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April 1, 2026

Mr. Thomas Sulich
Chairman
Fifth District AHEPA Cancer Research Foundation
305 Worth Street
Brick, NJ 08724

Dear Mr. Sulich,

It is my pleasure to submit our 2026 Mid-Year Progress Report for the grant generously awarded by the Fifth District AHEPA Cancer Research Foundation. On behalf of my research team, I extend our sincere gratitude for your continued and steadfast support. I am pleased to share the progress we have achieved for our project, *Meaningful Connections 2025–2026: Screening for an Anti-Stroma Potential Drug as a Means to Intercept Pancreatic Cancer Development*.

Our team has made significant progress in the first half of the 2025–2026 funding period, including completing key research aims, generating early in vivo results, publishing findings linked to a clinical trial, and advancing new small molecule and peptide drug development programs. With your continued support, we are now moving forward with screening AI-designed candidates and advancing preclinical studies aimed at identifying a first-in-class therapy to help prevent pancreatic cancer in high-risk individuals.

Since September 2025, support from the Fifth District AHEPA Cancer Research Foundation has been acknowledged in five manuscripts (published, in press, or under review) and five invited national and international presentations. These efforts directly support our primary goal: developing a drug that can normalize the tumor microenvironment—the surrounding "neighborhood" of cells and tissues around a tumor—and restore its natural ability to suppress cancer growth.

Background: What We Are Doing and Why

Pancreatic cancer is one of the most lethal cancers, with only about 1 in 8 patients surviving five years after diagnosis. One major reason is that the disease is typically detected too late, when treatments have limited impact. For this project, our team is focused on *prevention*. Specifically, on intercepting pancreatic cancer before it fully develops in people who are genetically at risk.

Our approach targets not the cancer cells themselves, but the supportive tissue that surrounds them; what we call the "neighborhood." In previous funding periods, we discovered that the main cellular residents of this neighborhood, called cancer-associated fibroblasts (CAFs), express a pair of proteins in the pancreas that are normally found only in the brain, where they play an important role in neural cell communication. These pre-synaptic and post-synaptic-like proteins are absent in healthy pancreatic tissue, but we discovered that these appear in pre-cancerous

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and cancerous lesions, where they act as a key switch that flips the neighborhood from a naturally protective state to one that actively encourages cancer to grow. Blocking this switch is the central goal of our AHEPA-funded project.

Over the course of this multi-year project, we have progressed through three phases:

- **Aim 1 (completed):** Identified the most effective antibodies capable of restoring the neighborhood's natural tumor suppressive function in our laboratory models by blocking these brain-derived synaptic-like proteins in neighborhood cells (CAFs) isolated from patient surgical samples.
- **Aim 2 (completed this period):** Tested those top antibodies as well as prototype peptides (short protein fragments designed to interfere with the pre/post-synaptic protein interaction) in laboratory models that mimic cancer survival supported by the CAFs, confirming their ability to prevent cancer cells gaining a foothold while supported by tumor promoting neighborhood cells.
- **Aim 3 (initiated this period):** Began our first animal studies to determine whether these therapeutic candidates can prevent or delay pancreatic cancer development in living systems.

Major Accomplishments: First Half of 2026

Completion of Aim 2

We are pleased to report that **Aim 2 has been successfully completed**. Using our specialized three-dimensional (3D) laboratory cultures, in which CAF cells grow within their own self-generated collagen scaffolds, closely mimicking conditions inside the human body, we rigorously tested our top antibodies and prototype peptides. Our bioengineered human pancreatic cell models, which carry genetic variants that predispose individuals to pancreatic cancer, were used to measure whether these agents could prevent the neighborhood from supporting cancer cell survival.

The results confirmed that our lead antibodies significantly outperform commercially available controls in blocking the pre/post-synaptic protein interaction and, therefore, in denying the microenvironmental advantage that a tumor-promoting neighborhood provides. These findings lay a solid foundation for moving forward with improved drug candidates.

Fully Automated Screening Assays: A Major Technical Advance

A cornerstone achievement of this period has been the development, by Dr. Aleksandr Dolskii, of fully automated, medium-throughput in vitro survival and interception assays. Completing and validating these assays was a central goal of the 2025–2026 proposal, and, we are happy to report that they are now fully operational.

Dr. Dolskii independently built an automated system for multi-color 3D confocal microscopy that captures images of dozens of experimental conditions simultaneously, and paired it with a custom digital image analysis algorithm (publicly available at https://github.com/alexdolskii/FIA-tools, v1.1) that scores proliferating versus dying cells without human bias. The complete assay and pipeline were published as an open-access protocol so that other laboratories worldwide can adopt and build upon our methods (Dolskii, Shitik, Dmitrieva, Williams et al., *protocols.io*,

2025). These same automated tools will be used again in the second half of 2026 when we screen our new drug candidates; meaning the infrastructure built for Aims 1 and 2 directly enable all future screening activities.

From the Lab to Patients: The HOST-Factor and the PLDR Clinical Trial

One of the most significant milestones of this reporting period is the formal publication of a study that connects our AHEPA-supported laboratory work directly to pancreatic cancer patient care at Fox Chase Cancer Center.

This paper, Franco-Barraza, Dmitrieva, Luong et al., Gastro Hep Advances, 2026, provides the scientific proof-of-principle that justified our PLDR clinical trial (NCT04452357), in which a modified radiation approach was tested to see whether it can reprogram the tumor neighborhood from cancer-promoting to cancer-suppressing in actual patients. Critically, this publication formally cites Dr. Dolskii's automated imaging pipeline (FIA-tools), demonstrating how AHEPA-supported tools are enabling not only drug screening but also clinical analyses.

The paper also introduces the **HOST-Factor;** a comprehensive scoring system our team developed to measure the overall "mood" of the tumor neighborhood. Negative HOST-Factor scores describe neighborhoods that are hostile to cancer growth (like dry, infertile soil), while positive scores indicate neighborhoods that are fertile ground for cancer progression. The PLDR trial, which was recently completed, is now being evaluated using this HOST-Factor framework and results from control samples are already available (see the accompanying Figure).

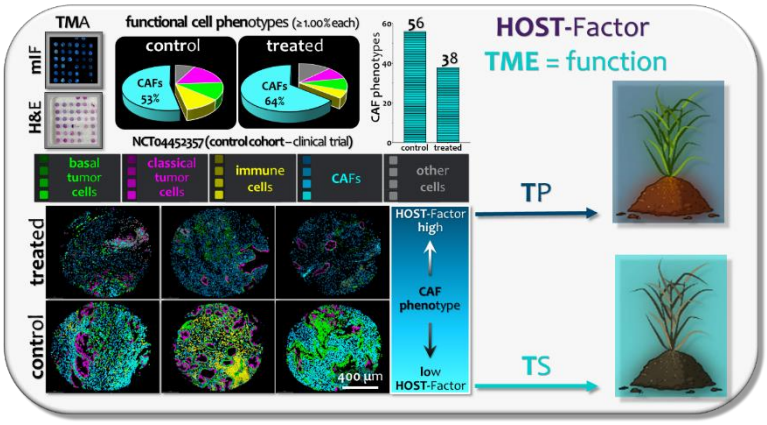


*Figure denoting how our AHEPA supported stromal research in the laboratory connects to patient care at Fox Chase Cancer Center. This figure shows the functional "neighborhood" differences between untreated pancreatic cancer patients and patients who received standard pre surgical chemotherapy plus conventional continuous radiotherapy, as measured by our sequential immunofluorescence profiling platform (the **H**armonic **O**utput of **S**tromal **T**raits Factor; HOST-Factor). Color coded "tumor mass maps" (in the bottom) show each cell type: green and magenta = cancer cells (darker tones = more aggressive), yellow = immune cells (darker tones = more pro tumoral), cyan = CAFs (tumor neighborhood cells; darker tones = more tumor promoting). After standard treatment, cancer cells are reduced but become more aggressive, CAFs increase in proportion (from 53% to 64% of the neighborhood) and become more uniformly tumor promoting (fewer diverse protective states), and immune cells diminish while the few remaining show pro tumoral immunosuppression. The HOST-Factor scores shown on the right summarize this shift: positive (fertile) scores indicate the neighborhood has become more, not less, cancer supporting after standard treatment. This is exactly the problem our AHEPA funded drug discovery project is designed to solve, by targeting the neighborhood and not just the cancer cells. For individuals*

with a cancer predisposition, the neighborhood needs to transition to tumor promoting for cancer to develop, and finding ways to prevent this switch is the goal of our multiyear proposal.

This finding powerfully reinforces why our approach matters: standard therapies kill cancer cells but inadvertently make the surviving neighborhood more dangerous. Our AHEPA-funded work aims to develop drugs that normalize the neighborhood, preventing it from fostering cancer in the first place and use cancer interception as an initial goal.

Initial *In Vivo* (in mice) Results: Encouraging Proof-of-Principle

With Aim 2 completed and our two mouse models established and validated, we initiated a **first round of *in vivo* (in living organisms) interception experiments** using the KC mouse model; a well-established genetically engineered model in which precancerous lesions (called PanINs, similar to those found in high-risk human patients) develop predictably and can be accelerated using a pancreatic irritant.

These pilot experiments were encouraging. We observed approximately a **40% reduction in high-grade precancerous lesions** in mice treated with our lead antibodies compared to controls. This confirms that targeting the tumor-promoting neighborhood can genuinely influence disease progression; exactly the proof-of-concept we needed. However, the effect, while meaningful, was more modest (using the antibodies) than what we achieved in our laboratory cell culture systems, which importantly lack any immune components. In addition, using the peptides in a different but also telling mouse model revealed an important technical issue with the prototype peptides: the **peptide controls** used in this study showed signs of triggering an immune reaction in the animals, which was also somewhat disappointing. This kind of immune response, a known challenge with first-generation protein-derived therapeutics, can confound results and limit the usefulness of these particular peptide designs in living systems.

Rather than proceed to larger animal studies with agents that carry this limitation, we have made the scientifically sound decision to first develop significantly improved prototype drug candidates that could serve as alternatives to the antibodies and peptides tested thus far. To this end, both small molecules and next generation peptides are now being designed and developed. For this, we will need to reenter the laboratory screening and *in vivo* testing phases, yet all models and assays are now established, making this approach both feasible and potentially much more meaningful. Because all approaches proposed in all three aims, including the interception mouse model, were validated during this half funding period, the next step is to equip these validated systems with better ammunition.

Plans for Second Half of 2026: Two Complementary Drug Development Tracks

The lessons from our pilot i*n vivo* study have led us to pursue **two parallel, complementary approaches** to developing better drug candidates. Both tracks will use the same automated laboratory assays built and validated during Aim 2; the technology platform AHEPA helped build is now the engine for our next phase.

Track 1: AI-Designed Small Molecules

Working closely with the Molecular Modeling Facility at Fox Chase Cancer Center, we have used artificial intelligence based computational methods to design small molecules capable of

blocking the pre and post synaptic protein interaction that drives the tumor promoting neighborhood.

The process involved three main steps. First, we identified a unique structural pocket on the presynaptic protein that is distinct from a related brain protein that, based on our evidence, may render CAFs more tumor suppressive, which we therefore want to avoid inhibiting. This ensures that any drug we develop would selectively block only the pro tumoral CAF functions. Second, we generated an ideal theoretical molecule that would fit this pocket. Third, we ran iterative artificial intelligence training cycles to identify candidate small molecules that match these ideal features and can be efficiently synthesized in the laboratory.

These 19 candidate molecules have been requested for chemical synthesis and are expected to be delivered during the second quarter of 2026. We will screen all 19 using our automated platforms, as previously done for the antibodies and peptides in the original aims 1 and 2. Depending on the results:

- If clear top performers emerge, they will advance directly to *in vivo* testing in our established mouse models, as originally planned for aim 3.
- If results are promising but the molecules need refinement, we will use the screening data to inform a second computational design cycle, improving their binding properties and overall potential drug ability before synthesizing and testing next generation compounds again in the laboratory screens, as in aims 1 and 2.

Small molecules offer significant practical advantages over antibodies for eventual clinical use: they are smaller, can more easily penetrate tissues, may be taken orally, and are generally less expensive to manufacture; all important factors for a future preventive drug for high-risk patients.

Track 2: Next-Generation Peptides via Computational Protein Design

In parallel, we have initiated a new collaboration focused on **sophisticated computational peptide design** to develop next-generation peptide drugs with improved properties. The immunogenicity issue we observed with our prototype control peptides pointed us toward an already thriving field: modern computational methods can now engineer peptides that avoid triggering immune responses, are more stable in the body, and penetrate tissues more effectively, while still blocking the specific protein interaction we are targeting.

The remarkable success of drugs like semaglutide (*Ozempic/Wegovy*) and tirzepatide (*Zepbound*), peptide-based medicines for diabetes and weight management that are now household names, demonstrates that properly designed peptides can be genuinely powerful and clinically viable drugs. We are drawing inspiration from these advances to design a next generation of peptide candidates that block the pre/post-synaptic protein interaction with greater precision, safety, and durability.

By pursuing both small molecules and next-generation peptides as independent, orthogonal strategies, we increase our probability of identifying at least one truly effective and clinically translatable drug candidate, since each class has distinct biological advantages.

Publications (September 2025 – March 2026)

The Fifth District AHEPA Cancer Research Foundation has been acknowledged in the following **5 publications** during this reporting period:

1. **Franco-Barraza, J., Dmitrieva, M., Luong, T., Egleston, B. L., Raghavan, K., Wong, J. K., Vendramini-Costa, D. B., Francescone, R., Gardiner, J. C., Handorf, E., Dolskii, A., Reddy, S. S., Meyer, J. E., & Cukierman, E.** (2026). Pulsed Low-Dose-Rate Chemoradiation Induces Stromal Reprogramming in Pancreatic CAF-Generated ECM: Quantification by the HOST-Factor. *Gastro Hep Advances*, in press. *(Pre-clinical foundation for the PLDR clinical trial; cites Dr. Dolskii's automated imaging pipeline.)* https://doi.org/10.1016/j.gastha.2026.100902
2. **Dolskii, A., Shitik, E., Dmitrieva, M., Williams, O., Miano, M., Ma, G., Luong, T., Franco-Barraza, J., & Cukierman, E.** (2025). Fibroblast/ECM functional units: A medium-throughput assay and digital analysis pipeline. *protocols.io*, Protocol ID 218562. https://doi.org/10.17504/protocols.io.e6nvwqyz7vmkv1 *(Open-access methods paper enabling global reproducibility of our screening platform.)*
3. **Dolskii, A., Alcantara dos Santos, S. A., Andrake, M., Franco-Barraza, J., Dunbrack, R. L., & Cukierman, E.** (2025). Exploring the potential role of palladin in modulating human CAF/ECM functional units. *Cytoskeleton*, 82(3), 175–185. https://www.ncbi.nlm.nih.gov/pubmed/39239855
4. **Dolskii, A., & Cukierman, E.** (2025). FABP4-tastic Pancreatic Stellate Cells Coddle KITL to Uphold Inherent Microenvironmental Tumor Suppression. *Cancer Discovery*, 15(5), 872–874. https://pubmed.ncbi.nlm.nih.gov/40304501/
5. **Shah, B., Franco-Barraza, J., Cai, K., Dmitrieva, M., Messmer, M., Yang, Y., Wasik, M., Cukierman, E., & Nejati, R.** (2025). EBV-positive Hodgkin lymphoma with immunosuppressive microenvironment during IL-23 inhibitor therapy for psoriasis. *medRxiv*, 2025.04.08.25325422. https://www.ncbi.nlm.nih.gov/pubmed/40297411

Scientific Presentations (September 2025 – March 2026)

Research supported by the AHEPA Cancer Research Foundation was presented at **6 invited national and international venues** during this reporting period:

2025

1. Israeli Society for Cancer Research (ISCR) Annual Meeting: Understanding Cancer Complexity: Advances in Cancer Mechanisms and Evolution, **Keynote Speaker**. Invited by Neta Erez and Yuval Shaked. Weizmann Institute of Science, June 10, 2025, Rehovot, Israel.
2. Cold Spring Harbor Laboratory's *Biology of Cancer: Microenvironment & Metastasis* conference. Invited Speaker. September 16–20, 2025. Cold Spring Harbor, NY.
3. AACR 2025 Special Conference on Advances in Pancreatic Cancer Research. **Conference Co-Chair**. September 28 – October 1, 2025. Boston, MA.
4. The Supriya & Shyam K. Saha Memorial GI Seminar Series, Fred Hutchinson Cancer Center. Invited Speaker. November 19, 2025. Seattle, WA.

2026

5. European Nordic Bioscience and the ECM Pharmacology Community. Invited Webinar. January 26, 2026.
6. Fox Chase Cancer Center/Temple Health Leadership Meeting Invited Speaker. Invited by Dr. Uzzo. March 20, 2026. Philadelphia PA.

Continued Impact and Recognition

Our research continues to generate national and international recognition. Among the most notable developments:

- **Appointment to the NCI Working Group on Extramural Research Concepts and Programs (2025–2028):** One of only 35 national experts appointed to advise the National Cancer Advisory Board and the NCI Director on the direction of federally funded cancer research.
- **Chair, AACR Tumor Microenvironment Working Group (2024–2026):** Steering the field's research agenda and annual meeting programming for the tumor microenvironment community.
- **Principal Investigator, NIH EMPOWER Fellowship (R25 CA259244, starting 2026):** Leading an undergraduate research training program in partnership with the University of Delaware, with a special emphasis on students from under-represented backgrounds.
- AACR 2026 Annual Meeting. **Co-Chair of the Scientific Program Committee** and **Chair of the Educational Program Committee**. April 2026. San Diego, CA.

These leadership roles directly benefit our AHEPA project: they provide visibility, foster collaborations, and create opportunities to advocate for pancreatic cancer interception strategies at the national level; opportunities seeded by the foundational research this foundation has supported since 2018.

Closing Thoughts

We believe that the completion of Aim 2, the encouraging (if modest) first *in vivo* results, the formal publication connecting our laboratory work to a completed clinical trial, and the launch of our dual-track small molecule and next-generation peptide programs together represent substantial progress in this first half of the 2025–2026 funding period.

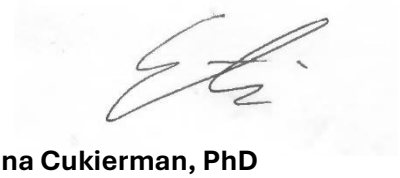
The automated laboratory tools built with AHEPA support have proven their value not once but twice; first in the drug screening studies that are the heart of this project, and now in the analyses of our clinical trial patients. That ripple effect from laboratory to clinic is a direct testament to what your foundation's investment makes possible.

As we enter the second half of 2026, we plan to initiate the screens for the 19 AI-designed small molecule candidates and advance our new peptide design collaboration (in silico), using the same validated assay platforms we have spent years building and are now fully automized. The interception model in mice is ready and waiting. The goal now is to identify the best possible therapeutic candidates before we commit to the definitive animal studies that will bring us

closest to a first-in-class drug for preventing pancreatic cancer in people who carry the highest risk.

We are deeply grateful for the Fifth District AHEPA Cancer Research Foundation's unwavering support across now our 30+ year relationship with Fox Chase Cancer Center. We look forward to continuing this enormously fruitful collaboration.

With deepest appreciation and respect,



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