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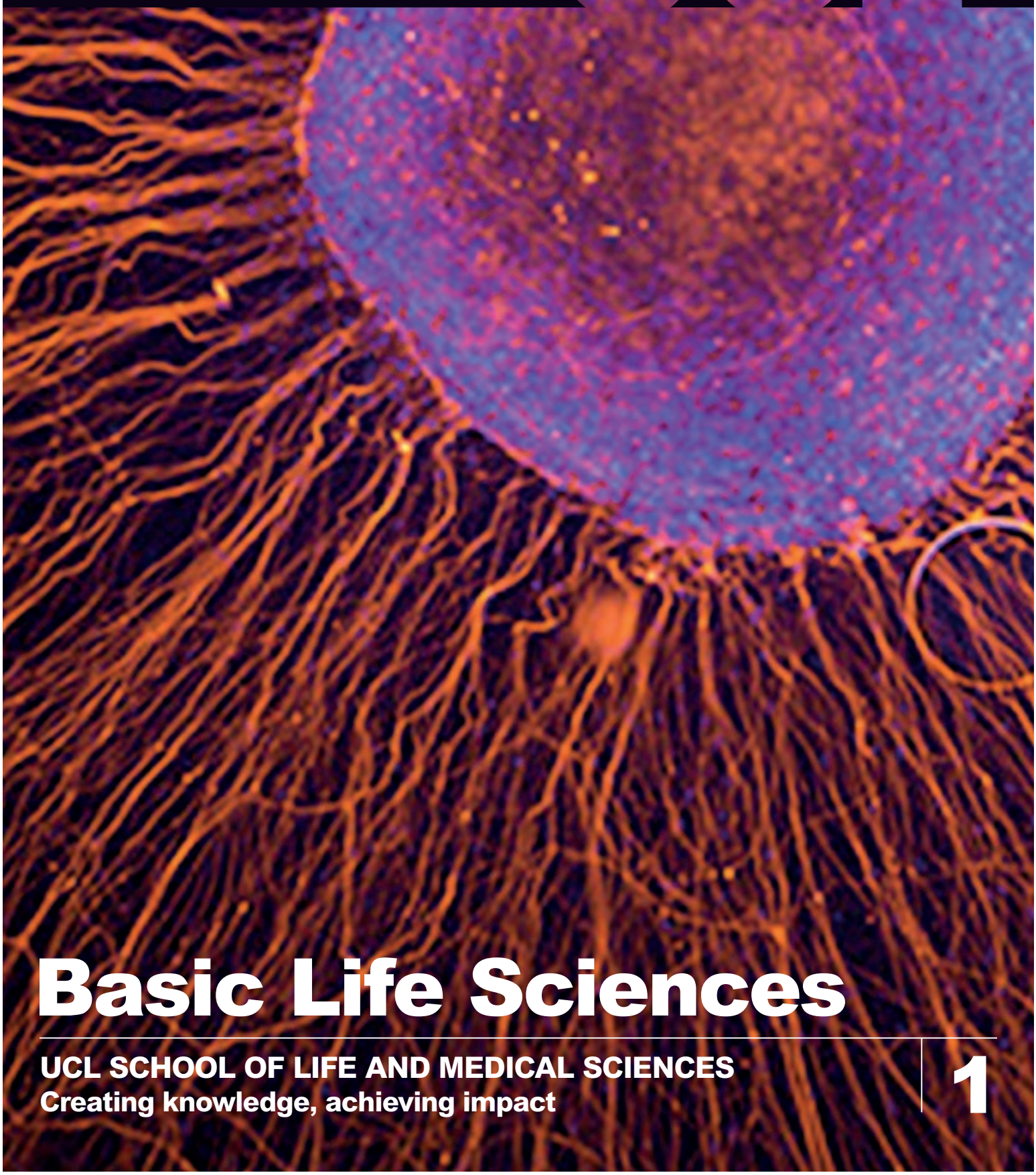

Basic Life Sciences

UCL SCHOOL OF LIFE AND MEDICAL SCIENCES
Creating knowledge, achieving impact

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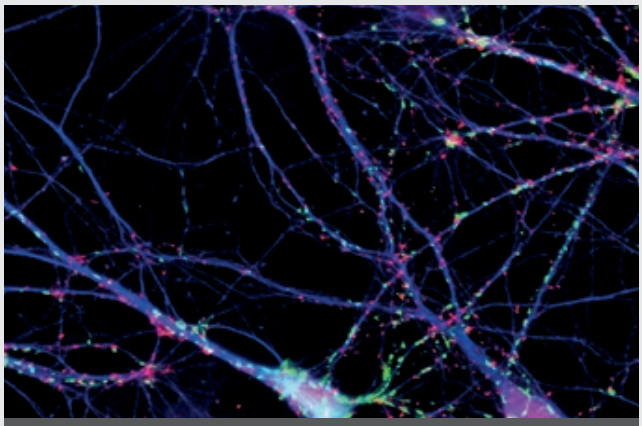

Synapses on hippocampal neurons.

WNTS BUILD A SYNAPSE

Wnt signalling has a surprising role to play in strengthening synaptic connections.

The Wnt cell signalling pathway is one of the most widely studied in biology. It has been implicated in an enormous diversity of biological processes, during development and in adult organisms. In part, this flexibility arises from the variety of both Wnt signalling proteins – around 20 in humans – and Wnt receptors. Wnt proteins repeatedly turn up in key biological processes, and **Professor Patricia C Salinas** and colleagues have recently added another – control of synaptic strength.

Wnt signalling is well known to be critical to development of the embryonic nervous system and to the formation of synaptic connections. The latest work suggests that Wnt proteins can also modulate the strength of connections after they have been established.

In 2005 Professor Salinas showed that one particular Wnt protein, Wnt7b, promoted the formation of new dendrites in cultured hippocampal cells. Furthermore, this effect depended on a specific signalling pathway, through the scaffold protein known as Dishevelled (Dvl). Later work in knockout mice revealed that Wnt7a promoted fine modelling of complex synapses in the cerebellum, again by acting through the Dvl pathway.

Recent work has expanded on these findings. In particular, Wnt7a appears to be playing a significant role in 'synaptic plasticity' – changes in the properties of synapses after they have transmitted a signal, an important factor in learning and memory.

During the formation of new synapses in the mouse hippocampus, Wnt7a signalling was found to be dependent on the Wnt receptor, Frizzled-5 (Fz-5). Furthermore, neuronal activity led to increased numbers of Fz5 receptors at the synapse, enhancing Wnt signalling.

Interestingly, Wnt7a appears to enhance connections at excitatory but not inhibitory synapses (at the latter, neurotransmitter release inhibits rather than activates neurons). These effects at excitatory synapses depended on calcium signals and the calcium/calmodulin-dependent protein kinase II, which had previously been implicated in modulation of synaptic strength.

The results suggest that Wnt7a, unlike other Wnt proteins, promotes the formation of just certain types of synapse. Potentially, abnormal Wnt function could therefore contribute to conditions in which the balance between excitatory and inhibitory signalling is disturbed, such as epilepsy.

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Artificially coloured carbon nanotubes.

CATCH THE TUBE

Carbon nanotubes are exciting new tools with many potential applications in biomedicine.

First rising to prominence in the 1990s, carbon nanotubes consist of sheets of carbon atoms rolled up into tubes just a nanometre or so in diameter. Among their many possible uses is as a delivery platform for therapeutic agents – an area where **Professor Kostas Kostarelos** and colleagues have generated highly promising results.

Although pure carbon nanotubes are insoluble, they can be chemically modified to increase their solubility. They can also have biologically active molecules chemically attached to them – anything from anti-cancer drugs to DNA for gene therapy.

Crucially, such 'functionalised' carbon nanotubes offer advantages over existing delivery technologies. In 2007, Professor Kostarelos and colleagues found that, although some nanotubes are taken up by standard endocytotic mechanisms, others penetrate the membrane directly, acting as a kind of 'nano-syringe'. This would allow material to be delivered directly into the cytoplasm – one of the major challenges in cell engineering.

This advantage is tempered somewhat by difficulties in targeting – receptor–ligand binding tends to promote endocytosis rather than direct entry. So Professor Kostarelos has looked for applications where biochemical targeting is not required, with a focus on 'small interfering RNAs' (siRNAs) to silence the expression of target genes.

One exciting possibility is delivery of siRNA to localised areas of the brain. In rodent models of stroke, for example, the approach has been used to inhibit programmed cell death after oxygen starvation, thereby limiting tissue damage and promoting recovery. And in Parkinson's disease, surgical techniques could be used to deliver siRNA directly to the dopamine-containing cells affected in the condition – a strategy being explored in collaboration with neurosurgeon Professor Marwan Hariz at the Institute of Neurology.

It remains early days for nanotube-based therapeutics. In the long term their clinical use will hinge on safety as well as efficacy, so Professor Kostarelos is also studying the fate of carbon nanotubes within the cell and in body tissues. With extensive programmes in nanoscale delivery systems, he also aims to convince others of their enormous potential. One possible use is the reprogramming of cells into a pluripotent state, bringing carbon nanotube technologies into the burgeoning area of cellular engineering.

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