




## Albert J. Wong, M.D.

Professor of Neurosurgery

 NIH Biosketch available Online

### Bio

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#### ACADEMIC APPOINTMENTS

- Professor, Neurosurgery
- Member, Stanford Cancer Institute

#### PROFESSIONAL EDUCATION

- B.A., Johns Hopkins University , Bioengineering/Medicine (1980)
- M.D., Johns Hopkins School of Medicine (1983)

### Research & Scholarship

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#### CURRENT RESEARCH AND SCHOLARLY INTERESTS

The goal of this laboratory is to define targets for cancer therapeutics by identifying alterations in signal transduction proteins and then translate these findings into important clinical tools, including one of the first effective peptide vaccines against cancer. The major type of cancer that we study is glioblastoma multiforme, the most common and devastating of the human brain tumors, but this work has also had implications for lung, breast, ovarian and prostate cancers.

Our research direction originated when we first identified a spontaneously occurring mutant EGF receptor in glioblastoma. Known as EGFRvIII (pronounced “E-G-F-R-v-three”), this molecule represents a deletion of exons 2 through 7 in the extracellular domain of the EGF receptor. This removes 273 amino acids and creates a novel glycine at the fusion junction. We have engaged in both very basic studies on the signal transduction pathways initiated by EGFRvIII, as well as translational work to create diagnostic tools and therapies around EGFRvIII.

Our basic science studies on understanding EGFRvIII signaling have led us to discover the Gab1 docking protein. Originally discovered as a substrate for the EGF receptor, we and others have found that Gab1 is a substrate for numerous tyrosine kinase receptors, and in turn Gab1 recruits several proteins with SH2 domains. It is now clear that it is a vital link for multiple growth factor and cytokine pathways and has a role in diverse phenotypes such as cell survival, the cellular response to stress, and the cellular entry of parasites.

As another result of our efforts on signaling pathways, we have discovered that glioblastoma tumors preferentially utilize the JNK pathway, unlike many other tumors that use the ERK pathway. More specifically, only one of the 12 known JNK isoforms is highly expressed, JNK2a2. Co-incidentally, we have uncovered that this isoform is constitutively active and that it has a specific activation domain. JNK2a2 also upregulates TGF- $\alpha$ , a ligand for the EGF receptor that is frequently overexpressed in glioblastomas.

Our translational work has encompassed both diagnostics and therapeutics. We have developed antibodies that specifically recognize EGFRvIII and not EGF receptor and have also developed rapid RT-PCR based assays to detect EGFRvIII. Using these tools, we have discovered that expression of EGFRvIII is not limited just to glioblastoma tumors but it is also found in breast, lung, prostate and ovarian tumors.

We were the first to show that a peptide vaccine based on the cancer specific epitope found in EGFRvIII is an effective anti-tumor drug (originally called ALT-110). In animal models, this vaccine can both prevent tumors and induce the regression of existing tumors. We also played a major role in initiating the first clinical trial in humans using this peptide vaccine. Three trials have now been completed with highly interesting results. A Phase II clinical trial at Duke and MD Anderson for glioblastoma patients has shown median survival of 30 months vs. 14 months for conventional therapy in a matched cohort.

An expanded Phase II/III trial for brain tumors using the vaccine (now called CDX-110) is currently enrolling which is sponsored by Celldex Therapeutics. If you have questions about this trial, please visit the NCI trials website at <http://clinicaltrials.gov/ct/show/NCT00458601> or [www.avantimmune.com](http://www.avantimmune.com).

Disclosure: Dr. Wong is the inventor of EGFRvIII and CDX-110, holds other patents related to EGFRvIII, and owns equity in Celldex.

## CLINICAL TRIALS

- Phase I Rindopepimut After Conventional Radiation in Children w/ Diffuse Intrinsic Pontine Gliomas, Not Recruiting

## Teaching

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### COURSES

#### 2019-20

- Cancer Biology Journal Club: CBIO 280 (Spr)

#### 2018-19

- Cancer Biology Journal Club: CBIO 280 (Spr)

#### 2017-18

- Cancer Biology Journal Club: CBIO 280 (Spr)

### GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Cancer Biology (Phd Program)

## Publications

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### PUBLICATIONS

- **Targeting a Glioblastoma Cancer Stem-Cell Population Defined by EGF Receptor Variant III.** *Cancer research*  
Emlet, D. R., Gupta, P., Holgado-Madruga, M., Del Vecchio, C. A., Mitra, S. S., Han, S., Li, G., Jensen, K. C., Vogel, H., Xu, L. W., Skirboll, S. S., Wong, A. J.  
2014; 74 (4): 1238-1249
- **EGFRvIII gene rearrangement is an early event in glioblastoma tumorigenesis and expression defines a hierarchy modulated by epigenetic mechanisms.** *Oncogene*  
Del Vecchio, C. A., Giacomini, C. P., Vogel, H., Jensen, K. C., Florio, T., Merlo, A., Pollack, J. R., Wong, A. J.  
2013; 32 (21): 2670-2681
- **Chimeric antigen receptor containing ICOS signaling domain mediates specific and efficient antitumor effect of T cells against EGFRvIII expressing glioma** *JOURNAL OF HEMATOLOGY & ONCOLOGY*  
Shen, C., Yang, Y., Han, E. Q., Cao, N., Wang, Y., Wang, Y., Zhao, Y., Zhao, L., Cui, J., Gupta, P., Wong, A. J., Han, S.  
2013; 6

- **Breakpoint analysis of transcriptional and genomic profiles uncovers novel gene fusions spanning multiple human cancer types.** *PLoS genetics*  
Giacomini, C. P., Sun, S., Varma, S., Shain, A. H., Giacomini, M. M., Balagtas, J., Sweeney, R. T., Lai, E., Del Vecchio, C. A., Forster, A. D., Clarke, N., Montgomery, K. D., Zhu, et al  
2013; 9 (4)
- **Breakpoint analysis of transcriptional and genomic profiles uncovers novel gene fusions spanning multiple human cancer types.** *PLoS genetics*  
Giacomini, C. P., Sun, S., Varma, S., Shain, A. H., Giacomini, M. M., Balagtas, J., Sweeney, R. T., Lai, E., Del Vecchio, C. A., Forster, A. D., Clarke, N., Montgomery, K. D., Zhu, et al  
2013; 9 (4)
- **Expression of epidermal growth factor variant III (EGFRvIII) in pediatric diffuse intrinsic pontine gliomas** *JOURNAL OF NEURO-ONCOLOGY*  
Li, G., Mitra, S. S., Monje, M., Henrich, K. N., Bangs, C. D., Nitta, R. T., Wong, A. J.  
2012; 108 (3): 395-402
- **A novel epidermal growth factor receptor variant lacking multiple domains directly activates transcription and is overexpressed in tumors** *ONCOGENE*  
Piccione, E. C., LIEU, T. J., Gentile, C. F., Williams, T. R., Connolly, A. J., Godwin, A. K., Koong, A. C., Wong, A. J.  
2012; 31 (24): 2953-2967
- **Epidermal Growth Factor Receptor Variant III Contributes to Cancer Stem Cell Phenotypes in Invasive Breast Carcinoma** *CANCER RESEARCH*  
Del Vecchio, C. A., Jensen, K. C., Nitta, R. T., Shain, A. H., Giacomini, C. P., Wong, A. J.  
2012; 72 (10): 2657-2671
- **Immunohistochemical discrimination of wild-type EGFR from EGFRvIII in fixed tumour specimens using anti-EGFR mAbs ICR9 and ICR10** *BRITISH JOURNAL OF CANCER*  
Modjtahedi, H., Khelwatty, S. A., Kirk, R. S., Seddon, A. M., Essapen, S., Del Vecchio, C. A., Wong, A. J., Eccles, S.  
2012; 106 (5): 883-888
- **Targeting EGF receptor variant III: tumor-specific peptide vaccination for malignant gliomas** *EXPERT REVIEW OF VACCINES*  
Del Vecchio, C. A., Li, G., Wong, A. J.  
2012; 11 (2): 133-144
- **Hedgehog-responsive candidate cell of origin for diffuse intrinsic pontine glioma** *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA*  
Monje, M., Mitra, S. S., Freret, M. E., Raveh, T. B., Kim, J., Masek, M., Attema, J. L., Li, G., Haddix, T., Edwards, M. S., Fisher, P. G., Weissman, I. L., Rowitch, et al  
2011; 108 (11): 4453-4458
- **The role of the c-Jun N-terminal kinase 2-alpha-isoform in non-small cell lung carcinoma tumorigenesis** *ONCOGENE*  
Nitta, R. T., Del Vecchio, C. A., Chu, A. H., Mitra, S. S., Godwin, A. K., Wong, A. J.  
2011; 30 (2): 234-244
- **Rindopepimut, a 14-mer injectable peptide vaccine against EGFRvIII for the potential treatment of glioblastoma multiforme** *CURRENT OPINION IN MOLECULAR THERAPEUTICS*  
Del Vecchio, C. A., Wong, A. J.  
2010; 12 (6): 741-754
- **IDENTIFICATION AND TARGETING OF GLIOBLASTOMA STEM CELLS USING EGFRvIII** *Advances in Inflammatory Bowel Diseases Crohn's and Colitis Foundations National Clinical and Research Conference*  
Wong, A. J., Del Vecchio, C., Mitra, S., Han, S., Holgado-Madruga, M., Gupta, P.  
OXFORD UNIV PRESS INC.2010: 123-123
- **Development of an EGFRvIII specific recombinant antibody** *BMC BIOTECHNOLOGY*  
Gupta, P., Han, S., Holgado-Madruga, M., Mitra, S. S., Li, G., Nitta, R. T., Wong, A. J.  
2010; 10
- **Pineal Parenchymal Tumor of Intermediate Differentiation: Clinicopathological Report and Analysis of Epidermal Growth Factor Receptor Variant III Expression** *NEUROSURGERY*  
Li, G., Mitra, S., Karamchandani, J., Edwards, M. S., Wong, A. J.  
2010; 66 (5): 963-968

- **MEASURING THE CONSTITUTIVE ACTIVATION OF C-JUN N-TERMINAL KINASE ISOFORMS** *METHODS IN ENZYMOLOGY, VOLUME 484: CONSTITUTIVE ACTIVITY IN RECEPTORS AND OTHER PROTEINS, PART A*  
Nitta, R. T., Badal, S. S., Wong, A. J.  
2010; 484: 531-548
- **The Epidermal Growth Factor Variant III Peptide Vaccine for Treatment of Malignant Gliomas** *NEUROSURGERY CLINICS OF NORTH AMERICA*  
Li, G., Mitra, S., Wong, A. J.  
2010; 21 (1): 87-?
- **Targeting brain tumor stem cells using a bispecific antibody directed against CD133+and EGFRvIII** *45th Annual Meeting of the American-Society-of-Clinical-Oncology (ASCO)*  
Wong, A., Mitra, S., Gupta, P.  
AMER SOC CLINICAL ONCOLOGY.2009
- **Constitutive Activity of JNK2 alpha 2 Is Dependent on a Unique Mechanism of MAPK Activation** *JOURNAL OF BIOLOGICAL CHEMISTRY*  
Nitta, R. T., Chu, A. H., Wong, A. J.  
2008; 283 (50): 34935-34945
- **IDENTIFICATION OF EGFRVIII IN BRAIN TUMOR STEM CELL ANALYSIS SUGGESTS A BISPECIFIC ANTIBODY TARGETING STRATEGY** *13th Annual Meeting of the Society-for-Neuro-Oncology (SNO)*  
Mitra, S., Del Vecchio, C., Han, S., Gupta, P., Skirboll, S., Wong, A.  
OXFORD UNIV PRESS INC.2008: 899-99
- **EGF receptor variant III as a target antigen for tumor immunotherapy** *EXPERT REVIEW OF VACCINES*  
Li, G., Wong, A. J.  
2008; 7 (7): 977-985
- **The scaffolding adapter Gab1 mediates vascular endothelial growth factor signaling and is required for endothelial cell migration and capillary formation** *JOURNAL OF BIOLOGICAL CHEMISTRY*  
Laramee, M., Chabot, C., Cloutier, M., Stenne, R., Holgado-Madruga, M., Wong, A. J., Royal, I.  
2007; 282 (11): 7758-7769
- **A variant epidermal growth factor receptor protein is similarly expressed in benign hyperplastic and carcinomatous prostatic tissues in black and white men.** *West African journal of medicine*  
Olapade-Olaopa, E. O., Moscatello, D. K., MacKay, E. H., Ogunbiyi, J. O., Shittu, O. B., Terry, T. R., OKEKE, L. I., Wong, A. J., Habib, F. K.  
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- **c-Jun NH2-terminal kinase 2 alpha 2 promotes the tumorigenicity of human glioblastoma cells** *CANCER RESEARCH*  
Cui, J., Han, S., Wang, C., Su, W., Harshyne, L., Holgado-Madruga, M., Wong, A. J.  
2006; 66 (20): 10024-10031
- **beta(1) integrins modulate cell adhesion by regulating insulin-like growth factor-II levels in the microenvironment** *CANCER RESEARCH*  
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- **Identification of a specific domain responsible for JNK2 alpha 2 autophosphorylation** *JOURNAL OF BIOLOGICAL CHEMISTRY*  
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- **Host adaptor proteins Gab1 and CrkII promote InlB-dependent entry of Listeria monocytogenes** *CELLULAR MICROBIOLOGY*  
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- **Gab1 is an integrator of cell death versus cell survival signals in oxidative stress** *MOLECULAR AND CELLULAR BIOLOGY*  
Holgado-Madruga, M., Wong, A. J.  
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- **Targeting of cells expressing wild-type EGFR and type-III mutant EGFR (EGFRvIII) by anti-EGFR MAb ICR62: A two-pronged attack for tumour therapy** *INTERNATIONAL JOURNAL OF CANCER*  
Modjtahedi, H., Moscatello, D. K., Box, G., Green, M., Shotton, C., LAMB, D. J., Reynolds, L. J., Wong, A. J., Dean, C., Thomas, H., Eccles, S.  
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- **Constitutively active forms of c-Jun NH2-terminal kinase are expressed in primary glial tumors** *CANCER RESEARCH*  
Tsuiki, H., Tnani, M., Okamoto, I., Kenyon, L. C., Emlet, D. R., Holgado-Madruga, M., Lanham, I. S., Joynes, C. J., Vo, K. T., Wong, A. J.  
2003; 63 (1): 250-255
- **Expression of constitutively activated EGFRvIII in non-small cell lung cancer** *CANCER SCIENCE*  
Okamoto, I., Kenyon, L. C., Emlet, D. R., Mori, T., Sasaki, J., Hirotsako, S., Ichikawa, Y., Kishi, H., Godwin, A. K., Yoshioka, M., Suga, M., Matsumoto, M., Wong, et al  
2003; 94 (1): 50-56
- **Elevated JNK activation contributes to the pathogenesis of human brain tumors** *ONCOGENE*  
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- **Proteolytic cleavage of the CD44 adhesion molecule in multiple human tumors** *AMERICAN JOURNAL OF PATHOLOGY*  
Okamoto, I., Tsuiki, H., Kenyon, L. C., Godwin, A. K., Emlet, D. R., Holgado-Madruga, M., Lanham, I. S., Joynes, C. J., Vo, K. T., Guha, A., Matsumoto, M., Ushio, Y., Saya, et al  
2002; 160 (2): 441-447
- **Proteolytic release of CD44 intracellular domain and its role in the CD44 signaling pathway** *JOURNAL OF CELL BIOLOGY*  
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- **New approaches to the molecular biology, classification, and therapy of nervous system tumors: a workshop of the National Institutes of Health Pathology B study section.** *American journal of pathology*  
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- **The tyrosine phosphatase SHP-2 is required for sustained activation of extracellular signal-regulated kinase and epithelial morphogenesis downstream from the Met receptor tyrosine kinase** *MOLECULAR AND CELLULAR BIOLOGY*  
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- **Epidermal growth factor receptor vIII enhances tumorigenicity in human breast cancer** *CANCER RESEARCH*  
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