In the mouse olfactory bulb, mitral cells initially extend multiple dendrites to multiple glomeruli, but developmentally they prune all but single primary dendrites. It has remained unknown how they establish just one primary dendrite. Here we show that genetically silencing neuronal activity in mitral cells, but not neurotransmission from olfactory sensory neurons, precludes developmental dendrite pruning. Glutamatergic spontaneous activity generated within the olfactory bulb is essential. We also find that the activity-dependent dendrite pruning is mediated by NMDARs and Rho GTPases. FRET imaging experiments show that glutamatergic synaptic inputs via NMDARs locally suppress RhoA, but globally activate it within a mitral cell to selectively prune weaker dendrites. Thus, activity-dependent long-range lateral inhibition via Rho GTPases establishes just one primary dendrite in a mitral cell.

S-36

Control of astrocyte dispersion in the developing cerebral cortex

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Astrocytes are among the most abundant cell types in the mammalian brain. They play essential roles not only in the mature brain but also during development, including in neural network formation by regulating synapse formation, maturation, and elimination. Despite their importance, the mechanisms involved in astrocyte production and distribution throughout the brain during development are poorly understood. Here, we showed that, during development of the mouse cerebral cortex, proliferative astrocyte progenitors migrated by switching between a newly identified migration mode, erratic migration, and a blood vessel-guided migration mode. During erratic migration, astrocyte progenitors moved rapidly and almost randomly within the intermediate zone and the cortical plate (CP). These cells divided frequently, and the daughter cells exhibited the same irregular pattern. Astrocyte progenitors also adopted blood vessel-guided migration, especially in the superficial CP. These cell behaviors of astrocyte progenitors were also confirmed using two-photon in vivo imaging of intact living embryos. Interestingly, angiogenesis itself was supported by astrocyte progenitors that bridged neighboring blood vessels during blood vessel-guided migration. The progenitors involved in these two migratory behaviors were generated in the prenatal stages and eventually differentiated into protoplasmic astrocytes in the cortical gray matter, whereas fibrous astrocytes in the white matter were generated postnatally. When the molecular mechanisms that underlie the blood vessel-guided migration of astrocyte progenitors were inhibited in vivo, the final position of astrocytes in the CP was affected. Our results demonstrated that astrocyte progenitors in the CP were highly motile and that the combination of erratic and blood vessel-guided migrations, as well as the mutual dependency between astrocyte progenitors and blood vessels, facilitated the even and ubiquitous distribution of astrocytes throughout the CP.

S-37

Molecular and functional heterogeneity of neural stem cells

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Neural stem cells generate new neurons throughout life in distinct regions of the mammalian brain. This process, called adult neurogenesis, is critically involved in certain forms of learning and memory. In addition, failing or altered neurogenesis has been associated with a number of neuro-psychiatric diseases such as major depression and cognitive aging. We aim to characterize the cellular and molecular mechanisms regulating neural stem cell activity and behavior on a single cell level. We present new approaches to study the cellular principles underlying life-long neurogenesis using imaging-based tools and single cell molecular profiling. Further, we provide evidence for novel molecular mechanisms governing the neurogenic process in the mammalian brain. Thus, the data presented provide new insights into the cellular principles of hippocampal neurogenesis and identify novel mechanisms regulating the behavior of rodent and human neural stem cells.

S-38

Novel mechanisms of neurogenesis – the centrosome as a dynamic RNA processing hub in neurogenesis

Magdalena Götz

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We study the mechanisms of neurogenesis in order to implement them for neuronal repair. I will briefly summarize our work on a novel centrosomal protein, Akna, that is regulated with great precision in subsets of neural stem cells and turned off again when young neuroblasts leave the subventricular zone. This suggested high specificity in centrosome protein association which prompted us to determine the total proteome of human neural stem cells and neurons derived from human induced pluripotent stem cells. Determining the spatial proteome of the centrosome by using 10 different baits that are located at different positions at the centrosome and examining their reproducible interactors unraveled an unprecedented centrosome heterogeneity in human neural cells with 60% of all centrosome interactors so far never detected at the centrosome. This is due to the fact that no centrosome proteome of any brain cells had ever been determined and comprised novel hubs of interactors related to RNA processing. Strikingly, we observed again a 60% change between the centrosome proteome from neural stem cells to neurons. revealing and verifying novel disease candidates. Analysis of neurodevelopmental disease cohorts identified a significant overrepresentation of NSC, but not neuronal centrosome proteins with variants in patients with periventricular heterotopia (PH). Expressing the PH-associated mutant splicing factor PRPF6 reproduced the periventricular misplacement in the developing mouse brain, highlighting mis-splicing of transcripts of the MAP-kinase SAD-A at centrosomal location as essential for the phenotype. Collectively, cell-type specific centrosome interactomes explain how genetic variants in ubiquitous proteins may convey brain-specific phenotypes and highlight the yet unappreciated highly dynamic composition of the centrosome.

S-39

Functional rejuvenation of aged neural stem cells by Plagl2 and anti-Dyrk1a activity

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Regenerative potential of neural stem cells (NSCs) declines during aging, leading to cognitive dysfunctions. This decline involves up-regulation of senescence-associated genes, but inactivation of such genes failed to reverse aging of hippocampal NSCs. Because many genes are up-regulated or down-regulated during aging, manipulation of single genes would be insufficient to reverse aging. Here we searched for a gene combination that can rejuvenate NSCs in the aged mouse brain from nuclear factors differentially expressed between embryonic and adult NSCs and their modulators. We found that a combination of inducing the zinc finger transcription factor gene *Plagl2* and inhibiting *Dyrk1a*, a gene associated with Down syndrome (a genetic disorder known to accelerate aging), rejuvenated aged hippocampal NSCs, which already lost proliferative and neurogenic potential. Such rejuvenated NSCs proliferated and produced new neurons continuously at the level observed in juvenile hippocampi, leading to improved cognition. Epigenome, transcriptome, and live imaging analyses indicated that this gene combination induces up-regulation of embryo-associated genes and down-regulation of age-associated genes by changing their chromatin accessibility, thereby rejuvenating aged dormant NSCs to function like juvenile active NSCs. Thus, aging of NSCs can be reversed to induce functional neurogenesis continuously, offering a way to treat age-related neurological disorders.

P-1

Spatial genome organization during neurogenesis

Yuki Fujita

University of Pennsylvania

Gene expression regulated by spatial chromatin organization and nuclear architecture plays crucial roles in the development of the brain. We have focused on the role of the cohesin complex, which is chromosome-associated multi-subunit proteins, in embryonic and adult neurogenesis.
Cohesin is a highly conserved nuclear protein complex composed of four subunits, Smc1, Smc3, Scc3, and Scc1 (Rad21), which form a ring structure.
The cohesin complex is well known for its role in sister chromatid cohesion to maintain the proper cell cycle process, through its inclusion of the sister chromatid into its ring-like structure. However, the cohesin subunit proteins continue to be expressed in postmitotic cells, including NeuN-positive neurons. Cohesin mediates chromatin loop formation, which has a role in regulating gene expression. Loss of cohesin function causes disruptions in chromatin loops, with subsequent effects on transcriptional regulation.
Mutations that perturb the function of cohesin or the proteins that regulate cohesin function cause Cornelia de Lange syndrome (CdLS), a rare malformation syndrome characterized by mental retardation, limb abnormalities, and distinctive facial features. Most of these mutations do not cause overt defects in cohesion or chromosomal segregation.
To investigate the potential role of cohesin in terminally differentiated cells in vivo, we generated conditional Smc3-knockout mice. We observed craniofacial abnormality and decreased spine density in cortical neurons of heterozygous Smc3-knockout mice. Heterozygous Smc3-knockout mice exhibited increased anxiety-related behavior, which is consistent with a symptom of Cornelia de Lange syndrome. Thus, neuronal cohesin contributes to neural network formation, and cohesin deficiency leads to higher brain dysfunction.

P-2

Intracellular trafficking of Notch orchestrates temporal dynamics of Notch activity in the fly brain.

Miaoxing Wang, Makoto Sato

Kanazawa University

Notch signaling is evolutionarily conserved from fly to human and plays diverse biological processes. Delta acts as a ligand for Notch signaling. It activates Notch receptor only in neighboring cells (*trans*-activation) and autonomously represses Notch activity through the process of *cis*-inhibition. However, the molecular mechanism and biological significance of *cis*-inhibition remain largely elusive. The wave of differentiation in the Drosophila brain, the 'proneural wave', is an excellent model for studying Notch signaling in vivo. A previous paper in Sato lab showed that Delta expression and Notch activity is upregulated at the wave front of the proneural wave and restricts the speed of wave propagation. However, Notch is reactivated behind the proneural wave forming the twin peaks of Notch activity. In this study, we found that strong nonlinearity in *cis*-inhibition reproduces the second peak of Notch activity behind the proneural wave in silico. Based on this, we demonstrated that Delta expression induces a quick degradation of Notch in late endosomes and the formation of the twin peaks of Notch activity in vivo. Indeed, the amount of Notch was upregulated and the twin peaks were fused forming a single peak when the function of Delta or late endosomes was compromised. Additionally, we demonstrated that the second Notch peak behind the wavefront controls neurogenesis. Thus, intracellular trafficking of Notch orchestrates the temporal dynamics of Notch activity and the temporal patterning of neurogenesis.

P-3

The role of PcG in regionalization of the mouse telencephalon

Yusuke Kishi, Hikaru Eto, and Yukiko Gotoh

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During brain development, neural stem-progenitor cells (NPCs) in different brain regions produce different types of neurons, and each of these regions plays a different role in the adult brain. Therefore, precise regionalization is essential in the early stages of brain development, and irregular regionalization has been proposed as the cause of neurodevelopmental disorders. The mechanisms underlying brain regionalization have been well studied in terms of morphogen-induced expression of critical transcription factors for regionalization.
We recently revealed that Polycomb group proteins (PcG) play a key role in establishing ventral identity in the mouse telencephalon. Knockout of Ring1, an essential protein in PcG function, in neuroepithelial cells induces ectopic expression of dorsal genes, including those for BMP and Wnt ligands, as well as attenuated expression of the gene for Shh, a key morphogen for ventralization, in the ventral telencephalon. We performed RNA-seq and epigenomic profiling analyses of NPCs isolated from each brain region and found the role of PcG in region-specific gene expression in the developing mouse telencephalon.

P-4

Mechanical modeling of brain morphogenesis caused by multicellular dynamics

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The cerebrum and cerebellum have convoluted cortexes composed of highly-organized neural layers, which are closely associated with brain functions. The cortical folding is assumed to be mechanically triggered by differential growth between cortex and subcortex, where tissue growth and deformation are caused by cooperative neuronal activities, including proliferation, migration, and axon elongation. Therefore, to clarify the mechanism of how brains robustly acquire their complex structures and functions, comprehensive understanding of the spatiotemporal mechanical behavior of brain tissues and the underlying multicellular dynamics is of great importance. In this study, we have developed a mathematical model of brain morphogenesis that links tissue growth and deformation to cell proliferation and migration. The tissue growth and deformation were formulated based on a theory of continuum mechanics. The cell proliferation and migration were modeled using a balance equation for cell number density, and incorporated into the above tissue model. By utilizing the proposed mathematical model, we simulated foliation in cerebellar cortex caused by proliferation and migration of granule cells and investigated the mechanism of folia lengthening. The simulation results showed that radial migration of granule cells guided by Bergmann glial fibers, whose orientation depends on the surrounding tissue deformation, is a critical factor to produce elongated folia accompanied by a granule layer with non-uniform thickness. Our mathematical model is a promising framework to explore the emergence of brain structure and function from mechanical and biochemical viewpoints, and potentially help clarify the mechanism of various neurological diseases.

Keyword: Brain morphogenesis, Cell proliferation, Cell migration, Mathematical model, Computer simulation

P-5

Development of fluorescent indicators for visualization of N-cadherin interaction across cells

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For the formation and maintenance of tissues and organs and synaptic transmission, cell adhesion plays an essential role in multicellular organisms. At the interface of adhering cells, the intercellular interaction of adhesive molecules attracts adjacent cells. One of the adhesive molecules neural cadherin (N-cadherin) belonging to the classical cadherin family mediates Ca^{2+}-dependent cell adhesions. N-cadherin contributes to a broad range of biological processes, including ontogenesis, cell migration, neurite outgrowth, and synaptic potentiation. Despite its importance, there is a lack of suitable imaging techniques to detect these interactions. Therefore, there are difficulties to obtain spatiotemporal information, when and where N-cadherin interactions occur. To address this situation, we developed fluorescent indicators to visualize N-cadherin interaction. The indicators are composed of N-cadherin and dimerization-dependent fluorescent proteins (ddFPs). Through the interaction of N-cadherin moieties across cells, dimerization of ddFPs, which leads to fluorescence emission, is induced. Our ddFP based N-cadherin interaction indicators (ddFP-NCad) with reversible property overcome the limitations of indicators based on the irreversible reconstitution of split fluorescent proteins. We demonstrated the ability of reversible detection of ddFP-NCad by monitoring the formation and disruption of N-cadherin interaction through the approach and dissociation of the living cells. We also successfully visualized N-cadherin interactions in primary neurons and spheroids consisting of multi-layered cells. The ddFP-NCad can be applied to a wide range of specimens and could provide useful insights regarding the spatiotemporal dynamics of N-cadherin interactions in various biological processes, including the development of the neural system and higher brain functions.

P-6

Contractile oscillators regulate the spatial patterning of gut motility

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The contractile waves on the gut, called peristalsis, play an important role in effective food transport and digestion in many animals. The location where the peristaltic waves emerge is confined at specific sites of the gut, which enables effective food transport. However, the patterning mechanism remains to be elucidated. Here, we set up the Ca^{2+} imaging system (based on GCaMP6s) for the embryonic chicken guts and observed Ca^{2+} traveling waves that propagate across guts. In the mature gut, Ca^{2+} waves were associated with the contraction of smooth muscles (SMs). Interestingly, even in the younger guts which show little muscle contraction, spontaneous Ca^{2+} waves were observed. The origins of Ca^{2+} waves tend to emerge at a specific position which seems to be linked to the initiating point of peristalsis in the mature gut, therefore the Ca^{2+} waves we observed here may contribute to establishing the functional gut movement. Furthermore, we imaged Ca^{2+} waves likely derived from interstitial cells of Cajal that function as pacemakers of the peristalsis. In this meeting, we will discuss how pacemaker waves interact with the spontaneous Ca^{2+} waves in SMs to achieve functional peristalsis.

P-7

Elucidation of the internal state-dependent modulation of the nociceptive escape behavior

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Adequate behavioral responses to noxious stimuli are essential for organismal survival. *Drosophila* larvae exhibit a stereotypic rolling behavior to escape from nociceptive stimuli (e.g., attacks of a parasitoid wasp; Hwang et al., 2007). Although external environmental factors like the wing beat of the wasps facilitate the escape behavior (Ohyama et al., 2015), little is known about how it can be modulated by internal states. Here we report that the gene *belly roll* (*bero*) negatively regulates the nociceptive escape behavior, and we examine the possibility that a subset of *bero*-expressing neurons integrates environmental humidity, a factor influencing body fluid osmolality, into the modulation of the escape behavior.

We noticed that the magnitude of the escape behavior varies significantly between commonly used wild-type strains. Prompted by this finding, we performed genome-wide association analyses of the nociceptive responses and identified *bero* as a candidate gene. We found that *bero* knockdown larvae showed enhanced escape behavior upon noxious thermal stimuli. *bero* is expressed in the multiple peptidergic interneurons in the larval central nervous system, including the abdominal leucokinin neuropeptide-producing (ABLK) neurons that respond to nociceptive stimuli and modulate the escape behavior (Hu et al., 2020). To explore the physiological roles of *bero* in ABLK neurons, we first examined the neural activities of the neurons using Ca^{2+} imaging. We found that the neurons respond not only to noxious stimuli but also to extracellular osmolality, and that *bero* promotes the hypoosmolality-induced neural activities. Our preliminary data suggest that the hypoosmolality-induced activity of ABLK neurons inhibit their own nociceptive responses.

Outside of their habitat (e.g., fermenting fruit), *Drosophila* larvae cannot hide themselves from the parasitoid wasp and are also desiccated, thereby causing hyperosmolality. We discuss the possibility that the hyperosmolality-dependent facilitation of the escape behavior might promote larval survival.

P-8

Thalamocortical axons control the cytoarchitecture of neocortical layers by area-specific supply of VGF

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The adult mammalian neocortex is entirely composed of six layers of neurons, yet the laminar structure is not uniform throughout the neocortex; the thickness and cellular composition of the layers differ among cortical areas. For instance, in the sensory cortex, layer 4, which is the main recipient layer of sensory information from the thalamus, is thick and dense, whereas it is thinner in the motor area. These features are considered to be crucial for proper functions of the cortical areas, therefore the developmental mechanisms that regulate the formation of the regionally distinct laminar architecture has long been a major issue in developmental neurobiology. While some of area-specific features are controlled by intrinsic cues such as morphogens and transcription factors, the exact influence and mechanisms of action by cues extrinsic to the cortex, in particular the thalamocortical axons (TCAs), have not been fully established. Here, we investigated the influence of TCAs on cortical laminar formation by ablating TCAs from ventrobasal (VB) nucleus at birth. We found that the number of layer 4 neurons was decreased in the primary somatosensory area (S1), the target area of TCAs from VB, during postnatal stages. This was rescued by overexpression of TCA-derived secreted protein VGF in cortical layer 4 of S1. Furthermore, genetic disruption of *Vgf* resulted in a reduction of the layer 4 neuronal number in the sensory areas. Collectively, these results indicated that TCAs are required for the formation of sensory area-specific laminar structure by regulating the number of layer 4 neurons through VGF. Thus, highly site-specific axon projection, which depends on initial regional patterning of the target fields, in turn contributes to generation of further regional diversity and complexity within the target tissue.

P-9

Neuronal delamination and outer radial glia generation in neocortical development

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During neocortical development, many neuronally differentiating cells are generated at the apical/ventricular surface by the division of neural progenitor cells (apical radial glial cells, aRG). Neurogenic cell delamination, in which these neuronally differentiating cells retract their apical processes and depart from the apical surface, is the first step of their migration. We recently found that the microtubule-associated protein Lzts1 is expressed at the AJ of the apical endfeet of the nascent neuronally differentiating cells. It activates actomyosin systems with reduction N-Cadherin localization at the AJ and induces neuronal delamination. Moreover, we also found that low-level Lzts1 induces the oblique division of aRGs to generate outer radial glia (oRGs)-like cells: oRGs, also called basal radial glial cells (bRGs), are another type of undifferentiated neural progenitor cell with long radial fibers extending to the basal side, and their cell body exists in the SVZ, where they divide multiple times.
In addition to neuronal delamination and oblique division, there are various cell departure patterns from the apical surface in the developing cerebral wall. Interestingly, these diverse cellular behaviors appeared in response to the level of overexpressed Lzts1, suggesting that the various cellular departure events might be understood as a continuous phenomenon linked to common molecular mechanisms, likely as a spectrum. Our observations further suggest that some neuronal differentiation-related genes, such as Lzts1, play important roles in cell positioning and histogenesis, even in neural progenitor cells.

P-10

A FOXG1-dependent critical period for autism-associated GABAergic circuits

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Abnormalities in GABAergic inhibitory circuits have been implicated in the etiology of autism spectrum disorder (ASD). However, when and how defects in inhibitory circuit development can lead to ASD-related social behavioral impairments is unclear. Here, we utilize mouse genetics to determine how modulation of the ASD-linked gene *FoxG1* during specific developmental windows results in dysregulated GABAergic circuits and abnormal social behavior. Consistent with both duplication and haploinsufficiency of *FOXG1* observed in syndromic forms of ASD, increased or decreased *FoxG1* expression levels result in social impairments in mice but only when alterations take place in both excitatory and inhibitory populations, indicating a pre-and postsynaptic role for *FoxG1* in GABAergic circuit formation. We observe that the second postnatal week is the critical period for *FoxG1* expression to establish juvenile inhibitory circuits and to prevent subsequent ASD social phenotypes. We further show that transplantation of GABAergic precursor cells prior to this critical period ameliorates the circuit and social behavioral defects of the FoxG1 ASD model, whereas reduction in GABAergic tone via *Gad2* mutation exacerbates them. Our results provide insight into the developmental timing and inhibitory circuit mechanisms that are promising avenues for therapeutic intervention in ASD.

P-11

Parallel anatomical connections for song memories between two regions of the zebra finch higher auditory cortex

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Male zebra finches learn to sing by listening and memorizing, and then mimicking their tutor's song during the developmental critical period. The caudomedial nidopallium (NCM) and caudomedial mesopallium (CMM) comprise the zebra finch higher auditory cortex. The NCM has been evidenced as a site of tutor song memories (Yanagihara and Yazaki-Sugiyama 2016), while the neighboring CMM has been also reported to correlate with memory formation and directly project to the song motor area, HVC. It has been hypothesized that the NCM and CMM may act as parallel auditory memory places for tutor song, however the connections between these two regions and how the location of tutor song memory may change as birds develop their own song has yet to be understood. Here, we separately labeled the neurons responding to tutor song and the ones responding to bird's own song by using a newly optimized AAV-cFos TetON/TetOFF system (AAV2/9 cFos TetON-EGFP and AAV2/9 cFos TetOFF-mRFP) in both the NCM and CMM of adult male zebra finches.

Anatomical analysis has revealed the distinct neuronal populations were activated by either tutor song, bird's own song, or both in both the NCM and CMM. The proportions of the tutor song and/or bird's own song responsive neurons were not differ between the adult NCM and CMM ($n=3$ birds, $p>0.05$). Our further tracing analysis revealed tutor responsive neurons in the NCM projected to the CMM and vice versa, suggesting an important interaction between these two regions in storage of tutor song memory.

These suggest that both the NCM and CMM involve neuronal substrates of tutor song memory, and they are interacting with each other.

P-12

The neural basis for overcoming failure: a dopamine circuit facilitates switching toward new goals

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How can we eventually achieve our goals despite failures? Humans and animals have the ability to learn from failures (unsuccessful outcomes), cope with them appropriately, and move forward. This adaptive ability to overcome failure is a key to achieving a goal, ultimately maximizing the number of achieved goals. However, the neural basis of the ability is poorly understood. We developed a task in rats to precisely monitor active behavioural switching toward the next reward after failure to obtain reward, based on our previous work (Ogawa M., et al, Neuron, 2013). We then combined this task with cell-type-specific recording, dopamine measurement, and circuit-specific optogenetics. We discovered that a population of dopamine neurons in the ventral tegmental area (VTA) exhibited increased responses to unexpected failure to obtain reward (no-reward) and decreased responses to unexpected reward. This bidirectional surprise signal for no-reward was also evident in the dopamine level in the nucleus accumbents (NAc). The responses were opposite to and slower than those of the well-known reward-responsive dopamine neurons important for value-based reward seeking. The higher the responses to the failure, the faster the switching toward the next reward. The timing of the correlation became earlier when no-reward was certain earlier, suggesting that the timing of the switch was adjusted based on past experience of failure. Further, this correlation appeared even after the transition to a task in which no-reward could be processed passively, but it gradually weakened. These findings demonstrate that the dopamine circuitry from the VTA to NAc drives active switching toward new goals after failure, thereby providing the adaptive ability to overcome failure. As such, the dopamine circuitry, in cooperation with the value-based reward-seeking function, enables robust and efficient achievement of goals.

P-13

From Retrospective to Prospective: Integrated Value Representation in Frontal Cortex for Predictive Choice Behavior

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Animals must flexibly estimate the value of their actions (action-value) to successfully adapt to a changing environment. The brain is thought to estimate action-values from two different sources, namely the action-outcome history (retrospective value) and the knowledge of the environment (prospective value). How and which brain region reconciles these two different estimates of action-values to make a choice is not well understood. By combining behavior modeling with reinforcement learning and two-photon calcium imaging, here we show that as a mouse learns the state-transition structure of a decision-making task, retrospective and prospective values become jointly encoded in the preparatory activity of neurons in the anterior lateral motor (ALM) cortex. Suppressing this preparatory activity in expert mice returned their behavior to a naïve state. These results reveal the neural circuit that integrates knowledge about the past and future to support predictive decision-making.

P-14

Visual instrumental learning without primary visual cortex

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Blindsight is an ability of visually guided behavior after lesion of the primary visual cortex (V1), despite the loss of visual awareness. The ability of the visual pathways bypassing V1 has been investigated in various visual functions, but an ability to drive instrumental conditioning has not been investigated. We used macaque monkeys with unilateral V1 lesion, a model of blindsight, to investigate whether visual conditioned stimulus (CS) on the affected visual field by the V1 lesion can play a role of secondary reinforcer to drive instrumental conditioning. Here, the monkeys were required to locate a hidden target area (HA) on a blank monitor in an oculomotor search task. If monkey's gaze moved to and remained in the HA, the reinforcing visual CS was presented at an edge of the screen in a location different from the HA. Even when the CS were presented in the affected visual field, behavior to locate a HA were promoted. Not only did their gaze get into the HA more quickly as they learn, but the saccades entering the HA also converged on one or two vectors in each session. It indicates that the visual CS acted as secondary reinforcers, reinforcing both the location of HA and the vector of saccades made immediately before the CS presentation. Reinforcement learning is thought to be driven by the activity of dopamine neurons, which encode reward prediction error signals. Dopamine neurons of the substantia nigra pars compacta (SNc) in V1 lesion monkeys showed phasic responses to visual CS of hidden target area search task presented in the affected visual field. These results indicate that the visual inputs via the residual visual pathways after V1 lesions can access fundamental neural mechanisms of reinforcement learning.

P-15

Regulation of synaptic nanodomain and nanocolumn by liquid–liquid phase separation

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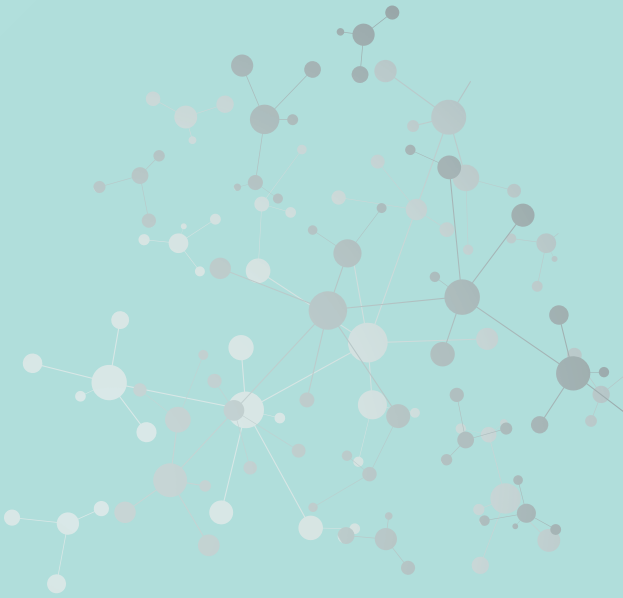
The regulation of synaptic glutamate receptors is the basis for memory formation. Observations with super-resolution microscopies have revealed an activity dependent reorganization of nanoscale segregations of glutamate receptors, so called nanodomains, at postsynaptic density (PSD). Furthermore, postsynaptic nanodomains of glutamate receptors align with presynaptic vesicle releasing sites to form a trans-synaptic nanocolumn, which regulates the efficacy of synaptic transmission. However, the mechanisms underlying the formation of nanodomain and nanocolumn remained unclear.

Here we found that calcium/calmodulin-dependent protein kinase II (CaMKII) undergoes liquid-liquid phase separation (LLPS) with NMDAR subunit GluN2B through the multivalent interaction contributed by its dodecameric structure in a calcium-dependent manner. Also, autophosphorylation of CaMKII contributes to maintain this protein condensate by locking CaMKII in an active conformation. Interestingly, the incorporation of CaMKII into *in vitro* PSD protein condensate composed of PSD-95, GluN2B and Stargazin, an auxiliary subunit of AMPAR, resulted in the formation of a core-shell structure, while CaMKII-GluN2B forms shell phase and PSD-95-Stargazin forms core phase. Furthermore, Neuroligin-1 (NLGN1), a neuronal adhesion molecule, which clusters with presynaptic neurexin, also segregates together with AMPAR. The segregation of AMPAR and NMDAR was also observed in living neuron with dual-color direct stochastic optical reconstruction microscopy (dSTORM). This segregation was disrupted by membrane-permeable CN21 (tat-CN21), a CaMKII inhibitor, which competes and disrupts CaMKII-GluN2B interaction. In addition, the segregation between NLGN1 and NMDAR nanodomains was also reduced by tat-CN21.

Taken together, these results suggest that the incorporation of CaMKII into PSD and the interaction between CaMKII and GluN2B is critical for the formation of AMPAR and NMDAR nanodomains and the trans-synaptic nanocolumn. Therefore, here we propose that calcium-induced and persistent formation of LLPS by CaMKII, as an activity-dependent crosslinker for postsynaptic proteins, can be a novel mechanism for synaptic plasticity, and serves as molecular basis of memory formation.



ASHBi
WPI Kyoto University

脳構築における発生時計と場の連携

Interplay of developmental clock and extracellular environment in brain formation

KYOTO UNIVERSITY

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