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

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 pediatrician and 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 funded by NIH for 19 years and have authored over 140 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 Nobel laureate 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 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** (G_2 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 11 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 58 publications in the first 7 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. A special feature of cc-TDI is recently published in ***Nature***.

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
2014 - 2020	Affiliate (adjunct) Faculty, Colorado State University, Department of Clinical Sciences
2013 -	Adjunct Member, Shriner Hospital for Children Research Center, Portland, OR
2014 -	Scientific Director, Children's Cancer Therapy Development Institute, Beaverton, OR
2017 -	Affiliate (adjunct) Faculty, Legacy Research Institute, Portland, OR
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 - 2015	Physician License, State of Texas (inactive since 2015)
2009 -	Full Member, Children's Oncology Group, Soft Tissue Sarcoma Cmte (associate 2001-08)

2014 - Steering Cmte, Children's Oncology Group, Soft Tissue Sarcoma Cmte
2010 - 2016 Co-Chair, Children's Oncology Group, CNS-DVL cmte(brain tumor developmental therap.)
2009 - 2016 Editorial Board, *Pediatric Blood & Cancer*
2015 - 2020 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 (independent of IBM in 2022)

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 and the muscle tissue microenvironment. 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).
    a. Xiaolei Lian, Steffan Bond, Narendra Bharathy, Sergei P. Boudko, Elena Pokidysheva, Jack F. Shern, Melvin Lathara, Teagan Settelmeyer, Megan M. Cleary, Ayeza Bajwa, Ganapati Srinivasa, Christopher P. Hartley, Hans Peter Bächinger, Atiya Mansoor, Sakir H. Gultekin, Noah Berlow, Charles Keller. Defining the Extracellular Matrix of Rhabdomyosarcoma. **Frontiers in Oncology**. 2021 Feb 23;11:601957. doi: 10.3389/fonc.2021.601957. eCollection 2021 [PMID 33708626; PMC7942227]
    b. Megan M. Cleary, Narendra Bharathy, Jinu Abraham, Erin R. Rudzinski, Joel E. Michalek, Charles Keller. Interleukin-4 receptor inhibition targeting metastasis independent of macrophages. **Molecular Cancer Therapeutics.** 2021 May;20(5):906-914. doi: 10.1158/1535-7163.MCT-20-0199. Epub 2021 Apr 14. [PMID: 33853867; *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. Arthur O Frankel, … Paul H Huang, Robin L Jones, Brian P Rubin, Morgan A Darrow, Ganapati Srinivasa, Erin R. Rudzinski, Sonja Chen, Noah E Berlow*, Charles Keller*. Machine Learning for Rhabdomyosarcoma Histopathology. **Modern Pathology**. 2022 Apr 21. doi: 10.1038/s41379-022-01075-x. [PMID 35449398]
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. These models were the topic of my mentor's 2007 Nobel lecture.
    a. Samuel V. Rasmussen, Noah E. Berlow, Atiya Mansoor, Stefano Cairo, Sandra Rugonyi, Charles Keller. Preclinical Therapeutics Ex Ovo: Quail Eggs as an Automation Ready Platform. **Sci Rep.** 2021 Dec 2;11(1):23302. doi: 10.1038/s41598-021-02509-3. [PMID 34857796 *open access*]
    b. Koichi Nishijo, Tohru Hosoyama, Christopher R.R. Bjornson, …, 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]
    c. 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*

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). 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. Xiaolei Lian, Dina Kats, Samuel Rasmussen, Leah R. Martin, Anju Karki, Charles Keller* and Noah E. Berlow. Design considerations of an IL13Rα2 antibody-drug conjugate for diffuse intrinsic pontine glioma. **Acta Neuropathol Commu***,* 2021 May 17;9(1):88. doi: 10.1186/s40478-021-01184-9. [PMID: 34001278; PMC8127302] (*co-corresponding authors)
    b. 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*]
    c. 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)
    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. Andrew D. Woods, Noah E. Berlow, Michael V. Ortiz, Filemon Dela Cruz, Armaan Siddiquee, Diego F. Coutinho, Reshma Purohit, Katherine E. Tranbarger Freier, Joel E. Michalek, Melvin Lathara, Kevin Matlock, Ganapati Srivivasa, Brigitte Royer-Pokora, Renata Veselska, Andrew L. Kung, Charles Keller. Bromodomain 4 inhibition leads to MYCN downregulation in Wilms tumor. **Pediatric Blood & Cancer**. 2021;e29401. doi/10.1002/pbc.29401 [PMID *pending*; PMCID n/a]
    b. 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

c. 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)

d. Samuel V. Rasmussen, Jia xiang Jin, Lissett R. Bickford, …, Paul H. Huang*, Thomas G. P. Grünewald*, Noah E. Berlow*, Charles Keller*. Functional genomic analysis of epithelioid sarcoma reveals distinct proximal and distal subtype biology. **Clinical and Translational Medicine**. 2022 Jul;12(7):e961. doi: 10.1002/ctm2.961. *co-corresponding authors [PMID 35839307]

Complete List of Published Work in MyBibliography (140+ 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) 05/14/2021 - 04/30/2026 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) 01/01/20 – 12/31/22 0.6 calendar
Anonymous donor
SEF Functional Genomics
The goal of this project is to define the functional genomic landscape of sclerosing epithelioid fibrosarcoma.
Role: PI

No number Keller (PI) 05/01/20 – 04/30/23 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) 07/01/21 – 11/30/23 0.6 calendar
Megan Bugg Citizen Scientist Project – Crowdfunding
Preclinical Testing for COG Phase 2 Clinical Trial of Entinostat
The goal is to preclinically test entinostat plus chemotherapy testing to justify a Phase 2 pediatric trial.
Role: PI

No number Keller (PI) 05/01/21 – 04/31/23 0.9 calendar
Megan Bugg
Citizen Scientist Project
The goal of this project is to repurpose or rapidly develop treatments for rhabdomyosarcoma.
Role: PI

No number Keller (PI) 01/01/20 – 12/31/22 0 calendar
Macy Easom Foundation
Macy Easom Foundation Fellow
The goal of this program is to use a quail egg, biomimetic assay or hepatoblastoma drug development.
Role: PI

No number Keller (PI) 01/01/20 – 12/31/22 0.8 calendar
WCG (IBM initiated program), Nurix Therapeutics & Golf Fights Cancer
All in the Family - finding an Achilles' Heel common to many Sarcomas
Goal is to develop a computationally-discovered small molecule inhibitor of transcription in EWSR1 cancers.
Role: PI

Redacted – research agreement with Genentech-Roche, Cardiff Oncology and in-kind collaborations below.

OVERLAP - none; COI – Dr. Keller has sponsored research or joint ventures with Novartis, Roche/Genentech, Eli Lilly, Syndax Pharmaceutics, Edding Pharma and Nurix Therapeutics, and is co-founder of Tio Companies and Artisan Biopharma. An institutional conflict of interest management plan is in place for Dr. Keller.

ERIKA ELLIS

Biologists and engineers worked together to create an inexpensive quail-egg platform to quickly test large numbers of drugs in living tissue.

CHANGING CHILDHOOD CANCER'S DEADLY CALCULUS

A non-profit organization merges engineering and biology to accelerate drug development for childhood cancers. **By Esther Landhuis**

In a single motion, a sliding blade slices the bottoms off six speckled quail eggs, and their yolks plop into a six-well dish.

Quail eggs aren't common in research, and most biomedical scientists have never seen this guillotine-like device. But at the biotechnology laboratory of the Children's Cancer Therapy Development Institute (cc-TDI), just outside Portland, Oregon, these eggs are helping researchers to quickly prioritize drug candidates for long, costly mouse studies. Last December, cc-TDI published a description of this platform[1] in *Scientific Reports* – just one example of how the nonprofit organization is breaking norms in cancer research as one of the only freestanding research labs focused on developing drugs for paediatric cancer.

Each year, some 400,000 children and adolescents around the world develop cancer. In the United States, cancer kills around 1,800 young people annually, more than all other diseases combined. Yet, since 1978, fewer than a dozen drugs developed specifically for childhood cancers have earned US Food and Drug Administration approval. (On average, 12 drugs for adult cancers reach the market every year.)

It's a cruel economic conundrum: despite their huge collective impact, individual childhood cancers are rare, and few companies are willing to invest the millions of dollars required to develop a drug with a tiny market. "How on Earth are you going to make money treating 300 kids a year with rhabdomyosarcoma?" asks Charles Keller, scientific director and founder of cc-TDI, referencing a rare type of cancer that forms in muscle and other soft tissues and that affects mostly children.

A physician-researcher with a background in biomedical engineering, Keller launched cc-TDI in 2015 to change that calculus. Partnering with biotech and pharmaceutical companies to vet experimental therapies for clinical testing, the institute has already helped to move a pair of drug candidates into nationwide phase I trials, including one for diffuse intrinsic pontine glioma, a lethal brain tumour for which the survival rate and treatment options have not improved in several decades.

Flexible funding

Federal grants don't typically fund drug-validation and preclinical-development studies, so researchers aren't financially incentivized to complete them. A new mechanism, a promising drug target, perhaps a candidate drug – those are the kinds of project

that tend to attract government investments.

cc-TDI runs on a lean US$2.5-million budget — of which just $350,000 is supplied by grants from the US National Institutes of Health (NIH). The bulk comes from foundations, families and philanthropy. "It takes just as much work to steward a relationship of trust with a donor as it does to write an NIH grant," Keller says. One young woman raised more than $980,000 for cc-TDI before dying of rhabdomyosarcoma in March, a month shy of her 21st birthday. A Portland-area philanthropist gave $270,000.

Philanthropy and private donations can fund high-impact preclinical research that would struggle to attract federal dollars. With funding from multiple foundations, for instance, cc-TDI laid the groundwork for repurposing a class of antibiotic compounds called fluoroquinolones to prevent relapses in Ewing sarcoma, a rare cancer for which two drugs have failed clinical trials. Fluoroquinolones could enter clinical trials once cc-TDI secures funding to identify promising compounds and test them in more cell and animal models.

An engineer's perspective

For tools to get the job done, the institute turns to engineers. Noah Berlow came on board in 2015 after obtaining an electrical engineering PhD at Texas Tech University in Lubbock. In his research, Berlow used applied maths and artificial intelligence to find cancer therapies, as part of a collaboration between Keller, then at the Oregon Health & Science University in Portland, and Ranadip Pal, an electrical engineer and Berlow's thesis adviser at Texas Tech.

At cc-TDI, engineers and biologists work together to analyse drug-testing results alongside DNA- and RNA-sequencing data of tumours — resulting in massive data sets. Berlow says the engineer's role is to help make sense of them. When intriguing features in the data emerge, biologists can work out what they mean. Although engineers rely on biologists' expertise to contextualize what might appear as a smattering of stray data points, an engineer's scant biomedical knowledge — and their fresh perspective — can prove advantageous.

"When you start making assumptions that you know how things work, cancer has a way of turning that on its head," Berlow says.

Berlow co-developed an automated screening tool that ranks by diagnosis likelihood all the possible cancers a person could have. This helps pathologists to decide quickly which confirmatory tests to conduct, and could prove especially useful in rural areas and developing countries that lack pathologists[2]. Trained on 424 tissue slides of sarcoma tumours, the model is more than 88% effective at detecting all tested sarcoma subtypes.

Another engineer, Samuel Rasmussen, joined cc-TDI fresh out of university, where he studied mechanical engineering. Rasmussen put himself through Portland State University in Oregon by working nights at a local distribution warehouse of the farm-equipment manufacturer John Deere. He was part of a team of undergraduates doing a senior research project in early 2016 under Keller's supervision. Their charge: create a device to crack eggs without breaking the yolk.

The team's design didn't work, but Rasmussen kept tinkering. Experimenting over a mixing bowl at the student union, he determined that removing the bottom of the egg with a knife could release the yolk unscathed. Within days, Rasmussen created a working prototype. Keller offered him a summer internship — and, six months later, hired him full time.

Rasmussen was first author of the *Scientific Reports* paper[1], in which he and colleagues placed drug-treated tumour cells onto shell-free quail embryos growing in lab dishes, providing a quick and inexpensive way to screen drugs on living tissue. Data from an 11-day quail-egg assay, which uses up to 200 eggs per screening at around 35 cents an egg, agreed with mouse data, even when results from mouse and lab-dish experiments differed, Keller says. That suggests the quail-egg system could be used to reliably select candidates for testing in studies using mice implanted with human tumours. Those mouse studies take ten or more weeks and cost tens of thousands of US dollars.

Because mouse studies "are really expensive and time-consuming", says Maya Ridinger, a biologist at Cardiff Oncology, a biotech firm based in San Diego, California, scientists can investigate only a limited number of compounds, doses and models. Cardiff Oncology is working with cc-TDI to test onvansertib, a drug designed to treat a childhood liver cancer called hepatoblastoma. "I think the quail-egg system is a great opportunity," says Ridinger.

Mission minded

Rasmussen's work was funded by a John Deere dealership owner who gave money to cc-TDI after losing a niece to childhood cancer. The John Deere link was coincidental, but Keller has a knack for rallying diverse people to a singular mission — getting drugs into paediatric-cancer trials. In addition to nurturing connections with families and funders, Keller maintains close ties with pharmaceutical collaborators and groups that run clinical trials, to focus cc-TDI's preclinical work on what is potentially translatable. "You probably can't overstate that, because we've been curing cancer in mice for many years," says Douglas Hawkins, a paediatric haematologist-oncologist at Seattle Children's in Washington. Hawkins, who chairs the Children's Oncology Group, a federally funded clinical-trial network that is conducting one of the cc-TDI trials, adds: "Trying to take whatever we've learnt in the lab and apply it to humans, that's been one of the harder things."

Since 2004, the US National Cancer Institute has funded a preclinical research programme to evaluate compounds — mostly pharmaceutical drugs previously developed for adult cancers — for inclusion in paediatric cancer trials. For the five-year funding cycle that began in July 2021, the Pediatric Preclinical In Vivo Testing Consortium (PIVOT) provided $5 million per year to a coordinating centre and seven research teams to test specific compounds in models in the lab. Among more than 140 drugs studied by the programme, only a few have proceeded to clinical testing, says paediatric oncologist and PIVOT director Malcolm Smith.

At cc-TDI, Keller aims to beat those odds by focusing on team diversity and his belief that a great scientist can come from anywhere.

Andy Woods, for example, is a former tile contractor who left his business and moved his family to Oregon in 2017 to work at cc-TDI as a senior research associate. In October 2021, he published a paper[3] on his daughter's kidney cancer, Wilms' tumour, describing how he and his colleagues used genomics to identify drug candidates for a subtype of the disease that responds poorly to standard therapies.

Another recent addition to cc-TDI is Tim Brown, a former vice-president of biotech company Genentech, based in South San Francisco, California. In 2015, Brown's 20-year-old son died from Duchenne muscular dystrophy. Brown connected with Keller through a cc-TDI research assistant who was part of the team that helped his son, then an undergraduate at the University of Portland, with eating, dressing and daily tasks as his disease progressed. Brown began volunteering at cc-TDI last October to honour his son's memory by applying his supply-chain and manufacturing expertise to projects such as automating the quail-egg assay.

The multidisciplinary team and culture of innovation were a big draw, Brown says. "There's really good connection between us folks who have a few years of experience in different industries, and these young scientists."

By casting a wide net, the institute "was, and always is, an experiment", Keller says. Its junior board of directors, which helps to plan local events and fundraising efforts, is open to young people aged 7 to 17. It has former vice-presidents of the semiconductor manufacturer Intel on its board of directors. And it hosts annual summer 'nanocourses', weeklong crash courses in the basics of childhood cancers, drug development and clinical trials, to train members of the public to liaise between cancer researchers and the community. "This is a grass-roots cause," Keller concludes, "where a few people who care a lot about a rare condition come together because they're driven by the mission."

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