NOVEMBER 3-5, 2022

15TH

International VHL Medical/Research Symposium

VHL Alliance

vhlsymposium.com

welcome

Welcome to the 15th VHL Medical/Research Symposium!

Von Hippel Lindau disease was first recognized as a rare disorder running in families in the late 1800s. Patients present with tumours involving the brain, spine, retina, kidney and adrenal gland, along with cysts in various parts of the body such as the pancreas and reproductive organs. In 1993, the VHL gene was identified providing a critical advancement in the understanding and treatment of VHL disease. It is estimated that VHL has a frequency of 1 in 30,000-40,000 people, but this is likely an underestimate. More pervasive genetic testing has led to identification of previously underrecognized cases. The VHL gene is involved in many biological pathways, and is one of the most frequently altered genes in kidney cancer; involved in polycythemia, and importantly, the hypoxia inducible (HIF2alpha) pathway. This led to the discovery of belzutifan, a HIF2alpha inhibitor, and the first precision cancer medicine for VHL patients, approved in 2021. This monumental discovery led to William Kaelin, Peter Ratcliffe and Gregg Semenza receiving the 2019 Nobel Prize for their discoveries of how cells sense and adapt to oxygen availability.

In parallel to these scientific and clinical progressions, the VHL patient community has been critical to advancing the VHL field. More than twenty-five years of work has helped shape the VHL Alliance into the pre-eminent resource for patients, caregivers, researchers, and the medical community. In addition, the VHL Alliance is part of an international network serving an estimated 15,000 people worldwide, in 108 countries.

Feelings of isolation among patients and their families, particularly during the pre-internet era, was the primary motivation for forming the VHL Alliance. Creating a sense of connection helped relieve some of the stress of the unknown as well as the frustration caused, in part, by the lack of knowledge of healthcare professionals about this rare condition. As such, the organization made its mission to connect and educate VHL patients and their families while providing information to healthcare providers to advance VHL diagnosis, treatment, and quality of life. Likewise, the Canadian VHL Alliance's vision is to improve the quality of life of Canadian VHL patients and families. They have been active for over 20 years and have partnered with the US VHL Alliance on key initiatives. Additionally, the organization is affiliated with twenty-two International VHL Alliances globally.

On a biennial basis, the VHL community holds an International Medical Symposium aimed at updating VHL researchers and clinicians on the most recent advances in research, and current best practices of clinical care. The virtual 15th International VHL Medical/Research Symposium (Nov 3-5, 2022) is held in partnership with the Canadian VHL Alliance and the Toronto VHL Network. We are excited by the enthusiasm this research community has generated during the nearly three decades of these biannual meetings. The last few years especially have seen enormous advances in both understanding the molecular events consequent to VHL inactivation, as well as clinical understanding and treatment of VHL manifestations. We are looking forward to the presentation of new data that will enable VHL-mutation carriers to lead normal lives and generate insights into the fascinating molecular biology.

The VHL Alliance, the Toronto VHL Network, and the Canadian VHL Alliance are delighted to host another successful VHL International Conference.

With Gratitude,

Raymond Kim MD/PhD, FRCPC, FACMG, FCCMG Chair, 15th International VHL Medical/Research Symposium Committee, *Medical Geneticist Associate Professor*, University of Toronto

Alexandra Volenik, MSc, CGC, CCGC, *Genetic Counsellor* Bhalwani Familial Cancer Clinic, Princess Margaret Cancer Centre

Anders Bjella, Geordyn Coker, Rhiannon Lewis, Joshua Mann, MPH, Jordan McGuire and Kelsey McQueen, Staff, VHL Alliance

Stephen Parrott, Chair, Canadian VHL Alliance

accreditation and contact info

CEC and CEU Accreditation

This conference has been approved by the Canadian Association of Genetic Counsellors (CAGC) for 14.0 CECs. If you are in need of proof of attendance, please contact us at info@vhl.org.

This conference has also been approved for 1 CEU through the National Society of Genetic Counselors (NSGC). If you would like to claim this credit, please contact jordan.mcguire@vhl.org by November 21st.

Contact Information

For any general questions, please contact Jordan McGuire at jordan.mcguire@vhl.org or via phone +1 360 584 0574

For technical questions or concerns, please contact the team at support@webinarsolutions.ca or via phone at +1 844 992 2297

sponsor

program

Day 1 | Thursday, November 3 2022

INTRODUCTIONS

8:00 ET	Welcome	**Raymond Kim, MD, PhD, FRCPC, FACMG** *Medical Geneticist*, Associate Professor, University of Toronto, Ontario, Canada
8:15 ET	*Keynote Address:* VHL: Gene to Pathway to Precision Management to Therapy	**W. Marston Linehan, MD** *Chief of Urologic Surgery and the Urologic Oncology Branch*, Center for Cancer Research, at the National Cancer Institute, National Institutes of Health, Bethesda, MD.
9:15 ET	*Break*	

SESSION TITLE: BASIC SCIENCE
Chair: Michael Ohh, PhD

9:30 ET	Natural History and Treatment of Hemangioblastomas in VHL Patients: The MGH Experience	**Othon Iliopoulos, MD, PhD** *Clinical Director,* von Hippel-Lindau Disease/Familial Renal Cell Cancer Program, Massachusetts General Hospital Cancer Center, Boston, MA, USA *Associate Professor of Medicine*, Harvard Medical School, Boston, MA, USA
10:00 ET	Investigating Plkfyve and Lysosomes as Target in VHL Disease	**Sandra Turcotte, PhD** *Canadian Cancer Society Research Chair*, Canada *Researcher in Residency*, Atlantic Cancer Research Institute, Canada *Associate Professor*, Department of Chemistry and Biochemistry, New Brunswick Centre for Precision Medicine, Canada
10:30 ET	*Proffered Abstract:* Tumor heterogeneity analysis using single-cell transcriptomics in Von Hippel-Lindau related renal cancer	**Isaline Rowe, PhD** *Staff Scientist, URI - Urological Research Institute, IRCCS San Raffaele Hospital , Milan, Italy*
10:45 ET	*Break*	

program

11:00 ET	**The Quest after the Oncogenic Drivers for VHL-Related Pancreatic Neuroendocrine Tumors**	**Amit Tirosh, MD** *Associate Professor of Medicine*, Aviv University Faculty of Medicine, Tel Aviv, Israel *Director*, ENTIRE Translational Research Center for Endocrine Cancer, Sheba Medical Center, Israel
11:30 ET	**Psychosocial Impact of VHL - New Insights and Challenges**	**Rachel van Leeuwaarde, MD, PhD** *Department of Endocrine Oncology*, University Medical Center Utrecht, The Netherlands
12:00 ET	**Patient Corner**	**Jess**
12:30 ET	*Lunch Break*	
1:00 ET	**Nontraditional Tumor Associated Antigens in ccRCC**	**William Y. Kim, MD** *Rush S. Dickson Professor of Medicine*, Genetics, and Pharmacology, Division of Oncology *Co-leader* Cancer Genetics Program, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, NC, USA
1:30 ET	**VHL and Other Emergent Pseudohypoxic Diseases: Lessons from pVHL/HIF2a and PHD2/HIF2a Crystal Structures**	**Fraser Ferens, PhD** *Post-Doctoral Fellow*, Ohh Laboratory, University of Toronto, Toronto, Canada
2:00 ET	**VHL-Independent Heterogeneity of Hypoxia Signaling in Renal Cell Carcinomas**	**Hamed S. Najafabadi, PhD** *Canada Research Chair*, Systems Biology of Gene Regulation *Assistant Professor*, Department of Human Genetics, McGill University, Canada
2:30 ET	**Closing Remarks**	**Othon Iliopoulos, MD, PhD,** VHLA Board Member **Stephen Parrott,** CVHLA Board Chair
2:45 ET	*Break*	

SESSION TITLE: POSTER SESSION

3:00 ET	**Poster Session**
3:30 ET	**Poster Session**
4:00 ET	**Poster Session**

program

Day 2 | Friday, November 4 2022

SESSION TITLE: CLINICAL MANIFESTATIONS IN VHL
Chair: Jesse Pasternak, MD

7:55 ET	Welcome	**Raymond Kim, MD, PhD, FRCPC, FACMG** *Medical Geneticist*, Associate Professor, University of Toronto, Ontario, Canada
8:00 ET	FDA Approval of Belzutifan	**Eric Jonasch, MD** *Professor*, Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Texas, USA
8:30 ET	Tumor Surveillance for Children and Adolescents with Cancer Predisposition Syndromes: The Psychosocial Impact Reported by Adolescents and Caregivers	**Kalene van Engelen, MSc, CGC, CCGC** *Certified Genetic Counsellor*, London Health Sciences Centre, London, Ontario, Canada
9:00 ET	Patient Corner	**Andrew Gowan**
9:30 ET	Management of CNS Manifestations of VHL: Lessons from the NIH Natural History Study	**Prashant Chittiboina, MD** National Institutes of Health, Maryland, USA
10:00 ET	Breaking News in Pheochromocytoma and Paraganglioma Surgery	**Martin K. Walz, MD** *Head and Professor of Surgery*, Kliniken Essen-Mitte Academic Hospital of the University of Duisburg-Essen, Cologne Bonne Region, Germany
10:30 ET	Updates on the Journey of Testing Treatments of Ocular Hemangioblastomas Associated with VHL	**Emily Chew, MD** *Senior Investigator*, Division of Epidemiology and Clinical Applications, Clinical Trials Branch, National Institute of Health, Bethesda, MD, USA
11:00 ET	*Proffered Abstract:* Applying a disease-specific annotation protocol for VHL gene curation using Hypothes.is	**Sarah Ridd** *Clinical Research Study Assistant,* Department of Medicine, Division of Medical Oncology, University Health Network, Toronto, Ontario, Canada

11:15 ET	*Break*	
11:30 ET	Poster Session	
12:00 ET	*Lunch Break*	*CDMRP Presentation Will Occur in Main Room*

VHL TUMOUR BOARD

12:30 ET	VHL Tumor Board	**Toronto VHL Network team** https://webinarsolutions-ca.zoom.us/j/87931615922?pwd=OGxFMDVUanlGTHYyQWdHOTRjNHk3UT09 Meeting ID: 879 3161 5922. Passcode: 056541
2:30 ET	Closing Remarks	**Joshua Mann, MPH,** VHLA Director of Health **Patty Milburn,** CVHLA Secretary

Day 3 | Saturday, November 5 2022

SESSION TITLE: ENDOCRINE MANIFESTATIONS IN VHL
Chair: Karen Gomez Hernandez, MD

7:55 ET	Welcome	**Raymond Kim, MD, PhD, FRCPC, FACMG** *Medical Geneticist*, Associate Professor, University of Toronto, Ontario, Canada
8:00 ET	**Hypoxia-Inducible Factors Mediate Immune Evasion of Cancer Cells**	**Gregg L. Semenza, MD, PhD** *VHL Foundational Speaker* *C. Michael Armstrong Professor of Genetic Medicine*, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA *2019 Nobel Prize Recipient*, Physiology or Medicine
8:30 ET	**VHL and Oxygenases - Not Just Degradation?**	**Christopher J. Schofield, PhD** *Department Head and Professor*, Organic Chemistry, Department of Chemistry, University of Oxford, Oxford, England *Fellow of the Royal Society*, England

program

9:00 ET	*Proffered Abstract:* Organoid models of hereditary and sporadic pheochromocytoma	**Patricia Dahia, PhD** *Professor of Medicine,* University of Texas Health Science Center at San Antonio, Texas, USA
9:15 ET	*Break*	
9:30ET	Long-Term Outcomes in Survivors of Hereditary Childhood Cancer	**Paul Nathan, MD, MSc** *Head*, Solid Tumor Section *Director*, Aftercare Program, Division of Haematology/ Oncology, Hospital for Sick Children, Toronto, Canada *Professor*, Departments of Paediatrics and Healthy Policy, Management & Evaluation, University of Toronto, Toronto, Canada
10:00 ET	Patient Corner	**Jane**
10:25 ET	*Proffered Abstract:* Unique characteristics of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors by various diagnostic criteria	**Reut Halperin, MD, PhD** *Senior Clinical Associate,* VHL Clinical Care Center, Division of Endocrinology, Diabetes and Metabolism and ENTIRE - Endocrine Neoplasia Translational Research Center, Sheba Medical Center, Israel *Senior Physician,* Faculty of Medicine, Tel Aviv University, Israel
10:40 ET	Endocrine Manifestations of VHL disease: Pathologist's perspective	**Ozgur Mete, MD, FRCPC** *Professor*, University of Toronto, Department of Laboratory Medicine & Pathobiology - Anatomic Pathology, Canada
11:00 ET	Management of VHL-Associated Pheochromocytoma or Pancreatic Lesions Including Pancreatic Neuroendocrine Tumors	**Electron Kebebew, MD, FACS** *Professor of Surgery*, Harry A. Oberhelman, Jr. and Mark L. Welton Professor, Stanford University School of Medicine, California, USA *Chief*, Division of General Surgery, Stanford Medicine, California, USA
11:30 ET	Update on Hereditary Pheochromocytoma	**Karel Pacak, MD, PhD, DSc, FACE** *Senior Investigator*, Division of Intramural Research, National Institute of Health, Bethesda, MD, USA
12:00 ET	Closing Remarks	**Jennifer Galenkamp,** VHLA Board Member **Stephen Parrott,** CVHLA Board Chair
12:15 ET	*Break*	
12:30 ET	Poster Session	

speaker bios

Emily Y. Chew, MD
Senior Investigator, Division of Epidemiology and Clinical Applications, Clinical Trials Branch, National Institute of Health, Bethesda, MD, USA

Emily Chew is the director of the Division of Epidemiology and Clinical Applications and the Chief of Clinical Trials Branch, at the National Eye Institute/National Institutes of Health. She received her medical degree and her ophthalmology training at the U. of Toronto, School of Medicine. She completed her fellowship in Medical Retina at the Wilmer Eye Institute, the Johns Hopkins Medical Institutes and the U. of Nijmegen, the Netherlands. She has designed, conducted, and completed clinical trials and epidemiologic studies in retinovascular diseases including several large randomized trials: the Age-Related Eye Disease Study (AREDS)/ AREDS2, the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study, and the clinical trials of the international Macular Telangiectasia Project (Mac Tel Project) for the treatment of age-related macular degeneration, diabetic retinopathy and macular telangiectasia type 2, respectively. She also conducted clinical trials in the ocular disease of von Hippel Lindau disease. She collaborates with colleagues at the National Library of Medicine (NLM/ NIH) utilizing of artificial intelligence/deep learning on detecting, classifying, and predicting the progression of ophthalmic diseases. She is the Editor-in-Chief for Ophthalmology Science.

Prashant Chittiboina, MD
National Institutes of Health, Maryland, USA

Dr. Chittiboina earned his M.D. from Goa University (India) in 2000 and a Master of Public Health from Idaho State University in 2004. He completed his residency in neurosurgery at Louisiana State University in 2012. During his residency, Dr. Chittiboina also completed a year-long research fellowship studying neuro-vascular disease. He came to NINDS in 2012 as a translational research fellow, becoming a Staff Clinician in the Surgical Neurology Branch in 2013. He became an Assistant Clinical Investigator in 2015 and a Tenure Track Investigator in 2020. His laboratory studies neurosurgical disorders of the pituitary gland and inheritable tumor syndromes. His current work is focused on improving the outcomes of neurosurgical disorders through translational research approaches.

Patricia Dahia, MD, PhD
Professor of Medicine at UT Health San Antonio

Patricia Dahia, M.D., Ph.D., is a Professor of Medicine at UT Health San Antonio. Dr. Dahia has clinical training in Endocrinology and Metabolism and laboratory training in Cancer Genetics, Cellular and Molecular Biology. Her career has been dedicated to research on the genetics of cancer, with emphasis on inherited tumor syndromes, particularly pheochromocytomas and paragangliomas. She has contributed to the discovery of many pheochromocytoma and paraganglioma susceptibility genes including SDHB, KIF1B, EPAS1(HIF2A), TMEM127 and others. Her studies helped define the basis for molecular classification of hereditary and sporadic forms of pheochromocytomas and paragangliomas, including those related to VHL disease. Other research contributions involve defining overlapping signaling among distinct genotypes, identification of new clinical-genetic paradigms, development of the framework for genetic testing and patient surveillance, and generation of new study models for therapeutic testing in these tumors.

speaker bios

Kalene van Engelen, MSc, CGC, CCGC

Certified Genetic Counsellor, London Health Sciences Centre, London, Ontario, Canada

Kalene is a genetic counsellor working in the Medical Genetics Program at London Health Sciences Centre in prenatal, cancer and neuro-genetics. Prior to obtaining her Master's degree in genetic counselling, she worked in clinical cancer genetics research at SickKids. It was this work in surveillance for rare hereditary cancer predisposition syndromes which inspired her Master's thesis project looking at the psychosocial aspects of surveillance.

Fraser Ferens, PhD

Post-Doctoral Fellow, Ohh Laboratory, University of Toronto, Toronto, Canada

Dr. Ferens works alongside Professor Michael Ohh at the University of Toronto's Department of Laboratory Medicine and Pathobiology. Dr. Ferens' focus is on studying the complex genotype-phenotype relationships of pseudo-hypoxic cancer disorders (VHL disease, HIF2-driven disease and PHD-driven disease) using biophysics, structural biology and cell models. The goal of his work is to provide information that will inform the treatment of individuals suffering from these cancer disorders, particularly informing precision medicine approaches, which will benefit from an understanding of how specific mutations in the components of the metazoan oxygen-sensing pathway are causative of disease.

Reut Halperin, MD PhD

Senior endocrinologist at the VHL Clinic and the Division of Endocrinology, Diabetes and Metabolism; *Senior Physician in Internal Medicine* at Sheba Medical Center, Israel

Her PhD thesis, in a direct track and published as a five manuscripts collectio, focused on uncovering how animals form a cognitive map of their environment (Faculty of Biology, Tel Aviv University 2009). She then pursued medical training in Tel Aviv University (2014) and continued to complete an internship in internal medicine (2018) and fellowship in endocrinology (2021) at Sheba Medical Center, Israel. Her clinical work involves an active and busy clinic for patients with neuroendocrine tumors (NET), both sporadic and as part of multiple endocrine neoplasia (MEN) syndromes such as von Hippel-Lindau disease and MEN (1, 2 and 4) syndromes and a clinic for general endocrinology. Her research interest focuses on neuroendocrine tumors as part of multiple endocrine neoplasia, mostly pancreatic NET, with several publications on the prognostic factors of pancreatic NET in VHL and MEN1, and a recent landmark article on characterization of MEN4, the newest member of the MEN syndromes.

speaker bios

Othon Iliopoulos, MD, PhD

Clinical Director, von Hippel-Lindau Disease/Familial Renal Cell Cancer Program, Massachusetts General Hospital Cancer Center; *Associate Professor of Medicine*, Harvard Medical School, Boston, MA, USA

Othon Iliopoulos is an oncologist at Massachusetts General Hospital, where he serves as the Clinical Director of the VHL Disease/Familial Renal Cell Cancer Program. He is also an Associate Professor of Medicine at Harvard Medical School and at the Center for Cancer Research at MGH. Dr. Iliopoulos is a VHL Alliance Research Grant Recipient and is a Clinical Investigator for the MK-6482 (formerly PT-2977) clinical trial. His lab is involved in research pertaining to the main mechanisms underlying the reprogramming of cancer cell metabolism and cancer angiogenesis with the goal to develop mechanism-based strategies for selectively killing cancer cells. Dr. Iliopoulos is the Chair of the Clinical Advisory Council and the Research Council.

Eric Jonasch, MD

Professor in the Department of Genitourinary Medical Oncology, Division of Cancer Center at the University of Texas M. D. Anderson Cancer Center in Houston, Texas.

Dr. Jonasch is director of the VHL Clinical Center at the MD Anderson Cancer Center and is involved in tissue-based translational research in renal cell carcinoma and VHL disease. He heads a number of investigator-initiated clinical trials and leads the Department of Defense Kidney Cancer Research and VHL Consortia. Dr. Jonasch is in charge on an ongoing laboratory research effort evaluating the determinants of response and resistance to therapy in renal cell carcinoma and VHL disease. Dr. Jonasch's current work focuses on understanding the drivers of renal cell carcinoma tumor ontogeny, and the development of informative models of tumor-microenvironmental interaction. Dr. Jonasch serves as Vice-Chair of the NCCN Kidney Cancer Guideline Panel and is a Board member of the International Kidney Cancer Coalition.

Electron Kebebew, MD, FACS

Professor of Surgery, Harry A. Oberhelman, Jr. and Mark L. Welton; *Professor*, Stanford University School of Medicine, California, USA; *Chief*, Division of General Surgery, Stanford Medicine, California, USA

Dr. Electron Kebebew is an internationally recognized expert in Endocrine Oncology and Surgery. He has performed more than four thousand operations on the adrenal, parathyroid, and thyroid glands, and for neuroendocrine tumors of the gastrointestinal tract and pancreas. He has given over 200 invited lectures and visiting professorships. His clinical and translational studies on endocrine and neuroendocrine tumors have been awarded more than $30 million in research funding. Dr. Kebebew has authored and coauthored over 400 scientific articles, 50 book chapters, and edited or co-edited four textbooks. His scientific contributions include the use of molecular markers in thyroid nodule to refine diagnosis and prognostication, identification of novel target for endocrine cancer therapy, implementation of genetic testing and advanced imaging modality to optimize the management of patients with endocrine neoplasm and to allow the practice of precision surgery, and the identification and characterization of inherited endocrine and neuroendocrine syndromes, and their susceptibility genes.

speaker bios

Raymond Kim, MD, PhD, FRCPC, FACMG, FCCMG

Clinician Scientist, Princess Margaret Cancer Centre; *Leader* OICR's Ontario Hereditary Cancer Research Network (OHCRN)

Raymond Kim is an internal medicine and medical genetics specialist at the University of Toronto. He is Associate Professor of Medicine and Provincial Head of the Provincial Genetics Program at Ontario Health. He is Medical Director of Cancer Early Detection and Familial Cancer at Princess Margaret Cancer Centre. He is a staff medical geneticist at the Hospital for Sick Children and Sinai Health System and Project Lead of the Ontario Hereditary Cancer Research Network at the Ontario Institute for Cancer Research. His clinical interests lie in transition of care, complex multidisciplinary care and adult hereditary disorders including patients with Von Hippel Lindau disease. With the support of a VHL Alliance Clinical Research Grant, his group has published a large scale machine learning analysis of over 2882 VHL patients. He also chairs the Clinical Genome Resource VHL Variant Curation Expert Panel. His other research interests incorporate novel genomic technologies in clinical care including whole genome sequencing and circulating DNA.

William Y. Kim, MD

Rush S. Dickson Professor of Medicine, Genetics, and Pharmacology, Division of Oncology; *Co-leader Cancer Genetics Program*, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, NC, USA

Dr. Kim is a laboratory-based physician-scientist whose research and clinical practice focuses on bladder and kidney cancers. After completing his clinical oncology training and post-doctoral fellowship at Dana-Farber Cancer Institute Dr. Kim joined the Division of Oncology at the University of North Carolina at Chapel Hill in 2006. During his time at UNC Dr. Kim has been awarded a number of prestigious grants and awards including the Damon Runyon Clinical Investigator Award, the AACR Kure It Grant for Kidney Cancer Research, and the inaugural Bladder Cancer Advocacy Network (BCAN) Innovation Award. When in clinic Dr. Kim adheres to the philosophy passed down to him from his father: treat patients as if they were your family member.

Rachel van Leeuwaarde, MD, PhD

Endocrinologist and Clinical Epidemiologist Department of Endocrine Oncology, University Medical Center Utrecht, The Netherlands

Rachel van Leeuwaarde is an endocrinologist and clinical epidemiologist at the University Medical Center of Utrecht. She is the chair of VHL multidisciplinary tumor board and the coordinating VHL specialist at the UMC Utrecht. Her research is directed to epidemiology, quality of life related studies, and novel therapies for genetic tumor syndromes, with a special interest in VHL and MEN syndromes. She is a leading investigator of the Prospective Dutch VHL cohort which involves a national prospective registrry and biobank.

speaker bios

W. Marston Linehan, MD

Chief of Urologic Surgery and the Urologic Oncology Branch, Center for Cancer Research, at the National Cancer Institute, National Institutes of Health, Bethesda, MD.

W. Marston Linehan, M.D. received his internship, residency, and fellowship training at Duke University Medical Center. He began his career at the National Cancer Institute in 1982 with positions as Senior Investigator and Urologist-in-Charge, NCI. He is Chief of the Urologic Oncology Branch at the National Cancer Institute, National Institutes of Health, Bethesda, Maryland. He has had a long-standing interest in identification of the genetic basis of cancer of the kidney. By studying patients and families with kidney cancer, he and his colleagues identified 8 kidney cancer genes, including the VHL gene for von Hippel-Lindau syndrome and showed that the VHL gene is also the gene for clear cell renal cell carcinoma. He and his colleagues identified the gene for Hereditary Papillary Renal Carcinoma (MET oncogene, type I papillary renal carcinoma) the FLCN gene (Birt Hogg Dubé syndrome, chromophobe renal carcinoma), the gene for TFE3 kidney cancer, IDH2 kidney cancer and described the germline fumarate hydratase and succinate dehydrogenase B/C/D mutations in the North American families with hereditary leiomyomatosis renal cell carcinoma (HLRCC) and SDH-RCC and described eight new diseases. This work has provided the basis for the development of new therapeutic strategies for the different types of kidney cancer based on understanding the molecular pathway of the specific cancer genes associated with the different types of kidney cancer. He and his colleagues have defined the methods for surgical and clinical management of kidney cancer associated with the hereditary forms of kidney cancer, von Hippel Lindau, Hereditary Papillary Renal Carcinoma and Birt Hogg Dubé syndrome and Hereditary Leiomyomatosis Renal Cell Carcinoma and Succinate Dehydrogenase Renal Cell Carcinoma.

Dr. Linehan and his colleagues' work, showing that "VHL associate.... with elongins B and C and.....that VHL is found in a complex with the CUL-2 proteins....revealed a potential link between VHL and protein degradation", was cited by the Nobel Assembly at Karolinska Institutet in 2019 as providing the critical foundation for the discovery of "H ow Cells Sense and Adapt to Oxygen Availability". He has published over 800 scientific articles and is a member of the National Academy of Medicine. He has received the Joseph H. Burchenal Memorial Award for Outstanding Achievement in Clinical Cancer Research from the American Association of Cancer Research, the Dr. Nathan Davis Award from the American Medical Association, the Lila Gruber Award for Cancer Research from the American Association of Dermatology, the NIH Director's Award for discovery of the VHL Kidney Cancer and Oxygen Sensing Gene, the Barringer Medal from the American Association of Genitourinary Surgeons, the Gold Cystoscope Award, the Distinguished Contribution Award and the Ramon Guiteras Award from the American Urological Association, the Huggins Medal, the SUO Medal and the Whitmore Lecture Award from the Society of Urologic Oncology and the Andrew C. Novick Award from the Kidney Cancer Association. He is or has been on the editorial board of 15 journals

speaker bios

Ozgur Mete, MD, FRCPC

Consultant Endocrine Pathologist at the University Health Network; *Professor* in the Department of Laboratory Medicine and Pathobiology at the University of Toronto

As a Clinician Investigator, Dr. Mete's research focuses on the translation of basic findings to clinical tests that provide diagnostic, prognostic, and predictive biomarkers for endocrine tumors. His other interests involve development of practice guidelines, digital pathology, and innovative teaching designs. In 2013, Dr. Mete received the Danny Ghazarian Resident Teaching Award, and in 2014 and 2017 the prestigious Wightman-Berris Academy Award for excellence in undergraduate and postgraduate medical teaching at the University of Toronto. In 2018, Dr. Mete received the teaching excellence award of the MD program at the University of Toronto as well as the undergraduate teaching award of the Laboratory Medicine and Pathobiology at the University of Toronto. Dr Mete is currently the Anatomic Pathology Residency Site Director at the University Health Network.

Dr. Mete has lectured in many international meetings, has co-edited 5 pathology textbooks, and authored over 140 textbook chapters, and more than 230 peer-reviewed journal articles in endocrine pathology. Dr Mete has been appointed as one of the expert editors for the 5th series of the WHO endocrine and neuroendocrine, and the WHO head&neck bluebooks. In addition, Dr Mete served as a leading author in several chapters for the 4th and 5th editions of the WHO classification of endocrine and neuroendocrine tumors, and he has been actively involved in endocrine chapters in the 5th series of the WHO central nervous system, pediatric, genitourinary, and head and neck bluebooks. Dr. Mete is currently the Editor-in-Chief of Endocrine Pathology Journal and has been the President of Endocrine Pathology Society (March 2020-March 2022). Dr Mete is also a member of the College of American Pathologists (CAP)'s Cancer Committee and has been appointed to lead the CAP endocrine tumor protocols since 2019.

Hamed Najafabadi, PhD

Canada Research Chair, Systems Biology of Gene Regulation; *Assistant Professor*, Department of Human Genetics, McGill University, Canada

Dr. Hamed Najafabadi obtained his PhD from McGill University in 2012, followed by a postdoctoral fellowship in University of Toronto. He joined McGill University as a faculty member in 2016, where he is now an Associate Professor of Human Genetics and holds a Canada Research Chair in Systems Biology of Gene Regulation. Dr. Najafabadi's research encompasses the study of transcription factors, RNA-binding proteins, and non-coding RNAs in the context of cancer. His lab uses data-driven computational methods to characterize the role of these gene regulatory factors in determining cell identity and function, and combines them with patient omics data to uncover the basis for development and progression of cancer.

speaker bios

Paul Nathan, MD, MSc

Head, Solid Tumor Section; *Director*, Aftercare Program, Division of Haematology/Oncology, Hospital for Sick Children, Toronto, Canada; *Professor*, Departments of Paediatrics and Healthy Policy, Management & Evaluation, University of Toronto, Toronto, Canada

Dr. Paul Nathan is Director of the AfterCare clinic and the Section Head of the Solid Tumor section in the Division of Pediatric Hematology/Oncology and a Senior Associate Scientist in the Research Institute at the Hospital for Sick Children. He is a Professor of Pediatrics and Health Policy, Management and Evaluation at the University of Toronto. Dr. Nathan completed his medical degree in 1991 from the University of Toronto. His research is focused on health care utilization by adult survivors of childhood cancer, as well as specific "late effects" of cancer therapy, including cardiac disease and second malignant neoplasms. He is a member of the American Society of Clinical Oncology, the Children's Oncology Group, and the International Society of Pediatric Oncology (SIOP), as well as clinical committees focused on research, clinical care, and policy creation for long-term survivors of childhood cancer.

Karel Pacak, MD, PhD, DSc, FACE

Chief, Section on Medical Neuroendocrinology, NICHD, NIH; *Head*, Developmental Endocrinology, Metabolism, Genetics and Endocrine Oncology Affinity Group

I graduated summa cum laude from Charles University of Prague, Czech Republic where I received my MD, PhD, and DSc degrees (the last two degrees I received were based on my scientific work at the NIH). I have established a nationally and internationally recognized patient-oriented pheochromocytoma and paraganglioma research program at the NICHD/NIH in Bethesda, MD, where my laboratory has accumulated major findings and publications over the past 22 years. I promote clinical and scientific collaboration on a national and international level. I have established The International Symposium on Pheochromocytoma (ISP), a series of international pheochromocytoma conferences, in which I served as the President in 2005 and was elected again in 2020. These conferences have opened doors for extraordinary collaborations between the United States and other countries. I later expanded this collaboration by co-founding and/or playing a vital role in the PheoPara Alliance, the Asian Alliance for the Study of Neuroendocrine Tumors, PRESSOR (Pheochromocytoma Research and Support Organization), the Working Group on Endocrine Hypertension, European Society of Hypertension, and most recently, the American-Australian-Asian Adrenal Alliance (A5).

speaker bios

Sarah Ridd

Clinical Research Study Assistant, Department of Medicine, Division of Medical Oncology, University Health Network, Toronto, Ontario, Canada

Sarah Ridd is a Clinical Research Study Assistant for the University Health Network in Toronto, Ontario, Canada. She joined the organization shortly after graduating from McMaster University in 2021. Since then, she has been a part of the VHL data curation project under Physician-Scientist Dr. Raymond Kim, including helping with biocuration efforts on the VHL ClinGen VCEP. Sarah is passionate about the study of genetics and oncology.

Isaline Rowe, PhD

Staff Scientist, URI - Urological Research Institute, IRCCS San Raffaele Hospital , Milan, Italy

Dr. Rowe earned a master's degree in Molecular and Cellular Genetics in 2000 and a Ph.D. in Life Sciences in 2004 from Paris' Pierre et Marie Curie University. In 2004 she moved to the San Raffaele Hospital in Milan in Italy with a Marie Curie Excellence Grant team member as post-doc fellow to work on Autosomal Polycystic Kidney Disease (ADPKD). She discovered that metabolic reprogramming was a central feature of polycystic kidney disease which opened new therapeutic perspectives for a therapy using the glycolytic inhibitor 2-deoxy-D-glucose (2DG). Next she joined the URI - Urological Research Institute in the San Raffaele Hospital in Milan in Italy in 2019 as a staff scientist to conduct translational research on Von Hippel-Lindau related renal cell carcinoma. She is focusing on the analysis of tumor microenvironment and metabolic features in hereditary ccRCC to find markers of response to systemic agents and potential new therapeutical targets.

Christopher J. Schofield, PhD

Department Head and Professor, Organic Chemistry, Department of Chemistry, University of Oxford, Oxford, England; *Fellow of the Royal Society*, England

Dr. Schofield studied for an undergraduate degree in chemistry at the University of Manchester Institute of Science and Technology. He moved to Oxford for DPhil studies with Jack Baldwin on the synthesis and biosynthesis of antibiotics. He subsequently became a Departmental Demonstrator in the Dyson Perrins Laboratory, and in 1990 Lecturer in Chemistry and Fellow of Hertford College. In 1998 he became Professor of Chemistry and he served as Head of Organic Chemistry from 2011 to 2021. He is a Fellow of the Royal Society and Head of Chemistry at the Ineos Oxford Institute for Antimicrobial Research.

His research group works at the interface of chemistry, biology and medicine. His work has opened up new fields in antibiotic research, oxygen sensing and gene regulation in organisms ranging from bacteria to plants and animals. His work has identified new opportunities for medicinal intervention that are being pursued by numerous academic and commercial laboratories.

speaker bios

Gregg L. Semenza, M.D., Ph.D.

VHL Foundational Speaker; C. Michael Armstrong Professor of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; *2019 Nobel Prize Recipient*, Physiology or Medicine

Dr. Semenza is the C. Michael Armstrong professor of genetic medicine, with joint appointments in pediatrics, radiation oncology, biological chemistry, medicine, and oncology at the Johns Hopkins University School of Medicine. He serves as the founding director of the Vascular Program at the Johns Hopkins Institute for Cell Engineering and the founding director of the Armstrong Oxygen Biology Research Center. Dr. Semenza received an A.B. (in Biology) from Harvard University and M.D. and Ph.D. (in Genetics) degrees from the University of Pennsylvania. He completed pediatrics residency training at Duke University Medical Center and postdoctoral training in medical genetics at Johns Hopkins. He has been a member of the Johns Hopkins faculty since 1990.

Dr. Semenza's lab discovered hypoxia-inducible factor 1 (HIF-1), a transcription factor that controls the expression of thousands of genes in response to changes in oxygen availability, for which he was awarded the 2019 Nobel Prize in Physiology or Medicine. His current research interests include investigating the molecular mechanisms of oxygen homeostasis and the role of HIF-1 in cancer progression. He has authored more than 450 research articles and book chapters, and his work has been cited by other scientists more than 175,000 times. Dr. Semenza is co-founder of HIF Therapeutics Inc., which is focused on the development of HIF inhibitors for the treatment of cancer and blinding eye diseases. In addition to the Nobel Prize, Dr. Semenza has received the Albert Lasker Basic Medical Research Award (2016), Wiley Prize in Biomedical Sciences (2014), Lefoulon-Delalande Grand Prize from the Institut de France (2012), and the Canada Gairdner International Award (2010).

Amit Tirosh, MD

Associate Professor of Medicine, Aviv University Faculty of Medicine, Tel Aviv, Israel; *Director*, ENTIRE Translational Research Center for Endocrine Cancer, Sheba Medical Center, Israel

Amit Tirosh graduated from the Hadassah Medical School (2007) and specialized in Internal Medicine (2012) and Endocrinology (2015). Dr. Tirosh specialized in managing endocrine cancer and cancer bioinformatics at the U.S. National Cancer Institute between 2015-2018. After his return to Israel, Prof Tirosh established the neuroendocrine tumors unit and the VHL Clinic at Sheba Medical Center, Israel, and opened a research lab focusing on hereditary endocrine cancer syndromes, and specifically on VHL-related endocrine tumors. In 2018 the VHL Clinic was recognized as a VHL Clinical Care Center by the VHL Alliance. Prof. Tirosh published works on endocrine cancer genomics in highest-tier journals, including JAMA Oncology, Gastroenterology, Cancer, and the Journal of Clinical Endocrinology and Metabolism, and has been awarded grants by the leading professional societies, including the VHL Alliance (2020), the Israel Cancer Research Fund (2021), the Neuroendocrine Tumors Research Foundation Pilot Grant (2021), and the Israel Science Foundation grant (2022). Amit was a member of the expert team developing the clinical recommendations for VHL management for the VHL Alliance and led the subcommittee responsible for the VHL-related pancreatic manifestations management recommendations, that were published in 2021.

speaker bios

Sandra Turcotte, PhD

Canadian Cancer Society Research Chair, Canada; *Researcher in Residency*, Atlantic Cancer Research Institute, Canada; *Associate Professor*, Department of Chemistry and Biochemistry, New Brunswick Centre for Precision Medicine, Canada

She completed her PhD in Biochemistry at the Université du Québec à Montréal and Post-doctoral Fellowships at Stanford University in California and at the CRCHUM in Montreal. Her research focus on identifying new therapeutic targets for kidney cancer associated with VHL mutations. Her studies identified a small molecule that kill VHL-mutated cancer cells by disrupting lysosome dynamics. Her laboratory utilized a variety of methods in molecular biology such as CRISPR-Cas9 to study the role of important genes involved in kidney cancer, particularly the von Hippel-Lindau gene its implication in autophagy.

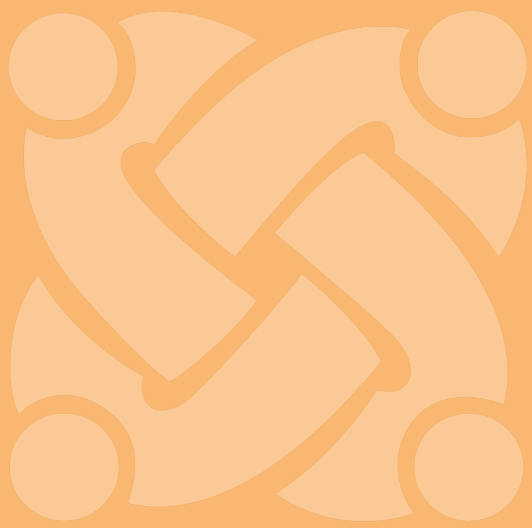
Dr Turcotte hold a Canadian Cancer Society Research Chair in New Brunswick since 2011. Her research funding is coming from provincial and national organisms including the Canadian Institutes for Health Research (CIHR), the Kidney Foundation of Canada (KFOC), the Cancer research Society and the New Brunswick Health Research Foundation (NBHRF).

Martin K. Walz, MD

Head and Professor of Surgery, Kliniken Essen-Mitte Academic Hospital of the University of Duisburg-Essen, Cologne Bonne Region, Germany

Dr. Walz is Head and Professor of Surgery at the Kliniken Essen Mitte Academic Hospital of the University of Duisberg-Essen in Germany. After completing his studies and basic military service, Professor Walz initially took up a position as an assistant doctor at the Institute for Pathology at Essen University Hospital in 1982. In 1984 he moved to the surgical clinic, where he worked as a research assistant until 1999. Clinical and scientific focal points are oncological surgery, endocrine surgery, minimally invasive surgery and surgical intensive care medicine. His list of publications includes over 700 publications. In 2002 he was appointed professor at the University of Duisburg-Essen, and in 2004 he received an honorary doctorate from the Victor Babes University in Timisoara/Romania.

poster and proffered paper abstracts



Metastatic pheochromocytoma/paraganglioma in a child with von Hippel-Lindau disease: An uncommon cause of paediatric hypertension

Joshua Stanley[1]* and Jonathan Wasserman[1]

[1]Department of Pediatrics, Division of Endocrinology, The Hospital for Sick Children, Toronto, ON, Canada

*Correspondence: joshua.stanley@sickkids.ca

Background: Catecholamine-secreting chromaffin tumours are common among individuals with germline predisposition. Von Hippel-Lindau (VHL) disease is the most common genetic cause of pediatric pheochromocytoma/paraganglioma (PPGLs). While tumours may be multifocal (either synchronous or metachronous), metastatic PGGL are rare outside of carriers of germline SDHB variants, with an estimated rate of 5-8% in VHL disease. We present the case of a previously healthy male with multiple incidental secreting tumours, including a suspected metastasic lesion. We describe his diagnostic evaluation and treatment course.

Case Report: A 6-year-old boy was referred for evaluation of bilateral undescended testicles. Abdominal-pelvic ultrasound demonstrated an incidental retroperitoneal mass in the right supra-renal fossa. More detailed evaluation demonstrated three retroperitoneal masses. During his evaluation, asymptomatic hypertension with peak systolic blood pressure of 149 mmHg was noted. He had no other symptoms of catecholamine excess or family history of PPGLs or endocrine neoplasms. Biochemistry was notable for elevated serum normetanephrine (>7.5 nmol/L; ref. range <0.9 nmol/L) and urine VMA (12.8 mmol/mol Cr; ref range <=5.0 mmol/mol Cr) with normal levels of remaining serum metanephrines. He was diagnosed with PPGL. MRI abdomen confirmed three discrete heterogeneously enhancing lesions, ranging from 1.1-2.6 cm in the right adrenal gland, midline retroperitoneum and adjacent to the right liver. 68Ga--DOTATATE scan showed similar somatostatin-avid lesions and an additional mid-retroperitoneal focus. Pre-operative alpha-blockade was initiated with doxazosin, as was salt-loading and hyperhydration. He underwent an uncomplicated complete right adrenalectomy and excision of multiple paragangliomas. Multiple intra-adrenal pheochromocytomas, one extra-adrenal paraganglioma with negative excision margins and one subdiaphragmatic lesion with positive resection margins were identified. Given the rarity of metastatic disease in VHL, particularly at this young age, careful histological examination of the subdiaphragmatic lesion was performed. This was felt to be consistent with metastatic, as opposed to synchronous, tumour due to its atypical site, extensive infiltration of connective tissue and vascular space and a solitary lymph node containing tumour cells. Germline analysis demonstrated a de novo c482G>A variant in the VHL gene and a variant of uncertain significance in the FH gene. As germline FH variants have been associated with PPGL predisposition, it is unclear whether the FH variant in this child is disease-modifying or an incidental finding. Post-operatively, he remains normotensive with normal metanephrines and no residual disease on repeat imaging.

Conclusion: This patient highlights the importance of histologic scrutiny with PPGLs located in atypical locations and of germline analysis for any child presenting with PPGL, to allow for pre-symptomatic surveillance to minimize morbidity attributable to associated lesions.

Unique characteristics of von Hippel-Lindau disease-associated pancreatic neuroendocrine tumors by various diagnostic criteria

Reut Halperin[1],[2*], Liat Arnon[1], Yehudit Eden-Friedman[3], Amit Tirosh[1],[2]

[1]ENTIRE Endocrine Neoplasia Translational Research Center, Sheba Medical Center, Tel Hashomer, Israel, [2]Tel Aviv University Faculty of Medicine, Tel Aviv, Israel, [3]Division of Endocrinology, Diabetes and Metabolism, Sheba Medical Center, Tel Hashomer, Israel

*Correspondence: reutavni@gmail.com

Background: Von Hippel-Lindau (VHL) disease includes hemangioblastomas (HB), renal cell carcinomas (RCC), pheochromocytomas, and pancreatic neuroendocrine tumors (vPNET). Diagnosis is based on International (two HB, one HB and one visceral lesion, or VHL family history plus HB\visceral lesion) or Danish criteria (two clinical manifestations, or VHL family history\pathogenic variant plus HB\visceral lesion). Unlike sporadic PNET (sPNET), most vPNET are non-functioning, have lower grade and fewer metastases, yet head-to-head comparisons are scarce.

Objective: To compare the characteristics of vPNET and sPNET and test the hypothesis that VHL diagnosis by International or Danish criteria comprise two distinct populations.

Material and Methods: PNET diagnosis was identified using the MDClone platform and data collected included demographics, tumor characteristics and VHL clinical features and family\genetic diagnoses. Patients were sub-grouped to sPNET, and to those diagnosed with VHL according to the International (IC) and Danish criteria (DC).

Results: The cohort included seventeen (58%) patients with vPNET out of 29 with VHL, and 65 with sPNET. Patients with vPNET were younger at diagnosis compared with sPNET (50.1±4.7 vs 62.8±1.5 years, $p<0.001$), and the tumors were comparable in terms of stage and grade, but sPNET were more frequently located to pancreatic body/tail ($p = 0.048$). Patients in IC group were younger at diagnosis with VHL, vPNET and RCC than the DC group. Presenting manifestation was HB (52%) and PPGL (31%) in the IC group vs. RCC (62%) and PNET (30%) in the DC group. Finally, 90% of the patients in the IC group had a pathogenic variant in the VHL gene and 2/3 had a family history of VHL, none in the DC group had either ($p<0.05$ for both).

Conclusion: Patients with vPNET diagnosed by IC and DC form distinct clinical groups, with greater similarity of the DC group to sPNET. It is thus possible that diagnosis based on the Danish clinical criteria may include patients with sporadic disease. We therefore suggest that all patients with clinically based diagnosis of VHL should undergo genetic validation of VHL diagnosis.

Applying a disease-specific annotation protocol for VHL gene curation using Hypothes.is

Sarah Ridd[1]*, Kirsten M. Farncombe[2], Veronica Andric[1], Safa Ansar[1], Sean Delong[1], Eric Li[1], Samantha Macpherson[1], Neta Pipko[1], Dena Salehipour[1], Deborah I. Ritter[3], Courtney Thaxton[4], Raymond H. Kim[5]

[1]Department of Medicine, Division of Medical Oncology, University Health Network, Toronto, Ontario, Canada. [2]Toronto General Hospital Research Institute, University Health Network, Toronto, Ontario, Canada. [3]Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas, United States. [4]Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, United States. [5]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Sinai Health System, Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, Ontario Institute for Cancer Research, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

*Correspondence: Sarah.Ridd@uhn.ca

Background: Von Hippel-Lindau (VHL) disease is a rare, inherited disorder that predisposes individuals to develop tumors in various organs throughout the body. Variants of uncertain significance in the VHL gene continue to be encountered despite the Clinical Genome Resource VHL Variant Curation Expert Panel (VCEP)'s best efforts to efficiently classify them for clinical decision making. To address the challenges associated with the lack of variant and clinical phenotype data-sharing among clinicians and scientists, the VHL VCEP is developing gene-specific conditions for VHL variants with the aim of improving patient care. We have adapted ClinGen's current standard operating procedure (SOP) for variant curation to account for specific characteristics and disharmony observed within VHL.

Material and Methods: Hypothes.is is an online platform which presents a centralized hub to house aggregate information on VHL variants, systematically highlighting the variants found in the clinical literature and emphasizing American College of Medical Genetics (ACMG) standards. Our protocol standardizes legacy VHL variants, and highlights patient-specific information including age, family information and inheritance, disease assertion and phenotypic associations, and population database frequencies. We have screened for 504 unique patient-specific VHL genotype-phenotype publications dated up to April 2022.

Results: Our team has currently used the Hypothes.is platform to annotate 457 of the 504 papers. We have identified 616 unique variants in VHL with accompanying genotype-phenotype information. Of these, only 45% (279) were associated with ClinVarIDs, while 47% (288) had at most a CAID, and 8% (49) were not found on either of these notable databases, yet still determined to be relevant by our team.

Conclusion: The considerable variability in VHL variant access across platforms poses a challenge to researchers and clinicians. We successfully established an accessible hub of genotype-phenotype information for VHL disease at a patient-specific level through our adaptation of a VHL-specific Hypothes.is annotation protocol. This standardized approach to annotating VHL variants has been a successful tool integrated into the VHL VCEP and their efforts towards curation and pathogenicity classification. Using Hypothes.is, we strive to mitigate the challenges imposed on VHL treatment by bringing together the strew of information on potentially causative VHL variants found in patients.

Organoid models of hereditary and sporadic pheochromocytoma

Alice Soragni[1],[2], ZiMing Cheng[3], Huyen Thi-Lam Nguyen[1], Ahmad Al Shihabi[1], Hector Gonzalez-Cantu[3], Qianjin Guo[3], Maneesha Thaker[4], Paul Boutros[4],[2], Nicole Bechmann[5], Graeme Eisenhofer[5], Mio Kitano[6],[7], Yanli Ding[7],[8], Patricia L.M. Dahia[3],[7]*

[1]Dept. Orthopaedic Surgery, University of California Los Angeles (UCLA); [2]Jonsson Comprehensive Cancer Center; [3]Div Hematology and Medical Oncology, Dept. Medicine, University of Texas Health San Antonio (UTHSA), San Antonio, TX; [4]Dept of Human Genetics, University of California Los Angeles (UCLA); [5]Institute of Clinical Chemistry and Laboratory Medicine, Medical Faculty Carl Gustav Carus, Universität Dresden, Germany; [6]Dept.Surgery (UTHSA); [7]Mays Cancer **Center** (UTHSA), [8]Dept. Pathology, (UTHSA).

*Correspondence: dahia@uthscsa.edu

Background: Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine-secreting neuroendocrine tumors known for their high heritability and genetic diversity that is reflected in discrete molecular subgroups. Metastatic and recurrent PPGLs have few therapeutic options, in part due to the lack of appropriate study models.

Material and Methods: We established viable organoids from n=6 distinct pheochromocytomas and performed histological, immunohistochemical, molecular, biochemical, functional, genomic and drug response characterization.

Results: The six pheochromocytomas were obtained from patients with distinct clinical history and of diverse ethnic and genetic background. Viable organoid cultures were successfully generated using fresh and processed frozen surgical material. Organoids were developed in a format compatible with histologic characterization and high-throughput drug screening. We observed cellular diversity with immunohistochemical expression of the neuroendocrine marker chromogranin A (n=6/6), sustentacular cell marker S100 (n=5/6, matching primary tumor pattern), and vascular marker CD34 (n=3/3). Five samples were developed into short and long-term cultures. Catecholamines and metanephrines were detected by LC/MS/MS in the media and matched the primary tumor pattern, suggesting that these organoid models are functionally active for at least one month. We also evaluated the response of tumor organoids from six PPGLs by measuring their viability after 48h exposure to a panel of 25 drugs spanning a broad chemical space, including both standard-of-care chemotherapy as well as targeted agents. The resulting drug sensitivity profiles highlighted shared responses but also tumor- and culture-specific differential responses. We will also discuss high-depth genomic sequencing comparison of the primary tumors and matched short- and long-term organoid cultures for a subset of cases.

Conclusion: PPGL organoids are functionally active models that recapitulate aspects of neuroendocrine biology and can be used to investigate PPGL pathogenesis and drug responses.

Paired germline and somatic mutations in VHL in a patient with recurrent endometrial cancer: driver for therapeutic targeting?

Gloria J Morris[1],[2]*, Jeffrey S Ross[3], Bonnie Braddock[1], Jason A Shandler[1], Rinki G Agarwal[1],[4]

[1]The SUNY Upstate Medical University Cancer Genetics Program, [2]Department of Medicine, [3]Department of Pathology, and [4]Department of Gynecologic Oncology (RGA)

*Correspondence: morrisg@upstate.edu.

Background: The tumor suppressor VHL gene is associated with autosomal dominant von Hippel-Lindau syndrome, classically known to increase risks of renal cell cancers (RCCs), pancreatic neuroendocrine tumors, retinal and CNS hemangioblastomas, with sensitivity to HIF-1 inhibitors. Other mutations in the VHL gene can cause autosomal recessive familial erythrocytosis (ARFE), without increased risks of these cancers.

Case Report: We present a case of a postmenopausal Caucasian female with history of early-stage breast cancer at age 44 and then a high-grade papillary serous adenocarcinoma of the endometrium at age 53. Given her personal history of 2 cancers, with family history of throat cancer and leukemia in paternal second-degree relatives, as well as unknown maternal history, she underwent a germline testing (sent as a 47-gene panel), which ruled out mutations in BRCA1 or PTEN, but detected a heterozygous pathogenic variant in VHL (c.598C>T [p.Arg200Trp]), reportedly associated with ARFE, with classic VHL syndrome in only 1 family in the literature (including the VHL Alliance compilation), and seen in 1/20 individuals with Chuvash heritage. In addition, from a genetic counseling perspective, offering cascade testing for this germline variant to offspring is addressed, the tracking of which may assist surveillance for family members. Upon progression of her disease, and difficulty tolerating chemotherapy, genomic sequencing of the original tumor was sent, and identified the same alteration in VHL (VAF 74%), as well as microsatellite stability, low tumor mutational burden (TMB) at 6 mutations/Mb, ERBB2 amplification, and alterations in PIK3CA and TP53, the latter not seen in her germline testing. There were no other actionable targets at that time, but recommendation for participation in other early phase clinical trials overlapping with mTOR pathway was suggested for multiple tumor types. The patient succumbed due to multifactorial conditions in late 2019.

Conclusion: Mutations in VHL are rare in endometrial cancer (Xu et al, Int J Gynecol, 2011), and have been identified in only 0.3% of all 12,895 endometrial carcinomas and 0.3% of 3,221 papillary serous carcinomas in the Foundation Medicine database. Belzutifan, a HIF-2a inhibitor is now FDA approved since 2021, for use in patients with VHL related malignancies. Given the high tumor VAF for VHL mutation, exceeding 50%, we pose the question as to whether this patient with this inactivating VHL mutation (for which experimental data has shown disruption of the hypoxia response pathway) would now have been eligible for further therapeutic intervention, and whether evaluating this pathway in endometrial cancer would now have clinical benefit.

Tumor heterogeneity analysis using single-cell transcriptomics in Von Hippel-Lindau related renal cancer

Isaline Rowe[1], Alessandro Larcher[1], Federico Belladelli[1], Andrea Ieva[1], Roberta Lucianò[2], Miriam Sant'Angelo[2], Giulia Maria Scotti[3], Irene Franco[4], Claudio Doglioni[2], Umberto Capitanio[1], Francesco Montorsi[1], Andrea Salonia[1]

[1]Department of Experimental Oncology, Urological Research Institute (URI), IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; [2]Department of Pathology, IRCCS Ospedale San Raffaele, Vita-Salute San Raffaele University, Milan, Italy; [3]Center for Omics Sciences, IRCCS Ospedale San Raffaele, Milan, Italy; [4]Division of Genetics and Cell Biology, IRCCS San Raffaele Scientific Institute, Milan, Italy

*Correspondence: rowe.isaline@hsr.it

Background: Patients with Von Hippel-Lindau (VHL) disease have risk of developing multiple primary clear cell renal carcinomas (ccRCC). Our hypothesis stated that multiple independent tumors from one VHL patient might display inter-tumoral heterogeneity characterized by differences in tumor grade, metabolic, stromal, and immune cell features that may cause different response to systemic therapy. Using tissues obtained from nephrectomy performed on a VHL patient we investigated the molecular and microenvironmental factors in five independent primary tumors.

Material and Methods: Samples from each primary tumor and from a non-tumoral region were independently processed for single-cell RNA sequencing (scRNAseq) and histology. Diagnosis, staging and grading of ccRCC were assessed by a dedicated genitourinary pathologist. For scRNAseq, cells were isolated and captured using Chromium 10x, then sequencing data were processed with the UMI tools pipeline. Unsupervised clustering was performed using the Seurat R package, and the identified cell populations were manually annotated via marker genes.

Results: Histological analysis revealed that the biggest tumor of 5.5 cm resulted pathologic tumor stage 3a (pT3a) Grade2 (G2) ccRCC, the tumor of 3.0 cm resulted pT1a G3 ccRCC whereas the three smallest lesions of 0.5, 0.9 and 2.0 cm were pT1a G2. For scRNAseq, 10,574 cells were retained after quality filtering and integrative analysis identified 15 different cell clusters. Use of cell type markers allowed to identify cancer cells; immune cells including CD8 positive T cells, regulatory T cells, T cell natural killer like, tumor-associated macrophages (TAM), monocytes, dendritic cells, mast cells, natural killer Cells, B cells and stromal cells including myofibroblasts and endothelial cells. Each lesion had different cancer, immune and stromal composition, in particular the tumor with the highest-grade tumor had less CD8+ T cells and more TAM in comparison to the other lesions. At the level of the expression on of the therapeutical target genes, HIF-2alpha target genes VEGFA, IGFBP3, TGFA, SLC2A1 and CCND1 and immune check point targets PDCD1 (PD1), HAVCR2 (TIM3), LAG3, TIGIT and CTLA4 were expressed in the cancer cells and CD8+ T cells respectively from all the lesions with some notable differences between lesions notably lower expression of most the immune check points targets in the G3 lesion.

Conclusion: Inter-tumor heterogeneity within one VHL patient was revealed at the level of grade, stage and tumor microenvironment composition. Markers of potential response to systemic agents were expressed. This approach underlines the importance to study intra-patient heterogeneity.

Functional interaction between the von-Hippel Lindau protein and Androgen receptor in ccRCC

Antonella Falconieri[1]*, Chiara Boschelle[1], Giovanni Minervini[1], Silvio C.E. Tosatto[1,2], Maria Pennuto[1,3]

[1]Department of Biomedical Science, University of Padua, Padua, Italy; [2]CNR Institute of Neuroscience, Padua, Italy; [3]Veneto Institute of Molecular Medicine, Padua, Italy

*Correspondence: antonella.falconieri@unipd.it

Background: More than 80% of clear cell renal cell carcinoma (ccRCC) are linked to loss of function (LOF) mutations of the von Hippel-Lindau protein (pVHL). Males have a higher risk to develop renal cancer compared to females, implying a role for androgens in the etiology of the disease. The main mediator of androgen signaling is androgen receptor (AR). AR and pVHL have been reported to structurally and functionally interact with each other. However, how the functional relationship between AR and pVHL is regulated and how it impacts on ccRCC gender bias is unknown.

Material and Methods: We paired molecular, cellular and biochemical analysis to characterize pVHL/AR interaction in different ccRCC cell models.

Results: We found that AR interacts with both the full-length pVHL30 and the shorter pVHL19 isoform, and this interaction is subjected to androgen binding. By inhibiting protein synthesis and measuring the AR turnover, we show that pVHL expression influences AR stability in a isoform-specific manner. We confirmed that reintroduction of pVHL in RCC-pVHL- cells decreases cells proliferation, and activation of AR results in the recovery of cell proliferation. This finding suggests that AR in its active state may act as pro-proliferative factor in ccRCC.

Discussion: Taken together, our results indicate that both pVHL30 and pVHL19 interact with AR. Furthermore, the AR activity state has a key role in the regulation of AR/pVHL association, suggesting that the interplay among these proteins plays a role in determining ccRCC sex discrepancy.

Structural Characterization of Hypoxia Inducible Factor α - Prolyl Hydroxylase Domain 2 interaction through MD Simulations

Giorgia F. Camagni[1], Giovanni Minervini[1], Silvio C.E. Tosatto[1]

[1]Dept. of Biomedical Sciences, University of Padova, Via Ugo Bassi 58/B, Padova 35121, Italy

*Correspondence: giorgiafrancesca.camagni@phd.unipd.it

Introduction: Prolyl Hydroxylases (PHDs) are an enzymatic family regulating cell oxygen-sensing. Under physiological oxygen concentrations, PHDs hydroxylate the hypoxia-inducible factor α (HIFs-α) protein family allowing their recognition by the von Hippel-Lindau tumor suppressor protein (pVHL) and subsequent proteasomal degradation. Hypoxia inhibits PHDs activity, thereby stabilizing HIFs-α which initiate the transcription of genes involved in cell metabolism adaptation to hypoxia. As a main hallmark of cancer, hypoxia promotes abnormal angiogenesis, cell proliferation, and survival. The PHDs isoforms (PHD-1,2,3) are thought to have a variable and cell-dependent impact on tumor progression. All isoforms hydroxylate HIF-α (HIF-1,2,3α), however, with different affinities. What determines these differences and how they pair with tumor growth is poorly understood.

Material and Methods: Here, molecular dynamics (MD) simulations and computational tools were used to identify and characterize the PHD2 substrate specificity. In particular, we investigated the binding property of PHD2 in complexes with HIF-1α and HIF-2α. We also characterized the role of the phospho-Thr405 (TPO) localizing on the PHD2 C-terminus in acting as a molecular switch. In parallel, conservation analysis and binding free energy calculations were performed for all complexes to better understand PHD2 substrate affinity.

Results: Our data suggest a direct association between the PHD2 C-terminus and HIF-2athat is not observed in the PHD2/HIF-1α complex. Further, our results indicate that phosphorylation of Thr405 (TPO) is causative of a variation in binding energy, albeit this PTM has only a limited structural impact on PHD2/HIFs-α complexes. In contrast, we observed a statistically significant difference in binding energy between complexes formed by PHD2/HIF-1α and PHD2/HIF-2α that pair with a number of inter-molecules interactions specific for each substrate. Collectively, our findings suggest a C-terminus role in modulating PHD2 substrate specificity.

Conclusion: Our findings suggest that the PHD2 C-terminus may potentially act as a molecular regulator of PHDs activity. Further, the presence of a phororylation site in this region is suggestive of a fine regulative switch. Our data show that specific conserved residues allow the enzymatic discrimination between different substrates, suggesting that mutations in these sites emerging in cancer may interfer with the binding of a single substrate, ideally conferring an adaptative advantage rather than compromising the entire PHD2 enzymatic activity.

Patient-specific Phase-Field modeling and simulation of Retinal Hemangioblastoma provides new perspectives on the role of anti-VEGF therapy

Franco Pradelli[1]*, Giovanni Minervini[1], Silvio C.E. Tosatto[1]

[1]Department of Biomedical Sciences, University of Padova, Padova, Italy

*Correspondence: franco.pradelli94@gmail.com

Background: Retinal Hemangioblastoma (RH) is the most frequent and the earliest manifestation of the von Hippel-Lindau disease (VHL). It usually presents as a vascular and slowly growing tumor but can lead to life-threatening consequences. RH likely originates from the loss of heterozygosity in the VHL gene, which leads to angiogenic factors' (AFs) overexpression and abnormal proliferation. The effect of RH-driven angiogenesis (RHdA) could be recently observed in greater detail thanks to Optical Coherence Tomography Angiography (OCTA), which can detect the capillaries inside RHs much better than traditional fundus angiography. However, the absence of an animal model limits the study of RH Development (RHD) in time. Computational methods are rising as a valid alternative to study cancer dynamics, and, among all, Phase Field Models (PFMs) have proved remarkable results in reproducing tumor growth and angiogenesis. Thus, we used PFMs to model and simulate RHD and RHdA. More precisely, we simulated the coupled effect of tumor growth, AFs overexpression, and angiogenesis, exploiting OCTA images from an actual patient's RH to validate our results.

Material and Methods: We selected the OCTA images from a recently published case report describing an early-stage RH. Given the extent of the RH, we could estimate the initial capillaries conformation and use that as the hypothetical initial condition. Then, we used our model to simulate RHdA and RHD, exploiting the FEniCS computational platform and our recently developed software, Mocafe. We estimated the model's parameters from experimental evidence reported in the literature. Finally, we validated our model using the patient's OCTA images.

Results: The simulations analysis is in progress, but our model seems able to reproduce the RH observed in the patient (Figure). Considering different credible values for the model's parameter, we could confirm that a slowly growing population of tumor cells overexpressing AFs is the simplest explanation for RHD. Our early observations further suggest that the RHdA might be sudden and rapid, leading to complete tumor perfusion in the order of days. The velocity of RHdA might explain the discouraging results of AF inhibition therapy for RH (e.g., anti-VEGF, anti-PDGF). Indeed, RH is usually diagnosed upon fundus examination, so when RH becomes visible, the RHdA might be already too advanced.

Conclusion: To our knowledge, this is the first application of a mathematical model for studying RH. Our preliminary results align with the agreed RH pathology and experimental observations. These do not exclude other RH pathology possibilities but strengthen the mainstream theory. The simulated speed of RHdA is coherent with several studies on sprouting angiogenesis in vivo and in vitro and provides a new perspective on the applicability of AF inhibition therapy for RH. In conclusion, our work suggests that combining PFMs with OCTA provides a valuable tool for studying RH, partially filling the absence of an animal model.

A *RET::GRB2* fusion in pheochromocytoma defies the classic paradigm of RET oncogenic fusions

Cynthia M. Estrada-Zuniga[1,#], Zi-Ming Cheng[1,#], Purushoth Ethiraj[1,#], Qianjin Guo[1], Hector Gonzalez-Cantu[1*], Elaina Adderley[2], Hector Lopez[1], Bethany N. Landry[1], Abir Zainal[2], Neil Aronin[2], Yanli Ding[3], Xiaojing Wang[4,5], Ricardo C.T. Aguiar[1,6,7] and Patricia L.M. Dahia[1,6*]

[1]Division of Hematology and Medical Oncology, Department of Medicine, University of Texas Health San Antonio (UTHSA), San Antonio, TX, USA; [2]Division of Endocrinology, University of Massachusetts Worcester, Worcester, MA, USA [3]Department of Pathology, UTHSA, San Antonio, TX, USA; [4]Department of Population Health Sciences, UTHSA, San Antonio, TX, USA; [5]Greehey Children's Cancer Research, UTHSA, San Antonio, TX, USA; [6]Mays Cancer Center, UTHSA, San Antonio, TX, USA; [7]South Texas Veterans Health Care System, Audie Murphy VA Hospital, San Antonio, TX 78229, USA; [#]These authors contributed equally

*Correspondences: dahia@uthscsa.edu; gonzalezcant@livemail.uthscsa.edu

Background: Pheochromocytomas and paragangliomas are highly heritable neural-crest derived tumors that are components of VHL disease and other hereditary syndromes. About 2/3 of the tumors are sporadic, and their main drivers remain poorly known. Disruptions of the tyrosine kinase receptor *RET* are known driver events in neural crest tumors and epithelial cancers, including mutations in pheochromocytomas, where sustained cell proliferation is maintained by constitutive *RET* signaling.

Material and Methods: Here we report the characterization and experimental validation of a novel driver oncogenic *RET* fusion with *GRB2*, a physiological *RET*-signaling partner protein, in a sporadic pheochromocytoma.

Results: The *RET::GRB2* fusion architecture positions *RET* as the 5' partner, retaining its kinase domain, while losing critical C-terminus motifs, a configuration not seen in *RET* fusions detected in epithelial cancers. *RET::GRB2* endows oncogenic competence via constitutive, ligand-independent signaling that is both kinase and *GRB2* dependent. Translationally, *RET::GRB2*-transformed cells are sensitive to clinical grade selective *RET* inhibitors, thereby broadening the therapeutic scope of these agents towards another type of *RET* oncogenic fusion.

Conclusion: The characterization of the role *RET::GRB2* in pheochromocytoma presents a novel oncogenic driver event in these tumors with potential therapeutic implications, and an additional target for genetic screening.

Characterisation of HIF-mediated genoprotection in clear cell renal cell carcinoma

Sameh ElBadry[1]*, Sherif El-Khamisy[1], Freek van Eeden[1]

[1]School of Biosciences, University of Sheffield, Sheffield, UK

*Correspondence: skamohamed1@sheffield.ac.uk

Introduction: Clear cell renal cell carcinoma (ccRCC) is the most common form of renal cell carcinoma (RCC). Patients with ccRCC often have a remarkably high resistance to traditional radiotherapy and chemotherapy. Hypoxic cores are a common marker of various tumours, which trigger a genetic cascade causing the upregulation of genes crucial to cell survival, such as angiogenesis, cellular proliferation, and altered metabolism. Previous work suggests that increased resistance to radiotherapy/chemotherapy may be due to high levels of hypoxia-inducible factors (HIFs), which under normoxic conditions are targeted for degradation by the von-Hippel Lindau protein (VHL)/E3 ligase complex. Under hypoxia, HIF levels accumulate, allowing them to activate hypoxic response elements downstream.

Mutations in VHL, which are commonly seen in ccRCC patients, cause constant upregulation of HIFs. Therefore, pathways promoting cell survival are constitutively upregulated, initiating tumour formation. This project seeks to understand what pathways are involved in HIF-mediated genoprotection and whether or not high levels of HIF provide a genuine genoprotective effect in humans.

Methods: DNA damage assays, such as comet assays, clonogenics and cell titre blue assays were used to compare the DNA damage response between RCC4 VHL -/- and RCC4 VHL WT cell lines. Western blot and qPCR was used to compare protein expression between cell lines, focusing on VHL, HIFs, and DNA repair proteins

Results: The expression levels and activity of a key regulator of DNA damage response was highly upregulated in RCC4 VHL -/- cells, which correlates with high HIF expression. By knocking down HIF1a or HIF2a separately, I demonstrate that HIF2a is key for this upregulation. RCC4 VHL -/- cells show greater resistance to two DNA damaging agents: camptothecin and olaparib, both of which demonstrate anti-cancer properties. However, initial results indicate that HIF knockdown is insufficient to resensitise RCC4 VHL -/- cells to camptothecin treatment.

Discussion: Although HIF2α expression promotes expression of an important DNA repair protein, this is not solely responsible for the DNA damage resistance in RCC4 VHL -/- cells. The VHL/HIF pathway interplays with multiple pathways that also need to be modulated to see a substantial impact on DNA damage response. HIF levels in RCC4 cells may need to be altered on a long-term basis to accurately mimic patient cells. This may be achieved by CRISPR mutagenesis of HIF1a/HIF2α, which is currently being implemented. Further work will also focus on the other pathways that HIF1α and HIF2α interact with, as well as the HIF-independent roles of VHL that may contribute to the increased radiotherapy/chemotherapy resistance in ccRCC patients.

Characterization of the pVHL interactome in human testis using high-throughput library screening

Giovanni Minervini[1]*, Antonella Falconieri[1], Federica Quaglia[2], Geppo Sartori[1], and Silvio C.E. Tosatto[1]

[1]Department of Biomedical Sciences, University of Padova, 35121 Padova, Italy; [2]Institute of Biomembranes, Bioenergetics and Molecular Biotechnologies, National Research Council (CNR-IBIOM), 70126, Bari, Italy

*Correspondence: giovanni.minervini@unipd.it

Introduction: The von Hippel-Lindau (pVHL) tumor suppressor is a protein involved in the physiologic cell adaptation to low oxygen concentrations. Inherited mutations promoting a functional impairment of pVHL are causative of a familiar increased risk to develop cancer. As E3 substrate recognition particle, pVHL marks the hypoxia inducible factor 1a (HIF-1a) for degradation in normoxic conditions, thus acting as a key regulator of both acute and chronic cell adaptation to hypoxia. In male mice model, VHL gene conditional knockout yelds significant abnormalities in testis development paired with defects in spermatogenesis and infertility, indicating that pVHL may exerts testis-specific roles. Here we aimed to explore whether pVHL could have a similar role in human.

Methods: We combined the yeast two-hybrid (Y2H) assay, a high throughput screening approach, with in-depth bioinformatics analysis. In particular, we performed a testis-tissue library screening and identified a preliminary dataset including 61 pVHL30 interactors. Bioinformatics analysis about molecular function and subcellular localization for each interactor were performed by search against UniProtKB and Gene Ontology (GO). Cytoscape were used to construct protein-protein interaction network around the here identified pVHL30 interactors and integrated with data from from STRING and BioGRID databases. Clusters of functionally correlated proteins were identified with MCODE, while analysis of biochemical pathways, GO terms and association with human diseases was performed with Enrichr and ClueGo.

Results: Here, we identified 55 new pVHL interactors directly involved in pathways regulating spermatogenesis, cell differentiation and reproductive metabolism. Our in-depth computational investigation of these novel interactors identified multiple pVHL-specific binding motifs and demonstrated that multiple somatic mutations described in human cancers localize in these binding regions. Collectively, our findings suggest that, in addition to its role in cancer formation, pVHL may be pivotal in the correct gonads development also in human.

Discussion: We described the testis-specific proteome around the human pVHL30 obtained by library screening. Our approach identified 55 novel pVHL30 interactors, with multiple proteins directly involved in spermatogenesis, reproductive metabolism and cancer. Albeit further study is warranted to elucidate the exact role of these new interactions, we demonstrated that the isoform pVHL30 can bind tissue-specific interactors and suggested novel roles for this oncosuppressor protein.

The identification of distinct haplotypes in VHL tumor-predisposition syndrome and congenital erythrocytosis

Jihyun Song[1], Jorge Di Paola[2] and Josef T. Prchal[1]

[1]University of Utah and [2]Washington University in St. Louis, USA

Von-Hippel-Lindau (VHL) gene, tumor suppressor, is a negative regulator of hypoxia inducible factors (HIFs); HIFs are involved in many biological processes including unique energy metabolism of tumors (Warburg effect), erythropoiesis, iron metabolism, and vasculogenesis. Loss-of-function mutations in VHL gene cause VHL tumor-predisposition syndrome (VHL-TPDS) or congenital erythrocytosis phenotype (CEP) but not both. VHL-TPDS is caused by autosomal dominant mutations, leading to malignant tumors such as pheochromocytoma, renal cell carcinoma, paraganglioma, and hemangioblastoma after another somatic mutation in trans occurs in the VHL locus. First described congenital erythrocytosis due to an autosomal recessive mutation in VHL (R200W) was Chuvash erythrocytosis (CE), with high erythropoietin (EPO) levels caused by stabilization of HIFs`a subunits under normoxia. However, neither the patients with CE nor the patients with different VHL mutations causing erythrocytosis, ever developed any VHL tumors. Therefore, it is unknown why mutations in the same gene cause tumors versus erythrocytosis but never both.

Our data and other evidence indicate that this phenotypic difference between VHL-TPDS and congenital CEP is not due to the location of the mutations. Importantly, some individuals with compound heterozygosity for the Chuvash VHLR200W mutation and other missense VHL mutations known to be associated with VHL-TPDS would be expected to develop tumors, yet those individuals do not develop VHL tumors. The novel VHL mutations generate increased levels of a previously unrecognized cryptic VHL transcript composed of a portion of intron 1 and exon 2 of VHL. The increased levels of this transcript were associated with either germline intronic mutations or synonymous germline mutations in exon 2, which facilitate alternative splicing that generates the aberrant transcripts of VHL gene. Surprisingly, the same changes were associated with CEP in some families but not in other families with VHL-TPDS.

We analyzed published haplotype of VHL gene in 4 samples with VHL-TPDS, 13 with CEP, 15 with CE (homozygote for Chuvash VHLR200W), and 19 healthy controls. Genomic DNA was isolated from granulocytes collected from whole blood by density gradient method. We genotyped 7 single nucleotide polymorphisms (SNPs) including rs1056286, rs776517, rs779805, rs2600005, rs166538, rs458952, rs378630 located between 226 kb upstream and 100 kb downstream of VHL gene using Taqman SNP genotyping assays (Thermofisher). The 4 patients with VHL-TPDS had same genotype of five SNPs located between 3`kb of upstream to 8kb of downstream of VHL gene, which is different from patients with Chuvash VHLR200W. However, other CEP patients did not have same haplotype.

We postulate that there are functional genetic variants including single nucleotide polymorphisms (SNPs) and genome structural variants (SVs), such as copy number variation, insertion, deletion, or duplication that predispose to the VHL-TPDS, while other variants also increase HIFs signaling and EPO production, leading to CEP but prevent tumor development. These two haplotypes conferring two distinct phenotypes and their role in VHL-TPDS in tumorigenesis remain to be defined.

Multi-omics Profiling to Assess Signaling Changes upon VHL Restoration and Identify Putative VHL Substrates in Clear Cell Renal Cell Carcinoma Cell Lines

Xuechun Wang[1], Jin Hu[2], Yihao Fang[3], Yanbin Fu[4], Bing Liu[5]*, Chao Zhang[6]*, Shan Feng[3]*, Xin Lu[2]*

[1]Department of Biological Sciences, Boler-Parseghian Center for Rare and Neglected Diseases, Harper Cancer Research Institute, University of Notre Dame, Notre Dame, IN 46556, USA

[2]Mass Spectrometry & Metabolomics Core Facility, Key Laboratory of Structural Biology of Zhejiang Province, Westlake University, Hangzhou, Zhejiang, China, 310024

[3]Department of the Applied and Computational Mathematics and Statistics, University of Notre Dame, Notre Dame, IN 46556, USA

[4]Department of Plastic and Reconstructive Surgery, Shanghai Institute of Precision Medicine, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, 200125

[5]Department of Urology, Eastern Hepatobiliary Surgery Hospital, Shanghai, China, 201805

[6]Shanghai YangZhi Rehabilitation Hospital (Shanghai Sunshine Rehabilitation Center), Shanghai Key Laboratory of Signaling and Disease Research, School of Life Sciences and Technology, Tongji University, Shanghai, China, 200092

Inactivation of von Hippel-Lindau (VHL) is critical to clear cell renal cell carcinoma (ccRCC) and VHL syndrome. VHL loss leads to stabilization of hypoxia-inducible factor α (HIFα) and other substrate proteins, which together drive various tumor-promoting pathways. There is inadequate molecular characterization of VHL restoration in VHL-defective ccRCC cells. The identities of HIF-independent VHL substrates remain elusive. We reinstalled VHL expression in 786-O and performed transcriptome, proteome and ubiquitome profiling to assess the molecular impact. The transcriptome and proteome analysis revealed that VHL restoration caused downregulation of hypoxia signaling, glycolysis, E2F targets and mTORC1 signaling, and upregulation of fatty acid metabolism. Proteome and ubiquitome co-analysis together with the ccRCC CPTAC data enlisted 57 proteins that were ubiquitinated and downregulated by VHL restoration and upregulated in human ccRCC. Among them, we confirmed the reduction of TGFBI (ubiquitinated at K676) and NFKB2 (ubiquitinated at K72 and K741) by VHL re-expression in 786-O. Immunoprecipitation assay showed the physical interaction between VHL and NFKB2. K72 of NFKB2 affected NFKB2 stability in a VHL-dependent manner. Taken together, our study generates a comprehensive molecular catalog of VHL-restored 786-O model, and provides a list of putative VHL-dependent ubiquitination substrates including TGFBI and NFKB2 for future investigation.

attendees

First Name	Last Name	Email
Abigail	Green	abigail@vhl.org
Adit	Desai	adit.desai@merck.com
Alejandro	Sanchez	alejandro.sanchez@hci.utah.edu
Alexandra	Volenik	Alexandra.Volenik@uhn.ca
Alfredo	Aguilera	aaguilera11@yahoo.es
Allyson	Morgan	allmorga@wakehealth.edu
Amit	Tirosh	amit.tirosh@sheba.health.gov.il
Amy	Maesch	amy.lynn.maesch@merck.com
Anders	Bjella	anders.bjella@vhl.org
Andrea	Shields	akshields@usf.edu
Angel	Cuesta	angcuest@ucm.es
Angel	Serafini	aserafin@wakehealth.edu
Anilda	Dsouza	anilda.dsouza@merck.com
Anita	Villani	anita.villani@sickkids.ca
Anna	Matynia	matynia@jsei.ucla.edu
Antonella	Falconieri	antonella.falconieri@unipd.it
Antonio	Finelli	Antonio.Finelli@uhn.ca
Ariel	Madrigal Aguirre	ariel.madrigalaguirre@mail.mcgill.ca
Bernadette	van Nesselrooij	b.p.m.vannesselrooij@umcutrecht.nl
Betty	Gardie	betty.gardie@inserm.fr
Bonnie	Braddock	braddocb@upstate.edu
Brianna	Murphy	bkmurphy@wakehealth.edu
Bryan	Burkauskas	bryan.burkauskas@merck.com
Carol-Anne	Moulton	Carol-Anne.Moulton@uhn.ca
Christopher	Schofield	christopher.schofield@chem.ox.ac.uk
Corina	Andreescu	corina.andreescu@uzbrussel.be
Courtney	Davis	cordavis@wakehealth.edu
Cristina	Rodriguez-Antona	crodriguez@cnio.es
David	Malkin	david.malkin@sickkids.ca
Dong-Kyu	Kim	dong-kyu.kim@sickkids.ca
Donna	Kimbark	donna.m.kimbark.civ@health.mil
Dylan	Allen	dylanmichael@usf.edu
Eamonn	Maher	erm1000@medschl.cam.ac.uk
Electron	Kebebew	kebebew@stanford.edu
Elizabeth Romelia	Viera Rama	erviera@fundacio-puigvert.es
Ellen	van Rensburg	8vrhjj@queensu.ca
Emily	Chew	echew@nei.nih.gov
Emily	Henderson	emily.henderson@icahn.mssm.edu
Emily	Stuebing	Estuebing@mghihp.edu

attendees

First Name	Last Name	Email
Eric	Jonasch	ejonasch@mdanderson.org
Erika	Ward	eeward@wakehealth.edu
Evelynn	Vergauwen	evelynn-v@hotmail.com
Franco	Pradelli	franco.pradelli@phd.unipd.it
Fraser	Ferens	franco.pradelli@phd.unipd.it
Gelareh	Zadeh	Gelareh.Zadeh@uhn.ca
Geordyn	Coker	geordyn.coker@vhl.org
Giorgia Francesca	Camagni	giorgiafrancesca.camagni@phd.unipd.it
Giovanni	Minervini	giovanni.minervini@unipd.it
Gloria	Morris	morrisg@upstate.edu
Gregg	Semenza	gsemenza@jhmi.edu
Gretchen	Thone	gthone@geisinger.edu
Haifeng	Yang	haifeng.yang@jefferson.edu
Hamed	Najafabadi	hamed.najafabadi@mcgill.ca
Hector	Gonzalez Cantu	gonzalezcant@livemail.uthscsa.edu
Heidi	Rothenmund	hrothenmund@hsc.mb.ca
Helen	Hernandez	helenwhernandez@kalresearchinitiatives.com
Irene	Franco	franco.irene@hsr.it
Isabel	Anez	isabel.anezbruzual@pennmedicine.upenn.edu
Isaline	Rowe	rowe.isaline@hsr.it
Jane	Beasley	mtnbeas@aol.com
Jane	Green	janeg@mun.ca
Jasmine	Dhaliwal	jasmine.dhaliwal@myriad.com
Jason	Shandler	shandlej@upstate.edu
Jasper	Chen	jrchen@mdanderson.org
Jesse	Pasternak	jesse.pasternak@uhn.ca
Joanne	Ngeow	jongeow@gmail.com
John	Wallace	wallyjohnmd@gmail.com
Jonathan	Wasserman	jonathan.wasserman@sickkids.ca
Jonathan	Wickiser	jonathan.wickiser@utsouthwestern.edu
Jordan	McGuire	Jordan.McGuire@vhl.org
Josh	Mann	josh.mann@vhl.org
Joshua	Stanley	joshua.stanley@sickkids.ca
Julieann	Puleo	julieann.puleo@merck.com
Juliet	Milani	milanij@pennmedicine.upenn.edu
Kalene	van Engelen	kalene.vanengelen@lhsc.on.ca
Karel	Pacak	karel@mail.nih.gov
Karen	Gomez Hernandez	karen.gomez-hernandez@uhn.ca
Kari	Thorsen	kthorsen@mghihp.edu
Karishma	Prakash Bharwani	kbharwani@usf.edu

attendees

First Name	Last Name	Email
Kaycee	Carbone	kcarbone@mghihp.edu
Kelsey	McQueen	kmcqueen@mghihp.edu
Kim	Braz Gomez	kimberly.braz.gomes@merck.com
Kimberly	Gaiser	gaiser.kimberly@gmail.com
Kimberly	McGreevy	kimberlymcgreevy@yahoo.com
Kirsten	Farncombe	kirsten.farncombe@uhn.ca
Kristen	Pauley	kristen.pauley@hci.utah.edu
Lorena	Yapur	farak77@gmail.com
Lulwa	Saket	lelsaket@mgh.harvard.edu
Lulwa	El Saket	lulwasaket@gmail.com
Macy	Calvasina	mcalvasi@wakehealth.edu
Madison	Badje	mbadje@wakehealth.edu
Madison	Young	mcyoung@wakehealth.edu
Mandy	Yuen	mandy.yuen@uhn.ca
Marianne	Dubard-Gault	mdg2019@uw.edu
Markus	Holling	hollingm@ukmuenster.de
Markus	Wagner	markus.wagner@msd.de
Marston	Linehan	linehanm@mail.nih.gov
Martin	Walz	chirurgie@kliniken-essen-mitte.de
Mary	Fuentes	mefuentes@mdanderson.org
Maryam	Soleimani	maryam.soleimani@bccancer.bc.ca
Mei Yee	Koh	mei.koh@utah.edu
Melissa	Perrino	melissa.perrino@stjude.org
Michelle	Lunger	michela.lunger@merck.com
Minmin	Li	minmin.li@health.nsw.gov.au
Minseo	Jeong	minseo.jeong04@gmail.com
My Linh	Thibodeau	mylinh.thibodeau@bccancer.bc.ca
Nadia	De Rosa	nadia.derosa@merck.com
Nadia	Nikolova	nadia.nikolova1@nhs.net
Natalie	Waligorski	natalie.waligorski@seattlechildrens.org
Norma	Masson	norma.masson@ndm.ox.ac.uk
Olivia	Lopez	oclopez@wakehealth.edu
Othon	Iliopoulos	oiliopoulos@partners.org
Ozgur	Mete	Ozgur.Mete2@uhn.ca
Paul	Nathan	paul.nathan@sickkids.ca
Prashant	Chittiboina	prashant.chittiboina@nih.hhs.gov
Rachel	Van leeuwaarde	r.vanleeuwaarde@umcutrecht.nl
Raymond	Jang	Raymond.Jang@uhn.ca
Raymond	Kim	raymond.kim@uhn.ca

attendees

First Name	Last Name	Email
Renee	Hofstedter	raizely@gmail.com
Reut	Halperin	reutavni@gmail.com
Rhiannon	Lewis	rhiannon.lewis@vhl.org
Riham	Elshazli	riham.elshazli@merck.com
Rolf	Ponader	rolf.ponader@sana.de
Roya	Mostafavi	Roya.Mostafavi@stjude.org
Ruhee	Dere	ruhee.dere@bcm.edu
Salma	Elhaissouni	selhaissouni@bwh.harvard.edu
Sameh	ElBadry	skamohamed1@sheffield.ac.uk
Sandra	Turcotte	sandra.turcotte@umoncton.ca
Sarah	Ridd	sarah.ridd@uhn.ca
Shunsaku	Takayanagi	takayanagi-nsu@umin.ac.jp
Simson	Hui	simson.hui@merck.com
Stephanie	Naas	st.naas@gmx.de
Stephen	Parrott	sparrott@valuebasedplanning.com
Steven	Raman	sraman@mednet.ucla.edu
Steven	Waguespack	swagues@mdanderson.org
Sven	Glaesker	glasker@web.de
Tania	Cruz Marino	taniacruz@hotmail.ca
Thomas	Krohn	tom.krohn@viz.ai
Tom	Hundsberger	thomas.hundsberger@kssg.ch
Valéna	Karaghiannis	valena.karaghiannis@univ-nantes.fr
Vera	Swanson	swan1858@umn.edu
Wendy	Morton	wendy.morton@merck.com
Wendy	Wolters	w.p.g.wolters-2@umcutrecht.nl
Werner	Kovacs	werner.kovacs@biol.ethz.ch
William	Kim	william_kim@med.unc.edu
Xuechun	Wang	xwang53@nd.edu
Yuval	Yossef	yuvalyosssef@mail.tau.ac.il

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