Human Cardiac Tissue Models to Understand and Target Macrophage-Mitochondrial Communication in Failing Hearts

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Background

Heart failure is a common and complex syndrome with diverse aetiologies that converge on common pathological pathways. The elucidation and modulation of these shared pathways has been instrumental in developing current foundational therapies licensed across the full spectrum of disease. One universal and maladaptive feature of failing hearts that remains untargeted therapeutically is *cardiac mitochondrial dysfunction and energetic deficit*, which is tightly linked with adverse outcomes and symptom severity. Recent evidence from our labs and others establishes key roles for cardiac macrophages in sustaining cardiac mitochondrial health, with evidence of human relevance and maladaptive reprogramming in heart failure.

To gain mechanistic insights with human relevance, sophisticated humanised model systems are needed to probe macrophage-cardiomyocyte interactions while preserving patient-specific genetic backgrounds and tissue architecture. We have established an advanced human cardiac tissue system incorporating key cell types like cardiomyocytes and macrophages providing an ideal and state-of-the-art foundation to interrogate the role of macrophage-mitochondrial dynamics in the context of human heart failure.

The successful applicant will be based at the Oxford Organoid Hub, which is equipped with a range of excellent cell culture and imaging systems optimised for cell work. You will lead on the construction and experimental profiling of humanised cardiac tissue, incorporating genetic and environmental bases of heart failure. You will quantify macrophage-mediated mitochondrial transfer and clearance dynamics in real-time using live imaging probes and characterize the molecular mechanisms by which macrophage mitochondrial dysfunction affects cardiomyocyte health and function in vitro. You will also have access to single cell and spatial atlases from failing human hearts to cross-reference findings for translation.

Elucidating fundamental mechanisms of macrophage-mitochondria dynamics will yield novel therapeutic targets, while also establishing a framework to model immunometabolic crosstalk in humanised cardiac tissue. Ultimately, successful reprogramming of macrophages to rejuvenate mitochondrial health would represent an entirely new paradigm for heart failure treatment.

1.Nicolas-Avila et al, PMID: 32937105 2.Margara et al, PMID: 36577774 3.Psaras et al, PMID: 38095849

Supervisor's recent relevant publications

Lewis

Energetic basis for exercise-induced pulmonary congestion in heart failure with preserved ejection fraction
Burrage MK, Hundertmark M, Valkovič L, Watson WD, Rayner JJ, Sabharwal N, Ferreira VM, Neubauer S, Miller JJ, Rider OJ and **Lewis AJM**
Circulation. 2021;144:1664–1678

Retained metabolic flexibility of the failing human heart
Watson W, Green P, **Lewis AJM**, Arvidsson P, De Maria G, Arheden H, Heiberg E, Clarke W, Rodgers C, Valkovic L, Neubauer S, Herring N, Rider O
Circulation 2023; 148:109-123

Neutrophils incite and macrophages avert electrical storm after myocardial infarction
Grune J, **Lewis AJM**, Yamazoe M, Hulsmans M, Rohde D……Ellinor P and Nahrendorf M
Nature Cardiovascular Research 2022;1(7) 649-664

Recruited macrophages elicit atrial fibrillation
Hulsmans M, Schloss M, Lee I, Bapat A, Iwamoto Y, Vinegoni C, Paccalet A, Yamazoe M, Grune J, Pabel S, Momin N, Seun Hg, Kumowski N, Pulous F, Keller D, Bening C, Green C, Lennerz J, Mitchell R, **Lewis AJM**, Casadei B, Iborra-Egea O, Bayes-Genis A, Sossalla S, Ong C, Pierson R, Aster J, Rohde D, Wojtkiewicz G, Weissleder R, Swirski F, Tellides G, Tolis G, Melnitchouk S, Milan D, Ellinor P, Naxerova K, Nahrendorf M
Science 2023; 381:231-239

Simões

Lin HC, Makhlouf A, Vazquez Echegaray C, Zawada D, **Simões F.C.#** (2023). *Programming human cell fate: overcoming challenges and unlocking potential through technological breakthroughs*. Development
150(24):dev202300.

Reyat JS, di Maio A, (...), Psaila B, **Simões F. C.**, Rayes J, Khan AO. (2023). *Modelling the pathology and treatment of cardiac fibrosis in vascularised atrial and ventricular cardiac microtissues*. Front Cardiovasc
Med. 10:1156759.

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PMC6992796.

Simões, F.C.# and Riley, P.R.# (2022). *Immune cells in cardiac repair and regeneration.* Development 149 (8): dev199906.

Weinberger, M.*, **Simões, F.C.***, Gungoosingh T, Sauka-Spengler T, Riley PR. (2024). *Distinct epicardial gene regulatory programs drive development and regeneration of the zebrafish heart.* Developmental Cell S1534-5807(23)00692-5.

Toepfer

Zhang Y, Tan CMJ, **Toepfer CN**, Lu X, Bayley H. *Microscale droplet assembly enables biocompatible multifunctional modular iontronics.* Science. 2024;386(6725):1024-30. Epub 20241128. doi: 10.1126/science.adr0428. PubMed PMID: 39607936.

Margara F, Psaras Y, Wang ZJ, Schmid M, Doste R, Garfinkel AC, Repetti GG, Seidman JG, Seidman CE, Rodriguez B, Bueno-Orovio A & **Toepfer CN**. *Mechanism based therapies enable personalised*

treatment of hypertrophic cardiomyopathy. Sci Rep. 2022;12(1):22501. Epub 20221228. doi: 10.1038/s41598-022-26889-2. PubMed PMID: 36577774; PMCID: PMC9797561.

Psaras Y, Margara F, Cicconet M, Sparrow AJ, Repetti G, Schmid M, Steeples V, Willcox JA, Bueno-Orovio A, Redwood C, Watkins H, Robinson P, Rodriguez B, Seidman JG, Seidman CE, **Toepfer CN.** *CalTrack: High Throughput Automated Calcium Transient Analysis in Cardiomyocytes.* Circ Res. 2021. Epub 2021/05/22. doi: 10.1161/CIRCRESAHA.121.318868. PubMed PMID: 34018815.

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