BIOGRAPHICAL SKETCH

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NAME: David H. Chang

POSITION TITLE: Associate Program Director, Post Graduate Medical Education in Heart Failure and Transplantation

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of California Berkeley, Berkeley, CA	BA	1995	Immunology
University of California Irvine, Irvine, CA	MD	2002	
University of California Davis, Davis, CA		2005	Medicine Residency
		2006	Chief Resident
University of California Los Angeles, Los Angeles, CA		2009	Fellowship, Cardiology
University of California Los Angeles, Los Angeles, CA		2010	Chief Fellow
Cedars Sinai Medical Center, Los Angeles, CA		2010	Fellowship, Heart Failure/Heart Transplantation

A. Personal Statement:

Since 2011, I have been fortunate to serve as a Cardiologist at the Cedars Sinai Smidt Heart Institute and California Heart Center with emphasis in the care of patients with end stage heart disease. This focus allows me to diagnose and treat patients with heart failure and mechanical circulatory support and care for patients after heart transplant. As Associate Program Director for Post Graduate Medical Education in Heart Failure and Transplantation, I am involved in the selection and training of our ACGME fellows, which allows me to continue educational efforts both at the bedside and in a formal didactic manner. In my training and as an attending physician, I have always valued the life-long learning process that encompasses a life in medicine and leads itself to teaching moments. My experience in basic science has stimulated an interest in clinical and translational research and a career that integrates immunology and clinical medicine.

Positions and Employment

2014 – Present	Associate Program Director, Post Graduate Medical Education in Heart Failure and Transplantation Smidt Heart Institute at Cedars-Sinai Medical Center, Los Angeles, CA
2011 – Present	Cardiologist, Attending California Heart Center, University Cardiovascular Medical Group
2011 – Present	Assistant Clinical Professor of Medicine, Department of Medicine Division of Cardiology University of California Los Angeles

Board Certifications
Board Certified in Advanced Heart Failure and Transplant Cardiology
Board Certified in Cardiovascular Disease
Testamur, National Board of Echocardiography, 2014-2024

B. Positions and Honors:

Small working group in Cardiology (SWiG), Cedars Sinai Medical Center, Co-Chair, 2017- present
Clinical Policy and Procedure Committee, Cedars Sinai Medical Center, Member, 2018 to present
"In recognition of service as Chief Fellow to the Division of Cardiology Fellowship Program" 2009-2010.
"Recognition for Outstanding Accomplishments in Teaching" UCLA, Division of Cardiology, 2007-2008, 2008-2009.
"Outstanding Professionalism Award, Junior Resident" UC Davis, Department of Internal Medicine, 2003-2004.
"Associated Medical Student Government Gold Headed Cane Award" in recognition of commitment and devotion to patient care. UC Irvine, College of Medicine, 2001-2002.

C. Contributions to Science:

The longitudinal care of patients after mechanical circulatory support and heart transplantation remains critical to quality of life improvements and survival. Survival has continued to improve due to refinements in care post mechanical support and after heart transplant. Drug-drug interactions with immunosuppressant medications can lead to short and long term adverse outcomes post transplant. Keen attention to minimization of poly pharmacy and drug-drug interactions should lead to continued improvements in post transplant care. Fostering a nurturing role for the care-giver will improve quality of life after mechanical circulatory support and after heart transplant. Infection remains a constant hazard after heart transplantation. As we move further into precision medicine, there is a role for continued improvements in immunosuppression to balance the risk of over-immunosuppression that contribute to infection post heart transplant. Current projects include assessment of prevalence, risk and morbidity of infections post heart transplant. These projects cover viral and fungal infections post heart transplant. In the first citation listed below, I supervised a fellow in training and a transplant pharmacist in the completion of a review paper describing drug drug interactions after heart transplant. The second citation references a book chapter that was published in a book edited by Dr. Jon Kobashigawa. The third reference describes an abstract accepted to the International Society of Heart Transplantation meeting. I supervised this project which was led by Dr. Bernice Coleman and included contributions from mechanical circulatory support coordinators, social workers, and nurses. The fourth reference describes a case report initiated by me and written by a colleague. I was involved in the care of patients and in abstract review of the fifth reference.

1. Xie Y, Dilibero D, **Chang DH**. Review of Major Drug-Drug Interactions in Thoracic Transplantation. *Current Transplantation Reports.* 2018 September; 5(3): 220-230.

2. **Chang D,** Kobashigawa J, Luu M. Outpatient Management and Long-Term Complications in Heart Transplantation. Clinical Guide to Heart Transplantation pp171-183. Springer. 2017.

3. Coleman, B, Martinez, B, Barone, H, Williams, M, Aronow, H, Sandau, K, Ansryan, L, Felice, J, Hajj, J, Olanisa, L, Huie, N, Fishman, A, Olman, M, White, M, Pamu, J, **Chang, D.** (2019). Vanishing MCS Caregiver: Insights into the Impact of Machines on the Caring Relationship. The Journal of Heart and Lung Transplantation. 38. S303.

4. Dong E, Morris K, Sodhi G, **Chang D**, Czer L, Chung J, Zabner R, Klapper E, Kobashigawa J, Nurok M. Neuroinvasive West Nile Virus Post Heart Transplantation. *Transplantation Proceedings, 50, 4057-4061 (2018)*

5. Geft D, Patel J, Kittleson M, **Chang D**, Rafiei M, Osborne A, Czer L, Esmailian F, Kobashigawa J. Use of Cylex Immune Monitoring Score to Guide Immunosuppression After Heart Transplantation Reduces Infection Risk. *J Am College of Cardiology.* 2013; 61(10) Suppl A: 196

Antibody sensitization creates immunologic barriers to the possibility of heart transplantation. The increased use of mechanical circulatory support prior to transplant is one factor behind the increased rates of antibody sensitization that have been demonstrated over the past decade. The team at Cedars Sinai is performing ground breaking work to allow for successful heart transplantation across immunologic barriers. Prior to heart transplant, desensitization therapies for highly sensitized patients broaden the donor pool to permit the possibility of heart transplant to patients previously deemed too high risk for heart transplant. We have completed projects that demonstrate acceptable risks for desensitization therapies and influence induction strategies at the time of heart transplant. The first reference listed below is an article written by me and supervised by Dr. Jon Kobashigawa. In the second article, I was responsible for data collection regarding infectious complications of this particular form of desensitization therapy. In references 3-5, I participated in manuscript review, abstract concept, and care of the patients involved in the project, respectively.

1. **Chang DH**, Kobashigawa J. Desensitization strategies in the patient awaiting heart transplantation. *Curr Opin Cardiol*. 2017 May; 32(3):301-7

2. Patel, J, Everly, M**, Chang, D** et al. Reduction of alloantibodies via proteosome inhibition in cardiac transplant. *J Heart Lung Transplant* 2011; 30: 1320-1326.

3. Patel J, Kittleson M, Rafiei M, Stern L, **Chang D**, Czer L, Trento A, Kobashigawa J. Desensitization Therapy with Immunoglobulin (IVIG) and Rituximab for Patients Awaiting Heart Transplantation. *J Heart and Lung Transplant.* 2012; 31(4): S161

4 Neyer J, Kittleson M, Patel J, Czer L, Aintablian T, Rodriguez G, Jocson R, Runyan C, **Chang D**, Moriguchi J, Trento A, Kobashigawa J. Desensitization in Total Artificial Heart Patients. *J Heart Lung Transplant*. 2016.

5. Rafiei M, Kittleson M, Patel J, Osborne A, **Chang D**, Czer L, Reinsmoen N, Esmailian F, Kobashigawa J. Anti-thymocyte Gammaglobulin May Prevent Antibody Production after Heart Transplantation. *Transplant Proc.* 2014;(10):3570-4

Cardiac Allograft Vasculopathy (CAV) remains a significant co-morbidity after heart transplantation. CAV is likely the third leading cause of death long term post heart transplant. Traditional risk factors for coronary artery disease likely contribute to the formation and progression of CAV. There are likely immune factors that promote and propagate this disease process as well. Surveillance for CAV remains important and treatment with percutaneous intervention and modulation of immunosuppression likely impact outcomes in patients with CAV. Future mechanistic work into the immune factors that contribute to CAV will be an important area of investigation. These references reflect a book chapter and articles written by me under the supervision of Dr. Jon Kobashigawa.

1. **Chang D,** Kobashigawa J. Cardiac Allograft Rejection, Surveillance, and Treatment. Clinical Guide to Heart Transplantation pp157-170. Springer. 2017.

2. **Chang D**, Kobashigawa J. Cardiac allograft immune activation: current perspectives. *Transplant Research and Risk Management.* 2015: 7 13-22.

3. **Chang DH**, Kobashigawa JA. Current diagnostic and treatment strategies for cardiac allograft vasculopathy. *Exp Rev Cardiovasc Ther*. 2015 Oct; 13(10): 1147-54.

4. **Chang DH**, Kittleson MM, Kobashigawa JA. Immunosuppression following heart transplantation: prospects and challenges. *Immunotherapy* (2014); 6(2): 181-194.

5. **Chang D**, Kobashigawa J. The use of the calculated panel-reactive antibody and virtual crossmatch in heart transplantation. Curr Opin in Organ Transplant 2012 Aug;17(4): 423-6.

The evidence basis for care of patients with heart failure with reduced ejection fraction (HFrEF) is broad and expansive. Given the morbidity and mortality rates associated with HFrEF, there remain opportunities to continue improvements in the medical care of these patients. As part of my role in the Smidt Heart Institute, I am the principal investigator for three current phase 3 clinical trials for HFrEF patients. Two of these trials examine the use of intramyocardial injection of stem cells for patients with left ventricular dysfunction. The DREAM HF trial has completed enrollment and will be completed this year. This trial examines use of Allogeneic stem cells. A currently enrolling stem cell trial, the CardiAMP trial, examines use of Autologous stem cell injections to the left ventricle for patients with symptomatic ischemic cardiomyopathy. A third important trial for HFrEF patients is the large 8,000 patient Galactic (Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure) trial, which examines the use of Omecamtiv mecarbil (OM) for patients with symptomatic heart failure. OM is a novel small molecule cardiac myosin activator. I was involved in manuscript review and revision of the citation listed below.

1. Westerdahl DE, **Chang DH**, Hamilton MA, Nakamura M, Henry TD. Allogeneic mesenchymal precursor cells (MPCs): an innovative approach to treating advanced heart failure. Expert Opin Biol Ther. 2016 Sep;16(9):1163-9. doi: 10.1080/14712598.2016.1206526. Epub 2016 Jul 8.

The Notch protein has been conserved in evolution and is involved in the development of a diverse range of animals including Drosophila melanogaster, Caenorhabditis Elegans, mice and humans. In mice, Notch signaling is critical for T cell development. Work in transgenic mice demonstrated the role of Notch protein signaling in the lineage determination of Alpha-Beta versus Gamma-Delta T cells. Additional work in transgenic mice demonstrated the role of Notch in the development of CD4 and CD8 T cell lineages. Notch signaling in humans is important for the regulation of normal and variant hematopoiesis. Given its role in lineage development, Notch regulation and signaling control may, in the future, impact stem cell transplantation, and by extension, care of patients with solid organ transplant. In the projects referenced below, I was a staff research associate of the basic science Immunology lab under the supervision of Dr. Ellen Robey. I participated in care and analysis of work done with transgenic mice and in manuscript review of these articles.

1. Chang, D. et al. MHC Recognition in Thymic Development: Distinct, Parallel Pathways for Survival and Lineage Commitment. *Journal of Immunology* 2000; 165(12): 6710-6715.

2. Washburn, T. Schweighoffer, E. Gridley, T**. Chang, D**., Flowlkes, BJ, Cado, D and Robey, E. Notch Activity Influences the Alpha-Beta Versus Gamma-Delta T Cell Lineage Decision. *Cell* 1997; 88: 833-843.

3. Robey, E, **Chang, D**. et al. An Activated Form of Notch Influences the Choice between CD4 and CD8 T Cell Lineages. *Cell* 1996; 87: 483-492.

D. Additional Information: Research Support and/or Scholastic Performance

<u>Ongoing Research Support</u>:

Mesoblast Chang (Site PI) 11/06/2014 – Present
DREAM HF - C41750/3100: A Double-blind, Randomized, Sham-procedure-controlled, Parallel-group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells (rexlemestrocel-L) in Patients with Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of either Ischemic or Nonischemic Etiology

Bio Cardia, Inc Chang (Site PI) 09/01/2019 – Present
CardiAMP Heart Failure Trial: Randomized Controlled Pivotal Trial of Autologous Bone Marrow Mononuclear Cells Using the CardiAMP Cell Therapy in Patients with Post Myocardial Infarction Heart Failure.

Amgen Chang (Site PI) 06/01/18 - Present
GALACTIC: A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Assess the Efficacy and Safety of Omecamtiv Mecarbil on Mortality and Morbidity in Subjects with Chronic Heart Failure with Reduced Ejection Fraction

NIH/Duke University Kransdorf (Site PI) 11/01/17-Present
EntrestoTM (LCZ696) In Advanced Heart Failure (Life Study). The purpose of this study is to evaluate the effects of LCZ696 (Entresto) compared to valsartan by evaluating NT-proBNP levels. The hypothesis is that patients with symptomatic heart failure due to left ventricular systolic dysfunction, treatment with LCZ696 for 24 weeks will improve NT-proBNP levels. The study is a randomized, double-blinded trial of advanced heart failure subjects.
Role: Co-Investigator

Abbott Ramzy (site PI) 11/13/2015 to present
MOMENTUM 3 (Multi-Center Study of Maglev Technology in Patients Undergoing MCS Therapy with HeartMate 3™
Role: Co-Investigator

Abbott Ramzy (site PI) 11/11/2016 to present
MOMENTUM 3 CAP Multi-Center Study of Maglev Technology in Patients Undergoing MCS Therapy with HeartMate 3™ Continued Access Protocol: Post-Approval Continued Follow-up
Role: Co-Investigator

United Therapeutics Hage (PI) 12/29/17 – present
Southpaw 301 - A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) in Heart Failure with Preserved Ejection Fraction (HFpEF).
Role: Co-Investigator

United Therapeutics Hage (PI 12/29/17 - present
Southpaw 302 - An Open-label Extension Study of Oral Treprostinil in Subjects with Pulmonary Hypertension (PH) Associated with Heart Failure with Preserved Ejection Fraction (HFpEF) - A Long-Term Follow-up to Study TDE-HF-30

Alexion Inc. Patel (PI) 2014-Present
The DUET Cardiac Trial - The De-novo Use of Eculizumab Alongside Conventional Maintenance Therapy in Presensitized Patients Receiving Cardiac Transplantation: An, Open-Label, Investigator-Initiated Pilot Trial. Investigational pilot trial to determine the safety and efficacy of the de-novo use of eculizumab to prevent symptomatic antibody (AMR≥1) and/or cellular mediated rejection (≥2 Grade 2R) in highly sensitized cardiac transplantation recipients (PRA>70%).
Role: Co-Investigator

Pfizer, Inc. Patel (Site PI) 3/24/17-3/23/2020
ATTR- EXT - A Phase 3 Multicenter, Randomized, Double-Blind, Extension Study To Evaluate The Safety Of Daily Oral Dosing Of Tafamidis Meglumine (Pf-06291826) 20 Mg Or 80 Mg In Subjects Diagnosed With Transthyretin Cardiomyopathy (Ttr-Cm)
Role: Co-Investigator

Alnylam Pharmaceuticals Patel (site PI) 02/01/2020 – 01/31/2022
APOLLO-B - A Phase 3, Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Patisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)

Eidos Pharmaceuticals Patel (site PI) 05/21/2019 – 05/20/2022
Eidos AG10-301/ATTRIBUTE-CM – A prospective, randomized, multicenter, parallel-group study will evaluate the efficacy and safety of AG10 in symptomatic subjects compared to placebo, administered on a background of stable heart failure therapy