BIOGRAPHICAL SKETCH

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NAME: Suzie Chen

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

POSITION TITLE: Distinguished 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
Trinity College, Hartford, CT	B.S.	05/73	Mathematics
Albert Einstein College of Medicine, Bronx, NY	M.S.	10/76	Genetics
Albert Einstein College of Medicine, Bronx, NY	Ph.D.	10/79	Genetics
Columbia University, New York, NY	Postdoctoral Fellow	10/79-06/83	Cell Biology/Virology

A. Personal Statement

The focus of my research is to study how ectopic expression of an otherwise normal neuronal gene in melanocytes results in spontaneous melanoma development *in vivo.* The detection of this neuronal receptor, GRM1, in human melanoma cell lines and biopsies but not normal melanocytes prompted us to investigate the oncogenic potential of GRM1 in human melanocytes *in vitro* and *in vivo*. I have the background and expertise to successfully carry out the *in vivo* animal model experiments. As a graduate student at Albert Einstein College of Medicine, my graduate research was focused on the development of spontaneous lymphoma in the progeny of two inbred strains of mice with no known predisposition to lymphoma. We had demonstrated that the onset of spontaneous T-cell lymphoma in the progeny was a result of genetic complementation. Subsequent to attaining my Ph.D. in Genetics I carried out my postdoctoral training at Columbia University where I began work on cell transformation and DNA tumor virus, SV40. We identified a specific rearranged form of SV40 which was always detected only in cells which were also have acquired the anchorage-independence growth characteristics. While at Columbia University, I became interested in the regulation of cell differentiation and I adopted an adipocyte differentiation system developed by Dr. H. Green as our model. Through utilizing molecular cloning techniques and functional assays we identified two small fragments of genomic DNA each one has the ability to induce adipocyte differentiation when introduced into a variety of fibroblasts. I took this project with me when I began my independent position at Rutgers University. I expanded the studies in whole animals by making transgenics with cloned DNA fragments. One out of five founder mice developed spontaneous melanoma due to “insertional mutagenesis”. We identified and confirmed that ectopic expression of GRM1 in melanocytes is sufficient to induce spontaneous melanoma development *in vivo*. We also demonstrated that about 60% of human melanoma cell lines and biopsies showed aberrant GRM1 expression. Using an FDA approved drug that inhibits the release of glutamate, the natural ligand for GRM1, led to a decrease in the number of viable melanoma cells *in vitro* and *in vivo*. These laboratory-based findings were translated to the clinic for stages III/IV melanoma patients in one Phase 0 Clinical Trial, one Phase I Trial and one Phase II Trial at CINJ. All were supported by R21 grants from NCI. We showed that riluzole as a monotherapy has modest anti-tumor activities and no adverse reactions were found in patients. Combining riluzole with a multi-kinase inhibitor, sorafenib yielded synergistic responses in human melanoma cell xenografts in immuno-deficient mice. Results from this pre-clinical study were translated to a Phase I/II trial initially for late-stage melanoma patients then extended to other solid tumors. Results of this trial were recently

published. It is clear from all three trials that riluzole as a single agent has modest anti-tumor efficacy but combining this non-toxic reagent with another modality such as immunotherapy may enhance efficacy and improve outcomes, this concept was awarded with a SBIR grant with our industry partner.

1. Pollock, P.M., Cohen-Solal, K.A., Sood, R., Namkoong, J., Martino, J.J., Koganti, A., Zhu, H., Robbins, C., Makalowska, I., Shin, S.S., Marin, Y., Roberts, K.G., Yudt, L.M., Chen, A., Cheng, J., Incao, A., Pinkett, H.W., Graham, C.L., Dunn, K., Crespo-Carbone, S.M., Mackason, K.R., Ryan, K.B., Sinsimer, D., Goydos, J., Reuhl, K.R., Eckhaus, M., Meltzer, P.S., Pavan, W.J., Trent, J.M. and Chen, S. (2003) Melanoma mouse model implicates metabotropic glutamate signaling in melanocytic neoplasia. Nat Genet. 38:108-112. PMID 12704387
2. Yip, D., Le, M., Chan, J., Lee, J., Mehnert, J., Yudd, A., Kempf, J., Shih, W., Chen, S. and Goydos, J. (2009) A phase 0 trial of Riluzole in patients with resectable stage III and IV melanoma. Clin. Can. Res. 15: 3896-3902. PMCID: PMC2812866
3. Mehner, J., Silk, A., Wen, Y., Lee, J., Dudek, L., Jeong, B., Li, J., Schenkel, J., Sadimin, E., Kane, M., Lin, H., Shih, W., Zloza, A., Chen, S. and Goydos, J. (2018) A phase II trial of riluzole, an antagonist of metabotropic glutamate receptor 1 (GRM1) signaling, in patients with advanced melanoma. Pig. Cell Mel. Res. 31: 534-540.
4. Shah, R., Singh, S., Eddy, K., Fillipp, F. and Chen, S. Concurrent targeting of glutaminolysis and metabotropic glutamate receptor 1 (GRM1) reduce glutamate bioavailability in GRM1^{+} melanoma. Cancer Res.m79: 1799-1809. 2019.

B. Positions, Scientific Appointments and Honors

Positions and Employment

1976-1979 Pre-doctoral Study at Albert Einstein College of Medicine, with Dr. Frank Lilly, Bronx, NY
1979-1983 Postdoctoral Fellow, Biological Sciences, Columbia University, with Dr. Robert Pollack, New York, NY
1984-1986 Research Scientist, Biological Sciences, Columbia University, New York, NY
1986-1991 Associate Research Scientist, Biological Sciences, Columbia University, New York, NY
1991-1992 Senior Research Scientist, Biological Sciences, Columbia University, New York, NY
1992-1998 Assistant Professor, College of Pharmacy, Rutgers University, Piscataway, NJ
1998-2005 Associate Professor, College of Pharmacy, Rutgers University, Piscataway, NJ
2005-Present Professor, School of Pharmacy, Rutgers University, Piscataway, NJ
2016-Present Physiologist, VA New Jersey Healthcare System, East Orange, NJ
2020-present Chair, Department of Chemical Biology, School of Pharmacy, Rutgers University, Piscataway, NJ
2021-present Distinguished Professor, Department of Chemical Biology, School of Pharmacy, Rutgers University, Piscataway, NJ

Honors

2005 May Keynote Speaker at Brain Tumor Center Seminar Series MD Anderson Cancer Center, Houston TX
2005 May Rutgers University Board of Trustees Award for Excellence in Research, Piscataway, NJ
2007 Nov Second International Melanoma Congress Best Abstract Award, New York, NY
2014 March Speaker, Keystone Symposia on Molecular and Cellular Biology, G protein-coupled receptors: structural dynamics and functional implications, Snowbird, UT.
2016 AAAS Fellow, "For significant contributions in translational research in melanoma biology, particularly for identifying the critical role of glutamatergic signaling in the etiology of melanoma"

Other Experience and Professional Memberships

2005-present *Journal of Molecular Signaling*
2013-present Scientific Advisory Board for GPCR Targeted Screening Conferences: Global Technology, Monrovia, CA
2014-present *PLoS ONE*
2014-2017 Council member of PanAmerican Society for Pigment Cell Research
2017-present. Frontiers Cell and Developmental Biology
2017-present. Frontiers Oncology

2019-present Pigment Cell and Melanoma Research
2020-present Frontiers Oncology, Skin Cancer
2020 President-elect PanAmerican Society for Pigment Cell Research

Patents:

U.S. Patent Number: 7,385,103
Animal model, cells, and treatment for malignant melanoma, June 10, 2008
U.S. Patent Number: 7,691. 377B2
Methods and compositions for treating melanoma, April 6, 2010
U.S. Patent Number: 8, 835, 473
Methods and compositions for treating cancer, September 16, 2014
U.S. Patent Number: 9, 725, 427
Prodrugs of riluzole and their method of use, August 8, 2017
U.S. Patent Number: 10, 562, 870
Prodrugs of riluzole and their method of use, February 18, 2020
U.S. Patent Number: 10, 864, 271
Combination therapy using riluzole to enhance tumor sensitivity to ionizing radiation, August 13, 2020
U.S. Patent Number: 8, 444, 026
Prodrugs of riluzole and their method of use, November 24, 2020

C. Contributions to Science

Since my initial exposure to laboratory research in high school, I have been fascinated with the thrill of discovery and the excitement of exploiting the complexity of the building blocks of life. We pioneered and developed the transgenic animal model system for malignant melanoma. We identified downstream signal targets in transformed melanocytes induced by the aberrant expression of a neuronal receptor, metabotropic glutamate receptor 1 (GRM1) on the cell surface. The normal function of GRM1 is in learning and memory in the central nervous system. We found that one of the consequences of deregulated GRM1 expression is cell transformation *in vitro* and tumor formation *in vivo*. We have demonstrated these unique properties of GRM1 in melanocytic and epithelial cell systems. We have performed preclinical experiments in the mouse system and have extended into human melanoma. I have an ongoing collaboration with Dr. James Goydos, Professor of Surgery and Director of Melanoma Research at the Rutgers-Cancer Institute of New Jersey (RCINJ) since 2001. Since then we have several joint publications and have completed three clinical trials and with one more trial anticipate in 2020. The goal for a basic researcher like myself is to be able to advance human health no matter how minute. I believe that I have achieved parts of this goal by translating the discoveries from my laboratory into the clinic in collaboration with physicians at Rutgers CINJ. Together with Drs. Goydos and Mehnert we have completed two single-agent Phase 0 and Phase 2 trials with late stage melanoma patients. Based on the preclinical results from my laboratory we have initiated a Phase 1 combinatorial trial, which is just completed. All three trials were supported by grants from the National Cancer Institute (NCI) and Cancer Therapy Evaluation Program (CTEP) at NCI. In a separate collaboration with Drs. Khan and Haffty, radiation oncologists at Rutgers CINJ, we showed enhanced radiation sensitivity when one combines a radiosensitive drug with irradiation in preclinical studies. We again translated these laboratory-based results to the clinic and have an ongoing trail for patients receiving irradiation. Our recent studies in small vesicles, exosomes pointed to altered cell characteristics by exosomes from $GRM1^{+}$ cells but not $GRM1^{-}$ cells, suggesting possible uses of exosomes as diagnostic markers in melanoma patients in clinical trials.

a. Wen Y, Li J, Koo J, Shin S-S, Lin Y, Jeong B-S, Cohen-Solal K , Mehnert J. M, Chen S. and Goydos J. S. (2014) Metabotropic glutamate receptor 1 activation leads to downstream pro-angiogenic signaling and enhanced angiogenesis in melanoma. Cancer Res. 74: 2499-2509. pMID:2449180
b. Kulkarni, A., Al-Hraishaw, H., Hirshfield, K., Chen, S., Pine, S., Jeyamohan, C., Sokol, L., Slrai, A., Lung, T., White, E., Rodriguez, L., Mehnert, J. and Ganesan, S. (2017) BRAF fusion as a novel mechanism of acquired resistance to vemurafenib in $BRAF^{V600E}$ mutant melanoma. Clin. Can. Res. 23:5631-5638. PMID:28539463
c. Isola, A., Eddy, K., Zembrzuski, K., Goydos, J. and Chen, S. (2017) Oncotarget 9: 1187-1199. PMCID: PMC5787429
d. Khan, A., LaCava, S., Mehta, M., Schiff, D., Thandoni, A., Jhawar, S., Danish, S., Haffty, B. and Chen, S. The glutamate release inhibitor riluzole increases DNA damage and enhances cytotoxicity in human glioma cells, *in vitro* and *in vivo*. Oncotarget, 10: 2824-2834, 2019.

In addition to the contributions described above, in collaboration with two physician scientists in breast cancer we have extended our studies in glutamatergic signaling to cancers of the epithelial cell origin including kidney and breast cancers. Our results from these studies demonstrated that the involvement of aberrant glutamate mediated signaling might be more common than previously envision. Recently other groups have linked glutamate signaling to prostate cancer. It has been postulated that abnormal glutamate levels in the cells initiates a cascade of rewiring of the metabolic pathways, which is a new and exciting direction that my laboratory begun to embark on.

a. Martino, J. J., Wall, B. A., Mastrantoni, E., Wilimczyk, B., La Cava, S., Degenhardt, K., White, E. and Chen, S. (2013) Metabotropic glutamate receptor 1 (Grm1) is an oncogene in epithelial cells. Oncogene 32: 4366-4376.
b. Mehta, M., Dolfi, S., Bronfenbrener, R., Bilal, E., Chen, C., Moore, D., Lin, Y., Rahim, H., Aisner, S., Kersellius, R., Teh, J., Chen, S., Toppmeyer, D., Medina, D., Ganesan, S., Vazquez, A. and Hirshfield, K. (2013) Metabotropic glutamate receptor-1 expression and its polymorphic variants associate with breast cancer phenotypes. PLoS ONE. 8(7): doi:10.1371/journal.pone. 0069851. PMID: 23922822
c. Teh, J., Shah, R., La Cava, S., Dolfi, S., Mehta, M., Kongara, S., Price, S., Ganesan, S., Reuhl, K., Hirshfield, K., Karantza, V. and Chen, S. (2015). Metabotropic glutamate receptor 1 disrupts mammary acinar architecture and initiates malignant transformation of mammary epithelial cells. Breast Cancer Research and Treatment. 151:57-73. PMID: 25859923

Partial List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/41163234/