TALK ABSTRACTS

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Alternative splicing regulation by snRNA modifications

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Alternative splicing is a critical mechanism generating transcript diversity and is closely linked to organismal complexity. Multicellular organisms exhibit diverse patterns of alternative splicing that can be specific to particular cells and tissues, as well as developmentally regulated, with multiple pathways involved in the regulation of alternative splicing. Likewise, many diseases are associated with alterations in transcript splicing patterns. However, splicing errors and alternative splicing are not always discernible. RNA splicing is carried out by the spliceosome, which comprises over a hundred proteins and five snRNAs named U1, U2, U4, U5, and U6. All spliceosomal snRNAs are highly modified, yet the function of these modifications is not well understood. We recently showed that the m6A modification on U6 snRNA is essential for recognising 5′ splice sites with adenosine at the +4 position in *C. elegans* and humans (1). In the absence of m6A modification on U6 snRNA, 5′ splice sites shift from a +4A position to a +4U position. However, our analysis suggests that this shift in splice site position is not random. We found that 5′ splice sites of transcripts with +4A and +4U positions can be conserved across millions of years. We will present a new alternative splicing mechanism that relies on snRNA modifications.

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Metabolist Architecture: Science, Fiction, and Interdisciplinary Exchange

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Scientific metaphors and disciplinary crossovers can be powerful engines for leaping into the unknown—but they can also generate confusion or misalignment. This workshop explores the productive frictions and conceptual pitfalls that emerge when terminology from one field is adopted in another. I explore *Metabolist Architecture*, a postwar Japanese movement that borrowed the language of biological metabolism to reimagine buildings and cities as living, evolving systems—capable of growth, renewal, and adaptation over time. Through this biological metaphor, the Metabolists aimed to challenge the rigidity of postwar planning and to envision a dynamic, future-oriented built environment.

But did the metaphor of *metabolism* truly capture the processes they hoped to design for? This reflection opens up a broader question about the limits of metaphor itself: can a metaphor suffice for interdisciplinary engagement, or must we go further—toward genuine intellectual dialogue with the discipline from which the concept is drawn?

Metabolist Architecture is not alone. Architectural theory relies on borrowed concepts for forward thinking, extending to Modernist use of *space-time* to break with history and geography and Digital Architecture use of computer science metaphors and models. Conversely, Systems Biology used the term 'network *motif*', borrowed from art and architecture history.

I ask what happens to meaning, precision, and disciplinary integrity when terms migrate across fields? How do these borrowed metaphors shape not only the recipient field's theoretical language but also its practical ambitions? And how might we map strategies for more reciprocal, critical, and imaginative forms of interdisciplinary exchange.

Selfish genes and us

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I will talk about selfish genes and host systems designed to counteract their activity, but sometimes converted into selfish genes themselves. Transposable elements that are propagated by moving from one place to another in the genome are considered the ultimate example of selfish genes. All organisms have multiple genome defense systems that are able to recognize and suppress transposons. The most flexible and precise defense systems - piRNA and siRNA pathways in eukaryotes and CRISPR and pAgo in prokaryotes - use small non-coding RNA guides to recognize their targets. The interaction of transposons with the host defense systems is often described as an arms race, which leads to a fast evolution of both components. In a broader sense, popularized by Richard Dawkins, any gene, not just transposons, is potentially selfish and 'cares' only about its own propagation. I argue that the real dynamic of transposons and host defense systems is complex, and the primary function of many 'defense systems' might be the integration and productive use of transposon sequences for the benefit of the organism, rather than their suppression. On the other hand, defense systems themselves might evolve in the direction of selfishness. Finally, selfish genes are frequently born from normal cellular genes (not transposons), and this process happens often and fast on the evolutionary scale. Defense systems then work to identify and suppress new threats generated by these newborn selfish genes.

Pattern formation during Hydra aggregate self-organization

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During development, groups of cells generate patterns. To study self-organization in the absence of pre-patterning, we use the regenerative abilities of the cnidarian Hydra vulgaris, which displays a striking planar pattern of actin fibers at the organism scale. Cellular aggregates of Hydra cells have initially lost all cell actin polarity yet can regenerate a long-range actin pattern within a week. We measure the appearance of the actin pattern over days and show that the actin field evolves from a disordered symmetric state to an ordered state in which rotational symmetry is broken and translation symmetry is partially broken, with the associated order parameters (resp. nematic and smectic) increasing over days. On shorter time scales, the actin field displays spatial heterogeneity in the nematic order parameter and ordered domains progressively grow and fuse. To better understand the mechanism driving the ordering, we perturb the tissue physical constraints, and show that while topology and geometry do not have a direct effect, stretch can strongly bias the pattern of the actin field within hours. The bias happens without the appearance of a matching Wnt organizer, suggesting a direct mechanical role in the alignment of the actin fibers. Overall, we show *in vivo* the physical properties and constraints of a self-organized supracellular actin pattern.

Causality and reversibility of epigenetic information loss in aging and disease

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Two seemingly unrelated questions in the field of aging are “Is aging a disease?” and the role of epigenetic information loss during aging. While the first is often viewed as almost a philosophical question, the second concerns the exact roles of a well established driver of aging. We demonstrate that tissue-specific DNA methylation patterns, a form of epigenetic information, are lost during normal aging. Furthermore, this information loss is a shared characteristic of various, but not all, diseases, where it primarily affects the diseased organ. Moreover, at least in the liver, this loss is both reversible and enriched for causal sites. These results suggest that from an information-loss standpoint, aging can be considered a disease. Moreover, several diseases can be viewed as instances of organ-specific aging.

On development-defense dynamics in plants/ stunningly naive science

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Talk + Other- "other" will be an informal session entitled "stunningly naive", where people can participate by asking the most naive questions, scientific or otherwise, that they would like feedback on, or even would just like to voice out loud- but have never had the guts. I am still developing the idea. Inspired by a recent grant review. Alternatively, my talk can be changed to this topic rather than the science, if this type of session does not work out. I have many examples of stunningly naïve scientific questions :) that have been laughed at (or that I didn't have the strength to voice out loud). I would like to either present a scientific abstract along these lines, like in the previous woodstock; or focus only on the plant communication project (see below) with my one slide; or, present a talk about naivety in science and (crowd) philosophize on why it's important to preserve naivety- either as a prelude to the "stunningly naive" session I would like to organize, or, if that doesn't work out- instead of it. Could also do both :)

Scientifically: the Bar Lab is dedicated to uncovering new insights into plant immunity mechanisms. Our research encompasses several key areas: Plant-to-plant communication: Investigating how plants convey developmental status and species identity to neighboring plants. Development-defense trade-offs: Studying how plants balance growth with defense mechanisms against environmental stressors. Roles of plant hormones in fungal biology: Investigating the functions of plant hormones in both pathogenic and beneficial fungi. Architectural effects in plant-microbe interactions: Exploring how variations in plant organ shape can influence microbiome composition and susceptibility to pathogens.

Divining promoters: How AI rediscovered TATA box and nucleosome positioning signal (and a bit more)

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What a time to be alive to witness an arms race in genomics: who can build the biggest, flashiest AI model to decode our DNA. Everyone's throwing transformers and deep learning at the genome, stacking up parameters like it's a contest (because it is), and claiming their model "performs best." And sure—these genomic AI models are making real progress. They can now predict where transcription starts down to a single base pair. Impressive, right? However, promoter people are not convinced that these models understand promoters. While these models are excellent at pointing out *where* transcription begins, they're still pretty clueless about *how* it's organized. Specifically, the whole business of promoter architecture—the reason why a gene starts being transcribed from one particular "sharp" spot like a sniper or a "broad" region like a shotgun—remains underexplained, to say the least. Since promoter shape closely regulates genes, why wouldn't we ask AI to answer this? So, instead of building a *bigger* model, we tried to test what existing ones can do when asked a different question. We fine-tuned the Nucleotide Transformer on zebrafish promoter regions from the DANIO-CODE project. Using CAGE data to label promoters as "broad" or "sharp," we asked the model to figure out the difference using sequence alone. The results? As any decent promoter researcher, we rediscovered the TATA box as a classic marker of sharp promoters. However, in broad promoters, we found that the strongest features sit about 50 bp downstream of the transcription start site and comprise a ~10 bp WW dinucleotide periodicity. As you might've already guessed, we also rediscovered nucleosome positioning signal. However, our rediscoveries uncovered something new as well: CpG islands might be a bit overrated. It turns out that promoters have a type, and AI can figure it out with a bit of training. This study shows that beyond just calling transcription start sites, these models can actually help us *understand* promoter architecture, by detecting both sequence motifs and the physical DNA properties shaping gene regulation.

Zany Idea Collider

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Having jumped from grad work in protein structure to a postdoc in teaching and learning, I've gone full-blown interdisciplinary. In the spirit of Night Science, for this session we'll figure out some outlandish possible research projects to end all projects, with brand-new collaborators! Hurrah!

PS- if you want to talk about my research, come find me! These days I study how we can do a good job teaching university level science - whether we have 5 students or 500. I have a bunch of projects on the go -- investigating how students make high-stakes decisions together when they disagree; helping graduate students learn how to be conference poster judges; teaching CRISPR guide RNA design at the intro level. I've also got a super-new research question and a bit of data that I'd love your help interpreting. Does what you wear, as an instructor, have any kind of impact on your students learning and experience in your class?

Does sex matter? Invasive female and male trophoblasts in the placenta

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In mammalian development, the placenta forms the mechanical and physiological link between maternal and fetal blood. Specialized placental cells called trophoblasts, derived from the trophectoderm of the blastocyst, perform many of the placenta's transport, endocrine, and immunogenic functions. An invasive trophoblast celltype, called an extravillous trophoblasts (EVT), coordinates nutrient accessibility for the embryo and modulates the maternal immune response to the fetus. Like the fetus, trophoblasts are typically either chromosomally male (XY) or female (XX). Interestingly, pregnancy disorders and outcomes like pre-term birth show a bias rooted in the biological sex of the fetus. This indicates that the conceptus interacts with the mother through distinct sex-specific responses. To examine if the biology of invasive male and female human trophoblast differ, transcriptomic signatures of EVT harvested at distinct developmental timepoints across the first trimester of pregnancy were measured. Applying both bulk and single-cell RNA-seq platforms, we find that prior to week 10 of gestation male and female EVT are transcriptionally indistinguishable from each other. At this early developmental time-point, male and female EVT show enrichment of genes predominately associated with cell proliferation; the only sex-related gene differences are attributable to the cell's sex chromosome complement. However, following 10 weeks' of pregnancy, significant autosomal gene differences appear between male and female EVT. Computational modeling suggests that sex-dependent gene differences at this latter developmental period influences how invasive trophoblast interact with maternal cell types of uterus. Male EVT, for example, show elevated activity of immuno-modulatory *MIF* and *CD99*, as well as angiogenesis-associated VEGF signaling. These preliminary findings suggest a timepoint in human pregnancy when gene differences in male and female invasive cells of the placenta can be detected. These findings highlight a possible sex-based bifurcation in how male and female placenta cells interact with maternal environment.

Cell as a watermill – What is the thermodynamics of metabolism?

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Cells just die when you don't feed them. The reason behind this seemingly trivial fact is, though, not trivial at all, and connects to the very fundamental forces operating the biosphere, i.e. thermodynamics. You can imagine cells and life in general as watermills placed on a stream running downhill – the stream is the energy gradient, be it a photon from the sun or the chemicals that sea-bed black smokers spit out. They dissipate energy from more concetrated forms to less concentrated forms, i.e. they increase entropy. The watermill is the cell metabolism, diverging part of the flowing energy into its own body for own selfish purposes. Continuing this analogy, removing the stream stops the mill, as removing the flow of energy kills the cell.

Now, you have probably heard a lot about the nitty-gritty details of stream kinetic energy transformation into rotational movement of axes inside the mill – those are biochemical reactions transforming the energy of nutrients or light into ATP. But what we still have little clue about is the design and architectonic plan behind all these watermills. Like, what streams can you place them on? What happens if the stream gets stronger, will the mill operate proportionally faster and at what point will it break? Are all mills equal in terms of efficiency, or are some excellent and some rubbish in harvesting the stream power? Is there a common design principle, or are they inherently different?

I'm trying to figure this out for human tissue culture – there is some body of literature for simple bugs like yeast and E. coli, but basically nothing for more complex cells. First, I put together the tools that help me to measure and understand the transformations the mill does: this would be all the inputs (nutrients and oxygen) and the outputs (new mills = new cells, heat, waste molecules). From these, I can calculate how well does the mill perform, what energy it requires and what power it outputs, and how does it compare to what we know about other mills.

I won't spill the beans here, if you got interested in mills and what I do with them, come talk to me!

CK1ε and DVL in Wnt Signaling: A Scatman Story of (un)structure, sync, and signal

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Casein kinase 1 epsilon (CK1ε) is a positive regulator of the phospho-protein Disheveled (DVL), the central hub of the Wnt/β-catenin signaling pathway. In cells, DVL has been shown to phase separate into punctate structures, known as "puncta", which dissolve upon DVL phosphorylation mediated by CK1ε. Interestingly, CK1ε activity is also regulated by autophosphorylation of its long C-terminal tail. However, the cascade of CK1ε (auto)phosphorylation events leading to DVL puncta disassembly is still unclear.

Here, we explored the molecular factors that control DVL phosphorylation by CK1ε. We used NMR in a binary system to investigate how multisite phosphorylation of the enzyme and/or the substrate modulates their interaction. We identified a DVL2 epitope conserved across the Dishevelled isoforms that mediates binding to CK1ε. Notably, the interaction is not dependent on the phosphorylation events, suggesting a novel scaffolding function for the kinase. The kinetic analysis revealed that the enzyme-substrate (auto)phosphorylation within the DVL-CK1ε complex occurs synchronously. Indeed, CK1ε autophosphorylation does not exclude DVL processing and *vice versa*. Last, we pinpointed a single residue in DVL as the critical determinant of CK1ε-DVL complex formation. Mutating this residue completely abolished CK1ε binding *in vitro* and disrupted DVL phosphorylation in cells, ultimately affecting the distribution of the puncta.

Our findings unveil a DVL phosphorylation mechanism in Wnt signaling that depends on the scaffolding function of Ck1ε.

Abstract moral: every relationship is a combination of up ("binding") and down ("no binding"), good ("even") and bad ("just puncta") moments. We must find the right "epitope" and let the story become a joyful "happily phosphorylation ever after"!

Scatman's moral: Like in scat, the message is in the rhythm, and the logic lies not in the catalysis but in a synchronized phospho duet!

PS: I forgot to introduce myself: I'm Sara, a biochemist who plays with NMR to understand the intricate world of phosphorylation mechanisms!

Don't Stop Me Now!

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Premature Termination Codons (PTC) are among the leading causes of heritable genetic diseases. Their treatment, as treatment of any genetic disease, is currently very limited and relies on the gene-tailored genetic therapy or administration of toxic readthrough inducing drugs. An alternative approach involves the use of engineered tRNAs that can suppress PTCs. Even these, however, currently have low efficiency. Fortunately, there are multiple examples of species with reassigned genetic codes. This means that they utilize termination codons as regular sense codons. Our goal is to find out what tricks are used by these organisms to be able to decode termination codons with a high efficiency and potentially use them to our benefit. The availability of genetic codes allowed us to discover several players involved in the reassignment. Specifically, we discovered functional adaptations in ribosomal proteins of the A-site, release factors, and suppressor tRNAs. When tested in yeast model system a significant effect on PTC decoding can be observed.

This embedding doesn't mean what you think it means

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Are you using AI models for protein or nucleotide sequences? Did you maybe forget that their embeddings are themselves predicted representations of biomolecules and come with no obvious measure of reliability? Imagine how much standard sequence analysis methods would suffer if source genome or protein sequences were subtly randomized via unflagged processing errors. This is exactly what happens if we use low-quality embeddings. We propose the RNS (random neighbors) score as a means to score embedding reliability! Using RNS drastically improves the next steps in model use, e.g. variant effect prediction, structure modeling, function annotation, etc. Can better embeddings help your question too?

Building Brains with More Neurons: From the Womb to the Grave

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My group has found that the length of the G1 phase of the cell cycle influences the fate of somatic stem cells [1]. This allowed the expansion of neural stem cells during development [2] and adulthood [3], thus increasing the number of neurons generated in the mammalian brain. This finding was important to reveal the contribution of progenitor subtypes in the evolutionary expansion and gyrification of the mammalian cortex [4] as well as the role of adult neurogenesis in promoting sensory discrimination [5] and cognitive performance thereby rejuvenating hippocampal function over the course of life [6, 7]. In short, and as our most used approach, viruses are injected in the mouse brain that promote the expansion of neural stem cells and neurogenesis. As a result, the increase in neuron number makes mice smarter... pretty much like in "The Planet Of The Apes" movie, except that our mice are not as aggressive, thus far. Our next ambition is to understand '*how*' does an increase in the number of neurons promote the computational performance of our more complex organ and gain insights into the basis of cognitive processes [8].

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Chromatin Dynamics in Plants: At the Crossroad of Genetics and Epigenetics, surprises can arise

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While chromatin dynamics is anticipated as key determinant of organogenesis, the precise sequence of molecular events taking place in the nucleus from the change in a chromatin mark to changes in developmental gene expression, remains unclear.

My group studies switches in chromatin states from trithorax-activated to Polycomb-repressed (and vice versa), that accompany key developmental transitions in the plant *Arabidopsis thaliana*.

Some of our previous discoveries indicate that changes in histone active marks, driven by the trithorax complex, may be pioneer for gene expression (Engelhorn *et al.*, 2017; Yan *et al.*, 2019). In particular, during flower morphogenesis, the H3K4me3 mark (trimethylation at Lysine 4 of Histone 3) is highly dynamic as compared to the Polycomb-deposited H3K27me3 mark.

With the aim of contributing to a comprehensive, dynamic view of the epigenetic roadmap for plant developmental transitions, we have both taken a candidate-focused approach as well as a more general approach implementing histone epi/genetic edition tools. I will discuss our recent discoveries in the function of one chromatin component and its dual role in regulating the abundance of H3K27me3 marks at target genes that are central to specific cell fate changes (Geshkovski *et al*., BioRxiv 2024 and unpublished data). I will also present our latest advances in the development of tools to address the chromatin, expression and developmental changes driven by modifications at H3K27 (Fal *et al.*, 2023; Fal *et al*., 2025).

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Neurons must spike or die. A metabolic imperative for spontaneous activity.

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While conventionally viewed as processors of synaptic input into action potentials, neurons frequently exhibit spontaneous spiking and diverse firing patterns, often with no apparent functional role, particularly in vitro. This raises a fundamental question: why do neurons expend significant metabolic energy on seemingly irrelevant activity during periods of inactivity? Here, we propose a novel hypothesis: intrinsic neuronal excitability serves as a survival mechanism to mitigate the accumulation of toxic byproducts from cellular energy metabolism. Specifically, we posit that in neurons, when mitochondrial ATP production is limited by ADP availability, the electron transport chain nearly stalls and generates damaging reactive oxygen species (ROS). To counteract this, neurons may engage in "metabolic spikes" that produce ADP, thereby restoring mitochondrial ATP production and reducing ROS. We will explore the validity of this hypothesis using computational models that simulate both synaptic and metabolic spiking, with a particular focus on dopaminergic neurons and their degeneration in Parkinson's disease. Finally, we will outline testable predictions that could confirm or refute this theory.

SEX DIFFERENCES IN MITOCHONDRIAL FATTY ACID OXIDATION PATHWAY IN HEALTHY HUMAN CARDIOMYOCYTES

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Human females and males differ in cardiac physiology and pathology, even after controlling for sex differences in anthropometrics, lifestyle, and environment. For example, females and males differ in cardiac stroke volume and ventricular thickness, and they exhibit different rates and symptoms of heart disease. Less is understood about molecular differences in female and male hearts, such as sex differences in gene expression. We present an integrative framework utilizing both bulk and single-nucleus RNA-sequencing data to study sex differences in the cardiac transcriptome. We report that genes of the mitochondrial fatty acid oxidation (FAO) pathway, the primary source of energy in the heart, are expressed more highly in healthy female than in healthy male hearts. We demonstrate that this sex difference is due to cardiomyocyte-specific, female-biased expression of FAO genes and cannot be explained by sex differences in cardiac cellular composition or number of mitochondria, where FAO takes place. Finally, using cardiac metabolomic data from patients without heart failure, we observe increased cardiac flux and energetic utilization of free fatty acids in female compared to male hearts. Our findings highlight fundamental differences in mitochondrial metabolism between male and female hearts that likely contribute to sex differences in cardiac physiology and pathology.

From Embryogenesis to Aging: Sculpting Life through Waves of Cell Death

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Biological systems encode fundamental principles through which nature enables resilience, functionality, and adaptability. At the molecular level, our previous work showed that feedback interactions between metabolites and signaling proteins generate multistability in cellular redox state, enhancing resilience to oxidative stress (Huang, Co et al. 2021, *Molecular Systems Biology*). At the cellular level, these multistable systems can be spatially coupled, allowing for coordinated cell death across large populations during embryogenesis (Co, Wu et al. 2024, *Nature*). Cell death coordination is mediated by the propagation of ferroptosis, an iron-dependent form of cell death, which spread across cells in a spatially-infinite manner through trigger waves. While such large-scale ferroptosis is important for sculpting tissues during embryonic development, emerging evidence also suggests ferroptosis as a driver many aging-related pathologies, including neurodegenerative and cardiovascular diseases. This raises a fundamental question: could the same ferroptotic programs that drive proper embryonic patterning also imprint long-term consequences on tissue function and aging? Recognizing the developmental origins of aging, I am interested in investigating how ferroptotic events during embryogenesis influence the aging trajectory. By identifying the molecular circuits and signaling pathways that govern large-scale cell death, we aim to uncover how developmental programs regulate aging and lifespan determination.

Open Flower: reimagining Arabidopsis as a platform for floral design

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The Open Flower project seeks to transform *Arabidopsis thaliana*, the major model organism for plant science, into ornamental flower varieties. By treating floral development as a programmable design space, we apply biotechnology tools to engineer new types of flowers at the intersection of art, education, and science. The resulting engineered flowers have two primary functions: (1) further research on the developmental biology of flowers by leveraging and extending existing models and (2) producing novel and interactive phenotypes that effectively support education and outreach. Through this integration of aesthetics and synthetic biology, we explore new possibilities for Arabidopsis developmental research, creative expression, and public engagement in plant science.

Science, Art & Creativity

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Science and Art - two disciplines that seem far apart at first glance, but have more in common than widely appreciated. Creativity is important in both domains, and upon closer inspection one might arrive at the conclusion that there are many more similarities and overlapping skills useful for the two seemingly disparate fields.

Is Science creative, or does research merely uncover the pre-conceived laws of nature? Is the process of creating an artwork guided by scientific principles? Can artistic insight catalyze scientific understanding and vice versa? As a former scientist-turned-artist with a background in Genetics and Developmental Biology, I will explore these questions and offer a personal perspective on the intersection of Science and Art.

Using historic and contemporary examples, as well as experience from my own work, my goal is to inspire scientists to adopt a more creative approach to their research and provide practical tools for effectively communicating complex ideas in ways that resonate both intellectually and emotionally.

From Helpers to (Serial) Killers: Uncovering the Cytotoxic Potential and Plasticity of Helper T Cells in the Gut

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Segmented filamentous bacteria (SFB) are anaerobic, spore-forming, Clostridia-like microbes. Their adhesion to the intestinal epithelium triggers a strong immune response, characterized by the accumulation of Th17 cells and increased IgA secretion by plasma cells. Recently, we reported that helper T cells reactive to SFB can also differentiate into induced intraepithelial lymphocytes and begin to express cytotoxic molecules.

Traditionally, the helper versus cytotoxic role of T cells was believed to be hardwired. However, the mechanisms enabling this transition are only now being uncovered. Using genetic models, we identified the antigen-presenting cells and molecular pathways responsible for driving the shift from helper T cells to cytotoxic intraepithelial lymphocytes, as well as their functional implications in gut physiology.

These findings advance our understanding of host–gut microbiota interactions and reveal the cellular mechanisms underlying the unconventional transition of $CD4^+$ T cells into cytotoxic intraepithelial lymphocytes. Understanding these processes provides valuable insights into gut barrier regulation and may offer new avenues for manipulating intraepithelial lymphocytes to benefit host health.

Peeling an onion – Influence of phase separation on RNA folding

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Long non-coding RNAs form often complex structures which are necessary for their relative functions. However, unlike protein folding, which is at least partially solved, RNA folding is still a topic of ongoing research. In their biological context, RNAs are typically in contact with RNA-binding proteins (RBPs), many of which have a tendency to form condensates by liquid-liquid phase separation. This gives rise to the question, how phase separation plays a role in RNA folding.

An especially interesting case for this is the ribosome, with the ribosomal RNA being one of the best studied structured RNAs. Further, ribosomes are formed in the nucleolus, which is a phase separated organelle. While ribosomal proteins are necessary for the stability of the ribosome, it is unknown if they form condensates. Finally, the ribosome has been described to be like an onion: the peptidyl transferase center at its core is highly conserved over all domains of life, with approximated evolution layer by layer.

Using this test case, single molecule experiments and numerical predictions, we try to unpeel how the interactions with RBPs and condensates might help RNAs to find and shape their structure.

Night Science: the Neurobiology of Lucid Dreaming

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Lucid dreaming refers to the phenomenon of becoming aware of the current dream state during ongoing sleep. The neurobiology of lucid dreaming has been studied under laboratory conditions already since half a century, however is still poorly understood, particular due to the rarity of the phenomenon: only about half of the population knows lucid dreaming from own experience, and few individuals dream lucidly more often than every couple of weeks.

In this talk, I will introduce into the current state of the neurobiology of lucid dreaming, including electrophysiological, neuroimaging, pharmacological and brain stimulation studies. I will further highlight how to learn and train lucid dreaming, and explore future directions of this small but rapidly growing field of neurobiological research, leveraging recent advances in wearable neurotechnology, large-scale collaborations, and citizen neuroscience approaches.

Literature:

Zerr P, Adelhöfer N, Dresler M. The neuroscience of lucid dreaming: past, present, future. *Neuron* 2024, 112: 1040-1044. doi:10.1016/j.neuron.2024.03.008

Uncovering the Epigenetic Basis of Psychedelic Therapy for Depression

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Major Depressive Disorder (MDD) is a pervasive psychiatric condition affecting millions worldwide. Current treatments, such as selective serotonin reuptake inhibitors (SSRIs), often fail to achieve complete remission and are associated with delayed therapeutic effects and adverse side effects, including weight gain and sexual dysfunction. Consequently, there is an urgent need for novel therapeutic approaches. Psilocybin, a psychedelic compound, has demonstrated rapid and sustained antidepressant effects, yet the underlying molecular mechanisms remain poorly understood.

This research hypothesizes that psilocybin induces significant epigenetic changes, particularly in DNA methylation (5-methylcytosine, 5mC) and hydroxymethylation (5-hydroxymethylcytosine, 5hmC) within key brain regions associated with mood regulation, such as the prefrontal cortex (PFC). These changes are anticipated to influence gene expression related to neuroplasticity and stress response, thereby contributing to psilocybin's therapeutic effects.

Preliminary findings from this pilot study support this hypothesis. Mice treated with psilocybin exhibited significant changes in 5hmC patterns in the PFC, especially in genes linked to synaptic transmission and neuroplasticity. These results suggest that psilocybin induces rapid epigenetic modifications that may underlie its antidepressant effects. This research provides a foundation for understanding the molecular basis of psychedelic therapy and could inform the development of novel, targeted treatments for MDD.

Developmental Biology a la Søren Kierkegaard

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Developmental Biology is traditionally described as a field that studies how a single-cell develops into a complex organism. Therefore, a typical undergraduate course or text book begins with fertilization, early cleavages, and works its way through gastrulation and neurulation to morphogenesis and organogenesis. In approaching development in such a chronological fashion we require students to imagine objects and processes they never encounter in their day-to-day lives. As children, we don't grow up surrounded by zygotes and gastrulae. We do, however, have lasting memories of butterflies and sea shells. I propose restructing Developmental Biology courses to begin with familar patterns. Students being by learning how to 'read' a butterfly wing or a sea shell. 'Eye spots', 'stripes' and other discrete features and patterns tell a story of development; of intersecting gradients and regualtory interactions. Students then progress to learning the genetics of *Drosophila* wing development and with that are introduced to a host of signalling pathways that become relatable since the meaning behind Wingless, Notch or Decapentaplegic becomes evident. The acquired literacy in cellular movements and signalling pathways, rooted in familar encounters then enables students to tackle processes and genes that are removed from immediate experience. In reversing Developmental Biology instruction we are reminded with Kierkegaard's insight, "Life can only be understood backwards; but it must be lived forwards."

Beyond the histone code: an unexpected function of SetDB1 in heterochromatin spreading and maintenance

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Heterochromatin plays an essential role in nuclear organization and regulation of gene expression by directing the 3D genome organization, regulating lineages-specific gene expression and ensuring repression of transposable elements and endogenous retroviruses. Functionally and structurally different chromatin domains are discriminated by the so-called histone code, combinations of post-translational modifications of histones that are deposited by code-writers and recognized by code-readers. The main mark of heterochromatin, trimethylation of histone H3 tail at lysine 9 (H3K9me3) is deposited by histone methyltransferases, such SetDB1, and provides a binding platform for readers, most significantly, HP1 family proteins. How heterochromatin spreads from nucleation sites to establish large repressive domains and how these domains are stably maintained is not fully understood.

Using a reporter to monitor dynamics of heterochromatin establishment and maintenance, we show the existence of a feedback mechanism by which the reader of the H3K9me3 mark, HP1, attracts the writer, SetDB1. Recruitment of SetDB1 by HP1 requires their direct physical interaction, which depends on posttranslational modifications of SetDB1. These modifications of SetDB1 are critical for the spreading and stable maintenance of heterochromatin.

A condensate link between translational regulation and microtubule transport

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Human YBX1 is a critical RNA-binding protein with a simple domain architecture comprising a Cold Shock Domain (CSD) and intrinsically disordered regions (IDRs). The CSD and IDRs facilitate RNA binding, while the C-terminal IDR enables liquid-liquid phase separation (LLPS) and condensate formation. Despite its known involvement in early embryonic development and neural tube formation, the specific role of the CSD in RNA binding and the contribution of the IDRs had previously remained unclear. Our study explores the role of YBX1 in translational regulation and its interaction with axonally transported mRNAs, including α-synuclein and β-actin, *in vitro*. We demonstrate that YBX1 represses the translation of these mRNAs in a concentration-dependent manner. Furthermore, we show that both the CSD and IDRs are essential for efficient RNA binding. Mutations in key residues of the CSD weaken RNA binding but do not affect LLPS.

Previous reports identify YBX1 as the most abundant axonal protein at the mRNA level and as an interactor of tubulin/microtubules. We demonstrate that condensed YBX1 colocalizes with RNA and free tubulin, and shows a strong affinity for microtubules *in vitro*. However, this interaction is significantly reduced when the C-terminal tails of microtubules are enzymatically removed. Notably, we also find that RNA outcompetes microtubule binding of YBX1, highlighting YBX1's dominant affinity for RNA. While the CSD contributes significantly to RNA binding, it plays a reduced role in microtubule interaction. Finally, we observe that YBX1 forms mutually exclusive islands with Tau (MAP), suggesting spatial segregation within axons.

These findings offer new insights into the multifaceted roles of YBX1 in mRNA packaging, microtubule-based transport, and localized translation in neurons—processes essential for neuronal function. Disruption of YBX1's interactions with RNA or microtubules may contribute to the pathogenesis of neurodegenerative diseases.

Ancestral auxin phospho-cascade targets the plant microprocessor complex

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Auxin is a chief phytohormone that orchestrates plant multicellularity and development. Classic examples of auxin action are the aesthetically pleasing arrangement of leaves around a stem (phyllotaxis) or the self-organization of vascular systems. Notwithstanding auxin's prominence in plant biology, the signaling cascades it triggers remain poorly understood. Classic works identified slow transcriptional auxin responses occurring on the timescale of hours and underlying most developmental functions of auxin. The past three years, however, have seen the identification of a rapid phosphorylation-based cascade that predates the emergence of complexity in extant plants. I shall discuss my recent work on this auxin phospho-response, specifically, why unicellular algae evolved auxin-mediated phosphorylation in the first place. My data suggest that the ancestral function of auxin might have been the phosphorylation of SERRATE subunit of the microprocessor complex responsible for miRNA biogenesis.

ARTIS - Art Inspired Science

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The ARTIS Program provides WIS Scientists with a unique space to explore Creative Scientific Thinking through artistic mediums, guided by leading figures from the Israeli art world. Through Music, Movement, and Culinary Arts, participants work closely with artists, engaging in hands-on creative processes. The program integrates Art-based Research methods to help participants reflect on and deepen their artistic and scientific journey.

This year's art focus is on using our senses to build awareness and personal intuition. Artists have spent many years training their senses to be creative and develop their own unique styles. This connection between senses and creativity should be talked about more in science, as it shows how artists and scientists are similar in how they explore and create.

Different art forms connect to different senses:

- Culinary Art connects to Memory
- Movement Art connects to Being
- Music connects to Listening

For example, the culinary art medium raises questions such as:

- How do memories of food change how we see things?
- How does the food we eat help make us who we are?
- Are our memories the main part of our life stories?
- How is making food similar to doing science?

Please watch our video from last year to see ARTIS in action:

ARTIS VIDEO 2024: https://youtu.be/nw-aSeocTOo?si=LGbf_3ejb22RT3KL

You can also visit our website connected to Weizmann:

ARTIS WEBSITE: http://www.weizmann.ac.il/artis/

The cytoplasm makes and Oocyte an Oocyte

Christoph Gaebelein[1], **Ashid Amarsanaa**[1], **Jay Goodman**[1], **Sergio Guerrero-Castillo**[2], **Liam Holt**[3], **Ruth Lehmann**[1]

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The Oocyte is a terminally differentiated cell, capable of producing thousands of embryonic stem cells. Oogenesis, the formation of an Oocyte, is a cell differentiation program not regulated by a specialized transcriptional program, as the Oocyte nucleus is transcriptionally silent. Instead, the Oocyte cell state is organized by a sequence of signaling cues originating in the cytoplasm. Our work aims to decipher this code and its connection to the unique ability of the Oocyte to give rise to a new organism. We found a conserved program that changes the biophysical and metabolic properties of the Oocyte cytoplasm, which is also required to induce the transition between an Oocyte and the embryo. Furthermore, our data suggests that OXPHOS activity is not strictly required during late oogenesis and early embryogenesis, confirming the dogma that mitochondrial activity is connected with stem cell differentiation, but not necessarily maintenance.

Exciting Hematopoietic Stem Cells

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Hematopoietic Stem Cells (HSCs) are the source of blood and immune cells. During everyday healthy life, HSCs are mostly quiescent in the bone marrow. Following blood-loss, or inflammation, HSCs can gain activation, presumably accelerating the generation of the needed blood and immune cells. Surprisingly, however, our knowledge regarding the ability of various pathogens' to perturb HSCs is minimal. Moreover, the early- and late-effects of HSCs' activation are only beginning to reveal.

We revealed surface markers of immune-activated HSCs, namely CD69 and CD317 (also called BST2). Utilizing improved identification of activated HSCs is providing us with molecular insights, and better ability to follow HSC's status dynamically. We recently found that HSC's activation is much faster, and broader, than previously thought -- evident as early as 2 hours for both Stem- and progenitor-cells. The response is systemic, highly sensitive, and dose-dependent down to a surprisingly low amounts of stimulant. Interestingly, other recent studies challenge the concepts of HSCs' contribution to emergency hematopoiesis, highlighting further interests in understanding the acute phase of stem cells activation.

Chronic activation, on the other hand, can deplete HSCs' potency, and might further increase the risk of malignancies. We find extraordinary impact following prolonged bacterial infection in a novel mice model, and even more exciting ability for recovery following clearance of the pathogen. Single-cell analysis is letting us additional insights into molecular states of naïve, potent-less, and recovered HSCs.

Changing concepts of hematopoiesis are fundamental for the generation of new immunocytes through health and disease. New data will allow for preserving the potency for a longer and healthier life.

Keywords: *Hematopoiesis, Hematopoietic Stem Cells, Immune Activation, Transcriptome analysis*

RNA-binding proteins as mediators between genome evolution and gene regulation

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Transposable elements (TEs) contribute 1.5 billion bases to the human genome, and half of them are located inside annotated genes. These TEs are transcribed, in sense- or antisense orientation, together with their host genes, but are generally not included in the mature RNA products as they are removed together with introns. However, TEs carry sequences and form structures that can interfere with co- and post-transcriptional processing of nascent transcripts, and we study how RNA-binding proteins (RBPs) suppress or leverage these effects. ADAR and DHX9 are RBPs that bind double-stranded RNA (dsRNA) structures, which are often formed by TEs, and melt them by introducing nucleotide mismatches or by actively unwinding dsRNAs stems. We show how the loss of ADAR and DHX9 alters transcriptional output of many genes and disrupts splicing integrity without introducing new splice sites. We aim to identify individual intronic dsRNA stems that alter splicing outcomes, and explore the evolutionary implications of dsRNA burden in introns. RBPs also bind TEs in a sequence-dependent manner, and we show how SAFB binding protects genomes from retrotransposition of intron-embedded L1 elements, without compromising pre-mRNA processing. By masking exonization signals and cryptic splice sites, SAFB proteins prevent exonization of intronic L1 elements, regulate the inclusion of long exons and suppress activation of premature polyA sites in hundreds of genes in cell lines and human tissues. Taken together, our results show how TE insertions direct post-transcriptional gene regulation, and how cells use RBPs to intercept or co-opt these signals.

Food to brood: metabolic origins and circulation of nutrients in ant colonies

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Many insect orders, and most ant species, exhibit eusocial behavior, i.e., individuals live in groups, coordinated through cooperative action and reproductive division of labor. One of manifestations of eusociality is presence of socially exchanged nutritious fluids. In this way, the exchange of readily available molecular building blocks (biomass precursors) opens opportunities for distributing the metabolic labor among colony members: different individuals could specialize in production of compounds for the whole colony. However, both biosynthesis of biomass precursors in situ, and production of them to be shared, come with distinct investments and benefits. So, what profile of (re)distribution of biomass precursors through fluids are the most beneficial to the colony?

To answer this question, we combined multi-omics analyses with computational metabolic modeling. We sampled individuals and socially exchanged fluids from 5 ant species for proteomics and metabolomics analyses. We have found that despite very different lifestyles, the metabolic capacity encoded in the genomes of ants was largely overlapping. We observed colony tissue- (also known as caste) specific proteome composition and different small molecules exchanged via fluids. By combining the computational models with multi-omics data, we identified metabolic objectives of colony tissues, reasoning that the division of labor among colony tissues fosters overall colony growth. We have correlated this with the observational data which suggests that species with more elaborate division-of-labor patterns perform better, i.e. can sustain larger colony sizes, than their more primitive counterparts (up to several orders of magnitude).

Notes on Biochemistry

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I work on the intracellular distribution of metabolic pathways in algae with complex plastids. When I was an undergraduate student, every academic bookstore had "The Biochemists' Songbook" by Harold Baum. I never bought it, even though I played guitar already back then. I guess I found it intimidating, after all I hadn't even cleared my biochemistry exam, and frankly, I was more interested in algae anyway. Little did I know that a couple of years later, my interest in algae would bring me back to biochemistry. Woodstock of Biology inspired me to finally check out the pathways of the Biochemists' Songbook, and in this presentation I would like to share my findings.

- The Biochemists' Songbook by Harold Baum (publisher's site): https://doi.org/10.4324/9780203482988
- The Biochemists' Songbook can be borrowed at: https://archive.org/details/biochemistssongb0000unse
- For Ansgar's serious science, check out https://asafind.jcu.cz/

What does evolution make? Learning in living lineages and machines

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The multiscale architecture of intricate patterns of form and function observed in living organisms is a testament to the complex interplay between genetic information and developmental processes shaped by natural selection and evolution [1, 2]. Here [3], we explore the profound connections between evolution and learning, and view biological development as fundamentally agential, literally reframing the genome as a generative model rather than a rigid algorithm or blueprint. This interpretation suggests deep analogies between evolutionary and developmental genetics and generative machine learning, departing from traditional mappings of genes to traits. On the contrary: the genome embodies compressed latent variables shaped by evolution and natural selection and dynamically decoded by collaborative cells of the developing embryo. This perspective allows us to interpret development as a hierarchical generative process - with the genome at its creative bowtie - that adapts context-aware across scales. This notion draws strong parallels with cognitive systems - especially regarding the construction of the mind - and with generative AI, spanning autoencoders, intrinsically distributed neural cellular automata, or cutting-edge diffusion models. We will discuss the implications of these models for enhancing our understanding of various tiers of biological evolution and self-organization, as well as their potential applications in biomedicine, bioengineering, and both artificial and biological intelligence.

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The dynamics of ergosterol biosynthesis in pathogenic Candida species

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Representatives of the genus *Candida* are known as leading causative agents of opportunistic fungal infections. Current treatment options include drugs affecting cell surface: cell wall of plasmatic membrane. While human cell membranes contain cholesterol as the major sterol lipid, fungi possess ergosterol. Lanosterol 14-alpha-demethylase, one of the enzymes of the ergosterol biosynthesis pathway, is a target of azole-based antimycotics, including a widely used drug fluconazole. Resistance to antimycotic treatment has been of concern. Its mechanisms including efflux pumps or chromosomal rearrangements have been extensively studied. Less attention has been turned to sterols themselves and their content in the cells of *Candida* species differing in susceptibility to fluconazole. We analyzed the composition of sterol lipids, namely lanosterol, ergosta-5,7,22,24(28)-tetraenol and ergosterol in *C. albicans*, *C. parapsilosis*, *C. glabrata* and *C. guilliermondii* and monitored changes occurring during cultivation of these yeasts under laboratory conditions. The yeast species differed not only in the ergosterol content, but also in the changes of ergosterol concentrations during the culture growth. While *C. glabrata* and *C. parapsilosis* showed slight gradual decrease of ergosterol concentrations, *C. albicans* and *C. gulliermondii* displayed a more complicated pattern with maxima and minima of ergosterol concentrations occurring over time. The dynamics of the key sterol biosynthesis reflects differences in the lifestyle, which are likely to contribute to differences in antimycotic susceptibility of the individual yeast species.

Regulatory RNAs that interact with RNA polymerase in bacteria

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Bacterial transcription is an important target of antibiotics. Rifampicin, which inhibits bacterial RNA polymerase (RNAP), is the first-line drug to treat tuberculosis. We propose that in nature, bacteria have evolved their own mechanism to reversibly sequester and potentially inhibit RNAP by 200 - 400 nt long, structured RNAs. These RNAP-associated regulatory RNAs are highly abundant in specific growth conditions and show a high variability between different species.

For example, in *Mycobacterium smegmatis* and *Mycobacterium tuberculosis*, the majority of RNA associated with RNAP during the stationary phase of growth are Ms1 and MTS2823 RNAs, respectively. We have established a method to detect these RNAs. Now we are asking whether molecules based on these RNAs (or their partial sequences) could be used as antibacterial compounds targeting RNA polymerase in the future. The advantage of such compounds is their potential species specificity - they could target only bacterial pathogens without affecting other bacteria in the human microbiome.

ENDOTHELIAL PYRIMIDINE SYNTHESIS DEFICIENCY PROMOTES TUMOR GROWTH

Petra Hyrossova[1], **Isidora Milisav**[1,2], **Silvia Novais**[1], **Mirko Milosevic**[1,2], **Jakub Rohlena**[1], **Katerina Rohlenova**[1]

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Cancer cells depend on nucleotide synthesis for proliferation. Antimetabolites targeting nucleotide metabolism remain the basis of cancer therapy. Despite their success, antimetabolites suffer from high rates of resistance, possibly due to interactions with stromal cells. To test the impact of altered nucleotide metabolism in the tumor microenvironment, we suppressed de novo pyrimidine synthesis in mice by whole-body inducible knockout of DHODH, its essential enzyme. Here we report that such manipulation results in an accelerated growth of orthotopic lung tumors. Single-cell transcriptomics data from tumor-bearing lungs revealed that systemic DHODH deficiency impacts stromal cells, including immune cells and, unexpectedly, endothelial cells. To explore the specific effect on the endothelium, we generated a mouse model of inducible endothelial DHODH deficiency. Surprisingly, the ablation of de novo pyrimidine synthesis in the endothelium paralleled the whole-body model results and created a more permissive environment for cancer cells, as evidenced by accelerated lung tumor growth. Transcriptomic analysis of the endothelial-specific model revealed changes in the immune repertoire of the tumor microenvironment, particularly in monocytes, while metabolic imaging points to possible metabolic crosstalk with endothelial cells. We are now developing these findings further to identify mechanisms responsible for the pro-tumorigenic effects of pyrimidine synthesis-deficient endothelium. To summarize, our results suggest a paradoxical, pro-tumorigenic effect of pyrimidine synthesis inhibition in endothelial cells, which could impact the effectiveness of anti-cancer therapy.

How do Plants Recover from Drought Stress?

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All organisms experience stress as an inevitable part of life, from single-celled microorganisms to complex multicellular beings. The ability to recover from stress is a fundamental trait that determines the overall resilience of an organism, yet stress recovery is understudied. To investigate how plants recover from drought we examined a fine-scale time series of bulk RNA sequencing starting 15 minutes after rehydration following moderate drought. We reveal that drought recovery is a rapid process involving the activation of thousands of recovery-specific genes. To capture these rapid recovery responses in different leaf cell types, we performed single-nucleus transcriptome analysis at the onset of post-drought recovery, identifying a cell type-specific transcriptional state developing independently across cell types. Furthermore, we reveal a recovery-induced activation of the immune system that occurs autonomously, and which enhances pathogen resistance *in vivo*in *A. thaliana*, wild tomato (*Solanum pennellii)* and domesticated tomato (*Solanum lycopersicum* cv. M82).Since rehydration promotes microbial proliferation and thereby increases the risk of infection1-2, the activation of drought recovery-induced immunity may be crucial for plant survival in natural environments. These findings indicate that drought recovery coincides with a preventive defense response, unraveling the complex regulatory mechanisms that facilitate stress recovery in different plant cell types.

Snowball Earth, the birth of a condensate and the rise of conscious metazoans

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Earth. 700 million years ago. The Cryogenian. Four ice ages – Sturtian, Marinoan, Gaskiers, and Baykonur – repeatedly shock-freeze the planet for eons. Closed ice sheets cover oceans and continents. The cold is unbearable. Life is almost wiped out. Proteins that mitigate cold stress – especially RNA chaperones – are under extreme and prolonged evolutionary pressure. What is the result? Only a few organisms will survive in a handful of spots on land or deep in the ocean. But what was once a world of slime before this severe environmental stress will soon explode into every complex living body plan we see around us today. How did life survive the cold? How did WE survive so spectacularly?

Fast forward to 2006. Researchers in Japan knock out an RNA-binding protein in mice. The embryos die after a few weeks with a malformed, undersized brain. Close analysis reveals that the protein in question has large disordered regions. However, these regions flank a central folded domain that binds complex regulatory RNAs in mammals (3'-UTRs, lncRNAs, etc.). Surprisingly, this is the same cold shock domain that may have helped save us 700 million years ago. Further analysis shows that the four amino acids that contact the RNA are part of an ultra-conserved RNA-protein interface found throughout the tree of life. The four aromatic amino acids that contact the RNA have not changed in 4 billion years.

Combining single-molecule biophysical experiments with RNA molecular biology and bioinformatics, our team is tracking RNA-protein interactions along evolutionary trajectories. Our goal is to better understand how a fully folded stress response protein to a severe environmental thread (prolonged cold) that does not form any condensates has evolved into an essential factor in brain development in higher organisms with long IDRs that easily condense into beautiful, liquid-like droplets. I will take you on a journey involving cold RNAs, hot optical tweezers, and microtubule-bending droplets, illustrating how even prolonged and severe stress can sometimes provide an opportunity for recovery and growth.

Unveiling the choreography of human brain development with morphodynamics in human brain organoids

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Brain organoids enable mechanistic study of human brain development and provide opportunities to explore self-organization in unconstrained developmental systems. We have established long-term light sheet microscopy on unguided multi-mosaic neural organoids (MMOs) generated from fluorescently labeled human induced pluripotent stem cells (iPSCs), which enables tracking of tissue morphology, cell behaviors, and subcellular features over weeks of organoid development. We demultiplex multi-mosaic neural organoids using morphometrics to provide quantitative measurements of tissue and cellular dynamics, using Actin, Tubulin, plasma membrane, nuclei, and Lamin labels, and show that the organoids exhibit tissue state transitions through neural induction, lumenization, and regionalization. We find that despite morphological heterogeneity, different organoids exhibit lumen formation and expansion at a consistent time, coinciding with early neurectoderm switching to late neurectoderm fate. This morphological tissue transition coincides with a switch in underlying gene regulatory networks (GRNs) involving extracellular matrix (ECM) pathway regulators. Presence of a basement membrane rich external ECM promotes cell polarization, cell alignment to form a neuroepithelium, lumen expansion and leads to formation of telencephalic progenitors. However, in absence of external ECM, the tissue transition switch is perturbed forming a heterogenous neuroepithelium with mixed cellular alignment and polarity. This promotes formation of increased neural crest cells and non-telencephalic progenitors. Finally, we show ECM induced patterning guidance is linked to modulations of the WNT and HIPPO signaling pathway, including spatially restricted induction of WLS and YAP1. Altogether, our work provides a new inroad into studying human brain morphodynamics, and supports a view that mechanosensing dynamics play a central role in constraining brain regionalization.

Data visualization against facism

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Data visualization is a tool of enlightenment and empowerment: it makes the invisible visible, particularly in biology. Charles Darwin famously used a branching diagram to illustrate his theory of common descent, offering a revolutionary view of evolution and our shared ancestry. But data visualization has also served the common good in public health and society. John Snow mapped cholera outbreaks in London to reveal the source of contamination, and Florence Nightingale devised graphics to persuade policymakers to improve hygiene in military hospitals, drastically reducing soldier mortality during the Crimean War. In the 20th century, Otto Neurath and Marie Reidemeister developed the ISOTYPE system, Emojis of the 19th century, to communicate socioeconomic realities and inequalities accessible to low-literate, oppositing fascist propaganda by promoting clarity, education, and transparency. I will present community-developed guidelines and work towards increasing interpretable, reproducible, and trustworthy image figures and charts. I also talk about the clinical work, using data visualizations to support those most vulnerable, the cancer patients, and increasing their equity in care. Truthful communication of biological data is not just a scientific necessity, but a civic responsibility in an era shaped by misinformation.

Nicotinic acetylcholine receptors expressed by individual neuronal populations of the mouse prefrontal cortex show specific effects on behavior

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Nicotinic acetylcholine receptors containing beta2 subunit (beta2* nAChRs) are widely expressed in the mouse prefrontal cortex (PFC). The expression pattern is complex and changes according to the specific neuronal types, cortical layers and subregions. In addition, beta2* nAChRs in the PFC control cognition and behavior associated with this brain region, including attention and memory, cognitive flexibility and social and anxiety-like behavior. Although the functional significance of beta2* nAChRs in the PFC is broadly accepted, the possibly distinct roles of beta2* nAChRs expressed in specific neuronal populations are poorly understood. To address this knowledge gap, we wanted to compare the effects of the knockdown (KD) of beta2* nAChRs expressed in different neuronal types in the PFC. First, we used fluorescent in situ hybridization (FISH) to examine the expression of beta2* nAChRs in different neuronal populations of the mouse PFC. Then, we used a CRISPR-based approach to induce the KD of the beta2 nicotinic subunit in selected neuronal populations. The KD of the beta2 subunit in a mixed (excitatory and inhibitory) population of the deep cortical layers affected the exploration of novel environments and led to working memory impairment and decreased social interactions. Importantly, the severity of behavioral changes was correlated with the number of neurons affected by the CRISPR-induced KD. In contrast, the KD in a homogeneous inhibitory population of the upper cortical layers led to an increased interest in social stimuli, while it showed little effect on other domains. Finally, we used the Cre/loxP system to induce general beta2 KDs affecting large neuronal populations. Surprisingly, the general KDs showed relatively little effect. In conclusion, more restricted and regional- and neuronal-type-specific modulation of nAChRs may be more efficient in the control of behavior, including behavioral symptoms related to PFC-associated neuropsychiatric disorders.

A Key Metabolic Sensor Meets Chromatin in Neurons — But Does the Brain Care?

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The metabolic level of a nerve cell adjusts, on the one hand, to the neuronal activity of the surrounding network of nerve cells and, on the other hand, to the availability of nutritional and energy resources of the given cell. One of the key proteins that enables the integration of these two types of information and the appropriate adjustment of cellular metabolism in eukaryotic cells is the protein kinase mTOR (mammalian target of rapamycin). mTOR is absolutely crucial for the development and physiology of neurons, and disturbances in its activity underlie numerous neurodevelopmental and neuropsychiatric disorders.

mTOR is commonly considered to be a cytoplasmic protein activated at the lysosomal membrane. However, increasing evidence points to its physical presence in the cell nucleus and the associated changes in nuclear processes, although exactly how these are regulated by mTOR remains poorly understood.

Our previous research has shown that high activity of the neuronal network causes a transient accumulation of mTOR in the nucleus, which inspired us to ask what function this may serve. We have subsequently demonstrated that one of the nuclear targets of mTOR in neurons is the phosphorylation of the Brg1 protein, an enzyme crucial for the activity of the BAF complex, which actively modulates DNA accessibility. mTOR activity leads to the degradation of Brg1 in the nucleus. At the network level in vivo in zebrafish, this results in increased neuronal network activity.

The aim of my presentation is, on the one hand, to present these previously unpublished findings, and on the other hand, to engage in a discussion with participants of Woodstock Bio2 about the still-unanswered question: why does a nerve cell require a transient reduction of Brg1-dependent BAF complex activity in the cell nucleus?

Disordered epigenetics: Single-molecule long reads for methylation entropy as a biological biomarker

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DNA methylation plays a critical role in regulating gene expression and maintaining genomic stability, with aberrant patterns often linked to disease. Micro-arrays and short read sequencing commonly measure the local degree of methylation as the average methylation value of a specific methylation site. The mean methylation level, commonly termed the methylation Beta value, ranges from zero to one and reflects a population average without retaining information regarding the contribution of individual DNA molecules or the correlation between neighboring methylation events. Methylation entropy—a measure of the disorder in methylation patterns—offers a promising biomarker for assessing epigenetic dysregulation. Oxford Nanopore Technologies (ONT) long-read sequencing allows to infer methylation entropy, relying on the methylation patterns along individual DNA molecules, in addition to the mean methylation level.

In this work we explore methylation entropy as a potential biomarker and highlight common pitfalls in its analysis methods. We show the impact of limited read coverage when combined with CpG density and binning strategy, potentially misrepresenting genomic complexity, and introduce methodologies to enable accurate assessment of epigenetic heterogeneity. Our strategy is validated through synthetic data benchmarks in a biologically-relevant genetic context. We showcase our approach in a comparative analysis between normal pancreatic and pancreatic ductal adenocarcinoma (PDAC) samples, demonstrating its potential for cancer detection. By assessing differential methylation entropy regions, we show that methylation entropy provides a complementary measure to differential methylation level, potentially increasing the sensitivity for tumor detection and classification. This validation not only underscores the influence of CpG density on entropy metrics but also illustrates the potential of our method to reveal biologically meaningful epigenetic alterations associated with tumor development.

Dual regulation of the unfolded protein response by IGF2BP3 during ER stress

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Misfolded protein accumulation in the endoplasmic reticulum (ER) perturbs cellular homeostasis, causing pathological ER stress. While a transcriptional response is paramount for the Unfolded Protein Response (UPR), which counters ER protein overload, multiple UPR-linked mRNAs are post-transcriptionally regulated. However, the mechanisms mediating this regulation remain unclear. Here, we reveal specific interactions between the conserved RNA-binding protein IGF2BP3 and transcripts encoding UPR effectors. During ER stress, IGF2BP3 destabilizes many of its target transcripts, including UPR effectors. Mechanistically, ER stress enhances IGF2BP3's association with the mRNA decapping complex and the ER stress sensor RNase IRE1, correlating with a shift toward mRNA destabilization. Unexpectedly, prolonged depletion of IGF2BP3 inhibits UPR via decreased transcription of UPR target genes. Together, our findings suggest that IGF2BP3 contributes to proteostasis during ER stress through dual mechanisms: directly promoting mRNA degradation to reduce translation and folding burden and indirectly supporting transcriptional activation of the UPR.

The complex (IV) relationship of Dr. Jekyll, Mr. Hyde and their friends

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COX6B1 (Dr. Jekyll) is a subunit of complex IV that assembles as a part of MTCO3 module. Previously known patient mutations implicated its role in the late stage of the assembly, however our HEK293T cell line knock out model unexpectedly showed greatly diminished levels of complex IV proteins resembling models of COX4, an early assembling subunit, knock out. Expression of alternative oxidase (AOX) partially restores the assembly of the complex and helps to pin-point the role of COX6B in it as levels of MCTO1, MTCO2 and even parts of the MTCO3 modules increase in comparison to the knock-out. COX6B2 (Mr. Hyde) is a non-canonical isoform of COX6B1and can be found only in testis and, according to some reports, in cancer. However, despite their similarities, COX6B2 does not rescue the COX6B1 knock out phenotype and does not assemble into complex IV in any cell line transfected with the expression vector containing it. We have developed a new solubilization protocol for boar sperm cell and found COX6B2 assembled in complex IV that, together with other respiratory system complexes possessed a unique separation pattern on BN-PAGE.

My Favorite Animal: The Living Fossil Amphioxus

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Since ancient times, people have been curious about their origins. For centuries, they honored their ancestors, and religion was often the main explanation for the origin of life. Then came the 19th century, when Charles Darwin suggested something radical: that all species on Earth share a common ancestor. And if we zoom out even more, we now know that all phyla — the major body plans of animals — also trace back to common ancestral phyla. This is how we can explore the origin of species, and even the origin of major groups like vertebrates. So if we ask: Where did vertebrate traits come from? Traits like the brain, cranium, vascular system, and sensory organs — all the things that make vertebrates, well, *vertebrate*. To answer that, nature has kindly preserved a perfect model organism: the humble amphioxus. It looks like a **living fossil**, and it functions like a **natural control** — a simple version of a chordate, without all the fancy vertebrate upgrades. Studying amphioxus helps us understand how complex features evolved in vertebrates by comparing them to what was already likely present in the common ancestor.

Does energy drive growth, or does growth regulate energy intake? Insights from snake development

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Classical energy budget models assume that food availability dictates growth and sexual size dimorphism, with energy intake limiting developmental trajectories. However, mounting evidence suggests that growth is regulated by intrinsic physiological mechanisms rather than immediate energy availability. Here, we test this hypothesis in a long-term experiment on a highly sexually dimorphic snake species (sand boa), tracking growth, body mass, and feeding behavior in control and steroid-treated individuals. Contrary to the assumption that snakes exhibit plastic growth dictated by food intake, we found that individuals regulate feeding based on body condition, cycling through prolonged feeding and non-feeding phases lasting for months. The length of these phases differed between sexes and treatment groups, with faster-growing groups exhibiting shorter non-feeding intervals. Crucially, the body condition thresholds for initiating or ceasing feeding remained constant across groups. Our findings challenge the classical view that energy intake dictates growth, instead suggesting that growth itself determines feeding needs as a function of maintaining homeostasis. This reversed causality has profound implications for ontogenetic growth models, life-history theory, and the fundamental understanding of energy allocation in vertebrates.

Extreme gene expansion and diversification of the broadly antiviral effector Tetherin in Myotis bats

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Bats are reservoirs of numerous zoonotic viruses and have been linked to recent disease outbreaks, including SARS-CoV-2 pandemic. During evolution, countless virus-host encounters may have shaped bat immunity leading to diverse balances between tolerance and defense to viral infections. One of the first barriers against invading pathogens is innate immunity, including antiviral proteins, which inhibit the viral replication in the host cells. Recent research on bats showed the diversification of several antiviral effectors, suggesting their pivotal role in bat immunity, yet their evolutionary history and functional consequences remain largely unknown.

In this study, we describe the genetic expansion of the locus encoding antiviral protein Tetherin in *Myotis* bats. *Myotis* bats are found worldwide and are natural hosts of viral families with zoonotic potential, including flaviviruses, rhabdoviruses, and coronaviruses. Tetherin is an interferon-stimulated restriction effector that physically binds newly formed viral particles to the host cell membrane and thus blocks virus transmission. In most mammals, it is present as a single copy. However, the analysis of the Tetherin*/BST2* genomic locus between *PLVAP* and *MVB12A* genes in 30 bat species revealed a varying number of *Tetherin* copies in *Myotis* and *Pipistrellus* bats, up to 20 copies. Several copies represent putatively functional Tetherins, while others acquired deleterious mutations. We further found important protein structural differences between Tetherin copies, strongly suggesting functional divergence during evolution. Moreover, bat *Tetherin* has evolved under strong positive selection during bat evolution, as well as within the Myotis radiation, suggesting its involvement in virus-host evolutionary arms race and the presence of Tetherin antagonists from pathogenic viruses that have shaped *Myotis* evolution through past/recent epidemics.

Taken together, we identified numerous *Tetherin* copies in high-quality genomes of closely related *Myotis* bat species, which will uniquely enable us to determine the complex evolutionary history of Tetherin duplications and divergence. The functional consequences remain to be determined and future work will determine if and how Tetherin duplication and divergence contribute to bat innate immunity.

The unbearable predictability of kcat

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The catalytic rate constant *k*_cat is widely seen as an evolvable trait reflecting enzyme efficiency and fitness. Since amino acid sequence determines enzyme function, we expected *k*_cat to be best predicted from sequence. Instead, using machine and deep learning models, we found that the biochemical reaction alone predicts *k*_cat more accurately than the enzyme's sequence. It seems that *k*_cat is less a feature of the protein than of the reaction it catalyzes – as if evolution drives enzymes toward a reaction-specific optimal *k*_cat. But what defines this optimality? And why does evolution converge so predictably?

A genetic gatekeeper of epigenetic inheritance in mammals

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Epigenetic information carried in the gametes can modify phenotype in the next generation. Mammalian sperm contain RNA, protamines, nucleosomes, and covalent DNA modifications, all of which have the potential to transmit regulatory information to the zygote and influence developmental trajectories. Nearly all of this non-genetic information is reset at fertilization, clearing the way for genetically encoded programs to robustly and reproducibly control development. Under stress conditions, however, it can be advantageous for epigenetically encoded information about the parental environment to reach the offspring, even at the cost of increased developmental variability. We found that the histone demethylase KDM6A (also called UTX) acts as a genetically programmable barrier to epigenetic inheritance in the mouse male germ line. Loss of KDM6A during sperm development impacts phenotype in offspring even when they do not inherit the mutant allele. F1 offspring of *Kdm6a* mutant fathers ('Kdm6a F1s') have shorter lifespans, higher cancer rates, and altered gene expression compared to genetically identical controls. We found that KDM6A forms a germline-specific partnership with specific histone methyltransferases during a short window in sperm development to deposit the histone modification H3K4me1 at promoters. Loss of KDM6A in spermatogenic precursors abolishes H3K4me1 at hundreds of sites in the genome. This epigenetic shift impacts gene expression in the early embryo and in normal-appearing adult tissues. We hypothesize that KDM6A acts as a genetic switch that allows the parent to tune how much epigenetic information will be passed on to offspring. Interestingly, other members of the histone demethylase gene family have been reported to act as barriers to epigenetic information in diverse organisms including yeast, plants, and invertebrate animals, suggesting that this function may be deeply conserved.

The Last of the Worms

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What happens when our brain realizes we are trapped and cannot move any longer? To address this question, we record brain wide activity of *C. elegans* worms when they get trapped
by a natural predator, the fungus *A. oligospora*. When trapped, the worms attempt to escape from the deadly lasso traps with vigorous movements. If they don't succeed, they die. Using this system, we find that worms respond to trapping by elongating specific movements and intensify their forward undulations. In the brain, we find a highly distributed response, where multiple reversal-related neurons prolong their shared activity state, and many motor neurons intesify their activity.

In the second chapter, we wondered: How do such innate behaviors evolve? To tackle this, we exposed genetically diverse worm populations to fungal traps as a selection pressure. After multiple generations, we obtained several populations that became more efficient escapers. Next, we characterized the genetic changes in these super-escaper populations and set out to study the candidate alleles in terms of their corresponding changes in brain-wde activity and behavior.

Together, our projects shine light on how life-or-death behavioral strategies are distributed and modulated throughout the brain, and show possible pathways of how evolution shapes this innate behavior and its neuronal underpinnings.

A Mathematical Model for Pseudo-Progression in CAR-T Therapy of B-cell Lymphomas

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CAR-T therapy, where T cell are genetically modified to respond to CD19-presenting B cells, has revolutionized the treatment of several blood cancers. The immediate effect of this immunotherapy is associated with a significant inflammatory response in the patient, sometimes leading to a tumor that seemingly swells in the days following CAR-T cell injection. This is referred to as pseudo-progression, and in this project we present a mathematical model of CAR-T cell therapy where pro-inflammatory cytokines play a crucial role. The model is capable of capturing a wide range of behaviors, including long-term successful treatments, failed treatments and pseudo-progression. The parametrization of the model maps on to measurable patient characteristics, and we discuss how these parameters impact the long term behavior of the model.

Pre-empting resistant infections based on pathobiome profiling

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The rising prevalence of antibiotic resistance commands that the antibiotic treatment be tailored to the sensitivity of the infecting strain. However, direct measurements of infection sensitivities are not always routinely performed and are costly in terms of lost therapeutic time; in absence of a resistance profile, an inappropriate antibiotic is often administered. Here, we show that antibiotic resistance in future urinary tract infections (UTIs) can be predicted by pre-profiling the resistance of a patient's pathobiome: the reservoir of infection-capable strains residing in a microbiome. Inspired by recent evidence that certain types of infections are commonly seeded by patients' pathobiomes, we assembled a unique collection of same-patient stool samples and urine cultures for 477 patients. Whole-community and single-clone genotyping of pathogen-enriched stool samples showed that pathobiomes are diverse and highly person-specific. Furthermore, these pathobiomes often harboured the genome of a strain found in future urine cultures, with matching resistance profiles. Critically, we found that genotypic mapping of resistance genes in a patient's pathobiome is predictive of an antibiotic-specific resistance in urine isolates of the same patient even months later. Finally, we developed a simple whole-community resistance profiling method and showed that pathobiome community resistance predicts antibiotic resistance in future urine isolates. Our findings pose the opportunity for a personalised, resistance-curbing infection treatment strategy based on microbiome testing that can be performed well ahead of infection, and hint at a future where infections are preempted rather than treated.

Cells decrease their volumes and cell cycle progression rates during formation of multicellular structures

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Cell proliferation is essential for healthy tissue homeostasis and repair and is achieved through the coordination of cell growth and division. Before a cell can divide, it must grow by replicating its genome and cellular material, which occurs over the cell cycle. This growth can be observed as an increase in cell mass and volume. These changes in volume over the cell cycle are not merely passive byproducts, but rather actively contribute to its regulation. The regulation of volume and cell cycle happens in conjunction and is essential for regulating proliferation. However, this precise regulation of proliferation is disrupted in a diseased state like cancer. Tumors are marked by increased cell proliferation. This can be explained by the disruption of cell cycle regulation in cancer cells. While numerous studies have investigated cell cycle progression in the context of cancer, the direct relationship between changes in cell volume and tumor progression remains underexplored. So, it is still unclear how cancer cells modulate their volume (and cell cycle) as they proliferate to give rise to a multicellular tumor. As this would be technically challenging to study *in-vivo*, in this study we form tumor spheroids from single cancer cells in a physiologically relevant 3D matrix. Single cells from multiple cancer cell lines were embedded in PEG-heparin hydrogels and allowed to form spheroids. Using high resolution confocal imaging and image segmentation, we observed that single cells drastically reduced (by 40-60%) their cellular and nuclear volumes when they formed multicellular tumor spheroids. We show these changes are not due to compressive stress or inhibition of growth. Rather these changes in volume were attributed to changes in the cell cycle and water efflux. Interestingly, when observing invading spheroids in 3D, the invaded single cells had a higher nuclear volume compared to the cells in the spheroid. Thus, either when single cells form multicellular structures or when they escape from a multicellular structure, they are larger in volume compared to the multicellular entity. Mechanical measurements also show these single cells to be more compliant.

Expression of 13 Secreted Novel AID/APOBEC-like Deaminases (SNADs) Genes During Embryogeneis of Common Carp (Cyprinus carpio) in the Context of Immune System Development

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The AID/APOBEC family comprises zinc-dependent cytidine deaminases that catalyze the deamination of cytidine to uridine in nucleic acids. Within this group, the *Secreted Novel AID/APOBEC-like Deaminases* (SNADs), distinguished by the presence of a signal peptide, are unique compared to classical intracellular AID/APOBECs, which are central to antibody diversification and antiviral defense. To date, SNADs remain poorly characterized, with limited information available regarding their biochemical properties and biological functions. However, our previous studies have demonstrated catalytic activity of SNAD1 and its involvement in various immunological processes, including immune responses to viral and bacterial infections, as well as temperature acclimation. The aim of this study was to investigate the expression patterns of all 13 currently identified SNAD1 genes in common carp (*Cyprinus carpio*) during ontogeny. Using multiplex PCR, we analyzed gene expression at key developmental time points: 0 hpf, 17 hpf, 26 hpf, 49 hpf, 74 hpf, 98 hpf, 123 hpf, 147 hpf, 170 hpf, 190 hpf, and 10 dpf. Our results revealed dynamic, stage-specific changes in SNAD gene expression, suggesting their potential involvement in early immune system development in carp. This study provides the first comprehensive overview of SNAD gene expression during vertebrate ontogeny and lays the groundwork for future functional analyses of this novel deaminase family.

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Exercise immunometabolically reprograms the brain blocking melanoma brain metastasis formation

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Brain metastases represent a critical challenge in cancer progression, with melanoma patients comprising the second most affected population. Despite their clinical significance, effective therapeutic strategies for melanoma brain metastases (MBMs) remain limited. Using our previously developed exercise paradigm, we show that sustained aerobic activity robustly suppresses MBM formation. While the underlying molecular mechanisms remain to be fully elucidated. Our data reveal that exercise induces profound immunometabolic remodeling of the brain microenvironment, rendering it less permissive to metastatic colonization. This includes an altered metabolic signature, striking structural changes detectable through MRI-DTI analysis, and hints in our preliminary data that suggest that a yet to be identified factor is actively attacking metastasasizng melanoma cells. Together, these findings suggest that exercise triggers systemic and local adaptations that create a neuroenvironment hostile to melanoma cells. Through a multidisciplinary approach—integrating proteomics, in vivo models, in vitro systems, spatial metabolomics, and human epidemiological data—we aim to dissect the complex interplay between brain metabolism, immune responses, and metastatic progression. Ultimately, this work positions exercise not only as a potential non-pharmacological intervention but also as a discovery tool for novel therapeutic targets in the prevention and treatment of MBMs.

Plasticity in flexibility

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A key concept for understanding plastic traits has been the reaction norm, an idea that emerged in the early 20th century and has since become a very important ool for all sorts of biologists. Part of the power of the reaction norm concept derives from its mathematical simplicity, that it can easily partition sources of complex phenotypic variation into genetic (G), environmental (E), and interactive (GxE) causes. The success of the reaction norm idea, however, has also given false hope because much if not most plasticity is quite dynamic, contingent and even cognitive over the lifetime of an individual. Here I argue that we might yet rescue the reaction norm method despite these issues, but only after we shift our focus upstream of the regulated traits themselves. In other words, instead of trying to decompose highly dynamic phenotypes, we could instead first describe the latent landscape of phenotypic variation available to an individual for the trait of interest, then study plasticity in this landscape of flexibility in the conventional reaction norm framework. I briefly discuss one example using this approach, namely the regulation of glucocorticoids in response to stressors. Although this approach will probably be viable for most complex molecular and physiological traits, glucocorticoids are exceptionally pleiotropic, and my group has begun to apply this plasticity in flexibility method effectively to these hormones already.

"Non-canonical" functions of signaling molecules

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Signaling pathways are often studied through the lens of their conserved, canonical mechanisms. However, increasing evidence points to evolutionary novelties and context-specific functions that challenge this framework. In our studies, we explore the emergence of novel, non-canonical roles of the Notch signaling pathway, focusing on the Notch1 receptor and Notch ligand, Jagged1. We identified a vertebrate-specific amino acid in Notch1 that acts as an interaction interface for Casein Kinase 1 alpha (CK1α), a Wnt signaling pathway component, suggesting crosstalk between these two major developmental pathways. Additionally, we investigate disease-associated variants of Jagged1, linked to Alagille syndrome and biliary atresia. When introduced into mouse models, these mutations elicit divergent effects on liver vasculature and distinct, selective outcomes on the biliary system, yet notably preserve the canonical signaling capacity of the ligand. Together, ours and others' findings challenge the conceptual framework used to define intercellular communication, with implications for both developmental biology and disease modeling.

Microbes just want to have fun (IBD edition)

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(Meta)genomic profiling of human-associated microbiomes has been increasingly used as a way to understand how microbes are physiologically relevant to their hosts. As sequencing cost decreases, metagenomic profiling is more and more accessible, but without good design, background knowledge, computational experience or experimental validation, often microbial fishing expeditions end up being low impact association studies. In such studies, where typically subjects affected by some disease are compared to Controls, “good” bacteria are reduced and “bad” bacteria are increased in the disease compared to Controls.

From an ecological perspective, this dichotomous view is deceiving, to say the least.In any community of organisms, balance between species is determined by resources availability, not intentions. My work stems from this premise and the overarching goal of refocusing on bacteria and their ecological drives.

When I started my phD I wasn’t aware, but soon I realized how useful studying a disease is: it provides a model system. My model system is Inflammatory Bowel Diseases (IBD) which are characterized by chronic inflammation of the gut.

I will present computational metagenomic analyses that started as a thought experiment, in which I imagined being a bacterial cell myself: what would I experience in an inflamed gut? In my analysis I compare samples coming from Control subjects with samples from IBD patients, and I ask: Do species within an IBD gut mutate more than in a healthy one?

Molecular snapshots of transcription factors "in action" in their native chromatin environment

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Transcription factors (TFs) distinctly mark genes for expression and are the pillars of cell identity. Yet, even at the basic level of DNA recognition by TFs, we know little about how this is achieved. Eukaryotic DNA is wrapped around histone proteins to form nucleosomes which occlude large parts of the DNA surface. While it has been long known that some TFs engage DNA motifs when 'hidden' in chromatin, the mechanisms have remained elusive. I will describe our recent structural insights into how diverse TFs, including those involved in circadian rhythms, read out specific DNA sequences within a chromatinized genome.

A mechanism by which selective-autophagy regulates plant development and fruit ripening

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Ethylene and autophagy play pivotal roles in plants, including in senescence and responses to stress. Although several studies have suggested their crosstalk, direct evidence is still lacking. We speculated that this might be further clarified in a climacteric fruit ripening context. Through the evaluation of tomato Neighbour of BRCA 1 (NBR1) and Autophagy-related 8 (ATG8) protein dynamics together with ripening-context silencing of essential autophagy genes (*SlATG2*, *SlATG7*, and *SlATG4*), we show that autophagy restricts ripening via repression of ethylene production. Notably, a similar outcome was observed, beyond ripening, in *Arabidopsis* root elongation context, wherein *atg5* and *atg7* knockout seedlings showed increased ethylene emission and sensitivity to its precursor, 1-aminocyclopropane-1-carboxylate (ACC).

Furthermore, assays performed to identify *Arabidopsis* ATG8-interacting proteins, coupled with proteomics analysis of autophagy-deficient tomato fruits, highlighted two ethylene biosynthesis proteins (for convenience, collectively termed here ETBPs) as autophagy degradation targets. Consistently, ETBPs contain a distinct ATG8-Interacting Motif (AIM) in a structurally exposed region for ATG8 recognition and are associated with endomembranes, including the tonoplast and the endoplasmic reticulum. We, therefore, propose that autophagy represses ethylene production by selectively degrading ETBPs.

Collectively, our research describes the crucial role of autophagy in ethylene production, which deepens our understanding of the autophagy-ethylene crosstalk in plants.

Deciphering the early events of retroviral expression - do they dare to burn to fade away?

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A legend once wrote that "It's better to burn out than to fade away." —but what about retroviruses? After integration, do they make a fiery entrance with a burst of transcription, only to dim into latency, or do some proviruses silently slip into the shadows from the very start?

In retroviral infections, a curious subset of cells harbors proviruses that remain transcriptionally silent—no viral genes, no detectable signals, just a quiet presence. Parsing this latent population is no easy feat. Current approaches mostly rely on sorting out expression-negative cells, often ending up with a muddled mix of defective, silenced, or entirely absent proviruses.

Our project flips the script with a function-driven approach to uncover a unique class: the "brief burners." These are proviruses that sparked with early expression but quickly faded into latency—neither truly burned out nor inherently silent. By isolating cells marked by this fleeting transcriptional activity, we aim to define the genetic and epigenetic fingerprints of the proviruses responsible.

This new lens—focused on expression history rather than mere presence—will reveal the early post-integration events that set the stage for viral latency. Ultimately, it could deepen our understanding of the latent reservoir and point the way toward better strategies for controlling viral reactivation and rebound.

Do you believe in Got(s)? (glutamic oxaloacetic transaminases)

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Cancer cells rewire their metabolism to meet the heightened demand for building blocks required for rapid proliferation within tumors. Among these metabolic adaptations is an increased dependence on the endogenous synthesis of aspartate, a non-essential amino acid required for nucleotide and protein biosynthesis. Interestingly, enzymes that produce aspartate (glutamic oxaloacetic transaminases 1 and 2, Got1 and Got2) participate in the malate–aspartate shuttle, a metabolic system that transports cytosolic NADH into mitochondria. Hence, aspartate synthesis by GOT1/2 provides not only biosynthesis, but also the cytoplasmic redox.

Indirect interventions that reduce aspartate levels by redox modulations impair tumor growth, but the direct effect of specifically targeting aspartate synthesis in tumors is less well understood. In this study, we investigated whether simultaneous ablation of both Got1 and Got2 (Got2-1 dKO) compromises tumor growth in mice and explored potential metabolic adaptations that might help cancer cells overcome Got2-1 dKO induced aspartate limitation.

Contrary to expectations, growth kinetics of Got2-1 dKO tumors were comparable to parental controls. Analysis of GOT1/2 dKO tumors and nutrient manipulations in vitro revealed that the primary metabolic limitation of GOT1/2 dKO cells is the altered cytoplasmic redox state (e.g. reduced NAD^+/NADH ratio) and not a defect in aspartate synthesis. Evidently, aspartate is provided by alternative synthesis pathways. Consistently with dysregulated redox state, GOT1/2 dKO cells rely on exogenous pyruvate for cytoplasmic redox maintenance. Loss of function CRISPR screen suggested that in the absence of pyruvate GOT1/2 dKO may rely on transsulfuration to maintain their cytoplasmic NAD^+/NADH ratio via endogenous production of alpha-ketobutyrate.

These findings demonstrate that simply blocking aspartate synthesis is not sufficient to inhibit tumor growth, as cancer cells dynamically adapt to maintain key metabolic processes, notably NAD^+/NADH homeostasis. A deeper understanding of these compensatory mechanisms will be essential for developing more robust, multi-targeted therapeutic strategies to disrupt cancer cell metabolism and prevent tumor progression.

The role of transposons in genome evolution

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Will discuss some new examples from vertebrates and invertebrates. A bit of theory, a bit of philosophy and actual data.

Innovation and Conservation in Plant Immunogenomics

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The perpetual conflict between hosts and pathogens propels rapid evolution and biological innovation across all living organisms. Genes involved in host immunity stand out as the most hypervariable and diverse gene families in the genomes of plants, animals, and bacteria. Remarkably, despite this extraordinary diversity, recent studies have identified a set of ancestral immune modules conserved across the tree of life—from bacteria to plants and animals.

Our research focuses on leveraging these dual characteristics of immune genes to uncover novel immune components in plant genomes. Deep homolgy and conceptual conservation of immunity allows us to detect plant genes that are homologs of immune genes in other organisms - we then directly test the hypothesis that this conservation in sequence or domain composition implies a conserved role in immunity. On the other end of the evolutionary spectrum, we use new datasets of high-quality fully assembled plant genomes to identify rapidly evolving loci, and ask if genes of unknown functions in these loci are involved in immunity. We find cool stuff using both approaches, which is nice.

May the force be with you: How lasers unfold complex RNA structures

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PEW PEW PEW. Lasers. They can be so powerful they can destroy planets. But they can also be used in the name of Science! What is a laser beam focused by lenses? That's right – It's a trap! A so-called optical trap, to be precise. This trap can catch and move small objects or even single molecules! With piconewton and nanometer precision, you can see in real-time how the molecule changes its conformation when Force is applied. Any disturbance in the Force represents an unfolding event through which we can understand the structure of the studied molecule. Such a method can be used to examine biomolecules like DNA, proteins or even RNA.

Despite its relatively simple composition, RNA's functional versatility underscores the crucial role of RNA structure. Proper folding enables distant segments of the RNA molecule to come into close proximity, facilitating essential biological functions. However, some RNA species—such as mRNAs, rRNAs, and lncRNAs—can be over 1000 nucleotides long. This raises a fundamental challenge: how do living organisms ensure the robust and accurate folding of long regulatory RNAs?

In our quite literal tour de Force approach, we aim to understand how long RNA molecules fold into their complex structures and what is the role of RNA-binding proteins in that. By employing methods like optical tweezers, fluorescence correlation spectroscopy, or confocal microscopy, we want to dissect key aspects of the dynamic folding process of complex RNAs. Much to learn about RNA folding, we still have…

Phenotypic errors and their impact on evolution

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The genetic code serves as a molecular mapping function, translating triplets of nucleotides into the 20 amino acids that comprise proteins. The Central Dogma of Biology outlines the processes of transcription of DNA into RNA and the subsequent translation of RNA into proteins. Decoding of information within genes occurred through codons—triplets of nucleotides in RNA that are interpreted by tRNA molecules with complementary anticodons.

While accurate execution of this code is essential for producing unique protein sequences from each gene, the inherent molecular processes within cells inevitably lead to errors.

We present new experimental and computational methods for mapping errors that occur during transcription and translation. These errors include the incorporation of incorrect amino acids, shifts in the reading frame that alter the resulting amino acid sequence due to a single nucleotide shift, and the violation of translation stop codon signals leading to unintended protein extensions. We further discuss post-synthesis chemical editing of RNA molecules, which modulates the genetic information encoded in DNA and allows a single gene to produce multiple protein products.

One of the primary challenges we face is distinguishing between neutral, deleterious, and beneficial errors and edits. While some events may have no selective advantage, and even disadvantage, evolution appears to favor instances where diversity confers adaptability. We provide compelling examples illustrating how translation errors enable organisms to create and propagate protein diversity faster than DNA mutations can generate genetic variation.

Our findings suggest that errors and edits within the Central Dogma represent a newly recognized mechanism through which evolution fosters functional diversity, upon which natural selection can act.

The evolution of somatic genome evolvability

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Somatic genome evolution is dependent on the underlying genome, which affects the location of DNA damage accumulation and the accumulation of mutations, as well as their selection through somatic growth advantages. DNA sequence preferences of somatic DNA damage and mutation accumulation are dependent on the underlying epigenome and sequence content. Also, transcription and replication, which themselves have a strong relationship with the DNA sequence, determine sequence susceptibility to damage, repair preferences, and mutation. Together, these processes create a tissue-specific, individual, and species-specific balance between functionality and stability for somatic genomes. This leads to evolutionary pressures on the organismal level, particularly in relation to aging phenotypes and life-span. With the use of DNA-sequence-based deep learning, so called DNA language models, we aim to understand the relationship between the genome sequence and its somatic evolution.

EAGLE-MUT (Efficient Analysis with a Genome-wide LSTM to Evaluate per-nucleotide MUTation susceptibility) learns sequence context of single base substitution probabilities in individual samples of evolved somatic genomes. The fine-tuned foundation DNA language model GROVER (Genome Rules Obtained Via Extracted Representations) learns the impact of DNA sequence and the epigenome on the formation of DNA double strand breaks. With these models we provide information on the first step of somatic genome evolution, the accumulation of damage and mutations. On these, selective processes can act and promote somatic genome evolution, somatic overgrowth, and mosaicism as a consequence.

At Science Woodstock we would like to discuss how the evolvability of somatic sequence we observe may have shaped the genome sequence of organisms in the first place. How can evolutionary pressures on somatic genome evolvability shape the germ line genome sequence? What does this mean for the biology of ageing? Is the timing of somatic mosaicism programmed in our DNA through mutation probability at specific sites? Does this mean that ageing, life span, and cancer risk are programmed through somatic genome evolvability? How can we utilise our DNA language models to tackle such big questions in evolutionary theory?

The Mantis Shrimp: On the spectrum or off the spectrum?

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Although the Mantis Shrimp has intrigued the scientific world for a long time, the visual system of this animal just kept becoming more and more complicated. In order to show that animals such as the mantis shrimp indeed see beyond the human visible spectrum, absorption measurements were made directly on the eyes, complemented with behavioral studies, but no one was able to express and study the rhodopsins of this animal individually.

The mantis shrimp's eye mRNA underwent the most extensive sequencing attempt in 2020, which revealed an astonishing number of 33 rhodopsins. In this project, we attempted to express and characterize rhodopsins from mantis shrimp, find the red-shifted ones, and explore their potential as optogenetic tools. Far red-absorbing rhodopsins are useful since the red wavelengths penetrate the tissue and scatter more in the neuronal tissue. Far-red-absorbing rhodopsins are scarce in nature, and one of their bearers are stomatopod crustaceans (a famous member is the peacock mantis shrimp), which can detect wavelengths ranging from UV (310 nm wavelength) to infrared (over 700 nm) by using different rhodopsins and light filtration systems in their eyes. In a collaboration with Prof. Megan Porter in Hawaii, we received a collection of almost 600 crustacean rhodopsins. These rhodopsins were sorted through a phylogenetic tree, and 25 representatives were synthesized artificially and expressed in HEK293 cells, along with 16 proposed long-wave sensitive (LWS) opsins from *Neogonodactylus oerstedii.*

During the project, we figured out the spectrum and G protein sensitivity of these rhodopsins, finding out that they can switch between two stable states very well. The middle-wave-sensitive ones turn on with blue light and turn off with red light, while the long-wave-sensitive ones do the opposite. The middle-wave-sensitive ones are activated by blue light and deactivated by red light, while the long-wave-sensitive ones act in the opposite direction.

In true Mantis Shrimp fashion, the more research is conducted, the more questions emerge about this intriguing and complex visual system.

Blossoming early in a dry world: interaction of Abscisic-Acid and photoperiodic pathways in Arabidopsis thaliana

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Drought caused the anticipation of flowering in the model plant Arabidopsis as well as in several crops, at the cost of productivity. The Abscisic Acid pathway, that responds to and relays drought stimuli, interacts genetically with the photoperiodic flowering one and in particular with its key component GIGANTEA (GI).

Using BiFC and Co-IP we find that GI interacts physically with group A bZIP transcription factors – to different extend final effectors of the Abscisic Acid pathway – e.g. Abscisic Acid responsive elements-Binding Factors (ABFs).

Using sequence and structural predictions we annotate GI and ABFs to explain their functions and interactions. On one hand, we hypothesize on how ABFs can act as activators under ABA signalling and on what could be the function of GI in this as it is found to be part of the ABA gene regulatory network. On the other hand, GI cold be annotated for the first time with an Armadillo domain and thus structural predictions of complexes between this domain and ABFs or ABFs in complex with their General Regulatory Factors partners are analysed in detail.

The latter point is also explored with preliminary and ongoing interaction assays leveraging on mutated forms of bZIPs and with the Armadillo truncation of GI. We reconcile the resulting observations with unpublished data of our lab where GI affects the stability ABFs. Altogether we produce a working model to falsify the role of GI in ABFs transcriptional complexes.

Further studies are needed to gain a detailed understanding of the complex systems under study at different levels. Still in-silico predictions together with literature data provide the basis for exciting and testable hypotheses, to unravel the how drought signals are integrated into the photoperiodic flowering pathway and shed light on the key but long enigmatic GI.

The Missing Disorder: A Cold Take on Bacterial Stress Responses

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Evolution has enabled the gradual transition from unicellular life forms to complex multicellular organisms over approximately 3.5 billion years. There are many potential pathways by which Nature may have turned the knobs to facilitate this change of organismal life forms from a single cell species to intricate multicellular species. Conservation and modification of protein domains from bacteria to humans is one way evolution imparts robustness and functional diversity. This gives rise to proteins conserved in structure and function. The cold shock proteins (CSPs) are one such family of proteins native to almost every organism; examples of how Nature opts for the same domain to orchestrate multiple functions.

Our initial investigation of the structural differences in the protein family using bioinformatics revealed a striking trend: the bacterial CSP has no intrinsically disordered regions (IDRs), whereas the human CSP ortholog YBX1 is approximately 70 per cent disordered.

The bacterial CSP initiates a cold shock response in bacteria, enhancing their survivability.1 Curiously, the human counterpart YB-1 is a multifarious protein with many functions like translational control, transcriptional regulation, mRNA stabilization, mRNA splicing, and extracellular roles.2 This strongly suggests significant functional evolution of the protein family orchestrated by the introduction of IDRs.

To explore this functional aspect of this IDR expansion, we are designing an *in vivo* bacterial system to investigate the effect of CSP orthologs from different organisms on the bacterial cold shock response. Through our study, we aim to gain novel insights into how the absence or presence of IDRs shapes environmental adaptation responses in organisms.

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Cellular Domestication: In-Vitro Evolution as a Tool for Cultured Meat Advancement

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Cellular agriculture could become a major part of our nutrition in the coming decades. However, the transition from farm to bioreactor presents new biological challenges: mammalian cells must grow and differentiate *ex-vivo* into muscle and fat tissues—functions they were never naturally selected to perform outside the body. Can we adapt these cells to thrive in this novel environment and reliably produce high-quality, meat-like products?

To tackle this question, we conducted the first genome-wide CRISPR knockout screen in bovine mesenchymal stem cells (bMSCs). By applying targeted selection pressures, we are uncovering key genes and pathways that govern cell proliferation and differentiation *in-vitro*. Our goal is to optimize bMSCs for the unique demands of cultured meat production, advancing both the science of cell domestication and the future of sustainable protein.

Studying ageing as a two-phase process, the path towards identifying public mechanisms

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Aging is a complex, multifaceted process influenced by genetic, molecular, and environmental factors that is generally defined as a time-dependent decline of an organism's physiological functions ultimately leading to its death. In the past ten years, the breakdown of intestinal barrier function, as demonstrated in Drosophila, has become a critical indicator of systemic aging. The alteration of intestinal controlled permeability dubbed "Smurf phenotype" predicts hallmarks of ageing such as inflammatory responses and metabolic dysregulation better than chronological age, as well as ultimately mortality.

Its broad evolutionary conservation across *Caenorhabditis elegans*, *Danio rerio* and mice has led us to propose a model of ageing being a two-phase process and assess its role on the evolution of an "ageing function".

Together, these studies illustrate the importance of considering the two-phase model of ageing for better understanding healthspan and identify potential targets for therapeutic strategies aimed at enhancing resilience against age-related diseases.

How Function Emerges from Behaviour: Synchronization and Collective Motion in Active Systems

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Emergent behavior occurs when local interactions between individual components lead to large-scale collective patterns that are not encoded at the level of the individual agent. A ubiquitous example in biology is synchronization, where interacting oscillatory units autonomously coordinate to pulsate in unison. However, synchronization alone does not constitute a function. An emergent behavior transitions into an emergent function when coupled to its environment. For instance, the synchronized contractions of muscle cells coupled to a fluid can drive directed flow, as in the heart. This principle underlies many biological processes, yet a predictive framework to engineer emergent function remains lacking.

In this work, we demonstrate how synchronization drives collective motion in both cell assemblies and macroscopic active spheres via coordinated force transmission to the substrate. We show that by measuring the energy consumption of each agent, we can reconstruct the flow of energy throughout the system and link it to the emergence of self-organization. We propose that an emergent function can be directly engineered by shaping how energy flows through the system—from input to dissipation. Ultimately, by guiding these energy pathways, it may be possible to establish a framework that allows for the design of active materials with tailored functions.

A watery grave

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The practice of earth burial has been well established for centuries. Human bodies are laid into coffins which in turn are laid into a burial plot for a period of time to decay naturally. Decay is based on microbiota and edaphic species breaking down organic and inorganic matter. This process takes place in soils, which also act as a transport medium for precipitation into the deeper ground. When this decay process is hindered, it can lead to a variety of problems.

On the one hand, challenges may arise from a place of burial with poor drainage. Decay has to take place in aerobic, moist conditions. A high groundwater surface level and wet conditions can lead to anaerobic conditions, halting microbial activity. On the other hand, human bodies themselves increasingly prove more challenging to be broken down. A higher body-fat amount leads to the interruption of hydrolysis. An increased use of drugs and antibiotics may increase life quality but inhibit microbial activity. Declining decay rates can already be found in various burial grounds throughout Germany through combinations of these factors. This raises the question, whether cemeteries in combination with a decline in decay rate pose risks for the quality of drinking water sources such as groundwater.

This presentation proposes the investigation of the influence of human decay on groundwater quality through different methods. The quantification of a human decay-footprint on groundwater bodies can be achieved through groundwater sampling and istope analysis. This also includes an assessment of the soil hydraulic properties of burial plots. Such assessments should be ideally carried out in a variety of climates, geological formations and soils in which cemeteries are placed. Subsequently, a risk analysis for potential contaminant efflux into groundwater bodies will be carried out for normal and extreme circumstances, to avoid future contamination and insure the proper decay of human bodies.

Clonal evolution in planarian flatworms?

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Planarian flatworms are fascinating creatures. Abundant adult pluripotent stem cells are the only division-competent cells in adults; many species can regenerate entire animals from tiny pieces of tissue; asexual reproduction by literally ripping themselves in half and subsequent regeneration is common; and while asexually reproducing strains do not appear to age, the lifespan of sexual species may be limited to one reproductive season. Similarly, planarian genomes are highly unusual in terms of extreme compositional biases of >70% A/T, the presence of giant transposable elements, and rapid structural evolution, presumably without syntenic constraints. My talk will present recent data on the genomic consequences and putative causes of asexual reproduction in the model species *S. mediterranea*. In addition, I will discuss our initial attempts to explore the extent of somatic mosaicism and the potential for multi-level selection phenomena among the many pluripotent adult stem cells within a single individual, which pose interesting challenges for the maintenance of genomic self in these animals.

The MicroVirome- The secret lives of viruses and phages in the Plant Holobiont

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Eukaryotic organisms harbour large communities of microorganisms forming an holobiont, considered to be a single ecological and evolutionary unit. In recent years, bacterial community dynamics and their effect on the plant holobiont have been the subject of many studies. In spite of this, little is known regarding the role that bacteriophages play in shaping those bacterial communities. In my work I intend to set the basis for understanding the role of bacteriophages, The Microvirome, by studying Arabidopsis thaliana-associated bacteria and phages, in laboratory and natural settings. We isolated novel lytic bacteriophages infecting the ubiquitous plant pathogen Pseudomonas viridiflava and we are assessing their impact in plant colonization and development. Additionally, P. viridiflava strains host distinct families of prophages, which might be involved in their host's ability to defeat competitors and other phages. Following a multilevel approach, I expect to gain a mechanistic understanding of the way phages affect plant-associated bacterial communities, deepening our basic understanding of the plant holobiont, and phage-host interactions in an oligotrophic environment. These findings can be projected to other significant plant-microbes systems, and be the foundation to design phage-based solutions to pest management in agriculture.

Protein folding is a limiting factor in metabolic reprograming

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Cells change their state during differentiation and adaptation by altering their metabolism. To do so, cells fine-tune the expression of metabolic enzymes, primarily in the cytosol and mitochondria. In most cases, proteins are imported into the mitochondria in a linear, non-folded state, after which they are folded by mitochondrial chaperons. Ecological network analysis of gene expression in multiple cancers shows that mitochondrial proteins and chaperones are found in two major clusters, suggesting that specific mitochondrial proteins may depend upon specific chaperones for their proper folding. However, the precise nature of these dependencies and the potential for mitochondrial chaperones to act as a bottleneck in metabolic adaptation remain largely unexplored. We addressed this knowledge gap by investigating the mitochondrial chaperone HSPD1 and its role in folding the crucial one-carbon metabolism enzyme, MTHFD2. Using gene manipulation techniques in cancer cells, we demonstrate that MTHFD2 folding, and consequently, one-carbon metabolism, is critically dependent on HSPD1. Our findings establish that mitochondrial protein folding is not merely a passive process, but a potentially rate-limiting step in metabolic reprogramming. This highlights the importance of chaperone availability and specificity in dictating cellular metabolic capacity, with implications for biological scenarios where cells change their state, such as during cancer progression.

Behavioral modulation in Shank3 mice with autism spectrum disorder through skin ultraviolet exposure

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Chronic exposure to low-dose ultraviolet B (UVB) radiation has been shown to enhance social behavior and reduce anxiety through skin-mediated pathways. Given that autism spectrum disorder (ASD) is characterized by social deficits, elevated anxiety-related behavior, and repetitive behaviors, we hypothesized that UVB exposure might affect these core symptomes. In this study, we found that chronic low-dose UVB exposure significantly improved social preference in Shank3 mutant mice bearing the human InsG3680(+/+) mutation, resulting in behavioral performance comparable to that of wild-type counterparts. UVB treatment also normalized anxiety-related behaviors in mutant mice compared to mock-irradiated controls. Proteomic analyses of the brain, skin, and immune organs provided insights into the molecular changes potentially underlying these behavioral improvements, which are currently being further investigated. Additionally, statistical analysis of data from children with ASD revealed an inverse correlation between vitamin D levels—elevated by UVB exposure—and the capacity for behavioral improvement. Together, our findings offer a novel model for identifying modulators of ASD-associated behaviors and suggest a potential pathway through which solar radiation could be used as a modulator of neuropsychiatric conditions.

Two lipids, one membrane

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The cell membrane organizes and protects life, serving as a responsive interface and selective barrier. Lipids—the fatty, amphiphilic molecules forming the bilayer—are fundamental to membrane function. Yet, we still don't understand why cells tightly regulate the synthesis of hundreds of distinct membrane lipids, especially when just one lipid can form a bilayer. What is all this complexity good for, and can we learn to harness lipid diversity to engineer membranes for synthetic life? The specific combination of lipids defines a membrane's physical properties, influencing membrane function and ultimately cellular fitness. Although one lipid is sufficient to assemble a membrane, multiple lipids are necessary for a membrane to adapt its properties optimally to physiological and environmental demands.

In my lab, we've established genomically minimal bacterial systems, particularly pathogenic mycoplasmas and the Minimal Cell (JCVI-Syn3), as experimental platforms to dissect and manipulate membranes. This approach lets us systematically tune and minimize lipidomes, demonstrating that two lipids are sufficient (but far from optimal) for life. Using these minimal organisms as a starting point, we can systematically reintroduce genomic and chemical complexity to elucidate the crucial components of a functional cell membrane. My long-term ambition is to unravel how the essential material properties of membranes are genomically encoded and to determine how this knowledge can be leveraged to program synthetic membranes.

Unravelling the antigen-specificity and functionality of CD8 Tregs

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Conventional CD8 T-cells are specialized in eliminating pathogen-infected or cancerous cells upon recognizing molecular imprints, displayed on the cell surface by the major histocompatibility class I (MHC-1) molecules, through their unique T-cell receptors (TCR), However, a substantial subset of CD8 T-cells expresess Killer Ig receptors (KIRs). Recent reports suggest that these KIR expressng CD8 T-cells function as regulatory T-cells (CD8 Tregs) especially in the context of autoimmune diseases. However, we don't know the interplay between TCR and KIR interaction and the related antigen-specificty in healthy as well as in a specific disease setting.

Using large-scale peptide-MHC analysis in viral infection as well as in auoimmune conditions we identified antigen-secifity of CD8 Tregs and established an effective assay system to evaluate the dynamics of antigen-stimulation and functional impact of KIR+ CD8 T-cells. Our data may not neccessarly align with the current understanding of this CD8 T-cell subset, but identifies antigen-specific activation of KIRs, serving as an aditional inhbitory molecule.

The art of insects, immunity and idealism

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Humans often consider themselves the dominant life form on Earth, yet insects have been playing the game of evolution for more than 250 million years before the appearance of the first mammal. Their resilience suggests they may endure long after humans are gone. After all, they have witnessed the rise and fall of dinosaurs.

Our research has been exploring how insects respond to viral infections, not only through classical immune pathways but also via metabolic adaptations, stress responses, and tissue repair. Our findings challenge the traditional view of the immune system as merely a defense against pathogens, proposing instead that it serves as a sophisticated sensor of internal and external environments. Today, I will discuss the lessons learned over 16 years at the Institut Pasteur and reflect on how fostering a nurturing environment is essential for unlocking intellectual creativity and driving scientific discovery in unexpected directions.

Mechanics of circulating tumor cells and its clusters.

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Abstract :

More than 90% of cancer-associated mortality is caused by tumour metastasis. This complex multistep process lays on the dissemination of tumour cells, known as circulating tumor cells (CTCs) that reach distant tissues via the bloodstream and initiate growth of secondary tumours. Recent studies have shown that CTCs clusters increase the metastatic potential by 50 times in comparison to single CTCs and are able to pass through narrow capillaries, by deforming themselves whilst experiencing and resisting mechanical stresses at different rates. Resources are being directed towards detection and phenotyping of these rare CTCs in the bloodstream, as they appear as potential non-invasive biomarkers for cancer diagnosis and prognosis. Nevertheless, little is known about their mechanical properties. We hypothesis that inter-cellular adhesion plays a pivotal role in modulating the underlying mechanical response of CTCs cluster. We use an atomic force microscopy (AFM) to charectise both the static and dynamic viscoelastic response of CTC's and its clusters.

Message to the oraganisers:

I got lost in the thought of the bohemian woods, daydreaming and overthinking for way too long. Thus, finally ended up on the waiting list.
I just hope I can make my way up this list and finally attend the#TheConferenceToEndAllConferences .

P.S.
Imagine my work as a conversation between a physicist, a data enthusiast, and an experimental cancer biologist.
Also this work is not enough to be published, but it is also not insignificant enough to be ignored.

Like a stack of dominoes – the coupling mechanism of respiratory complex I

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Complex I is the first and largest (1 MDa) membrane protein complex of mitochondrial and bacterial respiratory chains. It couples NADH:ubiquinone oxidoreduction to the translocation (across the membrane) of four protons per catalytic cycle by a mechanism which is still hotly debated. Recently we presented cryo-EM structures of ovine and *E. coli* complex I in different conditions, including catalytic turnover [1, 2]. We have shown that, unexpectedly, out of three antiporter-like subunits, only the distal ND5 is capable of ejecting protons into intermembrane space (IMS). Dramatic conformational changes around the quinone (Q) binding cavity couple the redox reaction to proton translocation during "open" to "closed" state transitions of the enzyme. In the "open" state Q cavity is widely open, allowing quinone to come in/out. In the "closed" state the cavity is tightly enclosed around bound quinone but is connected by a newly formed water wire to the E-channel and the rest of the central hydrophilic axis of the membrane domain. Therefore, the protons needed to complete quinone reduction have to come from the central axis. This initiates a "domino effect"-like cascade of electrostatic interactions within the antiporter-like subunits, ultimately resulting in the ejection of four protons per catalytic cycle from subunit ND5 into IMS. Thus, the mechanism of complex I is an unexpected combination of conformational changes and electrostatic interactions.

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Spatially distributed and regionally unbound cellular resolution brain-wide processing in mice

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Until recently, it has been possible to examine activity in the brain globally through regional averaging or locally at cellular resolution. These studies characterized regions as functionally homogeneous entities (e.g. V1 for extracting low-level visual features) or single neurons in a region as heterogeneously tuned (e.g. mixed selectivity). Here, we leverage the unprecedentedly dense IBL electrophysiological recordings in mouse brains during a sensorimotor decision-making task and computationally combine these to generate a global event-aligned high temporal precision cellular-resolution functional map. We cluster individual neural responses and obtain intuitive response categories; tracing these to anatomical regions reveals tremendous functional heterogeneity in the distribution of cellular response types within each region. Indeed, we find that every functional class is present in essentially all areas. Quantitatively, functional tuning can barely be predicted by fine or coarse cytoarchitectural boundaries, 3D spatial coordinates, or subcortical and cortical layer structure, or vice versa. At most, the brain exhibits moderate distributional similarities of cell responses at nearby locations. In terms of correlated communities, neurons form distributed and shifting alliances over phases of each trial, similar to the identification of "mode networks" at the region level through fMRI. Our analysis identifies a novel set of mode networks, however network membership is much finer-grained than regional, comprising subsets of cells in each brain region. These results point toward the idea of spatially wide-ranging dynamical processing -- winding through most brain regions and involving a subset of neurons in each -- to carry out basic functions, and contrast with the idea that brain areas are functionally specialized units.

A dynamic view of the E. coli chromosome using single-cell Hi-C

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The *Escherichia coli* chromosome is a highly dynamic structure, constantly reorganized by essential processes like gene expression, replication, and segregation. Despite its central role, the functional importance of the chromosome's specific 3D architecture in bacteria remains largely unclear. A major hurdle is that most existing methods for studying chromosome structure lack temporal resolution, yet with rapidly growing bacterial cells, understanding chromosome dynamics is key to linking organization with biological function.

In my other ongoing research, we use live-cell 3D fluorescence imaging to track the dynamics of multiple chromosomal loci, and we use this data to inform a data-driven dynamic polymer model of a replicating chromosome. This model demonstrates the dynamic nature of known chromosomal interaction domains, and surprisingly also predicts new transient long-range interactions. However, as extraordinary results require extraordinary evidence, we sought to validate this prediction with an independent method.

As no such method existed for bacteria, we had no choice but to develop a novel single-cell Hi-C (scHi-C) technique tailored for bacteria. In this presentation, I will introduce the first dynamic Hi-C contact maps for *E. coli*, generated using our scHi-C method. We achieve temporal resolution by inferring each cell's precise stage in the cell cycle through marker frequency analysis, which utilizes replication-associated biases in local genome copy number.

Moving forward, combining live-cell imaging with single-cell sequencing-based methods will allow us to investigate how various genetic and environmental perturbations impact chromosome dynamics.

Growth factors-infused cellulose scaffolds support cost-efficient proliferation and differentiation of bovine stem cells for cultivated meat.

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Cultivated meat, which aims to replicate traditional meat using tissue engineering and stem cell biology, is a promising approach to sustainably supplementing traditional meat production to meet increasing global demand. The production of cultivated whole-cut meat is not trivial; it requires a complex structure that supports cell growth, enables nutrient and waste exchange, and mimics natural texture. Here, we develop a biocompatible, porose, and anisotropic scaffold, based on directional freezing of nano and microcrystalline cellulose, which supports the growth and differentiation of bovine mesenchymal stem cells toward fat and muscle lineages. Furthermore, we show that preloading the scaffolds with growth factors directing the cells for proliferation or differentiation is a promising alternative to conventional media delivery since these pretreated scaffolds yield similar proliferation and differentiation efficiencies using at least 10 times lower masses of prohibitively expensive factors, and thus may significantly lower one of the primary boundaries to price parity with traditional meat. Together, these findings propose a method for the production of cultivated whole-cut meat—a sustainable and ethically preferable alternative to meet the growing demand for a highly sought-after product.

CENTROSOME RESILIENCE TO MECHANICAL STRESS

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Centrosomes are complex protein assemblies in animal cells that exhibit remarkable mechanical resilience, withstanding persistent tension and compression exerted primarily by the cytoskeleton. When centrosome integrity is compromised, chromosomal instability arises during cell division – a defining feature of cancer. The underlying causes of this mechanical failure remain unclear, revealing gaps in our understanding of centrosomal biomaterial properties and how they evolve throughout the cell cycle. Due to their structural complexity and small size, centrosomes have long eluded direct mechanical investigation. Yet, given their constant exposure to cytoskeletal forces, it is essential to study them under mechanical stress. My approach integrates cutting-edge microscopic and molecular techniques to uncover how centrosomes preserve their structural integrity. Using atomic force microscopy, we quantify their stiffness. Through acoustic Brillouin microscopy, we assess their viscoelastic properties. By manipulating microtubules nucleated from centrosomes in optical trap microscopy, we aim to determine, for the first time, whether microtubule anchors are mechanically stiffer than the centrosome itself. But what gives centrosomes their unique biomaterial properties? Is it the specific bonding between structural components within the centrosome or the anchoring of microtubules? While microtubules consist of globular tubulin proteins, centrosomal scaffolds are primarily made of fibrillar, intrinsically disordered proteins. Intriguingly, could this mechanical design principle also operate in other contexts beyond mitosis or in other species? Water bears (Tardigrada) cells survive extraordinary environmental stresses during desiccation. In response to dehydration, they form protective cytoplasmic phase-separated gels, however, the mechanical strain on all cytoskeletal components is likely high. How centrosomes regulate the microtubule cytoskeleton during such conditions is unknown. In our project, we aim to study centrosomes in both human and water bear cells to get insight into the principles governing biophysical properties and functions of the centrosome under stress.

Photons can do a lot of jobs, but is there a bright future for them in biology?

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Folks in photophysics, photochemistry and other related fields, including ourselves, love to say that our systems promise, will be, or are already used in many applications in (bio-)medical research and beyond. Indeed, rationally designed small molecular chromophores based on posterchilds like fluorescein or indocyanine green can do a lot of wonders as far as (potential) use in research, diagnostics and therapies. Few such examples from our own research (and beyond) will be shown, e.g., tunable and most often bright fluorophores, large Stokes shifts, pH, viscosity, and other media influences. Interactions tracked in tissue transparent window, where mammals' tissues are fairly transparent, delivery of safely caged molecules, clicks and other tricks, too. Many of these under a guise of building tools for others, promising a bright future or just bringing something better than what is in use right now. But then an inevitable question will follow, one that I do not hear often – is it really worth to pursue such research now and in future with such bold reasoning (or an excuse, who knows?), or are the contemporary and future biologists more than happy with the available toolbox and the research questions are really somewhere else and require completely different tools? Or is there a need for a specific, yet non-existent tool?

#TheIdeaToEndSomeIdeasOfPhotochemistsAndPhotophysicists

Bodies In Motion: Somatic Modeling of Cellular Dynamics

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Communicating and understanding cell biology is not easy. Cells and proteins are three-dimensional assemblies that are constantly in motion, and these structural movements underlie all biological processes. However, textbooks and graphical models typically use abstract shapes to represent biomolecules such as proteins, lipids, nucleosides, and phosphate groups. Static shapes connected by arrows fail spectacularly to communicate the true dynamic nature of cell signalling. This is a particular problem for teaching students about cell migration, which relies on cycles of assembly/diassembly of macromolecular complexes in space and time. Abstract 2D diagrams may be understood as shorthand for 3D dynamic processes by experts, but do not convey this information effectively to students, and may even create more conceptual confusion. Arrows imply unidirectional processes, abstract shapes give no indication about how biomolecular interactions take place, and wiring diagrams poorly represent temporal cycles. Animated models derived from structural biology data help to illustrate the dynamics and mechanisms of biological processes, but these require specialist skills and tools to create.

But we all have dynamic 3D models available to us for communication. What happens when we move away from of the powerpoint slide to involve our physical bodies? Can a 'somatic pedagogical' approach stimulate creative thinking and enhance understanding? While not precisely replicating the real forms of proteins, human bodies moving in space and time may provide more accurate depictions of biomolecules than circles and squares with letters attached. On a pedagogic level, using movement to convey concepts in cell biology translates the invisible to the visible, the abstract to the concrete. Audience participation and novelty can increase memorability and integration of new information. And, importantly, moving around has been shown to stimulate divergent thinking through increased blood oxygenation and changes in brain activity.

In this presentation, I will explore how using physical movement to communicate concepts about cell migration could be used to enhance science communication and stimulate creative thinking.

Cell-type-specific protein dynamics during seizures

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Epilepsy is a common neurological disorder with a high rate of pharmacological resistance. It can lead to psychiatric disorders, cognitive deficits, and increased mortality from the direct or indirect effects of seizures. Although little is known about the molecular mechanisms regulating the development and severity of seizures and epilepsy, it has been shown that protein synthesis plays a role. For example, alterations in protein translation mediated by the eukaryotic elongation factor 2 kinase (eEF2K) can affect the balance of excitatory and inhibitory synaptic transmission, leading to changes in seizure susceptibility and intensity. Additionally, seizures have been shown to disrupt protein synthesis, thereby impacting brain metabolism. The specific proteins and cell types that mediate these processes remain unknown. To study the complex interplay between protein synthesis and epileptic seizures we apply a technique for cell-typespecific labeling of nascent proteins during and following induced seizures in the zebrafish animal model.

The brain's immense complexity has so far interfered with our ability to study its protein dynamics in an unbiased manner. Various cell types and long neuronal processes are tightly entangled within the tissue, and neurons with their long axons and dendrites cannot be surgically dissected to allow cell-type-specific proteomic analysis. To overcome this challenge, we developed an approach, based on noncanonical amino acid tagging and click chemistry, to label nascent proteins in a cell-type-specific manner in zebrafish larvae. Zebrafish larvae exhibit seizures following various chemical and genetic manipulations. I will present our ability to induce seizures in zebrafish larvae, combined with the technique for cell-typespecific labeling of nascent proteins. This approach provides an ideal framework to identify the proteins synthesized in neurons and glia, measure global and local levels of nascent protein during seizures, and detect potential proteomic changes that occur at later stages following seizures.

Applied force enables integrins to identify ECM-context to alter cellular mechanotransduction within seconds

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The cellular ability to biophysically and biochemically recognize extracellular matrix proteins is fundamental to adhesion, mechanics, migration, and morphogenesis, and influences homeostasis and disease. However, the triggers underlying integrin-mediated mechanosensing based on the ligand context remain elusive. Here, we discover that within seconds of force-induced ligand-sensing in two separate contexts, αV-class integrins initiate and strengthen adhesion biphasically through complementary mechanotransduction pathways, which rely on single αVβ3 integrin bond behavior. Under low force application, mechanosensing requires αVβ3 and αVβ5 integrin-associated actomyosin and FAK activity, while αVβ5 integrin engages membrane and clathrin-mediated endocytosis. Upon applying higher force, mechanosensing requires αVβ3 integrin-led Arp2/3, cSrc, and PI3K signaling that dominates αVβ5 integrin in organizing the consensus adhesome on vitronectin. Simultaneously, αVβ5 integrin regulates the mechanical stiffening of fibroblasts. Thus, αV-class integrins exhibit rapid ligand-context and β-subunit-specific programs to synergistically guide mammalian cell adhesion and mechanics.

AGO1, a Key miRNA Protein, Helps Cells Grow by Acting in the Nucleolus

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Environmental changes trigger the formation of dynamic RNA-protein assemblies, or ribonucleoprotein (RNP) granules, in both the cytoplasm and nucleus. These membrane-less compartments arise through liquid-liquid phase separation of RNA-binding proteins with intrinsically disordered regions (IDRs), preceding major transcriptional reprogramming. Our lab previously showed that microRNAs (miRNAs) modulate stress responses and that miRNA biogenesis is highly stress-sensitive. Since Argonaute1 (AGO1)—the core component of the RNA-induced silencing complex (RISC)—is essential for miRNA function, we hypothesized that AGO1 behavior may change under stress. Using Drosophila S2 cells and oogenesis models, we found that AGO1 relocates under stress to cytoplasmic (stress granules, processing bodies) and nuclear (Cajal bodies, nucleolus) RNP granules. Notably, AGO1 consistently colocalizes with Fibrillarin in the nucleolus, suggesting a potential role in ribosome biogenesis. Small RNA sequencing revealed that AGO1 binds various small RNAs, especially C/D box snoRNAs, which guide rRNA modification. Fibrillarin, AGO1's nucleolar partner, is a core component of the C/D box small nucleolar RNP (snoRNP) complex required for pre-rRNA cleavage and rRNA modification. Given that nucleolar size reflects rDNA transcription and protein synthesis capacity, our findings support a model where AGO1, together with Fibrillarin, regulates rRNA processing and nucleolar size, thereby controlling protein synthesis and cell growth. We tested this model using follicular epithelium mosaic clones and found that AGO1 loss-of-function or downregulation led to reduced nucleolar and cell size. In contrast, depletion of Dicer-1 (Dcr-1), another key miRNA pathway protein, did not produce this phenotype. This suggests that AGO1 regulates cell growth independently of its canonical role in miRNA-mediated silencing, possibly through interaction with small RNAs such as snoRNAs.

Livin' on Thin Air

Chris Greening[6], **Rhys Grinter**[4], **Ville Kaila**[5], **Volker Müller**[3], **Jan Schuller**[2], **Sven T. Stripp**[1]

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The atmosphere is increasingly recognized as an energy source for microorganisms such as archaea and bacteria.[1] Key component is hydrogen gas (H2), which represents about 0.00005% of the gas mixture commonly known as air. With such a small piece of the cake, it is unsurprising that the oxidation of H2 into protons and electrons demands extremely sensitive enzymes. Enter Hydrogenase.[2]

Hydrogenases are gas-processing metalloenzymes loosely related to iron-sulfur proteins like ferredoxin and Complex I of the mitochondrial electron transfer pathway. Exploiting unique active site cofactors, hydrogenases catalyse H2 oxidation or H2 production with high affinity and virtually no electric overpotential.[3] These are the characteristics of extremely efficient enzymes. Accordingly, hydrogenases have inspired the design of various noble-metal-free catalysts that can be used in fuel cells for O2- and H2 evolution from water.[4]

At the example of a membrane-bound hydrogenase, I will explain how the enzyme plucks H2 from air and reduces the menaquinone pool of the membrane, used for O2 reduction by Complex IV (a.k.a. cytochrome c oxidase).[5] Another hydrogenase uses H2 for the purpose of electron bifurcation, *i.e.*, it unevenly distributes the reducing power of H2 to regenerate a low-potential acceptor like ferredoxin and a high-potential acceptor like NADPH.[6] I will focus on the role of infrared spectroscopy in my talk [7], which is not a standard technique in the biological sciences but a very helpful one nevertheless. The presented works highlight the importance of collaborative research between microbiology, biochemistry, structural biology, and biophysical chemistry.

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Mystery of the Missing Penis

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A while ago, our lab decided to develop a laboratory model from a terrestrial slug for expanding our research on adaptations of RNA silencing pathways in animals. Small RNA pathways, particularly the PIWI-interacting RNA (piRNA) play a crucial role in transposable element (TE) silencing across Metazoa. Yet, diversity and evolutionary adaptations of the piRNA pathway remain underexplored in mollusks – the second-largest animal phylum. I will report our analysis of the piRNA pathway in three different slug species. After initial experiments with the infamous invasive slug *Arion vulgaris*, we have found that palearctic slugs *Deroceras invadens* and *Deroceras laeve* have great potential for becoming slug laboratory models. Remarkably, while *D. invadens* slugs mate and cross-fertilize, a *D. laeve* individuals often lack penis (aphalics) and self-reproduce while *D. laeve* individuals with penis (euphalics) mate and cross-fertilize. This offers unique opportunity to study expansion and repression of TEs associated with the two distinct reproductive modes. So far, we generated chromosomal-level assembly for *D. invadens* and aphalic *D. laeve*, annotated genes and repetitive elements, and identified sources of small RNAs. This work included long and small RNA- sequencing and transcriptome assembly for all three slug species. 28-29nt long piRNAs were mostly derived from repetitive sequences and majority of them were primary piRNAs originating from <100 unidirectional piRNA clusters. Further sequence analysis identified a small population of secondary piRNAs. Combined analysis of primary and secondary piRNAs in the soma and germline, TE annotation, and distribution of DNA methylation in both *Deroceras* species provide a unique insight into variable pressure of mobile elements on genome integrity and their transcriptional and post-transcriptional silencing in cross-fertilizing and self-reproducing slugs.

Why do we age? DNA damage and age-related diseases

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Aging is the primary risk factor for diseases such as cancer, metabolic syndromes, and neurodegeneration. My lab studies the molecular changes that drive aging, particularly DNA damage accumulation, a key factor in age-related diseases. We aim to uncover the process from DNA damage formation to its resolution and identify intervention points for healthier aging.

The Sirtuin family prevents age-related diseases, including neurodegeneration, heart disease, and diabetes. Notably, SIRT6 knockout mice exhibit accelerated aging and premature death by three weeks, with metabolic defects, genomic instability, and a progeroid-like phenotype.

SIRT6 is a DNA damage sensor that recognizes double-strand breaks (DSBs) and initiates homologous recombination and non-homologous end joining, moreover, we compare its function to a sensor for HR and NHEJ and developed a dynamic network of interactions to understand the process of DNA repair from the sensor's point of view. Identifying the interchangeable network at each time point, the core of repair and specialized. Each sensor has a robust network with similar functions but different players, allowing the cell to navigate several pathways simultaneously.

To explore the consequences of accumulated damage and lack of SIRT6, we developed a mouse model lacking SIRT6 specifically in the brain, which exhibits accelerated brain aging with symptoms resembling Alzheimer’s and other tauopathies, behavioral changes, poor sleep quality, and metabolic changes, allowing us to investigate the causes of Age-related neurodegeneration. Strikingly, AD patients show a significant decline in SIRT6 levels in their brains.

Overall, understanding the consequences of DNA damage and its interactive network will allow us to understand the several processes malfunctioning as we age.

Universal rules of regulation

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I will argue that we are too arrogant about understanding biology. Instead of telling everyone that we will be waging wars on cancer, figuring out how the brain works or ameliorating all human disease, we ought to be more honest with politicians and the public, humbly admit that we know nothing and go back to figuring out basic principles of how life works. Or try dying, I mean, die trying. My presentation will be along those lines and will also involve bicycles. That's all I am willing to say at this moment.

Intergenerational control of ribosomes under dietary restriction

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Cells adjust their proteome to their environment. Most prominently, ribosome expression scales near linearly with the cellular growth rate to provide sufficient translational capacity while preventing metabolically wasteful ribosomal excess. In microbes, such proteome adjustments can passively perpetuate through symmetric cell division. However, in animals, a passive propagation is hindered by the separation between soma and germline. This separation raises the crucial question whether the proteome of animals is reset at every generation or can be propagated from parent to offspring despite this barrier. We addressed this question by exploring the intergenerational effects of dietary restriction in *C. elegans*, combining proteomics and live imaging. While most proteins showed no intergenerational regulation, ribosomal proteins remained reduced in offspring after maternal dietary restriction. When offspring of dietarily restricted mothers were raised under improved dietary conditions, this reduced ribosome content delayed their growth until normal ribosomal protein levels were restored. Soma-specific maternal inhibition of mTORC1 signalling replicated these effects, while other growth-reducing perturbations, such as reduced insulin signalling or maternal ribosome depletion, did not impact offspring ribosomes. Thus, mTORC1 signalling bridges across the soma-germline divide to regulate ribosome levels of the next generation, likely priming the offspring for the anticipated demand in protein synthesis.

Multimodal multiplexing with expansion microscopy as a path to molecular connectomics

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In brain mapping, the field has long largely relied on morphological information to infer the complex molecular makeup of cells and synaptic connections. Recent advances in expansion microscopy, multimodal multiplexing, optical morphological readouts [1], and neuronal barcoding now present a new path towards integrating molecular information.

My presentation covers progress towards building PRISM [2]: an optical multiplexing platform for brain tissue that integrates the readout of virally delivered protein barcodes, endogenous synaptic and cellular markers, and neuronal morphology.

I highlight the developments in expansion microscopy and multimodal molecular multiplexing that facilitate the readout of dozens of molecular targets at synaptic resolution.

[1] tinyurl.com/biorxiv-LICONN
[2] e11.bio/news/roadmap

The Age of Mega-Experiments: (Aging) Biology's Turn to Think Big

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Physics has CERN, LIGO, ITER, and the James Webb Space Telescope—billion-dollar mega-projects driven by clear scientific objectives and global collaboration. These initiatives weren't born overnight, but emerged as the field matured beyond what small-scale experiments could resolve. Biology, particularly aging biology, is nearing a similar inflection point.

We now have an encyclopedia of molecular mechanisms implicated in aging—but no unified system to connect them. Small-sample studies and fragmented datasets are no longer enough to tackle the most profound biological question of all: *why do organisms age so differently, and how can we control it?*

In this talk, I argue that the next phase of aging research must adopt the mega-project mindset: centralized, cross-disciplinary, and unapologetically ambitious. What would it take to coordinate a 10,000-mouse lifespan study? A 15-million-person global longitudinal aging cohort? A large-scale multi-omic comparative atlas across all mammals—capturing the genomic, epigenomic, transcriptomic, proteomic, and metabolomic signatures that shape lifespan and the biology of aging from shrews to whales?

I'll explore what such projects could look like, how they might be funded and governed, and why less fragmentation—and more focus—could mean fewer papers but better science, and a happier community of collaborating scientists. Most importantly, I'll ask: if we're serious about understanding aging, why are we still acting like it's a side project?

A breath of fresh air: evolution and development of breathing strategies in the paradise fish

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Demand for oxygen has been a main driver for evolution in Metazoans. While complex multicellular life first emerged in aquatic environments, the rise of atmospheric oxygen facilitated the repeated evolution of air-breathing strategies, granting access to this abundant and relatively stable resource. Indeed, recent research suggests that air-breathing evolved in fishes over 80 times independently. Paradise fish (*Macropodus opercularis*) is an air-breathing freshwater fish species, with a signature labyrinth organ (LO) capable of extracting oxygen from the air that helps adult fish to survive in hypoxic environments. The appearance of this evolutionary innovation in the group of anabantoid fishes resulted in anatomical innovations, and also contributed to the emergence of species-specific behaviors, such as parental care. While at the beginning of the 20th century zoologists were intrigued by the structure and function of the labyrinth apparatus, ultimately this research program petered out due to the lack of adequate molecular tools to address the questions related to the development of the LO. Using some of the latest technological developments, we revisit these questions to reveal the molecular and cellular landscape of a true evolutionary innovation.

On monsters and models - sculpting with stem cells to understand how embryos build themselves

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Morphogenesis emerges from the interplay between genetic programs and the physical, chemical, and geometric constraints of the embryonic environment. While classical models of evolution emphasize external selection pressures, recent work highlights the importance of internal generative rules that shape form independently of organismal function, as postulated by Pere Alberch in his seminal work "The logic of monsters" (1989). Studying the extent to which teratological systems—developmental anomalies with little adaptive value—exhibit structural order, offers a window into these generative rules. In our lab, we use stem-cell-based embryo models (SEMs), gastruloids and trunk-like structures, to provide mechanistic insight how physiological constraints govern robustness of body axes formation. We leverage that SEMs are minimal systems that mimic key features of in vivo development while allowing precise control and measurement, making it possible to dissect how minimal biochemical and mechanical inputs generate robust and reproducible patterning. We combine SEMs with live imaging, omics, biophysics, and data science, to uncover the feedback loops and boundary conditions that guide morphogenesis. Intrinsic variability in SEMs can further reveal the boundaries of morphospace and the constraints that shape development. I will discuss how such a bottom-up perspective can provide insights into how internal rules and physical context generate and limit possible phenotypic outcomes.

From Chaos to Order: Specificity in Nuclear Condensate Assembly

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According to many CNS papers, liquid–liquid phase separation appears to be ubiquitous and very important in nuclear processes. However, the belief that these condensates are sustained solely by non-specific interactions seems unlikely.

Uncovering Ap2N-Capped Human tRNAs and Their Fragments with Ap2N-RNA Sequencing

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Apart from the canonical eukaryotic mRNA cap, an increasing number of non-canonical caps (NAD, dinucleotide polyphosphates) have been discovered on other RNA types in both prokaryotes and eukaryotes. However, these RNA caps have not been detected in tRNA yet. Here, using LC-MS, we discovered the dinucleoside diphosphate (Ap2N) serving as 5' RNA cap in human cells. To gain insights into the Ap2N capping, we developed a specific Ap2N-RNA sequencing protocol and applied it on short RNA. The most prominent RNAs capped with Ap2N were tRNAs and previously unknown tRNA fragments. Our work suggests that Ap2N cap might be formed as an intermediate of a new type of RNA processing and provides the toolkit for studying its involvement in cellular physiology.

A model for cellular adaptation to stress

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The ability of cancer cells to consistently escape therapy remains a fundamental challenge for effective treatments. A longstanding debate in the field has centered on whether resistance arises primarily through genetic reprogramming or through cellular plasticity. Emerging evidence increasingly supports a “plasticity-first” model in which adaptive cellular states initially arise through a physiological response to environmental stress and are subsequently stabilized and extended by both epigenetic memory and genetic mutations. In this talk I will describe evidence that cancer cells can engage in an exploratory reprogramming of gene regulation as a means of adapting toward progressively resistant states. I will also offer our perspective on the mechanisms that drive this adaptive gene regulation, including stress-induced feedback responses, combinatorial regulatory networks, and systems for maintaining and recalling adaptive states. Finally, I will highlight the broader relevance of these mechanisms – extending beyond cancer to contexts such as inflammation and neurobiology – and the insights they offer into the origin and evolution of novel gene regulatory programs.

Structural studies of ferritin and its modification toward wild ideas

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Ferritin is an iron storage complex exist in all living organism. Naturally, ferritin is nanoreactor that is able to absorb iron ions and to mineraliza them into a amorpheus ferrihydrite mineral. Such mineralization protect the cell from toxic fenton reaction. To get better idea on ferritin formation and its manipulation, we initiated a wide study on ferritin and its engineering. Using natural ferritin from magnetotactic bacteria we established the link between evolutionary modulations and its assembly into a 24 mer oligomer from two distinct ferritin chains, in a non symmetric assembly. Using C-terminal extentions in the ferritin core we were able to get a first glimps on the interactions of proteins with minerals. One of our modification produces an open ferritin with a 1.2 nm openings that enables the movement of large molecules. Such ability to open ferritin can enable anti cancer treatment and modification of ferritin toward strange nano-devices. These ideas will be discussed in the meeting and together with the audiance we will apply night science to gain modifications and possible devices based on the community needs.

Fishing for Egg Quality Markers in Pikeperch

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Finfish eggs, due to their external fertilization and clearly defined oogenesis stages, serve as excellent models for studying non-genetic inheritance mechanisms that transmit crucial transgenerational signals to the developing embryo. Among various molecular contributors, maternally deposited mRNAs are known not only as essential regulators of early embryonic development - particularly before zygotic genome activation - but also as informative molecular indicators of egg quality and developmental competence. Egg-specific mRNAs, in particular, are considered highly robust markers, as they often participate in processes essential for fertilization and early development. However, their temporal expression during oogenesis remains largely unexplored, especially in non-model fish species.

In this study, we used a multi-layered transcriptomic approach to investigate the molecular underpinnings of egg quality in pikeperch (*Sander lucioperca*), a species of growing relevance in aquaculture. We generated transcriptomic profiles of oocytes during late vitellogenesis and final maturation and constructed a multi-tissue transcriptome atlas to identify transcripts uniquely present in the eggs. Additionally, we compared egg transcriptomes between virgin and experienced females to identify potential molecular drivers of reduced developmental competence observed in eggs from first-time spawners.

This integrative analysis revealed 147 egg-specific transcripts, with 129 being significantly upregulated immediately before ovulation -suggesting their importance in oocyte readiness and fertilization capacity. Among these, a cadherin-1-like gene (*cdh1*) was consistently underexpressed in eggs from virgin females. Given *cdh1*'s established roles in cell adhesion and epithelial organization, its reduced expression may reflect impaired structural or molecular preparation for fertilization.

Our results emphasize the power of combining developmental stage-specific and tissue-specific transcriptomics to identify functional markers of egg quality. *Cdh1* represents a promising candidate for future studies aiming to understand and improve reproductive outcomes in aquaculture species.

Like father, like daughter: epigenetic inheritance of cardiovascular disease

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Atherosclerotic cardiovascular disease (CVD) is the leading cause of death worldwide. Recent clinical studies suggest that parental environmental influences can affect offspring CVD risk. However, most existing studies focus on the impact of maternal exposures on the offspring health, and little is known about the adverse effects of paternal exposures on offspring cardiovascular health. We recently explored how unhealthy diet consumption in fathers affects offspring atherosclerosis development using the LDL receptor-deficient (LDLR-/-) mouse model. Male LDLR-/- mice were fed either a low-cholesterol or high-cholesterol diet before mating with female LDLR-/- mice to generate F1 offspring. We found, for the first time, that paternal high-cholesterol feeding led to significantly increased atherosclerosis in F1 female, but not male, LDLR-/- offspring. Consistently, transcriptomic analysis revealed that paternal hypercholesterolemia stimulated the expression of many pro-atherogenic genes in the intima of female but not male offspring.

Emerging evidence indicates that sperm small non-coding RNAs (sncRNAs), particularly tRNA-derived small RNAs (tsRNAs) and rRNA-derived small RNAs (rsRNAs), along with their diverse types of RNA modifications can respond to environmental exposures and act as causative agents in mediating offspring metabolic phenotypes. By using an innovative small RNA sequencing method, PANDORA-seq, we revealed an overall tsRNA/rsRNA-enriched sperm sncRNA landscape and uncovered high-cholesterol diel-induced sperm tsRNA/rsRNA changes. Moreover, those diet-altered sperm tsRNAs/ rsRNAs can induce early transcription changes in murine embryoid bodies, which may lead to adverse effects on cardiovascular development or increased atherosclerosis in the offspring. In addition to dietary exposure, we also demonstrated that paternal exposure to ubiquitous endocrine disrupting chemicals altered sperm tsRNA/rsRNA profiles and elicited inter- and trans-generational adverse effects on cardiometabolic health of their offspring. These findings increase our understanding of the etiology of CVD and other chronic human diseases originating from paternal environmental exposures.

Camillo Golgi Strikes Back: Evolution and Development of Neurons in Ctenophores

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The neuronal doctrine posits that nervous systems are composed of discrete cellular units - neurons - that communicate via synapses. This framework has recently been challenged by the discovery of a syncytial nerve net in ctenophores (comb jellies), whose neurons fuse to form a continuous network. As ctenophores occupy a basal phylogenetic position and sponges lack neurons entirely, it is likely that neurons in ctenophores evolved independently. However, the molecular identity and developmental origins of these syncytial neurons remain poorly understood. Here, we use single-cell RNA sequencing to profile cell type diversity across ctenophore development. We identify candidate progenitor populations and trace the emergence of major neural and non-neural lineages. Comparative analyses with other early-branching metazoans reveal both conserved and ctenophore-specific features of neurogenesis. Our findings provide molecular and developmental insights into the evolution of neurons in animals and challenge the universality of the canonical neuron doctrine.

Beta-glucan exposé: quantifying the diversity of yeast cell wall

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Think the yeast cell wall is just a boring outer shell? This “mere coating” takes up a quarter of the cell’s dry mass and a third of its volume – yet it remains under-investigated because, inconveniently, it sits on the “wrong” side of the cell membrane, beyond the reach of reliable, intracellular molecular biology tools. Moreover, nearly everything we know about it comes from a few *Saccharomyces cerevisiae* lab strains that have spent decades growing and waiting in rich media and sterile shake flasks – hardly reflecting a life in the wild or at the brewery. To perform a reality check, we took a diverse set of natural and domesticated *S. cerevisiae* isolates and unleashed flow cytometry and confocal imaging on their walls. Surprise: the ratios of β-glucans, mannoproteins, and chitin are all over the map, with textbook strains looking merely average. These outliers aren’t just biological curiosities – they’re prime candidates for probing fresh layers of microbe–environment interactions and developing next-gen surface display, i.e., remaking yeast outer surface into self-renewing enzyme-studded living material. In short, it’s time to give these wallflowers their moment in the spotlight.