Our research group is broadly interested in understanding how immunological tolerance to self is established in the thymus and how breakdown of this process results in autoimmunity.

In particular, we focus on a very unique population of the thymic stroma, called the medullary thymic epithelial cells (mTECs). Specifically, mTECs are endowed with an amazing and unique capacity to express, and subsequently present, essentially all body antigens, including those whose expression was originally thought to be restricted only to peripheral organs (e.g. insulin, casein, etc.). Such “promiscuous” expression of tissue-restricted-antigen (TRA) genes in the thymus “foreshadows” the self-antigens that T cells would encounter once they reach maturity and are released into the body.
We study the interactions and cross talk between crystals and biological environment, spanning several orders of magnitude from the molecular level to cell and tissue level. We focus on the ion pathways leading to the formation of mineralized tissues. Examples range from calcified coatings in green algae to sea urchin spines, to vertebrate bone. We focus on structure-function relations, in particular of unique optical devices in the eyes of mainly aquatic, but also terrestrial animals. We study cholesterol crystals in atherosclerotic plaques, trying to understand how they form and how they can dissolve.
To understand and treat genetic diseases we need to decipher, at the molecular level, the biochemical processes that drive them; processes such as gene expression, DNA replication, and DNA damage repair. Our goal is to obtain a deep molecular understanding of protein-DNA interactions involved in these fundamental processes, as well as their roles in physiology, disease, and evolution.

To accomplish this, we develop and use cutting-edge approaches to manipulate DNA molecules in high throughput and to introduce chemical and mechanical DNA perturbations that frequently occur in the genome.

We believe in a multidisciplinary view that closely integrates experimental and computational approaches.
The role of specialized metabolism in plant-environment interactions

The lab has four expertise clusters (biology, chemistry, microbiology & computation) that use a unique infrastructure.

MODEL ORGANISM
Plants

MAJOR METHODS
- High resolution mass spectrometry (metabolomics; proteomics; mass spectrometry imaging; metabolite purification)
- Transcriptomics and proteomics
- Microbiome analysis
- Genome editing
- Metabolic engineering

The term ‘METABOLOME’ describes the complement of all metabolites expressed in a cell, tissue or organism during its lifetime. We aim at understanding how plants make and regulate a tremendous diversity of small molecules and the role of these chemicals in plant-environmental interactions (e.g. pigments, anti-fungal, bacterial, herbivory metabolites and systemic signaling molecules). We study plant metabolites and their impact on above ground interactions mediated through the plant outer surface layers as well below ground in roots, their secretions and interactions with rhizosphere organisms. Experiments are conducted both indoors and recently outdoors, in nature (using genome edited plants).
What does it mean for a brain to perceive? What are the processes underlying the seemingly effortless acts of seeing, feeling, hearing, tasting or smelling? In our lab we try to answer some of these questions. We focus on the senses of touch and vision: we study them in rodents and humans, construct them in synthetic (robotic) and hybrid (brain-machine) agents, and substitute one with the other.
Circulating immune cells must exit blood vessels near specific target sites of injury, inflammation or tissue repair. The vessel wall at these sites displays specific combinations of traffic signals which operate to recruit specific circulating subsets with proper receptors to these signals. We use genetically manipulated mice, together with state-of-the-art imaging techniques, to dissect how these trafficking molecules promote context- and tissue- selective exit of immune cells through distinct blood vessels.

We also study how chemotactic and antigenic signals promote the stoppage of lymphocytes on dendritic cells during distinct infectious processes. We follow how specific subsets of lymphocytes use specific adhesion signals to undergo differentiation into efficient effector and memory cells.

A new avenue of research in our lab focuses on the trafficking mechanisms used by tumor specific T cells to enter metastatic lesions at various target organs, in particular the lungs. This information is critical for improved targeting of genetically-engineered tumor-specific T cells to sites of lung metastasis.
Understanding biological circuits that perform computations is a central problem in biology. Circuits can be made of proteins inside the cells, or cells that communicate with each other in a tissue. Our lab studies biological circuits using a combined experimental and theoretical approach, aiming to uncover general underlying principles that govern their functioning and evolution. Current projects in the lab focus on the role of senescent cells in human ageing, mortality and diseases incidence, principles of hormone circuits, origins of autoimmune diseases, origins and timescales of mood disorders, inflammation and fibrosis.
Ido Amit
Immunology

We are world leaders in developing single-cell genomic technologies and their application in immunology and medicine. Our lab pioneered the field of single cell genomics. Using these technologies, we revealed cellular localization, clonality, cell-cell interactions, signaling and regulatory circuits determining immune activity. These powerful single-cell tools enable us to uncover novel cell types, pathways and targets of immune regulation in the fields of development, cancer, metabolism, autoimmune and neurodegenerative diseases. Together these unique technology and knowhow enable us to develop the next generation of immunotherapies.

**What**
Applying advanced genomics and big data approaches to characterize the immune system and develop new immunotherapies

**How**
Our lab is a major driver in developing and applying cutting edge single-cell genomics technologies and advanced computational approaches. We apply these novel tools in animal models and human patients to uncover immune regulatory mechanisms and pathways in cancer, neurodegeneration, autoimmune and metabolic disease.

**Model Organism**
Mouse, human

**Major Methods**
Single cell genomic technologies, CRISPR and other genome engineering methods, modeling and computational analysis

**Keywords**
Single cell genomics
Cancer
Neurodegeneration
Immunometabolism
Autoimmune
CRISPR
Our lab studies cellular communication pathways that regulate differentiation and decision-making processes in cells, from a systems level perspective. We focus on the way extracellular information is perceived by individual cells and control their response. Using single cell quantitative tools, we study the encoding of the extracellular signals into few intracellular mediators, and map the spectrum of responses generated by a large space of combinatorial cues. Combining experimental approaches with mathematical modeling, we generate predictive bio-physical models, providing a deeper understanding of these cellular processes.
Programmed cell death (PCD) is a regulated cell suicide process that functions to eliminate unwanted or dangerous cells. Malfunction of PCD is associated with many diseases, including cancer and neurodegenerative disorders. Apoptosis, the most abundant form of PCD, is executed by proteases called caspases. However, activation of caspases does not always lead to PCD, and can promote a variety of non-lethal cellular processes (CDPs), whereas cell death can sometimes proceed in the absence of caspases by triggering alternative cell death pathways (ACDs). We discovered and study several developmental paradigms of CDPs and ACDs, with the aim of addressing some of the key questions in the field.
Our physiology and behavior are subject to daily oscillations that are driven by an endogenous circadian clock. Our main research interest is to identify daily metabolic cycles in mammals and mechanistically address their interplay with circadian clocks. Specifically, we are interested in the interaction between oxygen metabolism, mitochondrial function and exercise biology in the context of circadian rhythms. To this end, we employ a diverse arsenal of experimental approaches ranging from biochemical and molecular biology methods through in vivo imaging in cultured cells and living animals to metabolomics analysis and animal behavioral studies.
Biological membranes are universally conserved dynamic structures that constantly change their shape and composition to drive biological functions.

We are interested in understanding how cellular membranes gain their exquisite architecture and how subdomains of the membrane can be reshaped into functional structures that allow the trafficking of material and information in and between cells (e.g. endocytosis, exocytosis, exosomes). We are also fascinated by the process of cell-to-cell fusion, which is necessary for innumerable developmental processes such as fertilization, and myogenesis.

To gain previously inaccessible insight into the molecular mechanisms and physiological functions of membrane remodeling, we take a multimodal imaging approach combining several advanced imaging techniques including total internal reflection fluorescence microscopy (TIRF-M), confocal microscopy and correlated light and electron microscopy (CLEM), which we apply to a variety of cell culture and in vivo model systems.
By applying cross-disciplinary single-cell analysis platforms that collectively enable us to extensively profile and precisely monitor host-pathogen interactions within the context of in vivo infections, we aim to answer these Main questions:

- How bacteria regulate different virulence strategies to optimize pathogenicity in the host environment.
- How do innate immune cells recognize pathogens, integrate signals from bacterial ligands and determine cell fate.
- Ongoing improvement of the methodologies we apply to study host-pathogen interactions.
- Characterize the in vivo landscape of human infection at a resolution of individual host-pathogen encounters: why do some get sick and some don’t?
My primary interest is with saccadic eye movements. We can see detailed images only at the line of gaze. We thus can see in detail only serially, one object after another. To shift the line of gaze we make a saccadic eye movement; this is a fundamental design principle of primate vision. Many issues concern saccades; here are some open for study. (1) Fatigue in looking. (2) Interactions of the readout from visual and motor working-memories with the flow of sensation. (3) Communication by eye-contact and influence of emotion on looking. (4) Looking at night, while the line of daytime gaze is blind. (5) Changes of looking in disease (eye, brain, ‘mental’).
Cells are constantly "making decisions" - monitoring their environment, modulating their metabolism and 'deciding' whether to divide, differentiate or die. For this, they use biochemical circuits composed of interacting genes and proteins. Advances over the past decades have mapped many of these circuits. Still, can we infer the underlying logic from the detailed circuit structure? Can we deduce the selection forces that shaped these circuits during evolution? What are the principles that govern the design and function of these circuits and how similar or different are they from principles that guide the design of man-made machines? The interplay between variability and robustness is a hallmark of biological computation: Biological systems are inherently noisy, yet control their behavior precisely. Research projects in our lab quantify biological variability and identify its genetic origins, examine how variability is buffered by molecular circuits and investigate whether variability can in fact be employed to improve cellular computation. We encourage a multi-disciplinary approach, combining wet-lab experiments, dynamic-system theory and computational data analysis.
Cell-cell adhesion is a key biological process in multicellular organisms. We study the signals conveyed by cell-adhesion receptors that regulate gene expression. A tight coordination between cell adhesion and gene expression is found in normal tissues and this coordination is altered in invasive cancers.

We are investigating the Wnt/β-catenin pathway, because β-catenin has a dual role: as a major linker of cell adhesion receptors to the cytoskeleton, and as a key transducer of Wnt signaling to the nucleus where β-catenin activates target genes. Hyperactivation of this pathway is found in colon cancer. We are studying β-catenin target genes activated in colon cancer, especially those of the colonic stem cell signature and genes related to epithelial-mesenchymal transition. Our studies will shed light on both intestinal homeostasis and on development of metastatic colon cancer.
Macromolecular machineries residing within our cells mediate every aspect of cellular physiology in both health and disease. These machineries adopt complicated three-dimensional (3D) structures that are critical to their function. Our lab focuses on visualizing the complex architectures of macromolecular assemblies, with the aim of learning how their complicated structures contribute to their ability to mediate cellular functions. To do this we use a combination of structural, biophysical and biochemical techniques with an emphasis on high-resolution electron cryo-microscopy (cryo-EM).
We are interested in questions related to membrane protein biogenesis, structure, and function.

Biosynthetically, structurally and functionally, membrane proteins must follow interesting, dedicated principles. For example, unlike soluble proteins, most membrane proteins are translated by membrane-bound ribosomes and then assemble and function inside the lipophilic environment of the membrane.

We ask how cells produce membrane proteins and how various structural determinants affect their function: (i) How ribosomes and mRNAs target the membrane for localized translation of membrane proteins? (ii) What dictates the fascinating capabilities of multidrug transporters?
Signals arriving from the outside world play a key role in shaping a tissue. Disruption of the cellular equilibrium within the gut tissue may lead to various diseases, including food allergies, inflammatory bowel diseases, and cancer. To understand the intestinal tissue physiology at higher resolution, we are leveraging single-cell genomics and traditional experimental methods. We aim to decipher the role of epithelial-immune interactions in homeostasis and gut pathologies by 3D organoids, mouse and human samples. Our goal is to understand tissue basic principles and identify disease key pathways.

We focus on:
1. Epithelial stem cell biology.
2. Epithelial – immune interactions.
3. Inflammatory bowel diseases.
The ability of antibodies to detect pathogens and malignant cells, and trigger diverse immune effector functions make them central players in the immune response. Monoclonal antibodies have turned into a powerful drug platform at the front of cancer immunotherapy approaches. Our group studies the mechanisms that control the activity of both natural and therapeutic antibodies.

We are particularly interested in the roles of the Fc regions of these antibodies and in their various Fcγ Receptors (FcγRs) in mediating anti-tumor activities, For maximum clinical relevance we are studying human antibodies in mice humanized for FcγRs and other relevant human genes. We are exploring strategies to enhance the identified pathways and aim to create 2nd generation antibodies with improved activity.
Regulation of transcription and mRNA translation is fundamental to all biological activities and is frequently altered in diseases. Our broad research interests are (i) to elucidate how transcription and translation control the cellular response to environmental stimuli; (ii) to reveal the connections between these processes and (iii) to develop drugs to manipulate these processes for potential treatment of cancer, chronic inflammation and neurodegenerative diseases. We address these issues utilizing several biological systems:

• Spt4/Spt5 (DSIF), a transcription elongation factor involved in stress responses and neurodegenerative diseases
• Regulation of translation initiation by TISU (a transcription and translation regulatory element), stress and mitogenic signals
• RNA modifications as mediators of the crosstalk between gene expression stages
Our research group investigates how viruses infect cells, how the immune system combats viral infections, and how viruses evade effective immune responses.

We take a structural biology approach to address these questions. We elucidate the molecular structures of key viral proteins, investigate how they attach to and utilize various cellular receptors. We also examine the potential of a humoral immune response to combat viral infections and design novel immunotherapeutic reagents. We focus on enveloped viruses in general, emphasizing viruses from the Arenaviridae family that contain some notorious human pathogens.

Keywords: Viral infection, Immunotherapy, Molecular recognition, Molecular Structure.
Intracellular protein transport in membrane-bound vesicles is fundamental to cell physiology. Autophagy is a unique, highly conserved membrane trafficking pathway for degradation of excess or damaged macromolecules and organelles. It is induced by stress and implicated in apoptosis, cancer, infection and neurodegeneration.

In our lab we study the mechanism of autophagy and its role in health and disease, using mouse models, mammalian cell lines and budding yeast. Particular interests include elucidation of cargo-specific sequestration processes, establishment of mouse models for autophagy in neurodegeneration, and dissection of conserved mechanistic aspects by novel assays yeast genetics.
The material that makes up the bones in our bodies is constantly being produced by osteoblasts and being degraded by osteoclasts (OCLs), the only cells in our bodies that can fulfill this function. Balancing between bone production and degradation is essential for health and development. Excess OCL activity causes bone loss in, for example, osteoporosis and cancer, while loss of OCL activity causes the lethal genetic disease osteopetrosis.

Our goal is to understand the molecular and cellular mechanisms that drive and regulate the formation and function of OCLs in the context of health and in diseases. We aim to advance the basic knowledge of OCLs and bone biology, as well as to identify new targets, pathways, and strategies to treat bone disease.

Our studies encompass the molecular, cellular, and whole-animal level.
The mammalian intestine contains trillions of microbes, collectively termed the microbiome. Dysregulation of host-microbiome interactions predisposes to disease ranging from chronic inflammation, obesity, the metabolic syndrome and even cancer. The Elinav lab mechanistically studies in mice and in humans the factors participating in the reciprocal regulation between the host and the intestinal microbial ecosystem, using advanced genomics, metabolomics, proteomics, mouse and human experimentation. Understanding the molecular basis of host-microbiome interactions may lead to development of new microbiome-targeting treatments.
Our lab deciphers the dynamics of cellular metabolism at different disease states. In particular, we are interested in understanding the contribution of the urea cycle components to the metabolic changes that accompany disease pathogenesis. Urea cycle metabolites serve as metabolic junctions that directly contribute to distinct metabolic fluxes at different cellular states. Consequently, changes in the function of urea cycle proteins have important effects on cell growth, survival and proliferation. Identifying specific metabolic alterations during disease can potentially improve diagnosis, monitoring of progression, and therapeutic interventions.
Florigen is a systemic plant hormone produced in leaves and travels to apices to initiate flowering. In tomato, local production of antiflorigenic signals inhibit floral transition in a dose and position dependent manners. Hence, the florigen/antiflorigen balance in each bud determines if it will flower or, remain vegetative. Together, the two opposing hormones comprise a regulatory system that is environmentally tunable. We are looking for the direct targets of florigen by capturing the detailed events that follow its arrival to the target bud. In vivo genetic characterization of this process is used to understand the mechanisms underlying developmental transitions late in the plant life.
Neurons are the largest and longest cells in the body. How do neurons control their own growth, and what are the molecules or mechanisms that might allow their repair after injury? Can neurons sense their own size and length and how might they do that? Can we take advantage of such mechanisms to devise new approaches for repair and regeneration in the nervous system? Are mechanisms of size and growth control in neurons generalizable to other cell types? If these questions sound interesting, please get in touch.
Our lab studies enzymes that catalyze the formation of disulfide bonds during protein folding and assembly. Our research combines structural and molecular biology with experiments in vivo, allowing us to determine how catalysts of disulfide bonding contribute to animal physiology and, in certain cases, pathology. Controlling the activities of disulfide catalysts may have applications in medicine and tissue engineering, an avenue we are pursuing through the design of specific inhibitors of these enzymes.
Nature provides us with myriads of examples of exquisitely selective proteins that function as binders and enzymes. These proteins, however, are often formidably complex. For instance, a typical enzyme or the antigen-binding domain of an antibody comprise more than 200 amino acids and fold into complex three-dimensional conformations that depend critically on thousands of atomic interactions. By changing the protein sequence and structure or designing completely new proteins, we may generate desirable new enzymes for green chemistry, binders for research, diagnostics and therapeutics, and exquisite molecular sensors to measure metabolite concentrations. We develop methods for designing efficient and stable proteins with enhanced or new activities.
Pathogens and stressful environments rapidly induce reactive oxygen species (ROS) and activate cell death programs that include proteases and their inhibitors called serpins. We recently discovered a role for singlet oxygen, a special type of ROS that appears in many different stress reactions and activates cell death. Our research is meant to understand the origin the singlet oxygen, its effect and control so as to develop hardier plants.
At any given moment, thousands of proteins are produced and need to fold in the cell. But folding is an incredibly complex process that very often fails, resulting in numerous devastating diseases. To deal with this challenge, the cell is equipped with an array of chaperones and proteases, performing quality control functions to safeguard the cell. We combine biochemistry and genetics with high throughput mutagenesis, robotics, and computational biology, to investigate how these events unfold for membrane proteins, which make up a quarter of the proteome in every living organism.
Our laboratory works on sphingolipids, important membrane components. We focus on two main areas: (i) sphingolipid synthesis and signaling, particularly of ceramide and (ii) sphingolipid storage diseases, with an emphasis on mechanistic understanding of disease pathology and also on therapeutic approaches.
Unicellular algae in the oceans are able to produce minerals in shapes and compositions unequaled by any manmade material. The biological mineralization process is intracellular and proceeds under strict cellular control, giving rise to spectacular morphologies of the mineral.

We study mineralization processes in two of the most abundant algal groups of modern oceans: 1) diatoms - that form cell wall made of nano-patterned silica, and 2) coccolithophores - that form calcium carbonate scales with unprecedented control over crystal morphology.

Our main tool is state-of-the-art electron microscopy that allow to follow these intracellular processes in 3D and with nanometer scale resolution.
Adhesion to the extracellular matrix (ECM) or to neighboring cells regulates multiple cellular processes such as cell migration, morphogenesis, proliferation, gene expression and survival. Activation and regulation of these responses depends on multiple environmental cues, which are sensed and interpreted in specific cell-matrix and cell-cell adhesions. In our lab, we focus in particular on integrin- and cadherin-mediated adhesions, and study the mechanisms whereby they sense external surfaces, recognizing not only their chemical composition, but also their physical properties, including their topography, rigidity and ligand density. Systematic molecular modulation of the adhesion sites is used in an attempt to decipher the mechanisms whereby the adhesion-based molecular machinery integrates complex environmental information and triggers a coherent and robust response. Specifically, we combine a wide variety of molecular perturbation approaches with advanced, quantitative imaging technologies, to study cancer cell invasion and migration, osteoclast-mediated bone remodeling, platelet adhesion and activation, the formation and maintenance of the epithelial barrier function in the gut, the development of antigen-specific stimulatory surfaces that stimulate T-lymphocytes, and more.
Internal tumor heterogeneity is a major clinical challenge associated with tumor metastasis and treatment resistance. We aim to understand cancer complexity by combining mass spectrometry-based clinical proteomics, advanced computational analyses, and functional validations in-vitro and in-vivo. We further advance the proteomic technology and combine bulk tumor analyses with spatial and single cells analyses to decipher mechanisms of treatment resistance, that cannot be found using genomic approaches.
My lab studies the cell biology of RNA, namely how mRNA trafficking and localization are regulated and control basic cellular processes and cell physiology (e.g. protein translation, polarized growth, chemotaxis, mitochondria and peroxisome function, cell fusion, etc.). We use a wide variety of techniques, including fluorescence microscopy, RNA tagging and pull-downs, mass spectrometry, RNA-seq, whole translatome analysis, and genetic and biochemical techniques to understand the mechanisms involved. The work shows that mRNA trafficking and localized translation form a critical layer of organization within the cell responsible for protein localization and function.
We study viruses and we explore the creative strategies they use to maneuver their host cells. We are interested in deciphering the roles different viral elements are playing during infection, as well as how viruses interface with and commandeer cellular pathways to control gene expression. We study these complex interactions using mainly cytomegalovirus (CMV), a herpesvirus that infects the majority of the world's population, leading to severe diseases in newborns and immunocompromised adults. We anticipate that our studies will uncover new aspects of virus-host interactions, as well as reveal new cell biology principles.
The major research topics of our lab evolve around how mitochondria act as “headquarters” to coordinate cell fate decisions and the relevance to disease.
Chameleons, copepods, fish, and many other organisms, use organic crystals for an astonishing variety of optical functions. These crystals are formed by specialized cells, in which remarkable control over crystal shape, size, and assembly is obtained using strategies that are beyond the state of the art in materials science. While these cells were identified many years ago, almost nothing is known about their biology, particularly the cellular processes involved in organic crystal formation. We use biological tools together with physical and chemical methodologies to study the processes organisms use to produce either optically functional or pathological, bio-organic crystals. Our main model organisms for these studies are zebrafish and medaka.
We are an interdisciplinary group of scientists interested in understanding embryonic stem cell biology, early development and advance human disease modeling. Specifically, we investigate the process of cellular reprogramming, in which induced pluripotent stem cells are generated from somatic cells, and we investigate how pluripotency is maintained throughout development in mouse and human. We utilize in our studies a diverse arsenal of biological experimentation methods, high throughput screening, advanced microscopy and genomic analyses. We also seek to combine biological experimentation with computational biology, theory and modeling, to elucidate the biological processes involved.

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<th>WHAT</th>
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**KEYWORDS**

- Stem cells
- Epigenetics
- Reprogramming
- Fertility
- Bioinformatics
Hornstein lab investigates the molecular mechanisms underlying neurodegeneration. We are particularly interested in alterations in non-coding genetics and RNA metabolism of neurodegeneration. We study RNA-related neuro-protective functions and insufficiency in neuro-diseases, including amyotrophic lateral sclerosis (ALS) and FTD.

We use a multidisciplinary approaches, including computational data science, mouse genetics and iPS cell-derived human neurons. We also translate the molecular mechanisms we have discovered, that underlie neurodegeneration into potential therapies. We develop cell-free biomarkers and test a small molecule therapy based on our findings in a clinical trial.
The focus of our research activities is to understand the molecular basis of allosteric transitions in protein machines and how they relate to their function. Much of our work is centered on the GroEL and CCT/TRiC folding machines in E. coli and yeast, respectively. We are interested in understanding their substrate specificity, folding mechanisms and allosteric properties.
Mammalian tissues are composed of heterogeneous cells, interacting in highly structured microenvironments to achieve physiologic goals. We study how single-cell gene expression patterns serve to achieve these goals and how intercellular interactions are perturbed in disease such as diabetes and cancer. We apply an interdisciplinary approach, combining novel measurement techniques of single cells in intact tissues with mathematical models. We focus on the metabolic tissues – intestine liver and pancreas and apply cutting-edge technologies such as single cell RNAseq and single molecule microscopy.
Mononuclear phagocytes form a body wide network of myeloid immune cells devoted to the maintenance of health and immune defense of the organism. We study these monocytes, dendritic cells and macrophages in physiological in vivo context, providing detailed mechanistic insights into intercellular communication driving human pathologies. Current focus is given to the gut and brain. Specifically, we investigate cytokine circuits that control the hyper-activation of macrophages in small and large intestine, as well as brain microglia, which otherwise leads to detrimental pathologies such as inflammatory bowel disorders (IBD), sickness behavior and neuropathy.
How does our brain mediate persistent behavioral changes? To answer this central question in neurobiology, we investigate how monoamine systems, such as the serotonin (5-HT) and dopamine (DA) systems, orchestrate whole-brain neural dynamics during adaptive and maladaptive behaviors.

We approach this problem using zebrafish, whose tiny transparent brain is an excellent model for the basic functionalities of our brain. We apply advanced optical imaging, statistical analyses and genetics to examine how whole-brain neural activity dynamics mediate behavioral changes and how monoamine systems modulate such dynamics.
Human pathologies depend on the interplay between malignant cells, stroma, and the immune system. However, we have much better understanding of individual cells than of their cumulative behavior. Our research is focused on understanding how different cells interact as a system in health and disease to define progression and outcome in response to treatment. We develop new imaging tools to visualize the molecular composition of single cells in clinical specimens in unprecedented spatial detail. We combine these with artificial intelligence and clinical collaborations to study of trans-cellular interactions, with the ultimate goal of developing better treatments and diagnostics.
We are studying the neuronal and molecular mechanisms that govern reproductive behavioral patterns and social interactions.

The lab focuses on two main themes:

1. Elucidating how sexually dimorphic reproductive behaviors, such as mating, parental care and aggression, are encoded by the male and female brain, and regulated by environmental stimuli (focusing on olfactory signals).

2. Dissecting the mechanisms underlying social behaviors and group organization in neurotypical and autism spectrum disorders (ASDs)-related mouse models.
Our lab studies programmed cell death, a network of multiple cell death and survival pathways, whose complex coordination determines a cell’s decision to live or die. The following topics are being studied:

- Monitoring the global profile of protein-protein interactions of hundreds pairs of proteins, in cells in real time.
- Whole genome functional screens to identify drivers of alternative forms of programmed cell death.
- Mechanisms that suppress selective RNA translation to allow embryonal stem cell differentiation.
- Mechanisms of cell death in the developing mammalian embryo.
- Identifying the cell death signature of patient’s tumors and targeting point of vulnerability towards precision cancer therapy.
We discover new insights into how trees cycle water and nutrients between leaves, stems, and roots—including a “carbon trade” between roots of nearby trees. We quantified the transfer of carbon between mature trees of different species in the forest.

We investigate the drought-resistance mechanisms of trees. Even irrigation does not cancel out the exposure of fruit trees to drought, so the development of drought-resistant varieties of lemons, pears, and olives would allow them to grow in drier areas.

Studying trees matters if we understand that they are an essential part of the global water and carbon budgets. In order to mimic what greenhouse gases might have in store for life on Earth 50 years from now, we adapted greenhouses with double the concentration of CO2 we have today.
In nature, bacteria form complex and differentiated multicellular communities, known as biofilms. The coordinated actions of many cells, communicating and dividing labor, allow biofilms to attach to hosts and protect them from environmental assaults. Bacteria in a biofilm are up to 1,000 times more resistant to antibiotics than free-living bacteria. The mechanisms supporting this community resistance and the transition from free-living single bacteria to a differentiated biofilm colony are still poorly understood. We use single-cell imaging, genetics, transcriptomics, and biochemistry to identify novel bacterial developmental pathways. We study biofilm formation in beneficial bacteria as well as bacteria involved in persistent infections.
Cellular senescence, a permanent cell-cycle arrest, limits tumorigenesis and tissue damage. However, the long-term presence of senescent cells can paradoxically promote tissue damage and aging. These non-cell-autonomous effects are partially mediated by the secretion of soluble factors from senescent cells to their microenvironment.

In order to understand the role of cellular senescence in cancer, aging and more recently in embryonic development, our research aims to uncover the underlying mechanisms associated with the interaction of senescent cells with their microenvironment.

We study how immune systems regulates the presence of senescent cells and thus age-related diseases.
The neocortex plays a central role in higher brain functions, including perception, memory and motor control. Yet, basic anatomical and physiological features are similar across different cortical areas, suggesting that similar principles govern cortical functions. Our overarching research goal is to understand how tactile stimuli are represented by the somatosensory cortex and what enables their perception. Using in-vivo recordings, calcium imaging and optogenetics in awake mice, we study how neurons integrate excitatory and inhibitory inputs from local and distal sources and how their activity is affected by the history of stimulation as well as by the animal’s behavioral state.
We proposed a model for life’s emergence, involving assemblies of lipids that, upon biased accretion and fission, pass compositional information to progeny. Our computational chemistry formalism (GARD) depicts non-equilibrium catalytic lipid networks with homeostatic growth, showing reproduction with mutations, hence capable of selection and evolution. Thus, RNA and proteins may be the outcome, not prerequisite for life’s emergence. We now gather experimental evidence for catalysis in nanoscopic protocells, use Molecular Dynamics to support homeostatic growth, and employ advanced kinetics to show attractor behavior that could greatly enhance the probability of life in the universe.
Metabolic regulation of hematopoietic stem cell migration and development by their dynamic bone marrow (BM) microenvironment and BM neutrophil activation and recruitment. The role of daily circadian light and darkness onset, ROS, nitric oxide, lactate, mitochondria transfer, the endothelial BM/Blood barrier, TNF, Norepinephrine, Melatonin, CXCL12/CXCR4 interactions, proinflammatory Thrombin/PAR1 interactions, anti-inflammatory aPC/EPCR/PAR1 stem cell regulation, clinical stem cell mobilization, homing and repopulation are currently investigated.
RNA viruses including corona, zika and dengue are a major threat to human health. We study how RNA viruses interact with their host cells and transform them into viral manufactories. Our main model is enteroviruses (EVs), common human pathogens, that cause severe medical complications in young children. We tackle key questions including: How EVs that express only a handful of proteins take control over human cells with complex protein machineries? How EVs hijack host organelles and repurpose them into a makeshift virus factory? We aim to build a complete mechanistic picture of the EV replication process, that will help develop better antivirals, for a broad spectrum of RNA viruses.
Aberrant signaling networks commonly lead to uncontrolled cell growth, proliferation and motility, and consequently to cancer development and metastasis. We aim to identify tumorigenic alterations in signaling networks and target them for cancer therapy. We focus on triple negative breast cancer (TNBC), a highly aggressive subclass of breast cancer. We apply multidisciplinary approaches to gain molecular understanding of how TNBC develops, progresses and spreads to eventually identify highly effective therapeutic strategies for each individual patient.

Ongoing projects focus on:
(1) Ferroptosis
(2) Tumorigenic signaling networks
(3) EMT and drug resistance
(4) Synthetic lethal interactions.
We utilize zebrafish to investigate development and function of neurons that reside in the hypothalamus. These neurons regulate fundamental body functions including sleep, blood pressure, temperature, hunger and metabolism, thirst and satiety, stress and social behavior. We study the molecular and cellular processes underlying morphogenesis and function of oxytocinergic neurons that affect both peripheral and central nervous system activities. A primary research direction is the assembly and maintenance of the hypothalamo-neurohypophyseal system. This important neuroendocrine conduit between brain and blood contains multiple neurovascular interfaces that mediate the passage of hormones to the peripheral blood circulation.
Our understanding of biology has been revolutionized by the development of genomic and proteomic technologies, in particular with deep sequencing and mass spectrometry. Such technologies have been providing precise information about parts (DNA, RNA, proteins) that make up a cell. Remarkably, however, our understanding of how these parts self-organize and give rise to a living cell have been lagging behind. The overarching goal of our research is to characterize general principles by which proteins self-organize in space and time. In this endeavor, we develop computational as well as experimental approaches and bridge different fields of biology.
We focus on deciphering the mechanisms and kinetics of various biomolecular self-assembly processes. Quantifying the molecular and physical principles of the mechanisms of protein-protein and protein-DNA assembly is key to cracking the protein-DNA recognition code and improving the prediction of specificity and binding affinity.

Our goals are to predict new phenomena and principles from the physical and chemical perspective as well as providing molecular interpretation to basic cellular processes, for understanding diseases and ways to overcome them.
We study the molecular mechanisms by which DNA damage, caused by internal and external agents, is handled by human cells, including embryonic stem cells. We focus on the balance between error-free and error-prone mechanisms, and in particular the role of low-fidelity DNA polymerases, which we discovered, and which are a major source of mutations. In parallel we develop blood tests to measure DNA repair, and use them in clinical and epidemiological studies for prevention and early detection of cancer. Notably, we discovered that a DNA repair score combined of 3 DNA repair blood tests, is a strong risk factor for lung cancer, and can be utilized for prevention and early detection.
Brain-body communication requires interoception, the perception of internal bodily signals. Insular cortex is the main cortical site that integrates external cues with bodily signals. We seek to understand brain-body communication, and its role in regulating diverse behaviors, by focusing on insular within the brain-body loop. We focus on global physiological need states such as hunger and thirst, as well as on more specific signals such as gut nutrient sensing. We use cellular/sub-cellular imaging, with circuit-mapping, circuit manipulation and computational approaches. We combine these approaches with goal-directed behaviors, as well as measurements and manipulations of bodily physiology.
Covalent inhibitors have many advantages as chemical probes and drug candidates, discovery of new covalent inhibitors remains challenging, however. Our lab is interested in covalent molecular recognition, the development of technologies to design and discover such covalent inhibitors and their application to shed new light on biology. We have developed two leading technologies for covalent probe discovery. The first is DOCKovalent, a software that computationally screens huge libraries of putative covalent binders. The second is a complementary, empirical, electrophile fragment-based approach. Through both, we were able to rapidly discover covalent fragment hits for several protein targets. We now develop additional approaches related to targeted protein degradation, proteomic target identification and new screening modalities.
My lab members and I are passionate about trying to understand the cellular highways of energy and carbon transformations known as central carbon metabolism in quantitative terms. We employ a combination of computational and experimental synthetic biology tools. We also quantify the new geological era of the anthropocene from a holistic quantitative perspective to get insight and lead of action.
Our lab focuses on two different research areas: archaeology/anthropology and material farming. On the archaeology/anthropology, we are developing AI algorithms (in 2D and 3D) to infer past human behavior. On the material farming, we are combining the study of cotton natural biochemical pathways at different scales and hybrid synthetic biology-chemistry to exogenously “bioaugment” cotton fibers with unusual properties (e.g. fluorescence, hydrophobicity or magnetism).
The vascular bed is essential for survival of all multicellular organisms larger than a millimeter. Accordingly, structural and functional changes of tissues, in health and disease, during development or degeneration, are accompanied and often induced by vascular changes.

The aim of our work is to map the regulatory network controlling the growth and function of blood and lymphatic vessels. Novel MRI tools, accompanied by advanced optical modalities, allow us to non-invasively obtain dynamic information on activity of multiple steps in the angiogenic process and thereby improves our understanding of the key regulatory elements and critical checkpoints of vascular remodeling.
The p53 tumor suppressor gene is the most frequently mutated gene in human cancer. When functional, p53 drives a transcriptional program leading to elimination of cancerous cells. In contrast, cancer-associated p53 mutations not only abolish its anti-tumor activity, but also facilitate tumor progression through pro-oncogenic gain of function. Current research in our lab focuses on the involvement of wild type tumor suppressive p53 and mutant oncogenic p53 in transcriptional regulation, metabolism, shaping the tumor microenvironment and anti-cancer immunity.

We are also interested in the Hippo pathway, which is emerging as a master controller of tumor growth and metastasis.
Sexual dimorphisms in brain structure and function are evident across phylogeny, but little is known about sexually dimorphic features of individual neurons, and the mechanisms for establishment and maintenance of dimorphic neuronal circuits. The Oren lab investigates how sexually dimorphic patterns in the brain emerge, from synapse formation to animal behavior. We have developed a unique system that enables studies of sexual dimorphism at the synaptic, circuit, genetic and behavioral levels, across all developmental stages. We are also testing how sexual dimorphism is manifested in brain pathologies.
How can $10^{11}$ neurons, each forming $10^4$ connections with other neurons, work in concert to process information and underlie cognitive functions? What is the neural language/code? We focus on dynamics of networks during learning and memory formation. We combine electrophysiology in animals, fMRI in humans, and computational methods, to unveil mechanisms that underlie learning and memory formation.

We investigate phenomena as: reinforcement learning, generalization of learning, emotional modulation, extinction of memories, primitives of computation, social cognition. We develop models for pathologies that arise from abnormalities in learning and memory, as PTSD, Depression, Anxiety and Autism.
Myelin is an insulating membrane sheath produced by specialized glial cells; Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS). It enables fast and efficient nerve conduction, and provides essential trophic support to maintain axonal integrity and survival. Destruction of myelin leads to several neurological diseases such as multiple sclerosis, and is also associated with psychiatric and neurodegenerative disorders. We study the various aspects of myelinating glial cells biology, and in particular interested in the mechanisms that enable Schwann cells and oligodendrocytes to ensheath the axons they contact and to myelinate them.
High quality RNAseq data of 53 tissue types is available for >700 individuals. We are interested in examining unusual expression programs. Besides typical ‘normal’ expression of each gene in each tissue are fewer cases where individuals have much higher or lower expression values for some genes in some tissues. These cases might be due to individuals in atypical conditions that led to atypical expression. Identifying these individuals and genes requires analyses across all individuals, tissues, and genes. Finding the common pathway/s of these genes might determine what was the atypical condition that led to their unusual expression.
We study the structure, function and evolution of genetic regulatory networks in microbes and mammals. We use computational biology and theory to formulate hypotheses on evolution of regulatory networks. A main research paradigm is experimental evolution with which we evolve organisms in the lab to tackle basic questions on dynamics and mechanisms of evolution. We aim to distil genetic determinants of evolvability – the capacity of organisms to evolve. We use lab evolution to reveal the role of evolutionary mechanisms such as horizontal gene transfer, and reverse transcription. A major focus is on regulation of protein translation in which we study efficiency and fidelity of the process.
Integration is the hallmark of cognition. This is true both at the neural, and at the behavioral level. Even the single action potential is above all the product of large-scale integration across multiple brain regions. The simplest, everyday behaviors (for instance remembering a face, or opening a door) are in actuality incredibly complex, supported by multiple cognitive domains such as perception, action, memory, learning, and social cognition. Our group studies those large-scale interactions, and how they support the network level synthesis of interdependent cognitive processes in health and disease.
Malaria, caused by *Plasmodium falciparum*, is the most devastating parasitic disease, killing up to a half a million people each year. We have previously showed that malaria parasites can communicate between them using secreted Extracellular Vesicles (EVs). EVs capable of delivering cargo of proteins, lipids and nucleic acids by fusing with target distal cells, thus providing a secure and efficient mode for signal delivery. Little is currently known about the precise mechanisms of parasite-derived EV cargo delivery and function. With malaria continuing to be a major global disease, advances toward understanding the basic biology of *Plasmodium* remain essential.
We study:

- Structure, function & adaptability of photosynthetic machineries.
- Biogenesis and breakdown of the photosynthetic apparatus during leaf development and senescence.
- Structural, molecular and regulatory mechanisms of desiccation tolerance in resurrection plants.
- Engineering out toxins from drought-tolerant nutritious plants for human consumption.
- What is the relationship between environmental dynamics and population variability and survivability?
- To what extent is the ability of individuals to survive deterministic/stochastic?
- Can individuals, or communities as a whole, acquire new adaptive functions following training by synthetic feedbacks?
We study the process of embryonic brain development, and what goes awry during disease conditions. In the developing brain there is a relative change in the type of neuronal stem cells that are born; and neurons born in one position have to reach their final destination by active cell migration. These highly dynamic processes are regulated via the concerted action of multiple gene products. Through interdisciplinary approaches, combining molecular, biochemical, in vivo, ex vivo, and in vitro studies with mouse and human brain organoid models, we examine a wide range of human developmental brain malformations and diseases.
Ion flow through protein channels is one of the fundamental mechanisms of transmembrane signaling. Ion channels are involved in processes as diverse as development, hormone secretion, salt balance and memory. Abnormalities in channel function underlie a wide range of neural, muscular, cardiovascular and renal diseases. In order to understand the roles of ion channels under normal and pathological conditions, it is necessary to know how they regulate the flow of specific ions across the membrane and how other proteins affect their function. We address these questions by combining state of the art electrophysiological, molecular and imaging techniques, both in cultured cells and in native tissues.
The retina is a model system in neuroscience. It is easily accessible and its input can be fully controlled by the investigator. Its simple layered structure combined with the recent advances in microscopy, imaging and genetics place the retina in a unique position to study computations in neuronal circuits.

Recently, we found that retinal neurons can dynamically change their computation (=the visual property they report on). We study the mechanisms allowing anatomically-defined neural circuits to change their function, and investigate how retinal targets decode the dynamic signal.

We also aim to use the retina for early diagnostic of neurodegenerative diseases, such as Parkinson’s disease.
Our lab studies molecular machines in our cells, called chaperones, that can reverse the formation of toxic protein aggregates and amyloid fibers linked to a host of debilitating conditions, such as ALS, and Parkinson’s, Alzheimer’s, and Huntington's diseases. We use a combination of advanced NMR (magnetic resonance) techniques and biochemical and biophysical functional assays to obtain a structural and mechanistic understanding of how these chaperones work, and the conformational changes they impose upon their clients to do so. Through this research we aim to identify why, in certain cases, chaperones fail in their task - giving rise to disease.
Our aim is to delineate the interactions of melanoma cells with the immune system. To this end we have established an extensive melanoma genetic database and a pipeline to identify and characterize neoantigens using whole-exome and HLA peptidomics in order to further understand its functional implications. This allowed us to map both the neoantigenic and T cell receptor landscape, their immune reactivity and corresponding T cell identities. We have further established a powerful melanoma mouse model that allows us to identify novel clinically-relevant biomarkers and treatment options for melanoma patients.
The study of MRI and of functional MRI is a prime example of contemporary multidisciplinary science; where Physics, Chemistry, Biology and Engineering meet. In our lab we integrate these fields aiming to develop new imaging methods and new tools for functional brain measurements. The study relies on the one hand on a physics background, for the development of new MRI techniques, on the other hand on a neurobiology background, to perform the actual human volunteer studies. Our lab’s research focuses on ultra-high field MRI aiming to better understand the human brain function. To do so, we are looking for new biomarkers and contrast methods, as well as new methods of acquisition.
Specific protein-protein interactions are basic in all living processes. My laboratory studies structure/function relations of protein-protein interactions and how these relate to biological signaling. For this purpose, we adopted a multidisciplinary approach including biophysical and biological bench work, protein-engineering, bioinformatics and applied the gained knowledge towards solving biological questions. Recently, we started to work on the evolution of the SARS-CoV-2 virus, showing that its in vitro evolution parrots and predicts contagious mutation spread. Moreover, we successfully evolved a drug, that is now in animal experiments. Other research topics include the evolution of specificity of protein-protein interactions and the molecular understanding of the type I interferon system.
Our lab is interested in neuronal remodeling, which is critical for setting up the wiring diagram of the nervous system. When defective, it is implicated in a wide range of neuro-psychiatric disorders including autism, schizophrenia and Alzheimer’s. Remodeling involves both degeneration and regeneration. Therefore, our studies have the potential to shed light on axon degeneration and regeneration during development, in disease and following injury.

**WHAT**
Developmental Neuroscience

**HOW**
Mechanisms of axon growth, destruction and refinement during developmental neuronal remodeling

**MODEL ORGANISM**
Fruit Fly (*Drosophila melanogaster*)

**MAJOR METHODS**
- Genetics
- Confocal Imaging
- Mosaic analysis
- RNAseq
- Connectomics

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**KEYWORDS**
- Neuronal remodeling
- Pruning
- Neuronal degeneration
- Axon regeneration
- Circuit formation
A hallmark of eukaryotic cells is the presence of membrane-enclosed organelles that create optimized environments for chemical reactions required to sustain life. Although more than 20 years have passed since publication of the yeast genome sequence, over 30% of organelle proteins have never been studied and more than half do not have a known function. Most of these proteins are conserved all the way to humans and some have been implicated in diseases. We use novel methodologies to uncover the functions of these unstudied proteins, and to delineate pathways and networks that enable the function and communication of organelles.
RNA is modified by >100 chemical modifications. These modifications are, in some cases, highly ubiquitous, conserved and dynamically regulated in mRNA, imposing a unique and uncharacterized regulatory code. Our lab aims to crack this code, and understand how modifications on mRNA direct gene expression programs and cell state decisions. Our lab bridges experimental and computational aspects of biological research, combining genomic, genetic and biochemical approaches with tailored computational ones.
We are a multi-disciplinary lab of computational biologists and scientists focusing on microbiome, nutrition, genetics, and gene regulation in health and disease. We aim to develop personalized nutrition and personalized medicine using machine learning, computational biology, probabilistic modeling, and analysis of heterogeneous genomic and clinical data.
Microscopic algae that live in the ocean are fundamental in the global carbon, oxygen and sulfur cycles. In recent years we have begun to learn that microalgae associate with marine bacteria in exquisite ways; the whole range from mutualism to pathogenicity can be seen in algal-bacterial interactions. Our group studies how algae and bacteria communicate via organic and inorganic compounds. Through a unique combination of approaches from the Life and Earth sciences, we aim to understand how algae and bacteria influence each other, the marine environment, and the geological record of Earth.
Adaptive immunity depends on generation and maintenance of a pool of mature peripheral lymphocytes throughout life. Lymphoid homeostasis results from delicately balanced lymphocyte production, differentiation, sequestration, proliferation, and survival. Disturbing this balance can lead to autoimmune malfunctions such as autoimmune diseases and cancer evasion of the immune system.

Our studies focus on four main aspects of the regulation of immune cell maintenance:

1. Regulation of stem cell maintenance
2. Molecular pathways controlling immune cell survival in homeostasis and malignancies
3. Cross-talk of immune cell with their microenvironment
4. Control of regulatory B cells differentiation and function in autoimmune diseases and cancer
5. Regulation of anti-tumor immunity in hematological and solid tumors.

Finding of our studies can pave the way towards development of novel therapies for various malignancies and autoimmune diseases.
1. Antimicrobial peptides (AMPs) are innate immunity molecules in all life forms. We study their mode of action which allow us to design AMPs with high potency against planktonic bacteria and biofilms. Moreover, we study resistance mechanisms towards AMPs.

2. HIV is a viral pathogen which infects the host via the gp41 protein. We study the mechanism by which HIV infects its target cells and escape the immune response.

3. TLRs sense pathogens and initiate the immune response. Uncontrolled activation of TLRs might lead to pathologies ranging from cystic fibrosis, Crohn’s disease and cancer.

Importantly, these studied lead also to the design of peptides which block various steps in the function of the protein and hence can be developed to novel therapeutics to various diseases.
We aim to discover the mechanisms that control and coordinate the activity of molecular machines involved in the protein degradation pathway. To do so we apply novel native mass spectrometry approaches, in conjunction with fluorescence microscopy, biochemical and cell biology methods - generating an integrative mode of analysis combining in vitro and in vivo findings.
We study epigenetic events that contribute to cellular transformation and cancer. To address these fundamental questions, we develop and apply innovative cutting-edge single-molecule technologies. The activity of genes, and thus the establishment and maintenance of a cell’s identity, is regulated by their cell type-specific chromatin organization. We develop methodologies at the interface of genomics and proteomics, with the goal of paving the way towards deeper understanding of epigenetic regulation, as well as the development of therapeutic and diagnostic tools. We focus on pediatric brain cancers, breast cancer and lymphoma.
Aging of the human hematopoietic system is typically correlated with: 1) clonal hematopoiesis 2) myeloid malignancies 3) reduced T and B cell clonal diversity 4) reduced myeloid cells function 5) red to yellow marrow transition. Understanding the evolutionary principals driving these phenotypes is the first step in early diagnosis and treatment of hematopoiesis malfunction. Hematopoiesis failure in humans is a long process of somatic selection. Somatic evolution creates new clones exploring the fitness space. Without changes in the somatic environment new clones will loose to the young hematopoietic system which have been optimized over millions of years of germline evolution. Under changing environment, the fittest clones will gradually take over and in time due to antagonistic pleiotropy will lead to a disease. Our lab is a multidisciplinary lab composed of hematologists, evolutionary biologists and computationalsystem biologists all trying to understand the rules of human hematopoietic aging.
Chromosome abnormalities play an important role in cancer. Recent DNA sequencing efforts revealed the extent of cancer genome complexities. Our work identified how such abnormalities can drive cancer, and lead to therapy resistance.

We aim to uncover molecular mechanisms leading to catastrophic genomic events by developing chromosome manipulation approaches. This will help better understanding cancer evolution and drug resistance formation. Ultimately, we aim to identify vulnerabilities of cancer cells, specifically related to the role of DNA repair in initiating and maintaining chromosome abnormalities, with the intention of developing novel therapies that would prevent resistance formation.
For tumors to expand, metastasize, and evade immune surveillance, cancer cells must recruit non-malignant cells, including macrophages, fibroblasts and endothelial cells. These cells, collectively termed the tumor microenvironment, are reprogrammed to support the tumor at the expense of its host.

We hypothesize that this reprogramming is mediated by evolutionary conserved stress responses, and we aim to elucidate these underlying mechanisms.

Our goal is to understand how tumors develop into systemic malignancies, predict which tumors are more likely to do so, and design therapeutic strategies to overcome these malignancies by targeting genetically stable elements in the tumor microenvironment.
Long lasting protection from harmful pathogens depends on collaboration of multiple types of immune cells each with a unique function. These cells interact with each other in small confined niches in lymphoid organs and exchange molecular signals required for differentiation into cells with the capacity to eliminate invading pathogens. Protective antibodies evolve in lymphoid organs in sites known as germinal centers. In our lab we aim to understand this process and discover new antibodies and targets for cancer immunotherapy and for treatment of various infectious diseases.
Our group investigates how every cell and animal copes with stress that cannot be effectively alleviated by pre-existing adaptation, whether new adaptations can be acquired by semi-stochastic changes in the epigenome and microbiome, how these changes might affect the germline and how they can be inherited and stabilized as longer-term, evolutionary adaptations. Our focus is on testing predictions of a theory of individual-specific adaptation, which complements natural selection by explaining adaptation on every timescale and level of organization. It also explains induction of adaptive variations (a neglected gap in Darwin’s theory) and accounts for the frequently invoked, but never really explained notion of adaptive plasticity.
We study how phages attack bacteria, and how bacteria defend themselves against such attacks. We are interested in deciphering the molecular mechanisms providing bacteria with protection against phages, collectively known as the "immune system" of bacteria. Specifically, we study the CRISPR-Cas system, which is the adaptive immunity system of microbes, as well as new anti-phage defense systems discovered in our lab.

We also discovered that phages can use small-molecule communication in order to coordinate their infection dynamics - our lab studies the molecular mechanisms allowing such communication.
Our ability to adapt to and learn from experiences underlies many of our cognitive capabilities. We seek to identify the molecular mechanisms through which neural circuits adapt to experience and to understand how the cellular functions that are regulated by these molecular mechanisms generate an animal’s adaptive behavior. We focus in our research on signaling and transcriptional networks and apply genomic, molecular, biochemical, electrophysiological and in vivo imaging approaches to understand how experience-induced signaling and transcriptional networks in subtypes of cortical neurons regulate the connectivity and function of the cortex. We believe that our research will allow us to untangle how nature and nurture cooperate to regulate adaptive behavior and to understand how mutations in the genome might give rise to individual variation in cognitive capabilities and to psychiatric disorders.
Epigenetic modifications provide cells and organisms with remarkable plasticity. Yet, disentangling the Gordian knot of epigenetic cause and effect still remains a formidable task. Building on the recent developments in single cell genomics and epigenomics and moving forward, by developing systems for dissection of embryonic epigenetic function in-vivo, represents a deep and fundamental challenge our group is determined to engage. Specifically, we ask:

- How cell-specific epigenetic programs are established and maintained?
- How do epigenetic changes at regulatory regions modulate cell state and function?
- What are the effects of epimutations on development and disease?
Tumors are heterogeneous and are made of highly complex ecosystems. Accordingly, our studies reach beyond the tumor cells to include the multiple components of the tumor microenvironment, including stromal cells, immune cells and bacteria that are present inside tumors - the tumor microbiome. We use cutting edge technologies to characterize understudied components of the tumor microenvironment and the mechanisms that modulate the response to cytotoxic, targeted and immune-mediated anti-cancer therapies. We strive to develop better treatment options for cancer patients.
From the earliest proteins to modern synthetic biology and chemical biology, understanding evolution at the molecular level is fundamental to biology.

How do proteins evolve? Natural selection can create molecular machines with breath-taking performances, e.g., enzymes that accelerate the rate of chemical transformations by factors of $10^6$ up to $10^{17}$. Strikingly, new protein functions can evolve within years or even months, as happens with drug resistance, and with enzymes that degrade man-made chemicals. Why is this process, which is based on ‘trial and error’ so rapid and efficient? We lack the fossils of the protein world, but we can reproduce protein evolution in the laboratory and in real time, implementing the principles of Darwinian evolution to individual genes and enzymes. In doing so, we obtain crucial insights regarding the evolutionary intermediates and the routes and mechanisms that led to the highly proficient enzymes known to us today.
We leverage single cell technologies, computational approaches and clinical collaborations to study human tumors as a complex ecosystem in which diverse cancer and non-cancer cells interact and collectively determine tumor biology and response to therapies. We analyze the diversity of cells within human tumors, to identify important tumor subpopulations such as cancer stem cells, drug resistant cells and invasive cells. We then study their function, regulation and vulnerabilities, with the ultimate goal of developing better cancer treatments.
Ischemic heart disease is the leading cause of death in the Western world. We combine novel approaches to study and manipulate various aspects of cardiac physiology including cardiac muscle cells dedifferentiation and renewal, immune modulation and formation of new blood vessels to promote cardiac regeneration following injury. Aspiring towards the development of translational therapies, we have recently began work on a clinically relevant pig model of acute myocardial infarction (heart attack), to mimic the human setting as close as possible.

Our unique approach is to combine developmental biology and regenerative medicine aiming to develop novel therapies for mammalian heart regeneration.
We take a “Natural Neuroscience” approach, which aims to decipher the neural mechanisms of natural behaviors in freely-moving animals. We focus on studies of neural codes for space, time, and social behaviors – in flying bats – using wireless electrophysiology methods that we pioneered. We discovered novel neuronal representations in animals navigating in 3D or in huge environments (hundreds of meters), or engaged in social interactions. These include 3D place cells and 3D grid cells, as well as “vector cells” representing the direction and distance to goals, and “social place-cells” representing other animals. Going forward, we want to take brain research to evermore naturalistic behaviors.
The human genome produces tens of thousands of long noncoding RNAs (lncRNAs), which are molecularly similar to mRNAs, yet do not encode functional proteins. lncRNA expression varies across tissues and is commonly dysregulated in human disease, including cancer. Accumulating evidence shows that lncRNAs play pivotal regulatory roles in diverse biological processes. Our goal is to understand how these functions are carried out and how they are encoded in lncRNAs sequences and structures. We are also interested in how the post-transcriptional fate, including nuclear export, of mRNAs and lncRNA is controlled, and how chromatin remodeling dysfunction contributes to disease in neuronal cells.
The Vardi Laboratory aims at exploring the cellular mechanisms involved in sensing and acclimation to diverse environmental stress conditions during algal bloom dynamics in the ocean. Our research utilizes the recent advances in the field of chemical ecology (metabolomics and Mass spectrometry imaging) combined with single cell imaging and transcriptomic approaches to track cell-cell interactions at the micro(be)-scale. We study key biotic interactions (host-virus, host-bacteria, predator-prey and allelopathy) that regulate the fate of algal blooms, in order to discover novel signalling and metabolic pathways employed during these interactions. Newly identified genes and metabolites induced during specific host-pathogen interactions are used as functional biomarkers to assess the ecological impact of microbial interactions in structuring microbial food webs and potentially global nutrient cycles.
Contractile muscle fibers are multinucleated cells with highly organized cytoplasm and characteristic connections with tendons required for proper muscle function. Our lab studies mechanical aspects of muscle development using the fruit fly Drosophila as our major animal model. Major research topics studied in the lab: (1) The 3D architecture and epigenetics of muscle nuclei. (2) Nuclear mechanotransduction and its effect on cell cycle. (3) Dynamic measurements of nuclear deformations in response to force manipulations.
Pancreatic beta cells are the only cell type capable of producing the key metabolic hormone insulin: their function is essential for normal metabolic balance, and their dysfunction is central to the development of both major forms of diabetes.

In our research, we focus on the following aspects of beta cell function:

1. The transcriptional mechanisms underlying the normal embryonic development of beta cells and the functioning of mature beta cells
2. Manipulating pancreatic cellular identity: molecular mechanisms controlling exocrine to endocrine cell reprogramming
3. Dissecting the signaling mechanism that permit beta cells to respond to modulators of insulin secretion, in particular long chain and short chain fatty acids
Development of multicellular organisms is a complex process that requires several events of cellular proliferation, differentiation and organization to be executed in a stereotypic order. As development proceeds, progenitor cells undergo progressive fate decision steps, each refining their identity, until they reach a functional end state. Our work aims at understanding how endothelial cells become specified to generate functional blood and lymphatic vessels that support organogenesis and regeneration. To this end, we use the zebrafish, a transparent vertebrate, which on top of enabling high-resolution live-imaging and easy genetic manipulations, are able to regenerate most of their organs.
While the majority of tumors are initiated by genetic aberrations, all malignant lesions follow a subsequent step-wise progression phase, which involves growth factors. Unlike many oncogenic mutations, growth factors and their receptors are amenable to pharmacological interception. We focus on the group of EGF-like growth factors and their ERBB/HER family receptors. We study the principles of signal transduction networks and focus on the complex transcriptional programs that underlay EGF-to-ERBB signaling. This understanding offers opportunities for pharmacological targeting growth factor signaling, experimental strategies to retard metastasis and ways to overcome resistance to cancer therapies.
Standing at the intersection of immunology, biochemistry, and proteomics, our lab studies proteostasis regulation in cancer and immunity. We focus on elucidating regulatory mechanisms involving protein modification and degradation in biochemical, cellular and physiological levels. We utilize immunoproteomics, cell biology, in-vitro and in-vivo models to reveal novel control mechanisms of protein modification and degradation across different disease models. We combine our expertise to gain insight into basic and translational questions and develop cutting-edge technologies in epiProteomics and biochemical immunology to promote precision medicine and impact human health.
The wiring of the nervous system during development sets the pattern of connections that allow the organism to function in the world. This developmental program is composed of progressive events as guidance of axons to their targets, and regressive events in which axons and neurons are eliminated. Inappropriate execution of this program is in the basis of many neurodevelopmental disorders. In the lab we are studying the cellular and molecular mechanisms that control the wiring process through the use of in vitro neuronal cultures and the analysis of mutant mice.
Ada Yonath
Structural Biology

Keywords
Ribosomes
Antibiotics
Resistance
Evolution
Nucleic Acids

WHAT
Ribosomes function; Defected ribosomes in human diseases; Novel eco-friendly antibiotics; Origin of life

HOW
Mutated ribosomes structural analysis, Design of novel antibiotics, Prebiotic peptide bond formation

MODEL ORGANISM
Bacteria, parasites, diseased human cells

MAJOR METHODS
• Isolation of ribosomes from pathogenic bacteria and from healthy or disease carrying human cell by sucrose gradient ultracentrifugation
• Structure determination of normal, mutated and modified ribosomes by high-resolution Cryo-EM techniques
• Revealing mutations in ribosomal components by mass spectrometry
• Design of compounds complementing specific structural motifs of pathogens mainly by antisense technology following biochemical assays for detecting their protein synthesis inhibition
• Construct functional RNA "pockets", similar to the highly conserved ribosomal active site, resembling the prebiotic peptide bond formation machinery

We are striving to reveal ribosomal structural elements that are linked to medical issues and to origin of life. Specifically:


2. Studying mutated ribosomes that are associated with human diseases, anemia & cancer, aiming at removing or reducing tumor size alongside remote sensing of cancerous cells or metastases in body fluids.

3. Extending our studies, which suggest that the ribosomal site of peptide bond formation, a highly conserved pocket-like RNA feature, evolved from a prebiotic synthetic machinery, thus linking the RNA world and modern life.
The musculoskeleton is a tremendously sophisticated and complex biomechanical organ system. It allows vertebrates, including us humans, to display a vast repertoire of movement and postural patterns and, consequently, of behaviors and functions. Our main goal is to understand the biological and biomechanical principles governing musculoskeletal development and function, maintenance and regeneration, as well as aging and pathology. Deciphering the mechanisms underlying these processes will pave the way for development of new therapeutic approaches for treatment of numerous musculoskeletal diseases, including congenital and degenerative, and injuries.
We study how microbial ecosystems are affected by human-made artifacts. We apply the insights learned from these microbes to devise new ways to protect the environment. We take two complementary approaches:

First, we use metagenomic and metabolomic assays, combined with AI, to find new genes that microbes use to evade and metabolize pollutants. Using high throughput screening and automation we validate our findings in the lab.

Second, we study the stability of microbial ecosystems and how it is affected by human-made perturbations, in order to predict and prevent ecosystem collapses. We use simple experiments, sampling of natural microbial populations, and machine learning models.
We are interested in how memory information is coded in the brain, and about what happens, from the neural code’s perspective, to information “stored” in the brain over timescales that range from days to months. We investigate how memory information is coded by large neuronal populations in brain circuits that are important for memory processing. We do that by combining novel in-vivo optical imaging methodologies for longitudinal recordings of neuronal activity in freely behaving rodents, with genetic tools for manipulating specific molecular pathways or spiking activity in specific cell types, and behavioral assays of learning and long-term memory.