



## Professor Clive Orchard

Emeritus Professor

### Area of research

Regulation of cardiac-contraction coupling

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### Summary

My research is focused on cardiac excitation-contraction coupling and its regulation. Using a variety of techniques (for example voltage clamp, fluorescent ion indicators, whole cell and confocal microscopy, immunohistochemistry, RT-PCR and computer modelling) we are investigating how the rise of intracellular  $Ca^{2+}$  that causes contraction is initiated, and how it is regulated by intracellular 2nd messenger pathways. A particular interest is the role of the t-tubules (invaginations of the surface membrane of cardiac ventricular myocytes) in this process. We have recently developed a technique that allows us to physically and functionally uncouple the t-tubules from the surface membrane, enabling us to investigate their function.

Using this technique we have been able to show that the t-tubules form a specialised region of the cell membrane for ion handling: many of the key proteins involved in excitation-contraction coupling are found predominantly at the t-tubules, and the regulation of these proteins appears to be better coupled to second messenger pathways at the t-tubules than at the surface membrane. This work not only helps our understanding of cardiac cell function, but may also be important in understanding heart failure, in which t-tubule density decreases and ion channel expression and regulation are altered. We are also interested in how a variety of physiological and pathophysiological interventions, such as beta adrenergic stimulation and acidosis, alter excitation - contraction coupling and hence cardiac cell function.

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### Activities / Findings

- Tonic phosphorylation by PKA- and CamKII-dependent phosphorylation of L-type  $Ca^{2+}$  channels, which are localised at t-tubules, maintains I<sub>Ca</sub>
- $Ca^{2+}$  efflux from the sarcoplasmic reticulum via the  $Ca^{2+}$  ATPase occurs only at t-tubules
- Inhibition of either the NCX or SERCA blocked both spontaneous  $Ca^{2+}$  transients and action potentials in the AVN pacemaker

### Skills

- arrhythmia
- hypertension

### Methodologies

- Molecular Biology
- PCR
- $Ca^{2+}$  imaging

- Immunocytochemistry
- Immunohistochemistry
- Electrophysiological recording

## Memberships

### Organisations

[School of Physiology, Pharmacology & Neuroscience](#)

### Other sites

- [Bhi](#)

### Research Areas

- [Ion channels and cardiac function](#)

### Selected publications

- Du, C, El Harchi, A, Zhang, Y, Orchard, C & Hancox, J, 2011, '[Pharmacological Inhibition of the hERG Potassium Channel Is Modulated by Extracellular But Not Intracellular Acidosis](#)'. *Journal of Cardiovascular Electrophysiology*, pp. in press
- Chase, A & Orchard, C, 2011, '[Ca efflux via the sarcolemmal Ca ATPase occurs only in the t-tubules of rat ventricular myocytes](#)'. *Journal of Molecular and Cellular Cardiology*, vol 50., pp. 187 - 193
- Du, C, El Harchi, A, McPate, M, Orchard, C & Hancox, J, 2011, '[Enhanced inhibitory effect of acidosis on hERG potassium channels that incorporate the hERG1b isoform](#)'. *Biochemical and Biophysical Research Communications*, vol 405., pp. 222 - 227
- Orchard, C, Brette, F, Chase, A & Fowler, M, 2011, '[Role of the t-tubules in the response of cardiac ventricular myocytes to inotropic interventions](#)'. in: U Ravens, M Sanguinetti, O Tripathi (eds) *Heart Rate & Rhythm*. Springer

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### Recent publications

- Kong, CHT, Bryant, SM, Watson, JJ, Roth, DM, Patel, HH, Cannell, MB, James, AF & Orchard, CH, 2019, '[Cardiac-specific overexpression of caveolin-3 preserves t-tubular I<sub>Ca</sub> during heart failure in mice](#)'. *Experimental Physiology*, vol 104., pp. 654-666
- Kong, CH, Bryant, SM, Watson, JJ, Gadeberg, HC, Roth, DM, Patel, HH, Cannell, MB, Orchard, CH & James, AF, 2018, '[The Effects of Aging on the Regulation of T-Tubular I<sub>Ca</sub> by Caveolin in Mouse Ventricular Myocytes](#)'. *Journals of Gerontology, Series A*, vol 73., pp. 711-719
- Bryant, S, Kong, C, Watson, J, Gadeberg, H, Roth, DM, Patel, H, Cannell, M, James, A & Orchard, C, 2018, '[Caveolin-3 KO Disrupts T-Tubule Structure and Decreases T-Tubular I<sub>Ca</sub> Density in Mouse Ventricular Myocytes](#)'. *AJP - Heart and Circulatory Physiology*, vol 315., pp. H1101-H1111
- Bryant, SM, Kong, CH, Watson, JJ, Gadeberg, HC, James, AF, Cannell, MB & Orchard, CH, 2018, '[Caveolin-3 dependent loss of t-tubular I<sub>Ca</sub> during hypertrophy and heart failure in mice](#)'. *Experimental Physiology*, vol 103., pp. 652-665
- Kong, C, Rog-Zielinska, E, Kohl, P, Orchard, C & Cannell, M, 2018, '[Solute movement in the t-tubule system of rabbit and mouse cardiomyocytes](#)'. *Proceedings of the National Academy of Sciences of the United States of America*, vol 115., pp. E7073-E7080
- Lewis, M, Szobi, A, Balaska, D, Khaliulin, I, Adameova, A, Griffiths, E, Orchard, CH & Suleiman, MS, 2018, '[Consecutive isoproterenol and adenosine treatment confers marked protection against reperfusion injury in adult but not in immature heart: A role for glycogen](#)'. *International Journal of Molecular Sciences*, vol 19.

[View complete publications list](#) in the University of Bristol publications system

### Networks & contacts

- Jules Hancox - Bristol
- Andrew James - Bristol