BIOGRAPHICAL SKETCH

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NAME: Gao, Jinming

eRA COMMONS USER NAME (credential, e.g., agency login): JINMINGGAO

POSITION TITLE: Professor of Biomedical Engineering, Cell Biology, Otolaryngology, and Pharmacology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Beijing University, Beijing, China	B.Sc.	1991	Chemistry
Harvard University	Ph.D.	1996	Physical Organic Chemistry
Massachusetts Institute of Technology (MIT)	Postdoctoral	1998	Biomedical Engineering

A. Personal Statement

My primary research interest involves harnessing nanotechnology and cancer biology to convert inherent tumor or immunological signals into precision cancer medicine. In the past decade, my lab has focused on the design and development of transistor-like nanoparticles to introduce an OFF→ON paradigm to magnify cancer specificity in therapy. These efforts are aimed at overcoming the on-target, off-tumor toxicity of conventional therapeutics that are 'always ON' in cancerous or healthy tissues. In image-guided surgical therapy, we incorporated molecular cooperativity concept to synthesize a library of proton transistor nanoparticles. These nanoparticles are 'silent' during blood circulation but turn on the fluorescent illumination in the acidic tumor microenvironment for occult disease detection. Pegsitacianine, one such pH-activatable nanosensor, recently received FDA Breakthrough Therapy Designation in cytoreductive surgery of peritoneal metastasis. A completed Phase 2 clinical trial show Pegsitacianine identified unresected residual diseases in over 50% patients after routine cancer surgery. The proton transistor nanoparticles also allowed safe delivery of potent immune cytokines (e.g., IL-2 Fc) with greatly increased therapeutic window. To activate the innate immune pathways, we also discovered a unique class of synthetic polymers (PC7A, PSC7A) that allow non-canonical STING activation via cooperative, polyvalent STING condensation. Polymer-induced STING activation prevents lysosomal degradation unlike small molecule agonists, thereby improving the antitumor immunity in multiple tumor models including immune cold tumors. In vaccine applications, these nanoparticles exhibited a robust Th1, Th2 and cytotoxic T cell response, surpassing traditional adjuvants such as Alum or CpG. We recently established a "shock-and-lock" STING activating nanoparticle and identified a subset of dendritic cells (cDC1) that are essential for STING-mediated tumor rejection. A related nanoparticle agonist (ONM-501) has been approved by the FDA for clinical evaluation in cancer patients with advanced solid tumors and lymphomas (NCT06022029). I am currently spearheading the UTSW U54 Nano-Immune-Engineering Center which converge immunological discoveries with technology innovation to advance cancer immunotherapy.

Recent research support:

U54 CA244719 9/24/19-8/31/24
Gao (PI)
Nano-Immuno-Oncology Approaches to Overcome Tumor Immune Evasion

NIH-NCI 1R01 CA289258 9/1/2023-8/31/2028
Gao (Leading Co-PI)
Tumor-activatable Interleukin-2 Superkine Nanoparticle Therapy

R01 CA216839 4/1/18-8/31/23
Gao (PI)
STING-Activating Synthetic Nanovaccine for HPV-induced Cancers
(A pending competing renewal received a 2% score)

RP220150 3/1/22-8/28/25
Cancer Prevention and Research Institute of Texas
Gao (PI)
Turn ON the Antitumor Immunity in Metastatic Cancers

R01 CA266146 12/1/21-11/30/26
Sumer (PI)
A pH Responsive Transistor-like Nanoprobe for Sensitive Detection of Unknown Primary Cancers of the Head and Neck

Citations:

1. Luo M, Wang H, Wang Z, Cai H, Lu Z, Li Y, Du M, Huang G, Wang C, Chen X, Porembka MR, Lea J, Frankel AE, Fu Y, Chen ZJ, Gao J. A STING-activating nanovaccine for cancer immunotherapy. ***Nature Nanotech.*** 2017, 12, 648-654.
2. Wang X, Wilhelm, J, Li W, Li S, Wang Z, Huang G, Wang J, Tang H, Khorsandi S, Sun Z, Evers B, Gao J. Polycarbonate-based ultra-pH sensitive nanoparticles improve therapeutic window. ***Nature Comm.*** 2020, *11,* 5828.
3. Li S, Luo M, Wang Z, Feng Q, Wilhelm J, Wang X, Wang J, Cholka A, Sumer BD, Yu HT, Gao J. A Prolonged activation of innate immune pathways by a polyvalent STING agonist. ***Nature Biomed. Eng.*** 2021, 5, 455-466.
4. Wang J, Li S, Wang M, Wang X, Chen S, Sun Z, Ren X, Huang G, Sumer BD, Yan N, Fu YX, Gao J. STING licensing of type I dendritic cells potentiates antitumor immunity. ***Sci. Immunol.*** 2024, 9, 3945.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2010-now	Professor of Biomedical Engineering (2023-), Cell Biology (2020-), Otolaryngology (2016-) and Pharmacology, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX
2019-now	Member of Steering Committee, Immune-Oncology Translational Network, NCI
2018-2022	Member of External Advisory Council, Center for Scientific Review, NIH
2014-2016	Chair, NIH Gene and Drug Delivery study section
2005-2010	Associate Professor of Oncology and Pharmacology with tenure, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX
2005-now	Adjunct Professor of Chemistry and Bioengineering (2010-), University of Texas at Dallas, Richardson, TX
2004-2005	Associate Professor with tenure, Departments of Biomedical Engineering and Radiology, Case Western Reserve University, Cleveland, OH
1998-2004	Assistant Professor, Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

Honors

2024	Fellow, American Institute of Medical and Biological Engineering (AIMBE)
2023	Fellow, National Academy of Inventors (NAI)
2020	Elaine Dewey Sammons Distinguished Chair in Cancer Research, in Honor of Eugene P. Frenkel, MD, UT Southwestern Medical Center
2019	Immuno-engineering to Improve Immunotherapy (I3) Center Award, Beau Biden Cancer Moonshot^{SM} Initiative, National Cancer Institute
2018-	Mendelson-Young Endowment in Cancer Therapeutics, UT Southwestern Medical Center
2018-2020	Robert B. and Virginia Payne Professorship in Oncology, UT Southwestern Medical Center
2011	Elkin lecture, Winship Comprehensive Cancer Center, Emory University

2011 Distinguished Scientist Award from the Society of Experimental Biology and Medicine
2000 Young Investigator Award from the Whitaker Foundation
1991 Highest Honor Guanghua Fellowship, Beijing University, Beijing, China

C. Contributions to Science

I. Molecular recognition and tissue engineering. My early graduate work with George Whitesides included trainings in physico-organic chemistry and protein biochemistry to study the roles of molecular recognition in biology. My thesis work focused on the investigation of hydrophobic effect (size and shape) and electrostatics (charge) on protein-ligand interactions. I invented a "protein charge ladder" to first determine the effective charges of proteins in solution, and further quantified the contribution of electrostatic interactions in molecular recognition. My postdoctoral work with Laura Niklason and Robert Langer started with surface modification of polymer scaffold to solve the problem of low cell seeding density and viability, which led to the first tissue engineered vascular prosthesis in a jar.

Selected publications:

1. Gao J, Gomez FA, Haerter, R, Whitesides GM. Determination of the Effective Charge of a Protein in Solution by Capillary Electrophoresis. ***Proc. Natl. Acad. Sci. USA***, 1994, *91*, 12027-12030.
2. Gao J, Mammen M, Whitesides GM. The Use of Protein Charge Ladders to Evaluate Electrostatic Contributions to Biomolecular Recognition. ***Science*** 1996, *272*, 535-537.
3. Gao J, Niklason L, Langer RS. Surface Hydrolysis of Poly(glycolic acid) Meshes Increases the Seeding Density of Vascular Smooth Muscle Cells. ***J. Biomed. Mater. Res***. 1998, *42*, 417-424.
4. Niklason L, Gao J, Abbott W, Hirschi K, Houser S, Marini R, Langer R. Functional Arteries Grown *In Vitro*. ***Science*** 1999, *284*, 489-493.

II. Molecular basis of cooperativity. Cooperativity broadly manifests itself from biology to society. In biology, cooperativity exhibits inter-dependent multi-component biological processes where the whole is bigger than the sum of its parts. In materials science, non-covalent self-assembly offers a versatile and modular strategy to generate functional architectures that often display dynamic, cooperative behaviors in response to environmental stimuli. Recently, our lab has discovered several unique cooperative systems with all-or-nothing bistable states without intermediates. In a representative example, hydrophobic micellization drove divergent proton distribution of transistor-like ultra-pH sensitive nanoparticles with a Hill coefficient of 51, by far the largest reported in the literature. We are elucidating the molecular underpinnings of cooperative systems and further applying these principles as a key design concept to innovate nanotherapeutics to improve the precision of medicine.

Selected publications:

1. Ma X, Wang YG, Zhao T, Li Y, Su LC, Wang Z, Huang G, Sumer BD, Gao J. Ultra-pH Sensitive Nanoprobe Library with Broad pH Tunability and Fluorescence Response. ***J. Am. Chem. Soc.*** 2014, *136*, 11085-11092. (*Using hydrophobic nanophase separation to fine tune threshold pH to achieve a library of nanosensors with tunable pH from 4.0 to 7.4; Selected as ACS Editors' Choice*) PMC4132961
2. Li Y, Zhao T, Huang G, Sumer B, Gao J. Molecular Basis of pH-Triggered Molecular Self-Assembly. ***Nature Comm.*** 2016, *7*, 13214. *(Uncovered molecular mechanism of pH cooperativity and identified unprecedented all-or-nothing proton distribution phenotype with a Hill coefficient of 51)* PMC5095283
3. Li Y, Wang Y, Huang G, Gao J. Cooperativity Principles in Self-Assembled Nanomedicine. ***Chem. Rev.*** 2018, *118*, 5359-5391. (*Theory on molecular origin of cooperative behaviors in nature and engineered systems. Implementation of cooperativity design in nanomedicine to achieve therapeutic precision and robust action*) PMC6524957
4. Wang M, Singh P, Feng Q, Wilhelm J, Bennett ZT, Huang G, Gao J. Elucidation of Protonation Cooperativity of STING-Activating Polymer. ***Adv. Mater***. 2023, 2305255. (*Characterization of cooperative protonation behavior of a STING-activating polymer and its development for pH-activatable drug delivery)* PMID: 37541432

III. Polymeric STING agonist for cancer immunotherapy. The stimulator of interferon genes (STING) pathway for cytosolic DNA sensing plays a key role in immune defense against cancer cells. Small molecule STING agonists have shown potent antitumor activities in mouse models; however, these agents have not yet demonstrated significant antitumor response in clinical trials. To overcome current limitations, we discovered a unique class of synthetic polymers (PC7A, PSC7A) that allow non-canonical STING activation via cooperative, polyvalent STING condensation. Polymer-mediated STING activation prevents rapid lysosomal degradation, thereby prolonging type I-interferon expressions over small molecule agonists. In vaccine applications, these

nanoparticles exhibited a robust Th1, Th2 and cytotoxic T cell response, surpassing traditional adjuvants such as Alum, CpG and Poly(I:C). We recently established a "shock-and-lock" STING activating nanoparticle that displays broad antitumor immunity including immune cold tumors over small molecule agonists (cGAMP, Adu-S100). Mechanistic studies illustrate the crucial role of conventional type 1 dendritic cells (cDC1) in STING-mediated tumor rejection. A related nanoparticle agonist (ONM-501) has been approved by the FDA for Phase I clinical trials in cancer patients with advanced solid tumors and lymphomas (NCT06022029).

Selected publications:

1. Luo M, Wang H, Wang Z, Cai H, Lu Z, Li Y, Du M, Huang G, Wang C, Chen X, Porembka MR, Lea J, Frankel AE, Fu Y, Chen ZJ, Gao J. A STING-activating nanovaccine for cancer immunotherapy. ***Nature Nanotech.*** 2017, 12, 648-654. *(Spatio-temporal orchestration of antigen delivery and innate stimulation using minimalist (single) polymer design with broad efficacy in multiple tumor models*) PMC5500418
2. Li S, Luo M, Wang Z, Feng Q, Wilhelm J, Wang X, Wang J, Cholka A, Sumer BD, Yu HT, Gao J. A Prolonged activation of innate immune pathways by a polyvalent STING agonist. ***Nature Biomed. Eng.*** 2021*,* 5*,* 455-466. (*Biochemical elucidation of STING activation by PC7A through biomolecular condensation. PC7A led to prolonged STING activation and sustained expression of proinflammatory cytokines over cGAMP, a natural agonist*) PMC8126516
3. Wang X, Wilhelm, J, Li W, Li S, Wang Z, Huang G, Wang J, Tang H, Khorsandi S, Sun Z, Evers B, Gao J. Polycarbonate-based Ultra-pH Sensitive Nanoparticles Improve Therapeutic Window. ***Nature Comm.*** 2020*, 11,* 5828. (*Design and syntheses of new biodegradable UPS polymers including STING-activating PSC7A with improved safety and T cell activation properties*) PMC7673035
4. Wang J, Li S, Wang M, Wang X, Chen S, Sun Z, Ren X, Huang G, Sumer BD, Yan N, Fu YX, Gao J. STING licensing of type I dendritic cells potentiates antitumor immunity. ***Sci. Immunol.*** 2024, 9, 3945. *(Identification of the essential role of cDC1 in STING-mediated tumor rejection and establishment of a STING-cDC1 biomarker in predicting patient response to immunotherapy)*

IV. Nano-Immuno-Oncology. Nano-immuno-oncology is an emerging cross field that harnesses nanotechnology's unique synergy with immunology to advance cancer immunotherapy. Human immune system has evolved to sense and respond to nano- and micro-particulates (e.g., viruses, bacteria). Through the versatile control of composition, size, shape, and surface properties of nanoparticles, nanotechnology approaches are uniquely positioned to mount appropriate immune responses against cancer. Our lab is leveraging the all-or-nothing protonation cooperativity of the ultra-pH sensitive nanoparticles and non-canonical STING activation to augment the cancer-immunity cycle toward anti-tumor immunity. These efforts include T cell vaccination by coordinating cytosolic delivery of tumor antigens to dendritic cells with simultaneous activation of STING, tumor-targeted delivery of acidotic inhibitors to overcome T cell retardation, and pH-activatable delivery of immune cytokines for cancer immunotherapy. Through an NCI-sponsored U54 Nano-Immune-Engineering Center Award, we are integrating nanotechnology, immune cell biology and tumor immunology to advance cancer immunotherapy.

Selected publications:

1. Luo M, Liu Z, Zhang X, Han C, Samandi LZ, Dong C, Sumer BD, Lea J, Fu YX, Gao J. Synergistic STING Activation by PC7A Nanovaccine and Ionizing Radiation Improves Cancer Immunotherapy. ***J. Controlled Release.*** 2019*, 300,* 154-160*. (Combination of nanoparticle vaccine with radiation therapy can overcome tumor immune resistance)* PMID: 30844475
2. Huang TY, Feng Q, Wang ZH, Li W, Sun ZC, Wilhelm J, Huang G, Vo T, Sumer BD, Gao J. Tumor-targeted Inhibition of Monocarboxylate Transporter 1 Improves T Cell Immunotherapy of Solid Tumors. ***Adv. Healthc. Mater****.* 2021, *10*, 2000549. *(Nano delivery of a tumor acidotic inhibitor reversed the immune suppressive tumor microenvironment, resulting in improved antitumor efficacy at dramatically reduced the dose by >200 fold over free drug alone)* PMC7674253
3. Wilhelm J, Perez MQ, Basava V, Gao J. Antigen Folding Improves Loading Efficiency and Antitumor Efficacy of PC7A Nanoparticle Vaccine. ***J. Controlled Release.*** 2020, *329*, 353-360. *(Micelle-induced antigen folding resulted in increased loading efficiency and T cell priming)* PMC7904583
4. Li S, Bennett ZT, Sumer BD, Gao, J. Nano-Immune-Engineering Approaches to Advance Cancer Immunotherapy: Lessons from Ultra-pH-Sensitive Nanoparticles. ***Acc. Chem. Res.*** 2020*, 53,* 2546-2557 *(Succinct review on the use of cooperative nanoparticles to boost cancer-immunity cycle)* PMC8201660

V. Threshold pH sensors for cancer imaging and surgery. Over 1 million cancer surgeries are performed in the US and 5 million worldwide each year. Obtaining tumor-free surgical margins is important to achieve disease-free survival while minimizing removal of normal tissues is equally important to preserve quality of life. To achieve clear margin delineation in a broad set of tumors with diverse tissue origin and cancer genotypes/phenotypes, we have developed a transistor-like pH threshold sensor to image tumor acidosis, a universal cancer hallmark downstream of deregulated energetics (e.g., Warburg effect). Fluorescence quenching was achieved at the micelle state to abolish imaging signals during blood circulation, but allow exponential activation in the mildly acidic tumor microenvironment. The signal amplification strategy allowed the detection of occult tumor nodules <1 mm in size. Real-time, fluorescence-guided surgery achieved >70% cancer cures in mice bearing head and neck tumors. Recently completed Phase 1/2 trials demonstrate the safety and effectiveness of the UPS nanosensor (Pegsitacianine) in tumor detection, which led to the Breakthrough Therapy Designation by the FDA.

Selected publications:

1. Wang Y, Zhou K, Huang G, Hensley C, Huang X, Ma X, Zhao T, Sumer BD, DeBerardinis RJ, Gao J. A Nanoparticle-based Strategy for the Imaging of a Broad Range of Tumours by Nonlinear Amplification of Microenvironment Signals. ***Nature Mater.*** 2014, *13*, 204-212. *(Demonstration of amplifying tumor microenvironmental signals as a universal strategy for tumor imaging)* PMC3946908
2. Zhao T, Huang G,Yang S, Ramezani, S, Li Y, Wang Y, Ma X, Xie XJ, Thibodeaux J, Sun X, Sumer BD, Gao J. A Transistor-like pH Nanoprobe for Tumour Detection and Image-Guided Surgery. ***Nature Biomed. Eng***. 2016*, 1*, 0006. *(Chemical transistor concept to achieve binary tumor margin delineation to improve cancer detection and surgery)* PMC5617128
3. Voskuil FJ, Steinkamp PJ, Zhao T, van der Begt B, Koller M, Doff JJ, Jayalakshmi Y, Hartung JP, Gao J, Sumer BD, Witjes MJH, van Dam GM. Exploiting metabolic acidosis in solid cancers using a tumor-agnostic pH-activatable nanoprobe for fluorescence-guided surgery. ***Nature Comm.*** 2020, 11, 3257. (*First-in-human clinical trial of pH threshold sensor ONM-100 in 30 cancer patients with breast, head/neck, colorectal and esophageal cancers. Imaging efficacy in all patients demonstrating the pan-tumor characteristics without severe adverse events*) PMC7320194
4. Feng Q, Bennett Z, Grichuk A, Huang TY, Faubert B, Huang G, Chen MY, DeBerardinis RJ, Sumer BD, Gao J. Severely polarized extracellular acidity around tumor cells. ***Nature Biomed. Eng*.** 2024, doi.org/10.1038/s41551-024-01178-7. (*Discovery of polarized secretion of lactic acid from cancer cells with a severe acidotic threshold much lower than literature report; new insights to exploit severe pH threshold for cancer diagnosis and drug therapy*)

Complete List of Published Work in MyBibliography (>150 publications, h-index 79, total citations >38,000): https://www.ncbi.nlm.nih.gov/myncbi/jinming.gao.1/bibliography/public/?sort=date&direction=descending.