BIOGRAPHICAL SKETCH

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NAME: Oro, Anthony Eugene

eRA COMMONS USER NAME (credential, e.g., agency login): oro.anthony

POSITION TITLE: Eugene and Gloria Bauer Professor of Dermatology, Assoc Director Center for Definitive and Curative Medicine; Co-Director Stanford Child Health Research Institute

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/YYYY	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	06/1985	Molecular Biology
University of California, San Diego, La Jolla, CA, Salk Institute with Prof. Ronald Evans	Ph.D.	06/1991	Molecular Genetics
University of California, San Diego Med School	M.D.	06/1993	Medicine
Stanford University School of Medicine	Residency	06/1997	Dermatology
Stanford University School of Medicine, with Prof. Matthew P. Scott	Postdoc	11/1998	Developmental Genetics

A. Personal Statement

As a practicing Dermatologist, I have focused for the last 18 years on determinants of epithelial development, morphogenesis, and tumorigenesis using the skin as a model system. Building on my graduate work on the role of nuclear receptors in early embryonic Drosophila development we have elucidated the role of the hedgehog signaling pathway in skin and hair stem cell biology, hair stem cell regulation and patterning, and epithelial-mesenchymal regulation. In the last 14 years in my own lab, we've studied the role of hedgehog and hedgehog-related target genes in Drosophila, mouse mutants, and human skin regeneration models. We have used genomics to interrogate the molecular basis of human tumor resistance, analyzing drug-resistant tumors from patients in our advanced basal cell carcinoma clinical trial center. In the past 7 years, we've begun to apply our knowledge of genomics, developmental biology, stem cell biology, genome editing, and epidermal biology to help patients with the debilitating disease Epidermolysis bullosa (EB). Our goal is to create the first-in-human corrected induced pluripotent cell (iPS)-based skin graft for Recessive Dystrophic EB patients. We have demonstrated the ability using Therapeutic Reprogramming to generate iPS cells and correct them by homologous recombination using a novel adeno-associated virus we helped identify (2014). I am the Associate Director of a new Center for Definitive and Curative Medicine at Stanford, a program I helped build to manufacture cell-based stem cell therapies using a state-of-the-art GMP facility. While we have developed a iPS-based differentiation protocol into epithelial sheets, a major roadblock is the lack of genomic-level insight into skin differentiation and the ability to predict which patient iPS cells we generate will efficiently make skin sheets. The goal of this proposal is to use the combined stem cell, skin biology, and bioinformatics expertise of our team to define the mechanistic basis of keratinocyte commitment and develop rational prediction tools to enhance our manufacturing process. Progress on this proposal will provide needed data for Pre-IND FDA meetings and lay the groundwork for pivotal safety trials. Along with two papers under review forming the preliminary data of this grant, additional relevant publications include:

A. Melo, S., Lisowski, L., Bashkirova, E., Zhen H., Chu K., Keene, D., Marinkovich, P., Kay, M., **Oro, A.E** (2014). Somatic scarless correction of junctional epidermolysis bullosa by a highly recombinogenic AAV virus. ***Mol Therapy,*** 22:725-33. PMCID: PMC3982486

B. Sebastiano, V, Zhen HH, Derafshi, BH, Bashkirova, L, Melo, S, Wang, P, Leung, T, Siprashvili, Tichy, A., Li,J, Ameen M., Hawkins, J., Lee, S., Li, L, Bauer, G., Lisowski, Kay, M., Kim, SK, Lane, AT,Wernig, M. and **Oro, AE** (2014) Corrected Induced Pluripotent Stem Cell Based Therapy for the Treatment of Recessive Dystrophic Epidermolysis Bullosa, ***Sci Transl Med*** 6:264-7. PubMed Central PMCID: PMC4428910.

B. Positions and Honors

Positions and Employment

1998-2006	Assistant Professor, Department of Dermatology, Stanford University, Stanford, CA
2006-	Associate member, Stanford Comprehensive Cancer Center
2006-2011	Associate Professor, Department of Dermatology, Stanford University, Stanford, CA
2008-	Associate member, Stanford Institute Stem Cell Biology and Regenerative Medicine
2011-2017	Professor, Department of Dermatology, Stanford University, Stanford, CA
2016	Associate Director, Center for Definitive and Curative Medicine, Stanford
2017	Eugene and Gloria Bauer Professor of Dermatology
2017	Co-Director Stanford Child Health Research Institute

Other Experience and Professional Memberships

1998-2000	Society for Investigative Dermatology, Board of Directors
2000-present	Society for Investigative Dermatology, Committee on Kligman Travel Fellowships
2000-present	National Institutes of Health, Ad Hoc grant reviewer
2007-2010	Board of Directors, North American Hair Research Society
2010-present	Chair, Nominating committee, North American Hair Research Society
2005-present	Medical Advisory Board, Gorlin's Syndrome Life Support Network
2006-present	National Alopecia Areata Foundation, Scientific Review Board
2007-2012	Program Committee, Society for Investigative Dermatology
2010-2014	Permanent Member, NIH ACTS Study Section
2010-present	American Skin Association, Medical Advisory Committee
2012-2017	Board of Directors, Society for Investigational Dermatology
2013-2017	Executive Committee, Society for Investigative Dermatology
2013	Vice Chair, Gordon Research Conference Epithelial Differentiation Barga, Italy
2015	Chair, Gordon Research Conference Epithelial Differentiation Sunday River, ME
2017-present	Organizer, Annual Center for Definitive and Curative Medicine Symposium

Honors

1981	Academic Scholarships, Stanford University
1985	Honors research degree, Stanford University
1985	Fox Award to Outstanding Science Student, Stanford University
1987	A. Baird Hastings Honor Society, University of California San Diego Med School
1988	Howard Hughes Medical Institute, Graduate Student Award
1996	Thomas Fitzpatrick Research Award, KAO Corporation
1999	Frederick E. Terman Research Award
1999	Charles E. Culpepper Medical Scholar
2006	Nature Publishing Prize, SID Meeting
2008	Stanford Stem Cell Regulatory Board
2010	Permanent Member, ACTS study section
2012	M.H. Samitz Lectureship University of Pennsylvania
2013	Co-chair Epithelial Differentiation Gordon Conference
2014	Marion B. Sulzberger Memorial Award and Lectureship, AAD
2015	Jeffrey Schechner Memorial Lecture, Yale University
2015	John Blaffer Lecture, MD Anderson Cancer Center, Houston, TX

2015 Chair, Epithelial Differentiation Gordon Conference
2016 William Montagna Lecture, Society for Investigative Dermatology
2017 NCI Center for Cancer Research Grand Rounds
2017 George Odlund Lectureship, University of Washington Medical Center

Selected Patents (out of 18)
11/1996 US Patent Application 5571696 for "RECEPTORS"
11/1996 US Patent Application 5578483 for "RECEPTORS TRANSCRIPTION-REPRESSION ACTIVITY COMPOSITIONS AND METHODS"
01/1998 US Patent Application 5710004 for "METHODS OF USING NOVEL STEROID HORMONE ORPHAN RECEPTORS"
08/2001 US Patent Application 6281330 for "MULTIMERIC FORMS OF MEMBERS OF THE STEROID/THYROID HORMONE SUPERFAMILY OF RECEPTORS WITH THE ULTRASPIRACLE RECEPTOR"
11/2005 US Patent Application 20060142245 for "INHIBITORS OF HEDGEHOG SIGNALING PATHWAYS, COMPOSITIONS AND USES RELATED THERETO"
10/2006 US Patent Application 7119077 for "MULTIMERIC FORMS OF MEMBERS OF THE STEROID/THYROID SUPERFAMILY OF RECEPTORS WITH THE ULTRASPIRACLE RECEPTOR"
07/2008 US Patent Application 12/075,944 for "BONE MORPHOGENETIC PROTEIN ANTAGONIST AND USES THEREOF"
07/2008 US Patent Pending, STAN-08-77, "NOVEL HAIR CYCLE REGULATORS FOR HAIR GROWTH'
08/2009 US Patent Pending, STAN-671PRV, "NOVEL HAIR GROWTH REGULATORS"
09/2009 US Patent Pending, STAN-S09-130 FOLLISTATIN-LIKE 1 PROTEIN TO PROMOTE HAIR GROWTH
02/2013 US Patent, 14/728,916 "INHIBITORS OF ATYPICAL PROTEIN KINASE C AND THEIR USE IN TREATING HEDGEHOG PATHWAY DEPENDENT CANCERS"
06/2015 USPATENT PENDING, STAN S15-273 SRF/MRTF INHIBITORS TO TREAT DRUG RESISTANT BASAL CELL CARCINOMAS.
02/2016 US Patent Pending, US2016/012735, "R-SPONDIN AGONIST-MEDIATED HAIR GROWTH"

C. Additional Contributions to Science

1. I helped identify and reinforce the **mechanistic links between the Hedgehog signaling pathway and human cancer**. Forward genetic studies in Drosophila identified key morphogenic pathways regulating cell growth and differentiation. In examining the roles for the hedgehog pathway in vertebrate skin, I demonstrated that overexpression in skin of the vertebrate hedgehog Sonic Hedgehog, was sufficient to induce basal cell carcinoma (BCC), a common human cancer. Along with additional human and mouse genetic data from the Scott lab and others linking Shh signaling with both syndromic and sporadic BCCs, medulloblastomas, and rhabdomyosarcomas, the work established the role for hedgehog signaling in human cancer and set the stage for hedgehog pathway targeted therapeutics.

A. **Oro, A.E.,** Higgins, K.M., Hu, Z., Bonifas, J.M., Epstein, E.H., and Scott, M.P. (1997). Basal Cell Carcinomas in Mice Overexpressing Sonic Hedgehog. ***Science,*** 276: 817-21. PMID 9115210.
B. Azsterbaum, M, Epstein, J., **Oro, A.,** Douglas, V., LeBoit, P.E., Scott, M.P., and Epstein, E.H. (1999). Ultraviolet and ionizing radiation enhance the growth of BCCs and trichoblastomas in patched heterozygous knockout mice, ***Nature Med*** *5*, 1285-1291. PubMed PMID: 10545995.
C. Huntzicker E.G., Estay I, Zhen H., Lokteva L.A., Jackson P. K., **Oro A.E.** (2006). Dual degradation signals control Gli stability and tumor formation. ***Genes Dev.,*** 20: 276-81. PMCID: PMC1361699.
D. Gomez-Ospina N., Chang A.L., Qu K., **Oro A.E.** (2012). Translocation affecting sonic hedgehog genes in basal-cell carcinoma. ***N Engl J Med.,*** 366(23):2233-4. PMCID: PMC3839666.

2. A current major focus in the lab centers around advancing knowledge of **human tumor therapy, resistance, and tumor evolution**. I helped form the Stanford BCC Consortium, a group of basic and clinical investigators that integrate genomics and therapy. Independent in vitro screens by several groups and companies have led to the discovery of Smo antagonists, the first hedgehog pathway inhibitor. Our group formed part of the team that tested Smo antagonists in syndromic and advanced sporadic BCCs, leading to FDA approval in 2012. I noticed that tumor response varied in each patient group, with syndromic patients exhibiting no resistance and advanced sporadic 40% resistance with 20% more per

year. With this knowledge we have focused on understanding tumor evolution and drug resistance pathways using human BCCs as a model. We have patented small molecules targeting some of these novel signaling pathways and have a significant effort to develop additional chemical matter to target these pathways.

A. Sekulic A., Migden M.R., **Oro A.E.,** Dirix L., Lewis K.D., Hainsworth J.D., Solomon J.A., Yoo S., Arron S.T., Friedlander P.A., Marmur E., Rudin C.M., Chang A.L., Low J.A., Mackey H.M., Yauch R.L., Graham R.A., Reddy J.C., Hauschild A. (2012). Efficacy and safety of vismodegib in advanced basal-cell carcinoma. ***N Engl J Med.,*** 366(23):2171-9. PMID: 22670903

B. Atwood, S.X., Tang, J., Chang, A., Li, M., and **Oro, A.E.** (2013). Gli activation by aPKC regulates BCC growth ***Nature,*** 494:484-8. PMCID: PMC3761364.

C. Atwood, SX, Sarin, KY, Whitson R, Li, JR, Kim, G, Rezaee, M, Ally,MS, Kim, J, Yao, C, Chang, ALS*, **Oro, AE***, and Tang, JY* (2015) Smoothened variants explain the majority of drug resistance in basal cell carcinoma, ***Cancer Cell*** 27:342-353 , PubMed Central PMCID: PMC4357167 ***co-senior authors**.

D. Zhao, X. Ponomaryov, T. Ornell KJ, Zhou, P., Kabral, SK, Pak, E., Li, W. Atwood, SX, Whitson, RJ, Chang ALS, Li, J, **Oro, AE**, Chan, JA, Kelleher, JF, and Segal, RA (2015) RAS/MAPK activation drives resistance to Smo inhibition, metastasis and tumor evolution in Shh pathway-dependent tumors, ***Cancer Res***, 75:3623-35. PubMed Central PMCID: PMC4558230

E. Mirza, AN, Fry, MA, Urman, NM, Atwood, SX, Roffey, J., Ott, GR, Chen B, Lee, A., Brown AS, Aasi, SZ, Hollmig, T, Ator, MA, Dorsey, BD, Ruggeri, BR, Zificsak, CA, Sirota, M, Tang, GY, Butte, A, Epstein, E, Sarin KY, and **Oro, AE** (2017) Combined inhibition of atypical PKC and histone deacetylase is cooperative in basal cell carcinoma treatment, J Clinical Invest Insight, in press.

3. I helped to elucidate the **early structure and function of vertebrate nuclear receptors**. As a graduate student in Ronald Evans lab studying glucocorticoid receptor structure and function, I was surprised to discover that dozens of other evolutionarily related "orphan" proteins existed in other organisms. I established that related and novel "orphan" receptors existed in Drosophila, and then used powerful fly genetics to understand their functions. I focused on two receptors, the gap genes *knirps/knirps-related*, which were involved in patterning the early fly embryo, and *ultraspiracle*, the fly Retinoid X receptor homolog that formed obligate heterodimers with other nuclear receptors to mediate transcriptional activity of the steroid molting hormone ecdysone. The work led to 9 patents and formed the basis of several companies aimed at identifying novel ligands for these receptors.

A. **Oro, A.E.,** Hollenberg, S.M., and Evans R.M.(1988). Transcriptional Inhibition by a Glucocorticoid receptor-ß-galactosidase Fusion protein. **Cell** *55*, 1109-1114. PubMed PMID: 3144438.

B. **Oro, A.E**., Ong, E.S., Margolis, J.S., Posakony, J.W., McKeown, M., and Evans, R.M.(1988). The Drosophila gene knirps-related is a member of the steroid receptor gene superfamily. **Nature** *336*, 493-496. PubMed PMID: 2848202.

C. **Oro, A.E.,** McKeown, M., and Evans, R.M.(1990). Relationship between the product of the Drosophila ultraspiracle locus and the vertebrate retinoic acid responsive transcription factor, the Retinoid X receptor. **Nature** *347*, 298-301. PubMed PMID: 2169594.

D. Yao, Tso-Pang, Segraves, W.A., **Oro, A.E.,** McKeown, M., and Evans, R.M.(1992). Transactivation by the ecdysone receptor requires the conserved heterodimerization function of ultraspiracle. **Cell** *71*, 63-72. PMID: 1327536.

4. I helped elucidate **the mechanistic understanding of hair follicle stem cell regulation**. The vertebrate hair represents an ideal model system to study vertebrate stem cell regulation due to the regular array and spacing on the epidermis. Work by others established the identity and location of the stem cells, but the timing of hair cycling and its regulation remained elusive. Our work helped established the importance of hair follicle stem cells signaling with their local dermal niche environment. We've shown that hedgehog signals to the underlying dermal organizer to maintain hair growth through the induction of the BMP antagonist noggin. Signal reception of Shh requires the microtubule-based organelle, the primary cilium (a focus of the present proposal). Our work showed that a Shh target gene, Missing in Metastasis (MTSS1), regulates cilia formation, Shh signaling and epithelial-mesenchymal interactions in hair regeneration assays. Finally, in a small screen for FDA approved drugs that regulate hair follicle cycling,

we identified the L-type calcium channel CACNA1, the basis of the Timothy syndrome, and showed the channel is expressed highly in the stem cells and responds to ligands to regulate BMP antagonist production and hair growth. Recently, we have begun to explore the basis of epithelial: immune interactions in the common hair disorder alopecia areata and have demonstrate a key role for the JAK pathway in follicle quiescence.

A. Bershteyn M, Atwood SX, Woo W-M, Li M, **Oro AE**. (2010). MIM and cortactin antagonism regulates ciliogenesis and Hedgehog signaling**.** ***Dev Cell.*** 19, 270-283. PubMed Central PMCID: PMC3108505.
B. Woo W-M, Zhen HH, **Oro AE.** (2012) Shh maintains dermal papilla identity and hair morphogenesis via a Noggin – Shh regulator loop. ***Genes Dev*** 26: 1235-46. PubMed Central PMCID: PMC3371411
C. Yucel, G, Altindag, B. Gomez-ospina, N. Rana, A. Panagiotakos, G., Lara, MF, Dolmetsch, R and **Oro, AE** (2013) State-dependent signaling by Cav1.2 regulates hair follicle stem cell function, **Genes Dev.** 27: 1217-22. PubMed Central PMCID: PMC3690395.
D. Kennedy Crispin M, Ko JM, Craiglow BG, Li, S Shankar, G, Urban JR, Chen JC, Cerise, JE, Jabbari, A, Winge, MC, Marinkovich, MP, Christiano, AM, **Oro, AE****, and King BA**(2016) Safety and Efficacy of the JAK Inhibitor Tofacitinib Citrate in patients with Alopecia Areata ***JCI Insight*** 1:89776

****Co-Senior Authors**

D. Research Support

RT3-07796 Oro (PI) 03/01/15-2/28/18
California Institute for Regenerative Medicine
A Chromatin Context Tool for Predicting iPS Lineage Predisposition and Tissue Graftability
The major goal of this project is to develop a tool to predict how iPS lines will perform.
Role: PI

TRAN1-10416 Oro (PI) 3/1/2018-8/31/2020
California Institute for Regenerative Medicine
The major goal of this project is to develop genetically-corrected patient-specific iPS-derived keratinocyte grafts into a clinically compatible method and have a successful pre-IND FDA meeting.

AR46786 Oro (PI) 04/01/17-03/31/22
NIH
Stromal Regulation of Basal Cell Carcinoma Formation
The major goal of this project is to understand the molecular basis of epithelial regulation of Shh signaling and the molecular basis of tumor evolution during drug resistance.
Role: PI

R01 AR54780 Oro (PI) 09/01/13-08/31/18
NIH
Regulating Gli Function in Hair Follicle Progenitors
The major goal of this project is to understand the regulation of Gli function in hair follicle stem cells
Role: PI

R01 AR052785 Oro (PI) 07/01/14-06/30/19
NIH
MIM Function in Epithelial Neoplasia
The major goal of this project is to understand how the I-BAR domain-containing MIM protein functions human cancer and neurodegeneration.
Role: PI

EB Research Partnership (Oro) 06/01/2017-05/31/2018
Epidermolysis Bullosa (EB) Therapeutic Reprogramming Consortium
This project aims to develop clinical grade genetically corrected, iPS-derived skin sheets to treat Epidermolysis Bullosa.
Role: PI