BIOGRAPHICAL SKETCH

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NAME: Jean R. Lopategui, MD

eRA COMMONS USER NAME:

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable*	Completion Date MM/YYYY	FIELD OF STUDY
Lycee Francais, France	Baccalaureate	06/1976	High School
University of Marseilles Medical School	MD	06/1984	Medicine
Georgetown University Hospital	Residency	06/1988	Anatomic and Clinical Pathology
Tufts University Medical Center	Residency	06/1992	Anatomic and Clinical Pathology
City of Hope National Medical Center	Fellowship	06/1994	Hematopathology

A. PERSONAL STATEMENT

Jean Lopategui is the Director of Translational Genomics and the Program Director of the Molecular Genetic Pathology (MGP) Fellowship at Cedars-Sinai Medical Center. He is a molecular pathologist and a hematopathologist. He has a keen interest in the molecular pathogenesis and treatment of hematopoietic malignancies and solid tumors. During the last 23 years, he has pioneered several novel molecular assays in hematopoietic neoplasms, solid tumors, genetics, and pharmacogenomics. In the last 10 years, he has focused his efforts in developing large next-generation sequencing (NGS) panels for solid tumors and hematopoietic malignancies in order to identify diagnostic, prognostic and predictive genomic markers of response to novel targeted therapies in solid tumors and hematopoietic malignancies. More recently, he has investigated through transcriptome NGS, image analysis artificial intelligence and machine learning, a new model for uncovering pathways of resistance in EGFR+ non-small cell lung cancers treated with tyrosine kinase inhibitors (TKIs). His preliminary results have uncovered a new pathway of resistance in NSCLC patients that is amenable to targeted therapies. In addition, I he is actively investigating immune checkpoint inhibitors (ICIs) predictive markers of response in solid tumors. PD-L1, microsatellite instability, and mutation tumor burden are frontline. Finally, he is also investigating T-cell (CD3, CD8) macrophage (CD68), vascular markers (CD34) and follicular dendritic cell (CD21) markers of response to ICIs. The targeted therapies and ICI studies mentioned are linked to clinical outcomes of real-world solid tumor patients treated with targeted therapies and ICI who have developed resistance to treatment at different times (early vs late resistance). This strategy allows for a clear distinction of pathways of resistance to TKIs and ICIs in the responder vs non-responder groups. Dr Lopategui has been the recipient of several grants from Cedars CS-MATCH $500,000, and $125,000 Precision Health (PH) in non-small cell lung cancer (NSCLC). CS-MATCH selected cancer patients with genomic variants in solid tumors for clinical trials with targeted therapies, and PH in NSCLC integrated transcriptome, image analysis, artificial intelligence and machine learning to predict early vs late relapse in EGFR+ patients treated with TKIs.

Dr Lopategui has trained many MGP fellows who occupy leading positions at major academic centers, NCI, and industry.

B. POSITIONS AND HONORS

Academic Appointments

1997-2017	UCLA, Assistant Clinical Professor of Pathology
2003-2013	Cedars-Sinai Medical Center, Assistant Professor of Pathology
2013-	Cedars-Sinai Medical Center, Associate Professor of Pathology
2017-	UCLA, Associate Clinical Professor of Pathology

Positions

1994-1995	Acting Director Flow Cytometry & Research Molecular Hematopathology The City of Hope National Medical Center, Duarte, CA.
1995-2003	Director Diagnostic Molecular Pathology, Hematopathology & Flow Impath, Western division, Los Angeles, CA
2003-2007	Director Molecular Hematopathology Director Hematopathology Outreach Cedars-Sinai Medical Center, Los Angeles, CA
2007-2018	Director Molecular Pathology and Cytogenetics Program Director Molecular Genetic Pathology Fellowship Cedars-Sinai Medical Center, Los Angeles, CA
2018-	Director Pathology Translational Genomics Program Director Molecular Genetic Pathology Fellowship Cedars-Sinai Medical Center, Los Angeles, CA

Board Certifications

1993	Anatomic and Clinical Pathology, American Board of Pathology
1998	Hematopathology, American Board of Pathology
2011	Molecular Genetic Pathology, American Board of Pathology

Honors and Awards

1984	Research Thesis "Cum Laude" and with "First Class Honors" Low-power Laser Applications in Cellular Biostimulation
2001	University of Paris, Rene Descartes Thesis director, First Class Honors and Jury's Gold Medal "Multiplex RT-PCR and Cytogenetics: A combination of two methods to refine detection of gene rearrangements in acute leukemias".
2007	American Society of Hematology Trainee Award Program
2009	Proclamation from City of Beverly Hills, CA Developed First-in-world Genetic Screening Program to test Persian Jews for four inherited disorders which are treatable and preventable if detected
2010	Sports Spectacular Endowed Fellowship Award, David Rimoin, MD, PhD
2011	Designated a Roche Molecular Center of Excellence (one of 25 in the nation) Who's Who Top doctors
2014	Sports Spectacular Endowed Fellowship Award, David Rimoin, MD, PhD
2016	Sports Spectacular Endowed Fellowship Award, David Rimoin, MD, PhD
2017	Sports Spectacular Endowed Fellowship Award, David Rimoin, MD, Ph
2019	NCI-designated testing site for solid tumors and NCI-MATCH program member

C. CONTRIBUTIONS TO SCIENCE

1. **In lung cancer**, I have extensively studied mutations in the EGFR, ALK and ROS genes to select companion drugs including Tarceva and Crizotinib, respectively. I have also demonstrated in a pilot study that NGS allows distinction between independent bilateral primary lung cancers from intrapulmonary metastases. This has important consequences for staging (I vs IV) of lung cancer, therapy (surgery with intent to cure vs palliative chemotherapy) and prognosis (excellent vs poor).

I have also investigated through transcriptome NGS, image analysis artificial intelligence and machine learning, a new model for uncovering pathways of resistance in EGFR+ non-small cell lung cancers treated with tyrosine kinase inhibitors (TKIs). Our preliminary results have uncovered a new pathway of resistance in NSCLC patients that is amenable to targeted therapies. In addition, I am actively investigating immune checkpoint inhibitors (ICIs) predictive markers of response in solid tumors. PD-L1, microsatellite instability, and mutation tumor burden are frontline. In addition, we are also investigating T-cell markers of response (CD3, CD8) and well as macrophage markers (CD68), vascular markers (CD34) and follicular dendritic cell markers (CD21). All these studies are linked to clinical outcomes of solid tumor patients treated with targeted therapies and ICI. This allows for a clear distinction of pathways of resistance to TKIs and ICIs in the responder vs non-responder groups.

a. Gupta, AM Dastane, F Forozan, A Riley-Portugues, FChung, **JR Lopategui** and AM Marchevsky. Evaluation of EGFR abnormalities in patients with pulmonary adenocarcinoma: the need to test neoplasms with more than one method. Modern Pathology advance online publication 7 November 2008; 10.1038, Mod Pathol.2008, 128-133. PMID: 18997733.
b. Snehal Patel, Wendy Kadi, Ann E. Walts, Alberto M. Marchevsky, Andy Pao, Angela Aguiluz, Tudor Mudalige, **Jean Lopategui.** Next Generation Sequencing: A Novel Approach to Distinguish Multifocal Primary Lung Adenocarcinomas from Intrapulmonary Metastases. J Mol Diagn. 2017 Nov;19(6):870-880. doi: 10.1016/j.jmoldx.2017.07.006. Epub 2017 Sep 1. PMID: 28866070.
c. Gaurav Khullar, Kevin Baden, Rohit Khullar, Shimon Farber, Jie Tang, Yizhou Wang, Di Wu, Jane Tianran Jia, Chintda Santiskulvong, Esther Guerrido, Arkadiusz Gertych, Eric Vail, David Engman, Alberto Marchevsky, and Jean R Lopategui. TGFB1 Pathway Activation Predicts Early Relapse in EGFR-sensitive NSCLC patients treated with EGFR TKIs. JMD poster presentation 2019.

2. **In solid tumors**, I have over the last 3 years tested over 500 solid tumors at Cedars-Sinai using a 50 cancer-associated gene panel. The genetic information is displayed in the CS Intranet website for clinical and research use. Over 60% of solid tumors sequenced have been shown to display actionable ("druggable") mutations in the clinic or in clinical trials using investigational therapies. This database has been used by over 30% of our clinicians. **In prostate cancer**, we have collaborated with the Warschaw prostate cancer center for a clinical trial on PCA3 levels in post-radiation prostate cancer. **In breast cancer**, we have pioneered in collaboration with the department of breast surgery at Cedars, intra-operative real-time PCR detection of breast cancer micrometastases in sentinel lymph nodes, as a molecular adjunct to frozen sections.

3. **In colorectal cancer (CRC)** I have studied the role of KRAS mutational status and the role of RAS extended testing for the selection of the companion drug Cetuximab. I have also used targeted next-generation sequencing to identify in a pilot study unique molecular pathways in metastatic CRC amenable to targeted therapy. I also have a major interest in pharmacogenomics in oncology and we were among the early adopters for Irinotecan testing in CRC.

a. H Wang, **J Lopategui,** M Amin, S Patterson. KRAS mutation testing in the era of personalized medicine. Adv Anat Pathol 2010, 17(1):23-32. PMID: 20032635.
b. Raju K. Pillai, MD, **Jean Lopategui**, MD, Deepti Dhall, MD, Maha Guindi, MD, Scott Patterson, PhD. The State of the Art in Colorectal Cancer Biomarker Molecular Testing. Adv Anat Pathol 2016;23:92–103. PMID: 26849815
c. Snehal B Patel MD, PhD, Navid Farahani MD, Myriam Chevarie-Davis MD, Andy Pao CLS, Angela Aguiluz CLS, and **Jean R Lopategui MD**. Next Generation Sequencing Identifies Mutational Distinction between Primary and Metastatic Colorectal Carcinoma: Potential Therapeutic Implications. Poster USCAP 2017, San Antonio, TX.

4. **In pharmacogenomics**, I was one of the early adopters for warfarin, Plavix, tamoxifen, and irinotecan individual genetic variation testing to determine optimal dosage and efficacy and reduce adverse drug

events. In collaboration with the College of American Pathology Pharmacogenomics committee I developed national guidelines and a College of American Pathologist web-based curriculum for precision medicine and pharmacogenomics.

5. **In genetics**, I developed at Cedars the first-in-class Persian Jewish genetic screening for four preventable and treatable hereditary diseases. This was commanded by the Beverly Hills City

    a. M Kaback, **J Lopatequi**; AR Portuges, C Quindipan, M Pariani, N Salimpour-Davidov, DL Rimoin, Genetic screening in the Persian Jewish community: A pilot study. Genet in Med 2010: 12(10):628-33. PMID: 20733503

Complete List of Publications in Pubmed

https://www.ncbi.nlm.nih.gov/pubmed/?term=lopategui+j

D. ADDITIONAL INFORMATION: RESEARCH SUPPORT

Ongoing Research Support

Precision Health Initiative Engman, Lopategui, Gertych (MPI) 01/01/18-6/30/20
Machine learning approach to integrating disparate clinical, molecular, cellular and tissue data for more precise disease management and predictive therapeutic response in non-small cell lung cancer
The objective of this project is to advance precision health through development of a prototype pipeline for integrating clinical and omic information into a more accurate picture of human health and disease.
Role: Co-PI

IIT2015-20-MITA-CSMCMatch Mita (PI) 06/01/17-06/01/20
Personalized Cancer Care at Cedars-Sinai Medical Center Samuel Oschin Comprehensive Cancer Institute
The major goal of this study is a prospective comparison of clinical outcomes in the treatment of solid tumors using matched therapies selected by Targeted Next-Generation Sequencing vs conventional chemotherapy/ radiation in advanced refractory cancer patients.
Role: Co-I