The HFSP science digest 2021

The Human Frontier Science Program (HFSP) is unique in supporting international collaboration to undertake innovative, risky, basic research at the frontier of the life sciences. Special emphasis is given to the support and training of independent young investigators, beginning at the postdoctoral level.

The Program is implemented by the International Human Frontier Science Program Organization (HFSPO), supported financially by Australia, Canada, the European Commission, France, Germany, India, Israel, Italy, Japan, New Zealand, the Republic of Korea, Singapore, Switzerland, the United Kingdom of Great Britain and Northern Ireland, and the United States of America. Since 1990, over 7000 researchers from more than 70 countries have been supported. Of these, 28 HFSP awardees have gone on to receive the Nobel Prize.

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Letter From HFSP Secretary General,
Pavel Kabat

It is with great pleasure that I announce the publication of HFSP's first Science Digest covering some of the world's most bold and pioneering research in the life sciences today. That's a big claim to make, but then this is what HFSP was chartered to do: we push the boundaries of life science research, explore unknown ideas and unproven approaches, and we do so on a global scale promoting excellence and courageous efforts by the world's most creative scientists. This is what we mean by "frontier research."

In the last two years, as we have faced COVID-19 at all levels of personal and societal life, public opinion has refocused on the vital importance of basic research. I'll venture to say that not since the 1950s and the race for space, has the general public been as riveted on the need for funding and carrying out creative, life-changing basic research. Thus, we thought it was timely and important to showcase these advancements.

In this first edition, the HFSP Science Digest presents frontier research carried out through HFSP-awarded grants and fellowships in 2021. In this edition, you'll find studies on cell biology aided by bioengineering, new inroads in the fight against cancer, and studies that explain cognition, social behavior and evolution, among other work. It is not enough to study the world around us for the benefit of all humankind – it is also vital to understand how human decision-making affects the choices we make as we live in this closed system, Planet Earth.

Indeed, if there is anything we have learned during COVID-19 and in recent decades with increasing levels of global connectivity, it's that humans are as much subject as observer. Given the mounting global challenges we face, promoting high risk, high reward research is an essential part of our ability to grow and overcome obstacles.

Whether you are a colleague to those presented in this volume, a government official, a clinician, a developer with a pharmaceutical company, or a citizen with a healthy curiosity for science, I hope you will derive inspiration and great pleasure from the work pioneered by these HFSP scientists.

Thank you for your interest in HFSP and frontier science.

Best Regards,

Pavel Kabat

3.4.2 A bridge over troubled synapses in neurological diseases

By HFSP grant team members Michisuke Yuzaki (Keio University, Tokyo, Japan), Alexander Dityatev (DZNE Magdeburg, Germany), Radu Aricescu (Cambridge University UK, RGP0065 / 2014)

Synapses, which are the connections between nerve cells, are formed, maintained, and remodeled, not only during organism development, but also throughout life by molecules termed synaptic organizers. Many neuropsychiatric or neurological disorders, such as autism spectrum disorders, schizophrenia, and Alzheimer's disease, are considered to be caused by an imbalance of excitatory and inhibitory signaling at synapses; however, there are still no therapeutic methods for directly controlling the formation of synapses with defined functional properties.

In their HFSP-funded project, **Michisuke Yuzaki** (Keio University, Tokyo, Japan), **Alexander Dityatev** (DZNE Magdeburg, Germany) and **Radu Aricescu** (Cambridge University, UK) have developed a new synthetic synaptic organizer that restores synaptic connections and improves pathological conditions of cerebellar ataxia, Alzheimer's disease, and spinal cord injury in mouse models.

This organizer, named CPTX, combines structural elements from an organiser previously developed by Yukazi's team and another synaptic protein. It can establish 'molecular bridges' that link pre-synaptic terminals to post-synaptic ion channels belonging to the AMPA receptor family. Application of CPTX to mouse models of cerebellar ataxia, Alzheimer's disease, and spinal cord injury could successfully restore glutamatergic excitatory synapses and improve motor coordination, spatial and contextual memories, and locomotion associated with these disease models, respectively.

Structure-guided design of synthetic synaptic organizers targeting distinct pre- and post-synaptic molecules may inspire the development of a variety of innovative molecular tools that can repair or remodel a wide range of neural circuits. These tools are expected to illuminate the mechanisms of synapse formation and maintenance as well as promote the development and application of new treatments for neuropsychiatric or neurological disorders.

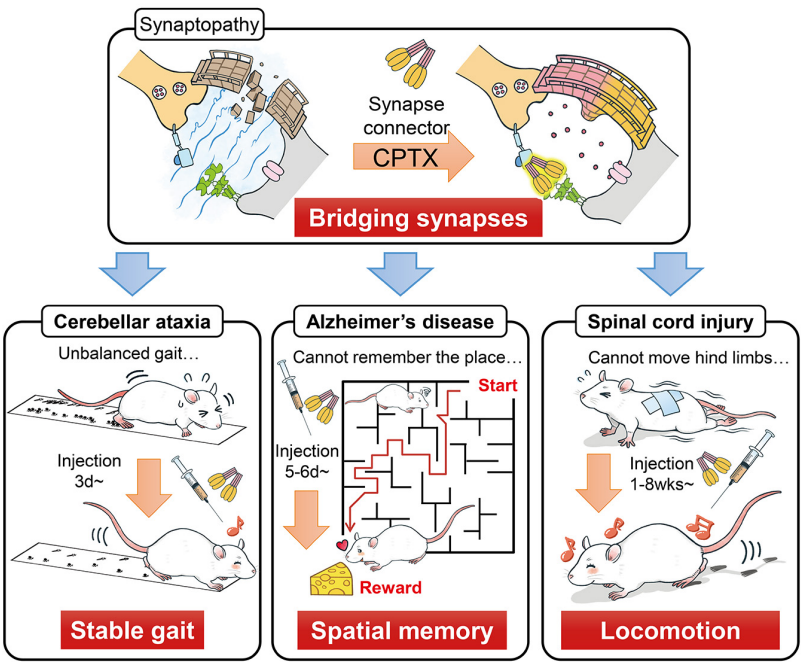

Figure 3.9: CPTX restores neural circuits and improves motor coordination and spatial memory. **A broad range of neuropsychiatric and neurological disorders are thought to be caused by abnormalities in synapses and referred to as synaptopathy (upper panel). CPTX administered to mouse models of cerebellar ataxia, Alzheimer's disease, and spinal cord injury could successfully restore synapses and improve motor coordination, spatial and contextual memories, and locomotion associated with these disease models, respectively (lower panels).**

Reference:

— Suzuki K, Elegheert J, Song I, Sasakura H, Senkov O, Matsuda K, Kakegawa W, Clayton AJ, Chang VT, Ferrer-Ferrer M, Miura E, Kaushik R, Ikeno M, Morioka Y, Takeuchi Y, Shimada T, Otsuka S, Stoyanov S, Watanabe M, Takeuchi K, Dityatev A, Aricescu AR, Yuzaki M. **(2020) A synthetic synaptic organizer protein restores glutamatergic neuronal circuits**. Science 369, eabb4853.

Link to HFSP highlight:

www.hfsp.org/hfsp-news-events/bridge-over-troubled-synapses-neurological-diseases

3.5 BEHAVIOURAL STUDIES USING NOVEL TOOLS AND METHODS

The recent years have seen developments of new methods allowing a deeper understanding of the neuronal mechanisms underlying behaviours such as avoidance of parasites, exploring a new habitat, or even body posture control. These include studies of multisensory behavioural control, but also robootics, computational methods and deep learning tools. The selected examples show that such new developments are favoured by post-doctoral fellows changing fields or by research grant teams integrating scientists from outside the life sciences.

3.5.1 How do fruit flies avoid parasitic wasps?

HFSP fellow Madhumala Sadanandappa (LT000933 / 2017-L)

Behavioural adaptation to environmental threats such as infectious diseases or predators increases the survival and fitness of an organism.

Parasitic wasps, which lay eggs in larvae and pupae, are responsible for high mortality of Drosophila. Following infection, if the host fails to mount an immune response to block the wasp's development, the wasp egg hatches and develops into an adult wasp that emerges from the Drosophila pupal case. In response to the parasitic selection pressure, fruit flies have evolved various behavioural and immunological defense mechanisms to reduce infection. Interestingly, while the parasitic wasp attacks larvae or pupae, the adult Drosophila identify the threat and modify their behaviour to decrease infection risk in their progeny.

Long-Term Fellowship awardee Madhumala Sadanandappa (Dartmouth School of Medicine, USA) asked how parental instinct is encoded in the adult flies that recognize and protect their progeny from the parasitic threat. He found that in the presence of wasps, Drosophila adult females retain their eggs and subsequently lay them in an area that is not infested with wasps. He could demonstrate that the mother's response requires both visual and parasitoid-specific olfactory cues. At the cellular level, Sadanandappa showed that this change in behaviour involves neuropeptide F (NPF) signaling in the central nervous system, which triggers retention of fully developed eggs and increases apoptosis of the developing egg chambers in the wasp-exposed ovaries, resulting in reduced egg-laying.

Interestingly, this alteration in reproductive behaviour is selective to wasps (*Leptopilina boulardi*) that infect the developing larvae, but does not occur in the presence of wasps that infect the pupae.

The outcomes of this report have broader implications in fields such as neuroethology and biocontrol.

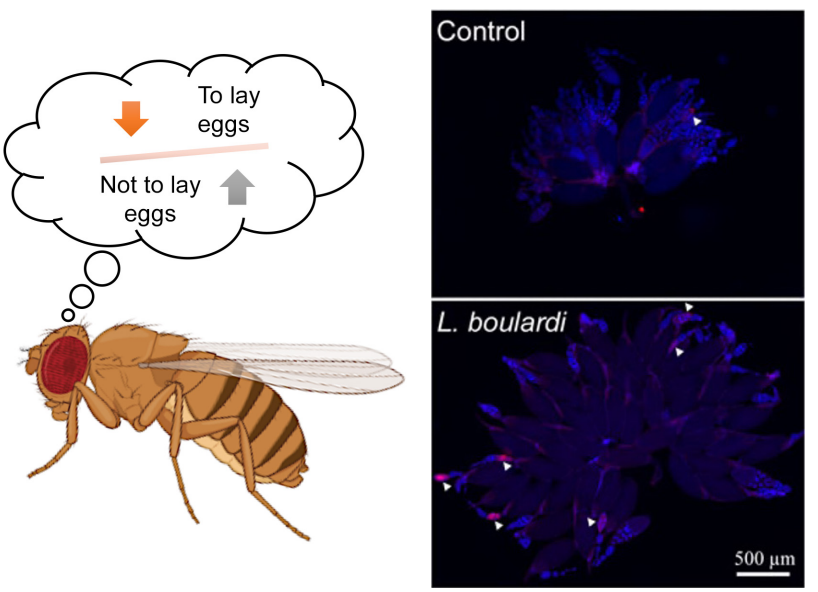

Figure 3.10: To reduce the rate of infection, Drosophila females modify their egg-laying behaviour in the presence of a parasitic wasp. Compared to controls, wasp-exposed female ovaries show retention of matured eggs and increased caspase-dependent apoptosis of the developing follicles.

Reference:

— **Sadanandappa MK**, Sathyanarayana SH, Kondo S, and Bosco G (2021) Neuropeptide F signaling regulates parasitoid-specific germline development and egg-laying in Drosophila. PLoS Genet. 17, e1009456.

Link to HFSP highlight:

www.hfsp.org/hfsp-news-events/how-do-fruit-flies-avoid-parasitic-wasps