Professor Mark Cannell
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Chair in Cardiac Cell Biology

Area of research

Computing and seeing a new solution to problems in the heart

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Summary

The bulk of my research has focussed on Ca signalling in cardiac cells, but I have also developed experimental and computational methods that are widely used in other biomedical research. I am probably best known for the discovery of Ca sparks, which are fundamental to thinking about (cardiac) Ca signalling. In subsequent work we described how the stochastic nature of Ca spark production and 'local control theories' can explain the voltage- and time-dependence of the Ca transient (which I first measured in 1987 after developing real time fluorescent Ca measurement in single cells in 1985).

By measuring Ca in single cells under voltage clamp, I also showed that Na-Ca exchange is the primary Ca extrusion system in ventricular muscle in 1990 (refuting the prevailing dogma that resting Ca was regulated by Ca ATPase).

We eventually developed a formalism for measuring EC coupling 'gain' based on Ca spark measurements and this was used to show a defect in microscopic EC coupling in heart failure. I suggested that this might arise from a reduction in co-localization between L-type Ca channels and sarcoplasmic reticulum Ca release channels, an idea that is steadily gaining importance with subsequent work showing disease-induced changes in the sub-cellular topology of the t-system in animal models and in human heart failure.

While stochastic Ca spark recruitment can explain the voltage- and time-dependence of the Ca transient, the key problem of Ca release termination has resisted our understanding for more than 20 years. We have recently proposed a new mechanism called 'induction decay' which provides a robust explanation for the termination of cardiac Ca release (Laver et al., (2013 J. Mol. Cell Cardiol. 54: 98–100). Therefore, in principle, the cellular basis of cardiac excitation-contraction coupling – from the initiation of Ca release to its termination – is now more clearly understood as a direct result of the research work I have enjoyed doing with many collaborators over the past ~30 years. With abundant evidence that defects in EC coupling and Ca cycling are major contributors to heart failure, the medical relevance of this basic science research is, I think, clear.

I also use detailed mathematical models to test hypotheses and enjoy developing new techniques and instruments.

Activities / Findings

My recent work has focussed in 4 main areas:

1) To clarify how Ca release from the intracellular Ca store is regulated

2) To improve methods for measuring local Ca signalling in cells -especially cardiac mycoytes

3) To apply high resolution imaging to clarifying how proteins are organized in the cardiac cell and how this orgnization affects function.

4) to try to undertsand how modufying electrical signalling can be exploited to improve contractility of the failing heart while also reducing the risk of sudden death.

Keywords

- Calcium imaging
- Heart muscle
- Muscle function

Memberships

Organisations

School of Physiology, Pharmacology & Neuroscience

Bristol Heart Institute

Other sites

- Bhi

Research Areas

- Ion channels and cardiac function

Selected publications

- Cannell, MB & Shang, W, 2014, 'Imaging Ca2+ Nanosparks in Heart with a New Targeted Biosensor'. *Circulation Research*, vol 114., pp. 412-420
- Laver, DR, Kong, HT, Imtiaz, M & Cannell, MB, 2013, 'Termination of calcium-induced calcium release by induction decay: An emergent property of stochastic channel gating and molecular scale architecture'. *Journal of Molecular and Cellular Cardiology*, vol 54., pp. 98-100
- Cannell, MB & Kong, HT, 2012, 'Local control in cardiac excitation-contraction coupling'. *Journal of Molecular and Cellular Cardiology*, vol 52., pp. 298-303
- Kong, HT, Laver, DR & Cannell, MB, 2013, 'Extraction of sub-microscopic Ca fluxes from blurred and noisy fluorescent indicator images with a detailed model fitting approach'. *PLoS Computational Biology*, vol 9., pp. 1-10

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Recent publications

- Cannell, M & Cox, G, 2019, 'Multiphoton microscopy'. in: Guy Cox (eds) *Fundamentals of fluorescence imaging*. Jenny Stanford Publishing Pte. Ltd., Singapore, pp. 63-80
- Cannell, M, Soeller, C & Baddeley, D, 2019, 'Practical aspects of localization microscopy'. in: Guy Cox (eds) *Fundamentals of fluorescence imaging*. Jenny Stanford Publishing Pte. Ltd., Singapore, pp. 347-381
- 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_{Ca} during heart failure in mice'. *Experimental Physiology*, vol 104., pp. 654-666
- Vicente, SL, Doray, A, Hancox, J & Cannell, M, 2018, 'Regulation of Kv4.3 and hERG potassium channels by KChIP2 isoforms and DPP6 and response to the dual K^+ channel activator NS3623'. *Biochemical Pharmacology*, vol 150., pp. 120-130
- Rog-Zielinska, E, Kong, CHT, Zgierski-Johnston, CM, Verkade, P, Mantell, J, Cannell, M & Kohl, P, 2018, 'Species differences in the morphology of T-tubule openings in cardiomyocytes'. *EP-Europace*, vol 20., pp. iii120-iii124
- 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

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