A. Personal Statement

I) Research description. The focus of my research program is to develop T cells into platform vector therapeutics that actively seek disease sites, assess disease burden, and synthesize proportionate amounts of therapeutic drugs. Central to this research is the role that T cells play in immune-surveillance. Upon sensing the chemotactic gradient created by the disease cells, they extravasate out of the blood vessels and actively traffic through multiple solid tissues to ablate the disease cells. This offers the possibility of directing the cytotoxic effect specifically to the diseased cells and preventing damage to healthy cells.

II) Technical expertise and personal attributes. My experience in the manufacturing industry and translational medicine provide me with the vision to conceive complex cross-disciplinary projects and skills to execute them efficiently. Driven by intellectual curiosity, I have taken risks to continuously explore outside my comfort zone. This is evident from my core expertise that is centered around cellular engineering\textsuperscript{1,2} and materials science\textsuperscript{3,4}, and broadly spans over biosciences and physical sciences. I use this expertise to conceptualize innovative solutions that are unbiased from the technological standpoint and focus on the critical unmet clinical needs. Meanwhile, my resilience empowers me to not quit and continue to stay invested in the career risks that I have taken. In the midst of difficult times, these attributes drive me to find innovative and lean approaches that extends the available resources. In better times, I continue to build upon this lean model. Together with my experience in translation of technologies from laboratory to the factory floor, this helps me in developing teams with individuals that bring their complementary strengths to the project. The breadth in my vision is further exemplified by the following projects encompass my current program:

1. T-cell Biofactory. Many host-defense peptides of non-human origin have anti-tumor activity and are not affected by the local immunosuppression of the tumor microenvironment. However, passive diffusion and high interstitial fluid pressure in the tumor limit their efficacy. When infused, they are quickly degraded, and administering high doses is toxic to normal cells. My group has proven the feasibility of engineering the T cell to synthesize non-human proteins directly at the disease site. We are now developing the T-cell Biofactory to respond to different physiological triggers and applying this platform to target solid tumors and viral infections.

2. Integrated Bioreactor. Targeting of self-antigen in healthy tissues by T cells engineered to express chimeric antigen receptors (CAR) causes on-target off-tissue toxicity. We have developed an inline electroporation device that transforms large populations of T cells with CAR mRNA, which is transient in nature. We are now developing an upstream bioreactor for selectively culturing chemotactically competent T cells and will thus manufacture CAR T cells with enhanced efficacy and safety.

III) Career Trajectory. I completed my PhD in Biomedical Engineering from Cornell University (2003-07). My research was in high-resolution photo-patterning of multiple proteins in hydrogel-based biomaterials, self-assembled monolayers, and polymer brushes. In this research, I capitalized on my expertise in microfabrication, micro-electro-mechanical systems and corrosion by applying it to biomedical applications. I also utilized this expertise to develop a multiplexed electrospray protein printer. I wanted to then apply my microfabrication expertise to medicine. Cell engineering was a natural choice because microfluidics offers a competitive advantage as the dimensions of cells match the feature size that can be produced by microfabrication. However, I wanted to first understand the process for transforming laboratory science into
usable technology. This is important to me because with an engineering mindset, it has been my prime career goal. Therefore, I joined Intel’s division of Portland Technology Development (2007-10). This is a world-class facility that pushes the limits of manufacturing sciences by experimenting with new methods in production planning and statistics on the factory floor. Here, I developed my expertise in technology scale-up that covered workforce training and statistical qualification of the semiconductor products, tools, and processes. Finally, I entered into the field of translational research as post-doctoral trainee at MD Anderson Cancer Institute with a joint position at Houston Methodist Research Institute (2010-12). During my postdoctoral work, I developed methods for imaging T cells by transfecting them with nanoparticle-based multi-modal contrast agents (radioactive, magnetic, fluorescence). In this research, I found that ~ 20 times more nanoparticles are transferred across the liver and spleen compared with direct injection. In my independent research (2012-current), this drove my initial plan to engineer the T cells to actively transport the nanoparticle-prodrug conjugates to their target sites and activate the prodrug through the intracellular T-cell activation cascade. With increased understanding of the T-cell immunity, I have transformed this strategy of engineering T cells into a platform vector therapeutics, i.e. T-cell Biofactories.

IV) Competitive advantage. My research is strengthened by my industry experience that provides solutions for translational roadblocks, including working with a large and diverse workforce for translating technologies from laboratory to manufacturing. The following two decisions continue to support my success:

1. Manufacturing industry experience. I joined Intel Corp. because I wanted to understand how to transform laboratory science into technology. I learned statistical techniques in Quality-by-Design and Design of Experiments; and managed large process trials on the factory floor for new product development. I contributed as a team member and gained managerial experience by coordinating a work force of ~ 30 technical operators on specific projects. The success of the project was, in part, a result of my focused efforts to help each operator gain visibility through their increased productivity.

These experiences form the cornerstone of my success. I used my managerial skills to develop a team of scientists and academic cores. I also cultivated a semiconductor statistics-based company (Stat-Ease, Inc.) to develop Design of Experiments for immunotherapies. Using this approach, I efficiently manage resources to swiftly generate the preliminary data and successfully competed for various grants.

2. Translational medicine experience. I wanted to identify important unmet needs in medicine that are barriers to effective treatment. Thus, I accepted a joint position in the laboratories of Dr. Laurence Cooper at MD Anderson and Dr. King Li at The Methodist Hospital in Houston, TX. I chose an area outside my comfort zone so I could acquire a new skillset and combine it later with my materials science expertise.

A transdisciplinary approach to target unmet needs in translational medicine now forms the foundation of my research. For example, I proved the feasibility of in situ T-cell mediated drug synthesis, which is an early step in the continuum of research I am currently pursuing.

* Indicates corresponding author


B. Positions and Honors

Positions and Employment

<table>
<thead>
<tr>
<th>Year</th>
<th>Position</th>
<th>Company/Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-1998</td>
<td>Quality Engineer</td>
<td>Star Wire (India) Ltd. Integrated Mini Steel Plant</td>
</tr>
<tr>
<td>2000-2002</td>
<td>Engineer</td>
<td>IBM Research, Magnetoelectronics</td>
</tr>
<tr>
<td>2007-2010</td>
<td>Senior Engineer</td>
<td>Technology and product ramp up to production, Intel Corp., Hillsboro, OR</td>
</tr>
<tr>
<td>2012-2015</td>
<td>Assistant Professor</td>
<td>Cancer Technologies, Ob/Gyn</td>
</tr>
<tr>
<td>2015-</td>
<td>Program Director</td>
<td>Cell-based Medicine, Biosciences Division, SRI International, Menlo Park, CA</td>
</tr>
</tbody>
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Awards

<table>
<thead>
<tr>
<th>Year</th>
<th>Award</th>
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<tbody>
<tr>
<td>1995</td>
<td>National Award for Science Innovation; Indian Institute of Technology (IIT), Kanpur, India</td>
</tr>
<tr>
<td>1995</td>
<td>Gold Medal for Scientific Lecture; Institution of Engineers, India</td>
</tr>
</tbody>
</table>
1997  Second Best All-rounder Student among 1500 BS students; NIT Warangal, India
2002  Achieved IBM First Invention Plateau; Hopewell Junction, NY
2003-2004  Cornell NanoBiotechnology Center Fellow; Ithaca, NY
2011  NSF Fellowship – Cancer Nanotechnology, Houston, TX
2013  Winner, InnoCentive Crowdsourcing: Metal processing for improved power transmission
2014  Fellowship – Cold Spring Harbor Laboratory – Synthetic Biology course
2014  Baylor's single nominee for 2014 Pew-Stewart Scholars for Cancer Research
2014  Edmund Optics Educational Award finalist
2016  Fellowship – Cold Spring Harbor Laboratory – Antibody Engineering & Phage Display course
2016  Nominee for the SRI Achievement Award
2017  Fellowship – Cold Spring Harbor Laboratory – The Genome Access course / Bioinformatics

Selected Invited Talks
Bio2Device, Palo Alto, CA, Jun 9, 2019; University of Massachusetts Horae Gene Therapy Center, Worcester MA, Jan 17, 2019; System Biosciences, Palo Alto, CA, Sep 19, 2018; SynBioBeta 2018, San Francisco, CA, Oct. 1-3, 2018; NCI’s 18th Annual IMAT Meeting, Bethesda, MD, Dec. 6-8, 2017; Biomedical Engineering, Texas A&M University, College Station, TX, Oct 20, 2017; Weill Cornell Medicine, New York, NY, Nov 16, 2017; Biomaterials Day, University of South Dakota, Sioux Falls, SD, May 11, 2017; Biomedical Engineering, University of South Dakota, Sioux Falls, SD, May 12, 2015; Houston Methodist Research Institute, Houston, TX, Mar 12, 2015; Roche – Nature Biotechnology Symposium 2014, Buonas, Switzerland, Sep 3-5, 2014 Fannin Innovation Studio, Houston, TX, Jul 7, 2014; All India Institute of Medical Sciences, New Delhi, India, Dec 24, 2013; Gulf Coast Consortia Keck Seminar, Rice University, Houston, TX, Oct 25, 2013; BioScience Research Collaborative, Rice University, Houston, TX, Sep 11, 2013; NCI’s Physical Sciences – Oncology Centers, National Cancer Institute, Bethesda, MD, Jul 29, 2013; International Translational Nanomedicine Conference, Northeastern University, Boston, MA, Jul 27, 2013; Banbury ThinkTank, Cold Spring Harbor Laboratory, Long Island, NY, Jul 14-16, 2013; Biomaterials Day, The University of Texas at Austin, Austin, TX, May 31, 2013; Translational Health Science and Technology Institute, Gurgaon, Haryana, India, Jan 17, 2012; IBM Almaden Research Center, San Jose, CA, Jul 16, 2010; Biosystems Research, Sandia National Laboratories, Livermore, CA, Nov 16, 2009; Techkriti ’95, Indian Institute of Technology, Kanpur, Apr 7, 1995

Press Releases
2018: Oct 24 – NIBIB Science Highlight: T-cell biofactories find, fight disease in one fell swoop
2019: July 16 – SRI International: Parijat Bhatnagar Wins Prestigious DARPA Young Faculty Award

Other Experience and Professional Memberships
Biomedical Engineering Society; American Society for Virology, Society for Immunotherapy of Cancer; Stanford Cancer Institute, Stanford University; American Association for Cancer Research; American Society of Mechanical Engineers; The Electrochemical Society; NACE International; Materials Research Society.

C. Contribution to Science
1. Modular antigen-specific T-cell Biofactory; antigen-presenting Artificial Disease Cells. I have developed an artificial cell-signaling cascade that transforms the T cell into a cell-based therapeutic delivery platform, i.e. T-cell Biofactory. The signaling cascade was designed as a single DNA sequence comprising three constant and two variable domains arranged in cis. The constant domains provide functionality to the T-cell Biofactory; and the variable domains can be exchanged to neutralize the pathology that triggered the T-cell Biofactory. To validate their function, I also developed Artificial Disease Cells that present live/dead markers along with disease biomarkers. This is innovative because of the simplicity of the artificial cell-signaling cascade design enables its separation from the complexities of the biological cell and transforms the cell into a vector for synthesizing engineered therapeutic proteins in situ. This “cellular medicine” is significant because it will actively locate disease sites, assess the disease burden, and synthesize a calibrated amount of protein-based therapeutic upon stimulation by the disease cells.

1. **Platform technology for ex vivo mass-screening and early detection.** Current approaches in disease detection relies on manifestation of clinical symptoms, which is not accurate and rarely early enough. Mass-screening for early detection offers an alternative strategy but is hampered by the lack of low-cost point-of-care sensor technology in low-resource settings. I have genetically engineered immortalized cell line into platform sensor-technology that can be rapidly expanded at low manufacturing cost for distribution. The innovation in this work lies in introducing a transmembrane receptor sensor that actuates the intracellular machinery to autonomously express a reporter transgene. This is significant because it will enable early diagnosis of many cell-based toxicities (cancer, autoimmune disorders, viral infections), which is critical in controlling the spread of epidemics and reducing the tissue/organ damage.


2. **Multi-modal (PET-MRI) imaging of adoptively transferred T cells; transport past the mononuclear phagocytic system (MPS).** Off-tumor trafficking of the T cells is responsible for various adverse events in the clinic and monitoring their biodistribution offers a way to mitigate this. I used controlled DMSO exposure to transiently permeabilize the T-cell membranes and used anionic PET-MRI-fluorescent nanoparticles to translocate through these membrane pores of cells that are negatively charged. This provides a solution to image adoptively transferred T cells with high sensitivity and high resolution. In this work, I made an additional discovery that 20 times more nanoparticles get across the MPS when loaded into T cells compared to their direct injection. This is innovative because I used a materials science approach to circumvent the barrier to enter the non-phagocytic T cells and found that T cells offer the potential to be used as vectors to transport nanomedicine across MPS. The significance is that it will make current T cell therapies safer and offers the potential for developing T cells as an in vivo vector for drug delivery.


   b. **Bhatnagar, P.**; Cooper, L.J.N (MD Anderson Cancer Center, USA). Image-Guided Adoptive T Cell Therapy Using Multi-Modal Contrast Agents. (2013); (licensed to Intrexon, Ziopharm)


3. **Photolithographic patterning of multiplexed proteins.** Study of the genesis of osteochondral tissue junction from mesenchymal stem cells requires patterning of multiple growth factors at micron-resolution. I developed a photosensitive hydrogel composite material stack assembly on a silicon wafer and used projection lithography to sequentially pattern proteins. This approach is innovative because current techniques to generate protein patterns do not provide high-resolution and result in denaturation of proteins. This is significant because generation of physiological junctions from stem cells, compared to the use of adhesive or sutures, improves the quality of graft and its integration with individual tissues in vivo. Additionally, the process can also be used to mass manufacture biosensors in microfabrication foundry.


4. **Micro-machined printer for additive manufacturing of high-resolution protein arrays.** Contact-
mode protein deposition systems are incompatible with soft hydrogel surfaces. Electrospray offers the advantage of non-contact deposition at high resolution. I used micromachining tools to create a device with multiple electrospray tips casted from a single silicon wafer and used it to generate multiplexed protein arrays from nanoliter volumes. This approach is innovative because we used micromachining for precision alignment that circumvents the placement issues in parallel electrospray tips where the current can follow the path of least resistance and render all but one tip non-functional. This is significant because this will lead to high-volume chip manufacturing for proteomics studies and enable a 3D printer for micrometer resolution.


**D. Research Support**

**Active**

1. **DP2 EB024245-01**
   - Bhatnagar (PI)
   - NIH – Director’s New Innovator Award
   - Title: Self-assembled therapeutics with spatiotemporal resolution.
   - Major goal: To transform T cells into a platform therapy for treating infectious diseases.
   - Role: Principal Investigator
   - Impact Score: 20
   - 9/30/2016-9/29/2021

2. **R21 CA236640-01**
   - Bhatnagar (PI)
   - NIH/NCI – Early-Stage Innovative Molecular Analysis Technology Development for Cancer Research
   - Title: T-cell Biofactories for targeting interstitial fluid pressure.
   - Major goal: To develop T cells that will normalize the intra-tumoral IFP.
   - Role: Principal Investigator
   - Impact Score: 21

3. **DARPA-RA-18-02-YFA-ES-170**
   - Bhatnagar (PI)
   - DARPA Young Faculty Award
   - Title: Remote Regulation of Cellular Medicine with Extracorporeal Devices
   - Major goal: To extra-corporeally control the immune system as prophylaxis against viral infections
   - Role: Principal Investigator
   - Impact Score: 21
   - 7/01/2019-6/30/2022

**Completed**

4. **R21 CA193064-01**
   - Bhatnagar (PI)
   - NIH/NCI – Early-Stage Innovative Molecular Analysis Technology Development for Cancer Research
   - Title: Cellular Biofactories for therapeutic protein synthesis in tumor microenvironment.
   - Major goal: Development of a molecular switch in T cells for autonomous regulation and biosynthesis of anti-tumor molecules selectively at the tumor site.
   - Role: Principal Investigator
   - Impact Score: 22
   - 6/1/2015-5/30/2018

5. Junior Faculty Seed Award
   - Bhatnagar (PI)
   - ARCO Foundation Young Teacher-Investigator Award and the Naman Family Fund for Basic Research
   - Title: Towards Natural-Orifice Based Early Detection of Ovarian and Fallopian Tube Neoplasia.
   - Major goal: To develop T cells as tumor seeking imaging agents.
   - Role: Principal Investigator
   - 7/1/2013-6/30/2014

6. **BWF 1012768**
   - Bhatnagar (PI)
   - Burroughs Wellcome Fund
   - Title: Development of Surgical Robotics for Single Port Laparoscopic Surgery for Uterine Myomectomy.
   - Major goal: To support application of existing camera technology to single-port myomectomy.
   - Role: Principal Investigator
   - Impact Score: 22
   - Awarded, but not accepted
   - 7/1/2013-5/31/2014

7. **U54 CA143837-05**
   - Ferrari (PI)
   - NIH/NCI – Center for Transport Oncophysics – PSOC Pilot Project
   - Title: Enhancing anti-cancer immunotherapy by combining Gene Research and Nano-Technology.
   - Major goal: Nanoparticles as pre-clinical imaging agents for T cells modified to target B-cell lymphoma.
   - Role: Principal Investigator (Pilot Project, Sub-Award)
   - Impact Score: 22
   - 9/24/2012-7/31/2013

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