South Coast Biosciences

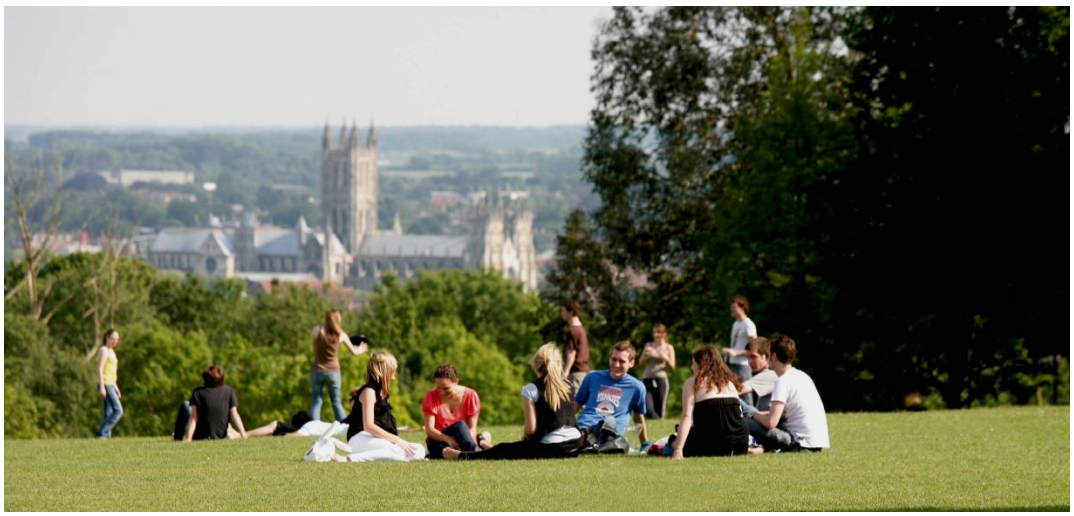
Doctoral Training Partnership

Programme, Abstracts & Networking Information

2024 Annual Conference

Hosted by the University of Kent

Tuesday 16th to Thursday 18th of April 2024



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Programme at a glance

Time	Session	Chair/Speaker	Location
Tuesday 16th April			
14:00-15:30	Thesis Writing workshop (yr4)	Profs Louise Serpell (Sussex)	Sibson LT2
14:30-15:30	Data management module Year 1 (in person)	Dr Rob Ewing	Sibson PC room 1
16:00-17:00	Plenary Talk: *'Nanotechnologies for Cell Manipulation'* Chaired by Johanna Fish	Dr Ciro Chiappini (Kings College London)	Sibson LT1
17:00-18:30	Reflexivity for the Biosciences: "Winning@Life" A session to help identify and celebrate your successes.	Dr Jenny Tullet (Kent)	Kennedy SR1
19:00	Dinner & networking catchup with academic leads from your institution		Dolche Vita (Keynes college)
Wednesday 17th April. Non-Case students.			
9:00-10:00	3-Minute Thesis (Year 2)		Sibson LT1 Chairs: William Edwards & Simon Thundow
10:00-10:40	Poster session (Year 3) and coffee		Sibson Foyer
10:40- 12:30	10-minute talks (Year 4)		Sibson LT1 Chairs: William Edwards & Simon Thundow
12:30- 12:40	Short intro to Personal Development plans		Sibson LT1
12:40- 13:30	Lunch incorporating Personal Development Plan Discussions		Sibson Foyer
13:30- 14:30	*I did it my way: An unconventional path to success in academia*	Sara Rankin – Imperial College London	Sibson LT1 Chaired by Johanna Fish
14:30- 15:00	Coffee		Sibson Foyer
15:00-16:30	10-minute talks (Year 4)		Sibson LT1 Chaired by Jo Haszczyn and Johanna Fish
16:30- 18:00	Organised (optional) trip to Whitstable	Wellbeing Champions (see poster in joining instructions)	Meet at Keynes Bus Stop B @16:45
19:00	Conference dinner (Canterbury town centre)		Cathedral lodge
Thursday 18th April. Industry day with CASE student talks.			
9:00-10:00	3-Minute Thesis (Year 2)		Sibson LT1 Chaired by Bree Streather & Jack Stubbs
10:00-10:30	10-minute talks (Year 4)		Sibson LT1 Chaired by Bree Streather & Jack Stubbs
10:30- 11:15	Poster session (Year 3 CASE) and coffee		Foyer
11:15-12.00	10-minute talks (Year 4)		Sibson LT1 Chaired by Bree Streather & Jack Stubbs
12:00-12.30	*"Dreams, Goals and Impact: Scaling and Commercialising a Seaweed Technology Company."*	Michelle Marin Chao – Nutri-San	Sibson LT1 Chaired by Charlotte Bilsby
12.30		Dr Barrie Rooney – Royal Society Entrepeneur in Residence	Sibson LT1 Chaired by Charlotte Bilsby
12:35-14:00	Discovery Park Networking Lunch with staff and students		Sibson Foyer
14:00-14:20	*'Spun out on Research – a Translators Journey'*	Renos Savva– Discovery Park	Sibson LT1 Chaired by Oya Canik and Anastasia Kolesnikov
14:20-14:40	*"UKRI and ICURe funding opportunities"*	Tobias Von der Haar – University of Kent	Sibson LT1 Chaired by Oya Canik and Anastasia Kolesnikov
14:40-15:10	*"There and back again: a tale about research in academia and industry"*	Diego Gomez-Nicola– University of Southampton	Sibson LT1 Chaired by Oya Canik and Anastasia Kolesnikov
15:10- 15:30	Industry Q&A panel Chaired by Oya Canik and Anastasia Kolesnikov	Renos Savva, Tobias Von der Haar, Michele Marin Chao, Diego Gomez-Nicola	Sibson LT1 Chaired by Oya Canik and Anastasia Kolesnikov
15:30	Concluding remarks		Sibson LT1
Depart			

Instructions for speakers, session chairs & microphone runners

Speakers

Please bring your talks on a data stick or email them to Anastasios Tsaousis (Tasos) on the day of your talk A.Tsaousis@kent.ac.uk

Session chairs

Liaise with Tasos prior to your session to make sure that all the talks are uploaded and you are familiar with the order of the speakers. If you are introducing an invited speaker, please make yourself familiar with their background, make them feel at home, and say a few nice introductory words about them prior to their talk. You can decide with your chairing partner who wants to introduce which parts of the session and then work together to make the session run smoothly and to time. Please keep an eye on the time and make sure speakers are aware if they are running over.

After each talk there should be time for questions (as long as the slot isn't running over). We suggest 1 question for a 3 MT talk and 2-3 for a longer talk – but it is great to have discussion so use your best judgement here.

Microphone runners

Please make yourself known to the session chairs and Tasos. We have enough microphones for you to take one each and pass it to whomever is asking the question. Check that you know how they work and that the batteries are full.

It is very important that everyone uses a microphone to speak (even if they say they don't need it).

FULL SPEAKER AND PRESENTER LIST

Wednesday 17th April. Non-Case students.			
9:00-10:00	3-Minute Thesis (Year 2) Chairs: William Edwards & Simon Thundow	1. Emily Woods (University of Sussex), 9:00 2. Natasha Ward (University of Kent), 9:04 3. Nikolaos Sideris (University of Sussex), 9:08 4. Matthew Shaw (University of Kent), 9:12 5. Tatum Sevenoaks (University of Sussex), 9:16 6. Annie Robertson (University of Sussex), 9:20 7. Matthew Rice (University of Kent), 9:24 8. Yomna Moqidem (University of Southampton), 9:28 9. Fiona Lancelotte (University of Sussex), 9:32 10. Anastasia Kolesnikova (University of Southampton), 9:36 11. Olivia Keers (University of Kent), 9:40 12. Abhishek Johan Issac (University of Southampton), 9:44 13. Ian Hunter (University of Portsmouth), 9:48 14. Johanna Fish (University of Southampton), 9:52 15. Callum Ellis (University of Southampton), 9:56	Sibson LT1
10:00-10:40	Poster session (Year 3) and coffee • Konstantinos TORNESAKIS (University of Portsmouth) • James WOODWARD (University of Sussex) • Austeja BAKULAITE (University of Portsmouth) • Matthew DAVIS-LUNN (University of Southampton) • Fiona DRESEL (University of Kent) • Amanda GILBERT (University of Southampton) • Jacob HUDSON (University of Kent) • Thomas PAIGE (University of Kent) • Sophie POWELL (University of Southampton) • Bree STREATHER (University of Kent)		Sibson Foyer
10:40-12:30	10-minute talks (Year 4) Chairs: William Edwards & Simon Thundow	1. Roman Urban (University of Kent), 10:40 2. Abigail Talbot (University of Sussex), 10:52 3. Anne Jeanette Romero (University of Southampton), 11:04 4. Fardina Rahimi (University of Southampton), 11:16 5. Klaudia Piotrowska (University of Southampton), 11:28 6. Letitia McMullan (University of Sussex), 11:40 7. Amy Lovegrove (University of Southampton), 11:52 8. Samuel Jones (University of Kent), 12:04 9. Steven Houghton (University of Southampton), 12:16	Sibson LT1
15:00-16:30	10-minute talks (Year 4) Chaired by Jo Haszczyn and Johanna Fish	1. Hope J. Haime (University of Sussex), 15:00 2. Laura Freeman (University of Kent), 15:12 3. David Fisher (NIAB EMR), 15:24 4. Brandon Coke (University of Southampton), 15:36	Sibson LT1

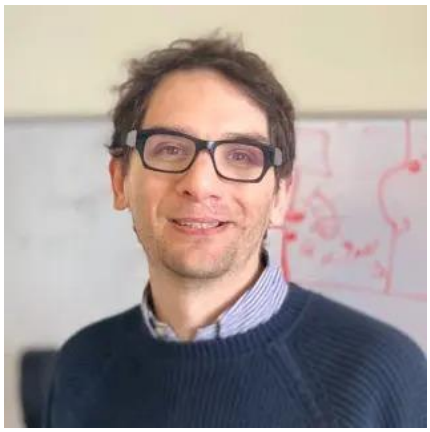
		5. Victoria Cheung (University of Kent), 15:48 6. Charlotte Bilsby (University of Kent), 16:00 7. Fiyin Adenekan (University of Southampton), 16:12	

Thursday 18th April. Industry day with CASE student talks.			
9:00-10:00	3-Minute Thesis (Year 2) Chaired by Bree Streather & Jack Stubbs	1. Simon Thundow (University of Kent), 9:00 2. Iolanta Spanner (University of Southampton), 9:04 3. Dmytro Prasolov (University of Kent), 9:08 4. Shubhangi Mahajan (University of Southampton), 9:12 5. Samuel Liu (University of Southampton), 9:16 6. Theo Hornsey (University of Southampton), 9:20 7. Charles Ellis (University of Southampton), 9:24 8. William Edwards (University of Kent), 9:28 9. Joseph Davies (University of Kent), 9:32 10. Alex Clarke (University of Southampton), 9:36 11. Oya Canik (University of Kent), 9:40 12. Rhianne Broadway (University of Sussex), 9:44 13. Ryan Boughton (University of Kent), 9:48 14. Dyuti Basu Choudhury (University of Southampton), 9:52 15. Shahd Al Balushi (University of Sussex), 9:56	Sibson LT1
10:00-10:30	10-minute talks (Year 4) Chaired by Bree Streather & Jack Stubbs	1. Chloe Uyl (University of Kent), 10:00 2. Robert Ulrich (University of Kent), 10:10 3. Paige Policelli (University of Southampton), 10:20	Sibson LT1

10:00-10:40	Poster session (Year 3 CASE) and coffee • Susmita AOWN (University of Sussex) • Alice CLARK (University of Sussex) • Matthew Irwin (University of Southampton) • Ryan Lawrence (University of Southampton) • Noviann MCLEAN (University of Kent) • Joanna RENAUT (University of Sussex) • Molly RUTT (University of Southampton) • Annabelle SOMERS (University of Southampton) • Erick GOMES OLIVEIRA (NIAB EMR) • Richard STACK (University of Kent) • Jack STUBBS (University of Southampton) • Lucy Sutton (University of Southampton) • Kaya TAYLOR (University of Sussex) • Jamie THOMAS (University of Southampton) •	Sibson Foyer

11:15-12.00	10-minute talks (Year 4) Chaired by Bree Streather & Jack Stubbs	1. Kseniia Pidisna (University of Kent), 11:15 2. Liam Jones (University of Southampton), 11:25 3. Johanna Haszczyn (University of Southampton), 11:35 4. Isabella R. Garcia (University of Kent), 11:45	Sibson LT1

Meet our Guest Speakers



Dr Ciro Chiappini:

'*Nanotechnologies for Cell Manipulation'*

Simple, controllable, and versatile access to the intracellular space is crucial to advancing biomedicine. Nanotechnologies are rapidly transforming our capacity to sample, sense, perturb, control and delivery to the intracellular environment. This talk will review our recent advances in developing nanomaterial-based approaches for cell and gene therapy and biosensing.

Dr Ciro Chiappini is Senior Lecturer in Nanomaterials and Biointerfaces, with a doctorate from the University of Texas, Austin. Prior to Joining King's, he has been Marie Curie and Newton International Fellow at Imperial College London. He joined King's College London in 2016, after completing his Marie Curie and Newton International Fellowship at Imperial College London.

His research blends nanotechnology, bioengineering and cell biology to develop functional materials that direct cell behaviour. These materials dynamically interact with the intracellular environment to detect, study, and manipulate biological processes at the molecular level.

Dr. Chiappini's work spans tissue engineering, precision medicine, and biointerface engineering. He focuses on precisely directing cell fate in vivo, developing novel nanotechnologies for rapid molecular profiling of diseases, and modulating biochemical and physical signals in both spatial and temporal dimensions.

Prof Diego Gomez-Nicola *"There and back again: a tale about research in academia and industry"*

Prof. Diego Gomez-Nicola (DGN) obtained a degree in Biological Sciences (Neuroscience) by the Complutense University of Madrid and his PhD in Molecular Biology (Neurosciences) at the Autonoma University of Madrid, obtaining the doctorate in 2008. After his first postdoctoral stage at the National Hospital of Paraplegics (Toledo, Spain), he joined the CNS Inflammation Group (University of Southampton, UK) as a postdoctoral fellow of the Spanish Ministry of Education and Science (MEC) and later as an EU Marie Curie fellow, under the supervision of Prof. Hugh Perry.

In 2013, thanks to a New Investigator Grant of the MRC, he started his independent research group, supervising since then several research lines, including the regulation of microglial proliferation and activation during chronic neurodegeneration, the control of neurogenesis in neurodegenerative diseases or the design of novel viral strategies for the study of CNS function. In 2019 he joined Eli Lilly as Head of Neuroimmunology to supervise the pre-clinical and clinical portfolio in neuroinflammation. At Lilly he designed and implemented the new strategy in neuroinflammation in AD, including prioritisation of target discovery programmes, and supervised a portfolio of preclinical projects for targeting neuroinflammation in AD and pain, across the UK and US.

Now, returned to the University of Southampton as full-time Professor at the School of Biological Sciences, leads a programme of research studying preclinical therapeutic targeting of neuroinflammation in Alzheimer's disease, as well as basic mechanisms of development of microglia in rodents and humans. Ongoing interests also include the study of the diversity of the microglial population in development and ageing, with a special interest on the mechanisms governing cell turnover. DGN is Deputy Chair of the Neuroscience and Mental Health Board of the MRC, and serves as member of multiple international committees and boards. More recently, he is the Deputy Head (Research) of the School of Biological Sciences, overseeing the research activity in Biosciences. More broadly, Diego has demonstrated a commitment to growing and shaping the ED&I agenda. From 2017-2019 he was Chair of the BioSci ED&I Committee and Staff Engagement Champion, leading the implementation of the action plan of the Athena Silver Award. He also contributed to the University Athena Swan Self-Assessment team, recently securing an Institutional Silver Award. While in Lilly, he was the site representative on a cross-site EDI working group, tackling issues such as disparity in maternity leave or flexible working policies.

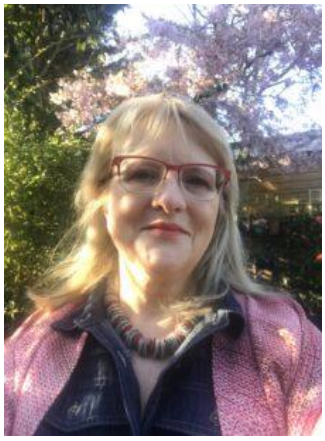
Dr Michelle Marín Chau

'***Dreams, Goals and Impact: Scaling and Commercialising a Seaweed Technology Company.***'

Dr Michelle Marín Chau is Communications Director and one of the founders of Nutri-San Ltd, a B2B seaweed bio-technology company. In 2023, she was granted the status of Honorary Academic in the School of Biosciences at the University of Kent.

Michelle started her career in academia, lecturing in Politics (University of York) and Development Studies (UEA), before moving into professional services. For over fifteen years she worked for global Executive Search firms in the UK and internationally.

In 2016, Michelle and her husband decided to set up Nutri-San Ltd and pursue their vision to build a sustainable seaweed technology business which, as well as producing products with environmental and health benefits for the animal feed and livestock industries, would also generate employment opportunities – particularly in marginalised coastal areas. It has operations in Vietnam, Zanzibar, and the UK.



Professor Sara Rankin FRSB

'*I Did It My Way: An Unconventional Path to Success in Academia*'.

Professor Sara Rankin FRSB has a first-class hons degree and PhD in Pharmacology from Kings College London. Having undertaken postdoctoral work at UCSD and CRUK she joined Imperial College London in 1995 where she is now Professor of Leukocyte and Stem Cell Biology. Her work is multisiciplinary, working with material scientist, engineers and Physicists, in the field of Regenerative Pharmacology.

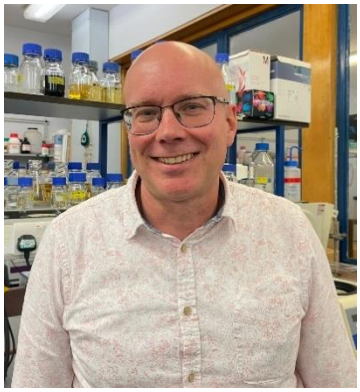
Throughout her Scientific career she has been committed to societal engagement and promoting diversity and inclusion in STEM. She has won awards for Leadership, Collaboration and Innovation in Societal Engagement and has worked collaboratively with artists and creatives on projects ranging from science pop-up shops, sci-art exhibitions and is Director of the first National Black Graduates Career Conference.

Prof Rankin is dyslexic and dyspraxic and her most recent work, supported by RSB, RSC and BPS seeks to promote neuroinclusion in STEM education and careers https://www.cacti.org.uk. She works to raise awareness of Neurodiversity in STEM businesses, research Institutes and Universities and support them in setting up ND networks. The network she setup in Astra Zeneca now has just under 3000 people in their Global network.

Dr Renos Savva

'Spun out on Research – a Translators Journey'

Renos is an experienced entrepreneur and bio-business lecturer, with a track record of supporting and mentoring successful startups and founders. Now Head of Innovation at Discovery Park, a leading science park in Kent and recognised Life Sciences Opportunity Zone. Amongst his many roles, Renos recently joined the SoCoBio DTP's Industry and Impact committee, where he is applying his vast expertise in the biotech industry to help direct and train our students.



Prof Tobias Von der Haar

'Business, Entrepreneurship and Innovation in the Biosciences: An introduction to the BBSRC ICURe Program'

Tobias von der Haar is Professor of Systems Biology at the University of Kent. His research group have studied how eukaryotic mRNAs are translated into protein, and how the process of protein synthesis is regulated, since 2006, combining experimental and computational approaches to address these problems.

The computational modelling work brought Tobias and his group in contact with companies interested in improving the efficiency of their protein expression systems, and his recent research interests focus on the design of efficient DNA and RNA sequences for industrial, environmental and medical applications. He currently holds a Royal Society Industry Fellowship to work on the development of more efficient RNA Therapeutics in partnership with Accord Healthcare. Tobias has held multiple roles relating to Innovation, Entrepreneurship and Career Development in these areas including serving on the BBSRC Skills and Careers Advisory Panel, as Director for Research and Innovation for the Division of Natural Sciences at Kent, and currently as PI for Kent's BBSRC-funded Impact Acceleration Account. In his talk he will introduce the BBSRC ICURe program which trains, funds, and supports researchers and research teams to determine whether there is a market for products or services that utilise their bioscience-based ideas, research, science, and technologies.

Dr. Barrie Rooney

Barrie is an experienced entrepreneur and leading tropical disease expert who spent many years working with Médecins Sans Frontières (MSF). While working with MSF on a range of humanitarian projects she travelled around the rainforests of central Africa diagnosing and treating African Trypanosomiasis OR Sleeping Sickness.

Winning the 2016 Innovator of the Year Award from the UK Biotechnology and Biological Sciences Research Council provided the means to set up the charity TroZonX17.
Barrie's entrepreneurial endeavours also include setting up ExCyte Ltd, a biotech company that characterised new drug targets emerging from the human genome project.

Most recently Barrie has carried out research on making accessible rapid diagnostic tests (RDT's) for Neglected Tropical Diseases and is an honorary lecturer in Infectious Diseases at the University of Kent. She collaborates extensively with academic researchers and organisations including the World Health Organisation (WHO) and is an 'Entrepeneur in Residence' for The Royal Society.

TROZON X17
Diagnostics for a Developing World

Industrial partners and Networking opportunities

A range of industrial partners are attending the conference, and we strongly encourage students to make the most of this occasion to build connections and learn about the opportunities available to them after their PhD.

We are joined by:

We are the independent scientific academy of the UK, dedicated to promoting excellence in science for the benefit of humanity. The Royal Society is a Fellowship of many of the world's most eminent scientists and is the oldest scientific academy in continuous existence.

The Royal Society Entrepreneur in Residence (EiR) scheme aims to increase the knowledge and awareness in UK universities of cutting-edge industrial science, research and innovation. The scheme provides opportunities for enthusiastic, highly experienced industrial scientists and entrepreneurs to spend one day a week at a university developing a bespoke project. The scheme provides a contribution to the basic salary for the EiR and towards travel and project costs.

Founded in 1911, we've been at the forefront of advancing molecular bioscience for over 100 years, promoting its importance as a discipline, facilitating the sharing of knowledge and expertise, and supporting molecular bioscientists across all career stages.

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Our SLS headquarters are in Nottingham, UK, with a regional footprint in Yorkshire, Scotland, Northern Ireland, Europe and Africa. SLS have advocated more sustainable laboratory practices for several years through their sustainability pledge. This pledge represents a continuous commitment to offering sustainable products that offer the highest levels of build quality and performance together with the longest lifespan and the lowest running costs. The dedicated SLS Sustainability Team continuously review the offering whilst ensuring their own practices meet the highest environmental standards.

Abstracts for 10 minute talks (year4)

Analysing the functional significance of a primate-specific glutamate receptor subunit

Steven Houghton, University of Southampton

All aspects of cognitive function require the excitatory neurotransmitter glutamate. One of the main receptors that binds glutamate is the NMDA receptor (NMDAR). NMDARs are Ca2+-permeable and contribute to long-term neuronal changes; playing a role in learning, memory, and neurodegeneration. NMDARs are tetramers within which the GluN2A subunit is incorporated. Our lab has recently found that a primate-specific GluN2A isoform (GluN2A-S), resulting from alternative splicing, is present abundantly within the human brain (Warming et al., 2019). GluN2A-S is as a shorter protein compared to the canonical GluN2A with a truncated C-terminal domain. As a result, GluN2A-S lacks a PDZ-binding motif and synaptic localization may be dependent upon the formation of tri-heteromeric NMDA receptors. Expressing human GluN2A results in a mix of protein, preventing study of the isoforms independently. I have generated a plasmid construct that only generates the canonical human GluN2A protein. This was by single nucleotide substitution within the 3' splice site for the rat GRIN2A equivalent site as the rat GRIN2A gene only generates one isoform. I will use it to answer whether GluN2A-S can localize synaptically and whether GluN2A-S contributes similar NMDAR properties. In rat GluN2A the opposing nucleotide change was not sufficient to generate two GluN2A isoforms. With this tool, we can study the impact of GluN2A and GluN2A-S separately in disease-associated GRIN2A mutants; such as the epilepsy-associated L812M missense mutation. Ultimately this work will allow us to gain insight into some of the human-specific intricacies of synapse function and plasticity in health and disease.

Applying large scale metanalysis of transcriptomic data to uncover hyper-responsive genes and prediction via machine learning

Brandon Coke, University of Southampton

Large scale meta-analysis of pre-existing RNA-seq and microarray datasets has revealed a subset of genes with higher intrinsic propensity for differential expression even stratifying by the tissues used in an experiment and the type of experiment conducted.

Assigning all genes within the human a prior that reflects this intrinsic propensity has been shown to improve the enrichment of more relevant differential expressed genes in studies exploring signalling pathways and enhance feature selection in scRNA-seq data.

Applying machine learning to understand the underlying genomic and transcript based features associated has identified a subset of features that highly enriched in hyperresponsive genes- genes that have a noticeably higher propensity for differential expression.

How does a mild decrease in oxygen availability constrain hippocampal function?

Letitia McMullan, University of Sussex

Baseline blood flow, oxygen saturation, red blood cell velocity (RBCV) and capillary density are lower in the hippocampus than other brain regions with similar neuronal activity; likely making it especially vulnerable to even a mild decrease in blood/ oxygen supply, as seen in early Alzheimer's Disease (AD) (~10-25%). However, little is known about how such a mild decrease in blood/ oxygen supply affects hippocampal neuronal function, and whether this may lead to subsequent hippocampal dysfunction and cognitive decline in AD. In adult mice of a C57BL/6J background, we modelled this by mildly reducing the fraction of inspired oxygen (FiO2) from 21%, down to 15% or 11%. Mice were either Thy1-GCaMP6f+ve, or received an intracranial injection of CAMK2-GCaMP6f virus, so that excitatory pyramidal neurons were labelled with a fluorescent calcium indicator dye. A cranial window was then implanted over the hippocampus or visual cortex. Peripheral oxygen saturation (SpO2) was monitored using a pulse oximeter. Brain haemodynamic measures, including blood flux and oxygen saturation, were recorded using a combined laser doppler flowmetry/haemoglobin spectroscopy probe (Oxy-CBF probe). The cerebral metabolic rate of oxygen consumption, a proxy for neuronal activity, was calculated. Neuronal calcium signalling was imaged under a 2-photon microscope. Changes in response to mildly reducing the FiO2 were recorded in awake mice. Mild hypoxia reduced peripheral and brain oxygen saturation, but increased brain blood flow, oxygen consumption and neuronal calcium signalling. Future experiments will investigate whether hypoxia induced hyperexcitability can be replicated ex vivo, and the underlying mechanisms will be explored.

Exploiting the natural diversity of the yeast Scheffersomyces stipitis for improved second generation bioethanol production

Chloe Uyl, University of Kent

More so than ever, are we noticing the impacts of global warming which is why it is crucial that action is taken now. A significant shift in our approach to energy and low carbon technologies will be required to meet net zero targets by 2050.

Biofuels produced from biomass play an important role in the decarbonization of the transport sector. Lignocellulosic represents one of the largest renewable sources of waste biomass which can be used to produce second generation bioethanol. The use of feedstocks such as lignocellulosic prevents compromising food security by using biomass that would have otherwise been combusted or left to decompose. Lignocellulose is a complex polymer consisting of cellulose, hemicellulose, and lignin. Hemicellulose is composed of various pentose and hexose sugars that can be fermented into ethanol for second generation biofuel by microorganisms such as yeast.

The non-conventional yeast Scheffersomyces stipitis has the highest native capacity for pentose fermentation of any known microorganism; and is therefore a suitable choice for second generation bioethanol production as it can ferment both pentose and hexose sugars. However, low ethanol tolerance and sensitivity to the inhibitory compounds generated during second generation biofuel production limit the potential application of Scheffersomyces stipitis.

In this study, a collection of Scheffersomyces stipitis natural isolates were screened in a range of industrially relevant conditions. Through this screening, several natural isolates were identified as superior bioethanol producers. Whole genome sequencing and CRISPR-Cas9 were used to link differences in genome organization to the different phenotypes observed.

Genetic basis of interspecies impacting the horticultural pest D. suzukii

Fardina Rahimi, University of Southampton

Fardina Rahimi1, Bethan Shaw2, Michelle Fountain2 and Herman Wijnen1

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Drosophila suzukii (Matsumura) or Spotted Wing Drosophila (SWD) is a fruit fly species native to Southeast Asia, that acts as an invasive pest in other parts of the world. SWD integrated pest management research has focused on finding biological controls against infestation of soft and stone fruit cultures. In this study we examined the deterrence of SWD egg laying by pre-exposure of egg laying substrates to the sister species Drosophila melanogaster, first noted by Shaw et al., (2017) and further characterized by Tsungadi et al., (2022). Experiments using D. melanogaster cultures raised in the presence of antibiotics or following dechorionation at the embryonic stage demonstrated that this interspecies deterrent signal was elicited by the bacterial microbiome of D. melanogaster. Notably, we identified an alternative lab D. melanogaster culture that possessed a bacterial microbiome that attracted rather than repelled subsequent SWD oviposition. Genetic crosses indicated that both the microbiome and the D. melanogaster genotype played a role in determining the valence of the interspecies signal. We will present metagenomics sequencing analyses of repellent and attractive D. melanogaster microbiomes and explain how this information may inform integrated pest management of SWD.

Discovering the form and function of ILF3

Abigail Talbot, University of Sussex

Interleukin enhancer-binding factor 3 (ILF3), is a multifunctional dual RNA and DNA-binding protein that plays critical roles in eukaryotic transcription regulation. ILF3 binds to specific DNA structures at promoter regions and exerts its regulatory functions through interactions with RNA molecules, including the regulation of RNA splicing, stabilization and export. ILF3 exhibits binding affinity for both RNA and A-form DNA. The presence of homologues of ILF3 across different eukaryotic organisms suggests evolutionary conservation due to functional necessity. Notably, ILF3 has been identified as an upstream promotor of the GATA2 gene, which is implicated in myelodysplastic syndrome-acute myeloid leukaemia. Despite the diverse roles attributed to ILF3 in gene expression and RNA processing, the exact molecular structure and mechanism of action remain elusive. In my research project, I have employed X-ray Crystallography to elucidate the structural characteristics of ILF3 in X.tropicalis and utilized the CRISPR-Cas9 system to generate ILF3 gene knockouts during the early stages of development. By utilizing Cryo-EM, I aim to unravel the comprehensive molecular architecture and mechanism of action of ILF3. This knowledge will significantly contribute to our understanding of ILF3's diverse roles in transcription regulation and RNA processing and provide valuable insights into the functional implications of ILF3 dysregulation.

An experimental microbiota that protects against multiple measures of age-related ill-health in the model organism C. elegans

Laura Freeman, University of Kent

With many advances in biomedical research, human lifespan has greatly increased whilst our health span has been left behind. It is known that the community of microbes in our gut, the gut microbiota, is a key factor in several physiological processes and its composition has been linked to diseases, frailty, and immune dysfunction. Since the gut microbiota undergoes considerable changes to its composition with biological ageing, whereby the species richness declines and the abundance of opportunistic pathogens increases, we believe that understanding how host-microbe interactions in the gut affect age-related phenotypes could lead to interventions promoting lifelong health. To examine molecular interactions between the host and gut microbiota during ageing, we have developed a new model system consisting of C. elegans combined with a simplified experimental microbiota of 11 bacterial strains, that have been isolated from the gut microbiome of wild C. elegans. The experimental microbiota effectively colonises the C. elegans gut, without negatively impacting host development, but slightly reduces body size, reproduction, and lifespan. By using a transgenic strain of C. elegans expressing amyloid-Î² in its body wall muscle cells, to model Alzheimer's disease, we have shown that our experimental microbiome reduces the amyloid-B toxicity, and the number of plaques observed in these C. elegans. Additionally, we have shown that our experimental microbiome protects C. elegans against Staphylococcus aureus. Genetic analysis has shown that this protection involves two evolutionary conserved immune pathways, namely, the p38 MAPK/PMK-1 cascade and TFEB/HLH-30.

Friendly fire: Identification of cis- and trans-acting elements involved in the regulation of the genome-editing enzyme, APOBEC3A

Paige Policelli, University of Southampton

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Aberrant activation of the apolipoprotein-B mRNA-editing catalytic polypeptide-like 3A (APOBEC3A) cytidine deaminase has been implicated as a major source of C>T and C>G mutations in cancer; in particular in carcinomas of the head and neck, bladder, lung, oesophagus, cervix and breast. To understand how APOBEC3A gene expression is regulated, we used two complementary approaches: (1) Circular Chromosome Conformation Capture (4C) to identify cis-acting regulatory elements that interact with APOBEC3A in a keratinocyte cell line (NIKS) and (2) prediction of transcription factors responsible for regulating APOBEC3A expression from single cell RNA sequencing data with validation in NIKS using short-interfering RNAs. Robust interactions between our 4C baits and regions up- and downstream of the APOBEC3A gene were detected, some of which (candidate silencers) are enriched in proliferating NIKS (low APOBEC3A expression) while others (candidate enhancers) are enriched upon APOBEC3A induction. Furthermore, knockdown of candidate transcription factors revealed a role for the Grainyhead-like transcription factor 3 (GHRL3) in regulating APOBEC3A expression. These findings significantly enhance our understanding of APOBEC3A regulation and how it becomes deregulated during cancer development.

Investigating Genome Packaging during Recombinant AAV (rAAV) Gene Therapy Viral Vector Production

Kseniia Pidlisna, University of Kent

Regioselectivity in the anaerobic biosynthesis of Vitamin B12.

Sam Jones, University of Kent

BzaC is an O-methyltransferase involved in the anaerobic biosynthesis of the lower ligand of Vitamin B12. Our approach to studying this enzyme/pathway involves the guided biosynthesis of potential pathway intermediates via the use of an engineered strain of E. coli. Characterisation of these molecules identified 5' and 6' isomers, in varying ratios depending on the intermediate. Subsequent analysis of BzaC reactions, via cobamide hydrolysis and HPLC/MS, has identified both 5' and 6' products, at varying amounts, demonstrating BzaC regioselectivity.

Investigations into a Potential Cancer-Testis Antigen

Isabella Garcia, University of Kent

"With 1 in 2 people facing a cancer diagnosis at some point in their lifetime, there is a critical need for new, effective treatments. Cancer-testis antigens (CTAs) are a family of tumour-associated proteins being investigated as a potential immunotherapy target. Under normal conditions, they are predominantly expressed in the testes, however, under aberrant conditions, they have also been identified in multiple tumour types with their expression also linked to worse clinical outcomes.

ZFY is a transcription factor encoded on the Y chromosome with functions linked to spermatogenesis, male development and male fertility. Interestingly, in humans, there are two variants of ZFY: a long variant expressed ubiquitously, and a second shorter variant missing an entire coding exon that is specific to the testes and is preferentially expressed in early proliferating germ cells. PCR confirmed the presence of the short variant in a male head and neck squamous cell carcinoma cell line, making it a cancer-testis antigen candidate.

Using transcriptomics, proteomics and evolutionary analysis the function of both ZFY variants was explored. Transcriptomics showed both variants acting on the ancient Wnt signalling pathway. Additionally, the shorter variant (ZFYS) seems to activate the ErbB signalling pathway, both of which are significant cancer-driving pathways when wrongly activated with downstream targets including PI3K-Akt and RAS/MAPK pathways. Moreover, the upregulation of pathways governing extracellular matrix regulation may suggest involvement in tumour microenvironment shaping and cancer progression. Although these findings are preliminary and demand further investigation, ZFYS holds potential as an intriguing CTA.

New Cell Regulators of Mitosis

Fiyin Adenekan, University of Southampton

"Mitosis, a fundamental process in higher organisms, leads to the generation of two genetically identical somatic daughter cells. This phase of the cell cycle encompasses crucial events such as cell rounding, chromosome condensation, and subsequent correct sister chromatid segregation. These processes rely on a tight control and regulatory mechanism to ensure their successful execution. The CDK1-cyclin B complex phosphorylates numerous proteins to govern mitosis.

A recent phosphoproteomics investigation in human cells has identified novel substrates exhibiting significant changes in phosphorylation levels upon depletion of cyclin B. Eight of these substrates are uncharacterised and we decided to investigate them further.

We employ CRISPR-based editing and RNAi techniques in conjunction with high-throughput fluorescence imaging to elucidate the roles of the identified proteins. SiRNA assays revealed that two out of eight candidates show mitotic phenotypes and I am currently investigating both in vitro and in vivo. Mass spectrometry will facilitate the identification and quantification of proteins that interact with my targets, while bioinformatics tools will enable statistical analysis and aid in deciphering their functional characteristics and protein-protein interaction networks. By integrating bioinformatic data with my experimental findings, I will perform comprehensive analyses to uncover patterns, correlations, and functional insights. This research seeks to expand our understanding of the molecular mechanisms underlying mitosis and elucidate previously unexplored interaction and regulatory networks associated with CDK1-cyclin B substrates.

Improving survivability of Pacific oysters to "Summer Mortality" with environmentally-modified, lipid-dense microalgal diet.

Amy Lovegrove, University of Southampton

"The invasive Pacific oyster (Magallana gigas) has become the most consumed oyster in the world, and have been commercially farmed in the UK since the 1890â€™s. They are now thriving in the UK's warmer waters, and we now produce ~3,000 tonnes per year. Despite their hardy nature, the Pacific oyster is vulnerable to a Summer Mortality which primarily comprises Ostreid herpesvirus (OsHV-1) and Vibrio spp. bacteria. These mortality events frequently cause 80 -100% mortality within European oyster farms, and are managed with over stocking, and broad-spectrum antibiotic treatment. The aim is to create a sustainable alternative to M. gigas disease management in aquaculture using environmentally modified microalgae diet. Key findings include:

- Preferential selection of brown alga Isochrysis galbana when offered a mixed diet, shown by 15N stable isotope analysis,

- Significantly heavier mass, but lower shell weight in oysters fed I. galbana,

- Significant up-regulation of calcification inhibitor nacrein in oysters fed I. galbana shown by RT-qPCR,

- A reduction of NaNO3 concentrations to 25% in culture media results in a 75% increase in expression of three essential immune polyunsaturated fatty acids in I. galbana shown by GC-MS,

- Oysters fed lipid-dense I. galbana had significantly higher metabolic rates, despite no differences in mass, to those fed the unmodified diet,

- Current RT-qPCR assays indicate up-regulation of innate immune gene Caspase8 in oysters fed modified I. galbana.

The final stage currently being undertaken assesses survival rates of M. gigas to various Vibrio species when fed the modified microalgae."

C. elegans as a model for nerve agent intoxication as a platform for medical mitigation

Jo Haszczyn, University of Southampton

Nerve agents exert their toxicological effect via inhibition of acetylcholinesterase. This inhibition results in excessive cholinergic signalling in vivo where the signs and symptoms are associated with paralysis and cessation of breathing. Current therapies for nerve agent poisoning antagonise the ensuing overstimulation of muscarinic acetylcholine receptors with atropine and use benzodiazepines to enhance inhibition as a counter to increased excitability. We recently showed that C. elegans can be effectively used to assess the toxic effects of acetylcholinesterase inhibition by paraoxon that use the same mode of action as organophosphate nerve agents. We showed that the C. elegans neuromuscular junctions that control feeding, and motility serve as a bioassay of intoxication in the intact animal. This is reinforced by measuring the OP inhibition of acetylcholinesterase activity in homogenates extracted from treated worms. Here, we extend these studies and identify that soman, sarin and VX efficiently inhibit extracted worm homogenate with an order of potency of S>S>VX. Importantly, this order of potency is maintained in feeding and motility behaviours in nerve agent intoxication. Interestingly, recovery of the worm's behaviours after removal from drug is more effective than the recovery of the in vitro inhibited enzyme. Interestingly, we show that this recovery observed in vivo maps onto the biochemically extracted acetylcholinesterase activity recovered across the in vivo recovery time-course. These data support the use of C. elegans to model nerve agent intoxication and highlight pathways to mitigation and new treatment regimens to nerve agent poisoning.

Single molecule investigation of DNA repair protein dynamics and their inhibition.

Roman Urban, University of Kent

DNA is an amazing molecule present in all known organisms and is often referred to as the molecule of life. It acts as the genetic manual on how the organism should function and reproduce, thus preservation of the integrity of the genome is vital. Being an inherently reactive molecule DNA is highly susceptible to damage, accumulation of which can lead to deleterious effects on the organism, such as cell death, mutations, and diseases like cancer. Thus, cells have developed a variety of pathways to repair DNA damage and maintain a healthy genome. One such pathway is nucleotide excision repair (NER). NER repairs DNA damage caused by UV irradiation as well as alkylating agents like benzo[a]pyrene. These, in turn, create bulky lesions that distort the DNA helix preventing the normal function of such regions. NER functions by excising DNA stretches containing such adducts and patching them up using the healthy strand of the double helix as a template. Deficiencies in NER proteins result in impaired damage repair and transcription, leading to disease. As such it is of vital importance to understand as much as possible about these processes. Furthermore, the mechanism of action of some drugs that are used for cancer chemotherapy is generating DNA damage that is repaired primarily by NER. Developing NER inhibitors to be used as adjuvants in chemotherapy could enhance the efficacy of the treatment while reducing the side effects.

ATM inhibition increases cancer-associated fibroblast-mediated CD8 T-cell infiltration into the tumour microenvironment

Klaudia Piotrowska, University of Southampton

ATM inhibition increases cancer-associated fibroblast-mediated CD8 T-cell infiltration into the tumour microenvironment

The success of immune-checkpoint blockade (ICB) is limited to a fraction of cancer patients, highlighting the need to identify targetable resistance mechanisms to improve its clinical effectiveness. Non-responsiveness to ICB can result from a limited T-cell infiltration mediated by the tumour microenvironment (TME). Cancer-associated fibroblasts (CAFs) are a key component of the TME and due to their heterogeneity CAFs have diverse functions. Myofibroblastic CAFs (myCAFs) have been recently found in the immuno-excluded tumours from patients responding poorly to ICB. Although, myCAFs are associated with poor outcome in most solid tumours, the molecular mechanisms regulating myCAF accumulation remain unclear, limiting potential for therapeutic intervention. Previous findings show that during TGF-1-induced differentiation, myofibroblasts upregulate genes associated with DNA repair. The aim of our research is to study the role of Ataxia-Telangiectasia Mutated (ATM) in regulating the myCAF phenotype.

To investigate the role of ATM, we treated fibroblasts with TGF-1 and examined activation of the myofibroblastic markers (SMA, fibronectin, collagens). In vitro, targeting ATM pharmacologically suppressed and reversed myCAF differentiation. In vivo, targeting fibroblast ATM suppressed myCAF-rich tumour growth and promoted intratumoural CD8 T-cell infiltration.

Our findings show that ATM inhibition normalises myCAFs by downregulating genes associated with the deposition of desmoplastic stroma rich in collagens and alters the secretome composition, both of which facilitate T-cell movement. This work identifies a novel pathway regulating myCAF differentiation and provides a rationale for using ATM inhibitors to overcome CAF-mediated immunotherapy resistance.

Investigating a novel role for DIS3L2 within the cellular stress response

Hope Haime, University of Sussex

DIS3L2 is a highly conserved 3'-5' exoribonuclease, with a crucial role in regulating RNA stability and mutations resulting in overgrowth disorders. We have previously demonstrated a role for DIS3L2 within PI3K/AKT/mTOR signalling, which are core signalling pathways involved in cellular stress and cell proliferation. In confirmation, our recent findings suggest DIS3L2 may be involved in regulating cellular stress by increasing the survival and resistance of Drosophila melanogaster and human cells against nutrient deprivation. To investigate this, we conducted RNA-sequencing on Isogenic Control and DIS3L2 knockout HEK-293T cells to monitor transcriptomic changes over time in response to nutrient deprivation and Endoplasmic Reticulum stress. Our analysis revealed distinct temporal transcriptomic responses in cells under starvation or ER stress and has identified a specific role for DIS3L2 in regulating stress-responsive transcripts. We have validated several of these targets, which include NIBAN1, BMP2 and a novel uncharacterised lncRNA using qPCR. Interestingly, the lncRNA responds only to starvation stress in the absence of DIS3L2. These findings support DIS3L2 having an underlying regulatory function within the stress response. Further characterising the role of these novel targets within the cellular stress response will allow us to unravel their mechanism of action, as well as elucidate the role of post-transcriptional regulation in aiding cell survival against cellular stress and to unpick the regulatory role that DIS3L2 plays within this. Our findings will further our understanding of disease pathologies associated with DIS3L2 in addition to those associated with cellular stress, such as neurodegeneration and cancer.

Development of a standard integrated model system to investigate biofilms and microbiologically influenced corrosion.

Liam Jones, University of Southampton

Corrosion poses a significant challenge across various industries like non- and renewable energy, water systems, and marine environments. Microbiologically influenced corrosion (MIC) is a leading cause of pipeline failures in the oil and gas sector, primarily due to biofilm formation on metal surfaces. However, understanding and predicting MIC is hindered by the lack of robust model biofilm systems and standardized evaluation methods for control strategies. MIC accelerates metal corrosion rates, leading to substantial repair and management costs, estimated at $500 billion in the US alone. Identifying MIC mechanisms is complicated by diverse corrosion pathways (biotic or abiotic) making threat assessment and mitigation challenging. This research aims to develop and validate a representative model biofilm system which mimicks industrial conditions, enabling the testing of biocides and antimicrobial compounds. Through molecular microbiological methods, image analysis, corrosion tests, and electrochemical techniques, a multidisciplinary approach is employed to comprehensively understand the biofilm-metal degradation relationship. Investigations focus on changes in biofilm viability, species prevalence, and corrosion rates. This holistic approach seeks to offer insights into biocide effectiveness and potentially innovative biocide development strategies.

Optimising Health or Avoiding Disease? A Snapshot of Current Vitamin C Security and Individual's Vitamin C Status Across the United Kingdom.

David Fisher, National Institute of Agricultural Botany

Central to physiochemical processes including wound healing, neurotransmitter synthesis, and immune function, the importance of vitamin C cannot be overstated. But do you get enough of it?

We aimed to illustrate the current state of vitamin C security in the United Kingdom through analysis of the supply and distribution of vitamin C dense foods. Blood-biomarker data from the National Diet and Nutrition Survey (NDNS) was used to study how vitamin C supplies translated into the vitamin C status of individuals across the UK.

Analysis of market data identified a nationwide autumnal dip in vitamin C consumption, during which vitamin C intake dropped to 37mg/day, 7.5% below the UK RDI of 40mg/day. People in the south consumed over 20% more vitamin C than people in the North, resulting in Northen regions consuming less than 90% of the UK RDI in the autumn.

From the NDNS years 1-11 cohort (n=15655), 46% of the cohort were identified to have inadequate levels of plasma vitamin C: 14% and 4% of those individuals fell below the cutoffs for moderate and severe deficiencies respectively. We also propose an estimated average requirement of 75mg/day to achieve adequate vitamin C status, almost doubling current government recommendations.

Clearly, despite ample supplies, vitamin C is not being distributed equitably across the population. Ongoing work seeks to understand the costs of vitamin C inadequacy, improving micronutrient monitoring systems, and trialling targeted interventions to help individuals overcome barriers to accessing and benefitting from a diet rich in vitamin C.

Genomic constraints on domestication: Why are so few species domesticated?

Anne Romero, University of Southampton

Crop domestication is an evolutionary process transforming wild progenitors into cultivated crops. We explore the role of plasticity and transposable elements (TEs) in the facilitation or constraint in the domestication of wild species, focusing on the domesticated (D), progenitor (P) and never-domesticated wild (W) tomato species.

Plasticity is the ability of an organism to respond to different environments through multiple phenotypes. A plasticity pot experiment and differential gene expression analysis revealed that more traits and genes were plastic in P compared to W. We found evidence that confirms our hypothesis that plasticity can promote gene expression divergence during tomato domestication. We found a significant overlap between the genes that were divergent between D and P and plastic in P, compared to genes plastic in W.

TEs are major drivers of evolution in plants and therefore could play a role in domestication. We explored the TE landscape in tomato species, comparing the TEs in D tomato with multiple P and W species. Genes associated with TEs were enriched for functions related to the regulation of gene expression. Comparing D and P genomes identified TE insertions that may have been selected during tomato domestication and these were located near genes involved in plant defence and stress response. Novel TE insertions were more common in P compared to D and W, suggestive of recent mobilisation activity and faster transposition rates.

These mechanisms, known to be adaptive for wild species, may have aided the early adaptation of tomato progenitors to a cultivated environment.

Understanding the Membrane-Bound Structure of CLIC1 and Developing Selective CLIC1 Inhibitors with Antiproliferative Activity for the Treatment of Glioblastoma Multiforme

Victoria Cheung, University of Kent

Glioblastoma multiforme (GBM) is the most aggressive and prevalent form of primary brain cancer and its poor prognosis makes GBM a public health concern. Increasingly, evidence points towards Chloride Intracellular Channel 1 (CLIC1) promoting oncogenic development with its high level of activity and expression during tumorigenesis. CLIC1's unique (moonlighting) abilities means that it may serve separate functions at both the cytoplasm and membrane. Intriguingly, the metamorphic nature of CLIC1 serves as a biological switch for malignant transformation in which only the membrane-bound form is carcinogenic. This distinct feature could pave way for a new selective, conformation-specific cancer therapy which would potentially spare normal cells making CLIC1 a highly promising pharmacological target.

Our research focuses on understanding the membrane-bound structure of CLIC1 as this is currently unknown and developing selective CLIC1 inhibitors with antiproliferative activity for the treatment of glioblastoma. To explore the structure of the membrane-bound form, we have used CryoEM with CLIC1 inserted into nanodiscs. To detect drug binding, we have performed solution-state NMR and X-ray crystallography of the soluble form of CLIC1 to a panel of FDA-approved compounds derived from an in silico drug screen. To test drug inhibition, we performed viability assays in human glioblastoma cells.

Abstracts for 3 minute thesis talks (year 2)

CypHer5E-POS; a novel pH-sensitive probe to investigate lysosomal proteolysis in retinal pigment epithelium (RPE) cells

Charlie Ellis, University of Southampton

Lysosomes play a pivotal role in cellular homeostasis by orchestrating the degradation and recycling of cellular waste. Central to their function is maintaining an intraluminal acidic environment (pH 4.5-5.5) which is critical for optimal enzymatic activity and cargo processing. We present the novel CypHer5E-POS probe, comprised of CypHer5E Mono-NHS- Ester conjugated with photoreceptor outer segments (POS). POS molecules are internalised daily by retinal pigment epithelium (RPE) cells in the eye to co-localise in lysosomes. We show CypHer5E as a powerful tool for dynamic, real-time investigation of lysosomal cargo processing, and a novel means to identify defective lysosomes linked with neurodegeneration.

Cultured RPE cells (ARPE-19) were fed 4g/cm2 of CypHer5E-POS. LysoTracker-GreenTM was used to identify lysosomes by live-confocal microscopy. Lysosomal volume with (n=35) and without POS cargos (n=115) was calculated via Nyquist correction. A pH calibration curve (3.5-7.5 pH buffer range) was used to evaluate CypHer5E fluorescence activity which reported mean/median grey intensities as outputs for comparison.

CypHer5E-POS co-localised with 0.812Â±0.080 of lysosomes, indicating lysosomal specificity. Lysosomes without CypHer5E-POS cargos measured 0.335Î¼m3Â±0.125, whilst those containing CypHer5E-POS cargos were 0.471Î¼m3Â±0.163 (1.4-fold increase, p=<0.0001). Our pH calibration studies identified a significant increase in CypHer5E fluorescence at pH 4.5.

We show evidence of the novel CypHer5E-POS conjugate faithfully co-localising with RPE lysosomes, providing a robust readout of lysosomal size as well as intraluminal pH which is optimal for functional lysosomes. As these are key features linked with lysosomal impairment, we will harness this tool to study the dysfunction of these important organelles in neurodegenerative diseases.

Killing Intracellular Pathogens with Antibiotic Nanocapsules

Alex Clarke, University of Southampton

Background

Antimicrobial resistance (AMR) is an increasing problem worldwide, with a predicted 10 million deaths a year from antibiotic resistant infections by 2050, and no new antibiotics have been approved for over 20 years. An alternative method for overcoming AMR is the repackaging of existing therapies to improve their efficacy and reduce toxicity. Nanocapsules made of polymer (polymersomes) loaded with antibiotics can be used to effectively eliminate intracellular bacterial infection, without affecting uninfected cells.

Methods

Polymersomes made of PEO-b-PCL loaded with doxycycline and rifampicin were made by nanoprecipitation. Drug-loaded polymersomes were added to free-living Mycobacterium smegmatis and Mycobacterium tuberculosis cultures and the absorbance at 600 nm and luminescence measured over time to indicate bacterial growth. The effect of polymersomes on bacterial growth was compared to that of free antibiotic and polymer alone.

Results

Polymersomes containing doxycycline were 97.89 nm Â± 7.00 in diameter, had a mean polydispersity index (PI) of 0.1026 Â± 0.019, and contained a mean drug concentration of 38.7 ug/ml Â± 42.4. Rifampicin loaded polymersomes were 89.88 nm Â± 5.06, had a mean PI of 0.09 Â± 0.027, and contained a mean drug concentration of 22.45 ug/ml Â± 10.27.

The minimum inhibitory concentration of doxycycline and rifampicin against M. smegmatis were identified as 0.125 ug/ml and 16ug/ml respectively, and against M. tuberculosis were 4 ug/ml and <0.03125 ug/ml respectively. Polymersomes loaded with either doxycycline or rifampicin exhibited no inhibitory effect against free-living planktonic M. smegmatis or M. tuberculosis.

Conclusions

Doxycycline and rifampicin can easily and consistently be encapsulated within polymersomes. Although free drug can effectively kill M. smegmatis and M. tuberculosis, encapsulated drug does not kill free-living bacteria.

Accessing and recording task-related neuronal activity in the cerebral cortex: using targeted recording configurations.

Shahd Al Balushi, University of Sussex

One of the principal goals of neuroscience is to underpin the mechanisms in which both sensory and non-sensory information are encoded in the cerebral cortex. Thus, sensory signalling and animal behaviour have been examined at length using head restrained rodents with the help of optogenetic stimulation. We attempt to simulate a naturalistic environment for freely moving mice via a modular labyrinth without restricting the animal's movement or nutrition to explore foraging behaviour. We show that mice exhibit exploratory behaviour in the maze and are able to learn arbitrary sequences of tactile cues that lead to a reward. We have optimised the maze's modularity by automating the stimulus presentation, reward delivery and animal tracking. We aim to further quantify their behaviour and learning performance with the inclusion of electrophysiological tools that record brain activity in the somatosensory and barrel cortex. The project will also involve a collaboration with Scientifica Ltd.

Good Vibrations: Using Molecular Dynamics and Vibrational Spectroscopy to Shed Light on the Mechanism of Tau Aggregation in Alzheimer's Disease

Callum Ellis, University of Southampton

The precise mechanisms by which tau aggregates and forms pathogenic oligomers and fibrils has remained a mystery since their implication in the onset and progress on Alzheimer's Disease (AD) and other tauopathies. The conformational changes the protein undergoes are unique to each tauopathy1 and so understanding the processes by which these conformational changes happen, could pave the way to designing drugs to combat the aggregation. This aggregation in AD is driven by two 6 amino acid sequences2, PHF6 and PHF6* and these motifs are the focus of our work.

Through use of a carbonyl vibrational probe, and using vibrational solvatochromism in Raman spectroscopy in range of parameterised solvents, we hope to further categorise the vibrational frequency shift of the probe in response to a range of dielectric conditions, thus allowing calculation of the electric field experienced by the probe.3 The electric field experienced by a molecule can be thought of as the sum of all the interactions experienced on the molecule, including solvent interactions, hydrogen bonding, dipole interactions etc. and gives a good description of the environment experienced by the molecule at a given time.

The calculation of the electric field can then be compared to those predicted by Molecular Dyanamics (MD) simulations in order to validate and calibrate the results of MD simulations.

Choice of the probe of choice has been critical, in addition to choice of experimental technique to isolate the probe's Raman spectra from that of the solvent, and much work has gone into choice of probe and experimental set-up and conditions, allowing probe Raman signal to be extracted from solution at modest concentrations.

Through this technique we hope to validate the results of tau aggregation in-silico MD experiments and thus potentially provide a framework to apply to other protein aggregates and a platform to test potential therapeutics.

Identifying microRNA-mRNA networks involved in carboplatin resistance in lung and ovarian cancer.

Nikolaos Sideris, University of Sussex

Carboplatin is a platinum-based DNA-damaging agent utilized in chemotherapeutic regimens for the treatment of various malignancies, especially lung and ovarian cancers. Despite improvements in survival most patients are eventually faced with relapse due to the development of resistance, but the mechanisms involved in its development are not fully understood. In recent years microRNAs have emerged as key players in the initiation and progression of cancer. MicroRNAs are small non-coding transcripts which repress gene expression at the post-transcriptional level. Accumulating evidence has shown their involvement in chemoresistance against various drugs across multiple cancers through regulation of genes crucial to this process but their role in the induction of carboplatin resistance has not been fully investigated. Our hypothesis is that networks of miRNA-mRNA interactions are involved in the formation of carboplatin resistance in these cancers. The purpose of this project is to interrogate these cellular networks. We performed small RNA sequencing to identify relevant RNA and we will define the mRNA targets of these miRNAs to identify potential microRNAs and their targets that are dysregulated in carboplatin resistance. At this stage we have selected common differentially expressed microRNAs for validation and further characterization. Additionally, our future plans include utilizing CRISPR-Cas9 to study how changes in these microRNAs affect carboplatin resistance. Understanding the evolutionary processes governing the formation of resistance is the key to developing new effective methods to overcome it. Therefore, identifying the networks involved in these processes will provide new insights and open the door to identifying new prognostic biomarkers and developing therapeutic avenues.

Controlling meaning for new memories

Fiona Lancelotte, University of Sussex

As we age, our general knowledge and appreciation of meaning improves while our memory for specific occurrences declines. We may know that a seagull is a thief of chips but forget a recent visit to the beach. Older people may be less able to control how this prior knowledge is used, however, not all types of control are impacted equally. It's likely that with age the relationship between knowledge and memory changes with control processes playing a key role. It is still unclear how processing for meaning impacts what we remember and the conditions in which it may help or hinder older adultsâ€™ performance.

My research investigates how controlling access to meaning may change how memories are represented in the brain, and what representations influence what we remember and forget. Using generalised linear mixed models, we have found that controlled access to knowledge increased generic memory (e.g., you saw an apple), but at the expense of specific memory (e.g., the specific apple) compared to a form of control focused on retrieving task-relevant information, which may help in remembering other aspects about the event (e.g., where you saw the apple).

Using behavioural and functional imaging methods we will next investigate the processes and brain representations that contribute to remembering, focusing on how controlled access to meaning may shape our memories. This work will provide valuable insights into how knowledge collected over the lifespan supports memory performance, and how this effect may change with age.

Unveiling the role of ApoE in microglial development

Dyuti Basu Choudhury, University of Southampton

Microglia are the CNS's first responders, surveilling for threats through morphological changes, enabling phagocytosis and protection. They play pivotal roles in brain development, regulating neural circuit formation, synaptic pruning, and myelination. Implicated in Alzheimer's disease (AD) pathogenesis, microglia exhibit APOE upregulation, especially in APOE4 carriers. APOE4 disrupts lipid homeostasis in microglia, leading to inflammation and impaired phagocytosis, and potentially hindering AÎ² and tau clearance. Microglial dysfunction associated to APOE4 may manifest during adulthood or in response to challenges, affecting brain health. Analyzing an integrated atlas of microglial cells across the lifespan, We show a selective upregulation of APOE expression in microglia during development, specifically around the ages P4-P7. Now, we aim to study whether the presence of two different APOE alleles (3 vs 4) influences the functionality of microglia across the embryonic, post-natal and adult ages. Using targeted replacement mice carrying the human APOE3 or E4 alleles, we found an increase in the density of microglia in the corpus callosum at P7 in E4 mice compared to the E3 mice. We also observed differences in microglial morphology between the E3 and E4 mice. The next steps would be to analyze the transcriptomics of microglia with the different alleles through single cell RNA sequencing, comparing early postnatal and adult mice, to see whether allelic differences cause differential profiles of microglia linked to altered functions during development, which in turn affects brain homeostasis in later stages.

Development of AAV gene therapy and their manufacturing for treatment and prevention of disease

Oya Isilay Canik, University of Kent

The use of gene therapy products for the treatment of a large range of indications and as potential vaccines in the clinic shows great promise but producing high titer viral vectors and manufacturing at scale remains a challenge and contributes to the cost of these therapies. The primary aim of the project is to increase the amount of functional titer (correctly assembled and packaged) of rAAV2 (Recombinant Adeno-associated virus serotype 2) vectors for gene therapy and to reduce its cost of production with HEK293F cells and to create novel, industrially relevant HEK293 cell lines for enhanced AAV production. Recent research in the literature highlights the work on AAV plasmid ratios in transfection as a factor in making a difference in functional AAV titer. My data so far contributes to this output and especially Rep2/Cap2 plasmid sequences are under investigation to enhance the higher functional titers of rAAV for gene therapies.

Risky decision-making: Revealing the neural mechanisms of behaviour selection to maximise survival.

Annie Robertson, University of Sussex

To maximise their chance of survival, animals need to combine sensory inputs from their environment with information about their internal state (e.g. how hungry they are) in order to select the most appropriate action. However, in many instances the nature of these inputs can lead to conflicts in decision making. How does a hungry animal that is under the immediate threat of predation decide whether to feed or flee? The mechanisms by which the circuits in an animal's brain computes the best response to keep an animal alive, are therefore of great interest but remain poorly understood. Here, by taking advantage of the pond snail, Lymnaea stagnalis, a classic experimental model system with simple behaviours and accessible brain circuits, we are able to investigate the key decision-making processes in exhaustive detail. We show that the presence of predator cues causes fed animals to suppress feeding and initiate escape behaviours, while hungry animals reverse these actions to maximise food-searching at the increased risk of predation. Using methods based on electrical recordings from single neurons in the brain, we are now investigating how threat-conflicts are computed and how this remarkable reconfiguration of behavioural output is achieved. In parallel, we are developing a novel recording method, based on fluorescent imaging, that will allow us to assay hundreds or thousands of neurons simultaneously, providing unique insights into how decision-making is processed across the nervous system.

Environmental and genetic determinants of Brassica crop damage by the agricultural pest Diamondback moth

Shubhangi Mahajan, University of Southampton

"Environmental and genetic determinants of Brassica crop damage by the agricultural pest Diamondback moth

Shubhangi Mahajan, Dr Stephanie Bird, Dr Haruko Okomato, Dr Herman Wijnen

Annually US$4-5 billion damage to the world economy is caused by the diamondback moth (DBM) Plutella xylostella, a pest for Brassica crops. DBM is a widely distributed species that thrives on a broad host range of cruciferous plants. Its long-distance migration and high capacity for developing resistance to plant (host) defence mechanisms and insecticides make it arguably the most impactful lepidopteran pest. Prior studies in the lab have demonstrated the importance of clock-controlled pest-plant interactions in determining DBM herbivory.

The overarching aim of this study is to investigate how abiotic environmental factors and genetically encoded molecular properties of both DBM and its host plants determine crop damage by DBM. Specifically, I will conduct time course analyses of DBM caterpillars to identify how rhythmic host plant signals modulate their transcriptome. I will also use the model cruciferous plant Arabidopsis thaliana to identify genetic mutants impacting relevant plant defence pathways. Finally, in collaboration with the Royal Horticultural Society, the CASE partner for my project, I will test some of the predictions from my work in a field setting.

Investigating the effect of regenerative agricultural practices on the farm animal microbiome

William Edwards, University of Kent

My PhD is centred around investigation into the role of the microbiome of farm stock in the effectiveness of regenerative agricultural practices. My project has multiple angles, with work concerning insects cattle and bison. I will be presenting my work with cattle. Having established a lab at bank farm in Ashford, we have begun experimenting with the production and feeding of bio-charcoal (biochar) to cattle located at the farm. Feceal samples were collected from the cattle before and after the addition of the biochar, and extracted DNA was sequenced. The experiment looks at two aspects of the microbiome, the 16s-targetbale species (bacteria and archaea) which includes methanogens responsible for the production of the greenhouse gas methane. The second group of interest are the recently discovered and poorly understood phylum of anaerobic gut fungi (AGF), these are documented to interact and even potentially regulate the methanogens in the gut. Our experiment utilises a meta-genetics approach to sequence and investigate the microbiome of the cattle at bank farm. Our pilot study has yielded interesting results, with significant reductions in diversity of AGF, with notable reduction in orpinomyces and dominance by anaeromyces. post-biochar as well as major fluctuations in the bacterial and archaeal microbiome. There is seen to be a reduction in methanobrevibacter (the dominant methanogen) over the time course, possibly suggesting a reduction in methane production.

Unravelling the brain mechanisms behind how cognitive and physical stimulation dampens food cravings and food consumption in mice

Emily Woods, University of Sussex

Learned, environmental signals or cues that are linked with food availability help animals and humans survive by motivating us to seek out food sources. However, exposure to these cues may provoke undesirable reactions such as food cravings, which may promote unhealthy overeating. Research to date has primarily revealed how the brain responds to cues that promote food cravings and food-seeking. Yet there remains a significant gap in understanding how the brain can counteract these cues and suppress food cravings and food seeking. Previous research in mice has revealed that brief exposure to environmentally enriched (EE) housing that provides cognitive and physical stimulation reduces cue-induced food seeking and food consumption. Thus, EE likely dampens the motivational impact of food cues by decreasing food's rewarding value. We have currently identified that food cues activate sparse sets of neurons or neuronal ensembles in reward-related brain regions, such as the prefrontal cortex (PFC). The orbitofrontal cortex (OFC), which is part of the PFC, interprets information about reward value and guides motivated actions. Hence, our project aims to reveal how OFC neuronal ensembles coordinate EE's effects on attenuating cue-evoked food seeking. To this end, we will examine how EE modulates the activation patterns and plasticity (e.g. changes in neuronal morphology and connectivity) of OFC neuronal ensembles. With obesity posing a significant health burden globally, understanding how EE modulates neuronal activity to reduce food cravings holds promise for addressing this pressing public health issue.

The Evolutionary Role of Genome Instability in Fungal Pathogens

Matt Shaw, University of Kent

"Candida albicans a member of the healthy human microbiome and an opportunistic pathogen, causing infections ranging from superficial to systemic. During systemic infection, C. albicans can rapidly adapt to any niche in the body and can acquire drug resistance. These traits are partially attributed to its genomic instability, which generates diversity and allows selection of fitter genotypes. This is apparent from the diversity of karyotypes seen in clinical isolates which often have breakpoints around repetitive elements. Such elements include the Major Repeat Sequence (MRS), a repeat array occurring throughout the C. albicans genome. We hypothesise that repetitive elements including the MRS serve as instability hotspots to facilitate genomic rearrangements and rapid evolution.

This project aims to establish a cause-and-effect relationship between repeat-associated chromosomal rearrangements and generation of fitter genotypes. To this end, we have used CRISPR-Cas9 to generate double strand breaks within repetitive elements, inducing chromosome rearrangements. These unstable strains have then been phenotyped, and evolved in clinically relevant stresses, including antifungal drugs.

Long-read sequencing has then been used to characterise the novel genotypes. This has shown that CRISPR-Cas9 can be used to generate different classes of chromosomal rearrangement in C. albicans. Strains bearing rearrangements have morphological and fitness changes, indicating that rearrangements at repeat loci are sufficient to generate phenotypic diversity. Preliminary experiments demonstrate that these strains are also less stable and undergo more frequent karyotype changes during evolution experiments. Further work will look at the effect of this instability on their ability to adapt to stress. "

Understanding reward and withdrawal in habitual caffeine use

Tatum Sevenoaks, University of Sussex

"Caffeine sourced primarily in coffee stands as the most widely consumed psychoactive substance globally, yet we still have a poor understanding of the reward and withdrawal processes driving habitual caffeine use. Although caffeine's potential for abuse is low, habitual consumption results in markers of addiction and dependence, with symptoms of withdrawal occurring when deprived. Previous research has demonstrated the characteristics of caffeine in terms of its withdrawal effects on mood, cognition, and preference. However, fundamental questions persist regarding how habitual caffeine consumption effects brain activity between those that are acutely deprived and not deprived of caffeine and ultimately how caffeine fits into our current theories of addiction.

My research aims to address these gaps using a combination of both fMRI neuroimaging and behavioural techniques, with two major studies ongoing. The first aims to analyse the effects of habitual caffeine consumption and acute deprivation on mood, cognition, and brain activity. The second aims to test the Incentive-sensitisation theory of addiction, investigating the effects of habitual coffee consumption and acute deprivation on wanting and liking for coffee. The outcomes of this research aim to further our understanding of the basic mechanisms that underly our affinity to consume caffeinated products, contribute towards theories of addiction, and in turn provide insight into the impact of habitual caffeine consumption on mental and physical health outcomes."

Intracellular-targeting novel compounds and the exploration of mammalian cell membranes and membrane transporters

Olivia Keers, University of Kent

"It is estimated that in the UK, there are around 170,000 deaths a year attributed to cancer, which in 2021 was equivalent to one in four of all UK deaths1. Resistance to current cancer treatments is rapidly increasing meaning there is an urgent need for novel anticancer agents to tackle this crisis. Cancer cells can control what enters the cells through the use of transporters within the cell membranes. These transporters are attuned for specific cargo; thus, efforts are underway to produce anticancer agents which can access this transport system, in a trojan horse approach. Specifically, cancer cells, due in part to their uncontrolled proliferation, have been shown to have an increased expression of L-type amino acid transporters 1 (LAT1)2.

A series of molecules have been designed which utilise an amino acid residue, joined through a urea moiety to a known targeting group. The scope of this work is to demonstrate whether the self-association capabilities of these novel compounds can be utilised to disrupt intracellular organelle membranes, with the hypothesis that a lower concentration of compound would be needed to induce a cytotoxic effect on the target cells. This work will also investigate whether amino acid transporters can be used for the influx of compounds into the cell.

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Drug repurposing to target Mycobacterial cytochrome bd

Ryan Boughton, University of Kent

Computationally screening drug libraries containing hundreds of thousands of compounds using in silico methods to predict binding towards Mycobacterial cytochrome bd, before selecting key compounds for in vitro testing. Combining wild type and mutant knock-out strains of Mycobacterium smegmatis, we can experimentally quantify compound efficacy determining IC50 and bacteriostatic/cidal nature of each compounds. Additionally, we have cloned M. smegmatis cytochrome bd and expressed in E. coli expanding the suite of techniques available, including the ability to purify mycobacterial cytochrome bd protein complex. Utilising oxygen consumption measurements, viability assays and spectrophotometric kinetic assays we can confidently assess these compounds effects on purified protein, isolated membranes, and whole cells. This work has the potential to change the treatment of Mycobacteria with plans to expand into more ESKAPE pathogens, by discovering new inhibitors and repurposing drugs to overcome the current antimicrobial resistance pandemic.

Understanding the Antimicrobial Properties of Natural Plant Extracts and Potential Impacts on Upper Respiratory Tract Diseases and Health

Iolanta Spanner University of Southampton

Upper respiratory tract infections (URTIs) are among the most common diseases globally, and although most cases are not life-threatening, symptoms negatively affect quality of life and result in a huge societal burden, both economically and socially. Moreover, with the rise of antimicrobial resistance, there is a need to develop novel approaches to treat infectious diseases. To this day, tea remains a hugely popular beverage around the world, second only to water and currently, there is a vast amount of research documenting the plethora of benefits and antimicrobial properties of common tea ingredients. This project aims to explore the relationship between herbal tea and URTIs, in order to fill a gap in research knowledge regarding the impact of herbal products on human health, and how we can enhance our current repertoire of prevention and treatment options. Currently, this investigation utilises a wide range of techniques, including various antimicrobial assays, advanced microscopy techniques, such as Scanning/Transmission Electron Microscopy (SEM/TEM) and Confocal microscopy, and chemical analysis using High-Performance Liquid Chromatography (HPLC) to understand the composition of various antimicrobial natural extracts. More recently, work has been done to develop bacterial biofilm communities, which have then been visualised using Confocal and Episcopic Differential Interference Contrast (EDIC) microscopy, under different treatment conditions. As biofilms represent the cause of many persistent URT infections, leading to burdensome healthcare complications, further work will aim to investigate the anti-biofilm properties of these various natural extracts, thereby increasing the research impact and value to real-life instances of infection.

Safeguarding UK Hops from Verticillium Wilt

Simon Thundow, University of Kent

UK hop production has declined by over 70% since 1981, in part due to the emergence of highly-pathogenic strains of the wilt-causing fungus Verticillium nonalfalfae. Hop cultivars which had previously been considered resistant to Verticillium wilt have since exhibited susceptibility to the disease, suggesting the emergence of resistance-breaking strains of Verticillium nonalfalfae. However, the molecular mechanisms underlying this host-pathogen evolutionary arms race remain unclear. This study seeks to determine how UK-specific pathotypes of V. nonalfalfae have evolved and what molecular mechanisms underpin their increased virulence.

Using newly-generated whole genome assemblies from V. nonalfalfae isolates collected from UK hops, we aim to investigate the evolutionary relationships between isolates of different pathotype through phylogenomic analyses. We also hypothesise that genomic variation between pathotypes will reveal candidate effector genes which may be involved in virulence on hop. We also seek to determine whether molecular differences in pathotypes could be used to develop pathotype-specific diagnostic protocols which may allow rapid in-field identification of aggressive strains of V. nonalfalfae. Furthermore, by identifying effector genes specific to V. nonalfalfae strains we can suggest potential targets for novel fungicides or identify new plant resistance pathways through Host Induced Gene Silencing. Overall, our research aims to improve our understanding of Verticillium wilt and give us more tools to tackle the disease.

Modern warfare: optimising PROTACs to battle disease.

Johanna Fish, University of Southampton

The abundance of E3 ligase signalling enzymes in the Ubiquitin Proteasome System (UPS) provides a new modality to assist protein degradation through UPS catalytic hijackers, namely, PROteolysis-TArgeting Chimeras (PROTACs). These molecules comprise three parts: a protein of interest (POI) warhead and an E3 ligase targeting warhead connected by a linker. Despite the benefits of protein degradation over reversible inhibition and early promise in the clinic, their pharmaceutical properties are unsatisfactory. Thus, modifications to improve the bioavailability of this drug class are pertinent for their therapeutic viability.

We are optimising on of the lead E3 ligase warheads to recruit the von Hippel-Lindau (VHL) tumour suppressor protein, a ubiquitous and abundant component of an E3 ubiquitin ligase complex. Through structure-based design and in silico studies, we aim to identify new synthetic ligands of VHL to improve the physicochemical properties of their resulting PROTACs.

Our multi-disciplinary approach to early PROTAC drug discovery focuses on computational design and organic synthesis, alongside biochemical and cellular evaluation, and structural characterisation. The full PROTAC construct will then be considered and adjusted to improve the aforementioned properties, ready for further investigation. Future work will evaluate the potential of these next generation PROTAC molecules across a wider range of disease driving targets, could be significant for drug discovery and improving patient outcomes.

Domesticate this, not that: why are certain species more likely to be domesticated?

Anastasia Kolesnikova, University of Southampton

Out of the tens of thousands of edible species, only 250 species are considered domesticated. Before agriculture began in the Neolithic, humans in the Fertile Crescent exploited a large diversity of plants, collecting and cultivating them, but many were abandoned. While the development of agriculture is an essential part of history, an unanswered question remains. What made certain wild plants more likely to be successfully domesticated?

I am exploring three hypotheses to answer this question. The first is that the rate of mutation would have influenced domesticability - the variation in the ability of a species to undergo domestication. Domestication relies on novel phenotypes, therefore, if they arise more quickly in some species than others, humans may favour these species, continuing to grow them.

The second is that the genetic architecture influenced domesticability. If traits selected by humans are conferred by large effect loci and/or are linked on the same chromosome, then selection could proceed faster. In other species, beneficial traits may be controlled by small effect loci and/or be unlinked, leading to inefficient selection and abandonment.

The final hypothesis is that phenotypic integration influenced domesticability. Certain phenotypes can be linked to each other, for example, big seeds produce bigger and hardier plants. They may influence each other's expression under certain conditions, providing an advantage to certain species.

This work opens a discussion about whether certain species are predisposed to succeed under certain conditions, with implications for neo-domestication, food security, and biodiversity response in a changing climate.

Caught in a Trap: The Biochemical Characterisation of the TAXI-TRAP Substrate Binding Protein Vc0430 from Vibrio cholerae

Joseph Davies, University of Kent

Tripartite ATP independent periplasmic (TRAP) transporters are widespread in prokaryotes and are responsible for the transport of a variety of different ligands, primarily organic acids. TRAP transporters are secondary active transporters that employ a substrate binding protein to bind and present the substrate to membrane embedded translocation component. TRAP transporters can be divided into two subclasses; DctP-type and TAXI type, which share the same overall architecture and requirement of the SBP for transport, but their SBPs share no similarity. The DctP-type transporters are very well studied and have been shown to transport a range of compounds including dicarboxylates, keto acids, sugar acids. However, the TAXI type transporters are relatively poorly understood, with the range of transportable compounds still to be discovered and selectivity requirements for binding unknown. To address these shortfalls in our understanding, we have structurally and biochemically characterized VC0430 from Vibrio cholerae revealing it to be a monomeric high affinity glutamate binding protein.

Development of Novel Methods to monitor Drug Uptake

Matthew Rice, University of Kent

The growing threat of Antimicrobial Resistance (AMR) means that there is an ever increasing need to develop novel antimicrobial compounds. Also, with an aging population, cancer continues to pose a large threat to human health. Both fields have struggled with the development of new drug-based treatments for many years. Numerous compounds could effectively irradicate invasive organisms or cancers, however, these compounds are often limited by their ability to cross biological membranes and successfully carry out their mode of action. We have developed a novel technique which allows monitoring of small molecule permeation across clinically relevant biological membranes, including ESKAPE pathogens and cancer cell lines. The technique utilises Nuclear Magnetic Resonance (NMR) to observe unique spectral differences when compounds associate with a membrane, are passively permeable across a membrane or are completely impermeable. One of the mechanisms supporting AMR or cancer resistance involves the alteration of the lipid composition. To correlate lipid composition and small molecule permeability, we have designed a pipeline where we perform lipid extractions from the relevant cell lines/bacterial strains, quantify their lipid composition and measure drug passive permeation. By collecting this information on multiple types of lipid compositions and small molecules, we are determining the rules governing drug passive permeation in both eukaryotic and prokaryotic cells, which will inform the next generation of anticancer drugs and antimicrobials.

Raman Spectroscopy Coupled with Machine Learning Unveils Temporal Cell-Associated ECM Signatures for Early Classification of Osteosarcoma Cell Lines

Theo Hornsey, University of Southampton

Osteosarcoma (OS) is the most common and deadly malignant bone tumour. Its lethality is largely due to the slow and difficult diagnostic process, involving both biopsy and imaging. New approaches are required to improve diagnostics and patient outcomes. OS is characterised by an altered extracellular matrix (ECM) and vasculature for tumour progression into metastasis. We previously found that human OS cell lines can be distinguished from murine osteoblast (OB) cells using Raman Spectroscopy (RS). We now aim to combine RS with machine learning (ML) to predict the different OS grades via their ECM signatures. Human Soas-2 (low-grade), human MG63 (medium-grade) and human 143B (high-grade) OS cell lines were cultured in-vitro for up to 14 days; as were Murine OB cells (MC3T3). Raman spectra of individual cells (n=15 per subgroup) were collected at day 1,4 and 14. Random Forest ML models of spectra were developed in Python to classify a cell as OS or OB, including pathological grading. OS phenotypes were predicted with an average 79.87% accuracy both within and between timepoints, indicating that each cell produced a unique and temporally distinct cell-associated ECM as early as day 1 in development. Multiple ECM components including collagen, lipids, amide I and III were identified as important features for prediction between cell lines. Using machine learning on Raman spectra of the extracellular matrix, we can accurately predict the different grades of murine OS cells. This suggests that our developed technique may be used to improve osteosarcoma diagnosis, thereby leading to better patient prognoses.

Factor inhibiting hypoxia-inducible factor-1 (FIH) as a potential guardian of alveolar epithelial cells.

Yomna Moqidem, University of Southampton

Idiopathic pulmonary fibrosis (IPF) is a fatal disease characterized by irreversible lung scarring and disrupted gas exchange. Experimental and clinical evidence indicates that persistent injury to epithelial cells plays a crucial role in initiating the disease. Emerging studies suggest that hypoxia and hypoxia-inducible factors (HIF) contribute to disease pathogenesis. Although extensive research has been conducted on the role of the HIF pathway in IPF, the role of factor-inhibiting HIF (FIH), a hydroxylase modulating HIF, and ankyrin-repeat-domain proteins, remains unexplored. This study investigates the impact of FIH deletion on alveolar epithelial cell dynamics using CRISPR/Cas9-mediated gene knockout in A549 cells. Transcriptomic analysis post-FIH-knockout delineated significant alterations that predispose to fibrogenesis, including cellular senescence, mitochondrial dysfunction, and epithelial-to-mesenchymal transition (EMT) pathways. This pro-fibrotic microenvironment was characterized by the upregulation of genes encoding SASP and EMT-associated secretory proteins. Our findings suggest that FIH might act as a sentinel in alveolar epithelial cells, maintaining cellular integrity and homeostasis. The absence of FIH catalyzes a progression toward a fibrotic phenotype, elucidating a novel aspect of IPF pathogenesis. These insights suggest FIH as a critical therapeutic target, with its modulation offering a potential avenue to alter the trajectory of IPF. This study underscores the imperative for advanced research to validate these outcomes. Further deciphering FIHs regulatory mechanisms will open a new frontier in the treatment paradigm for IPF.

Identification of Novel Antifungals against Rhizopus microsporus

Jake Hudson, University of Kent

Collectively, Rhizopus spp. are responsible for 70% of cases of mucormycosis, which has a mortality of over 90% in a disseminated infection. Current antifungals and debridement have limited efficacy, with the latter causing life-long damage and scarring. Preventative antibiotic treatments in at-risk patients can increase the likelihood of a patient developing mucormycosis, hinting that bacteria in the wound may have been preventing an infection. Previous work from the Hall lab has demonstrated that one factor produced by Pseudomonas aeruginosa which inhibits spore germination are siderophores, however it appears that others remain. Here, we show that rhamnolipids produced by P. aeruginosa, which have demonstrated antifungal efficacy against Alternaria alternata, Mucor circinelloides and Verticillium dahlia, may also be effective at inhibiting the germination of Rhizopus microsporus spores. Therefore, they could present a promising avenue for developing a further treatment.

A novel interaction between Amyloid Precursor Protein and Talin

Natasha Ward, University of Kent

Around 1 in 10 people over 65 are living with dementia. Alzheimer's Disease (AD), the leading form of dementia, was first characterised by Alois Alzheimer in 1906. Since then an array of hypotheses have been put forward to explain the mechanism behind this disease, however testing of these has not yet led to a cure. Recent advances in genome wide association studies have uncovered a vast network of AD risk modulators, further emphasising the complexity of the disease mechanisms involved. We have discovered that one of the main proteins involved in AD, the Amyloid Precursor Protein (APP) can bind to the mechanosensitive protein Talin, suggesting a previously unreported bio-mechanical link to AD. I am developing an overarching hypothesis to understand the role of cellular biomechanics in AD, with the ultimate aim of devising new approaches for therapies and cures to this debilitating disease.

Targeting mitochondria for next generation antifungal compounds.

Dima Prasolov, University of Kent

Cryptococcus neoformans is an opportunistic fungal pathogen that predominantly affects immunocompromised individuals, causing as many as 181,000 deaths annually. One of the hallmark features of this fungus is its ability to persist within the host in a dormant state for decades. It has been observed that as many as 70% of children in densely populated areas in the USA are exposed to this yeast. The identification of multidrug-resistant strains as early as 1999, coupled with the recent inclusion of C. neoformans in the fungal priority pathogen list by the World Health Organization, underscores the urgent need for new drug development. One potential target for the development of novel drugs is the mitochondria, which play a central role in vital life processes such as energy production, ergosterol biosynthesis, and iron homeostasis. Unlike human cells, C. neoformans possesses an alternative oxidase system encoded by the AOX1 gene. In many fungal pathogens AOX allows them to maintain mitochondrial function despite oxidative stress. Nitric oxide is of particular interest as it is a compound naturally produced by macrophages to kill pathogens. Here we present evidence of our investigation of Aox1 function in C. neoformans. Our data suggest that Aox1 is important for production of virulence factors such as the capsule as well as for maintain oxidative phosphorylation

Caught in the act: Aptablotting for decoding the signals by two-component systems

Johan Issac, University of Southampton

Two-component signalling systems (TCSs) are main signalling pathways in bacteria, which control major physiological processes, particularly antimicrobial resistance. TCSs consist of a sensor histidine kinase (HK) and a response regulator (RR). The HK senses environmental stimuli, self-phosphorylates its own histidine residue, and finally transfers the phosphate to an aspartate residue of the RR. The phosphorylated RR binds to the promoter region of downstream genes, triggering transcriptional changes. Unlike kinase networks in eukaryotes, for which various specific antibodies for important phosphorylated kinases or proteins exist, the lack of proper tools hampers the progress in studying prokaryotic TCSs. This project aims to use aptamers, which are small oligonucelotides (20 to 80 bases long), instead of antibodies, to study the HptRS and SaeRS TCSs in Staphylococcus aureus. The Hpt TCS is known to produce key virulence factors, and Sae TCS has been found to aid in production of virulence factors, but a clear connection between the two in the progress of pathogenesis has not be established. The plan is to first use a well-established SELEX process, a method to screen for aptamers with affinity to desired targets (HK and RR of both TCSs) from a large oligonucleotide library. Once suitable aptamers have been generated, their binding affinities will be measured. Subsequently, their binding affinity, specificity and selectivity will be confirmed using S. aureus wild-type and TCS-specific knockout mutants. Finally, the fully characterised final aptamers will be used for aptablotting of S. aureus in various conditions affecting Hpt signalling, with the goal of probing cross-talk between the two TCSs.

Targeting potassium channels in oligodendrocytes to maintain myelin and a healthy brain across the lifespan

Ian Hunter, University of Portsmouth

Oligodendrocytes are specialized cells within the central nervous system that form myelin, the insulating layer around nerve axons, which is critical for efficient signal transmission and trophic support of neurons. In energetic terms, neurons are highly demanding, relying on a substantial supply of both oxygen and an expenditure of ATP to carry out their basic functions. Sustained maintenance of oligodendrocytes in addition to myelin integrity throughout life is essential for cognitive function and neuronal durability. Recently published studies demonstrated myelin loss alongside white matter disruption as significant contributors to brain-ageing, a significant contributor in age-related cognitive decline. Therefore, further insight into the mechanisms underlying life-long maintenance of oligodendrocytes and myelin is crucial to facilitating a healthy brain environment throughout the lifespan. We have identified that the novel inward rectifying potassium channel Kir7.1 is essential for preserving oligodendrocyte integrity, highlighting the key functions potassium channels play in oligodendrocytes. Thus, novel investigation targeting the modulation of channel activity is vital to further elucidating the functional significance of potassium channels in the genetic, pharmacological, and metabolic factors that promote oligodendrocyte function and integrity.

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Abstracts for Posters (year 3)

Enhancing integrin-mediated axon regeneration following spinal cord injury

Mathew Davis-Lunn, University of Southampton

"Spinal cord injuries can result in severe damage to the axonal fibres that allow the brain and body to communicate. Recovery of this communication is dependent upon regeneration of axons through the injury site, which is typically unsuccessful due to a combination of an inhibitory extracellular matrix (ECM), and lack of intrinsic ability of neurons to regenerate. Current regenerative therapies are limited, with most treatments only capable of minimising damage to the central nervous system. Delivery of a specific integrin receptor to regenerating neurons has emerged as a potential gene therapy approach, enabling axons to adhere to, and grow through, lesioned ECM. The integrin receptor binds the ECM, supporting the construction of intracellular protein complexes that mediate downstream signalling.

Our project targets the integrin adhesion complex, with the aim to enhance the efficacy of integrin-mediated neurite outgrowth in vitro. We combine the use of primary neuron culture, with combinations of both inhibitory and growth-promoting ECM substrates. Our results confirm multiple adhesion proteins are therapeutic targets to promote neurite outgrowth, and will contribute towards a mechanistic understanding of how integrin adhesion sites mediate neurite outgrowth in vitro. Further work is underway to develop novel technologies which can promote significant axon regeneration in vivo following spinal cord injury."

Utilisation of bacteriophage-based biofilm community editing techniques for the enhancement of wastewater treatment efficiency

Matt Irwin, University of Southampton

"Wastewater treatment plants (WWTPs) face increasingly stringent nutrient discharge standards to protect environmental water bodies and human health. Poly-phosphate accumulating organisms (PAOs) are microbes that mediate enhanced biological phosphorus removal (EBPR). PAO are however often outcompeted by glycogen accumulating organisms (GAOs), limiting total phosphorus removal. Previous research has identified a link between GAO abundance and elevated wastewater temperature. Current control mechanisms for limiting GAO require physical or chemical process alterations. However, these alterations have been shown to limit the performance of other aspects of biological nutrient removal (BNR) and enhance nitrogen-based greenhouse gas (GHG) emissions. With the advent of rising global temperatures more regions globally are expected to operate with elevated levels of GAO competition. In addition, some WWTPs already operate at elevated temperatures due to geographical location, seasonal temperature variations and/or heat-treated trade wastewater influent.

We aim to develop a novel bacteriophage-based approach that triggers lysis of GAO as a biological control mechanism for limiting competition between these organism groups. Additionally, with the advent of newly developed targeted genome editing tools, particularly DNA-editing all-in-one RNA-guided CRISPR-CAS transposase (DART), we are exploring new approaches for biological control and enhancement to improve EBPR efficiency. Collectively, this research will demonstrate how biological tools and control mechanisms can be a feasible approach for biofilm community editing and enhancement of WWTP performance."

Droplet microfluidics for time-resolved serial crystallography

Jack Stubbs, University of Southampton

Serial crystallography requires large numbers of microcrystals and robust strategies to rapidly apply substrates to initiate reactions in time-resolved studies. Here, we report the use of droplet miniaturization for the controlled production of uniform crystals, providing an avenue for controlled substrate addition and synchronous reaction initiation. The approach was evaluated using two enzymatic systems, yielding 3 Â µm crystals of lysozyme and 2 Âµm crystals of Pdx1, an Arabidopsis enzyme involved in vitamin B6 biosynthesis. A seeding strategy was used to overcome the improbability of Pdx1 nucleation occurring with diminishing droplet volumes. Convection within droplets was exploited for rapid crystal mixing with ligands. Mixing times of <2 ms were achieved. Droplet microfluidics for crystal size engineering and rapid micromixing can be utilized to advance time-resolved serial crystallography.

Biophysical Characterisation of Recombinant E. coli Vesicles

Bree Streather, University of Kent

Using a short peptide tag, we have developed a way of inducing production of recombinant membrane vesicles in E. coli, containing a protein-of-interest, which are often exported into the media. This enhances protein yield up to 100-fold, simplifies downstream processing and enables production of otherwise toxic proteins. My current focus is to carry out biophysical analysis of these recombinant vesicles and the cells they are produced from in order to gain further understanding of the mechanism of action.

Structural Basis for Acidic and Anaerobic Multidrug Efflux by MdtF

Ryan Lawrence, University of Southampton

Multidrug efflux pumps are inextricably linked to the development of antimicrobial resistant bacteria; inhibiting these pumps could therefore potentially recapitulate the activities of previously ineffective antibiotics. The membrane-spanning tripartite efflux pump MdtEF-TolC is upregulated in Escherichia coli within acidic and anaerobic conditions, akin to the gut or bacterial biofilms, where it provides a fitness advantage and confers drug resistance. Currently, no high-resolution structural information for MdtEF-TolC exists. Here, we report the cryo-EM structure of the inner membrane protein, MdtF, in both wildtype and V610F (a mutant which elicits an altered multidrug resistance phenotype) forms to a 3.56 and 3.28 Ã… resolution, respectively. We also present a 3.2 Ã… cryo-EM structure of substrate-bound V610F MdtF, revealing the development of a hydrophobic nook within the ligand binding site which facilitates the capture of planar, aromatic cationic substrates. Crucially, these structures were determined within styrene maleic acid lipid particles (SMALPs) which permits the capture of a membrane protein within its native-like lipid milieu, enabling us to resolve bound structural lipids. Collectively, these studies reveal new insights into the structure-function of an anaerobic multidrug efflux pump which plays key roles in detoxification of noxious substances and antibiotic resistance within acid and anaerobically grown Escherichia coli.

Investigating the Role of 5-Hydroxytryptamine Receptor Subtypes in the Modulation of Cell-specific Immune Function

Jamie Thomas, University of Southampton

"5-Hydroxytryptamine (5-HT), also known as serotonin or 3-(2-aminoethyl)-1H-indol-5-ol, is a phylogenetically conserved biogenic monoamine that can act as a neurotransmitter, hormone, and mitogen, in various locations throughout the body (e.g., nervous system, cardiovascular system, immune system, etc). 5-HT signaling is primarily mediated by the family of 5-HT receptors (1-7), which comprise 15 known mammalian subtypes, that facilitate the activation of numerous intracellular signaling pathways associated with a wide range of biological activities in different cell types [1]. Immunological studies show that almost all immune cells express one or more 5-HT receptor subtypes [2] and many immunological function have been attributed to 5-HT signaling, via specific 5-HT receptor subtypes in different immune cells - highlighting the essential role that 5-HT has within the immune system [3-6]. To date, the full extent of the expression and influence that different 5-HT receptor subtypes have on different immune cells remain relatively unknown. In this project, we aim to utilize a range of molecular, biochemical and cellular techniques to 1) investigate the expression of 5-HT receptor subtypes in a variety of immune cells, 2) characterize the immunomodulatory functions associated with 5-HT signaling, and 3) identify if these functions can be manipulated using known 5-HT receptor agonists/antagonists. This will develop our understanding of both the function of 5-HT and its roles within the immune system, which in turn could shed new light on our understanding of the immune system in general, alongside how it interacts with other organic systems (e.g., neuroimmune axis), under physiological conditions and in diseased states.

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Do frog(hoppers) like wine? Grapevines as host plants of Philaenus spumarius Meadow spittlebug, insect vector of Xylella fastidiosa

Susmita Aown, University of Sussex

"Froghoppers are sap-sucking insects that feed solely on plant xylem. Philaenus spumarius Meadow spittlebug is one of the most widespread spittlebugs in the UK. It feeds on over 100 dicot plants. Meadow spittlebug is the most important vector of Xylella fastidiosa, a bacterial pathogen that causes disease symptoms in plants, such as leaf scorch and plant dieback. Xylella fastidiosa and their insect vectors are a high priority in research as the bacteria caused an epidemic in Italian olive orchards in 2013, costing â‚¬6.3 billion a year. X. fastidiosa has not been found in the UK yet, but there is a high chance it might come from Europe to the UK.

My research is focused on understanding the feeding behaviour of P. spumarius, specifically the host plant preferences of the insect in the UK. P. spumarius feeds mainly on olives and grapevines in continental Europe and the USA, respectively; in California, the economic losses were estimated to be $104.4 million annually. Grapevines are a major commercial crop in the UK. However, we do not know whether the insect feeds on vines in the UK. In my project, I am working with vineyards in South England to study the host plant preference of P. spumarius, study the probing and feeding behaviour of this sap-feeding insect in real time using an electrical penetration graph, and determine if any natural enemies might be affecting the distribution of the insect in vineyards. "

Development of novel small molecule inhibitors of Tyro3 receptor tyrosine kinase

Auste Bakulaite, University of Portsmouth

"Tyro3 is a member of TAM (Tyro3, Axl and Mertk) family, a subfamily of receptor tyrosine kinases. TAMs are involved in promotion of cell proliferation, survival, migration, tumour angiogenesis and suppression of anti-tumour immunity. Tyro3 is overexpressed in multiple different tumours and it is associated with poor patient prognosis. This makes Tyro3 an attractive target in anti-cancer therapeutics. At the moment, there are no clinically approved selective Tyro3 inhibitors.

Previous work from our group using molecular docking analysis has identified a number of small molecules which virtually occupy the kinase ATP-binding pocket of murine Tyro3. Currently, we are working to test these hits as potential Tyro3 kinase inhibitors using both computer-based and experimental models.

We have conducted further searches of a compound library which has yielded hundreds of new molecules similar in size and structure to one of the previously identified hit molecules. The top hits in the docking analysis are subsequently being tested in vitro in a kinase activity assay against Tyro3 kinase activity as well as against kinase activity of other TAMs. Furthermore, novel molecules similar in structure to the docking hits have been synthesised, which we are also currently testing.

This work should yield a number of novel small molecules that are selective inhibitors of Tyro3, and which could subsequently be further studied for development as potential cancer therapeutic agents

Using Caenorhabditis elegans to investigate the potential benefits of Leptadenia hastata on metabolic health

Noviann McLean, University of Kent

“Obesity is a very serious issue worldwide. Current numbers are continuously increasing which has a knock-on effect on the incidence of type 2 diabetes and metabolic syndrome. There are pharmacological interventions available, however, many are associated with side effects, complications and are not readily accessible to rural communities. However, the use of traditional antidiabetic plants such as Leptadenia hastata has been a favoured alternative. This plant is widely distributed across tropical Africa and has shown great potential in metabolic health. Previous mouse studies have shown that Leptadenia hastata treatment led to a notable reduction in body weight, fat percentage, food intake, increased energy expenditure, and improvement in blood glucose and insulin levels. The aim of this study is to establish Caenorhabditis elegans as a good alternative for investigating the metabolic effects of Leptadenia hastata and further explore its benefits using a simpler model organism.

Here, we used a combination of biochemical assays and microscopy to examine: 1) the effects of Leptadenia hastata on mitochondrial health using oxygen consumption, mitochondrial network organisation and Beta-oxidation as readouts; 2) how Leptadenia hastata treatment affects energy stores such as body fat; and 3) how Leptadenia hastata supplementation impacts eating behaviour. The results so far have shown that this plant has a significant effect on mitochondrial health and proton leak, which are key targets for treating diseases such as obesity and diabetes. This study will give further insight into the therapeutic activities of Leptadenia hastata and support further development of the ingredient for future commercial application."

Extracellular vesicle release from the endometrium

Molly Rutt, University of Southampton

"Up to 3% of those attempting to conceive will experience recurrent pregnancy loss, clinically defined as three or more miscarriages. A large proportion of these remain unexplained, and limited medical investigation exists to treat or prevent pregnancy loss.

It is hypothesised up to 75% of these losses may be attributed to issues with embryo implantation, a process reliant on the concurrence of a viable blastocyst and receptive endometrium-the lining of the womb.

We propose extracellular vesicles (EVs) released by glands within the endometrium as a potential metric or regulator of endometrial receptivity, and attempt to characterise and compare EVs in those with recurrent pregnancy loss and those without fertility issues.

Endometrial tissue and fluid was collected from fertility clinics within the Princess Anne Hospital. Electron microscopy was used to visualise vesicles within the gland tissue or free vesicles released into endometrial fluid in the womb lumen. Flow cytometry was used measure size and number of large EVs in the endometrial fluid. qPCR and RNAseq are used to measure the miRNA composition of the vesicles.

Serial block-face scanning electron microscopy has shown EV secretion from gland epithelial cell microvilli, where they average 134nm in diameter, and measured EVs in the gland lumen of a reduced, average size of 77nm. Flow cytometry staining with EV-specific markers CD63 and CD9 suggests a large EV concentration of 5600 vesicles/µl endometrial fluid. EVs purified from endometrial fluid have been shown to contain distinct populations of microRNAs including miR-10b.

As signalling molecules, these microRNAs may be delivered to target cells of the embryo and reproductive tract to drive changes to cellular function or phenotype. Endometrial gland-derived EVs and their contents may be essential biomarkers for endometrial receptivity and as such, pregnancy success. By identifying differences in EVs from women with/without fertility issues we may be able to identify factors responsible for implantation failure or pregnancy loss."

Cohort analysis of Baited Remote Underwater Video (BRUV) and environmental DNA (eDNA) in monitoring marine ecological communities

Alice Clark, University of Sussex

Monitoring the diversity and distribution of species in an ecosystem is essential to assess the success of restoration strategies. Implementing biomonitoring methods, which provide a comprehensive assessment of species diversity and mitigate biases in data collection, holds significant importance in biodiversity research. Additionally, ensuring that these methods are cost-efficient and require minimal effort is crucial for effective environmental monitoring. In this study we compare the efficiency of species detection, the cost and the effort of two non-destructive sampling techniques: Baited Remote Underwater Video (BRUV) and environmental DNA (eDNA) metabarcoding to survey marine vertebrate species. Comparisons were conducted along the University of Sussex coast upon the introduction of the Nearshore Trawling Byelaw. This Byelaw aims to boost the recovery of the dense kelp beds and the associated biodiversity that existed in the 1980s. We show that overall BRUV surveys are more affordable than eDNA, however, eDNA detects almost three times as many species as BRUV. eDNA and BRUV surveys are comparable in terms of effort required for each method, unless eDNA analysis is carried out externally, in which case eDNA requires less effort for the lead researchers. We found that using both methods in conjunction provides a more complete view of biodiversity, with BRUV data supplementing eDNA monitoring by recording species missed by eDNA and by providing additional environmental and life history metrics. The results from this study will serve as a baseline of the marine vertebrate community in University of Sussex Bay allowing future biodiversity monitoring research projects to understand community structure as the ecosystem recovers following the removal of trawling fishing pressure.

Evaluation of thermostability and kinetic stability of HotPETase, a thermotolerant PET hydrolase, and its predecessors in the directed evolution design process

Konstantinos Tornesakis, University of Portsmouth

"Enzymatic recycling of PET plastic requires enzymes with high stability and increased catalytic efficiency, at high temperatures. IsPETase degrades PET polymers, to its monomers, at ambient temperatures, through a Serine-Histidine-Aspartic catalytic triad.

HotPETase, designed with directed evolution, is a thermotolerant variant of IsPETase able to degrade PET at 65 O C. In this project, experimental and computational approaches were used in order to investigate the thermostability and catalytic activity of these two enzymes, as well as their intermediates. Protein unfolding was studied with differential scanning calorimetry. Activation energy and activation temperature showed an increase during the evolution process. HotPETase and one predecessor (M10-HP) displayed increased thermodynamic properties and resilience to denaturation. The PET degradation rates of all enzymes were studied with time course assays, revealing different kinetic stabilities. The experimentally observed optimum temperature for activity was increased from IsPETase to HotPETase. HotPETase showed less degradation yield compared to M10-HP at 65 O C. Both enzymes were then tested in 100mL bioreactor reactions showing the same pattern. Analysis of the PET surface after degradation was performed with scanning electron microscopy. Binding of PET to the active site was investigated with molecular docking calculations. The best docked poses were further refined with molecular dynamics simulations to account for flexibility and temperature effects. Trajectory analysis of the molecular dynamics simulations of IsPETase, M10-HP HotPETase at 30 O C indicated the probability of PET obtaining the optimum distances within the active site. Finally, for simulations at 60 O C, HotPETase and M10-HP were found to have a significantly large probability of obtaining the necessary distances, whereas IsPETase was found to be incapable of retaining the PET in the optimum distances."

Identifying, categorising and exploiting Mycobacterium tuberculosis biofilm-derived phenotypes using a luciferase reporter biofilm model for novel drug discovery

Kaya Taylor, University of Sussex

"Mycobacterium tuberculosis (M.tb) is the causative agent of tuberculosis (TB). TB is the leading cause of death from a bacterial infectious disease. The World Health Organisation estimated that 10.6 million people fell ill with TB in 2021 and 1.6 million people died from active disease. Lengthy and toxic drug therapies are hampering efforts to control this disease, as is the emergence of antibiotic drug resistance. Therefore, the introduction of new drug regimens using novel drugs is fundamental to eradicating this disease.

M.tb has been observed to grow as aggregated clumps or clusters of bacilli both in vitro and in lung tissue, as a single organism biofilm. This aggregated biofilm-like growth causes changes to the phenotype of the bacilli, inducing phenotypic heterogeneity that may impact antimicrobial drug efficacy. Here, we describe the development of an M.tb biofilm model to mimic aggregated extracellular growth in lung lesions and to measure drug action using a luciferase reporter system alongside 16s RNA and CFU. As expected, biofilm-derived M.tb exhibited tolerance to isoniazid, other first line drugs including rifampicin, ethambutol and bedaquilline were also investigated. There were differences in drug tolerance observed between different media conditions, such as a decrease in pH and supplementation with cholesterol. M.tb biofilms will be further characterised by confocal microscopy and electron microscopy, and M.tb-derived populations investigated by flow cytometry and RNA profiling.

Identifying and characterising drug-tolerant M.tb populations will improve our understanding of the action of drugs in vivo and may help advance novel treatment-shortening drug regimens for TB."

Predicting novel drug targets that are synthetically lethal vs. SMAD4 loss in oesophageal adenocarcinoma

Joanna Renaut, University of Sussex

"Oesophageal cancer is a significant global health burden, ranking as the sixth leading cause of cancer mortality worldwide in 2020. The adenocarcinoma subtype (OAC) occurs predominately in the lower oesophagus and gastro-oesophageal junction and is influenced by risk factors such as obesity, smoking and the absence of infection with Helicobacter pylori. Despite advances in medical science, OAC survival rates have seen little improvement over the past five decades.

Standard OAC therapies encompass surgery, chemotherapy, radiotherapy, immunotherapy, and some targeted treatments, including cetuximab, bevacizumab, and trastuzumab, yet none that target the gene SMAD4 â€“ a gene for which loss of function has been challenging to address therapeutically. The introduction of synthetic lethality (SSL) as a treatment strategy has opened new avenues for research, particularly since the discovery in 2005 in its application in BRCA1/2 deficient cancers. SMAD4 has known SSL partners for colorectal cancer such as BET (BRD2 and BRD4), AURKA, KLF5 and, most recently, RAB10.

To further explore SSL partners for SMAD4, we utilised dependency data from the DepMap database to inform predictions of novel SSL pairs. Additionally, we analysed the shortest paths between these pairs using protein-protein interaction networks from STRING to uncover further potential SSL interactions. Each gene's drug target potential was then assessed using the canSAR.ai CPAT tool.

To validate our predictions, we carried out a series of experiments employing CRISPR-Cas9 knockouts and siRNA knockdowns. These experiments confirmed several new synthetic lethal interactions in relation to SMAD4 loss, which could lead to new therapeutic options with further exploration."

Growing complimentary crops and nutritionally rewarding cultivars to sustain insect pollinators and crop pollination on farms

James Woodward, University of Sussex

About 70% of crop plants grown globally rely to varying degrees on insects for pollination. These crops are responsible for 35% of worldwide food production and it has been estimated that ~153 billion of global food production would have been lost in 2005 if pollinating insects were absent. Wild pollinators have declined in abundance and diversity in North West Europe and North America. Pollination deficits for pollinator-dependent crops have been identified. Optimising pollination for pollinator-dependent crops is of great value to society as these crops produce many fruits, vegetables, seeds, nuts and oils which provide sources of micronutrients, vitamins and minerals for healthy human diets. Therefore identifying strategies to mitigate pollination deficits is of international importance. An approach to boost pollinators and pollination on farmland is to develop complementary cropping systems where sequentially flowering pollinator-dependent crops extend the period of forage availability for pollinators. This strategy could be further enhanced by identifying crop cultivars which are highly nutritious and attractive to pollinators. The benefits of this could be two-fold, improving the reproductive success of pollinators and supporting more efficient crop pollination in current and subsequent years. Identifying nutritious crop cultivars involves quantifying the nutritional quality of the floral resources nectar and pollen. Nectar mainly provides a source of carbohydrates, whereas pollen predominantly supplies proteins, lipids and micronutrients. This project investigates whether pollination deficits can be mitigated on farmland by selecting nutritious and attractive crop cultivars for complementary cropping systems."

Investigating the oligomeric state of the E.coli DedA protein YqjA

Tom Paige, University of Kent

Bacterial membrane homeostasis requires the regulated efforts of membrane proteins enacting both directly and indirectly to ensure membrane integrity, cell division, nutrient uptake as well as antimicrobial resistance. The DedA superfamily of integral membrane proteins have been shown to be important in maintaining several aspects of membrane homeostasis, this importance is further reinforced by their extensive inclusion in bacteria. Recent studies have shown several DedA family members are able to transport lipids and this ability to transport lipids has been shown to be highly important in a bacteria's ability to combat antimicrobials, meaning that the DedA family is a prime target for future antimicrobial studies. Limited data on DedA proteins involvement either directly or indirectly in membrane homeostasis means there is a need for structural data, especially for the development of new antimicrobials. Here we examine the oligomeric state of the well-studied Escherichia coli homologue YqjA using analytical ultracentrifugation (AUC), showing that YqjA primarily forms a dimer. We then utilised Alpha fold Multimer modelling to produce models to predict the dimer interface and identify any potential residues involved in dimerisation. The importance of each residue for dimerisation was screened using Copper Phenanthroline (CuPhen) crosslinking, with the outcome being several residues being identified that are key to YqjAs dimerisation. This data gives an insight into the oligomeric state of YqjA and other DedA proteins, this combined with the key dimeric interface residues will aid in furthering the collection of structural data and potentially the production of new DedA specific antimicrobials.

Manipulation of chloroplast density to enhance photosynthesis and nutritional value of tomato

Erick Oliveira, University of Southampton and National Institute of Agricultural Botany

As global population growth continues to put pressure on existing agricultural systems, improving photosynthetic efficiency becomes ever more important to achieve sustainable food security. The ability of crop plants to convert light energy into chemical energy to sustain plant growth is achieved through chloroplasts. In fruits, this is particularly interesting as the conversion from chloroplast to chromoplast during the ripening process is associated with chlorophyll degradation and the accumulation of carotenoids in the chromoplasts, leading to the production of the secondary metabolites associated with the fruit's organoleptic qualities. Therefore, the genetic manipulation of fruit chloroplasts could simultaneously improve both fruit size and quality traits. This study aims to manipulate chloroplast development and density in fruit to produce plants with higher pigment content, enhanced fruit photosynthetic performance, and increased yield. To achieve that, we have identified target proteins for the manipulation of chloroplast development. Overexpression of a MADS-box protein from Birch in Tobacco was shown to enhance chloroplasts growth and division rates, with transgenic plants exhibiting more than 2-fold higher rates of photosynthesis. Furthermore, various transcription factors expressed in Arabidopsis have been shown to increase chlorophyll content and chloroplast number. We have produced a variety of transgenic tomato plants (Solanum lycopersicum) with altered levels of the targeted proteins and will evaluate the impact of plastid number on fruit organic compound sequestration, nutritional value, and postharvest quality. The technology proposed in this project represents an important milestone in the genetic manipulation of fruit photosynthesis and could be utilised in other fruit crops.

The importance of quantifying microbes in the characterisation of low-biomass microbiomes.

Richard Stack, University of Kent

"The relationships between microbiota of the male reproductive tract, semen quality and fertility end-points are ill-defined, and clear characterisations of healthy microbial communities and dysbiosis remain elusive. Whilst the data-rich output of high-throughput sequencing technologies promise much, the sensitivity and power of these techniques create multiple opportunities for bias, especially in the context of communities of low microbial biomass. Some biological niches proposed to harbour a distinct microbial community have been refuted (e.g. the placenta), highlighting the importance of establishing a biological signal distinct from contaminant and background DNA. In addition, the compositional nature of microbial sequencing data presents a challenging statistical problem in determining which microbial organism(s) have most relevance to clinical outcomes.

Here we used qPCR to target the V4 region of the universal bacterial ribosomal RNA gene 16S, allowing us to quantify copy number in DNA extracted from boar semen. We confirmed its nature as extremely low in microbial biomass, yet established this as above the lower limit of detection; distinct from cycle threshold values obtained from negative controls. Quantitative data can feed into decisions on sequencing depth in order to minimise excessive amplification of contaminant templates and, when combined with host gene copy number, can provide a point of evaluation to optimise host DNA depletion; a method to enrich microbial DNA for shotgun sequencing. Finally, by combining quantitative with compositional data, we hope to gain a deeper insight into microbial dynamics and reduce the risks of false discoveries."

Investigating the effect of *PURA* missense variants on neurodevelopment in *X. tropicalis* frogs using CRISPR base editing

Sophie Powell, supervised by Prof. Diana Baralle, Dr Gabrielle Wheway (Faculty of Medicine, University of Southampton) and Prof. Matt Guille (European *Xenopus* Resource Centre, University of Portsmouth).

PURA is a gene encoding a single-stranded nucleic acid-binding protein, mutations in which are responsible for PURA syndrome, a severe neurodevelopmental disorder in humans with no known disease-modifying treatment[1-5]. Pathogenic variants span the length of Purα, but no strong correlation has yet been found between the type and localisation of these variants and the presence or penetrance of clinical features in patients[6-9], limiting inferences that can be made about patient diagnosis, prognosis and the scope of therapy design. A large number of *PURA* variants are contained within medical genetics databases, but the majority have uncertain significance. Recently, several AI-driven tools for *in silico* variant effect prediction (VEP) have been developed[10-12]. These tools offer saturation-level prediction of the likelihood of pathogenicity of missense variants, but their accuracy has not yet been validated *in vivo*.

Xenopus frogs have been estimated to share 79% of all known human disease genes, including *PURA*[13,14]. Knockout of *pura* in *X. tropicalis* produces a clear neurodevelopmental phenotype, effecting morphology, survival and working memory of resulting tadpoles (Guille and Godwin, unpublished). To determine their effect on neurodevelopment, C-to-T and G-to-A *PURA* missense variants from ClinVar, gnomAD and the literature will be precisely recreated in *X. tropicalis* frogs using C-to-T CRISPR base editing. By comparison with AI-generated VEP scores, phenotypic effects of *pura* missense variants in *Xenopus* will be used to inform the accuracy of the AI tools, and to further our understanding of the relationship between variant localisation and severity of phenotype in PURA syndrome.

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How does the incorporation of the primate-specific isoform of GluN2A affect the synaptic expression and internalisation of NMDA receptors?

Oreoluwa Fakeye, University of Southampton

"The activation of the NMDA receptor by the binding of its coagonists glycine and glutamate is an important mediator of the central nervous system function. The subsequent influx of calcium ions leads to intracellular changes that mediate long-term potentiation (LTP) and long-term depression (LTD), the cellular mechanisms of synaptic plasticity. NMDA receptor activity is important for normal physiological processes like learning and memory and changes to their function are associated with aging and disease.

NMDA receptors are tetrameric receptors formed of two obligatory GluN1 subunits and two other (GluN2 or GluN3) subunits and the subunit composition of the NMDA receptors determines their function. For example, PDZ binding domains present at the extreme the C-termini of the GluN2 subunits interact with the MAGUK PSD-95 to facilitate the synaptic expression of NMDA receptors. GluN2A subunits also express a SH3 binding domain which also binds to PSD-95 facilitating a more stable expression of GluN2A containing NMDA receptors at synaptic sites. There is also a PDZ binding domain present on the GluN1-3 and GluN1-4 isoforms of the GluN1 subunit, but it is unclear if this can also facilitate the synaptic expression of NMDA receptors.

In primates, there is a short isoform of the GluN2A subunit (GluN2A-S) that does not express the PDZ binding domain or the SH3 domain required for the synaptic expression of GluN2A containing NMDA receptors. It also lacks a leucine residue at position 1320 that is important for the clathrin mediated endocytosis of GluN2A containing NMDA receptors. The function of this primate specific isoform of GluN2A is currently unknown.

In this project I will use the whole cell patch clamp technique to record synaptic NMDA receptor currents from the layer2/3 neurons of a mouse model in which the endogenous GluN2A and GluN2B subunits can be removed in the presence of Cre recombinase (Grin2Afl/fl/Grin2Bfl/fl mice), to determine if the lack of the PSD-95 binding domains precludes the synaptic expression of GluN2A-S. I will also investigate the potential mechanisms that may facilitate its synaptic expression. These include its presence in triheteromeric receptors and its coassembly with the isoforms of the GluN1 subunit that contain a PDZ binding domain. "

Control of Listeria monocytogenes in the fresh food supply chain

Lucy Sutton, University of Southampton

Listeria monocytogenes is an opportunistic food-borne pathogen that can survive under harsh conditions such as refrigeration temperatures, low oxygen levels and low nutrient levels which is why it is a problem in the fresh food supply chain. Pathogenesis involves intracellular infection after which infection with L. monocytogenes can result in listeriosis which can be fatal in immunocompromised patients, pregnant women, new-born babies and elderly. This study aims to evaluate the efficacy of common sanitisation methods used in the fresh food supply chain, using appropriate laboratory models of Listeria biofilms. L. monocytogenes Scott A, L. monocytogenes CECT 936 and L. innocua biofilms were grown at 20Â°C or 4Â°C, on 1cm2 steel coupons for 7 days, and treated with 4 different concentrations of Cl2 (0ppm, 25ppm, 50ppm, 100ppm) on days 1, 3, 5, and 7. Coupons were then processed for culturable cell counts, EDIC microscopy, and Raman spectroscopy. The results of this study show that temperature effects biofilm growth; biofilms became established faster at 20Â°C, but could still form at 4Â°C. Temperature also influences chlorine efficacy, as 4Â°C biofilms were more susceptible to chlorine sanitisation. Overall, chlorine was not effective at treating Listeria biofilms at the concentrations used, however Raman spectroscopy did indicate a chemical response to treatment with chlorine. Future work would include increasing the concentrations of chlorine, and to investigate the stress response at the molecular level using transcriptomics. This work provides important information on sanitisation efforts in the fresh food supply chain, concerning factory temperature and age of biofilm.

Developing an in vitro model of liver zonation.

Amanda Gilbert, University of Southampton

"The liver is involved in diverse, often contrasting physiological roles. These include detoxification of substances, protein synthesis and glucose metabolism. To maintain efficiency, opposing functions are spatially separated through zonation of its key functional cell, hepatocytes. A key driver of this zonation is thought to be oxygen availability. As oxygenated blood flows from the hepatic artery towards the central vein, an oxygen gradient of 8.5-4% is formed. This shapes the microenvironment of hepatocytes. Hepatic zonation can be split into three areas: the periportal zone, found closest to the portal vein and hepatic artery, the pericentral zone located next to the central vein, and the mid-lobular zone, between the two.

Production of accurate, high fidelity in vitro models provides opportunities for the development of new treatments for liver disease, generation of material for transplantation and improved toxicity screening of potential drugs. Current 2D and 3D models often fail to recapitulate the zonated liver and are unable to generate fully mature hepatocytes. Through the alteration of oxygen availability to hepatocyte organoid culture, we aim to produce an in vitro model of liver zonation providing the ability to assess the development and functionality of mature hepatocytes."

Achieving micronutrient security in the UK - parsnips as a case study for dietary interventions.

Annabelle Somers, University of Southampton

"Access to sufficient, nutritious, and healthy food is fundamental for maintaining population health and wellbeing, and is something we take for granted in higher income countries. But how well does the UK actually do at feeding its people?

Examining national and international datasets, we discovered concerning trends, with up to 70% of teenagers in the UK exhibiting deficiencies in vital micronutrients like B vitamins. In response to this, we aimed to propose solutions for enhancing micronutrient intake while considering factors such as budget constraints, taste preferences, and convenience for consumers.

As a case study, we investigated variation in the preparation, storage, and consumption patterns of parsnips, a micronutrient-dense root vegetable. Our analysis revealed threefold variation in folate (vitamin B9) content among parsnip cultivars. This variance translated into significant differences in the nutritional value of a standard 100g serving of parsnips, ranging from 16% to 180% of a child's recommended daily nutrient intake.

Additionally, we explored the impact of incorporating parsnips into common school meals, such as 'bangers and mash'. Substituting potato mash with varying proportions of parsnip significantly affected the provisions of vitamins B1, B6 and B9. Leveraging the results of our cultivar experiment, we illustrated how varietal selection could amplify or negate the effects of such substitutions on vitamin B9 provision.

This work underscored the potential for simple measures to significantly improve nutrition security across the UK. Future work seeks to delve deeper into sources of variation in parsnip nutritional content and its broader implications in the food system.