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Lung Cancer Foundation of America
Grant Award Recipient:
Dr. Daniel Costa, Beth Israel Deaconess Medical Center, Harvard

Lay summary/progress report:

A decade ago oncologists lumped together all non-small-cell lung cancers (NSCLCs) as a single disease and treated them with similar ineffective regimens. Molecular discoveries in the last several years have made it abundantly clear that NSCLCs that look similar are molecularly diverse, and the differences from one tumor type to another are vast. In 2004, epidermal growth factor receptor (*EGFR*) mutations were identified in tumors from approximately 15%-20% of patients with NSCLC (more than 200,000 patients a year worldwide). This finding proved not merely scientifically interesting; it also changed clinical practice. Patients whose tumors harbored *EGFR* mutations experienced remarkable palliative improvement when they took oral drugs such as gefitinib or erlotinib, which block the kinase domain of the EGFR protein and are now approved for tumors that carry these mutations. However, not all *EGFR* mutations are predictive of response to EGFR inhibitors and in specific *EGFR* exon 20 insertions (the third most common type of *EGFR* mutations) constitute the majority of insensitive mutations. Our group is focused in studying why *EGFR* exon 20 insertion mutations are different than other *EGFR* mutations and on how to develop novel treatment strategies for tumors that harbor these changes. To understand the patterns of resistance to EGFR inhibitors of EGFR exon 20 insertion mutations, in the first phase of the grant period, our research team generated the most extensive preclinical database of representative mutations using *in vitro* systems, structural models and NSCLC cell lines with these specific *EGFR* mutations. With the support

of the LCFA grant, we now understand the basic structure of the most prevalent EGFR exon 20 insertion mutations and why drugs like gefitinib and erlotinib are unable to inhibit these mutations. We have further showed that all classes of EGFR inhibitors that in in clinical development are unable to inhibit common EGFR exon 20 insertion mutations. To circumvent the lack of precision therapies for this important group of recalcitrant lung cancers, we have confirmed that a new class of anti-cancer medications (called heat shock protein 90 inhibitors [Hsp90]) has activity against *EGFR* exon 20 insertion mutated lung cancers; and further clinical development is planned. We hope our expanding our research tools will be used to identify novel therapies that function as precision therapies for *EGFR* exon 20 insertion mutated lung cancers.

Progress Report 2014 LCFA/IASLC Grant in Translational Lung Cancer Research

(grant period one of two: 01/01/2013 to 12/31/2013) (grant period two of two:01/01/2014 to 12/31/2014)

Principal Investigator:

Daniel B. Costa, MD, PhD

Title: Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations: understanding mechanisms of sensitivity and resistance to EGFR inhibitors

Publications that were partially funded by the first period of the LCFA/IASLC grant: **1.** Yasuda H, Park E, Yun C-H, Sng NJ, Lucena-Araujo AR, Yeo W-L, Huberman MS, Cohen DW, Nakayama S, Ishioka K, Yamagichi N, Hanna M, Oxnard GR, Lathan CS, Moran T, Sequist LV, Chaft JE, Riely GJ, Arcila ME, Soo RA, Meyerson M, Eck MJ, Kobayashi SS, **Costa DB**. Structural, biochemical and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med 2013;5:216ra177. PMCID: PMC3954775. (http://www.ncbi.nlm.nih.gov/pubmed/24353160) **2.** Yamaguchi N, Vanderlaan PA, Folch E, Boucher DH, Canepa HM, Kent MS, Gangadharan SP, Majid A, Kocher ON, Goldstein MA, Huberman MS, **Costa DB**. Smoking status and self-reported race affect the frequency of clinically relevant oncogenic alterations in non-small-cell lung cancers at a United States-based academic medical practice. Lung Cancer. 2013;82(1):31-7. PMCID:PMC3800098. (http://www.ncbi.nlm.nih.gov/pubmed/23932486) **3.** Folch E, Yamaguchi N, VanderLaan PA, Kocher ON, Boucher DH, Goldstein MA, Huberman MS, Kent MS, Gangadharan SP, **Costa DB**, Majid A. Adequacy of lymph node transbronchial needle aspirates using convex probe endobronchial ultrasound for multiple tumor genotyping techniques in non-small-cell lung cancer. J Thorac Oncol. 2013;8(11):1438-44. PMCID: PMC3800048.

(http://www.ncbi.nlm.nih.gov/pubmed/24128714) **4. Costa DB.** Identification of somatic genomic alterations in circulating tumors cells: another step forward in non-small- cell lung cancer? J Clin Oncol. 2013;31(18):2236-9. (http://www.ncbi.nlm.nih.gov/pubmed/23669228) **Publications that were partially funded by the second period of the LCFA/IASLC grant: 1.** Jorge SE, Kobayashi S, **Costa DB.** Epidermal growth factor receptor (EGFR) mutations in lung cancer: preclinical and clinical data. Braz J Med Biol Res 2014;47(11):929-939 (http://www.ncbi.nlm.nih.gov/pubmed/25296354). **2.** Gerber DE, Gandhi L, **Costa DB**. Management and Future Directions in Non-Small Cell Lung Cancer with Known Activating Mutations. Am Soc Clin Oncol Educ Book 2014:e353-365.

(http://www.ncbi.nlm.nih.gov/pubmed/24857124) **3.** Vanderlaan PA, Yamaguchi N, Folch E, Boucher DH, Canepa HM, Kent MS, Gangadharan SP, Majid A, Goldstein MA, Huberman MS, Kocher ON, **Costa DB**. Success and failure rates of tumor genotyping techniques in routine pathological samples with non-small-cell lung cancer. Lung Cancer 2014; 84(1):39-44. PMCID: PMC3954776. (http://www.ncbi.nlm.nih.gov/pubmed/24513263)