Polyaromatic hydrocarbons (PAHs) and cardiovascular (CV) health

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Background

Low molecular weight (MW) PAHs like phenanthrene (Phe), as seen below in figure 1, are responsible for causing CV system dysfunction in fish and mammals. PAHs are found in or generated from combustion of fossil fuels and organics. Human exposure generally occurs via PAH adsorption to airborne PM2.5 pollution. Phe has direct effects on the CV system via excitation-contraction (EC) coupling and reactive oxygen species (ROS), as well as indirect effects via immune cell activation.

Immune response

Phe induces systemic Th1 response from exposure site resulting in production of pro-inflammatory cytokines by immune cells. Immune cell build-up contributes to atherosclerosis.

EC coupling

Phe inhibits L-type Ca^{2+} channels, decreasing cardiac contractility and prolonging action potential (AP) duration in fish, as seen in figure 4. This can lead to the phenotypes seen in figure 2.

ROS

PAHs activate NADPH oxidases which induce ROS formation. ROS contribute to inflammation, endothelial damage and atherosclerosis. Specific pathways of ROS production and related CV damage are again yet to be fully understood in range of mammalian models.

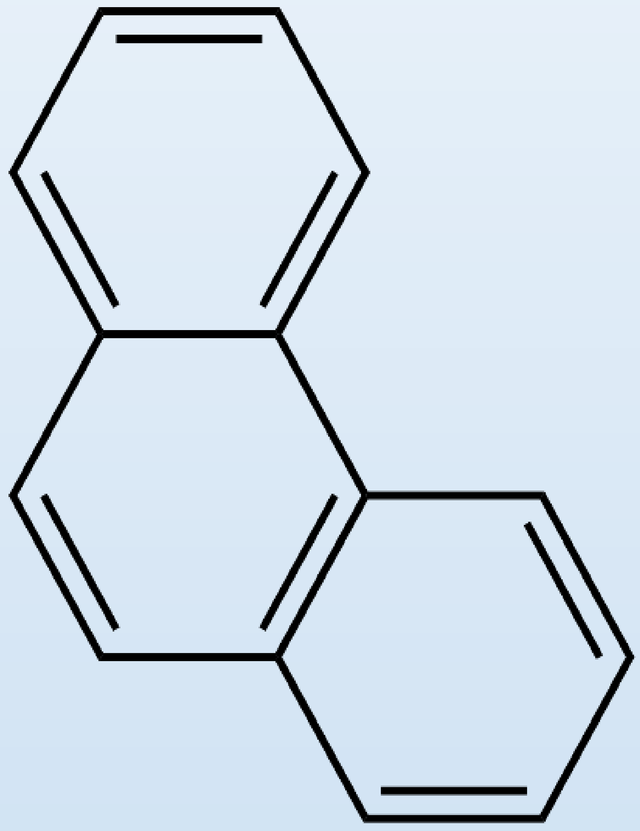

Figure 1. Chemical structure of phenanthrene.

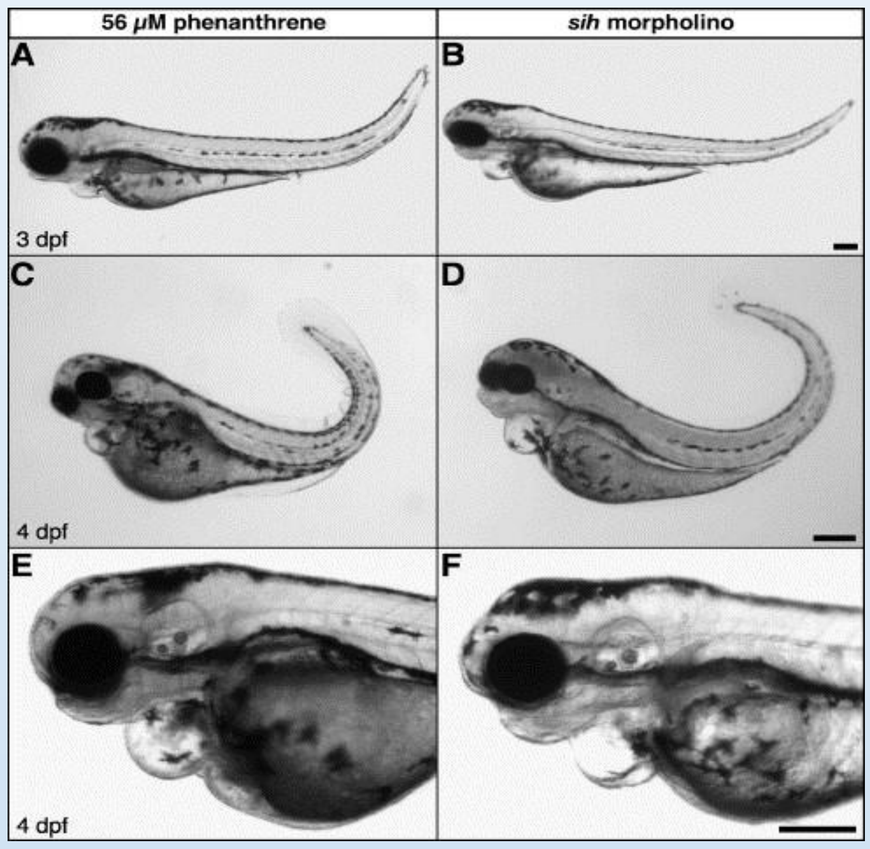

Figure 2. Phenanthrene effects on zebrafish larvae. Phe was found to cause almost identical malformations in zebrafish larvae as that induced by gene knockouts [1].

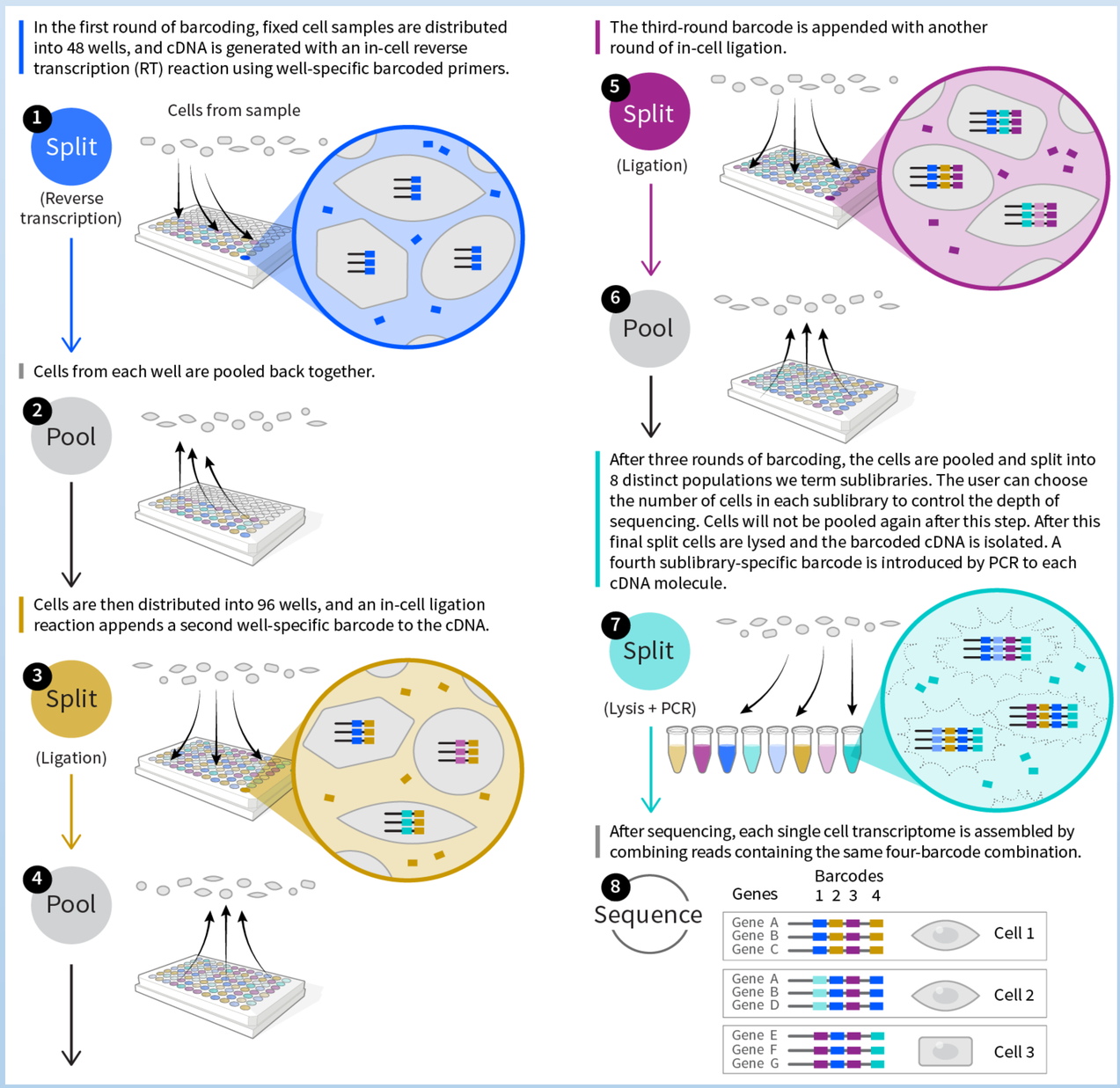

Figure 3. snRNA sequencing protocol. Taken from Parse Biosciences Single Cell Transcriptome Kit.

Programme and Methodology

Firstly, we will gain an understanding of changes in gene expression in mouse cardiac tissue following Phe exposure using snRNA-seq. This genomic profiling will reveal the long-term effects of PAHs at the expression level in cardiac tissue. The snRNA-seq process is outlined in figure 3.

Secondly, inflammatory and oxidative stress responses to Phe will be examined in human cell culture. Cytokine production, generation of damage-associated signals and ROS will be measured across a variety of cell types including macrophages, eosinophils and human-induced pluripotent stem cells. We will use a variety of techniques including IHC/ICC, RT-qPCR and flow cytometry.

In and ex-vivo analysis of chronically Phe-exposed mice will measure changes in CV electrical function, arrhythmogenic propensity, contractility, heart rate, AP duration, ion channel function and more. To help contextualise our findings, a real tire-wear PAH sample (Emissions Analytics) will be used in addition to pure Phe in as many experiments as possible.

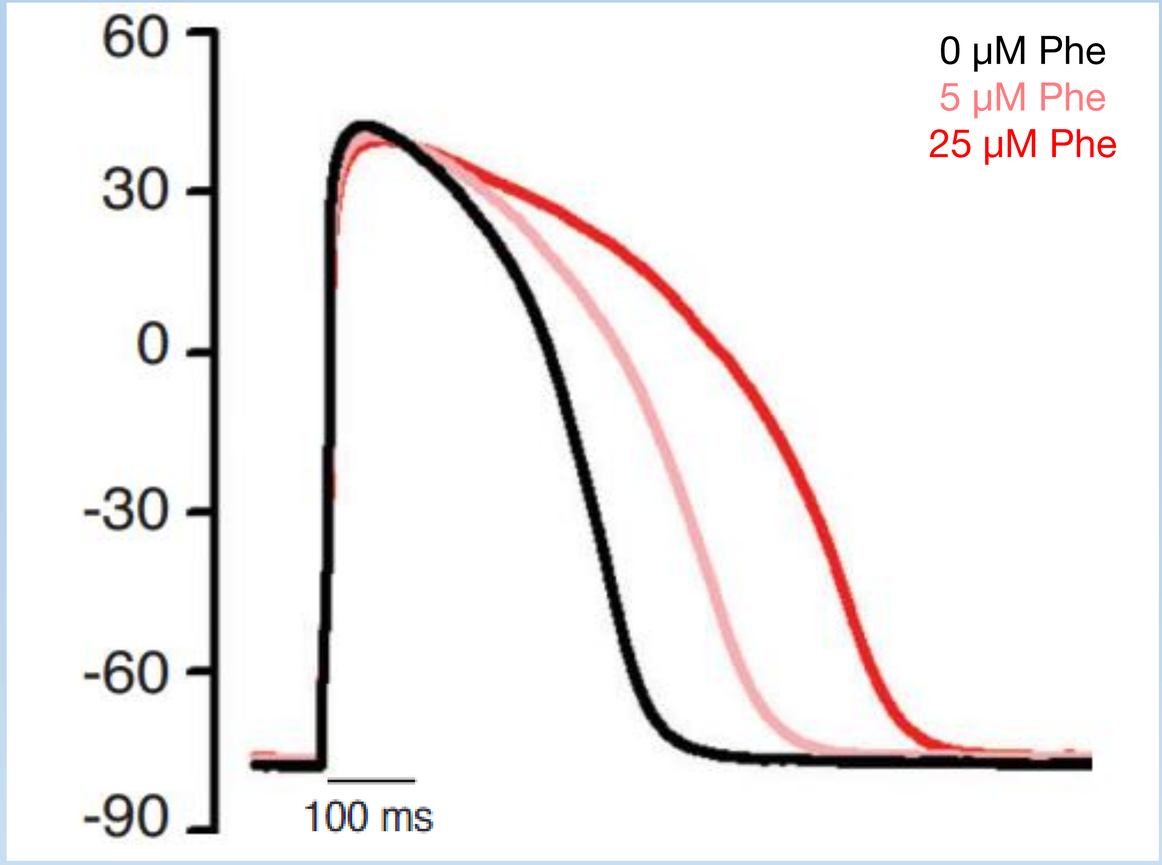

Figure 4. Prolongation of AP duration seen in bluefin tuna ventricular myocytes following 0 μM (black), 5 μM (pink), and 25 μM (red) phenanthrene exposure [2].

Responsible innovation and policy

This project has scope to inform environmental policy, such as shifting WHO-recommended guidelines by detailing mechanisms by which ambient air pollution may damage CV health. However, changing such policies could have knock-on impacts on the energy and transport sectors and may disproportionately affect those in the developing world. All work will strictly adhere to the Animals (Scientific Procedures) Act 1986 with establishment, project and personal licences in place.

References

[1] Incardona, J.P., Collier, T.K., & Scholz, N.L. (2004). Defects in cardiac function precede morphological abnormalities in fish embryos exposed to polycyclic aromatic hydrocarbons. Toxicology and Applied Pharmacology, 196(2), 191-205. https://doi.org/10.1016/j.taap.2003.11.026.

[2] Marris, C. R., Kompella, S. N., Miller, M. R., Incardona, J. P., Brette, F., Hancox, J. C., Sørhus, E., & Shiels, H. A. (2020). Polyaromatic hydrocarbons in pollution: a heart-breaking matter. The Journal of Physiology, 598(2), 227–247. https://doi.org/10.1113/JP278885