BIOGRAPHICAL SKETCH

NAME: Charles Keller, M.D.

eRA COMMONS USER NAME: KELLERC2

POSITION TITLE: Scientific Director, Children's Cancer Therapy Development Institute; and
Adjunct Member, Shriner Hospital for Children Research Center, Portland, OR

Interim CEO, Tio Companies (Therapeutics In Ovo)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
Tulane University, New Orleans, LA	B.S.E.	05/1990	Biomedical Engineering
Baylor College of Medicine, Houston, TX	M.D.	05/1995	Medicine
Baylor College of Medicine, Houston, TX	Residency	06/1995 - 06/1998	Pediatrics
University of Utah, Salt Lake City, UT	Fellowship	08/1998 - 07/2001	Pediatric Hematology-Oncology

A. Personal Statement

As a physician-scientist, my laboratory has been devoted to the development of novel molecular therapies for advanced childhood cancers associated with high morbidity or mortality. I have been continuously funded by NIH for 15 years and have authored over 120 peer-reviewed publications – but these milestones are secondary to our mission to bring basic science discoveries to clinical trials. The long-term emphasis of my laboratory's research is molecularly-targeted therapies to halt progression or induce regression for gross residual disease, metastatic disease and relapsed disease. To achieve these goals, as a past trainee of Mario Capecchi, my laboratory has traditionally utilized physiologically-accurate, genetically-engineered mouse models (GEMMs) of sarcomas and brain tumors. In parallel, we also develop primary tumor cell cultures of pediatric cancers for preclinical validation studies, including rhabdomyosarcoma. Our approach has been to study these childhood cancers in the context of developmental biology. By providing the scientific community a centralized knowledge base and experimental resources of validated and credentialed models, we hope to recruit not only cancer biologists but also developmental biologists, engineers and computer scientists to the investigation of these devastating childhood cancers. Our current lab group is intentionally half biologists, half engineers.

Below are our publications that highlight the leadership our group has sought to demonstrate by way of the disease models we have developed and investigated to uncover basic science & translational opportunities in sarcoma. Some of our sentinel findings include the first demonstration that **many translocation-mediated oncogenes are not expressed at a constant level, but are expressed in a cell-cycle phase specific manner** (G2 in the case of Pax3:Foxo1). We have also established that tumor-initiating mutations such as Pax3:Foxo1 are dispensable for tumor maintenance, but critically important for treatment resistance and tumor evolution through a process called **checkpoint adaptation**, which is borrowed by cancer cells from yeast. And although it might have seemed improbable at the onset, the **cell-of-origin** studies conducted by our laboratory have been the most informative in the development of potential new therapies for sarcomas. Specifically, the publications below have resulted in **3 clinical trial concepts and trials** for adults and children with rhabdomyosarcoma and the recently completed pediatric phase I trial for entinostat [NCT02780804/ADVL1513, a phase II trial for rhabdomyosarcoma now under consideration, and European study NCT03838042].

As founder & scientific director of the 501c3 Children's Cancer Therapy Development Institute (cc-TDI.org), modeled after the ALS-TDI, my team and I have endeavored to jumpstart drug development for childhood cancer (only 8 drugs have had primary FDA approvals since 1978). This effort has involved multi-scale leadership: basic science studies, NIH grant applications, business development with pharma & impact investors, communication with patients & families, partnership with our Intel spinout partners at omicsautomation.com, collaboration with medicinal chemists on a Novartis 640,000 screen, and clinical trial writing for a 200 children hospital cooperative group are all in a day's work. Our efforts have led to 46 publications in the first 6 years of

our startup as well as the 3 clinical trials and concepts described above – altogether in the context of a lean research organization on a $2.1M annual budget. cc-TDI was featured February 2019 as the cover article of the Portland Business Journal, which tells our unexpected backstory of innovation and opportunity as well as recent story on resilience and innovation in the pandemic.

1. Narendra Bharathy, Noah E. Berlow, Eric Wang, … Theodore J. Perkins, Christopher R. Vakoc, Joel E. Michalek, Charles Keller. SMARCA4-miR27a axis promotes expression of the PAX3:FOXO1 fusion oncogene in rhabdomyosarcoma. **Science Signaling**. 2018 Nov 20;11(557). pii: eaau7632. doi: 10.1126/scisignal.aau7632 [Cover Article] [PMID 30459282; PMC6432638] [COVER]
2. Bharathy N, Berlow NE, Wang E, Abraham J, Settelmeyer TP, Hooper JE, Svalina MN, Bajwa Z, Goros MW, Hernandez BS, …, Hawkins DS, Rudzinski ER, Mansoor A, Perkins TJ, Vakoc CR, Michalek JE, Keller C. Preclinical rationale for entinostat in embryonal rhabdomyosarcoma. **Skelet Muscle**. 2019 May 21;9(1):12. doi: 10.1186/s13395-019-0198-x. [PMID: 31113472]
3. Ken Kikuchi, Simone Hettmer, M. Imran Aslam, … Brian P. Rubin, Amy J. Wagers, Charles Keller. Cell-cycle dependent expression of a translocation-mediated fusion oncogene mediates checkpoint adaptation in rhabdomyosarcoma. **PLoS Genetics**, 2014 Jan;10(1):e1004107 [PMID 24453992; PMC3894165]
4. Jinu Abraham, Yaiza Nuñez-Álvarez, …, , Atiya Mansoor, Yidong Chen, Mònica Suelves, Brian P Rubin, Charles Keller. Lineage of Origin in Rhabdomyosarcoma informs Pharmacological Response. **Genes & Development,** 2014 Jul 15;28(14):1578-91 [PMID 25030697; *open access*]
5. Brian P. Rubin, Koichi Nishijo, …, Mario R. Capecchi, Joel E. Michalek, Lee Ann Zarzabal, Javed Khan, … Paul S. Meltzer, Yidong Chen , Charles Keller. Evidence for an Unanticipated Relationship between Undifferentiated Pleomorphic Sarcoma and Embryonal Rhabdomyosarcoma. **Cancer Cell**, Volume 19, Issue 2, 177-191, 15 February 2011 [Featured Article] [PMID 21316601; PMC3040414]

B. Positions and Honors

Positions and Employment

1995 - 1995	Predoctoral Fellow, MD Anderson Cancer Center, Houston, TX (PI. Francis Ali-Osman)
1995 - 1998	Intern & Resident in Pediatrics, Baylor College of Medicine, Houston, TX
1996 - 1997	Postdoctoral Fellow, MD Anderson Cancer Center, Houston, TX (PI. Francis Ali-Osman)
1998 - 2001	Fellow in Pediatric Hematology-Oncology, University of Utah, Salt Lake City, UT
2001 - 2004	Instructor in Pediatric Hematology-Oncology, University of Utah, Salt Lake City, UT
2002 - 2004	Director of Small Animal Imaging, University of Utah, Salt Lake City, UT
2003 - 2004	Associate Member, Utah Center for Advanced Imaging Research, Salt Lake City, UT
2004 - 2006	Adjunct Assistant Professor, Dept. of Bioengineering, University of Utah, Salt Lake City, UT
2005 - 2010	Assistant Professor, Dept. of Cellular & Structural Biology, UTHSCSA, San Antonio, TX
2005 - 2010	Adjunct Assistant Professor, Dept. of Pediatrics, UTHSCSA, San Antonio, TX
2005 - 2010	Investigator, Children's Cancer Research Institute, UTHSCSA, San Antonio, TX
2005 - 2010	Director of Small Animal Imaging, Children's Cancer Research Institute, San Antonio, TX
2006 - 2010	Adjunct Assistant Scientist, Southwest Foundation for Biomedical Research, San Antonio, TX
2008 - 2010	Director, Mouse Histology Resource, Children's Cancer Research Institute, San Antonio, TX
2008 - 2010	Core Faculty, UTSA/UTHSCSA Joint Graduate Program in Biomedical Engineering
2008 - 2010	Leader, Pediatric Preclinical Testing Initiative at GCCRI
2009 - 2010	Director, Small Animal Imaging Program, Institute for Integration of Medicine & Science, CTSA
2010 - 2014	Associate Professor, Department of Pediatrics, Oregon Health & Science University
2013 -	Adjunct Member, Shriner Hospital for Children Research Center, Portland, OR
2014 -	Scientific Director, Children's Cancer Therapy Development Institute, Beaverton, OR
2014 -	Affiliate (adjunct) Faculty, Colorado State University, Department of Clinical Sciences
2017 -	Affiliate (adjunct) Faculty, Legacy Research Institute, Portland, OR
2017 -	Co-Founder, First Ascent Biomedical LLC
2019 -	Co-Founder, Artisan Biopharma (public benefit corporation for childhood cancer drug dev.)
2021 -	Co-Founder, Tio Companies (Therapeutics In Ovo: childhood cancer drug dev. In quail eggs)

Other Experience and Professional Memberships

1998 - 2012	Board-Certification in Pediatrics, American Board of Pediatrics (ABP)
2004 - 2011	Board-Certification in Pediatric Hematology-Oncology, ABP
1998 -	Physician and Surgeon License, State of Utah (NPI #1053883181)

2005 - Physician License, State of Texas
2009 - Full Member, Children's Oncology Group, Soft Tissue Sarcoma Cmte (associate 2001-08)
2010 - 2016 Co-Chair, Children's Oncology Group, CNS-DVL cmte(brain tumor developmental therap.)
2009 - 2016 Editorial Board, *Pediatric Blood & Cancer*
2015 - Editorial Board, *Scientific Reports*
2009, 2011 ad hoc reviewer, NCI-F study section (June 23-24, 2009; February 22-23, 2011)
2011 - 2015 Standing Cmte Member, NCI-I Study Section
2017 ad hoc reviewer, TPM study section (October 30-31, 2017)
2010 Consultant, NCI CTEP Pediatric Preclinical Testing Program (PPTP)
2018 IBM world community grid *Smash Childhood Cancer* consortium

Honors

1996 Resident Research Grant, American Academy of Pediatrics
1998 NIH T32 Hematology Training Grant, University of Utah
1999 Molecular Biology in Clinical Oncology Travel Award, American Assoc. for Cancer Research
1999 Scott Carter Research Fellow, National Children's Cancer Foundation
2001 Postdoctoral Research Fellowship for Physicians, Howard Hughes Medical Institute
2001 Young Investigator Award, Children's Oncology Group
2001 – 2005 NCI K08-Funded Mentored Physician-Scientist, laboratory of Nobel laureate Mario Capecchi

C. Contribution to Science

1. My basic science research program in the biology of pediatric cancers has been focused on sarcomas. This has required a knowledge and engagement with normal developmental biology, as well as normal stem cell biology – particularly of muscle. Efforts to bridge these areas has led to frequent multi-disciplinary collaborations, in each case having diagnostic or therapeutic implications. We have made the first demonstration that **normal stem cells** (muscle stem cells) **are co-opted to facilitate cancer progression** (metastasis of muscle cancer). Of note, our studies often intersect pathways in age-related sarcopenia.

    a. Tohru Hosoyama, Guangheng Li, Koichi Nishijo, Suresh I. Prajapati, Charles Keller. Role of pRb in Skeletal Muscle Stem Cell Pool Homeostasis. **Journal of Biological Chemistry**, 2011 Jun 3;286(22):19556-64 [PMID 21478154; PMC3103335]
    b. Ken Kikuchi#, Eri Taniguchi#, Hung-I Harry Chen, Matthew N. Svalina, Jinu Abraham, Elaine T. Huang, Koichi Nishijo, Sean Davis, … Sherrie L. Perkins, Paul S. Meltzer, Atiya Mansoor, Joel E. Michalek, Yidong Chen, Brian P. Rubin, Charles Keller. Rb1 Loss Modifies but Does Not Initiate Alveolar Rhabdomyosarcoma. **Skeletal Muscle**, 2013 Nov 25;3(1):27 [PMID 24274149; *open access*]
    c. Guangheng Li, Ken Kikuchi, Charles Keller. IL-4 receptor blockade abrogates satellite cell - rhabdomyosarcoma fusion and prevents tumor establishment. **Stem Cells**, 2013 Nov;31(11):2304-12 [PMID 23897781; *open access*]
    d. Tohru Hosoyama#, M. Imran Aslam#, Jinu Abraham, Koichi Nishijo, Joel E. Michalek, Lee Ann Zarzabal, Laura D. Nelon, Denis C. Guttridge, Brian P. Rubin, Charles Keller. IL-4R Drives De-differentiation, Mitogenesis and Metastasis in Rhabdomyosarcoma. **Clinical Cancer Research**, 2011 May 1;17(9):2757-2766. [PMID 21536546; PMC3087179]

2. Model system development was an important early aspect of our laboratory. These technologies are key features of the mouse models being characterized by this grant application. At 5-11 alleles per model, our work is "genetically fine-tuned" to cover the spectrum of soft tissue sarcomas. We also work diligently to share these models.

    a. Koichi Nishijo, Tohru Hosoyama, Christopher R.R. Bjornson, Beverly Schaffer, Ali N. Bahadur, Mark S. Hansen, Mary C. Blandford, Amanda T. McCleish, Brian P. Rubin, Jonathan A. Epstein, Thomas A. Rando, Mario R. Capecchi, Charles Keller. Biomarker System for studying muscle, stem cells and cancer *in vivo*. **The FASEB Journal**, 23(8):2681-90, August 2009 [PMID 19332644; PMC2717773]
    b. Beverly S. Schaffer#, Marcia H. Grayson#, …, Joel E. Michalek, Charles B. Clifford, Anthony J. Infante*, Charles Keller*. Immune Competency of a Hairless Mouse Strain for Improved Preclinical Studies in Genetically-Engineered Mice. **Molecular Cancer Therapeutics**, 2010 Aug;9(8):2354-64 [COVER][PMID 20663932; PMC2921575]

MMHCC Repository Contributions and caMOD & GEO Participation
caMOD Model: Alveolar Rhabdomyosarcoma (Myf6Cre, Pax3:Fkhr, p53) (150064393)
caMOD Model: Embryonal Rhabdomyosarcoma (Myf6Cre, p53) (150068704)
caMOD Model: Medulloblastoma (Pax7Cre, Ptch1, p53) (150064532)
caMOD Model: Silent Corticotroph Macroadenoma (Pax7CreER, Rb1) (150065143)
caMOD Model: Spindle Cell Sarcoma - Embryonal Rhabdomyosarcoma (Pax7CreER, Ptch1, p53) (150065123)
MMHCC Strain Code 01XBL B6; 129-Myf6<tm2(Cre)Mrc>
MMHCC Strain Code 01XBM B6; 129-Pax3<tm1Mrc>
MMHCC Strain Code 01XBS - B6;129-Pax7<tm1(cre/Esr1*)Cklr>
MMHCC Strain Code tba; 129-Ptch1< *tm1Cklr* > Strain Submission ID #232
MGI Strains: 4453152 *Ptch1(tm1Cklr)*; 4437208 *Gt(ROSA)26Sortm1.1(CMV-luc,-ALPP)Cklr*; 4436914 *Pax7tm1(cre/Esr1*)Cklr*
Genome Wide Association Studies (GWAS) datasets:
GSE15489 (9 datasets): Mouse alveolar rhabdomyosarcoma and wild-type skeletal muscle
GSE22520 (60 datasets): Mouse Models of Alveolar/Embryonal Rhabdomyosarcoma & Spindle Cell Sarcomas

3. Our laboratory has sought to make basic & preclinical pediatric cancer research tangible at the national clinical trial level. This includes not only developing expertise in preclinical research, but also taking a leadership role in this area. Engagement of pharmaceutical companies, academic investigators and the public have been a key activity in this regard. *For example, the 13 institution International DIPG Preclinical Consortium that I led as co-chair of the CNS-DVL committee of the Children's Oncology Group resulted in the Nature Medicine publication below, an NIH Director Blog highlight, a Scientific American story, as well as a Phase I study of panobinostat (NCT02717455).* In other examples, we have worked diligently to improve materials for childhood cancer research by coordinating research autopsy programs with the families and the community (see NPR feature). Overall, the mission to provide real-time, validated pediatric cancer R&D to clinical trial investigators has been the motivation our academic-complementing non-profit biotech (cc-TDI).

    a. Matthew Svalina, Ken Kikuchi, … Jennifer Peckham, Yoon-Jae Cho, Joel Michalek, Brian Hernandez, Melanie Jackson, Daniel Guillaume, Nathan Selden, Darell Bigner, Kellie Nazemi, Sarah Green, Christopher Corless, Sakir Gultekin, Atiya Mansoor, Brian P Rubin, Randy Woltjer, Charles Keller. IGF1R as a Key Target in High Risk, Metastatic Medulloblastoma. **Scientific Reports** 2016 Jun 3;6:27012. doi: 10.1038/srep27012 [PMID 27255663; *open access*]
    b. Catherine S. Grasso#, Yujie Tang#, Nathalene Truffaux#, Noah E. Berlow, …, Charles Keller*,Ranadip Pal, Jacques Grill, Michelle Monje*. Functionally-defined Therapeutic Targets in Diffuse Intrinsic Pontine Glioma. **Nature Medicine**. 2015 May 4. doi: 10.1038/nm.3855. epub ahead of print [PMID 25939062; PMCID 4862411] (*co-corresponding authors)
    c. Elizabeth Sokolowski#, Claire B. Turina#, Ken Kikuchi, David M. Langenau, Charles Keller. Proof-of-Concept Rare Cancers in Drug Development: The Case for Rhabdomyosarcoma. **Oncogene**, 2014 Apr 10;33(15):1877-89 [PMID 23665679]
    d. Jennifer L. Alabran, Jody E. Hooper, Melissa Hill, Sandra E. Smith, Kimberlee K. Spady, Lara E. Davis, Lauren S. Peterson, Suman Malempati, Christopher W. Ryan, Rae Acosta, Sheri L. Spunt, Charles Keller. Overcoming Autopsy Barriers in Pediatric Cancer Research. **Pediatric Blood & Cancer**, 2013 Feb;60(2):204-9 [PMID 23015377, PMC3522778]
        Comment in: Jarzembowski JA, Hicks MJ. Pediatric autopsy consent: Helping families create hope out of despair. Pediatr Blood Cancer. 2013 Feb;60(2):173-4 [PMID 23109284]

4. Uncovering promising targeted therapies for childhood cancers has been an active area of our investigations. We reach out to investigators in many fields for these studies, including now fetal liver biologists.

    a. Dina Kats, Cora Ricker, Noah Berlow, Bénédicte Noblet, Delphine Nicolle, Katell Mevel, Sophie Branchereau, Jean-Gabriel JUDDE, Cody Stiverson, Christina Stiverson, Matthew Svalina, Teagan Settelmeyer, James Geller, Christopher Noakes, Ido Sloma, Narendra Bharathy, Stefano Cairo, Charles Keller. Volasertib preclinical activity in high risk hepatoblastoma. **Oncotarget**, 2019; 10:6403-6417. https://doi.org/10.18632/oncotarget.27237

b. M. Imran Aslam, Jinu Abraham, Atiya Mansoor, Brian J. Druker, Jeffrey W. Tyner*, Charles Keller*. PDGFRβ reverses EphB4 signaling in alveolar rhabdomyosarcoma. **Proc Natl Acad Sci U S A**, 2014 Apr 29;111(17):6383-8 [PMID 24733895; open access] (*co-senior authors)
c. Ken Kikuchi, Anuradha Soundararajan, Lee Ann Zarzabal, Capella R. Weems, Laura D. Nelon, Sheila T. Hampton, Joel A. Michalek, Brian P. Rubin, Alan P. Fields, Charles Keller. Protein Kinase C iota as a Therapeutic Target in Alveolar Rhabdomyosarcoma. **Oncogene**, 2013 Jan 17;32(3):286-9 [PMID 22349825; PMC3360112]
d. M. Imran Aslam, Simone Hettmer, …, Brian J. Druker, Amy J. Wagers, Jeffrey W. Tyner, Charles Keller. Dynamic and Nuclear expression of Pdgfrα and Igf1r in Alveolar Rhabdomyosarcoma. **Molecular Cancer Research**, 2013 Nov;11(11):1303-13 [PMID 23928059; PMC3834004]

Complete List of Published Work in MyBibliography (130+ publications)**:**
https://www.ncbi.nlm.nih.gov/myncbi/charles.keller.1/bibliography/public/

D. Research Support (selected)

ONGOING RESEARCH SUPPORT

1 R01 CA258720-01 Keller (PI/PD) 04/01/2021 - 03/31/2026 4 calendar mo
NIH/NCI
Clinical & Mechanistic underpinnings to reducing PAX:FOXO1 for alveolar rhabdomyosarcoma
The major goals of this project are to address the role of SMARCA4 and PAX:FOXO1 in rhabdomyosarcoma.

No number Keller (PI) 05/01/20 – 04/30/22 1.2 calendar mo
Vince Lombardi Cancer Foundation
Dynamic Regulation of Fusion Genes in Pediatric Cancers
The major goal of this project is to determine cell cycle specific function of translocated-mediated oncogenes.
Role: PI

No number Keller (PI) 05/01/20 – 04/30/22 0.3 calendar mo
Sam Day Foundation
CureFast Biobank and Registry
The major goal of this project is to develop research resources from relapsed and autopsy tumors.
Role: PI

No number Keller (PI) 10/01/19 – 09/30/21 0.85 calendar mo
Anonymous donor consortium
Ewing's Sarcoma Tumor Stem Cells & Maintenance Therapy
The major goal of this project is to define drugs that reduce recurrence from minimal residual disease.
Role: PI

No number Keller (PI) 01/01/20 – 12/31/22 0.6 calendar mo
Anonymous donor
SEF Functional Genomics
The goal of this project is to define the functional genomic landscape of sclerosing epithelioid fibrosarcoma.
Role: PI

PENDING

1 U01 CA263962-01 Keller, Geller, Lau (PI/PD) 07/01/2021 - 06/30/2026 1.5 calendar mo
NIH/NCI impact score 34; funding decision TBA
End-to-End Pediatric Cancer Preclinical Therapeutics
The goal of this project is to serve the PPTP for sarcoma, Wilms' tumor and hepatoblastoma drug testing.
Role: PI/PD

RECENTLY COMPLETED SUPPORT

NIH/NCI R01CA189299-01A1 Keller (PI) 08/11/15 – 08/10/20
Cytokine- and Satellite Cell-mediated Muscle Disease Promotion
This project's major goals are to determine mechanisms of IL-4R and muscle stem cell mediated metastasis.

OVERLAP none