OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 09/30/2024)

**BIOGRAPHICAL SKETCH**

**NAME**: Yu, Dihua

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

POSITION TITLE: Professor & Chair *ad interim*

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.)*

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| --- | --- | --- | --- | --- |
| INSTITUTION AND LOCATION | DEGREE | Completion | FIELD OF STUDY |  |
| Date |  |
|  |  |  |  |
| Capital Medical University, Beijing, P. R. C. | M.D. | 12/1982 | Medicine |  |
| Capital Medical University, Beijing, P. R. C. | M.S. | 12/1985 | Neuro-Cardio Physiology |  |
| Univ. of Texas Health Science Ctr., Houston, TX | Ph.D. | 04/1991 | Molecular Cancer Biology |  |

**A. Personal Statement**

This new R01 proposal focuses on investigating whether SHP1-modified dendritic cells-derived extracellular vesicles (S1-DCEVs) can be optimized and be effectively delivered to the brain to Impede breast cancer (BC) brain metastases (BrMs) and enhance ICT efficacy in BC BrMs by inducing strong antigen-specific T cell antitumor response. I have the vision, insight, creativity, leadership, expertise, and inspiration to succeed in the proposed research. I was trained as a clinician treating cancer patients from which I painfully realized that we could not save lives of many cancer patients due to late diagnoses and lack of effective treatments. This experience motivated me to obtain Ph.D. training in cancer biology so I could perform discovery research to pinpoint the Achilles’ heel of our enemy—CANCER and win our battle against cancer! My determination and my background in both clinical medicine and basic research have empowered me to develop a highly productive translational cancer research program at the M.D. Anderson Cancer Center (MDACC), where my laboratory functions as a bridge connecting basic/translational cancer research to important issues in cancer patient care. We aim to gain global understanding of the mechanisms of cancer initiation, progression, metastasis, and therapeutic resistance and develop mechanisms-based, rationally designed combinatorial prevention/intervention strategies and therapies for personalized cancer care. We use various preclinical models, *e.g.,* 2 dimensional (2D) and 3D cell culture, double and triple co-cultures, organoids, transgenic, knockout, and humanized mouse models, cancer cell xenograft and patient-derived xenograft (PDX) models, tissue and plasma specimens from patients, as well as big data (genomics, epigenomics, transcriptomics, proteomics, metabolomics, etc.) from patients.

Here I highlight some of my experience in, and contributions to, the BrM field (some are not included in Section C). During 2005-2012, I joined the DOD BrM Center of Excellence led by Dr. P. Steeg (NCI). My team has 1) established multiple new *in vivo* BrM models, including *in vivo*-selected brain-seeking mouse and human cancer cell lines and PDX models, and brain-seeking mammary tumor models from genetically engineered mice (MMTV-Neu/PTEN-null); 2) performed an unprecedented *in vivo* kinome (containing ~400 kinases) screen and uncovered novel kinases (>20 hits) that promote BC BrM in mice. We functionally and mechanistically defined an important role of Src kinase in promoting BC BrM and showed the high efficacy of targeting Src for intervention and treatment of BrMs (Can. Res. 73:5764, 2013). We revealed that in the brain microenvironment, astrocytes-derived exosomal microRNA induces a non-genetic, reversible PTEN loss in metastatic tumor cells, that leads to an increased secretion of CCL2, which recruits myeloid cells to reciprocally enhance BrM outgrowth (*Nature,* 11/2015). Recently, we discovered that EZH2 can promote BrM by immune suppression (*Science Transl. Med*., 5/2020). Lately, we found that Vitamin E enhances cancer immunotherapy by reinvigorating dendritic cells via targeting checkpoint SHP1 (*Cancer Discovery*, 7/2022). This application builds on these prior works. Additionally, I have supervised multiple projects in my team (research guidance, personnel and budget management, etc.), collaborated with researchers in and outside MDACC. I have also successfully led a Susan Komen Promise Grant team of investigators from multi-institutions (MDACC, Duke Univ. and Rice Univ.) and achieved all the proposed goals when the grant ended in 2015. My commitment and the above-mentioned experience promise continued productivity in pursuing the major goals of the research projects in my laboratory. Please see below for my four representative papers in the past few years.

1. Zhang L\*, Zhang S\*, Yao J, Lowery FJ, Huang W-C , Zhang C, Wang H, Palmieri D, Zhang Q, Cheerathodi M, McCarty JH, Huang S, Sahin AA, Aldape KD, Steeg PS, **Yu D**. Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. ***Nature***, 527(7576):100-4, 2015. PMCID: PMC4819404. (\*equal contribution).
2. Zhang L, Wei Y, Zhou Z, Yao J, Li P, Qu J, Badu-Nkansah A, Yuan X, Huang Y-W, Fukumura K, Mao X, Chang W-C, Saunus J**,** Lakhani S, Huse J T, Hung M-C, **Yu D.** Blocking immunosuppressive neutrophils deters pY696-EZH2-driven brain metastases. ***Sci Transl Med***, 12(545), 5/2020. PMCID: PMC7948522.
3. Li H\*, Xiao Y\*, Li Q, Yao J, Yuan X, Zhang Y, Yin X, Saito Y, Fan H, Li P, Kuo WL, Halpin A, Gibbons DL, Yagita H, Zhao Z, Pang D, Ren G, Yee C, Lee JJ, **Yu D**. The allergy mediator histamine confers resistanceto immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. ***Cancer Cell***, 40(1):36-52.e9, 1/2022. PMCID: PMC8779329. (\*equal contribution).
4. Yuan X, Duan Y, Xiao Y, Sun K, Qi Y, Zhang Y, Ahmed Z, Moiani D, Yao J, Li HZ, Zhang L, Yuzhalin AE, Li P, Zhang CY, Badu-Nkansah A, Saito Y, Liu XH, Kuo WL, Ying HQ, Sun SC, Chang JC, Tainer JA, Y, **Yu D**. Vitamin E Enhances Cancer Immunotherapy by Reinvigorating Dendritic Cells via Targeting Checkpoint SHP1. ***Cancer Discovery,*** 12(7):1742-1759, 7/2022. PMID: 35420681.

**Highlights of ongoing and recently completed projects**:

Ongoing Research Support

R01 CA231149

Yu (PI)

05/01/2019–04/30/2024

Combating Breast Cancer Brain Metastasis by Blocking the Two-Pronged Driver Kinase Function of CDK5

W81XWH2210060

Yu (PI)

12/01/2021-11/30/2024

Developing Strategies for Immunoprevention of Estrogen Receptor-Negative Breast Cancer

R01 CA266099-01A1

Yu (PI)

09/01/2022-08/31/2027

Exploring the function of MHC-II/Lag3 Axis in brain metastasis to develop novel therapeutic strategies

R01 CA27001-01A1

Yu (PI)

02/01/2023-01/31/2028

Exploring novel strategies for immunoprevention of estrogen receptor negative breast cancer

Completed (within the past three years)

R01 CA184836

Yu (PI)

03/13/2015–08/31/2020

Target p70S6K for Chemodietary Prevention/Early Intervention of ER- Breast Cancer

2019 METAvivor Research Grant

Yu (PI)

06/09/2020–06/08/2022

Inhibiting Breast Cancer Brain Metastasis by Blocking CCR2+ Myeloid Cell Infiltration

R01 CA208213

Yu (PI)

06/01/2017–11/30/2022

Inhibition of brain metastasis by blocking MAPK12 driver kinase functions

**B. Positions, Scientific Appointments, and Honors**

**Positions and Scientific Appointments**

07/19 - present Director, Cancer Biology and Metastasis program, CCSG, U.T. MDACC

02/19 - present Chair ad interim, Dept. of Molecular and Cellular Oncology, U.T. MDACC

02/19 - present Director, Functional Genomics Core, U.T. MDACC

08/2018-10/2020 President, Metastasis Research Society

11/2017-9/2020 Editor-in-Chief, American Journal of Cancer Research

01/2017 Co-Chair, 2018 Congress of Metastasis Research Society, Princeton University

06/2016 Co-Chair, AACR Annual Meeting 2017 Program Committee

01/14-12/2015 President, Society of Chinese Bio-scientists in America (SCBA)

02/2013 Member, DOD Review Panel, Collab. Scholars and Innovators-EOH Scholar-Innovator

Expansion, Washington DC

04/2012 NIH-NCI, Transformative R01 application SEP

08/2011 Member, DOD CDMRP EOH Scholar/Innovator Award Study Section

09/2010-11/2022 Board member, Metastasis Research Society (MRS)

09/2009-02/2019 Deputy Chair, Dept. of Molecular and Cellular Oncology, U.T. MDACC

09/2009 -present Hubert L. & Olive Stringer Distinguished Chair in Basic Science, U.T. MDACC

02/2009 Member, NIH-NCI, SPORE review Study Section, Washington DC

11/2006 -present Professor, Dept. of Molecular and Cellular Oncology, U.T. MDACC

11/2006-11/2010 Board member, Cancer Biology Training Consortium (CABTRAC)

9/2006 - 8/2009 Nylene Eckles Distinguished Professor in Breast Cancer Research, U.T. MDACC.

2005-2012 Associate Editor, Cancer Research

11/2005 Member, NIH Oncology Fellowship Study Section, Washington DC

8/2005 - 8/2011 Director, Cancer Biology Program, GSBS/MDACC and UTHSC

08/2005 Member, NIH PO1 Parental Sub-com. E. Cancer Epi., Prevent & Control, Bethesda, MD

10/2003-6/2006 Member, NIH-NCI, TPM Study Section, then returning as an ad hoc member 10/2008

9/2002-11/2006 Professor, Dept. of Surgical Oncology & Dept. of Mol. & Cell. Oncology, U.T. MDACC.

6/2001-11/2006 Director of Research, Division of Surgery, U.T. MDACC.

2001-2006 Pathobiology Rev. Committee, CBCRP (4/29/01, 2/26/03, 3/25/06)

2000-2007 Member, NIH PO1 Peer Review Panels, nine services (6/25/00, 6/1/01, 1/9/02, 2/13/02,

2/26/03, 2/17/04, 5/18/05, 6/13/05, 2/7/07).

04/06/2000 Chair, Review committee, California Breast Cancer Research Program (CBCRP)

10/1998-06/2003 Member, NIH Path B Study Section

9/1998-8/2002 Associate Professor, Dept. of Surgical Oncology & Dept. of Mol. Cell. Oncology, MDACC

05/4-5/1997 U.S. Army Breast Cancer Program Site Visit, U. Texas Health Sci. Ctr., San Antonio

11/13-15/1995 "Molecular Biology" Study Section, USAMRMC Breast Cancer Program

02/18-20/1994 "Detection and Diagnosis" Study Section, USAMRDC Breast Cancer Program

1/1994-8/1998 Assistant Professor, Dept. of Surgical Oncology & Dept. of Tumor Biology, U.T. MDACC.

9/1991-12/1993 Instructor, Dept. of Tumor Biology, U. T. MDACC.

5/1991-8/1991 Post-doctoral fellow, Dept. of Tumor Biology, University of Texas M.D. Anderson Cancer Center (U. T. MDACC), Houston, Texas

8/1986-4/1991 Graduate Student, Graduate School of Biomedical Sciences (GSBS), The University of Texas Health Science Center at Houston, Houston, Texas. (UTHSC)

1/1983-7/1986 Instructor, Capital Medical University, Beijing, China.

9/1981-12/1982 Internship, the International Red Cross Chao-Yang Hospital, Beijing, China.

**Honors** (a partial list)

12/2017 Impact Award, Breast Cancer Society, Taiwan

09/2016 The I. J. Fidler Innovator Award in Metastasis Research, Metastasis Research Society

08/2014 Awarded Sowell-Huggins Professorship in Cancer Research, UT-GSBS

05/2013 Achievement Award, Society of Chinese Bioscientists in America (SCBA)

11/2012 The Dallas/Fort Worth Living Legend Faculty Achievement Award in Basic Research, UT MDACC

10/2012 The Distinguished Faculty Research Mentor Award, UT MDACC

07/2012 Regents’ Outstanding Teaching Award, The University of Texas System

05/2012- University Distinguished Teaching Professor, U.T. MDACC

11/2011 Elected AAAS Fellow, American Association for the Advancement of Science (AAAS)

01/2011 Elected Academy Member, University of Texas Academy of Health Science Education

7/2010 Texas Business and Professional Woman Award, Texas Federation of Business and Professional Women

11/2007 & 5/2013 Faculty Educator of the Month, U.T. MDACC

2004-2006 Dean’s Excellence Award, Recipient of Honors Convocation of U. T. Health Science Center

3/2001 Health Science Center Honors Convocation Recipient

11/2000 E.N. Cobb Faculty Scholar Award for Research and Education Excellence, U.T. MDACC

5/1999 Research Award from Texas Business and Professional Woman Organization

10/1996 Overseas-Scholar Award from the National Natural Science Foundation of P. R. China.

1/1992 First Place Winner on Scientific Presentation, The Fourth SCBA International Symposium and Workshop in Singapore

3/1991 Upjohn Award, Travel Award from AACR

**C. Contributions to Science**

1. ***Revealed novel mechanisms of chemo-resistance*:**

Chemotherapy is the standard of care for cancer patients and chemo-resistance is a devastating clinicalproblem leading to cancer metastasis and poor patient survival. When I started my research program in 1994, one of my two research areas was to investigate the mechanisms of ErbB2-medicated chemo -resistance. Our studies provided “explanation of the clinically observed effect by which ErbB2 overexpression in cancer cells protects these cells from the often-used therapy of taxol,” (quote from a Reviewer). Later, we unexpectedly found that the ErbB2 membrane receptor tyrosine kinase (RTK) can directly phosphorylate Cdc2, the kinase required for mitotic cell division that functions in the nucleus, leading to Taxol resistance. This novel link between membrane RTK and nuclear Cdc2 brought a new concept to signal transduction and cell cycle fields.

1. **Yu, D.**, Jing T, …, McDonnell TJ, Hung MC. Overexpression of ErbB2 blocks Taxol-induced apoptosis byupregulation of p21Cip1, which inhibits p34Cdc2 kinase. ***Molecular Cell***, 2(5):581-91, 11/1998.
2. Tan, M., Jing, T., ..., Hung,M.C., **Yu, D.** Phosphorylation on Tyrosine-15 of p34Cdc2 by ErbB2 Inhibits

p34Cdc2 Activation and is involved in Resistance to Taxol-Induced Apoptosis, ***Molecular Cell****,* 9: 993-1004,

2002. **Note**: A figure from this paper was selected as the cover for ***Molecular Cell****.*

1. ***“Discovered why the cancer drug Herceptin fails in many patients*** *and may have hit on a way to**improve the therapy” (quoted from* ***Nature News****)*.

We made a novel discovery that PTEN activation is a critical component of the Herceptin therapeutic effect and that PTEN loss confers Herceptin resistance (***Cancer Cell***, 2004, cited >2147 times). This research has significantly impacted cancer treatment (see below). We also developed a new set of diagnostic markers,including PTEN-loss, activation of PI3K, Akt, p70S6K, and Src, that give increased predictive power for Herceptin response and survival of patients with HER2+ metastatic breast cancer (***Am. J. Pathol***. 2010; ***Cell*** 2012). We identified several PI3K inhibitors that reverse Herceptin resistance (***Clin. Cancer Res***. 2007). Based on our preclinical data, a phase I/II clinical trial was conducted at MDACC that brought significant clinical benefit to patients (***J. Clin. Onc***. 2011). We further identified “key nodes” in the Herceptin resistance network and developed strategies of targeting the “key node” to overcome resistance from multiple resistance mechanisms (***Nature Medicine***, 2011). We found that combining Herceptin and PI3K/Akt inhibitor for HER2+ BC also activated T-cell response, and T-cell checkpoint blockade by CTLA-4 antibody further enhanced the antitumor activity of the combination treatment (***Cancer Res***. 2012). Then, we developed a strategy of using biomarker in evolving resistant tumors to guide the application of targeted therapies in a sequential order that effectively target and reprogram the evolving resistant cancer signals and reduce toxicity during treatment (***Cell Res***. 2014). These findings have led to new clinical trials. These experiences inspire us to make new strides in conquering BC and BrM resistance to immunotherapies.

1. Nagata Y, Lan KH, …, Hortobagyi GN, Hung MC, **Yu D**. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. ***Cancer Cell*** 6:117-27, 2004.
2. Morrow PK, …, Hortobagyi GN, **Yu D**, Esteva FJ. Phase I/II Study of Trastuzumab in Combination With Everolimus in Patients With HER2-Overexpressing Metastatic Breast Cancer Who Progressed on Trastuzumab-Based Therapy. ***J Clin Oncol*** 29(23):3126-32, 8/2011. e-Pub 7/2011. PMCID: PMC3157979.
3. Zhang S, Huang WC, Li P, Guo H, Poh SB, Brady SW, Xiong Y, Tseng LM, Li SH, Ding Z, Sahin AA, Esteva

FJ, Hortobagyi GN, Yu D. Combating trastuzumab resistance by targeting SRC, a common node downstream

of multiple resistance pathways. ***Nature Med*** 17(4):461-9, 4/2011. PMCID: PMC3877934.

1. Sahin O, …, **Yu D**. Biomarker-guided sequential targeted therapies to overcome therapy resistance in rapidly evolving highly aggressive mammary tumors. ***Cell Research*** 24(5):542-59, 2014. PMCID:4011340

***3. Identified biomarkers and therapeutic targets of breast cancer metastasis.***

My team was among the first to provide direct experimental evidence that HER2+ enhances the metastatic potential of BCs and identified molecular targets for intervention of HER2-mediated metastasis (***Cancer Res***. 1993, 1994, 1997, 1999, 2006, 2009, ***Oncogene*** 2006, *etc.*). In our quest to identify key players in invasion and metastasis, we found that 14-3-3z cooperates with ErbB2 to promote the deadly transition from non-invasive DCIS to invasive BC conferring poor survival of BC patients (***Cancer Cell***, 2009, and ***Cancer Res***, 2008, 2011, 2014). We identified 14-3-3z as a molecular switch turning TGF-β from tumor suppressor to metastasis promoter, thus 14-3-3z and downstream signals may serve as therapeutic targets to block TGF-β signaling in metastases (***Cancer Cell***, 2015). Recently, we found that EZH2 and TGFβ signaling cooperate in the “vicious cycle of bone metastases” (*Nature Comm*., 5/2022). I have a vision: to reduce cancer mortality in this decade, we have to conquer brain metastasis, an emerging challenge in this new era of successful targeted therapies. Our research has brought novel insights on new diagnostic and therapeutic strategies (***Cancer Res***. 2013, **Nature**, 11/2015, Science Transl. Med., 2020). We aim to make bigger strides and breakthroughs to defeat brain metastasis.

1. Lu J, Guo H, …, Seewaldt VL, Muller WJ, Sahin A, Hung MC, **Yu D**. 14-3-3zeta Cooperates with ErbB2 to Promote Ductal Carcinoma In Situ Progression to Invasive Breast Cancer by Inducing Epithelial-Mesenchymal Transition. ***Cancer Cell*** 16(3):195-207, NIHMS[140388], 2009. PMCID: PMC2754239.
2. Zhang S\*, Huang W-C\*, Zhang L\*, …, Sahin A, Adalpe K, Steeg P, **Yu D**. Src family kinases as novel therapeutic targets to treat breast cancer brain metastasis. ***Cancer Research***, 73(18):5764-74, 9/2013. PMCID: PMC3781592
3. Xu J, Acharya S, Sahin O, Zhang QL, Yao J, Wang H, Li P, Lowery FJ, Saito Y, Kuo WL, Ensor J, Sahin A, Hung MC, Zhang JD, **Yu D**. 14-3-3ζ turns TGF-β's function from tumor suppressor to metastasis promoter in breast cancer by contextual changes of Smad partners from p53 to Gli2. ***Cancer Cell***, 27;177, 2015. PMCID: PMC4325275.
4. Zhang L, Qu JK, Qi YT, Duan YM, Huang YW, Zhou ZF, Li P, Yao J, Huang BB, Zhang SX, Yu D. EZH2 engages TGFβ signaling to promote breast cancer bone metastasis via integrin β1-FAK activation. ***Nature Commun*** 13(1):2543, 5/2022. doi: 10.1038/s41467-022-30105-0. PMCID: PMC9091212

***4. Development of novel early detection and prevention strategies for ER-negative (ER-) breast cancer.*** My research team has been tackling challenging problems of no effective prevention strategy for ER- BC. Although tamoxifen and aromatase inhibitors are effective in preventing ER+ BCs, there are NO efficacious agents to prevent ER- BC, which accounts for about 40% of women with early BCs. We found that RTK signaling and Src activation can drive the progression of ER- BC and tested strategies to target these pathways to prevent ER- BC. This research led to a multi-institutional PROMISE grant (PI: D. Yu) funded by Susan G. Komen for the Cure. With 6 years of hard work, we have validated that Src activation promotes ER-BC development and can serve as an early intervention target (***Cancer Res***., 2015). Our strong preclinical data have led to a phase II clinical trial using a Src inhibitor for secondary prevention of ER- BC in high risk women at MDACC (ClinicalTrials.gov identifier: NCT01471106). Meanwhile, we also tested targeting p70S6K and PI3K/Akt for ER- breast cancer prevention with important finding for potential clinical translation (see b, c below).

1. Jain S, …, , Arun B, Richards-Kortum R, Jia W, Seewaldt VL, **Yu D**. Src Inhibition Blocks c-Myc Translation and Glucose Metabolism to Prevent the Development of Breast Cancer. **Cancer Res**. e-Pub 9/2015. PMCID:4651709
2. Wang X, Yao J, Wang JY, Zhang QL, Brady SW, Arun B, Seewaldt VL, **Yu D**. Targeting Aberrant p70S6K Activation for Estrogen Receptor Negative Breast Cancer Prevention. **Cancer Prev. Res**. 10(11):641-650, 11/2017. PMCID:5668174. **Note**: A figure from this paper was selected as the cover for **Cancer Prev. Res.**
3. Zhou Z\*, Li M\*, Zhang L\*, Zhao H, Sahin Ö, Chen J, Zhao JJ, Songyang Z, **Yu D.** Oncogenic kinase-induced PKM2 tyrosine 105 phosphorylation converts non-oncogenic PKM2 to a tumor promoter and induces cancer stem-like cells. ***Cancer Research*** 78(9):2248-2261, 5/2018. e-Pub 2/2018. PMCID: PMC 5932213
4. Wang JY\*, Zhang Y\*, Xiao Y\*, Yuan XL, Li P, Wang X, Duan YM, Seewaldt VL, **Yu D**. Boosting immune surveillance by low-dose PI3K inhibitor facilitates early intervention of breast cancer. **Am J Cancer Res.** 11(5):2005-2024, 2021. e-Pub 5/2021. PMCID: PMC8167687.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/dihua.yu.1/bibliography/public/