Review of Current Activities

Dr. Artzi's distinguished accomplishments encompass science, education, leadership, and service. As the Head of Structural Nanomedicine at the Gene and Cell Therapy Institute at Harvard Medical School, she directs innovative research and clinical applications. Her role as one of twelve core faculty members at the Wyss Institute for Biologically Inspired Engineering highlights her commitment to advancing cutting-edge biomedical research.

A leader in structural nanomedicine, Dr. Artzi has made significant strides in developing tissue- and cell-responsive materials. Unlike static medical devices, her research introduces dynamic solutions that respond to patient variability and pathological conditions, exemplifying the next generation of precision medicine. These materials can adapt based on tissue interactions or release drugs on demand, optimizing therapeutic outcomes while minimizing side effects.

One of her key innovations is the development of adaptive adhesive hydrogels that sense local conditions to enhance adhesion and biocompatibility, effectively preventing leakage from sutures after surgeries. These materials enable localized, sustained drug delivery, overcoming barriers that limit systemic treatments for conditions such as brain cancer. When delivered in microneedle form, they can also treat skin conditions like melanoma and autoimmune diseases while allowing for noninvasive biomarker sampling.

Her groundbreaking work has led to the formation of three startup companies. With over 70 publications, she is backed by multi-million-dollar grants from the Advanced Research Projects Agency for Health (ARPA-H), foundations, and industry partners. A Fellow of both the American Institute for Medical and Biological Engineering (AIMBE) and the Controlled Release Society (CRS), she also teaches at Harvard Medical School and mentors students globally.

Contributions, Achievement, and Impact

- While pharmacokinetics and pharmacodynamics focus on how drugs behave in the body and how the body responds to them, the role of biomaterials has received relatively little attention. Dr. Artzi has demonstrated that dynamic materials that respond to tissues and cells enable precision medicine, leading to improved clinical outcomes. She coined the terms "material kinetics" and "material dynamics" (MK/MD), which are fundamental concepts for understanding how materials behave and interact with their environment under varying conditions. This knowledge is crucial for controlling material performance and behavior over time to meet specific functional requirements, paving the way for innovations in drug delivery, tissue engineering, and more.
  Her work, highlighted in numerous publications addressing the treatment of various conditions, has led to invited perspective articles in which Dr. Artzi discusses the significance of these concepts. Recently, her contributions were recognized with the 2024 Clemson Award for Applied Research.

- Soft-tissue surgical sealants are a class of materials that can be utilized to assess tissue-biomaterial interactions. Although sealants depend on binding to tissue surfaces for effective adhesion, target tissue properties have largely been overlooked in material design. As a result, a general formulation has been applied across various clinical applications, leading to suboptimal performance and, in some cases, failure. Dr. Artzi invented and chemically designed tissue-responsive adhesive materials that sense and respond to chemical and biological cues on tissue surfaces to maximize performance across different disease types and states. This innovation was achieved by creating two competitive chemical

reactions that occur simultaneously. The first, which takes place relatively quickly (within seconds), involves a reaction between chemical functional groups on a polymer solution and those on tissue surfaces to enhance adhesion. Meanwhile, the interaction of excess functional groups in that same polymer with functional groups on a second polymer solution forms a gel that continues to react and strengthen over many hours. Tissue-responsive materials have become an area of active investigation among scientists and engineers. This line of work has also led Dr. Artzi to establish a startup company, BioDevek, which provides biomaterial-based surgical solutions.

- The biocompatibility of materials is a crucial parameter for ensuring safety, as it determines whether a material can perform its intended function without causing adverse effects. Different types and families of materials exhibit varying levels of biocompatibility. Using the colon as a model organ, Dr. Artzi demonstrated that biocompatibility is not only an inherent property of a material but also context dependent. Baseline immunity and inflammation can alter the landscape and phenotype of cells interacting with a given material. This was evidenced by the differing responses to the same material when applied to healthy, colitic, and cancerous colons. Her work, published in *Science Translational Medicine*, reshapes how we develop and evaluate therapeutic materials and led to a FOCUS article by Prof. Buddy Ratner, known as the "father of biocompatibility," from the University of Washington.

- Drug delivery systems that respond to tissue and cellular triggers for on-demand drug release represent the next frontier in pharmaceutical development. Dr. Artzi has been instrumental in establishing the emerging field of "Structural Nanomedicine," which focuses on chemically designing and engineering nanostructures with controlled architectures. The arrangement of pharmaceutically relevant molecules and their chemical interactions with the core particle significantly influence construct stability, potency, and overall performance for both therapeutic and diagnostic applications. Dr. Artzi has developed advanced drug delivery systems that release therapeutics in response to specific chemical triggers, such as pH, enzyme activity, or the presence of molecules like mRNA. This approach enhances delivery specificity, maximizing therapeutic benefits while minimizing side effects. Her work has resulted in a series of high-impact publications and multiple national and international invitations to present her research.

- We have advanced the understanding of how biomaterials interact with the immune system through the use of novel constructs featuring chemically conjugated innate immune activators—specifically, a stimulator of interferon genes (STING) agonist. These constructs were fluorescently labeled to track their distribution within tissues after injection into mice with melanoma. The particles were found to accumulate not only in the tumor microenvironment but also in the spleen. To investigate the spleen's role in generating antitumor immune memory, we performed splenectomy on some mice and treated them similarly. The results revealed that the splenectomized mice could not generate immune memory; despite complete tumor elimination, they all succumbed when rechallenged with a subsequent tumor. In contrast, wild-type mice with intact spleens effectively rejected the tumor. This study was the first to demonstrate the spleen's critical role in immune memory generation, providing essential guidelines for chemically designing materials that engage with the immune system. This finding is particularly significant, as extra-tumoral drug delivery has previously been considered an undesirable effect that could lead to toxicity.

- While immunotherapy primarily targets immune cells, nanoparticles are also known to accumulate in cancer cells. Using STING agonist-conjugated constructs, Dr. Artzi investigated the fate of these stable and potent nanostructures to understand cell-to-cell communication. She uncovered a novel

phenomenon she termed the “paracrine transfer effect” (PTE), which describes how nanomaterials internalized by an initial “waypoint” cell (in this case, a cancer cell) are exported and subsequently re-internalized by a “destination” cell (here, immune cells), thereby influencing both cell types. Understanding and leveraging the PTE can significantly enhance the design and functionality of nanomedicine. Dr. Artzi has been invited to write a perspective on this finding, which is currently under review in *ACS Nano*, the journal of the American Chemical Society.

- Biological barriers to systemic drug delivery and the rapid clearance of nanoparticles from the body limit their efficacy in challenging diseases like glioblastoma—an aggressive brain tumor. Engineering macroscale materials, such as adhesive hydrogels, for local and sustained delivery of nanoconstructs and drugs can expand the therapeutic window and enable programmed delivery durations and sequences. Prolonged drug delivery is particularly important for fostering long-term antitumor immune memory to eliminate disseminated glioblastoma cells in the brain. By training immune cells to recognize and eliminate cancer cells throughout the body, this strategy enhances the immune response. Temporal drug delivery and prolonged exposure are essential for achieving long-term immune memory, as this process requires a cascade of events that unfolds over several days. Rapid clearance of drugs injected into the bloodstream—often occurring within minutes or hours—can hinder the development of this memory. This innovative approach has led to unprecedented efficacy in aggressive mouse models of glioblastoma and has laid the groundwork for the formation of a startup company, SpideRx, which aims to revolutionize outcomes for patients with glioblastoma.

- Despite the accessibility of the skin, conditions such as melanoma and autoimmune diseases like alopecia areata, vitiligo, and atopic dermatitis are often treated with systemic drug delivery. Topical creams struggle to penetrate the skin barrier, particularly the stratum corneum, resulting in low drug accumulation in the skin (often less than 1%) and potential systemic toxicity. This issue is particularly concerning when immunosuppressive agents are prescribed for autoimmune diseases, as indiscriminately suppressing the immune system increases the risk of cancer, cardiovascular diseases, and other complications. Dr. Artzi has designed and fabricated a polymeric microneedle patch—essentially a smart Band-Aid—for transdermal delivery that enhances efficacy and reduces side effects in mouse models of autoimmune diseases and melanoma. The patch can deliver a variety of therapies and is engineered to sample biomarkers in skin interstitial fluid—both soluble and cellular biomarkers—allowing clinicians to noninvasively monitor treatment responses over time. This innovative approach has led to the establishment of a startup company, LybraBio, which aims to revolutionize the treatment of autoimmune skin diseases.

- Tissue engineering approaches to regenerate tissues often depend on the delivery of growth factors, which can inadvertently support tumor growth in cases of osteosarcoma—bone cancer. Current therapies for osteosarcoma primarily rely on chemotherapy, such as doxorubicin, but its effects on bone regeneration have not been thoroughly studied. Dr. Artzi highlighted the importance of understanding how clinically available therapies interact with new and emerging treatments. She discovered that conventional chemotherapy could compromise the effectiveness of existing bone regeneration methods. In response, she developed a novel approach using miRNAs—master gene regulators—that promote osteogenesis (bone regeneration) while simultaneously suppressing tumor growth. Unlike growth factors, this miRNA-based strategy was not adversely affected by doxorubicin delivery. Her findings have led to invitations to present at tissue engineering conferences and seminars.

Reputation

Dr. Artzi is internationally acclaimed, as evidenced by prestigious awards, invitations to present at leading conferences, and her roles in organizing national and international events.

Dr. Artzi serves as an Associate Editor for *ACS Nano*, one of the leading journals in her field, and is on the editorial boards of multiple journals, including *Science Translational Medicine*, where she contributed highlights from recent literature, and *Advanced Materials*, where she served as a Guest Editor for a special issue on Materials for Precision Medicine. Additionally, she serves as an ad hoc reviewer for over 20 journals, including *Nature Nanotechnology*, *Nature Biomedical Engineering*, *Science Translational Medicine*, *and Advanced Materials*. She also evaluates grant proposals for organizations such as the NIH and the DOD, participating in various study sections and panels.

Dr. Artzi has actively engaged in national and international conferences, serving as chairperson for events such as the Gordon Research Conference, NanoDDS, and the Forbeck Forum. She has been invited to present her work globally, with notable presentations at the International Controlled Release Society in 2019, the World Biomaterials Conference in 2020 (where she received a mid-career award), and the International Conference on Nanomedicine Meets the Tumor Microenvironment in 2021. In 2021, she also participated in a Cell Press webinar on Biomaterials-Induced Immunoengineering, served as a panel moderator at the BioAsia conference, and gave an invited talk at the Nature Conference on Bio-Inspired Nano Materials. In 2022, she was a keynote speaker at the 5th International Conference on Recent Trends in Bioengineering in India, as well as at the Institute for Digital Medicine (WisDM) at the NUS Medicine Innovation Forum and the National University of Singapore. In 2024, she presented at the World Biomaterials Conference, where she received the Acta Biomaterialia Silver Medal and the Clemson Award for Applied Research, and at GlaxoSmithKline.

In the Society for Biomaterials, Dr. Artzi has held significant roles, including reviewer, treasurer, session organizer, session chair, and member of the program committee. She has also served as Chair of the Membership Committee and is currently the chair of the upcoming SFB meeting in Chicago in 2025. Additionally, she is dedicated to mentoring emerging scientists as a Young Scientist Mentor at the Controlled Release Society.

Her contributions have garnered numerous awards, including the Young Investigator Award from the Controlled Release Society in 2018, the Mid-Career Award from the Society for Biomaterials in 2020, the Award for Women Entrepreneurs from the MA Life Science Center in 2020, and the inaugural Kabiller Rising Star Award in Nanomedicine and Nanotechnology in 2021. She also received the 2024 Acta Biomaterialia Silver Medal, the highest honor for mid-career faculty members in biomaterials research, and the 2024 Clemson Award for Applied Research. Her status as a Fellow of both the American Institute for Medical and Biological Engineering (AIMBE) and the Controlled Release Society underscores her peers' recognition of her significant contributions to advancing biomedical engineering and drug delivery technologies.

Demonstration of Scholarship

Through her work, Dr. Artzi has established one of the most recognized programs in the development of tissue- and cell-responsive materials. Her research challenges the traditional "one-material-fits-all" approach, highlighting the importance of addressing inter- and intra-patient variability. In response, her lab has developed innovative material platforms that can detect changes in the biological environment—such as shifts in pH, enzyme activity, or redox states—and adapt accordingly. These

materials not only respond to these biochemical cues by modifying their properties but also promote tissue repair and provide real-time feedback on tissue health. This dynamic adaptability exemplifies the principles of personalized medicine, ensuring that therapeutic interventions are tailored to the specific needs of individual patients, thereby improving clinical outcomes and minimizing side effects.

Her work has demonstrated, for the first time, that biomaterial performance is contextual (Research Investigation 14), and that tissue healing via implanted polymeric biomaterials can be substantially affected by inflammation or disease (Research Investigation 19). These findings have enabled the design of tissue-responsive materials—materials that respond to their environment, for example, by thriving differentially based on the tissue they interact with in the body—, as well as to the design of nanostructures that carry therapeutic cargos and release the drugs in response to tissue- and cell-specific signals such as pH, enzymes, and reduction oxidation (redox) state (Research Investigation 21, 25, 29). Recognizing the importance of building stable and potent nanostructure, Dr. Artzi has helped develop the emerging field of structural nanomedicine, where the architecture and positioning of therapeutic components within a nanostructure, and not only the choice of components, is controlled. These affect stability, responsiveness, uptake, and release of drugs that dictate their ultimate efficacy and safety. Dr. Artzi serves as the head of structural nanomedicine at the Gene and Cell Therapy Institute of MGB, contributing to the core capability to manufacture GMP scale nanostructures to support the internal MGB community as well as promote external partnerships.

In a study published in *Nature Materials* (Research Investigation 27), Dr. Artzi achieved the formation of a triple-helix structure based on RNA, rather than DNA, for the first time. This innovative structure enables the delivery of two different miRNAs: a double-helix tumor suppressor (mature miRNA) and a strand of an antagomiR that silences a tumor-supporting miRNA. Together, these components work synergistically to eliminate tumors. The triple-helix configuration imparts greater structural stability and allows for higher drug loading per particle compared to the corresponding single and double helix components. To facilitate localized delivery of these drugs adjacent to a tumor, they were incorporated into an injectable adhesive hydrogel that releases the miRNAs over time. The self-assembled RNA triple-helix conjugates have demonstrated functionality both in vitro and in vivo, resulting in nearly 90% tumor shrinkage within two weeks post-gel implantation in a triple-negative breast cancer (TNBC) mouse model. In contrast, the separate delivery of the mature miRNA and antagomiR resulted in only 60% tumor shrinkage. These findings indicate that RNA triple-helix hydrogels can serve as an effective anticancer platform for locally modulating the expression of endogenous miRNAs in cancer. Building on these initial findings, her subsequent work has focused on designing macroscopic materials, such as this adhesive hydrogel, to overcome biological barriers to systemic delivery and enable the effective administration of combination therapies crucial for achieving cancer elimination.

Combination therapy is essential for effectively eliminating tumors; however, the translation of such therapies is often hindered by dose-limiting toxicities and inadequate tumor accumulation. In a study published in *Nature Materials*, Dr. Artzi demonstrated that the local delivery of a combination of gene therapy, drug therapy, and phototherapy can be achieved using a hydrogel patch. This approach resulted in complete tumor remission in a colon cancer mouse model when applied to non-resected tumors, and it prevented tumor recurrence when applied following tumor resection (Research Investigation 27). This local, triple-combination therapy can be adapted for various cancer cell types and molecular targets associated with disease progression. The paper also provides insights into the synergistic biological activity of the drugs through detailed gene expression analysis, emphasizing their clinical relevance. This analysis offers new methods for evaluating the toxicity and efficacy of potential combination therapies. While the

types of drugs and their combinations are crucial for controlling therapeutic efficacy, the duration of drug release may also significantly impact outcomes. In another study published in *Advanced Healthcare Materials* (Research Investigation 35), Dr. Artzi tested this hypothesis by utilizing an adhesive hydrogel that prolongs the release of drug-containing nanogels over time compared to systemic delivery of the same drug dose. This local and sustained delivery enhanced drug exposure at the site of interest (breast cancer tumors) while reducing systemic toxicity and improving tumor eradication compared to systemic drug delivery. Furthermore, the released nanogels were designed to specifically respond to cancer cell signals, including low pH and redox conditions, allowing for the targeted liberation of the drug within cancer cells, thereby improving safety and efficacy.

While chemotherapy and gene therapy show a lot of promise in cancer therapy, Dr. Artzi hypothesized that nanomaterials can be leveraged to target our body's own immune cells and reprogram them to recognize and eliminate cancer cells. This approach has the potential to generate long-lasting and self-propagating living therapeutics, as immune cells can be recruited to, and expanded at, the site of the tumor, circulate in the entire body to target metastatic lesions, and form antitumor immune memory, akin to a vaccine, preventing the tumor from coming back. This is the holy grail in cancer therapy. Indeed, her lab designed a nanostructure that can deliver an immune modulatory molecule, Stimulator of interferon (STING) agonist, that activates the cGAS-STING pathway (Research Investigation #37). This is a conserved pathway that activates a plethora of immune cells in our body in response to an infection by a virus or bacteria, and here was adapted to train the immune system to recognize and eliminate cancer cells. However, the high hydrophilicity and negative charge of the STING agonist (here, cyclic dinucleotides, or CDN) hinders their delivery into cells. Dr. Artzi developed a library of cationic polypeptide-modified dendrimer nanostructures to deliver CDNs efficiently in vitro and in vivo by affordin Here's a refined version of your text:

While chemotherapy and gene therapy hold significant promise in cancer treatment, Dr. Artzi hypothesized that nanomaterials could be harnessed to target the body's own immune cells, reprogramming them to recognize and eliminate cancer cells. This innovative approach has the potential to create long-lasting and self-propagating living therapeutics, as immune cells can be recruited and expanded at the tumor site, circulate throughout the body to target metastatic lesions, and form antitumor immune memory—similar to a vaccine—thereby preventing tumor recurrence. This represents the holy grail of cancer therapy. In her lab, Dr. Artzi designed a nanostructure to deliver an immune-modulatory molecule, a Stimulator of Interferon Genes (STING) agonist, which activates the cGAS-STING pathway (Research Investigation #37). This conserved pathway activates a variety of immune cells in response to viral or bacterial infections and was adapted to train the immune system to recognize and eliminate cancer cells. However, the high hydrophilicity and negative charge of the STING agonist (specifically, cyclic dinucleotides, or CDN) pose challenges for effective cellular delivery. To overcome this, Dr. Artzi developed a library of cationic polypeptide-modified dendrimer nanostructures designed for efficient CDN delivery in vitro and in vivo. This system enhances CDN packaging capacity, leading to higher activation of type I interferon (IFN-I) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) proinflammatory signaling pathways. The polypeptide-modified dendrimer platform provides a means for the efficient delivery of STING agonists in poorly immunogenic tumors and can be combined with other anticancer therapies, creating new opportunities for cancer eradication. However, while this structure enabled effective CDN complexation and intra-tumoral delivery, it lacked the stability necessary for systemic delivery, which is crucial for treating inaccessible tumors and ensuring the efficacy of repeated dosing.

This work was followed by an intensive study published in *Nature Nanotechnology*, where Dr. Artzi meticulously controlled the placement and architecture of the STING agonist (CDN) within a nanoparticle to enhance the stability, drug loading, and potency of her nanostructures (Research Investigation 48). In this study, CDN was chemically conjugated to polymer nanoparticles using a cleavable linker that releases the drug in target cells, thereby increasing the therapeutic window. Dr. Artzi demonstrated design parameters for nanostructures and generated guidelines for how innate immune activators, such as STING agonists, can elicit a long-term antitumor immune response. By fluorescently labeling these stable and potent nanostructures, Dr. Artzi tracked their fate following systemic delivery, studying their biodistribution in tissues and cells. While the primary target of the particles was immune cells, cancer cells, which are avid phagocytic cells, also took up the immune-stimulatory particles. She identified a phenomenon she termed the "paracrine transfer effect" (PTE), wherein nanoparticles that accumulated in cancer cells undergo exocytosis, followed by uptake by neighboring immune cells in the tumor microenvironment, contributing to cancer elimination. This finding has significant implications for nanostructure design. Dr. Artzi is currently preparing a perspective on PTE, describing how nanomaterials can be internalized by an initial "waypoint" cell, then exported and re-internalized by a distinct "destination" cell. This process can either positively or negatively influence both the waypoint and destination cells. It can be harnessed to intentionally block or enhance nanoparticle exocytosis for predetermined effects, accommodate a range of cargos released in a temporally controlled manner, or target mobile cells to exert their effects in specific locations. This calls for a renewed focus on the development of structural nanomedicines, where the architecture and spatial placement of medicinal components are as crucial as the choice of components themselves. In that same study, Dr. Artzi demonstrated, for the first time, the role of the spleen in generating long-term antitumor immune memory. She showed that systemically delivered particles accumulating in the spleen activated innate and adaptive immune cells, contributing to immune memory generation. In mice that had undergone splenectomy, the same therapy eliminated the primary tumor; however, upon rechallenge with another tumor, all mice died, unable to reject the tumor, indicating a lack of immune memory compared to wild-type mice. Dr. Artzi's synthesis of stable and potent particles has identified key mechanisms contributing to anticancer immune therapy that can be applied to a range of therapeutic approaches, informing future strategies in the field.

Dr. Artzi's interest in reprogramming the immune system extends beyond cancer therapy. Effective treatment of autoimmune diseases requires regulating the immune response rather than merely activating it. Patients with autoimmune skin disorders and those experiencing allograft rejection after transplantation often face poor outcomes due to the systemic delivery of immunosuppressive agents. These treatments result in only a small fraction of the drug reaching the target site, while their broad reactivity with immune cells suppresses the immune system indiscriminately. This leaves patients vulnerable to infections, cancer, and other complications, without addressing the underlying disease mechanisms, leading to high rates of recurrence. To enable specific immune regulation, Dr. Artzi developed a transdermal hydrogel patch that delivers factors designed to recruit and expand regulatory T cells (Tregs) in proximity to antigens in skin lesions, training these cells to form immune tolerance (Research Investigation 38). Microneedle-mediated local delivery of the chemokine CCL22 (to attract Tregs) and the cytokine IL-2 (to promote their expansion) enhances local immune suppression in the allograft without inducing systemic immune suppression. This approach also facilitates monitoring of the therapy response following skin transplantation. Additionally, this technology successfully restored hair regrowth in alopecia areata, another autoimmune skin disease where the body attacks hair follicles, resulting in focal hair loss (Research Investigation 54). The innovations in this area have generated

composition of matter and method of use intellectual property, leading to the foundation of LybraBio, a startup company that aims to translate this technology to treat patients with autoimmune skin diseases, such as alopecia areata, atopic dermatitis, vitiligo, psoriasis, and more.

The hydrogel-based microneedle technology is distinctive in that it enables both drug delivery and biomarker sampling from skin interstitial fluid (ISF). Dr. Artzi has leveraged this innovation for the transdermal delivery of cancer immunomodulatory drugs while simultaneously monitoring the response to therapy over time in skin ISF (Research Investigation 44). By integrating treatment with real-time diagnostics, this platform offers a personalized approach to cancer immunotherapy, enhancing treatment precision, reducing side effects, and potentially improving therapeutic outcomes. This work has generated significant interest from academic and industrial partners and is now being applied to the treatment and monitoring of autoimmune diseases, cancer, and infectious diseases—a strategy funded by a $27 million ARPA-H grant, on which Dr. Artzi serves as a principal investigator.

Such hydrogels can be utilized in conjunction with drugs or as standalone medical devices. For instance, hydrogels can serve as sealants to prevent complications after gastrointestinal and vascular surgeries, such as leakage from suture lines. Tissue-responsive materials that can adhere to varying surface chemistries and environmental conditions would enable their application across multiple organs and in patients with diverse pathological conditions (Research Investigations 12, 19, 42, 53, and 11 in Other Reviewed Publications). In one example, Dr. Artzi designs and synthesizes materials that interact with surfaces through multiple adhesion mechanisms, including ionic and covalent bonds, to maximize adhesion strength and performance in complex in vivo environments (Research Investigation 53). This versatility is particularly crucial in cardiovascular surgeries, where synthetic grafts are used for vascular reconstructions, necessitating strong adhesion between the graft and surrounding tissue. Such adhesion is vital for applications in wet and dynamic surfaces, such as the mucosal surfaces of the gastrointestinal tract following polyp and tumor resections (Research Investigation 53). A novel sprayable hydrogel provides a biocompatible solution that adheres effectively to both human tissues and synthetic grafts, reinforcing sutures and maintaining structural integrity under high vascular pressures (Research Investigation 42), peristaltic forces, and harsh biological conditions, such as those found in the stomach (Research Investigation 53). This work serves as the foundation for a startup company I co-founded, BioDevek, which translates this technology for surgical procedures in patients. Indeed, hydrogel-based biomaterials are increasingly employed as devices and for drug delivery applications in vivo. Furthermore, their high-water content and biocompatibility can be leveraged to model tissue microenvironments in vitro for drug screening purposes.

The ability to conduct in vitro experiments that accurately replicate the in vivo environment is crucial for obtaining results predictive of (pre)clinical performance. Dr. Artzi's lab has advanced this field by developing 3D spheroid models that incorporate multiple cell types to screen drugs and identify relevant conditions. This approach effectively mimics the 3D microenvironment of tumors. In one instance, Dr. Artzi developed an osteosarcoma model to study the complex interactions between tumor elimination and bone regeneration, which often presents significant therapeutic challenges (Research Investigation 39). By combining cancer cells with stromal cells, this model replicates the tumor microenvironment and elucidates the divergent effects of cancer treatments on tumor suppression and bone healing, providing critical insights into osteosarcoma progression and treatment dynamics. In a follow-up study, this model was utilized to screen combinations of drugs that could support both bone regeneration and tumor elimination (Research Investigation 46). The researchers examined a combination of chemotherapy and bone-inducing factors in both the spheroid and mouse models of osteosarcoma. Notably, standard chemotherapy was found to significantly hinder the bone's regenerative capacity, and this effect could

not be overcome by standard osteogenic growth factors such as bone morphogenic protein 2 (BMP-2). The study investigated the long-term effects of combined therapy involving the clinically used systemic chemotherapy agent Doxorubicin and hydrogel-mediated localized delivery of nanoparticle-complexed miR-29b, which has been shown to promote bone formation by inducing osteoblast differentiation in other models. This combination significantly reduced bone breakdown due to decreased tumor burden and preserved bone architecture, even in the presence of chemotherapeutics. This research demonstrates, for the first time, the immense potential of miRNA delivery to normalize bone homeostasis, as its pro-osteogenic effects are unaffected by the addition of chemotherapeutics, unlike BMP-2 delivery. Furthermore, it demonstrates the power of our in vitro spheroid model in predicting in vivo therapeutic outcomes.

In summary, Dr. Artzi's lab has been instrumental in establishing the field of structural nanomedicine by designing tissue- and cell-responsive materials that are uniquely stable, potent, and safe. Her lab has developed material platforms capable of sensing biological environments, enhancing tissue repair, and reporting on tissue states. These materials improve outcomes following surgery, overcome biological barriers to delivery, shuttle drugs to specific organs, and interact with target cells, such as cancer and immune cells, to modulate their phenotypes. Through the design of structural nanomedicines, her lab has created potent immune modulatory nanostructures that activate target immune cells, enhancing both specificity and efficacy. Dr. Artzi has also developed tunable, disease-specific materials and methodologies for noninvasive tracking of material erosion, drug distribution, and cell fate. She has refined biomaterial design by studying real-time material kinetics (MK) and dynamics (MD) in realistic in vivo environments. Dr. Artzi's group continues to explore innovative approaches for using chemically well-defined nanostructures for the delivery of immunomodulators and to investigate the effects of administration routes and spatiotemporal release kinetics on immune responses.

In a recent line of work (forthcoming publication), Dr. Artzi presents a novel and exciting paradigm for brain cancer therapy. Her approach utilizes an environmentally sensitive hydrogel as an implantable material to: 1) eliminate the need to cross the blood-brain barrier, and 2) enable controlled and sustained therapeutic release. This strategy underscores the significance of nanostructure design and architecture—not just the choice of components—in achieving the desired immunotherapeutic effect, representing a form of "rational vaccinology."

Grant/Other Funding Status

Dr. Artzi's lab is supported by a diverse range of funding sources, including federal, philanthropic, foundation, and industry grants. She currently serves as the principal investigator on a multi-million-dollar ARPA-H grant focused on a Disease-Agnostic Innate Immunotherapeutic RNA Platform. This project aims to develop a comprehensive discovery and translation platform for the creation, validation, delivery, and scalable manufacturing of RNA immunotherapeutics that activate the body's innate immune system for the treatment of cancer and infectious diseases.

Additionally, Dr. Artzi leads a sponsored research agreement with Johnson & Johnson to create a delivery system for the local treatment of lung cancer. She is also involved in a consortium dedicated to developing gene therapies for rare cardiovascular diseases and is part of an NCI consortium working on immune-targeted therapies for glioblastoma (GBM). Furthermore, she is the principal investigator on a program funded by the National Alopecia Areata Foundation (NAAF) and has secured multiple internal grants at MIT, Brigham and Women's Hospital (BWH), and the Wyss Institute at Harvard University.

Dr. Artzi has successfully completed funding from the NIH (NIH/NIAID R56) and has engaged in several multi-billion-dollar collaborations with industry partners. Her esteemed reputation and the expertise of her lab have attracted donations from pharmaceutical companies, further enabling advancements in the field of structural nanomedicine and tissue- and cell-responsive delivery.

Local Teaching and Education

Dr. Artzi teaches the highly regarded HMS course "Critical Thinking and Research Proposal Writing" (BBS 330). She has also contributed to Harvard Catalyst courses, including TRANSforming Care with Emerging Novel Devices (TRANSCEND) and the Innovation Training Program through One Brave Idea at Brigham and Women's Hospital (BWH). Additionally, she has provided instruction on novel diagnostic technologies to pathology fellows and residents at BWH.

Dr. Artzi runs multiple student exchange programs with Spain and Mexico, where students join her lab to conduct research for a year. She is passionate about teaching, mentoring, and witnessing the growth of her trainees. For instance, one student from the exchange program in Spain, Cristina Crespo Roman, currently serves as the Global Value and Access Director at Sanofi/Genzyme in Spain. Another exchange student, Nuria Oliva, became a PhD student in the MIT HST-MEMP program under Dr. Artzi's supervision and later a postdoctoral researcher in her lab at BWH. Nuria is now a professor at IQS in Spain. Postdoctoral student Joao Conde is now an Associate Professor at NOVA Medical School, while Shiran Ferber, another postdoctoral researcher from her lab, has become a Venture Partner at Target Global and the Director of Scientific Affairs at the GBC Foundation. Additionally, Alex Cryer, a postdoctoral fellow, has recently been promoted to Instructor and is on a fast track to becoming an assistant professor.

Dr. Artzi is dedicated to educating the next generation of scientists. She frequently presents cutting-edge technologies at the MGB WMIF as a First Look and Disruptive Dozen presenter, participates in the "Doctor is In" sessions, and engages in panel discussions. She has shared her work with the BWH scientific advisory board and is a sought-after speaker globally. Dr. Artzi also serves on the executive committee of the MD-PhD Admissions Committee at HMS, where she screens, interviews, and participates in selecting the cohort of students admitted to the prestigious Harvard-MIT MD-PhD program.

Significant Supporting Activity(ies) (SSA): Administration and Institutional Service

Dr. Artzi leads the Structural Nanomedicine program at the Gene and Cell Therapy Institute (GCTI) at Mass General Brigham, where she directs innovative research and clinical applications of nanomaterials. As a member of the GCTI leadership team, she plays a crucial role in ensuring the manufacturability of nanomaterials that can be developed as a service for the MGB community. Additionally, she attracts patients to MGB to participate in clinical trials that leverage cutting-edge science and technology. Dr. Artzi is instrumental in forming partnerships with industry and facilitating the translation of promising MGB technologies.

She also serves as the scientific advisor for the Stepping Strong Center for Trauma Research at Brigham and Women's Hospital (BWH) and is a member of the Center's medical advisory board. In this capacity, Dr. Artzi shapes the scientific direction of the Center, assists in selecting top programs for funding, helps plan and execute the annual Stepping Strong Symposium, and supports the translation of advanced inventions to patients.

Furthermore, as one of only twelve core faculty members at the Wyss Institute for Biologically Inspired Engineering, Dr. Artzi fosters collaborations between GCTI and the Wyss Institute on multi-million-dollar translational grants. This effort enhances the presence of Brigham and enables the application of GCTI's manufacturing capabilities and expertise across a range of promising applications.