BIOGRAPHICAL SKETCH

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NAME: **GIACCIA, Amato J.**

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

POSITION TITLE: **Professor and Division Director**

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/YY	FIELD OF STUDY
Lafayette College, Easton, PA	B.A.	1980	Biology
University of Pennsylvania, Philadelphia, PA	Ph.D.	1989	Pathology/Molecular Biology

A. Personal Statement

Qualifications to perform the research: The overall goal of radiotherapy is to eradicate the tumor and spare normal tissue damage. My research interests have focused on understanding the molecular mechanisms underlying the response of tumors and normal tissue to a reduced oxygen environment (hypoxia). Tumor hypoxia reduces the efficacy or radiotherapy and chemotherapy and increases the invasive and metastatic behavior of tumor cells. To this end, we have identified several small molecules that selectively kill tumor cells that have elevated levels of the HIF transcription factor. We are also developing new therapeutics to treat metastatic disease through the targeting of hypoxia-induced genes that involved in extracellular matrix remodeling such as lysyl oxidase.

B. Positions and Honors

Professional Experience

1992–1999 Assistant Professor, Dept of Radiation Oncology, Stanford University, Stanford, CA
1999–2003 Associate Professor (with tenure), Dept of Radiation Oncology, Stanford Univ, Stanford, CA
2003–present Professor, Dept of Radiation Oncology, Stanford University, Stanford, CA
2001–present Professor (by courtesy), Dept of Gynecology and Obstetrics, Stanford University, Stanford, CA
2004–present Director, Div of Radiation Biology, Dept of Radiation Oncology, Stanford Univ, Stanford, CA
2007–present Professor (by courtesy), Dept of Surgery, Stanford University, Stanford, CA
2012–2016 Member, Basic Mechanisms of Cancer Therapeutics Study Section, NIH Center for Scientific Review (Chair, 2015–2016)

Honors and Awards

1986–1989 NIH Predoctoral Trainee
1989 Alexander Hollaender Fellowship Awardee
1995 American Cancer Society Junior Faculty Research Award
1996 Howard Hughes Junior Faculty Award
1997 Michael Fry Research Awardee of the Radiation Research Society
2000 John Yuhas Award (Excellence in Radiation Oncology, University of Pennsylvania)
2006 Jack, Lulu and Sam Willson Professor of Cancer Biology
2010 MERIT Award NIH
2013 ASTRO Gold Medal
2015 NIH Outstanding Investigator Award, R35 CA197713
2015 National Academy of Medicine
2015–2016 Stanford Biosciences “Excellence in Mentoring and Service Award

C. Contributions to Science

1. When I first came to Stanford, the role of hypoxia in therapeutic resistance was a major theme of the department. However, I thought that hypoxia had additional roles than simply reducing the efficacy of radiotherapy, and hypothesized that it could act as a selective pressure in solid tumors for the expansion of tumor cells with diminished apoptotic potential. For example, in the well studied model of colorectal cancer, tumor cells with mutations in the p53 tumor suppressor gene occur and exist in small numbers compared to their wild-type p53 counterparts. Hypoxia fit the necessary criteria for a selective stress, as it induces

apoptosis in a p53 dependent manner, and the magnitude of this selection would be large enough to enhance the probability for mutant p53 tumor cells to become the predominant genotype in the tumor. My early studies focused on the role of hypoxia-induced apoptosis. In addition, we also demonstrated the mechanism of hypoxia-induced apoptosis was distinct from DNA damage induced apoptosis and regulated a very distinct set of target genes. These studies have important therapeutic implications, because hypoxia-mediated selection of cells with diminished apoptotic potential could also explain the in part the poor response of solid tumors to therapy. These studies have stimulated immense interest in understanding how hypoxia influenced the survival and malignant progression of tumor cells.

a. Graeber, T.G., Peterson, J.F., Tsai, M., Monica K., Fornace, Jr., A.J. and **Giaccia, A.J.** Hypoxia induces the accumulation of *p53* protein, but the activation of a G_1-phase checkpoint by low oxygen conditions is independent of p53 status. Mol Cell Biol 14:6264-6277, 1994 (PMID: 8065358).
b. Graeber, T.G., Osmanian, C., Jacks, T., Houseman, D., Koch, C.J., Lowe, S.W. and **Giaccia, A.J.** Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. Nature 379:88-91, 1996 (PMID: 8538748).
c. Zundel, W. and **Giaccia, A.J.** Inhibition of the anti-apoptotic PI(3)K/Akt/Bad pathway by stress. Genes Dev 12:1941-1946, 1998 (PMID: 9649498).
d. Hammond, E., Mandell, D.J., Salim, A., Krieg, A.J., Johnson, T.M., Shirazi, H., Attardi, L.D. and **Giaccia, A.J.** Genome wide analysis of p53 under hypoxic conditions. Mol Cell Biol 26:3492-3504, 2006 (PMCID: PMC1447427).

2. Hypoxia Induced Metastasis and the Premetastatic Niche. Niches are defined as particular regions within a defined environment where specialized inhabitants reside. The key points in this definition are "environment" and "specialized inhabitants". We have accumulated a significant amount of data that implicates an important role for hypoxia in recruiting bone marrow-derived tumor cells through the modulation of the extracellular matrix. Previous studies have suggested that tumor cell metastasis is facilitated by formation of "pre-metastatic niches" in destination organs, comprised of bone marrow-derived cells (BMDCs) such as CD11b+ myeloid cells recruited by poorly defined mechanisms. We found that lysyl oxidase (LOX) that is secreted by hypoxic tumor cells is essential for BMDC recruitment at pre-metastatic sites. LOX secreted by hypoxic breast tumor cells accumulates at pre-metastatic sites, cross-links collagen-IV in the basement membrane, and is essential for CD11b+ myeloid cell recruitment. Our findings demonstrate a critical role for hypoxia in formation of the pre-metastatic niche and metastatic disease. These studies were sufficient to stimulate Phase 1 and 2 clinical trials examining the role of LOX inhibition clinically. More recently, we have identified the receptor tyrosine kinase AXL as a critical modulator of invasion, metastasis and the desmoplastic response of tumors. Although we have not yet published these findings, it appears that AXL inhibition inhibits and reverses desmoplasia and fibrosis both in pancreatic tumor models as well as patient biopsies from idiopathic pulmonary fibrosis. We anticipate that clinical trials could be started on our clinical candidate in two years.

a. Erler, J.T., Bennewith, K.L., Nicolau, M., Dornhoefer, N., Kong, C., Le, Q-T., Chi, J-T.A., Jeffrey, S.J. and **Giaccia, A.J.** Lysyl oxidase is essential for hypoxia-induced metastasis. Nature 440:1222-1226, 2006 (PMID: 16642001).
b. Kariolis, M.S., Miao, Y.R., Jones II, D.S., Kapur, S., Matthews, I.I., **Giaccia, A.J.,** and Cochran, J.R. An engineered Axl "decoy receptor' effectively silences the Gas6/Axl signaling axis. Nat Chem Biol 10:977-983, 2014 (PMCID: PMC4372605).
c. Kariolis, M.S., Miao, Y.R., Diep, A., Nash, S.E., Olcina, M.M, Jiang, D., Jones, D.S. 2nd, Kapur, S., Mathews, I.I., Koong, A.C., Rankin, E.B. Cochran, J.R. and **Giaccia, A.J.** Inhibition of the GAS6/AXL pathway augments the efficacy of chemotherapies. J Clin Invest 127:183-198, 2017 (PMCID: PMC5199716).
d. Zhou, L., Liu, X.D., Sun, M., Zhang, X., German, P., Bai, S., Ding, Z., Tannir, N., Wood, C.G., Matin, S.F., Karam, J.A., Tamboli, P., Sircar, K., Rao, P., Rankin, E.B., Laird, D.A., Hoang, A.G., Walker, C.L., **Giaccia, A.J.** and Jonasch, E. Targeting MET and AXL overcomes resistance to sunitinib therapy in renal cell carcinoma. Oncogene 2015 Sep 14. doi: 10.1038/onc.2015.343. [Epub ahead of print] (PMID: 26364599).

3. Conditional Synthetic Lethality and Cancer Therapeutics. Identifying new molecular targeted therapies that specifically kill tumor cells while sparing normal tissue is the next major challenge of cancer research. Using a high-throughput chemical synthetic lethal screen, we identified several small molecule compounds that exploit the loss of the von Hippel-Lindau (*VHL*) tumor suppressor gene, which occurs in approximately

80% of renal carcinomas. One molecule STF-62247 induces cytotoxicity and reduces tumor growth by inducing autophagy. Interestingly, STF-62247 kills VHL deficient cells in a HIF independent manner. We also identified a second compound, STF-31 that also selectively kills cells with mutant *VHL* by specifically targeting glucose uptake and decreasing ATP production by glycolysis. Activity of STF-31 in these experimental renal cell tumors can be monitored by [18F]-fluorodeoxyglucose (FDG) uptake by microPET imaging and therefore may be readily translated clinically to human tumors. STF-31 is a particularly attractive targeted therapy for the treatment of renal carcinoma due to its unique mechanism of inhibiting glucose uptake and the ability to measure tumor response by FDG-PET. We have recently other tumor types such as ovarian cancers that are highly sensitive to killing by STF-31. These two small molecules that been licensed from Stanford and are being clinically developed.

a. Turcotte, S., Chan, D.A., Sutphin, P.D., Hay, M.P., Denny, W.A. and **Giaccia, A.J.** A molecule targeting VHL-deficient renal cell carcinoma that induces autophagy. Cancer Cell 14:90-102, 2008 (PMCID: PMC2819422).
b. Turcotte, S., Sutphin, P.D. and **Giaccia, A.J.** Targeted therapy for the loss of von Hippel-Landau in renal cell carcinoma: A novel molecule that induces autophagic cell death. Autophagy 4:944-946, 2008 (PMCID: PMC2803726).
c. Chan, D.A., Sutphin, P.D., Nguyen, P., Turcotte, S., Lai, E.W., Banh, A., Reynolds, G.E., Chi, J-T., Wu, J., Solow-Cordero, D.E., Bonnet, M., Flanagan, J., Bouley, D.M., Graves, E.E., Denny, W.A., Hay, M.P. and **Giaccia, A.J.** Targeting GLUT1 and the Warburg Effect in Renal Cell Carcinoma by Chemical Synthetic Lethality. Sci Transl Med 3:94ra70, 2011 (PMCID: PMC3683134).
d. Chan, D.A. and **Giaccia, A.J.** Harnessing synthetic lethal interactions in anticancer drug discovery. Nat Rev Drug Discov 10:351-364, 2011 (PMCID: PMC3652585).

4. Transform the Use of Radiotherapy to Treat Widespread Metastatic Disease. A patient presents with a primary pancreatic tumor that has metastasized to the liver. The liver is completely infiltrated with metastasis, and ultimately the metastasis will prevent the liver from functioning, and death will ensue. This is a frustrating situation, because we know where the metastases are located, we can image them, and attempt to treat them with cytotoxic chemotherapy. Unfortunately, chemotherapy only inhibits the metastasis in a short-term manner, and rarely eradicates the disease. Unlike chemotherapy, radiotherapy is highly effective in eradicating tumors, but it cannot be used to treat widespread metastasis in the liver due to normal tissue toxicity, especially at the doses of radiation needed to eliminate the metastasis. For radiotherapy to be used in such a manner, we need to develop effective radioprotectors that protect normal tissue, but not tumor tissue from radiation induced cell death. We have identified prolyl hydroxylase (PHD) inhibitors as promising agents that both stimulate erythropoiesis and protect the gastrointestinal tract from lethal doses of radiation without any effect on tumor radiosensitivity. Such agents will revolutionize the use of radiation for the treatment of metastasis, and most importantly would start to increase the long-term survival of patients with metastatic disease. So, our big idea for the next ten years is the identification of new molecules that selectively protect normal tissue from radiation-induced lethality. This is a completely different approach to the treatment of metastatic disease that is risky, but would be revolutionary.

a. Rankin, E.B., Wu, C., Khatri, R., Wilson, T.L.S., Andersen, R., Araldi, E., Rankin, A.L. Yuan, J., Kuo, C.J., Schipani, E. and **Giaccia, A.J.** The HIF signaling pathway in osteoblasts directly modulates erythropoiesis through the production of EPO. Cell 149:63-74, 2012 (PMCID: PMC3408231).
b. Taniguchi, C.M., Miao, Y.R., Diep, A.N., Wu, C., Rankin, E.B., Atwood, T.F. Xing, L., and **Giaccia, A.J.** PHD inhibition mitigates and protects against radiation-induced gastrointestinal toxicity via HIF2. Sci Transl Med 6:236ra64, 2014 (PMCID: PMC4136475).
c. **Giaccia, A.J.** Molecular Radiobiology: The State of the Art. J Clin Oncol 32:2871-2878, 2014.

5. HIF and Glucose and Lipid Metabolism. Insulin receptor substrate-2 (IRS2) is a critical component of the insulin signalling pathway. Decreased hepatic IRS2 expression contributes to diabetes in animal models of insulin resistance. Liver-specific knockouts of IRS2 show impaired glucose homeostasis in the fasted state. Thus, a great effort has been made to discover therapeutic pathways that would raise hepatic IRS2 levels and reverse hepatic insulin resistance. Unfortunately, many candidate molecules that increase IRS2, such as TFE3, SREBP1c or TORC2, are difficult to target pharmacologically. Hypoxia inducible factors -1 and -2 globally alter cellular metabolism and are regulated by three prolyl hydroxylase domain-containing proteins, PHD1-3. To understand the relative roles of the PHD proteins, we systemically deleted all combinations of the PHD proteins in the liver and found that the deletion of PHD1-3 (L-

PHD1/2/3KO) improved glucose tolerance, but led to severe hepatic steatosis and premature hypoglycemic death. The deletion of hepatic PHD3 alone (L-PHD3KO), however, improves insulin sensitivity without a fatty liver by increasing IRS2 in a HIF2 dependent manner. Overexpression of HIF2, but not HIF1, recapitulated nearly all the phenotypes of the L-PHD1/2/3KO including hepatosteatosis and death. Knockdown of HIF2 in L-PHD3KO mice normalized IRS2 expression and insulin sensitivity. Thus, modulating IRS2 through PHD3/HIF2 has tremendous therapeutic potential against type 2 diabetes, as long as HIF2 levels are carefully titrated to avoid hepatic steatosis and lethal hypoglycaemia. This could be accomplished through the selective inhibition of PHD3 or PHD1/3, which are investigating.

a. Taniguchi, C.M., Finger, E.C., Krieg, A.J., Wu, C., Diep, A.N., LaGory, E.L., Wei, K., McGinnis, L.M. Yuan, J., Kuo, C.J. and **Giaccia, A.J.** Cross-talk between hypoxia and insulin signaling via PHD3 regulates hepatic glucose and lipid metabolism and ameliorates diabetes. Nature Med 19:1325-1330, 2013 (PMCID: PMC4089950).
b. Wei, K., Piecewicz, S., McGinnis, L.M., Taniguchi, C.M., Wiegand, S.J., Anderson, K., Chan, C.W., Mulligan, K.X., Kuo, D., Yuan, J., Vallon, M., Morton, L.C., Lefai, E., Simon, M.C., Maher, J.J., Annes, J.P., McGuinness, O.P., Thurston, G., **Giaccia, A.J.** and Kuo, C.J. A liver HIF-2α/Irs2 pathway sensitizes hepatic insulin signaling and is modulated by VEGF inhibition. Nature Med 19:1331-1337, 2013 (PMCID: PMC3795838).

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/amato.giaccia.1/bibliography/40637446/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

P01 CA67166 (Giaccia) 06/01/13–05/31/18
NIH/NCI NCX
*Project 1 & Core A – (Project Leader)
Hypoxia: Molecular Studies and Clinical Exploitation
The major goals are to explore how to protect normal tissues to increase the efficacy of hypofractionated and fractionated radiotherapy, and how to specifically increase tumor radiosensitivity by manipulating mitochondrial metabolism and the unfolded protein response pathways.
Role: Principal Investigator

P30 CA124435 (Mitchell) 06/04/07–05/31/21
NIH/NCI
Stanford University Cancer Center
The Stanford University Comprehensive Cancer Center (Cancer Center) brings together, under a strong leadership team, a committed and talented group of investigators whose research focuses on the incidence, prevalence, etiology, prevention or treatment of cancer. The membership comes from 32 Departments and four Schools of the University and from the Northern California Cancer Center.
Role: Associate Director of Education & Program Leader

R35 CA197713 (Giaccia) 08/01/15–07/31/22
NIH Outstanding Investigator Award
The Impact of Mitochondrial Repression and Lipid Accumulation by HIF on Tumor Growth
The specific aims proposed are focused on developing a better understanding of the contribution of lipid and mitochondrial metabolism to tumorigenesis. Specifically, these studies will characterize the interplay between mitochondria and hypoxia-associated lipid accumulation, define the lipidomic profile of hypoxic cancer cells, interrogate the contribution of lipids to cell signaling in cancer cells and identify novel regulators of lipogenesis in cancer.
Role: Principal Investigator

R01 CA198291 (Giaccia) 04/01/16–03/31/21
NIH
Preclinical Testing of a Novel Therapy Targeting AXL in Advanced Kidney Cancer
The proposed studies will investigate the efficacy, survival benefit, and safety of sAXL alone or in combination with antiangiogenic agents to support its clinical development for the treatment of advanced ccRCC.
Role: Principal Investigator

Completed Research Support

R01 HL095571 (Wu) 02/01/10–11/30/14
NIH/NHLBI
Integrated Strategies for Treatment of Myocardial Ischemia
This project seeks to develop second generation minicircle vectors to improve safety and efficiency of transfection and to understand the mechanistic basis of HIF-1a therapy in preclinical models.
Role: Co-Investigator

R37-CA88480 (Giaccia) 05/1/10–07/31/15
NIH/NCI
Hypoxia and Gene Repression
The major goals of this project are to understand p53 dependent repression and identify p53-repressed genes that are involved in hypoxia-induced apoptosis.
Role: Principal Investigator

R01 AR065403 (Schipani) 10/01/13–10/31/18
NIH/NIDDK
HIF-1α, a Survival and Differentiation Factor for Cartilage
The aim of this proposal is to establish the role of metabolism both downstream and upstream of HIF-1α *in vivo* in the developing cartilage, which is a hypoxic tissue.
Role: Co-Investigator