SUSUMU TONEGAWA, PhD

Picower Professor of Biology and Neuroscience

Director, RIKEN-MIT Center for Neural Circuit Genetics (CNCG)

THE PICOWER INSTITUTE FOR LEARNING AND MEMORY

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Dear Dr. Sheinberg,

I am happy to write a strong letter of recommendation for **Dr. George Dragoi**, who is applying for Assistant Professor in the Department of Neuroscience at Brown University.

George joined my laboratory at the Picower Institute for Learning and Memory in 2003 as a Postdoctoral Associate after completing very productive Ph.D. thesis work in Gyorgy Buzsaki's laboratory at Rutgers University. This training prior to his arrival in my laboratory was almost exclusively on in vivo recording of standard (i.e., genetically unaltered) rats, and he wanted to extend this earlier training to mutant mice so that he could address at a deeper level the cellular and circuit mechanisms for hippocampal physiology relevant to learning and memory. Thus, in my lab, George initially picked a research project aimed at investigating the role of hippocampal CA3 NMDA receptors in the dynamics of place cell tuning in a novel track using the CA3-restricted NMDA receptor 1 knockout mice (CA3-NR1 KO), which was available in my laboratory. He almost single-handedly designed the experiment, obtained the CA1 place cell data and analyzed them, and found that the CA3-NR1 KO mice are significantly slower compared to the control littermates in tuning place cells upon exposure to a novel track, indicating that this receptor, and most probably the synaptic plasticity dependent on the CA3 NMDA receptors, play a crucial role in the rapid tuning of CA1 place fields under these conditions (i.e., de novo exposure to a novel environment). Interestingly, once the mice become familiarized with the novel track with intermittent rest/sleep periods and are then allowed to explore another linear track attached to the first track perpendicularly, but which had been unavailable during the earlier session due to a physical block between the two tracks, the mutant mice formed a new set of place fields in the L-shaped track as rapidly as the control littermates.

While these findings are very interesting with respect to the role of CA3 NMDA receptors in the rapid encoding of a novel space in the hippocampus, and the data will be submitted for publication, George made an even more intriguing discovery (see below) during this study with the control (i.e., genetically unaltered standard) mice—which is the reason why the submission of the NMDA mutant mice has been momentarily put aside.

According to the dominant model of hippocampal cell assembly activity, place cell firing order was established for the first time during the exploration to encode

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spatial experience, and is subsequently replayed during rest or slow-wave sleep for consolidation of the encoded sequence. But, contrary to this model, George found that temporal sequences of firing of place cells expressed during the resting or sleeping period preceding the novel experience, which we call "preplay." These results suggest that internal neuronal dynamics during resting or sleep organize hippocampal cellular assemblies into temporal sequences that contribute to the encoding of a related novel experience occurring in the future. Thus, preplay may contribute to accelerating learning when a new experience is introduced in multiple steps of increasing novelty. This work was recently published in Nature.

Because the claim of the preplay phenomenon went against the main establishment of the field, we encountered a great deal of scrutinization from some referees during the review process, which took nearly a year. During this process, George was highly resilient, conducting additional experiments and analyses, which the referees demanded. His confidence for the claim, which was the primary driving force during this grueling review period was the primary force for the final acceptance of the paper. I admire him for his resilience backed by exceptional intelligence. He is a man with a strong sense of independence—sometimes, a bit too much—but I should also quickly qualify this statement by pointing out that he commands respect from many of his peers and superiors. George has a total commitment to his academic career and is highly motivated to continue to conduct basic research at a high level. He has already demonstrated in two labs—Buzsaki's and mine—that he can accomplish very significant research, and I have no doubt that he will continue to do so.

For these reasons, I recommend his appointment to a faculty position enthusiastically and with no reservations. If I can be of more help, please do not hesitate to get in touch with me.

Sincerely,

Susumu Tonegawa
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