BIOGRAPHICAL SKETCH

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NAME: Chen, Shu-Hsia

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

POSITION TITLE: Professor

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
Shoo-Chow University, Taiwan, ROC	BS	07/1985	Microbiology
Nat'l Yang-Ming University, Taiwan, ROC	MS	07/1987	Microbiology & Immunology
Nat'l Yang-Ming University, Taiwan, ROC	PhD	07/1992	Microbiology & Immunology
Baylor College of Medicine, Houston, TX	Post-Doc	06/1995	Cancer Immunology Gene Therapy

A. Personal Statement

I have focused my career on gene therapy and tumor immunology to develop and identify novel therapeutic modalities that can reconstruct the antitumor response through the host immune system, and cancer immunobiology mechanisms. During the last decade at Icahn School of Medicine at Mount Sinai, I studied the mechanisms underlying the establishment of the immune suppressive tumor microenvironment, which remains the major hurdle to the success of immune-based cancer therapies. I am one of the pioneers in the identification of the myeloid derived suppressor cell (MDSC) subset populations and their roles in immune suppression in the tumor microenvironment. I am also an inventor for methods of using small compounds to enhance myeloid suppressor cell function for treating autoimmune diseases. Furthermore, my lab has identified and developed the recombinant adenoviral HSV-tk gene delivery for late-stage metastatic breast, lung colon cancer and glioma patients. Recently we conducted the phase II/IIb clinical trial with my MPI Drs. Chang, and Sun and Co-investigator Dr. Pan. The results have shown great promise of this ADV/HSV-tk therapy. To overcome the non-responder to become responder, we have designed an improved ADV/HSV-tk with tumor specific super-enhancers (HMR100). Intratumor delivery of HMR100 will activate immune cells in the neighboring areas of the tumor injection site to **enhance efficacy of immune checkpoint therapy and limit off-target toxicities associated with these drugs and counteracting on those non-responsive to therapy**. I have considerable experience in conducting clinical translational work and moving basic research to clinical application. I have been continuously supported by National Institutes of Health (NIH), Department of Defense, and company-funded research grants in both pre-clinical basic research projects and clinical trials. In this project with Drs. Sun, Chang and Pan, we will use my gene therapy expertise to develop HMR100 and immune checkpoint inhibitor to prolong antitumor immune response and biomarkers identification in metastatic or locally advanced HER2-negative cancer eradication. Overall, I am qualified to be an MPI on SPORE Project 1.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2017-present Center Director for immunotherapy Research
Professor of Institute of Academic Medicine, Methodist Research Institute, Houston Texas
Professor, Dep Physiology, Biophysics and System Biology (PBSB), Weil Cornell School of Medical Science, New York, NY

2010-present Professor, Department of Oncological Science, Dep. General Surgery, Mount Sinai School of Medicine, New York, New York

Professor, Department of Immunology, Weil Cornell School of Medicine, New York, New York

2005-2009 Associate Professor, Department of Gene and Cell Medicine, Dep. of Oncological Science, Dep. General Surgery, Mount Sinai School of Medicine, New York, New York

1997-2004 Assistant Professor, Institute for Gene Therapy and Molecular Medicine, Mount Sinai School of Medicine, New York, New York

1995-1996 Assistant Professor, Department of Cell Biology, Baylor College of Medicine, Houston, Texas

1992-1995 Research Associate, Howard Hughes Medical Institute/Department of Cell Biology, Baylor College of Medicine, Houston, Texas

Other Experience and Professional Memberships

2021-present Scientific Reviewer, Department of Defense (CDMRP), IMM6 grant review panel.

2018-2020 Regular member of Cancer immunology and immune therapy (CII) Study section, and NCI Program project reviewer, NIH

2017 NIH/NCI Program project review panel, NIH SBIR review Panel

2014-2017 Regular member for Outstanding Investigator grant reviewer NCI, R35

2014-present NCI, Reviewer for Small Business Innovative Research (SBIR) solicitation on contract proposals for "Development of Novel Therapeutic Agents that Target Cancer Stem Cells".

2013-present Advisory board member of the Emerging and Re-emerging Infectious Disease (EID) program of National Science Council, Taiwan

2013-present Advisory board member of the Emerging and Re-emerging Infectious Disease (EID) program of National Science Council, Taiwan

2012-present Visiting professor
National Health Research Institute (NHRI), Taiwan, ROC 1995-present Active Member, American Association for Cancer Research

2011, 12 Regular member for NIH (III) special emphasized Panel and Ad Hoc TTT study section

2010 University of Pittsburgh Cancer Institute and NIH designated Cancer Center site visit.
Primary reviewer for Cancer Immunology Program and share resource on immunological monitoring and cellular products laboratory, NCI, NIH

2009 Scientific Reviewer, Department of Defense (CDMRP), Prostate Cancer Research Program (PCRP), the Idea Development Award (IDA) and Synergistic Idea Development Award (SIDA).

2006-2009 Regular Member in Center for Scientific Review of Transplantation, Tolerance and Tumor immunology (TTT) study section, NIH.

2008 Scientific Reviewer for Department of Defense (CDMRP), Breast Cancer Research Program.

2007 Scientific Reviewer for Department of Defense (CDMRP), Prostate Cancer Research Program

2005 Ad Hoc member for Center for Scientific Reviewer in Transplantation, Tolerance and Tumor Immunology (TTT) study section, NCI, NIH.

2003 Grant reviewer in Experimental Immunology study section, NIH.

1995-present Active Member, American Association of Immunologist and AACR

Honors

2017-Present Emily Hermann endowed Professor in cancer immunotherapy

2023 Houston Methodist Presidential Research Award

2019-2022 2019, 2020, 2021,2022 High Impact in Cancer Research Grant Award, Houston Methodist Cancer Center

2013-2015 The Center for Therapeutic Antibody Discovery (CTAD) obtains the Award from Institute for Translational Sciences and the Office of Technology and Business Development, MSSM.

2010-2014 Journal of Immunology, Associate Editor

2010 Tisch Cancer Institute, Developmental fund award.

2006-2008 Black Family Stem Cell Foundation exploratory award.

2002 AACR annual meeting at San Francisco, Experimental Therapy Section Chair.

1996 Texas higher educational award. 1996-1998 $70,000/year.

1995 Selected presenter and travel award (offered by Bristol-Myers Oncology Division) to attend 1995 American Association for Cancer Research (AACR) Meeting, Toronto.

1992 Outstanding Research award, Dr. Ming-Lin Wang Biomedical Research Foundation, Taipei, Taiwan.

1991 Selected presenter and travel award (offered by Ministry of Education R.O.C.) to attend the international meeting on Molecular Biology of Hepatitis B Virus, Paris, France.

1990 The award of outstanding research of hepatitis and hepatoma in the 3rd annual Society of

Chinese Bioscientist Association Meeting (SCBA), Hong Kong.

C. Contributions to Science

1. **Cancer immune therapy through combination of innate and adaptive immunity through gene therapy and co-stimulatory molecules and cytokine gene delivery.**

My early research focused on immune activation through the adenovirus gene delivery and co-stimulatory activation, e.g. 4-1BB, OX40 and CD40, and immune gene therapy. I am a pioneer in this field and own a patent on adenoviral gene delivery for cancer immune therapy in conjunction with immune co-stimulatory activation.

a. Pan, P.Y., Ma, G., Weber, K.J., Ozao-Choy, J., Wang, G., Yin, B., Divino, C.M., & **Chen, S.H.** (2010). Immune stimulatory receptor CD40 is required for T-cell suppression and T regulatory cell activation mediated by myeloid-derived suppressor cells in cancer. *Cancer Res.,* 70(1), 99-108. PMID: 19996287
b. **Sun K**, Xu Y, Zhang L, Niravath P, Darcourt J, Patel T, Teh BS, Farach AM, Guerrero C, Mathur S, Sultenfuss MA, Gupta N, Schwartz MR, Haley SL, Nair S, Li X, Nguyen TTA, Butner JD, Ensor J, Mejia JA, Mei Z, Butler EB, **Chen SH,** Bernicker EH, **Chang JC** (2022) A Phase 2 Trial of Enhancing Immune Checkpoint Blockade by Stereotactic Radiation and In Situ Virus Gene Therapy in Metastatic Triple Negative Breast Cancer. *Clin Cancer Res.* Jul 25:CCR-22-0622.
c. Mai, S., Hodges, A., Chen, H.M., Zhang, J., Wang, Y., Liu, Y., Nakatsu, F., Wang, X., Fang, J., Xu, Y., Davidov, V., Kang, K., Pingali, S.R.V., Ganguly, S., Suzuki, M., Konopleva, M.Y., Prinzing, B., Zu, Y., Gottschalk, S., Lu, L., **Chen, S.H., Pan, P.Y.** (2023) LILRB3 modulates acute myeloid leukemia progression and acts as an effective target for CAR T-cell therapy. *Cancer Research* Dec 15;83(24):4047-4062.
d. Guan J, **Sun K,** Guerrero CA, Zheng J, Xu Y, Mathur S, Teh BS, Farach A, Zhang J, Butler E, **Pan PY,** Zsigmond E, Mei Z, Mejia J, **Chen SH**, Chang JC, Bernicker EH. (2024) A Phase 2 Study of In Situ Oncolytic Virus Therapy and Stereotactic Body Radiation Therapy Followed by Pembrolizumab in Metastatic Non-Small Cell Lung Cancer *Int J Radiat Oncol Biol Phys*. Apr 1;118(5):1531-1540. doi: 10.1016/j.ijrobp.2023.08.044. Epub 2023 Aug 24.PMID: 37625523

2. **Suppressive mechanisms of myeloid derived suppressor cells (MDSC) in tumor microenvironment**

I was one of the first to identify the MDSC population and its immune suppressive mechanisms in 2000, and I along with several tumor immunologists named this population MDSC. Recently, we have also found that DC-Sign play a role for TAM mediated immune suppression in tumor microenvironment.

a. Conde, P., Rodriguez, M., van der Touw, W., Jimenez, A., Burns, M., Miller, J., Brahmachary, M., Chen, H.M., Boros, P., Rausell-Palamos, F., Yun, T.J., Riquelme, P., Rastrojo, A., Aguado, B., Stein-Streilein, J., Tanaka, M., Zhou, L., Zhang, J., Lowary, T.L., Ginhoux, F., Park, C.G., Cheong, C., Brody, J., Turley, S.J., Lira, S.A., Bronte, V., Gordon, S., Heeger, P.S., Merad, M., Hutchinson, J., **Chen, S.H.,** & Ochando, J. (2015). DC-SIGN(+) macrophages control the induction of transplantation tolerance. *Immunity*, 42(6), 1143-1158. PMID: 26070485
b. Bronte, V., Brandau, S., **Chen, S.H.,** Colombo, M.P., Frey, A.B., Greten, T.F., Mandruzzato, S., Murray, P.J., Ochoa, A., Ostrand-Rosenberg, S., Rodriguez, P.C., Sica, A., Umansky, V., Vonderheide, R.H., & Gabrilovich, D.I. (2016). Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun.,* 7, 12150. PMID: 27381735
c. Chung, A.W., Anand, K., Anselme, A.C., Chan, A.A., Gupta, N., Venta, L.A., Schwartz, M.R., Qian, W., Xu, Y., Zhang, L., Kuhn, J., Patel, T., Rodriguez, A.A., Belcheva, A., Darcourt, J., Ensor, J., Bernicker, E., **Pan, P-Y**, **Chen, S.H,** Lee, D.J**., Niravath, P.A., Chang, J.C**. (2021). A phase 1/2 clinical trial of an inducible nitric oxide synthase inhibitor and taxane for treating chemoresistant triple-negative breast cancer. *Science Translational Medicine,* 15;13 (624).
d. Zhu Q, Balasubramanian A, Asirvatham JR, Piyarathna DWB, Kaur J, Mohamed N, Wu L, Chatterjee M, Wang S, Pourfarrokh N, Rasaily U, Xu Y, Zheng J, Jebakumar D, Rao A, **Chen SH,** Li Y, Chang E, Li X, Aneja R, Zhang XH, Sreekumar A. (2024) Integrative spatial omics reveals distinct tumor-promoting multicellular niches and immunosuppressive mechanisms in African American and European American patients with TNBC *bioRxiv* 2024 Mar 31:2024.03.17.585428. doi: 10.1101/2024.03.17.585428. PMID: 38562769

3. **Immune suppressive mechanisms mediated by tumor and myeloid cells and down regulation of effector cell function in the tumor microenvironment**

We are the first group to publish the seminal paper and identify that monocytic MDSC can activate the Treg population in the tumor microenvironment, thereby establishing the immune suppressive environment. We have identified a critical tumor factor, which is involved in the MDSC accumulation and test an FDA approved small compound, which can inhibit the MDSC accumulation and has been further tested in clinical patients.

a. van der Touw. W, Kang, K., Luan, Y., Ma, G., Mai, S., Qin, L., Bian, G., Zhang, R., Mungamuri, S.K., Hu, H.M., Zhang, C.C., Aaronson, S.A., Feldmann, M., Yang, W.C., **Chen, S.H.*,** and Pan, P.Y. (2018). Glatiramer acetate enhances myeloid-derived suppressor cell function via recognition of paired Ig-like receptor B*. J Immunol.,* 201(6), 1727-34. PMID: 30068593
b. Zhang, J., Hodges, A., **Chen, S.H*.**, and **Pan, P.Y**. (2021) Myeloid-derived suppressor cells as cellular immunotherapy in transplantation and autoimmune diseases. *Cell Immunol.*, 362:104300. PMID: 33582607
c. Butner, J.D., Dogra, P., Chung, C., Ruiz-Ramírez, J., Nizzero, S., Plodinec, M., Li, X., **Pan, P.Y**., **Chen, S.H.,** Cristini, V., Ozpolat, B., Calin, G.A., Wang, Z. (2022) Dedifferentiation-mediated stem cell niche maintenance in early-stage ductal carcinoma in stitu progression: insights from a multiscale modeling study. *Cell Death Dis.* 13(5):485. doi: 10.1038/s41419-022-04939-x.PMID: 35597788
d. Xu Y, Kang K, Coakley BA, Eisenstein S, Parveen A, Mai S, Wang YS, Zheng J, Boral D, Mai J, Pan W, Zhang L, Aaronson SA, Fang B, Divino C, Zhang B, Song WM, Hung MC, **Pan PY**, **Chen SH.** (2025) Modulation of tumor inflammatory signaling and drug sensitivity by CMTM4. *EMBO J.* 2025 Feb 13. doi: 10.1038/s44318-024-00330-y PMID: 39948411

4. **<u>The molecular mechanism regulating MDSC differentiation and reprograming</u>**

My lab and colleagues have identified that PIRB/LILRBs and its nature ligand ANGPTL-2, 5 are the critical regulatory cell surface receptor in MDSC differentiation into M1 vs. M2 macrophage. We are the first group to further demonstrate that reprogram of MDSC function could change tumor microenvironment that favors anti-cancer responses. Similar principle can be applied to enhance immune suppressive function of MDSC for treatment of autoimmune diseases. Currently my lab has developed the agonist and antagonist antibodies against human LILRBs. If it is successful, we will move these therapeutic agents into clinical application.

a. Zheng, J., Umikawa, M., Cui, C., Li, J., Chen, X., Zhang, C., Hyunh, H., Kang, X., Silvany, R., Wan, X., Ye, J., Cantó, A.P., **Chen, S.H.**, Wang, H.Y., Ward, E.S., & Zhang, C.C. (2012). Inhibitory receptors bind ANGPTLs and support blood stem cells and leukaemia development. *Nature,* 485(7400), 656-660. PMID: 22660330
b. Chen, H.M., van der Touw, W., Wang, Y.S., Kang, K., Mai, S., Zhang, J., Alsina-Beauchamp, D., Duty, J.A., Mungamuri, S.K., Zhang, B., Moran, T., Flavell, R., Aaronson, S., Hu, H.M., Arase, H., Ramanathan, S., Flores, R., Pan, P.Y., & **Chen, S.H.** (2018). Blocking immunoinhibitory receptor LILRB2 reprograms tumor-associated myeloid cells and promotes antitumor immunity. *J. Clinical Investigation,* 128(12), 5647-62. PMCID: PMC6264729
c. Singh, S., Lee, N., Pedroza, D.A., Bado, I.L., Hamor, C., Zhang, L., Aguirre, S., Hu, J., Shen, Y., Xu, Y., Gao, Y., Zhao, N., **Chen, S.H.,** Wan, Y.W., Liu, Z., Chang, J.T., Hollern, D., Perou, C.M., Zhang, X.H.F., Rosen, J.M. (2022) Chemotherapy coupled to macrophage inhibition induces T -Cell and B-cell infiltration and durable regression in triple-negative breast cancer *Cancer Res.* canres.3714.2021. PMID: 35442423
d. Hodges A, Dubuque R, **Chen SH**, **Pan PY.** The LILRB family in hematologic malignancies: prognostic associations, mechanistic considerations, and therapeutic implications. *Biomark Res.* (2024) Dec 19;12(1):159. doi: 10.1186/s40364-024-00705-7.PMID: 39696628

5. **<u>The targeting MDSC and in conjunction with chemo-, radiation, or oncolytic viral therapies/clinical trials</u>**

Based on our scientific findings on MDSC function and differentiation, we have conducted the clinical trial of overcoming the MDSC accumulation through FDA approved compound in conjunction with radiation therapy and monitoring the immune endpoints with human MDSC and Treg of blood samples from clinical trial cancer patients to correlate with clinical outcome. We have also developed a mathematical model to predict patient response to immunotherapy.

a. Chen, H.M., Ma, G., Gildener-Leapman, N., Eisenstein, S., Coakley, B.A., Ozao, J., Mandeli, J., Divino, C., Schwartz, M., Sung, M., Ferris, R., Kao, J., Wang, L.H., Pan, P.Y., Ko. E.C., & **Chen, S.H.** (2015). Myeloid-derived suppressor cells as an immune parameter in patients with concurrent sunitinib and stereotactic body radiotherapy. *Clinical Cancer Research,* 21(18), 4073-4085. PMID: 25922428
b. Liu, H.C., Gonzalez, D.D., Viswanath, D.I., Vander Pol, R.S., Saunders, S.Z., Di Trani, N., Xu, Y., Zheng, J., **Chen, S.H.**, Chua, C.Y.X., Grattoni, A. (2023) Sustained Intratumoral Administration of Agonist CD40 Antibody Overcomes Immunosuppressive Tumor Microenvironment in Pancreatic Cancer. *Adv Sci (Weinh)*;10(9):e2206873. PMID: 36658712
c. Hao, X., Shen, Y., Chen, N., Zhang, W., Valverde, E., Wu, L., Chan, H.L., Xu, Z., Yu, L., Gao, Y., Bado, I., Michie, L.N., Rivas, C.H., Dominguez, L.B., Aguirre, S., Pingel, B.C., Wu, Y.H., Liu, F., Ding, Y., Edwards,

D.G., Liu, J., Alexander, A., Ueno, N.T., Hsueh, P.R., Tu, C.Y., Liu, L.C., **Chen, S.H.**, Hung, M.C., Lim, B., Zhang, X.H. (2023) Osteoprogenitor-GMP crosstalk underpins solid tumor-induced systemic immunosuppression and persists after tumor removal. *Cell Stem Cell,* 4;30(5):648-664. PMID: 37146584

d. Liu Y, Yu D, Ge X, Huang L, **Pan PY,** Shen H, Pettigrew RI, **Chen SH**, Mai J. *(*2025) Novel platinum therapeutics induce rapid cancer cell death through triggering intracellular ROS storm. *Biomaterials.* Mar;314:122835. PMID: 39276409

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/shu-hsia.chen.1/bibliography/40691475/public/?sort=date&direction=descending.