



# Research Innovations vol. 5 Spring 2008

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**BAR - ILAN UNIVERSITY**  
The Office of the Vice-President for Research  
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## Research Innovations



It is my great pleasure and honor to preface this fifth issue of Research Innovations. The current collection is an eclectic mix of subjects that I am sure will interest everyone greatly. We are particularly proud that four of the articles come from the “Human” sciences. It is probably a well kept secret that in this part of the university which has a majority of the academic faculty, interesting and significant, high-level research is being conducted and published. Their innovations just don’t get the exposure and the interest that the Life and Exact Sciences attract. Research Innovations tries to redress the imbalance, and we call on all the researchers in the “Human” sciences to come forward, volunteer their articles, and share their accomplishments with everyone. In this way, the university community and the wider public will be exposed to the significant achievements of the greater part of the university. And to the readers of this issue we say: enjoy!

Prof. Harold Basch  
Vice-President for Research

# “Ironing out” the Problem - Bacterial Biofilm Development

Dr. Ehud Banin



The increase in bacterial antibiotic resistance is a major concern for clinicians and medical officials worldwide. One of the modes by which bacteria enhance their resistance is to create biofilms. Biofilms are surface-associated bacterial communities encased in an extracellular polymeric matrix. The problem of bacterial biofilm formation on abiotic surfaces (estimated to cost many billions of dollars each year) is common to a wide range of both medical and industrial problems. The prevalence of biofilm formation and the difficulties in biofilm removal, make biofilm prevention a major research challenge at the interface between

microbiology and materials science.

Dr. Banin's research focuses on understanding the basic aspects of the signals and processes involved in biofilm development with a goal of finding new methods of treating biofilm-related infections. A main interest in the laboratory is to uncover the role of iron in biofilm development.

Biofilm development is known to follow a series of complex but discrete and well-regulated steps (Fig 1).

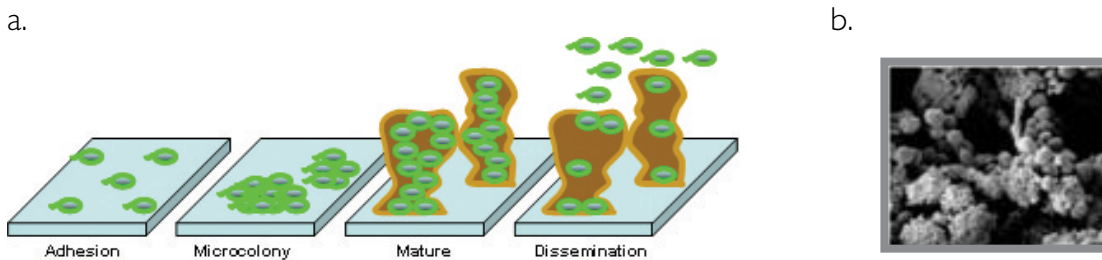


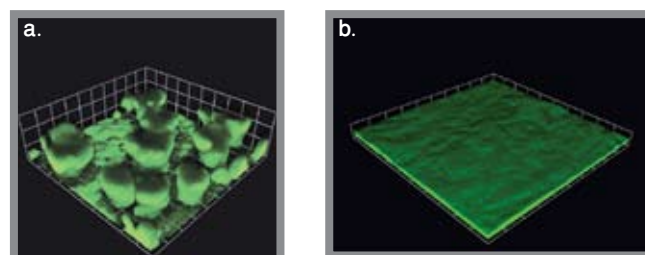
Fig. 1. Presentation of bacterial biofilm development on abiotic surfaces. (a) Adhesion initially involves reversible association with the surface. As this proceeds bacteria undergo irreversible attachment with the substrate through cell surface adhesions. In later stages bacteria will start secreting a protective extracellular matrix and form microcolonies that develop into mature biofilms. These structures protect the bacteria from host defenses and systemically-administered antibiotics. (b) An electron micrograph of a biofilm infected catheter.

An important characteristic of microbial biofilms is their innate resistance to immune system- and antibiotic-killing. This has made microbial biofilms a common and difficult-to-treat cause of medical infections. It has recently been estimated that over 60% of the bacterial infections currently treated in hospitals are caused by bacterial biofilms.

The number of implant-associated infections approaches 1 million/yr in the US alone and their direct medical costs exceed \$3 billion annually. Thus, there is an urgent need to find novel approaches to eradicate biofilms.

Iron is an essential element for most living organisms. Recent work has shown that iron concentration serve as a signal for biofilm development. By sequestering iron, sub-growth inhibitory concentrations of the mammalian iron chelator lactoferrin block the ability of *P. aeruginosa* biofilms to mature from thin layers of cells attached to a surface into large multicellular biofilm structures (Fig. 2). Dr. Banin's work has shown that *P. aeruginosa* requires active iron transport to support normal biofilm development and *P. aeruginosa* could effectively be killed and dispersed by exposing them to a strong chelator.

The discovery that iron acts as a critical checkpoint in biofilm development provides us with an important tool to investigate biofilm physiology. Dr. Banin is using iron as a valuable "switch" to intervene at defined points in the biofilm process, and he can now better understand both the role iron plays in mediating biofilm formation and gain significant knowledge of the basic processes required for successful biofilm development and maintenance. The genetic and genomic approaches Dr. Banin is taking are expected to reveal genes that are directly involved in biofilm formation and dispersal as well as genes involved in iron-regulation and signaling.



**Fig. 2 Iron and *P. aeruginosa* biofilm formation.** Visualization of mature biofilms grown under normal (a) and low (b) iron concentrations. Notice under the low iron conditions the difference in biofilm morphology compared to the normal iron conditions. Under normal iron concentrations, bacteria attach, multiply and develop into microcolonies that mature into structured biofilms. In low iron, the cells show increased surface motility, they attach and multiply but daughter cells move away from the point of replication and thus do not form microcolonies and structured biofilms. GFP-labeled *P. aeruginosa* were grown for 4 days in continuous culture flow cells. Images were acquired with confocal laser scanning microscopy (CLSM) and 3-D reconstruction was carried using Volocity™ software. Squares are 23  $\mu\text{m}$  on a side.

Another major theme in the laboratory is the search for novel antibiofilm agents.

Dr. Banin's preliminary findings suggest that by interfering with bacterial iron homeostasis we may be able to eradicate bacterial biofilms. Based on this, Dr. Banin is currently testing novel desferrioxamine-metallo complexes. Because *P. aeruginosa* possesses two uptake systems for ferrioxamine (the iron loaded form of desferrioxamine), there is reason to

predict there might be a synergistic effect of imposing iron limitation by directly delivering the toxic metal loaded in the DFO molecule to the cells via the ferrioxamine uptake systems (“Trojan horse” approach) and by sequestering any free available iron by the siderophore. Results show these complexes effectively block biofilm formation and can eradicate mature biofilms when combined with antibiotic treatment. Dr. Banin had similar success in vivo using a *P. aeruginosa* eye infection (keratitis) animal model. Topical addition of DFO-complex plus gentamicin decreased both infiltrate and final scar size by about 50% compared to topical application of the antibiotic alone.

Another approach Dr. Banin is taking to try and develop novel antibiofilm coating is based on nanotechnology. In collaborations with researchers in the Center for Advanced Materials and Nanotechnology at Bar-Ilan, Dr. Banin is utilizing novel surface nanofabrication techniques that allow us to change surface properties such as charge and topography as well as attach nanocrystals with antimicrobial activity in order to create sterile abiotic surfaces.

The recent advancements in biological research tools provide Dr. Banin with the opportunity to begin and explore fundamental aspects of bacterial life-style such as the processes that lead to the development of biofilms. At the same time there is an immediate necessity for discovery of novel antimicrobial agents as pathogenic bacteria rapidly gain resistance to existing antibiotics. These two paths converge as our improved knowledge on bacterial physiology and resistance can assist in developing novel therapeutic approaches.

## Therapeutic Advances in Treating Alzheimer's Disease

Dr. Shai Rahimipour



The prevalence of most neurodegenerative disorders increases dramatically with advancing age. Ischemic Stroke and Alzheimer's disease (AD) are the most prevalent of these disorders, affecting more than 20 million people worldwide today, and impact all aspects of society causing great suffering, death, and enormous financial burden. Despite the enormous efforts that are invested for discovering therapeutic agents, as of yet, only very few neuroprotective agents are approved for treatment. AD has been related to the accumulation of abnormally folded amyloid beta protein ( $A\beta$ ) in the brains of AD patients, which is believed to be toxic to the neurons. Removal of pathologically-produced aggregated  $A\beta$  is therefore a viable approach for developing new neuroprotective agents. The main thrust of Dr. Rahimipour's lab has been to use novel combinatorial approaches to design and construct self-assembled peptides/glycopeptides that inhibit the aggregation of the  $A\beta$  peptides or lower their concentration within the brain. Dr. Rahimipour's team will evaluate such self-assembled peptides/glycopeptides as therapeutic agents in Alzheimer's and other neurodegenerative diseases.

The main goals of their therapeutic strategy are: (1) Rational design and synthesis of novel peptides and glycopeptides that could selectively bind  $A\beta$  monomers or resulting aggregates. Such peptides are expected to interfere with the aggregation pathways of  $A\beta$  monomers or enhance the clearance of the resulted fibriles from the brain by increasing their solubility or by triggering the immune system. (2) Screening peptide libraries for their ability to inhibit the formation of  $A\beta$  aggregate and reduce their toxicity to neuron cells. (3) Probing the effect of the peptides to increase  $A\beta$  phagocytosis by microglia cells. (4) Determining the ability of the active sequence to cross the blood-brain barrier (BBB). (5) To evaluate the effect of the resulted peptides in Alzheimer animal models.

Dr Rahimipour's group employs "one-bead-one-compound" combinatorial libraries to synthesize such peptides. Following the synthesis of the libraries, they are screened for their ability to bind  $A\beta$  and inhibit its aggregation, using a high throughput screening method. Active peptides are then sequenced by a mass spectroscopic method and are synthesized in larger amounts for further chemical and biological evaluations. In order to increase the permeability of the peptides through BBB, they covalently attach different carbohydrates to their side chains of active peptides. These carbohydrates, which are known to enhance the BBB permeability, are designed and synthesized by different and complicated methods.

## Historical Roots of Ancient Islam

Dr. Deborah Tor



A day does not pass without media mention of the worldwide resurgence of Islam. To gain a deeper understanding of Islam's religious influence today on geo-political, military, and economic issues, we often need to delve into the source, the historical roots of ancient Islam.

Deborah Tor, who came to BIU from Harvard University, is a lecturer in the Department of Middle Eastern History.

Through her research, Dr. Tor offers us a panoramic view of medieval Islamic history. Her research is unusual in its wide

range, particularly for a young scholar. Her work spans the entirety of the so-called "Persianate Period" in medieval Islamic history, from the 8<sup>th</sup> to the 13<sup>th</sup> century, and covers social, political, and military institutions and issues ranging from chivalric holy warrior brotherhoods to imperial politics and tensions.

Dr. Tor wrote her first book (published by the Deutsche Morgenländische Gesellschaft [German Oriental Society] in May of 2007) on the puzzle of the poorly-understood but ubiquitous medieval armed bands known as 'ayyaran, demonstrating that the phenomenon arose in the volunteer holy warrior milieu of eastern Iran around the year 800, before eventually developing into chivalric Sunni brotherhoods by the mid-11<sup>th</sup> century. These groups served as the forerunner to today's jihad warriors.

Dr. Tor then moved on to a completely new field: her current research examines power institutions in the era of the Great Saljuq Dynasty, which ruled the eastern Islamic world in the eleventh and twelfth centuries; this change of periods and focus necessitated mastering an entirely new and unfamiliar source base. Her success in her new field is demonstrated both by her publication output and success in securing research grants from prestigious foundations: first from the American Institute for Afghanistan Studies and, most recently, a highly unusual double award from the Israel Science Foundation (ISF) and the German-Israeli Foundation Young Scientist program (GIF); the ISF grant will assist Dr. Tor in writing the first history of the long reign of the Saljuq Sultan Sanjar (1097-1157); and the GIF grant will enable Tor to explore the history of power relations and tensions between the caliph and sultan throughout the eastern Islamic world in the Great Saljuq period.



A digital photograph of dinar minted in Balkh in 1099-1100 in the name of the Great Saljuq Sultan Sanjar.

# Reversing Nerve Damage resulting from Neurodegenerative Diseases

Dr. Edward A. Stern

The focus of Dr. Stern's research is to understand the effects of neurodegenerative diseases on brain function at the neuronal network level. Dr. Stern, from our Neuronal Circuitry and Neurodegenerative Disease Laboratory and Gonda Multidisciplinary Brain Research Center, is particularly interested in the disruption of neuronal structure and function that occurs in neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease. Disruptions in the structure and function of specific neurons and connections underlie the specific neurological symptoms associated with each disease, such as dementia, memory loss, and tremor.

Using advanced electrophysiological and imaging methods, Dr. Stern monitors the effects of the disease process in the intact brain. In addition to providing a more complete understanding of neuronal operations in the normal and diseased brain, these methods allow Dr. Stern to apply novel therapeutic approaches such as passive immunotherapy to reverse the effects of the disease progress. Using these methods, Dr. Stern has shown that some of the effects of the disease process can be halted and reversed. In addition, we have shown that the nerve cells can recover from the disease process even in brains at advanced ages. Dr. Stern has thus demonstrated that brain structure and function is more plastic, or resilient, than previously suspected.

Supported by US National Institutes of Health AG024238



## New Data Structure in Electronic Design Automation

Dr. Osnat Keren

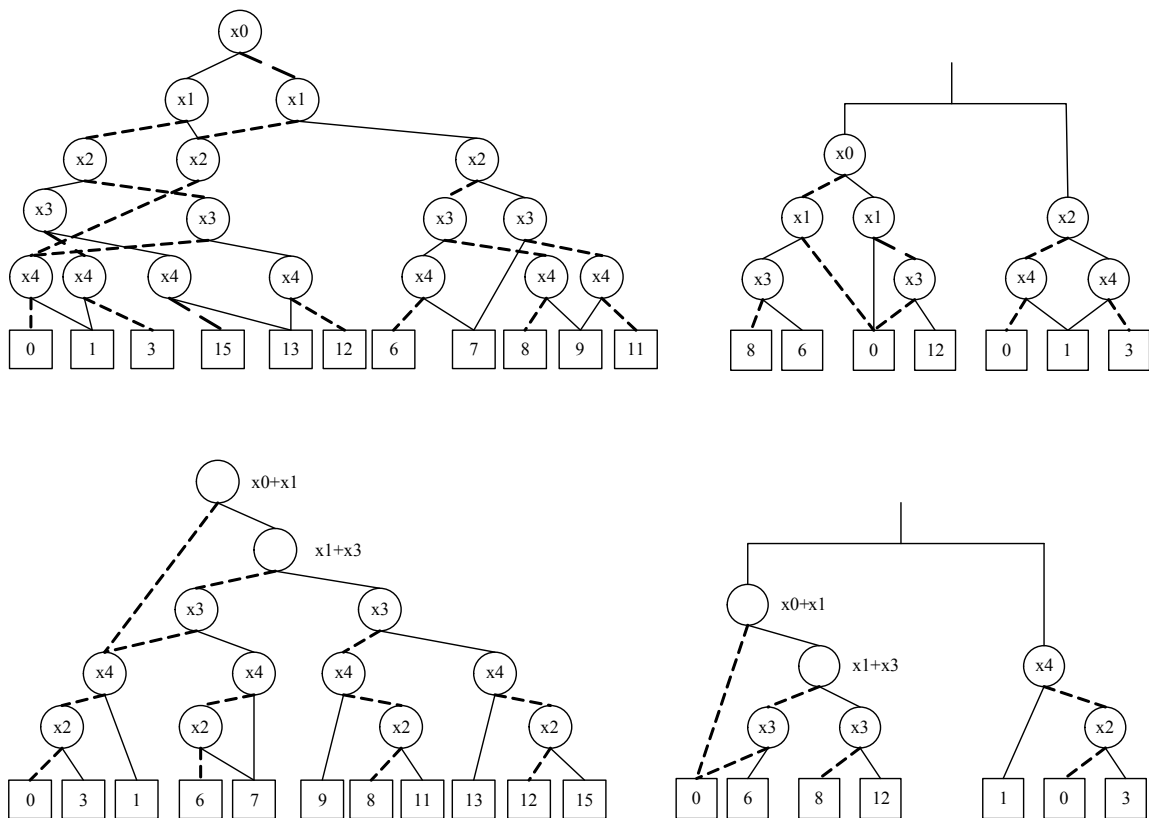


The progress in microelectronic introduces electronic systems with millions of transistors. Manual design of such systems becomes impossible. Electronic Design Automation (EDA) deals with development of sophisticated optimization algorithms for software tools of designing and producing electronic systems ranging from printed circuit boards (PCBs) to integrated circuits. Recently, in light of the emerging sub-micron and nanoelectronic technologies, the EDA becomes an especially important research area. Dr. Keren of the EDA research team of the School of Engineering is concentrating on developing innovative data structures for representation and efficient manipulation with logic functions. This research enables the creation of theoretical fundamentals both for present sub-micron technologies and for the future nanoelectronic design of digital circuits and systems.

In recent years, we have seen an enormous increase in system integration of VLSI (Very Large Integrated Circuits) designs. Moor's law, which states that the number of transistors on a chip doubles every 18 months, is still valid, and we do not see an end of this explosive growth. With modern integrated systems, traditional design techniques such as manual circuits design and simulation-based verification have become excessively time consuming and error prone. Instead, automated logic synthesis has largely replaced manual circuit design, while formal verification is increasingly used as a replacement of the simulation. Efficient algorithms and data structures to represent and reason about the circuit's functioning are a core requirement for automated synthesis and verification programs. In this area, even the most elementary tasks, such as determining whether two combinatorial circuits compute the same logic function, are intractable. Hence, we will most likely never find algorithms that are truly efficient, i.e., having worst-case polynomial complexity. Instead, we look for representations and algorithms that work reasonably well for problems of interest.

A central issue in providing computer-aided solutions to the problems mentioned above is to find a compact representation for Boolean functions on which basic operations and equivalence checks can be efficiently performed. The requirements of compactness and manipulability are generally conflicting. Currently, Binary Decision Diagrams (BDDs) serve as the most popular compromise between these conflicting requirements. In a multitude of cases of practical interest, a BDD representation of a Boolean function is exponential in the number of primary inputs. This limits the complexity of problems that can be solved using BDDs.

The Bar Ilan researchers' contribution in the Design Automation field can be characterized by pure analytical approaches for solving the research tasks. Dr. Keren's research results from the basics of Electronic Design Automation as a scientific discipline. Recently, our research team introduced a new data structure called Split Multi Terminal BDD. Her research team intensively investigate this data structure by using both the analytical methods and computational experiments based on extensive using of powerful computer resources. So-called spectral methods that use transformations of logical functions into the "frequency" domain play the central role in our research methodology. Dr. Keren's research is supported by two grants: one from the Israel Science Foundation and one from the US-Israel Bi-national Science Foundation. Intensive study of innovative VLSI data structures based on analytical research methods form the face of the Bar-Ilan Electronic Design Automation research team.



**Figure 1:** Four representations of the same Multi-output function: A standard implementation of a Multi-Terminal BDD (top-left), a linearized Multi-Terminal BDD (MTBDD) obtained from the standard MTBDD by reordering the inputs and/or replacing them by linear combinations of the inputs (bottom-left), a Split Multi-terminal BDD obtained by decomposition (top-right), and a Linearized Split MTBDD (bottom-right). The 4-bit output vectors are represented as integers. The terminal nodes in the Split MTBDDs and in the standard MTBDD are different. This results from the logical sum operation between the vectors of the original terminal nodes. For example, terminal node 7 in standard MTBDD (top-left) corresponds to two terminal nodes 3 and 6 in the Split MTBDD (top-right). The example demonstrates the significant reduction in the number of MTBDD nodes: the standard MTBDD has 17 non-terminal nodes, and after the splitting and linearization, this number is reduced to 6 non-terminal nodes (and 2 XOR gates).

# Foreign Home-care Workers and the Israeli Family

Dr. Liat Ayalon



Health, eco-demographic, and psycho-social forces, both within and outside the family unit, play a key role in how family members deliver home care to elderly patients.

Today, we are witnessing an increase in life span, a decrease in childbirth and changes in the family composition, including the entrance of women into the workforce, the high divorce rate, and the increasing popularity of the nuclear family. These forces have resulted in a shortage of available family caregivers. To compensate for this shortage, both in Israel and in other Western

countries, foreign home care workers have become a popular alternative to replace the shortage of family caregivers. The overwhelming majority of these foreign home care workers come from third world countries and provide caregiving services to frail but wealthier older adults. Israel has the second largest number of foreign workers relative to its population size in the world. Currently, almost all 24-hour paid care is provided by foreign workers, with Filipino home care workers capturing the majority of the market. Whereas Israel's official policy in recent years has restricted the number of foreign workers in the country, the one industry that has been steadily increasing in size and popularity, is the foreign home care industry.

To date, there has been only limited research on the topic. We know very little about the people who take care of our loved ones and about the challenges and advantages of this caregiving arrangement from the perspective of care recipients and home care workers. Dr. Liat Ayalon, lecturer in the School of Social Work, has been examining this phenomenon, and has focused on the quality of life of Filipino home care workers and the older adults they take care of. The overarching goal of Dr. Ayalon's research is to develop psycho-educational programs to improve the lives of older adults, their family members, and their foreign home care workers. Dr. Ayalon received a grant from the German Israel Foundation- Young Investigator's program to fund her work. In her study, Dr. Ayalon interviews Filipino home care workers, family members, and social workers about this to understand the challenges and advantages associated with such an arrangement.

# The Evolutionary Origin of Language and Gestures

Prof. Michal Lavidor



Upon returning in October 2006 from a six year research stay in the United Kingdom, Prof. Michal Lavidor from the Department of Psychology opened the Cognitive Neuroscience laboratory at BIU's Gonda Multidisciplinary Brain Research Center. Prof. Lavidor investigates the neural base of language and established her reputation by showing how initial visual stimuli (such as words or objects) is split between the right and left cerebral hemispheres. She has a worldwide reputation in magnetic stimulation studies of language where she uses her expertise in Transcranial Magnetic

Stimulation (TMS). For these achievements, Prof. Lavidor won the 2006 Marie Curie Excellence Award, and the 2007 NARSAD Independent Investigator Award.

Transcranial magnetic stimulation, a very promising avenue for influencing the living brain, has emerged in the last fifteen years, based on the use of pulsed magnetic fields. In practice, TMS is able to influence many brain functions, including movement, visual perception, memory, reaction time, speech and mood. The effects produced are genuine but temporary, lasting only a short time after actual stimulation has stopped. One reason why TMS is important in neuroscience research is that it can demonstrate causality.

Together with Ms. Dana Vainiger, a PhD research student from the Department of Psychology, Prof. Lavidor is studying the common base of words and gestures. First, functionality will be explored through a priming paradigm, as priming effects may reflect whether a gesture and a congruent word share semantic representation (see Fig. 1 for examples of gestures and words). Second, with the priming paradigm, Vainiger and Lavidor will employ a magnetic stimulation over Broca's area in the left hemisphere, in order to establish that this area is necessary for gestural comprehension. Overall, the research proposed here will prompt a more complete understanding of the neurocognitive mechanisms that enable gestures comprehension in natural language, and will shed light over the debate question whether gestures represent an evolutionary precursor of language.



**Fig 1.** Examples of gestural & verbal stimuli: [a] A symbolic gesture with a word corresponding in meaning; [b] A symbolic gesture with a word not-corresponding in meaning; [c] A meaningless gesture, without any semantic connotation.

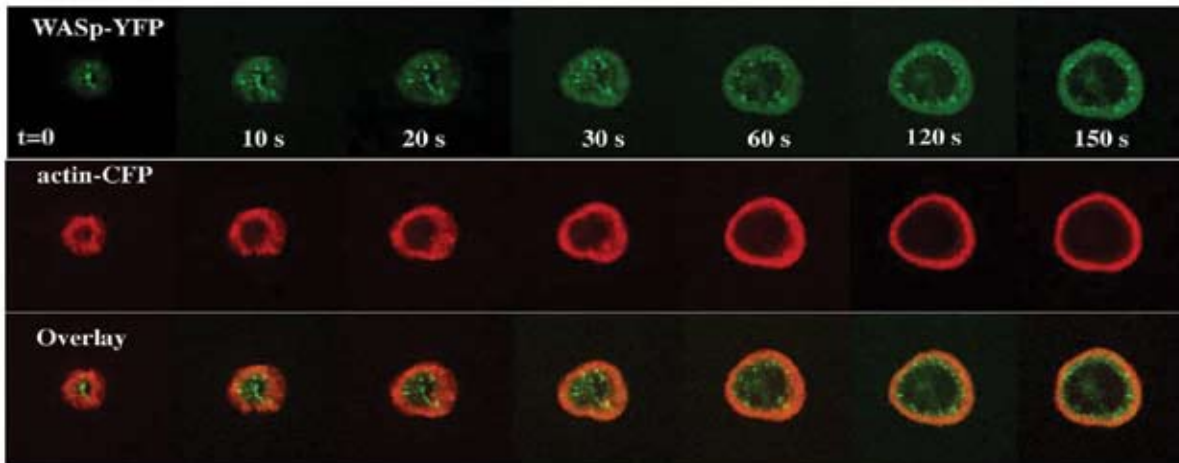
## Potential Usage of Specific Hematopoietic Cytoskeletal Proteins as Targets of Lymphoma

Dr. Mira Barda-Saad



Acquisition of the ability to migrate and invade tissues allows cancer cells to proliferate within organs, expand to adjacent tissues, and travel to distant sites. The actin cytoskeleton and its regulatory proteins are the primary mechanism of cell invasion and metastasis. Thus focusing on key regulatory proteins of the actin cytoskeleton, and in particular, actin regulation in cells of hemopoietic lineage, can provide a powerful tool for anticancer therapy of hematologic malignancies, which account for almost 10% of all cancers. The Wiskott-Aldrich syndrome protein (WASp) family proteins are primary players in the control of cell motility. Recently, four out of five members of this family were shown to be overexpressed in various non-hematologic cancers; thus, studying the role of the fifth protein WASp, exclusively expressed in hemopoietic cells in the motility of lymphoma cells is of major interest.

Dr Barda-Saad, Faculty of Life Sciences, is analyzing specific alterations in WASp gene expression in invading cells and to investigate whether aberrant regulation of WASp family protein expression or its function play a role in the motility and tissue infiltrating behavior of malignant lymphoma cells. Dr Barda-Saad's expertise lies in her ability to follow the dynamics of protein interactions in living cells, using bio-imaging techniques. While most bio-imaging studies have focused on non-neoplastic cells, we wish to examine the control of actin reorganization in cancer cells, using high resolution, and high speed microscopy for real time imaging of live cancerous cells.



Dynamics of WASp and actin following T-cell activation. Live T cells expressing WASp-YFP (green) and actin-CFP (red) were plated over stimulatory plane. Confocal images were collected during T-cell spreading. Real time imaging of T-cell activation site revealed that WASp-YFP and actin-CFP are at the point of initial T-cell membrane contact and after 1 min, by which time the actin ring is fully formed; WASp is located at the circumferential ring colocalized with F-actin. WASp is behind F-actin and in real time movie seems to push actin filaments outwards.

This research is supported by the Israeli Ministry of Health and by the Israel Cancer Association.

## Halakhic Literature of France and Spain during the 13<sup>th</sup> and 14<sup>th</sup> Centuries

Dr. Yehuda Galinsky



Dr. Galinsky, a lecturer in the Department of Talmud, has delved into the halakhic literature of France and Spain during the tumultuous 13<sup>th</sup> and 14<sup>th</sup> centuries. The historical events of this period that had impact on the development of halakhic literature include the famous trial and burning of the Talmud in Paris, the exile of the Jews from France, and the deterioration of Jewish life in Germany.

Dr. Galinsky's first project examined Sefer Misvot Gadol of Moses of Coucy, known by its acronym Semag, the primary legal code produced by the French Tosafists. The work was composed circa 1239-1247, at the same time that the Talmud was put on the witness stand, judged, and subsequently burned in Paris in a cooperative effort between the Catholic Church and the French monarchy. The impact of these traumatic events is evident in the long introduction to Moses' work where he defends the veracity and antiquity of the Talmud. A unique aspect of Moses' career was his preaching activity in the various Jewish centers in Western Europe, especially Christian Spain with the purpose of raising the spirits and the level of religious observance of the laity. One finds interspersed throughout his work portions of the sermons that he delivered during this time.

Dr. Galinsky has also studied the impact of a group of émigré scholars who left their homes at the beginning of the 14<sup>th</sup> century, either of their own volition or because they were exiled, and who settled permanently in the kingdom of Castile in Christian Spain. The primary figure of this group was the charismatic Asher b. Jehiel, known by his acronym the Rosh, who emigrated with his family from Germany in the year 1304 and settled in Toledo in 1305. In addition to serving as the primary legal authority of the kingdom of Castile, Rosh wrote in Spain Tosafot and Pesakim, both arranged largely according to the order of the Talmud. Two of his students, his son Yaacov, and Yeruham, an exile from Provence, composed user-friendly legal codes that "translated" the rulings of Rosh into accessible handbooks for the use of the Spanish rabbis and judges. Due to the activities of Rosh and his various students, much of Ashkenazi halakha was transferred to Castile, Spain. While working on the Tosafot of Rosh and their relationship to the previous collections of Tosafot, Dr. Galinsky found that despite the considerable research existing on the literature of the French Tosafot, no serious attempt was ever made to chart the change and development within the Tosafist movement, a movement that spanned close to 150 years (from the middle of the 12<sup>th</sup> to the beginning of the 14<sup>th</sup> century). There is a need to clarify

the ways in which the late 13<sup>th</sup> and early 14<sup>th</sup> century Tosafists, such as those of Peretz of Corbeil differ from their twelfth century predecessors, that is of Isaac of Dampierre and his students. Dr. Galinsky is researching what contributions the later scholars added in their approach to Talmud study, or did these later scholars essentially repeat the lore of the past. This basic question will be at the center of a new project, funded by the Israel Science Foundation that will attempt to clarify the unique features of French Talmudic creativity and halakhic literature composed in the second half of the 13<sup>th</sup> century. This study will center on the literary efforts of Peretz of Corbeil and those of his contemporary and townsman, Isaac, author of the influential Sefer Misvot Katan, the Semak.

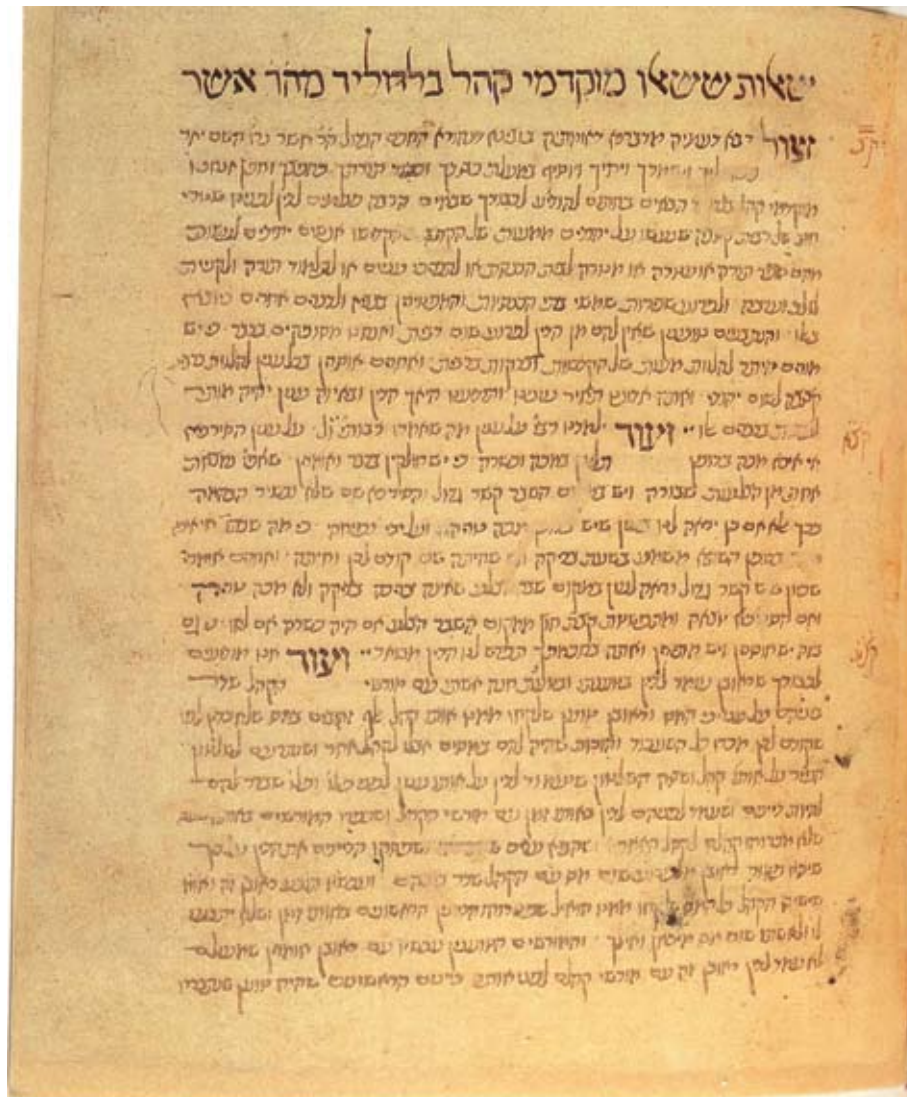
The study of the Tosafot, composed during the 12<sup>th</sup> and 13<sup>th</sup> centuries, has been a central component of Jewish culture and of Jewish learning, throughout the Middle-Ages until today's times, but rarely was the student sufficiently aware of the various layers that exist in the text and the stages in their development that took place within the batei midrash of the French Tosafists. This became even more so once the standard Tosafot were printed side by side with the Talmud (late 15<sup>th</sup> century and early 16<sup>th</sup>). From that time onward the perception of the student of the law has been to a large extent shaped by the printer's choice of texts. Through this study an attempt will be made to uncover something of the historic Tosafot, their change and development over time.



Tur Orah Hayim of R. Jacob b. Asher

Printed in Hajar by Eliezer b. Abraham Alantansi in the year 1485 is one of the earliest printings of this work in Spain. This printing and others printed in Iberia demonstrate the widespread popularity of Jacob's Turim amongst Sefardim during the 15<sup>th</sup> century.

Picture source: Rafael Weiser (ed.), Books from Sefarad (Hebrew), Jerusalem 1992, p.93



Responsa of R. Asher b. Jehiel (Rosh)

Manuscript (Jewish National Library 4° 1448) copied in Spain circa 1350, is considered to be the most important manuscript in reconstructing the original state of the Rosh's Responsa.

Picture source: Rafael Weiser (ed.), Books from Sefarad (Hebrew), Jerusalem 1992, p.91

## Biophysics: Studying the Organization of the Genome in the Nucleus

Dr. Yuval Garini



“DNA makes RNA, RNA makes protein, and proteins make us”

**Francis Crick**

How does a protein find its way toward a tiny piece of DNA that it has to bind to, as part of the normal function of the genome in the cell? The answer to this fundamental scientific question requires scientists to combine advanced optical experimental methods, biophysical analysis and modelling, and a biological system. Dr. Yuval Garini, a Bar-Ilan University biophysicist, is involved in such studies as well as related research

in biophysics. Dr. Garini's research focuses on nano-bio-photonics which includes nano-optics, single molecule detection and its utilization in biology and structural genomics. For many years, scientists believed that the existence of the genes guarantees that it will function correctly. Lately however, the three dimensional (3D) organization of the nucleus is also drawing significant interest and recent studies demonstrate that there is a non-random organization of chromosomes. This organization suggests functional relevance to proper gene expression and genome stability.

Dr. Garini's laboratory is studying telomeres, which are the ends of the chromosomes. Telomeres are constructed of a repetitive DNA sequences and a complex of proteins that cap the chromosome-ends in eukaryotic cells, protect it against enzymatic degradation and maintain the chromosome stability. Without telomeres, chromosomes may be lost during cell division or fuse with each other. Telomeres ascertain that the genome is replicated without loss of genetic information and they take part in maintaining the nuclear organization.

Dr. Garini and his collaborators found that telomeres of normal nuclei are organized in a cell-cycle dependent manner and form a disk-like shape during one of the cell-cycle phases (G<sub>2</sub>), Figure 1.

In tumor cells, Dr. Garini and his collaborators found that the telomeres form aggregates and a significant number of chromosome aberrations appeared. They showed that c-Myc deregulation in normal lymphocytes resulted in significant changes in the organization of telomeres and chromosomes, Figure 2.

For these studies Dr. Garini and his team performed comprehensive in vitro studies of telomeres organization in the nucleus, and developed an adequate image analysis program (TeloView) for that purpose.

Dr. Garini's lab is currently performing similar studies in living cells. Some of the relevant questions are:

1. What are the time-scales of protein binding to telomeres?
2. What is the mechanism that moves the fusing-telomeres towards one another? Is the mechanism due to random walk or is it a directed motion? Does it indicate on a nuclear structure that supports the motion? Are there other proteins that effect telomere fusion?

Achieving the described study requires the capabilities of an optical microscopy-based system with unique capabilities. The system that Dr. Garini is currently developing enables researchers to follow one or two entities in 3D at a high precision of 10 nm and high frequency. The system includes special optical components, a confocal microscope, as well as the use of fluorescent-based methods, such as fluorescence correlation spectroscopy (FCS).

### Figures

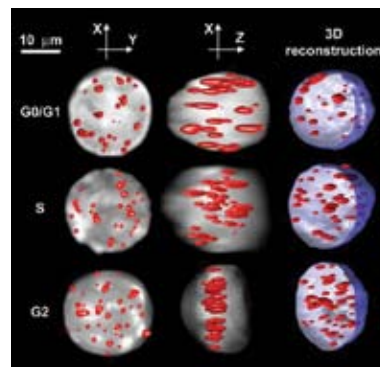


Figure 1 Organization of telomeres in the nucleus through the cell cycle. In G0/G1 and S phases the telomeres are distributed throughout the nucleus volume, but the telomeres form a disk-like shape during G2 phase. Published with permission from: Chuang, T.C.Y., Moshir, S., Garini, Y., Chuang, A.Y.-C., Young, I.T., Vermolen, B., Doel, R.v.d., Mougey, V., Perrin, M., Braun, M., Kerr, P.D., Fest, T., Boukamp, P. & Mai, S. The three-dimensional organization of telomeres in the nucleus of mammalian cells. *BMC Biology* 2:12, 1-8 (2004).

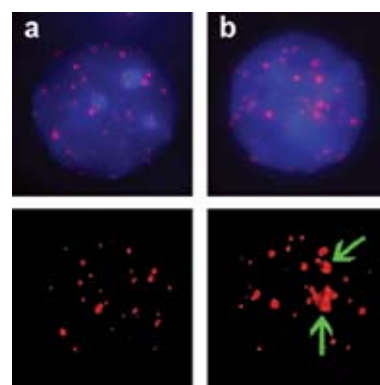


Figure 2 Appearance of telomere aggregates (left) in interphase nuclei shown in green arrow. Published with permission after: Louis, S.F., Vermolen, B.J., Garini, Y., Young, I.T., Guffei, A., Lichtensztein, Z., Kuttler, F., Chuang, T.C.Y., Moshir, S., Mougey, V., Chuang, A.Y.C., Kerr, P.D., Fest, T., Boukamp, P. & Mai, S. c-Myc induces chromosomal rearrangements through telomere and chromosome remodeling in the interphase nucleus. *Proceedings of the National Academy of Sciences USA* 102, 9613-9618 (2005).





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