

# The Concern Foundation Laboratories at the Lautenberg Center for Immunology and Cancer Research

Progress Report  
December 2025

## **Progress Report 2024–2025 – Executive Summary**

The 2024–2025 year was one of resilience, renewal, and remarkable scientific progress for the Concern Foundation Laboratories at the Lautenberg Center (LRC). Despite the ongoing war and its deep impact on our community, our scientists and students continued to advance discoveries that bridge fundamental immunology with translational and clinical applications.

### **Growth and Infrastructure**

The LRC now hosts over 170 trainees (19 MSc, 58 PhD, 13 postdocs).

Five new principal investigators joined, broadening our expertise and international collaboration:

- Dr. Inbal Benhar – neuroimmunology and retinal injury
- Dr. Miri Adler – computational and systems biology
- Prof. Alex Sigal – viral immunology
- Dr. Shlomo Elias – immune–hematopoietic interactions and cell therapy
- Prof. Carlos Caldas – breast cancer functional genomics (from the University of Cambridge)

Construction of a new 500 m<sup>2</sup> research floor, made possible through the generous support of the Concern Foundation and Michael S Kurtz, is completed.

### **Scientific and Clinical Achievements**

- *Translational Breakthroughs:*

Two LRC-developed drugs progressed to advanced clinical stages — a therapy for refractory AML (Phase II) and NTX1088, an immunotherapy currently in Phase I trials at five sites in Israel and the US (Sheba, Hadassah, City of Hope, MD Anderson, and Ochsner MD Anderson).

- *Mechanistic and Conceptual Advances:*

Research highlights include fibrosis circuit modeling (Adler), fragile gene regulation in cancer (Aqeilan), chronic inflammation and immune suppression (Baniyash), neuroimmune repair (Benhar), immunometabolism (Berger), breast cancer ecosystems (Caldas), epigenomics and liquid biopsy (Drier, Friedman), tumor evolution (Hofree), and immune-checkpoint splicing (Lotem).

- *Precision Oncology:*

Prof. Yinon Ben-Neriah's A51 inhibitor completed Phase I with exceptional responses in AML patients with RUNX1 mutations, now progressing to Phase II clinical trials.

Profs. Carlos Caldas and Alex Sigal launched a seven-year OR-ISF-funded program focused on breast tumor ecosystems, therapy resistance and virology.

### *People and Impact*

Over 20 PhD students completed their degrees this year. Despite national challenges, the LRC continued to grow, combining academic excellence with coexistence and collaboration among Jewish and Arab researchers. The center celebrated numerous achievements, including Prof. Ben-Neriah's 2025 Israel Prize in Medical Research.

### *Looking Ahead*

In 2025, our translational programs will expand, and collaborations will deepen — continuing our mission to advance discoveries that transform the understanding and treatment of cancer, infection, and inflammation.

### **Prof. Ofer Mandelboim**

Head, Concern Foundation Laboratories

Lautenberg Center for Immunology and Cancer Research

Hebrew University–Hadassah Faculty of Medicine

**REGULATORY DESIGN  
PRINCIPLES OF CELL  
CIRCUITS UNDERLYING  
TISSUE HOMEOSTASIS,  
FIBROSIS, AND CANCER**

Dr. Miri Adler



**Background**

Our tissues and organs are complex ecosystems in which diverse cell populations work in concert to perform joint functions. To function properly, cells must coordinate their behavior to regulate their relative proportions, spatial positions, and divide labor in a balanced way. Cells produce numerous signals, including contact-dependent cues and diffusible signals, to communicate and regulate each other's behaviors, forming a complex network of interactions. The central question we pursue is: how do the many cell types in a given tissue use this complex communication to coordinate their behaviors? Despite the explosion of single-cell and spatial data, the regulatory principles that organize this communication remain largely unclear. Our lab develops theoretical and computational frameworks, integrating concepts from dynamical systems, network and circuit theory, spatial ecology, and machine learning, to reveal these design rules for tissue-level processes in health and disease. In fibrosis, a common condition of excessive scarring, we used this approach to identify the conditions under which persistent scars evolve, predict two distinct classes of fibrotic disease ("hot" and "cold" fibrosis), and pinpoint new therapeutic targets. We are extending this approach in fibrotic conditions across lung, liver, heart, and skin and generalizing the theory to the tumor microenvironment (TME). The TME displays striking variability in cell composition, phenotypes, and spatial organization across patients and within tumors. Our models infer the circuit logic and control points that sustain immunosuppressive niches, predict how perturbations propagate through stromal-immune-cancer interactions, and highlight interventions to re-balance TME organization toward immune-permissive, therapy-responsive states. By turning descriptive maps into principles, we aim to provide a framework for rationally reshaping diseased states.

## Highlights of Recent Discoveries (2024–2025)

- **Hot/Cold fibrosis and target validation in cardiac and liver fibrosis:** We experimentally validated our theoretical prediction that fibrotic diseases can be classified into two distinct classes: “hot” and “cold”, distinguished by stromal and immune proportions in heart and liver fibrosis. In the heart, we discovered that myocardial infarction (MI) leads to cold fibrosis, whereas chronic heart failure results in hot fibrosis. Using a circuit-to-target strategy derived from our models, we identified TIMP1 as a key therapeutic target. Antibody-mediated TIMP1 blockade reduced the scar by ~2.5-fold in mice after MI, demonstrating that theory-driven predictions can be used to reprogram fibrotic outcomes.
- **Cross-tissue archetypes and a division-of-labor axis:** We developed a systemic framework to map cellular archetypes, extreme cell states that represent specializations in certain functions, for fibroblasts, macrophages, and endothelial cells across multiple human tissues, defining both universal and tissue-specific archetypes. This revealed a shared axis of tissue organization, a continuum of division-of-labor patterns among these common essential populations, that explains how different organs balance structural, immune, and vascular tasks, and how diseases shift tissues along this axis.
- **Network hyper-motifs for developmental circuit design:** We introduced the concept of network hyper-motifs, higher-order patterns of building-block network motifs (e.g., feed-forward loops, mutual inhibition, feedback loops) whose specific interconnections yield emergent dynamics (multistability, pulses, ordered transitions) that are not achievable by single motifs alone. Applying this framework to embryonic gene-regulatory circuits, we uncovered key design principles that produce robust timing and cell-fate decisions, offering a principled approach to disentangle and interpret complex developmental programs.

## Translational Impact

- **Fibrosis:** Using our theory-guided circuit framework integrated with single-cell/spatial data, we pinpointed TIMP1 as a therapeutic target in cardiac fibrosis. We will now apply the same pipeline across lung, liver, skin, and other organs to produce an organ-specific table of predicted targets, prioritized by circuit role and paired with candidate biomarkers to enable mechanism-matched therapies.
- **Cancer:** We are expanding our circuit-based methodology to cancer, where preliminary results reveal control points in stromal-immune-tumor interactions that shape TME composition and spatial organization. Our models predict interventions that shift the TME toward immune-permissive, therapy-responsive states. This yields testable strategies and rules based on TME circuit states rather than single markers. The goal is a predict-and-perturb pipeline that recommends patient-specific targets to reshape the TME and improve treatment response.

## Training & Leadership

I opened my lab in December 2023. I am currently mentoring 4 MSc students, 2 post-doctoral fellows, and one research associate.

## Looking Ahead

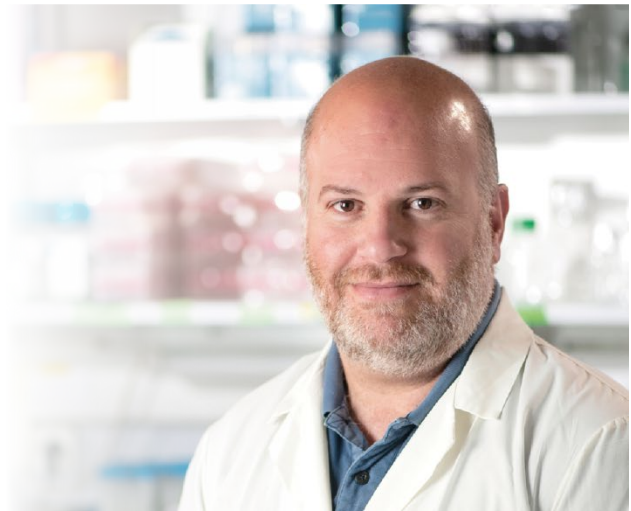
- Expand the fibrosis theoretical framework to consider feedback from the scar, interactions with additional cell types (e.g. damaged cells, endothelial cells, other immune cells, etc.), and spatial effects.
- Classify hot/cold fibrosis states across diverse organs including liver, lung, skin, and kidney, and pinpoint key therapeutic targets in each organ based on our theory.
- Develop theoretical models for multicellular circuits that represent interactions among cells in the TME and derive conclusions regarding their design principles and key parameters that control cell composition and spatial organization.
- Test our modeling predictions using single-cell and spatial data in cancers such as pancreatic ductal adenocarcinoma (PDAC) and triple-negative breast cancer (TNBC).

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# MOLECULAR BASIS OF CARCINOGENESIS AND TUMOR SUPPRESSION IS AND TUMOR SUPPRESSION



Prof. Rami Aqeilan

## Background

Our research focuses on fragile genes, including WWOX, that are prone to alteration and play a central role in cancer development and other diseases such as epilepsy and multiple sclerosis. We have developed advanced models and next-generation sequencing approaches to map DNA double-strand breaks, revealing transcription-associated mutagenesis as a key driver of early tumorigenesis. Our goal is to understand how these genes regulate genome stability and disease and to translate this knowledge into new targeted therapies.

## Highlights of Recent Discoveries (2024–2025)

- Identified the interplay between transcriptional stress, fragile sites, and genomic instability, showing how hypertranscribed cancer driver genes accumulate double-strand breaks (iScience 2024).
- Uncovered the relationship between WWOX and BRCA1 in mammary tumorigenesis and DNA repair pathway choice (Cell Death Discovery 2024).
- Established iPSC models from CTNNB1 mutation carriers to study neurodevelopmental disorders (Stem Cell Research 2025).
- Developed and disseminated sBLISS methodology for high-resolution mapping of physiological double-strand breaks (STAR Protocols 2024; Methods Mol Biol 2025).
- Linked c-MYC dysregulation to early osteosarcomagenesis from mesenchymal stem cells (Cell Death & Disease 2024).
- Explored the role of T cell DNA damage in immunity (Trends Immunology 2025).

## Translational Impact

Our findings are being translated into therapeutic avenues, with ongoing efforts to develop WWOX-based gene therapies for pancreatic cancer and neurodevelopmental disorders. These advances lay the groundwork for collaborations with biotech partners and future clinical applications.

## Training & Leadership

Between 2022–2025, the lab successfully graduated five PhD students (Housam Husaine, Rania Akkawi, Daniel Steinberg, Sara Oster, and Tirza Bidani) and five MSc students (Francis Mitri, Osama Hidmi, Kian Maroun, Dania Abdellatif, and Bara'a Abu-Diab). This highlights our strong commitment to mentoring the next generation of scientists.

## Looking Ahead

We will continue to explore the biology of fragile sites and transcription stress, with particular focus on their contribution to cancer and neurological disorders. Future directions include developing therapeutic strategies targeting WWOX loss, expanding iPSC-based disease models, and integrating cutting-edge genomic technologies to map genome instability.

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# CHRONIC INFLAMMATION- ASSOCIATED COMPLICATIONS: UNDERLYING MECHANISMS AND CLINICAL IMPLICATIONS

Prof. Michal Baniyash



## Background

Chronic inflammation is often referred to as the “silent killer” because it represents a persistent, low-grade process that gradually damages healthy cells and tissues, frequently without noticeable symptoms until significant harm has occurred. This systemic and sustained inflammatory state transforms a normal protective response into a pathogenic one, leading to numerous chronic diseases and complications, including cardiovascular disease, type 2 diabetes, cancer, Alzheimer’s disease, inflammatory bowel disease (IBD), immune suppression, and bone loss.

Our laboratory has uncovered several inflammation-associated complications and their underlying mechanisms, identifying chronic inflammation as a key driving force. These discoveries are now guiding translational efforts aimed at developing new diagnostic and therapeutic approaches.

## Highlights of Recent Discoveries (2024–2025)

- Inflammatory bone loss: Identified the underlying mechanisms driving inflammatory bone loss, a common complication in IBD, cancer, diabetes and additional chronic diseases, where no predictive biomarkers currently exist. (Preclinical discovery)
- IBD-colorectal cancer link: Uncovered a novel mechanism explaining why patients with IBD are at increased risk of developing colorectal cancer. We identified a unique crosstalk between bacteria invading the inflamed intestinal tissue and immune cells, which exacerbates inflammation and promotes tumor development. Key molecular players were identified. (Preclinical discovery)
- Chronic inflammation-induced immune suppression: Discovered how chronic inflammation suppresses immune responses, creating a major barrier to successful immunotherapies. Developed a novel tool that protects immune cells from inflammation-induced suppression. (Preclinical and translational discovery)

## Translational Impact

- Bone loss biomarkers: Implementing identified biomarkers for chronic inflammation-induced bone loss in clinical studies, in collaboration with the Orthopedic Department, Hadassah Hospital.
- IBD-CRC risk validation: Validating preclinical observations by analyzing biopsies from IBD and colorectal cancer patients in collaboration with the Gastroenterology Department, Hadassah Hospital.
- Therapeutic immune protection: Testing our immune cell-protective tool in human T and NK cells to optimize transduction, specificity, and efficacy under immunosuppressive conditions.

## Training & Leadership

- Graduated 2 PhD and 2 MSc students (2023–2024).

## Looking Ahead

- Establishing clinical proof-of-concept for inflammatory bone loss biomarkers and developing preventive treatment strategies.
- Advancing a newly discovered small molecule that blocks inflammatory activation of immune cells following bacteria-immune cell interactions; a potential therapeutic approach to prevent cancer development.
- Optimizing the immune-protective tool for T and NK cells to enable future clinical applications in inflammation-associated diseases and cancer.

## References (2022-2025)

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## NEUROIMMUNE INTERACTIONS UNDERLYING TISSUE INJURY AND REPAIR

Dr. Inbal Benhar



### Background

Our lab studies interactions between the nervous system and the immune system, mostly in the context of tissue injury. One main avenue of our research is understanding how we can harness immune responses to protect neurons from degeneration. We focus on the retina, which is the source and target of many blinding diseases.

As the body's control center, the central nervous system (CNS), which includes the brain, spinal cord and retina, is crucial for our survival and ability to function. Upon neuronal injury or in disease, many neurons are lost, and those that survive are generally unable to properly reconnect to their neighboring neurons. Consequently, such conditions may lead to devastating outcomes, including blindness, motor deficits or cognitive impairment. As such, major research efforts are aimed at finding ways to protect neurons or urge them to regenerate once they are damaged, in the hope of preserving or restoring function.

We posit that identifying barriers to neuronal survival and repair requires better understanding of events that occur in the injured tissue as a whole. Using mouse models of retinal injury, we leverage experimental and computational methods to analyze changes that occur in the tissue after injury across space and time. Collectively, we aim to understand how the signals that neurons receive from their non-neuronal neighboring cells impact their survival, hoping to uncover new ways to protect neurons.

### Highlights of Recent Discoveries

I joined the Lautenberg Center in September 2024 and received my newly renovated lab space in early 2025. This past year has mostly been dedicated to setting up the lab, establishing protocols, and recruiting the first team members. We have recently received preliminary results from our first experiments in a project that aims to elucidate the roles of the interferon response in retinal injury.

## Translational Impact

- Our findings of cellular and molecular changes that occur in the mouse retina after injury recapitulate findings in humans. This points to the potential of our research to ultimately inform the design of therapeutic interventions for glaucoma and other blinding diseases.
- I have recently forged a collaboration with clinicians at the Hadassah Ophthalmology Department to gain access to liquid biopsy samples from patients who undergo retinal surgery. We will analyze these samples through advanced proteomic and genomic methods to find biomarkers and predictors of visual outcome.

## Training & Leadership

- Noa Karp (PhD student); 2025-present.
- Kamar Basheer (MSc student); 2025-present
- Avital Abramtcik (MSc student); 2025-present

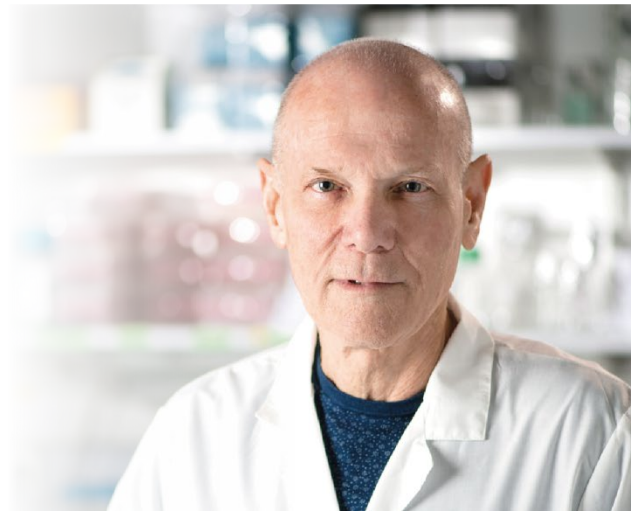
## Looking Ahead

- Explore the roles of the type-I interferon response in retinal neuroimmunology (immune cell recruitment, neuronal survival and microglia renewal).
- Establish the roles of a distinct subset of macrophages (termed Gpnmb macrophages) on survival and regeneration of retinal neurons after injury.
- We are currently introducing new methodology to the lab, including state-of-the-art spatial biology methods, which offer in-depth, high-throughput profiling of single cells in their native tissue context.

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- \*Equal contribution #Corresponding author

## TARGETING CANCER CELL VULNERABILITIES: BASIC AND TRANSLATIONAL ADVANCES.



Prof. Yinon Ben-Neriah

### Background

We developed a new type of kinase inhibitor as a potential anti-cancer drug. Whereas most other inhibitors target mutated oncoproteins, this new one targets as a single molecule a collection of cancer cell vulnerabilities - apoptosis inducers and blockers. Unlike most modern cancer drugs, our newly developed drug works like a cluster bomb that attacks simultaneously many leukemic proteins such as CKI□, CDK7 and CDK9. Consequently, we see robust activation of p53, with transcriptional shut-down of supper-enhancer (SE)-driven cancer drivers, such as Myc, Mdm2 and Mcl1, making it difficult for the leukemia cell to evade the therapy. Based on our preclinical studies at the Lautenberg Center, our drug moved to clinical trials and completed successfully Phase I at three major cancer centers in the US (MSKCC, MDA and City of Hope).

### Highlights of Recent Discoveries

- **Understanding clonal evolution towards the development of AML.** We have prepared several disease models, including specialized cell lines and mouse strains, displaying clonal evolution, particularly from clonal hematopoiesis (CH) to MDS and AML. During clonal evolution, prevailing hematopoietic clones accumulate mutations and epigenetic alterations that will increase vulnerability to cell viability offences and to transcriptional dysregulation, two major means by which A51 compromises transformed blood cells, preferentially over normal blood cells.

- **Resolving the significance of RUNX1 mutations in the therapeutic response of A51.** Runx1 mutations are thought to facilitate the progression of CH to malignancies. In addition, RUNX1 mutation appear to sensitize patients to A51 therapy. We found that A51 treatment abolish the RUNX2 SE in human and suppress RUNX2 transcription AML cells. RUNX1 and RUNX2 seem to play certain redundant roles, often targeting a similar gene set. Using the CRISPR-Cas9 system, we've created several RUNX1 KO AML cell lines and showed that RUNX1 KO cells are more vulnerable to A51 treatment than WT non-mutated isogenic cells, indicated by induction of apoptosis. These data may explain the outcome of our phase 1 clinical trial of A51 - why patients with Runx1 mutations responded better to A51 treatment.
- **Study the basis for the emergence of A51 resistance in AML therapy.** To investigate the mechanism of gaining resistance to A51 treatment and study the immediate adaptive response creating drug tolerance, we performed scRNA-sequencing of THP1 AML cells treated for 24hr with A51 followed by 3- and 10-days recovery. Our results show that cells respond and change its transcriptional program at Day 3 after treatment, however by day 10 this response is reversed, and cell transcriptional program becomes like that of untreated cells. GSEA analysis revealed that biological processes related to mRNA processing, splicing, and translation initiation are highly enriched by day 3 after A51 treatment, indicating the involvement of RNA metabolism and gene expression regulation in the immediate adaptive response.

### Translational Impact

Phase I study has successfully been concluded, documenting an unprecedented therapeutic effects in R/R AML patients who carry the RUNX1 mutation, frequently observed R/R AML and phase II combination study has begun. In addition, following successful preclinical trials in solid tumors we have also started in the Dana Farber Cancer Institute in Boston a clinical trial in liposarcoma, a type of tumor that has no effective medical therapy.

### Training & Leadership

- Mentored 3 PhD students who graduated (2024–2022).

### Recent Awards

- Elected Member of the Israeli Academy of Sciences and Humanities (2021)
- Elected Fellow: European Academy of Cancer Sciences (2022)
- Israel Prize for Medical Research (2025)

## Looking Ahead

### 1. Targeting cell-intrinsic transcriptional addiction (TA)-dependencies of A51-responsive cancer types

- a) Identify TA dependencies of cancer cells to A51 therapy by pharmacogenetic studies.
- b) Evaluate a potential synergy between A51 and RNA methylation inhibitors in AML and liposarcoma.

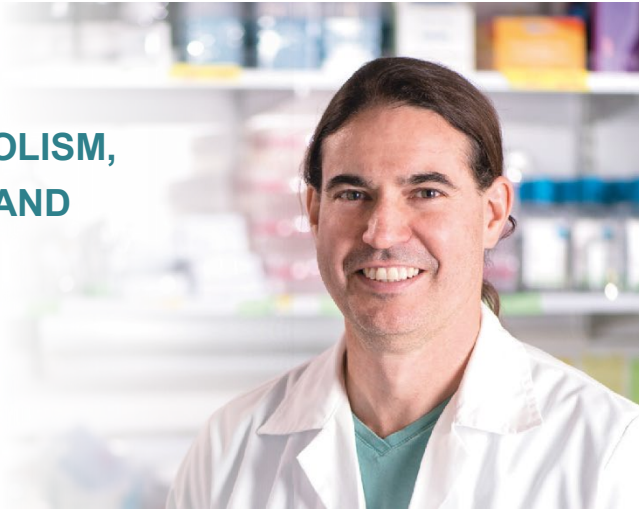
### 2. Targeting cell extrinsic factors to enhance the therapeutic effect of A51

- a) Evaluate if TA treatment-induced inflammatory cell killing is harnessed to recruit T cells for combating A51-responsive cancer
- b) Determine how T-cell immunity enhances A51 therapy.

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# METABOLIC STRATEGIES TO ENHANCE T-CELL FUNCTION: ADVANCES IN IMMUNOMETABOLISM, THERAPEUTIC ENGINEERING, AND IMMUNE DYSREGULATION



Prof. Michael Berger

## Background

Our research focuses on understanding how T cells, essential components of the immune system, use energy to fight infections and cancer. We aim to identify the energy requirements that influence their response to threats and explore how this knowledge can guide the development of new therapies. Additionally, we investigate mechanisms behind immune dysregulation in primary immunodeficiencies to uncover novel treatment options.

## Highlights of Recent Discoveries (2024–2025)

- **Boosting T-cell Power by Targeting Ant2:** Removing the protein Ant2 enables T cells to enhance their energy metabolism and improve their tumor-fighting ability, which may lead to improved cancer therapies.
- **Energy Deficiency in T-cells with NDUFS4 Mutation:** T cells carrying a mutation linked to Leigh syndrome exhibit impaired energy production and function, pointing to the need to address energy metabolism deficits to restore immune function.
- **Metabolic Enabling of T cells to Overcome Tumor Glucose Deprivation:** We engineered T cells to metabolize trehalose, an alternative sugar, enabling their survival and function in glucose-deprived tumor environments, highlighting a promising strategy to improve adoptive T cell therapy.
- **Immune Dysregulation in Baraitser-Winter Syndrome Type 1:**  $\beta$ -actin deficiency in T cells leads to immune dysregulation characterized by impaired activation and regulatory T cell loss; IL-2 and dupilumab treatments improved immune function and clinical outcomes, showing strong therapeutic potential.

## Training & Leadership

- Graduated three PhD students (2024–2025).

## Looking Ahead

- Optimize trehalose delivery to increase tumor bioavailability and bolster trehalose-metabolizing T cells to overcome metabolic barriers in melanoma.
- Advance understanding of mitochondrial metabolism in T cells to develop refined immunometabolic approaches that enhance T cell resilience and function in challenging tumor microenvironments.

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## BREAST CANCER TUMOR ECOSYSTEMS LABORATORY.



Prof. Carlos Caldas

### Background

Carlos Caldas graduated in Medicine from the University of Lisbon in Portugal and has been Professor of Cancer Medicine at the University of Cambridge in the UK since 2002 [where, since July 2025, he still holds a part-time position]. He was a Founding Senior Group Leader of the CRUK Cambridge Institute and the Founding Director of the Breast Cancer Program at the Cambridge Cancer Centre. He moved to the Lautenberg Center at the Faculty of Medicine of the Hebrew University of Jerusalem in April 2025.

He is a Fellow of the Academy of Medical Sciences, Fellow of the European Academy of Cancer Sciences, Fellow of the American College of Physicians, Fellow of the Royal College of Physicians, Fellow of the Royal College of Pathologists, and EMBO Member.

He has been distinguished by Web of Science as a Highly Cited Researcher yearly since 2018. He received the 2016 ESMO Hamilton Fairley Award, the 2021 European Society of Human Genetics Award, the 2021 Susan G. Komen Brinker Award for Scientific Distinction in Basic Science, and the ARC Foundation 51st Leopold Griffuel Award in Translational Cancer Research in 2023.

He has published over 450 manuscripts, including in Nature, New England Journal of Medicine, Nature Genetics, Nature Medicine, Nature Cancer, Nature Metabolism, Nature Immunology, Nature Communications, Cell, Cancer Cell, Cell Reports, and Science Translational Medicine.

His research focus is the functional genomics of breast cancer and its biological and clinical implications. His laboratory in Cambridge redefined the molecular taxonomy of breast cancer and showed that it determines the clinical trajectories of patients. He led the studies that established ctDNA as a monitoring biomarker and as a liquid biopsy. His laboratory pioneered and developed the use of patient-derived tumor explants as models of breast cancer. He is now using breast cancer xenograft models to study the regulation of cell fate and cell state in cancer.

## Highlights of Recent Discoveries (2022–2025)

- In a recent landmark paper using multi-omics and machine learning, he showed the biology of breast tumor ecosystems predicts response to therapy. [Nature 2022]
- Reported how applying a novel statistical model to serial ctDNA measurements from shallow whole genome sequencing in metastatic breast cancer patients produces a rapid and inexpensive predictive assessment of treatment response and progression-free survival. [Molecular Oncology 2025]
- Showed both B cell and T cell responses seem to coevolve with the metastatic cancer genomes and B cell clones associated with metastatic immunosurveillance and temporal persistence were more expanded and distinct from site-specific clones. Crucially B cell clonal immunosurveillance and temporal persistence are predictable from the clonal structure laying a foundation for prioritizing antibody sequences for therapeutic targeting in cancer. [Nature Immunology 2024]
- Reported how using an expressed lentiviral based cellular barcoding coupled with single-cell RNA sequencing one can track single-cell-derived cancer clones from patient-derived tumor xenograft models of human breast cancer. [Cell Reports 2025]

## Translational Impact

Phase I study has successfully been concluded, documenting an unprecedented therapeutic effects in R/R AML patients who carry the RUNX1 mutation, frequently observed R/R AML and phase II combination study has begun. In addition, following successful preclinical trials in solid tumors we have also started in the Dana Farber Cancer Institute in Boston a clinical trial in liposarcoma, a type of tumor that has no effective medical therapy.

## Training & Leadership

- Graduated 5 PhD students and two Masters.(2025–2022)

## Looking Ahead

Carlos Caldas has secured a prestigious OR-ISF grant which will fund an ambitious research program for the next 7 years:

Breast cancer is a constellation of 11 genomic driver-based subtypes with distinctive tumor ecosystems. The diversity of these tumor ecosystems represents a formidable challenge to study the biology of the disease and to translated into clinical applications.

The **OVERALL AIM** of the research program of my laboratory at the Lautenberg Center is to deeply phenotype breast tumor ecosystems at baseline and dynamically after perturbations to gain mechanistic insights into tumor dormancy, tumor recurrence, tumor metastasis, and tumor therapy resistance.

We have shown that patient-derived tumor xenografts (PDXs) are both genocopies and phenocopies of the corresponding matched human breast cancer. The working hypothesis is that mouse cell recruitment to the tumor microenvironment (TME) of PDXs is regulated by human malignant cell-intrinsic factors and the goal of the research program is to unravel the

mechanisms that enable human cancer cells to instruct the mouse TME to recreate the histological appearance of the original tumor. In PDXs individual malignant cell progeny can be tracked in space and time (using genetic barcoding) and tumor cellular communities can be comprehensively and longitudinally assayed at single cell and spatially resolved levels. The datasets that will be generated are highly complex and multidimensional and will require advanced algorithms and machine learning methods for their analysis. Importantly the scope of perturbations possible in the murine system will allow studying the dynamics of tumor ecosystem establishment and maintenance in vivo to unravel key processes such as metastasis, dormancy and therapy response.

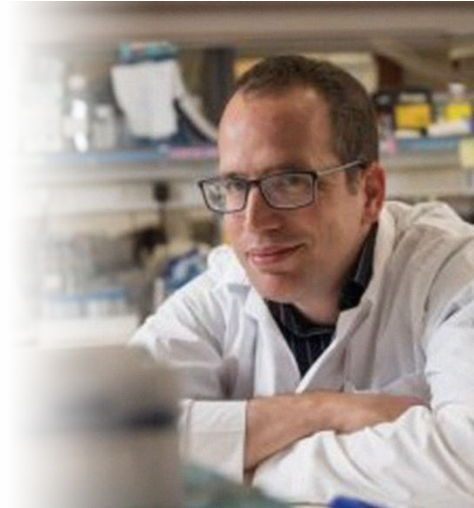
We plan to continually correlate the findings with clinical scenarios with both forward and reverse translation.

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## THE DRIER LAB FOR DISEASE EPIGENOMICS

Dr. Yotam Drier



### Background

In recent years extensive efforts revealed how changes in the DNA sequence of genes drive diseases and especially cancer. However, we still know very little about the function of epigenetic alterations- chemical alterations on top of the DNA that alter its function without changing its sequence, such as DNA methylation. We aim to systematically uncover both the causes of epigenetic dysregulation in disease, as well as their impact and role in disease pathogenesis. In particular, we are especially interested in epigenetic alterations of regulatory regions of the DNA – regions especially that do not code for genes, but instead regulate gene expression, splicing, DNA replication, and intra-chromosomal interactions. To systematically approach these questions, we rely on large scale publicly available data and on in-house epigenomic profiling of patient tissues, and develop computational and statistical approaches to utilize these data to predict functional, recurrent epigenetic alterations and its implication on gene expression and contribution to the disease. We also make these tools available to the broad research community.

### Highlights of Recent Discoveries (2024–2025)

- We uncovered the landscape of distal cis-regulatory elements (enhancers) of lung neuroendocrine tumors, revealing three regulatory subtypes. We characterized each subtype according to their regulatory signals- Proneural lung NETs, HNF+ lung NETs, and luminal-like lung NETs. Our analysis uncovered that the HNF+ subtype depends on FGFR signaling, and we were indeed able to show that small molecule inhibitors help stop tumor growth in mouse xenografts with HNF+ lung NET tumors (Davis E et al., PNAS 2024).
- Our efforts to improve computational tools to predict functional alterations in disease include the development of SiPSiC (Single Pathway analysis in Single Cells), a tool to accurately estimate pathway activity in single cells. We applied our tool to data of COVID-19 patients and cancer patients and demonstrated its accuracy and ability to identify functional and clinically relevant pathway alterations (Davis D, Wizel A and Drier Y, Genome Research 2024).
- We uncovered that SMCHD1 directly regulates alternative splicing, and SMCHD1 loss leads to aberrant splicing of multiple genes, including of DNMT3B. We demonstrated that

this shift in splicing of DNMT3B leads to hypomethylation of a macrosatellite repeat upstream of DUX4, causing aberrant overexpression of DUX4. This explains how mutations in SMCHD1 cause facioscapulohumeral muscular dystrophy (Engal E et al. Science Advances 2024).

### Translational Impact

- We are preparing to initiate a clinical trial with Hadassah Medical Center's Neuroendocrine Tumor Unit to test FGFR inhibitors in HNF+ lung NETs.
- SiPSiC uncovered several potentially targetable pathways, and we follow up on these results to further validate translational potential.
- We are exploring the potential of targeting SMCHD1 splicing by antisense oligonucleotides for FSHD and facioscapulohumeral muscular dystrophy and colorectal cancer.

### Training & Leadership

- Supervising 9 PhD students and 3 MSc students.

### Looking Ahead

We are working to multiple fronts to systematically the role of epigenetic alterations and heterogeneity in disease: We study the intratumor heterogeneity of HPV-related multiphenotypic sinonasal carcinoma, the interaction between adenoid cystic carcinoma tumor cells and their immune microenvironment, the impact of DNMT3B missplicing on DNA methylation and clinical course of colorectal cancer patients and beyond, the role of germline DNA methylation heterogeneity in effecting autoimmune disease risk, the epigenomic factors governing DNA breaks in breast cancer, and more.

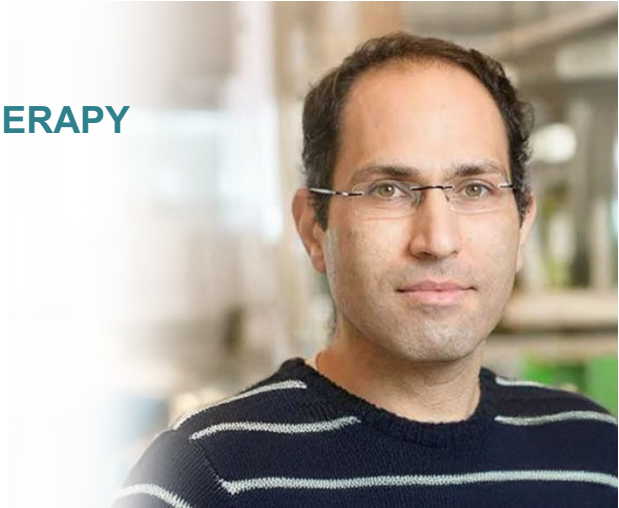
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2. Davis D, Wizel A, **Drier Y**: Accurate estimation of pathway activity in single cells for clustering and differential analysis. Genome Research. 2024
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## IMMUNE – HEMATOPOIETIC INTERACTIONS AND IMMUNOTHERAPY

Dr. Shlomo Elias



### Background

Our lab studies how immune cells in the bone marrow shape blood formation, focusing on regulatory T cells (Tregs) and natural killer (NK) cells. While immune cells are known to influence how new blood cells develop, many of these interactions remain poorly understood. By mapping these networks, we aim to uncover new ways to harness the immune system for therapy.

We also develop Treg- and NK cell-based immunotherapies. Tregs, which act as immune “brakes,” can prevent graft-versus-host disease (GVHD) after bone marrow transplants and may treat autoimmune disorders, but current Treg therapies are hard to produce. We work to improve their stability and clinical potential. NK cells, in contrast, are potent against cancer and infections and unlike traditional T cell therapies do not trigger life-threatening complications such as cytokine release syndrome (CRS) or GVHD, making them especially promising for next-generation therapies.

My background training includes both clinical and scientific education. I have clinical experience in bone marrow transplantation and immunotherapy, with additional basic research experience in immunology, and this combined expertise will assist me in achieving the goals of the lab.

### Highlights of Recent Discoveries (2024–2025)

Development of a novel cellular therapy based on an NK cell line (in collaboration with Prof. Mandelboim) (manuscript in preparation)

### Translational Impact

Not yet applied clinically.

## Training & Leadership

- Currently mentoring 2 PhD students and 2 MSc students.
- I plan to establish a new Immunotherapy course in the Faculty of Medicine for MSc and PhD students

## Looking Ahead

- Working on novel therapies based on Tregs for treating autoimmune diseases and GVHD.
- Working on a novel treatment against NK cell lymphoma.
- Studying the function of regulatory T cells in the bone marrow with a unique genetic mouse model.

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## EPIGENOMICS LIQUID BIOPSY: TRANSFORMING DISEASE DIAGNOSIS THROUGH CELL-FREE CHROMATIN



Prof. Nir Freidman

### Background

Cell-free DNA in blood is packaged as fragments of chromatin. Our lab developed technology to read chromatin modifications retained on these fragments, allowing us to determine both the role of DNA in the cell (e.g., active gene) and its sequence (which gene it is). From a single blood sample, we can report on the activity status of all genes in the genome in the cells that died and contributed to the cell-free DNA. This information reveals what type of cells are dying (due to cell-type specific gene activity) and their state (e.g., hypoxia or inflammation). This technology has opened a large range of medical applications from diagnosis of disease, monitoring disease progress, and predicting treatment efficacy, while providing new insights into basic questions about human biology.

### Highlights of Recent Discoveries (2024–2025)

- **COVID-19 epigenetic profiling:** Epigenetic liquid biopsies revealed elevated vascular endothelial cell turnover and erythropoiesis in asymptomatic COVID-19 patients. Monocyte/macrophage cfDNA, as well as lung epithelial and endothelial cfDNA, predicted clinical deterioration and duration of hospitalization.
- **Urinary cell-free chromatin:** Extended cfChIP-seq technology to human urine, demonstrating that cell-free nucleosomes in urine preserve multiple histone post-translational modifications. Identified primary tissues contributing to urinary cfDNA in healthy individuals and detected tumor-derived cell-free DNA in bladder cancer patients.
- **Multiple myeloma diagnostics:** Developed cell-free chromatin-based methods for diagnosis and prediction of precursor states in multiple myeloma, enabling improved patient stratification.
- **Computational advances:** Developed VarNMF, a non-negative probabilistic factorization method with source variation, improving analysis of complex epigenomic data.

## Translational Impact

- **Small cell lung cancer:** Demonstrated that liquid biopsy enables tracking disease extent and progress, and critically, differentiation between molecular sub-types that should be treated differently. Such subtyping is currently not performed in clinics due to the inaccessibility of molecular data from biopsies.
- **Non-viral liver diseases:** Established a large program collecting matched blood samples from patients undergoing liver biopsies. Results demonstrate accurate distinction between autoimmune hepatitis and non-alcoholic steatohepatitis (NASH) and other types of liver damage.
- **Immune activity monitoring:** Developed non-invasive approaches to observe immune cell activity at disease sites through cell-free DNA, addressing questions such as: When does immune-checkpoint therapy successfully activate immune attack? What dosage of immune-suppression is required for stabilizing transplanted organs?

## Training & Leadership

- Graduated 4 MSc students (2024-2025): Ronel Yaron, Noa Omer Vilks, Nadav Hermoni, Ella Frankel
- Currently training 6 PhD students and 2 MSc students in computational biology, epigenomics, and translational research

## Looking Ahead

- **Pregnancy tracking initiative:** Initiated a comprehensive longitudinal study collecting dense plasma samples from women with normal and high-risk pregnancies to investigate molecular trajectories of the placenta and mother during pregnancy.
- **Epigenomic atlas:** Embarked on a comprehensive project to construct an epigenomic atlas of relevant cell types and tissues, providing unprecedented insight into immune system dynamics through liquid biopsy.

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## TUMOR EVOLUTION THROUGH THE LENS OF MUTATIONS AND GENE-EXPRESSION STATES

Dr. Matan Hofree



### Background

In much the same way that every individual is genetically unique, so is each cancer tumor. Each is tumor shaped by unique genetic alterations and dynamic cellular interactions with the host patient. Our lab investigates this complexity by bridging DNA—the static genetic blueprint—and RNA—the dynamic record of cellular activity. Using advanced sequencing technologies and computational modeling, we study how genetic mutations and gene-expression programs influence tumor growth, immune evasion, and interactions within the microenvironment. By integrating genomics and transcriptomics, we aim to uncover principles of cancer evolution and advance precision oncology, tailoring treatments to the molecular profiles of individual patients.

### Highlights of Recent Discoveries (2024–2025)

- The lab was involved in several studies using scRNAseq to characterize senesce
- We show that spatial organization of immunity hubs in lung tumors, distinct from known tertiary lymphoid structures (and previously identified in CRC) is predictive of favorable outcomes with PD-1 immunotherapy.

### Training & Leadership

- Graduated: 1 MS student.
- 1 direct to PhD (Abish-Frenkel) student started in the lab
- 2 New MS students are set to start in October.

## Looking Ahead

- We are expanding our efforts into understanding the role of the microbiome in the tumor-microenvironment.
- We are developing a conceptually novel approach for the analysis of gene expression in cancer in a way that distinguishes between copy number-driven expression and expression changes due to other factors.
- We are developing a computational tool for cleaning ambient contamination in single-cell RNAseq studies.
- We are examining the mucosal barrier remodeling of the gut due to exposure with an enteric pathogen.

## References (2024-2025)

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# REGULATORY SPLICING OF IMMUNE CHECKPOINTS AND NEW APPROACHES TO IMMUNOTHERAPY

Prof. Michal Lotem



## Background

Alternative splicing is a post-transcriptional process that results in multiple proteins (isoforms) produced from the same gene. This mechanism plays a vital role in the normal function of human cells, and its dysregulation can lead to many severe diseases. Our lab elucidates and exploits this regulatory mechanism in immune cells to develop novel cancer immunotherapies.

## Highlights of Recent Discoveries (2024–2025)

- We demonstrated that T cell splicing dynamics are linked to patient responses to melanoma immunotherapy, highlighting splicing regulation as a promising avenue for novel immune-based treatments.
- We developed SpliceSeek, a CRISPR-based pooled screening platform that perturbs splice sites to redirect isoform usage and demonstrated that splicing manipulation of specific genes improved antitumor immune response, underscoring their potential as novel antitumor treatments.
- We showed that entrapment of splice-switching antisense oligonucleotides (SSOs) in lipid nanoparticles can improve their delivery and efficacy of immunotherapy.
- We generated several tri-specific molecules that simultaneously target SLAMF6, anti CD3, and selected immune checkpoints or tumor associated antigens for selective activation of tumor-specific lymphocytes while overcoming immune checkpoint-mediated suppression

## Translational impact

- The development of novel cancer immunotherapies based on the regulation of splicing isoforms.
- Anti SLAMF6-based tri-specific molecules show enhanced T-cell-mediated tumor cell killing.
- Ongoing clinical trials:

- Anti-NY-ESO-1 TCR-Gene Engineered Lymphocytes Given by Infusion to Patients With NY-ESO-1-Expressing Metastatic Cancers (NCT05296564).
- Modified Melanoma Vaccine for High Risk or Low Residual Disease Patients (NCT01861938).

## Training & Leadership

- One MD-PhD and one MSc student will graduate by the end of 2025, and six PhD and MD-PhD students are ongoing.

## Looking ahead

Establish the in vivo functionality and antitumor efficacy of tri-specific molecules in immune-deficient mouse models.

Deepen our research of top hit genes discovered using our SpliceSeek platform towards the development of new immunotherapy approaches.

Explore LNP encapsulation of immune-checkpoint targeting SSOs and TCR-mRNA to enhance treatment efficacy.

## Publications (2024 – 2025)

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## HARNESSING NK CELLS AGAINST CANCER AND INFECTION: SCIENTIFIC AND TRANSLATIONAL ADVANCES



Prof. Ofer Mandelboim

### Background

Natural Killer (NK) cells are powerful immune defenders, eliminating cancer, viruses, fungi, and bacteria. Our lab uncovered how tumors and pathogens evade NK cells and developed strategies to restore immune function. These discoveries are now moving into clinical applications, transforming basic immunology into new therapies for cancer and infection.

### Highlights of Recent Discoveries (2024–2025)

- Pathogen-informed immunotherapy:
- Fusobacterium proteins suppress NK cells — inspiring novel CAR-NK and antibody strategies.
- Candida and Fusobacterium Nucleatum studies revealed new NK checkpoints as drug targets.
- Pregnancy-trained NK cells: Found to protect pregnancies against harmful infections, suggesting unique approaches for maternal-fetal medicine.
- Viral evasion: HCMV tactics that disable host immunity, guiding antiviral immunotherapies.
- Next-generation NK therapies: Enhanced YTS NK cells (via lncRNA NeST) and a first-in-class NKp46 engager (CYT-303) showed strong preclinical anti-tumor activity.

## Translational Impact

- Companies established: Discoveries from our lab led to the creation of NectinTx (clinical-stage immuno-oncology) and HOPEC Pharma (developing modified -E.Coli targeted immunotherapies for bladder cancer).
- Clinical trials ongoing: Five NectinTx products are in development, including an anti-PVR antibody in Phase I trials in the US and Israel, with encouraging early results. HOPEC Pharma has just initiated its first Phase I clinical trial at Hadassah Medical Center.

## Training & Leadership

- Graduated 4 PhD students (2022–2024).

## Looking Ahead

- Explore pregnancy-trained NK memory as a blueprint for long-term protection.
- Deliver next-generation NK cell therapies to the clinic, reinforcing our role at the cutting edge of immunology and translational medicine.
- Exploring novel immune evasion mechanisms employed by fungi, bacteria, viruses, and tumors, with the goal of converting these insights into next-generation immunotherapies.

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## KEY DRIVERS AND NOVEL THERAPEUTIC TARGETS IN PANCREATIC CANCER



Prof. Oren Parnas

### Background

Pancreatic cancer is a deadly disease with a five-year survival of only 12%. We investigate the early stages of pancreatic cancer development to better understand this devastating disease, identify new markers for early detection, and uncover key drivers of tumor formation and metastasis.

### Highlights of Recent Discoveries (2024–2025)

We have profiled pre-malignant lesions using single-cell RNA sequencing and spatial transcriptomics. These lesions contain precursor cells that may progress to malignancy, making it crucial to determine under what conditions this transformation occurs and to identify potential risk factors. Our detailed spatial transcriptomic analysis revealed a potential mechanism underlying the formation of pre-malignant lesions. In addition, we found that epithelial cells, at the very early stage of transformation, interact with immune cells to prime an immunosuppressive microenvironment. We are now exploring the formation of premalignant pancreatic lesions in human samples following different stresses.

In our second project, we leveraged the large-scale genomic data we have collected to identify 82 genes expressed in both pre-malignant states and tumors in mouse and human. To evaluate the functional impact of these genes on tumor development, we conducted pooled CRISPR screens in vitro and in vivo. From this, we identified nine genes that are essential for tumor development and two that act as tumor suppressors. We are currently investigating the mechanisms and roles of each validated target. Furthermore, we performed a high-order Perturb-seq experiment to test whether combinations of these nine gene perturbations could further inhibit tumor progression. Notably, we found that co-targeting a gene involved in connecting the cell membrane and cytoskeleton, along with Kras had a stronger inhibitory effect than targeting either gene alone. Importantly, drugs exist for both targets, and their combination showed promising results in restricting cell growth in vitro. Our next step is to evaluate this treatment in vivo.

## Translational Impact

We have identified combinations of targets in immune cells and malignant cells that can enhance immune response and restrict tumor development. We are currently testing it in human samples, and we believe that this effort can lead to new treatments.

## Training & Leadership

In the last two years, three students graduated and four master's students finish their studies.

## Looking Ahead

We believe that the systematic approach will facilitate the discovery of effective combination therapies—both chemotherapeutic and immunotherapeutic—that can significantly improve current treatments by restricting the growth and spread of pancreatic tumors.

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## DRIVERS OF IMMUNE ESCAPE AND LONG-TERM PATHOLOGY OF PANDEMIC VIRUSES



Prof. Alex Sigal

### Background

We investigate virus–host interactions, with emphasis on viral countermeasures to innate and adaptive immunity and on the evolutionary routes by which pathogenic viruses adapt to humans. My group helped define SARS-CoV-2 variant evolution including the first isolation and phenotyping of the SARS-CoV-2 Omicron variant. Leveraging cohorts in a high-HIV-prevalence setting in Durban, South Africa, my lab revealed the role of advanced HIV disease immunocompromise in driving prolonged SARS-CoV-2 infection and evolution of variant-like viral strains, a mechanism of viral adaptation whose significance was not recognized before the Covid-19 pandemic. At HUJI, I am developing a program to investigate viral adaptation to and inhibition of the host immune response, with a view to using viral immune modulatory proteins to control aberrant immunity. We are focusing on two emerging viruses, chikungunya virus (CHIKV) and monkeypox virus (MPXV), which have divergent strategies for immune system escape.

### Highlights of Recent Discoveries (2024–2025)

- Advanced mechanistic studies on how persistent infection in immunocompromised hosts drives viral adaptation and immune escape, building on our prior evolution work.
- Leveraged South African clinical cohorts to identify host genes associated with strong neutralizing responses.
- Public engagement and standards: co-authored a Nature perspective urging unified safety standards among virologists to rebuild support of Virology research.

### Translational Impact

- Insights into viral evolution and neutralization support vaccine-strain selection and antibody countermeasures.
- CHIKV/MPXV gene-level screens aim to reveal innate-immune pathways that can be targeted in viral and non-viral arthritis.

- Leadership in high biocontainment research strengthens Israel's readiness via procedures, training, and risk assessment.

## Training & Leadership

I coordinate two HUJI courses (Basic Virology; Critical Reading for Medical Students), serve as academic head of the National BSL-3 Facility at HUJI, and mentor trainees in Israel and South Africa.

## Looking Ahead

Two goals will guide 2025–2027 efforts:

### Determinants of immune response and escape in pandemic viruses

- Identify viral adaptations during persistent infections in immunocompromise
- Determine genes associated with strong neutralizing antibody responses

### CHIKV and MPXV countermeasures against innate immunity

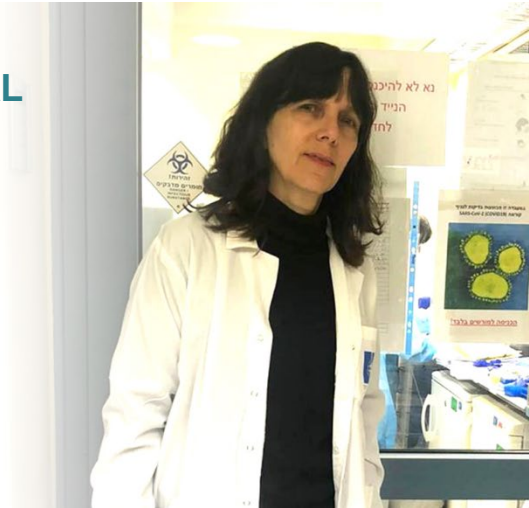
- Determine viral and host factors enabling efficient CHIKV infection of the joint
- Develop a screening approach for viral immunomodulatory genes
- Use viral immune-evasion genes as tools to probe non-viral arthritis

## References (2024–2025)

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# CONGENITAL CYTOMEGALOVIRUS (CMV) INFECTION: A TRANSLATIONAL RESEARCH APPROACH HIGHLIGHTING SCIENTIFIC AND REAL-WORLD ADVANCES



Prof. Dana Wolf

## Background

Cytomegalovirus (CMV) is the most common cause of congenital infection worldwide. It can lead to neurodevelopmental disabilities and hearing loss in the infant, which can manifest at birth or develop later during childhood. While the risk of materno-fetal CMV transmission and of congenital disabilities is relatively high following primary maternal CMV infection, nonprimary maternal infection (a common occurrence in pregnant women with preconception immunity) results in a much lower transmission rate.

Congenital CMV infection causes an immense global health burden and greatly affects women's and children's health, and has been recognized as a Tier 1 priority vaccine by the National Academy of Medicine. However, there is no available vaccine yet to prevent congenital CMV infection, and our understanding of the immune correlates of protection against transplacental transmission of CMV is still limited, in the absence of animal models for human CMV and in the absence of universal maternal and newborn screening for CMV infection.

## Highlights of Recent Discoveries (2024–2025)

Addressing these knowledge gaps as a physician scientist in Clinical Virology, my lab has employed a multi-faceted translational research approach - spanning basic-molecular and clinical real-world evidence studies; We have established a unique model of CMV infection in human placental tissues, representing the authentic materno-fetal transmission site. Our studies have uncovered the effective spread of the virus and the wide range of infected cells in the placenta - recapitulating natural infection and damage in the maternal-fetal interface. These findings have facilitated our recent discovery of new clinical biomarkers, which for the first time, can predict the severity of fetal brain damage before birth. We intend to apply these biomarkers to advance prognostic assessment and personalized treatment of infected fetuses. We have also revealed a new placental immune mechanism whereby immune cells

residing within the placenta can protect the developing fetus against congenital infection in women with preconception immunity.

### Translational Impact

Universal newborn screening of congenital CMV (cCMV) has been increasingly advocated to facilitate timely diagnosis and management. However, in the absence of a high-throughput screening test that can identify all infected neonates, the development of an accurate and efficient testing strategy for universal cCMV screening has remained an ongoing challenge. Towards this goal, building on our pooling pipeline that we successfully implemented during the COVID-19 pandemic, we developed a new pooling setup for cCMV detection and implemented it for large-scale screening of all the infants born at the Hadassah Hebrew University Medical Center for congenital CMV infection. This pioneering universal screening approach allows early diagnosis and treatment of (otherwise undiagnosed) cCMV. It further highlights the importance of universal screening in defining the true population prevalence of cCMV and in providing real-life evidence for a future vaccine. The data, recently presented at the NIH, and in the major European and US conferences for Virology / Infectious Diseases and Public Health and published in *Nature Medicine*, have attracted collaboration initiatives with leading global vaccine companies. The accompanying Nature Medicine Editorial summarized the findings, stating that “This paper presents a cost-effective, accurate and non-invasive method for cCMV testing, which could revolutionise the implementation of universal screening.”

We have recently summarized key performance and clinical-epidemiological outcomes derived from the routine implementation of our newly developed pooling setup for the universal cCMV screening of >48,000 infants over three years (**paper accepted for publication in The Lancet Infectious Diseases - the leading Infectious Diseases journal**).

### Training & Leadership

- Graduated two PhD students (with distinction) and one Master's student (2024-2025).
- Invited speaker and session chair:
  - American Conference for Pediatric Infectious Diseases (SLIPE) 2025, Chile,
  - European Congress of Clinical Microbiology and Infectious Diseases (34th ECCMID, now known as ESCMID Global), Barcelona, Spain, 2024
  - European Congenital CMV Initiative (ECCI), Leiden, Netherlands, 2024
  - 9th European Congress of Virology, Dubrovnik, Croatia, 2025

- European Society of Pediatric Infectious Diseases conference (ESPID) 2025, Bucharest, Romania, 2025
- Latin American conference for Pediatric Infectious Diseases (SLIPE) 2025, Chile, 2025

## Looking Ahead

- Identify real-world immune correlates of protection against congenital CMV
- Characterize the long-term clinical outcomes and true burden of congenital CMV
- Inform and lead public health prevention strategies and facilitate CMV vaccine development

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