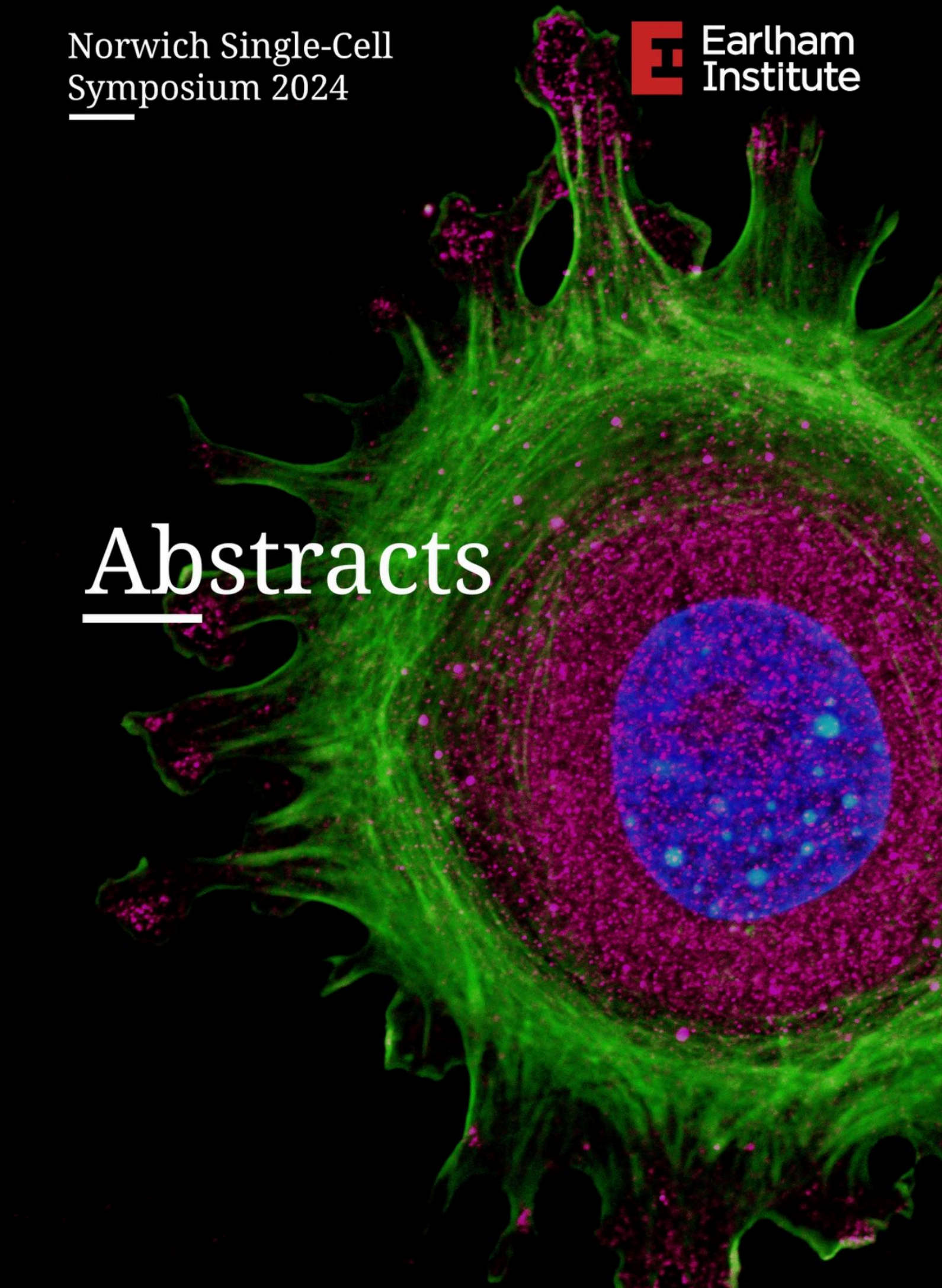
Norwich Single-Cell Symposium 2024

Earlham Institute



Abstracts

Genomics at the intersection of microbial communities and single cells

Tanja Woyke (Keynote Speaker)
DOE Joint Genome Institute

Microbial and viral diversity remains largely unexplored in laboratory settings. This underscores the continued importance of cultivation-independent methods for studying the genetic make-up of microbial and viral dark matter across diverse ecosystems. Metagenomics and single-cell sequencing are indispensable tools in microbiome research, offering insights into both the microbial identities present and the potential functions. In this presentation, I will discuss several studies conducted in my lab that use these approaches. While we use shotgun metagenomics, our focus also extends beyond traditional bulk techniques, as we try to find the needles in the haystack. To achieve this, we employ sorting and genome sequencing of individual environmental cells, using labelled probes or substrates as bait for targeted capture and investigations. Additionally, we explore genome sequences of microeukaryotes at the single-cell level, treating them as micro-consortia that may host bacterial endosymbionts or viral entities like giant viruses or virophages. This holistic approach helps us make predictions about inter-organismal interactions in the wild.

Using long reads to understand complexity and specificity of the transcriptomes.

Ana Conesa (Keynote Speaker)
Institute for Integrative Systems Biology

Long-read sequencing allows the capture of full-length transcripts in one read and the technology has been used to profile transcriptome diversity and isoform usage both in bulk and single-cell settings.

One recurrent aspect of the technology is the discovery of novel transcripts. However, these findings are compromised by the inaccuracy of the technologies and the presence of biological noise.

In my talk I will discuss the current work of my lab to unravel the potential of long-read sequencing to accurately resolve transcriptome complexity and cell-type specific isoform expression. Our results suggest that the community needs to re-think the definition of transcriptomes as a combination of proprietary and shared transcript models.

Long-read single-cell sequencing and its application to health and disease

Adam Cribbs (Invited Speaker)
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford

Adam Cribbs leads a computational biology team with a broad interest in systems biology, immunology and epigenetics. Research in the Cribbs lab is premised on the conviction that deepening our grasp of gene, protein, and biological pathway regulation is pivotal for unravelling the complexities of disease mechanisms. This foundational knowledge is expected to pave the way for identifying innovative therapeutic targets aimed at disease treatment. The methodologies employed by the Cribbs lab are applied to investigate various primary and secondary bone cancers, including multiple myeloma and Ewing's sarcoma. Notably, the lab has developed an array of tools for probing the biological underpinnings of these conditions. Among these, long-read single-cell sequencing stands out as a critical technique that offers substantial insights into the biological dynamics at play.

Abstract

Adam will deliver a comprehensive presentation on the applications and utility of long-read single-cell sequencing, emphasising its potential to yield profound biological insights. He will elucidate the significant advantages and inherent limitations of this technology, alongside strategies to mitigate these constraints. Through empirical evidence, he will demonstrate how long-read single-cell sequencing offers an enriched perspective on biological processes, facilitating the discovery of novel targets within Multiple Myeloma, a bone marrow cancer. This presentation aims to underscore the transformative impact of long-read single-cell sequencing in advancing our understanding of complex diseases.

Single-cell and spatial transcriptomics analysis of megakaryocytes in the healthy bone marrow

Sonia Fonseca[1] (Invited Speaker), Yuxuan Lan[1], Andy Goldson[1], Edyta Wojtowicz[1]
1 - Earlham Institute, Norwich Research Park, Norwich, Norfolk, NR4 7UZ, UK

Megakaryocytes (MKs) are highly polyploid, bone marrow and lung resident cells, producing more than 1 million platelets every second. They are a very diverse population of 2n-128n polyploid cells. To date, very few studies have investigated the cellular and molecular features associated with the *in vivo* polyploidisation process in mammals. Therefore, single-cell resolution analysis is key to provide biological insights into the cellular heterogeneity of MKs when studying the intrinsic and extrinsic factors determining their function.

Current single MK isolation protocols do not record information about cell morphology, limiting the discrimination of MKs containing/attached to neutrophils or platelets decorating other cells. We established robust MK isolation methods and obtained good quality single MK transcriptomes which provided unprecedented insight into the markers expressed by mature MKs, like *Mpig6b* or *Lrrc32*. We are using this dataset to provide a deeper understanding of the transcription regulation in polyploid genomes and consequences for function.

MKs reside in different anatomical locations, thus they are exposed to different conditions in terms of oxygen concentration, presence of pathogens and neighbouring cells. However, after single-cell isolation, the information about these extrinsic factors derived from the spatial context is lost. To study the influence of the microenvironment on MKs, we are using spatial transcriptomics, which allow us to investigate niches supporting polyploidization *in vivo* and cellular organisation within tissues.

Mapping Wheat Reproductive Development with Spatial Transcriptomics

Katie Long[1] (Invited Speaker), Ashleigh Lister[2], Max Jones[1], Nikolai Adamski[1], Chen Ji[1], Philippa Borrill[1], Wilfried Haerty[2], Jun Xiao[3], Xuemei Liu[3], Yuanrong Pei[1], Susan Duncan[1], Anna Backhaus[1], Iain Macaulay[2], Cristobal Uauy[1]

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At the beginning of its development, the inflorescence of *Triticum aestivum* starts as relatively uniform meristematic tissue. From this, complex structures arise during growth including the spikelets and floral organs, guided in part by spatially restricted gene expression. Despite initiating first, basal spikelets lag in their development, resulting in rudimentary basal spikelets and the characteristic 'lanceolate' shape of wheat. This trait is under genetic control, with an intron rearrangement and partial deletion of *VEGETATIVE TO REPRODUCTIVE TRANSITION 2* (*VRT-A2)* leading to a delayed initiation of spikelet meristems and increased rudimentary basal spikelets. The genetic regulation that balances the transition between vegetative and reproductive growth, and in turn leads to this effect, requires further characterisation. Through MERFISH (multiplexed error-robust fluorescence in situ hybridisation), we spatially resolve the expression patterns of 300 key genes to sub-cellular resolution in developing wheat spikes. With a particular focus on the genetic programme patterning the apical-basal axis of development, we show the localisation of spatially restricted gene expression networks, in addition to quantifying ectopic expression patterns in developmental mutants.

Using and learning from single cell atlases

Irene Papatheodorou (Invited Speaker)
Head of Data Science, Papatheodorou Group, Earlham Institute

Cell atlases represent comprehensive catalogues of cell types and their molecular characteristics within a given organism or tissue. These atlases, often constructed using single-cell RNA sequencing (scRNA-seq) technology, provide invaluable insights into cellular heterogeneity and function. With the availability of many different atlases available for a variety of species and conditions, it is now possible to utilise them in various fields, including developmental biology, immunology, and disease research. In this talk, I will discuss the different problems we work on and computational tools we develop to use available cell atlases in order to identify cell type abundance in diseases, pathogenic cell types, or explain anatomical relationships between species from different evolutionary distances.

HyDrop, an open-course droplet microfluidics platform for single-cell genomics

Koen Theunis (Invited Speaker)
Laboratory of Computational Biology, KU Leuven

Single-cell assays, such as transposase-accessible chromatin sequencing (ATAC-seq) and RNA-seq, are used extensively to create cell type atlases for a wide range of organisms, tissues, and disease processes. While current single-cell technologies enable parallel processing of hundreds to thousands of cells or nuclei, enhancing scalability, cost-efficiency, and assay customization remains essential.

The advent of microfluidics, exemplified by the widely adopted commercial platform from 10X Genomics, has revolutionized high-throughput single-cell processing. However, to further broaden accessibility, lower costs, and tailor assays to specific research needs, custom droplet microfluidics offer complementary solutions.

Therefore, we previously introduced HyDrop, an adaptable and open-source droplet microfluidic platform and demonstrated a significant improvement in throughput and sensitivity compared to previous open-source droplet-based scRNA-seq assays. Furthermore, with HyDrop-ATAC we introduced the first open-source droplet microfluidic assay for scATAC-seq. Now with HyDrop-v2, we further enhanced sensitivity and sequencing efficiency. Our platform provides a flexible and cost-effective solution for researchers to explore single-cell genomics.

Single cell transcriptomic analysis of the bone marrow niche during emergency haematopoiesis

Henry Xu (Invited Speaker)
Imperial College London

Haematopoiesis is a dynamic process by which mature blood and immune cells are generated throughout life. It is a hierarchical process that is sustained by a rare population called haematopoietic stem cells (HSCs).

HSCs contain functionally heterogeneous subsets in terms of their propensity for lineage-biased differentiation (Challen et al., 2010; Sanjuan-Pla et al., 2013). Stresses can induce different subsets of HSC to become transiently proliferative to replenish the blood compartments, in a process known as emergency haematopoiesis. (Baldridge et al., 2010; Essers et al., 2009; Ito & Suda, 2014; Sanjuan-Pla et al., 2013; Wilson et al., 2008). Leukaemia, viral infection, chemo- and radiotherapy can lead to platelet depletion. This induces specific emergency haematopoiesis, in which a subset of Lin^- $Sca1^+$ $c\text{-}Kit^-$ (LSK) $CD48^-$ $CD150^{high}$ HSCs (LT-HSCs or SLAM-HSCs) characterized by the expression of von-Willebrand factor (Vwf) is activated. Vwf^+ HSCs are megakaryocyte-platelet lineage-biased (Sanjuan-Pla et al., 2013). A recent study from our group has shown that the IL-$1R^+$ subset of $LepR^+$ perivascular niche cells in the central bone marrow stimulate Vwf^+ HSC to re-plenish platelets in response to acute platelet depletion (Luis et al., 2023).

During this conference, I will present the research findings which explored the precise molecular cross-talk between the $LepR^+$ perivascular cells and HSCs in response to platelet depletion stress.

Profiling ovarian development through single-cell RNA-sequencing analysis of paediatric ovaries

Authors: **James Ashcroft[1] (Selected Abstract)**, Luz Garcia-Alonso[1], Kevin Troulé[1], Cecilia Icoresi Mazzeo[1], Carmen Sancho-Serra[1], Nilay Kuscu[2], Valentina Lorenzi[3], Kenny Roberts[1], Callum Tromans-Coia[3], Elizabeth Tuck[1], Faranaz Auckburally[2], Elena Prigmore[1], Iva Kelava[1], Virginie Uhlmann[3], Suzannah Williams[2], Roser Vento-Tormo[1].

Ovarian development is poorly understood, principally because it starts in utero and is ongoing in many mammals for several decades. Understanding the changes that occur in ovarian tissue across the lifespan, including seminal events such as the transition from a non-ovulatory pre-pubertal ovary to an ovulatory post-pubertal ovary, are critical for understanding ovarian health and dysregulation.

In this study, we used single-cell RNA-sequencing to profile the transcriptome of pre-pubertal and post-pubertal ovarian cortex tissue. We computationally harmonised these datasets to create a single-cell atlas of ovarian development. We identified transcriptional clusters that delineate the cellular landscape of the human ovary, revealing new insights into specialised cell states that play a unique role in ovarian architecture and function. We identify granulosa cell compartments at various stages of follicular development, outlining dynamic changes arising during follicle formation, maturation, and regression. For the first time we reveal previously unreported cell subsets, including unique theca and stromal cell states, that are involved in a complex network of ovulatory signalling and oocyte maintenance. The interactions of these cell types, defined by their expression of complementary surface receptors and ligands, was interrogated revealing core regulatory programmes that control ovarian homeostasis.

This comprehensive mapping of ovarian cells not only enhances our understanding of ovarian biology, but also lays the groundwork for future studies on ovarian disorders including infertility and cancer. By uncovering the molecular signatures of ovarian cell types, this study opens new avenues for promising advancements in targeted therapeutic strategies and diagnostic markers for women's health.

Applying Single-nucleus Transcriptomics and Biosensor Imaging to Investigate Dormancy During Seed Development

William Bezodis[1] (Selected Abstract), Xiaochao Chen[1,2], Steve Penfield[1]

[1]Department of Crop Genetics, John Innes Centre, Norwich Research Park, Colney Ln, Norwich, NR4 7UH, United Kingdom

[2]Present address: Xianghu Lab, Hangzhou, Zhejiang, China

Seed dormancy refers to viable seeds not germinating despite permissive environmental conditions, and it is influenced by maternal environmental conditions during seed development. Low maternal temperatures during reproductive development have a strong dormancy-promoting effect on the progeny seeds in the model plant *Arabidopsis,* although the mechanism for this remains unclear. We have generated a single-nucleus RNA-seq dataset of developing fruits (containing the next generation as seeds) to investigate the responses of different zygotic and maternal tissues to temperature and dormancy. This is allowing us to investigate responses to temperature by specific maternal and zygotic tissues and dormancy-specific responses in the *lhp1* genotype which is non-dormant independently of temperature. In particular, tissue-specific signatures of nitrate and hormone signalling and transport may be particularly important. This is combined with single cell measurements of the dormancy-promoting plant hormone ABA, measured using a nuclear-localised fluorescent biosensor. These data, with the combination of single-cell transcriptomics and hormone levels, provide insights into maternal-filial communication during seed development and the intergenerational transmission of environmental information. We hope to use these data to gain a more complete picture of how dormancy is controlled during seed development and how the mother communicates environmental information to control the physiology of her progeny. Single cell approaches are particularly crucial due to the many small but important tissues with diverse functions, and the multiple genotypes and ploidies present that cannot easily be separated for whole-tissue approaches.

Analysis of single-cell somatic copy number variations in the brains of Parkinson's disease patients and healthy controls

Zeliha Gözde Turan (Selected Abstract), Ester Kalef-Ezra, Dominic Horner, Caoimhe Morley, Diego Perez-Rodriguez, Zane Jaunmuktane, Jonas Demeulemeester, Fritz Sedlazeck, Christos Proukakis

Parkinson's disease (PD) is the most common neurodegenerative movement disorder with partly unexplained etiology. The heritability of PD is ~30%, leading to further research into other potential contributors, such as somatic copy number variations (CNVs). To determine the role of CNVs on PD pathology, we generated and analyzed low-coverage single-cell whole genome sequencing data. We focused on neuronal (NeuN-positive) and non-neuronal (NeuN-negative) cell types from the cortex of three PD patients, three age-matched controls, and one individual with incidental Lewy body disease (ILBD). Out of the 532 analyzed cells, 90% passed the quality control criteria. Additional brains are being processed. The percentage of cells with at least one CNV was highest in the ILBD case (43.8%), followed by controls (14.1%), and then PD patients (7.6%) ($p<0.001$). Notably, in PD, the number of NeuN-negative cells with at least one CNV is 3.39 times greater than that of NeuN-positive cells ($p=0.004$). In contrast, this ratio is 1.37 for the control group ($p=0.37$). These findings suggest that neurons in PD might be more susceptible to the CNV load, potentially resulting in increased cell death. This could have significant effects on both the progression and severity of the disease. This study contributes to a better understanding of complex PD pathology and opens new avenues for further research into the factors influencing PD.

Grants: This research was funded in whole by Aligning Science Across Parkinson's [564669] through Michael J. Fox Foundation for Parkinson's Research.

Single-cell analysis in forensic science - the SCAnDi project:

Vanda Knitlhoffer, Lesley Ives, Andrew Goldson, Katherine Brown, Nick Dawnay, George Zouganelis, Michael Chen, Ardhendu Behera, Lorna Dawson, **Iain Macaulay (Selected Abstract).**

DNA profiling is a powerful technique in forensic science. However, the interpretation of samples arising from multiple contributors remains a significant hurdle, requiring computational deconvolution of the mixed DNA profile after it is generated.

DNA is transferred, and persists, as both cellular and acellular material. When DNA is recovered from a sample, any cellular material is lysed, resulting in a mixture of both cellular and acellular DNA molecules, and a complete loss of information of what cell the DNA originated from. In a forensic setting, linking cell phenotype linked with single-cell DNA analysis could be used to link DNA profiles with the tissue of origin (blood, sperm, or different epithelial cell types). This cell-of-origin information could be critical in deconvoluting mixed samples - especially higher order mixed samples, ascribing a narrative to where a DNA molecule came from, when it was transferred and by whom and resolving a major challenge for complex mixed samples.

In the SCAnDi project we are using single-cell approaches to study DNA transfer and persistence, linking cell-of-origin information with the DNA profile of the same cell, with the goal of identifying DNA profiles of specific individuals in cases where there are complex, mixed DNA profiles. We are using the BD S8 Discover to enable parallel cell isolation and phenotyping, linking this with whole genome amplification and DNA profiling using NGS approaches to link cell type with genetic identity of the contributor. In this presentation I will outline initial results from the project as well as a perspective on future developments.

Investigating the transcriptome and epigenome of embryonic hematopoiesis at single cell resolution

Authors: **Lydia Pouncey[1,2] (Selected Abstract)**, Emily Smith[1], Yuxuan Lan[2], David Swarbeck[2], Wilfried Haerty[2], Andrea Münsterberg[1], Iain Macaulay[2], Gi Fay Mok[1]

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Abstract (max 250 words): Cis-regulatory elements play a pivotal role in the intricate orchestration of gene expression and the precise determination of cellular lineage. In a developing embryo, the first hematopoietic stem cells (HSCs) are of mesodermal origin, and arise from the lateral plate mesoderm (LPM), undergoing an endothelial-to-hematopoietic transition (EHT), to become HSCs. However, the potential regulation of cis-elements and gene regulatory networks (GRNs) involved during the embryonic development of the vascular system remains largely unexplored. To address this question, we perform single-cell multiomic sequencing for the transcriptome (RNA-seq) and accessible chromatin (ATAC-seq) in embryonic day 1 (E1) and E2 chick embryos. We construct an initial atlas for the two developmental stages using well-established markers to identify different cell types. We further characterise the chromatin accessibility landscapes from the onset of gastrulation through to definitive and primitive hematopoiesis. We also find potential cis-regulatory elements associated with key hematopoietic genes such as Tal1, Gata2, Runx1 and Lmo2. Interestingly, we are able to identify putative transcription factor motifs within these elements. Collectively, we provide a valuable resource to understand early epigenome changes in embryogenesis.

Constructing a cross-species knowledge graph of the cell type pattern of gene expression

Yuyao Song[*1] **(Selected Abstract)**, Alvis Brazma[1], Irene Papatheodorou[*1,,2]

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Computational comparison of single cell expression profiles cross-species uncovers similarities and differences between cell types. Importantly, it offers the potential to refine evolutionary relationships based on gene expression. Our previous benchmark revealed that current data integration strategies are limited by the assumption of orthologs equivalency, and lose context given by non-orthologs. Here, we devise a novel analytical framework to redefine the analysis paradigm. We robustly classify genes by expression specificity and distribution across cell types to decode species batch effects. We revise the ortholog conjecture by evaluating the degree of class conservation among orthologs. We develop a contextualised similarity measurement of cell types by considering species-unique cell type specific genes. We consolidate gene classification results into a knowledge graph, allowing hierarchical depiction of cell types and orthologous groups to continuously integrate new data.

Comparative Analysis of Single-Nuclei Sequencing Reveals Cell Type Dynamics and Gene Rewiring in Nine Monophyletic Flaveria Species during C4 Photosynthesis Evolution

Authors: **Tianshu Sun1 (Selected Abstract)**, Leonie H. Luginbuehl1, Julian M. Hibberd1
1Department of Plant Sciences, University of Cambridge, United Kingdom

Compared with the ancestral C3 state, the C4 pathway allows higher photosynthesis rates due to reduced photorespiration. Water and nitrogen use efficiencies are also increased. Originating independently in over 60 lineages, C4 photosynthesis involves alterations to leaf anatomy and biochemistry that allow CO2 to be concentrated around RuBisCO. Most commonly this involves segregating photosynthesis genes between mesophyll and bundle sheath cells. Among the diverse lineages that have independently evolved C4 photosynthesis, the Flaveria genus stands out as a valuable resource, as it encompasses closely related species exhibiting C3, C3–C4 intermediate, C4–like, and C4 traits. Through an initial comparison of single-nuclei RNA sequencing (snRNA-seq) and single-cell RNA sequencing from protoplasts, we found that snRNA-seq captured more precise transcriptional profiles and a better representation of all cellular identities in the leaf. We then applied snRNA-seq to generate comprehensive cell-type-specific transcriptome atlases for nine monophyletic Flaveria species, including species that use C3, C3-C4, C4-like, or C4 photosynthesis. Our analysis revealed dynamic changes in cellular composition in mature leaves of Flaveria species as the C4 pathway evolves. Additionally, our data suggest that the evolution of the C4 pathway involves the compartmentalization of a specific set of genes, rather than the creation or loss of particular cell types in closely related species.

Unveiling cellular composition and gene signatures in melanoma for clinical outcome prediction

Lead author: **Vathrakokoili-Pournara(1) (Selected Abstract)**, Supporting Authors: Cardenas Galindo Paula Andrea(1,2), Brazma Alvis(1), Papatheodorou Irene(1,3)

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Immunotherapy has emerged as a promising avenue in the management of stage III melanoma post-surgical resection, yet recurrence remains a challenge despite available adjuvant systemic therapies. The efficacy of immunotherapy depends significantly on the intricate interplay among cells within the tumour microenvironment. Consequently, understanding the cellular composition of melanoma and the mechanisms underlying metastasis and therapeutic resistance is vital. Our study employed a comprehensive approach involving deconvolution of bulk expression data and single-cell RNA sequencing to infer cellular composition across six distinct melanoma cohorts. Our analysis unveiled substantial inter-sample heterogeneity in cell types, indicating diverse tumour microenvironments among patient subgroups. We identified a subset of patients harbouring tumours enriched in immune cells, correlating with improved overall survival outcomes. Leveraging single-cell and deconvolution results, we employed a composition-aware differential expression analysis to pinpoint genes serving as potential biomarkers attempting to separate genes associated with change in composition from genes whose change is owing to their distinct functional roles in the disease process. This carefully selected set of genes holds promise for effective patient stratification and accurate prediction of therapeutic response.

Single Cell Expression Atlas: a curated, standardised and multispecies single-cell data resource to facilitate scientific discoveries

Authors: Nancy George, Silvie Fexova, Alfonso Munoz Fuentes, Pedro Madrigal, Yalan Bi, Haider Iqbal, Upendra Kumbham, Nadja Francesca Nolte, Lingyun Zhao, Anil S Thanki, **Iris D Yu (Selected Abstract)**, Jose C Marugan Calles, Karoly Erdos, Liora Vilmovsky, Sandeep R Kurri, Anna Vathrakokoili-Pournara, Irene Papatheodorou, and Alvis Brazma

The Single Cell Expression Atlas (https://www.ebi.ac.uk/gxa/sc) is EMBL-EBI's knowledgebase for gene expression and localisation at the single-cell level. It provides standardised re-analysis results on curated, high-quality scRNA-seq datasets. Datasets are selected from public genomics archives, and include studies from hallmark projects like the Human Cell Atlas, the Fly Cell Atlas, and the COVID-19 Data Portal. The analysis pipeline utilises open-source tools for quantification, aggregation, and downstream processing, and its workflows are available in public repositories. The Single Cell Expression Atlas web application allows users to explore all available datasets via gene and metadata searches. In particular, the cell type wheel feature provides an enhanced metadata search capability that can facilitate the discovery, comparison, and broad understanding of gene expression profiles in particular cell types within specific organs and/or diseases. Individual experiments can be explored using a cell plot coloured by cell cluster membership, and a heatmap of marker genes that confer cluster identity. Experiments with high-quality metadata can also be visualised with interactive cell-level anatomograms and cell type gene expression heatmaps. Currently, the resource has 355 datasets containing a total of 10.5 million cells and representing 21 species of animals, plants, fungi, and protists. With a variety of high-quality datasets and various exploration options, the Single Cell Expression Atlas is a resource that can aid in scientific discovery