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EDITORIAL

John Squire: a leader and seminal contributor to experimental and theoretical muscle research for over 50 years

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This collection of papers aims to recognise and celebrate the life and scientific achievements of Professor John Michael Squire. A Memorial Meeting was held in his honour on 17 March 2022 at Imperial College London, and this brought together many eminent scientists from around the world. Many originated from the muscle field, but others came from related areas of research. Each had collaborated with or had been greatly influenced by John over the course of many years, and a selection of these scientists kindly agreed to write up their talks for this special issue.

John Squire was internationally renowned for his insights into the structural basis of muscle contraction. He performed cutting-edge research, both experimental and theoretical, over a very productive research career spanning some 51 years. During this time, he made world-leading contributions on the structure and function of muscle, and these include the steric blocking model of thin filament regulation (with David Parry) and a general model for the packing and assembly of myosin molecules in thick filaments. In addition, John was a prolific writer and editor of books and special issues of scientific journals that significantly advanced the fields of both muscle and fibrous protein research.

David Parry's association with John Squire goes back to the 1960s when both were undergraduates and PhD students at King's College in London. They met up again in 1971 in Oxford and collaborated on a model that explained how thin filament regulation might occur. In their concept they suggested that the movement of tropomyosin over the thin filament could allow or block myosin head binding (Parry 2022). This led to a ground-breaking paper that remains central to current understanding and which remained one of John's most important scientific contributions.

In 1971 John proposed a general model to explain the construction of all myosin thick filaments. Only very recently, however, has the technology been developed that has allowed his ideas to be verified. In so doing Ken Taylor used cryo-EM to examine in stunning detail the structure of insect flight muscle thick filaments. In his review (Taylor 2023), Ken discusses the molecular structure of the backbone of the myosin molecules and shows how the predictions of John's theoretical models have held up remarkably well in light of the new experimental findings.

One of the first projects that John Squire undertook when he joined Imperial College London in the early 1970s, was to elucidate the structural basis of the superlattice arrangement of myosin crossbridges that Hugh Huxley had predicted by X-ray diffraction of skeletal muscle (Huxley and Brown 1967). He assigned this challenging PhD project to Pradeep Luther. In his review with Rick Millane, Pradeep describes how the superlattice basis was indeed uncovered leading to the no-3-alike rules and the statistical superlattice (Millane and Luther 2023). Rick also describes his fortuitous meeting with John in the 1990s that led to his fascination with the superlattice arrangement and in recognising a parallel common phenomenon in physics (Millane and Luther 2023).

John introduced to the muscle community the use of cryosections of striated muscle to study its ultrastructure in scintillating detail (Sjostrom and Squire 1977). In their original paper, John's proteges, Pradeep Luther and Ed Morris, describe the cryo-electron microscopy analysis of refrozen cryosections of mammalian cardiac muscle to obtain insight

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into the structure and action of myosin binding protein C (Huang et al. 2023). Their sub-tomogram averaged images reveal the binding of MyBP-C to actin and the path of titin along the myosin filament backbone.

John and Ed Morris supervised Danielle Paul's PhD work on the single particle analysis of vertebrate thin filaments and the structure and orientation of the troponin complex. This formed the basis of Danielle's more recent work where she and her PhD student Marston Bradshaw, with John's continued involvement, used Volta phase plate cryo-EM data to analyse the structure of cardiac thin filaments from zebrafish. In their original paper, Bradshaw et al. describe this novel use of zebrafish cardiac thin filaments as a model for studying mutations leading to hypertrophic cardiomyopathy (Bradshaw et al. 2023).

Nancy Curtin and Tim West worked in the same department as John in the Faculty of Medicine at Imperial College London when he moved there from the Department of Physics in 1999. They describe in their original paper the energetics of striated muscles in catsharks (West et al. 2022). They discuss the high efficiency of the red slow fibres during routine swimming. John and Pradeep Luther studied the slow and fast fibres and made the startling discovery that in these cartilaginous fish, the slow muscle thick filaments were arranged on a simple lattice and the fast muscle thick filaments on a superlattice (Luther et al. 1996).

Steve Marston reflects on John's key role in elucidating the steric blocking mechanism of striated muscle regulation. The regulation of heart contractility to enable relaxation is called lusitropy. Steve reviews the role of PKA phosphorylation of Troponin I in affecting lusitropy (Marston 2022). He discusses the use of molecular dynamics simulations together with cryo-EM and NMR techniques to study the lusitropic effect.

The thick filament protein, myosin binding protein-C, is an important protein in cardiac muscle as mutations are a leading cause of inherited hypertrophic cardiomyopathy. It is a rod-shaped protein composed of 11 immunoglobulin and fibronectin type 3 domains. John had a great interest in this protein and collaborated with Lata Govada and Naomi Chayen to crystallise and solve the structure of one domain, C1, to a resolution of 1.55 Å. In their mini-review, Lata and Naomi describe the role of crystallography in structure determination of muscle proteins (Govada and Chayen 2023).

In addition to his seminal work on muscle, John made a significant contribution to the structural basis of vascular permeability. His collaborators, Charles Michel and Kenton Arkill describe his role, how the project was initiated at Imperial College in the early 2000s and restarted in Bristol in 2010. They review the structure of the endothelial glycocalyx and the state of the field at the present time (Arkill et al. 2022).

While no collection of papers can really cover the influence and achievements made by any one individual, in this case John Squire, it is to be hoped that his contributions as a scientist, as a mentor to his students, other team members and colleagues, as a conference organiser, writer and editor, and as a loving husband, parent and grandfather will remain with us. He deserves nothing less.

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