

'Exciting things are going on'

The impact of AKAPs in signal transduction pathways is becoming increasingly clear. Last year's paper of Scott's team, published in *Science*, was a crucial part of that. 'In the publication we suggest that the enzymes that bind to the AKAPs are much more organised than we thought. In fact, we calculated that molecular flexibility within the AKAP-kinase complex provides sufficient reach for the tethered kinase to command a zone with the width of two to four proteins. This mechanism of action is particularly important when kinases need to be confined to the cytoskeleton or mitochondria.'

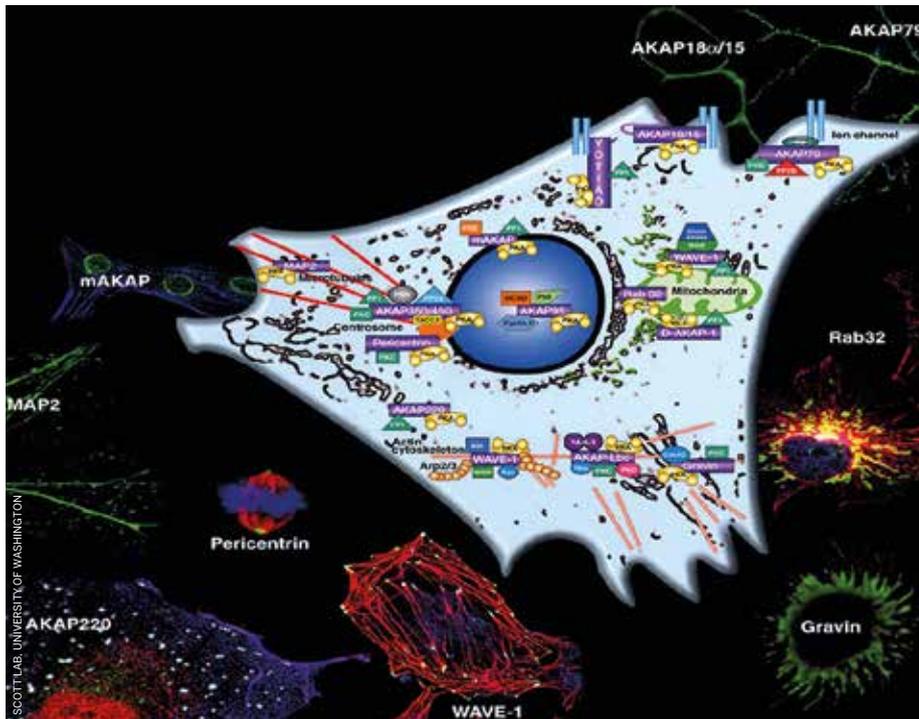
New frontier

The discovery also provides new ways for drugs to target enzymes involved in diseases. 'Most drugs on the market target the active site of a single enzyme', says Scott. 'But based on our discovery, one can design drugs that specifically target certain proteins within the AKAP-enzyme complexes. This prevents potential detrimental effects that occur when you target the enzyme everywhere in the cell.'

Scott is currently investigating how the anchoring proteins play a role in certain diseases. 'In breast cancer it turns out that one particular AKAP is upregulated in metastasising cancers cells but has low expression in stationary cells', he says. 'We are interested in how the protein is controlling cell mortality. In another project our team is studying how a combination of drugs can target specific enzymes within the AKAP complex in the case of a rare liver disease. A lot of exciting things are going on right now in this field and my friends and colleagues all over the world are embarking on this new frontier of science.' ●



LORENE LANGEBERG



Pioneering the study of anchoring proteins

Ariëns Award winner John D. Scott discovered the family of A-kinase anchoring proteins (AKAPs). These may hold the key to more specific therapeutic intervention.

Since 1985, the Dutch Society for Pharmacology (NVF) has been recognising the work of outstanding international pharmacologists with the annual Ariëns Award. It was named in honor of the Dutch professor Everhardus Jacobus Ariëns, one of the founders of the field of pharmacology. This year's winner is Professor John D. Scott of the University of Washington School of Medicine (US), appointed Edwin G. Krebs-Hilma Speights Professor.

Role in disease

Scott is best known for his identification of a new family of proteins called A-kinase anchoring proteins (AKAPs). These are

important for the organisation of signal transduction pathways inside the cell. He also deciphered their importance for the localisation of certain kinases, which will phosphorylate proteins at defined locations within the cell. The pioneering work explains why many colleagues refer to him as the 'father of his field'. Scott: 'About 25 years ago there were some indications that there were proteins that bind kinases to particular areas within the cell. My team and I systematically isolated their genes and biochemical properties. First in the context of synaptic membranes that underlie the molecular basis of learning and memory. Later, we began to investigate the role of AKAPs in other organs and tissues, like the cardiovascular system.'