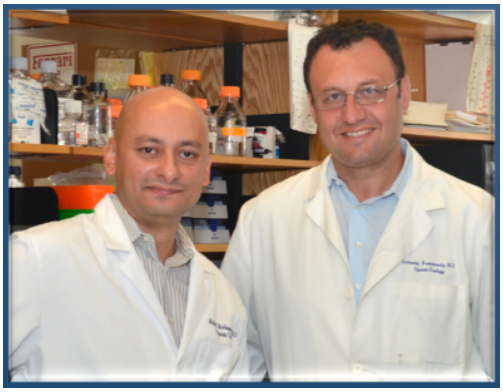
Sixth BHD SYMPOSIUM
and First International
UPSTATE KIDNEY CANCER SYMPOSIUM

SEPTEMBER 23–26, 2015

WELCOME ADDRESS



On behalf of the International Scientific Committee and the Local Organizing Committee, We are pleased and honored to welcome you to the Sixth BHD Symposium and First International Upstate Kidney Cancer Symposium in Syracuse on September 23 –26, 2015.

After Roskilde (2008), Washington (2009), Maastricht (2011), Cincinnati (2012) and Paris (2013), we are very proud to welcome the Symposium and will do our best to continue the successful series of excellent previous meetings.

This expanded symposium will provide a platform for excellent networking, exchanging ideas, and sharing challenges by gathering leading scientists, surgeons and experts in the field; all with a united goal of bringing innovative and progressive treatments to patients in the field of kidney cancer.

The symposium promotes the discovery of drug development, therapeutics and surgical management of patients with BHD and multi-focal renal tumors, as well as multidisciplinary approaches for patients with localized, locally advanced and metastatic renal cell carcinoma.

We wish you a fruitful conference and pleasant stay at the Upstate New York.

Sincerely yours,

Gennady Bratslavsky, MD
Chair, Organizing Committee
Chair, Department of Urology
SUNY Upstate Medical University

Mehdi Mollapour, PhD
Chair, Organizing Committee
Head, Renal Cancer Biology Section
SUNY Upstate Medical University

ACKNOWLEDGMENTS

The International Scientific Committee and the Local Organizing Committee are very grateful to the following sponsors for their financial support:

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We are grateful to Ms. Barbara McConnell and Ms. Susan Schulze for organizing this symposium. Thanks to Dr. Gennady Bratslavsky for the cover photo.

UPSTATE
MEDICAL UNIVERSITY
State University of New York

COMMITTEE

National and International Scientific Committee:

Fang-Ming Deng (New York City, USA)
Elizabeth Henske (Boston, USA)
Vera P. Krymskaya (Philadelphia, USA)
W. Marston Linehan (Bethesda, USA)
Eamonn Maher (Cambridge, UK)
Vesevolod Mateev (Moscow, Russia)
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Arnim Pause, (Montréal, CA)
Laura Schmidt, (Bethesda, USA)
John Solly (London, UK)
Danielle Stevenson (London, UK)
Andrew Tee (Cardiff, UK)
Robert G. Uzzo (Philadelphia, USA)

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Patricia Kane (Upstate)
Steve L Landas (Upstate)
Mehdi Mollapour (Upstate)
Gustavo de la Roza (Upstate)
Oleg Shapiro (Upstate)
Mark Woodford (Upstate)

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ORAL PRESENTATIONS

Speakers are noted

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Social Events

Wine tasting tour

Friday, September 23, 2015
Buses will depart promptly at 3:00pm in front of the Genesee Grande Hotel.

Winery 1– Goose Watch is one of New York's most unique wineries, for its setting as well as its wines. It is located at Cayuga Lake.
http://goosewatch.com/

Winery 2– The Toro Run is a vineyard located at Cayuga Lake. The owners, Chris and Jim's vision was to capture the essence of the Finger Lakes spectacular views and climate.
http://www.tororunwinery.com/

Dinner at the Belhurst Castle

Friday, September 23, 2015 at 7:30pm

Belhurst is located in the heart of the Finger Lakes Wine Region. With its rolling hills, beautiful lakes, stunning foliage and celebration of the arts, the Finger Lakes Region is the perfect getaway destination during any season.
http://www.belhurst.com/visit-us

Dinner Menu

For logistical reasons, please choose one of the following Entrees and inform the registration desk.

BEEF FILET – herb marinated 8oz filet of beef topped with maître d butter over gorgonzola whipped potatoes.

CHICKEN BRUSHETTA – Grilled boneless chicken breast topped with fresh tomato relish, served over garlic and olive oil dressed orecchietta pasta.

SESAME SALMON – Sesame crusted Atlantic salmon with miso-orange sauce over asparagus risotto.

TORTELLINI PRIMAVERA – Tri-colored tortellini tossed with charred grape tomatoes, asparagus, red onions, squash and shitake mushrooms in basil cream sauce.

Please choose one of the following desserts:

APPLE AWESOME – sugar topped, apple filled pastry tulip with a scoop of vanilla ice-cream

MOLTEN CHOCOLATE CAKE – with toasted coconut ice-cream

Sixth BHD Symposium and First International Upstate Kidney Cancer Symposium

September 23 – 26, 2015, Syracuse, USA.

	Wednesday, September 23, 2015	
4:00 – 6:00 pm	Registration	Tiffany Ballroom
6:00 – 9:00 pm	Cocktail Reception	The Bistro
	Thursday, September 24, 2015	
7:00 – 8:00 am	Registration / BreakfastBuffet	Tiffany Ballroom
8:00 – 8:15 am	IntroductionChairs, Organizing Committee Gennady Bratslavsky MD, Mehdi Mollapour PhD	Tiffany Ballroom
8:15 – 8:30 am	WelcomeRemarks - David B. Duggan MD Dean of the Medical School Upstate Medical University	Tiffany Ballroom
8:30 – 9:30 am	Keynote Speaker– W. Marston Linehan MD, National Cancer Institute, USA	Tiffany Ballroom
	Chairperson: Elizabeth Henske MD, PhD	
9:30 am	Elizabeth Henske MD, PhD, USA	Talk 1
9:50 am	Maria Czyzyk-Krzeska MD, PhD, USA	Talk 2
10:10 am	Vera Krymskaya PhD, USA	Talk 3
10:30 – 10:50 am	Break	Salon A
	Chairperson: Maria Czyzyk-Krzeska MD, PhD	
10:50 am	Arnim Pause PhD, Canada	Talk4 – Talk 5
11:30 am	Yu Jiang PhD, USA	Talk 6
11:50 am	Damir Khabibullin PhD, USA	Talk 7
12:10 am	Masaya Baba MD, PhD, Japan	Talk 8
12:30 – 1:30 pm	Lunch	Tiffany Ballroom
	Chairperson: Laura S. Schmidt PhD	
1:30 pm	Sunil Sudarshan MD, USA	Talk 9
1:50 pm	Haifeng Yang PhD, USA	Talk 10
2:10 pm	Laura Schmidt PhD, USA	Talk 11
2:30 pm	Jorge Toro MD, USA	Talk 12
2:50 – 3:10 pm	Break	Salon A
	Chairperson: Arnim Pause PhD	
3:10 pm	Angela Pacitto PhD, UK	Talk 13
3:30 pm	Adam R. Blanden, USA	Talk 14
3:50 pm	Diana Dunn, USA	Talk 15
4:10 pm	Mehdi Mollapour PhD, USA	Talk 16
5:00 – 7:00pm	Poster Session-Prize Presentation	Tiffany Ballroom
7:00pm	Dinner	Tiffany Ballroom

	Friday, September 25, 2015	
7:00 – 8:00 am	Breakfast Buffet	Tiffany Ballroom
	Chairperson: Brian Shuch MD, USA	
8:00 am	Ilene Sussman PhD, USA	Talk 17
8:20 am	Jo Robays MD, PhD, Belgium	Talk 18
8:40 pm	Mitsuko Furuya MD, Japan	Talk 19
9:00 am	Nishant Gupta MD, USA	Talk 20
9:20 am	Paul Johannesma MD, Holland	Talk 21
9:40 am	Irma van de Beek PhD, Holland	Talk 22
10:00 – 10:10 am	Break	Salon A
	Chairperson: Oleg Shapiro MD	
10:10 – 11:10 am	Keynote Speaker– Robert G. Uzzo MD (Fox Chase Cancer Center, USA)	
11:10 – 11:30 am	Break	Salon A
	Chairperson: Sunil Sudarshan MD	
11:30 am	Adam Metwalli MD, USA	Talk 23
11:50 am	Brian Shuch MD, USA	Talk 24
12:10 pm	Gennady Bratslavsky MD, USA	Talk 25
12:30 – 1:30 pm	Lunch	Tiffany Ballroom
	Chairperson: Gennady Bratslavsky MD	
1:30 pm	Jason Muhitch MD, USA	Talk 26
1:50 pm	Namitha Chittoria MD, USA	Talk 27
2:10pm	Fang-Ming Deng MD, PhD, USA	Talk 28
3:00 pm	Depart for Goose Watch Winery / Toro Run Winery	
7:00 pm	Dinner at the Belhurst Castle, Geneva, NY	

	Saturday, September 26, 2015	
	Translational – Clinical Program - Patients	
8:00 – 9:00 am	**Breakfast Buffet**	**Tiffany Ballroom**
9:00 am	**Introduction: Lindsay Middelton RN, USA** **Bonnie Braddock MPH, CGC, USA**	
9:20 am	**Nishant Gupta MD, USA**	
9:30 am	**Ilene Sussman PhD, USA**	
9:40 am	**Elizabeth Henske MD, PhD, USA**	
9:50 am	**Gennady Bratslavsky MD, USA**	
10:00 am	**Jorge R. Toro MD, USA**	
10:10 am	**Steve Landas MD, USA**	
10:20 am	**Panel Discussion**	
11:30 am	**Concluding Remarks** **Gennady Bratslavsky MD & Mehdi Mollapour PhD**	
12:00 pm	**Lunch**	**Salon A**

Thursday, September 24, 2015

GREEN = Basic/Translational Research
RED = Clinical Research
PURPLE = Patients

8:30–9:30am Keynote Speaker:
W. Marston Linehan MD,
Urologic Oncology Branch, National Cancer Institute, USA

9:30am T1– Tuberous sclerosis and Birt-Hogg-Dube: Connections in Pathogenesis and Therapy
Elizabeth Henske

9:50am T2 – VHL and FLCN kidney tumor suppressors are positive regulators of autophagic program targeting midbodies for lysosomal degradation.
Adam D. Price, Megan E. Bischoff, Emily Stepanek, Birgit Ehmer, Johnston Chu, Jarek Meller and Maria F. Czyzyk-Krzeska

10:10am T3 – Folliculin: Gene Function and Potential Therapeutic Targeting in the Lung
Vera P. Krymskaya

10:50am T4 – FLCN and AMPK confer resistance to hyperosmotic stress via remodeling of glycogen stores
Elite Possik, Andrew Ajisebutu, Sanaz Manteghi, Mathieu Flamand, Barry Coull, Kathrin Schmeisser, Tarika Vijayaraghavan, Thomas Duchaine, Maurice van Steensel, David H. Hall and Arnim Pause

11:10am T5 – FLCN Repression Induces Metabolic Reprogramming of White Adipose Tissue Through the AMPK/PGC-1α/ERRα Axis
M. Yan, É. Audet-Walsh, B. Walker, S. Manteghi, J. St-Pierre, V. Giguère, A. Pause

11:30am T6 – Tumor suppressor folliculin regulates mTORC1 through primary cilia
Xuwen Zhao, Mingming Zhong, and Yu Jiang

11:50am T7 – Role of the folliculin interacting protein Plakophilin 4/p0071 in cell adhesion and metabolism
Damir Khabibullin, Carmen Priolo, John Asara, Elizabeth Henske

12:10pm T8 – Xp11.2 translocation RCC mouse model
Masaya Baba, Ying Huang, Hisashi Hasumi, Mitsuko Furuya, Yukiko Hasumi, Masahiro Yao, Laura S. Schmidt, W. Marston Linehan

1:30pm T9 – Metabolic Regulation of the Kidney Cancer Epigenome
Sunil Sudashan

1:50pm T10 – Functional analysis of PBRM1 in ccRCC
Lili Liao, Wei Jiang, Essel Dulamir, Theodore Parsons, Kathik Devarajan, Qiong Wang, Raymond O'Neill, Haifeng Yang

2:10pm T11 – Germline FLCN mutation spectrum and phenotype analysis of 226 families with Birt-Hogg-Dube´syndrome: the NCI experience
Laura S. Schmidt, Lambros Stamatakis, Lindsay A. Middelton, Bonnie Braddock RN, USA, James Peterson, Cathy D.Vocke, Catherine A. Stolle, Edward W. Cowen, Maria J. Merino, Berton Zbar, Adam R. Metwalli, W. Marston Linehan

2:30pm T12 – Current and Emerging Techniques for Detection of FLCN Mutations
Jorge R. Toro, Bethany Friedman, Dolores Arjona, Sherri Bale

3:10pm T13 – LONGINg to broaDENN our understanding of the Folliculin/Fnip complex through its yeast orthologue Lst7/Lst4
Angela Pacitto, David B. Ascher, Louise H Wong, Beata K Blaszczyk, Ravi K Nookala, Nianshu Zhang, Svetlana Dokudovskaya, Timothy P Levine and Tom L Blundell

3:30pm T14 – Zinc Metallochaperone ZMC1 demonstrates a new drug mechanism for p53 reactivation and personalized chemotherapy
Adam R. Blanden, Xin Yu, Isabel Utschig, Darren R. Carpizo, Stewart N. Loh

3:50pm T15 – c-Abl Mediated Tyrosine Phosphorylation of Aha1 Activates Its Co-chaperone Function in Renal Cell Carcinoma
Diana M. Dunn, Mark R. Woodford, Andrew W. Truman, Sandra M. Jensen, Jacqualyn Schulman, Tiffany Caza, Taylor C. Remillard, David Loiselle, Donald Wolfgeher, Brian S.J. Blagg, Lucas Franco, Timothy A. Haystead, Soumya Daturpalli, Matthias P. Mayer, Jane B. Trepel, Rhodri M.L. Morgan, Chrisostomos Prodromou, Stephen J. Kron, Barry Panaretou, William G. Stetler-Stevenson, Steve K. Landas, Len Neckers, Gennady Bratslavsky, Dimitra Bourboulia, and Mehdi Mollapour

4:10pm T16 – Inhibition of the Hsp90 molecular chaperone ATPase Activity by the FNIPs Co-chaperones
Mark R. Woodford, Diana Dunn, Adam R. Blanden, Andrew W. Truman, Taylor C Remillard, Sarina Bottone, Rhodri M. L. Morgan, Steve Landas, Chrisostomos Prodromou, Dimitra Bourboulia, Laura S. Schmidt, Stewart N. Loh, Dimitra Bourboulia, W. Marston Linehan, Gennady Bratslavsky and Mehdi Mollapour

Friday, September 25, 2015

GREEN = Basic/Translational Research
RED = Clinical Research
PURPLE = Patients

10:10 – 11:10am **Keynote Speaker:**
Robert G. Uzzo MD,
Department of Surgery, FOX Chase Cancer Center, USA
"2015 update on management of Renal Cell Carcinoma"

8:00am T17 – Cancer in Our Genes International Patient Databank (CGIP)
Ilene Sussman and Suzanne Nylander

8:20am T18 – Oncogenetic testing, diagnosis and follow-up in Birt-Hogg-Dubé syndrome, development of a guideline in Belgium.
Jo Robays, Sabine Stordeur, Frank Hulstaert, Jean-François Baurain, Teofila Caplanusi, Kathleen Claes, Eric Legius, Sylvie Rottey. Dirk Schrijvers, Urielle Ullman, Tom Van Maerken, Bruce Poppe

8:40am T19 – A Clinicopathological Study of 264 Individuals in 102 Japanese BHD Families
Mitsuko Furuya, Reiko Tanaka, Masahiro Yao, Hisashi Hasumi, Naoto Kuroda, Yoji Nagashima, Yasuhiro Iribe and Yukio Nakatani

9:00am T20 – Cost-Effectiveness of HRCT Screening for Birt-Hogg-Dubé syndrome in Patients Presenting with Spontaneous Pneumothorax
Nishant Gupta, Dale Langenderfer, Francis X. McCormack, Daniel P. Schauer, and Mark H. Eckman

9:20am T21 – Pulmonary manifestations in Birt-Hogg-Dubé syndrome; An overview of results in the VU University Medical Center.
Johannesma PC, Houweling AC, van Beek I, Paul MA, van Waesberghe JHTM, Reinhard R, Starink ThM, Menko FH, van Moorselaar RJA, Postmus PE

9:40am T22- Renal imaging, follow-up and tumour characteristics in 164 patients with Birt-Hogg-Dubé syndrome.
Johannesma PC, van de Beek I, Reinhard R van der Wel JWT, Rozendaal L, Starink ThM, Waesberghe JHTM, Horenblas S, Postmus PE, Houweling AC, van Moorselaar RJ.

11:30am T23 – Surgical and functional outcomes of patients with multifocal RCC
Adam Metwalli

11:50am T24 – What is new in non-clear RCC.
Brian Shuch

12:10pm T25 – Role of a surgeon in management of metastatic RCC.
Gennady Bratslavsky

1:30pm T26 – Bolstering Anti-Tumor Immunity to Kidney Cancer with Current Clinical Approaches
Jason Muhitch

1:50pm T27 – Systemic therapy for advanced and metastatic non-clear RCC
Namitha Chittoria

2:10pm T28 – Updates on the Classification of Renal Cell Carcinoma
Fang-Ming Deng

Saturday, September 26, 2015

BHD/RCC Family session Agenda

9:00am	Lindsay Middelton RN and Bonnie Braddock MPH, CGC, Introduction
9:20am	Nishant Gupta MD, Pulmonologist
9:40am	Ilene Sussman PhD, Executive Director of VHL alliance
10:00am	Elizabeth Henske MD, PhD, Genitourinary Oncologist
10:20am	Gennady Bratslavsky MD, Urologic Oncologist
10:40am	Jorge R Toro MD, Dermatologist
11:00am	Steve Landas MD, Pathologist

ORAL PRESENTATIONS

T1 – Tuberous sclerosis and Birt-Hogg-Dube: Connections in Pathogenesis and Therapy

Elizabeth Henske

Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. 2 - Beth Israel Deaconess Medical

Notes:

T2 – VHL and FLCN kidney tumor suppressors are positive regulators of autophagic program targeting midbodies for lysosomal degradation.

Adam D. Price[1], Megan E. Bischoff[1], Emily Stepanek[1], Birgit Ehmer[1], Johnston Chu[1], Jarek Meller[2] and Maria F. Czyzyk-Krzeska[1]

[1]Department of Cancer Biology, [2]Departement of environmental Health, University of Cincinnati College of Medicine, Cincinnati, OH 45267

POSTER: 1

Abstract: Autophagy is a homeostatic function by which cells process their own organelles and proteins to eliminate defective molecules and to recycle nutrients. Many cancers become addicted to autophagy as a source of nutrients. There are three microtubule associated protein light chain regulators (MAP1LC3s, LC3A, LC3B and LC3C) essential for the formation of a functional autophagosome. LC3B/A and LC3C form separate autophagic vesicles, indicating independent functions. Here we show that both VHL and FLCN induce expression of LC3C but inhibit expression of LC3B. LC3C, but not LC3B, is specifically necessary for the autophagic destruction of midbodies. The mechanism of specificity involves the presence of a C-terminal peptide present in LC3C but not LC3B. Number of midbodies is augmented in cancer cells and stem cells indicating the role of midbodies, and therefore programs regulating their numbers, in cellular reprograming and tumorigenicity.

Notes:

T3 – Folliculin: Gene Function and Potential Therapeutic Targeting in the Lung

Vera P. Krymskaya

Pulmonary, Allergy & Critical Care Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Abstract:
Spontaneous pneumothoraces due to lung cyst rupture afflict patients with the rare disease Birt-Hogg-Dube´ (BHD) syndrome caused by mutations of the tumor suppressor gene *folliculin (FLCN)* by unknown mechanism. BHD lungs exhibit increased alveolar epithelial cell apoptosis. We show that *Flcn* deletion in lung epithelium leads to cell apoptosis, alveolar enlargement and impaired lung function. FLCN loss also impairs alveolar epithelial barrier function. *Flcn*-null epithelial cell apoptosis is the result of impaired AMPK activation and increased cleaved caspase-3. AMPK activator LKB1 and E-cadherin are downregulated by *Flcn* loss and restored by its expression. Flcn-null cell survival is rescued by AICAR or constitutively active AMPK. AICAR also improves lung condition of *Flcn*$^{f/f}$*:SP-C-Cre* mice. Our data show that Flcn regulates lung epithelial cell survival and alveolar size and suggest that lung cysts in BHD may result from an underlying defect in alveolar epithelial cell survival attributable to FLCN regulation of the E-cadherin-LKB1-AMPK axis.

Notes:

T4 – FLCN Repression Induces Metabolic Reprogramming of White Adipose Tissue Through the AMPK/PGC-1α/ERRα Axis

M. Yan[1,2], É. Audet-Walsh[1,2], B. Walker[1.2], S. Manteghi[1,2], J. St-Pierre[1,2], V. Giguère[1,2,3], A. Pause[1,2]

[1]Goodman Cancer Research Centre and [2]Department of Biochemistry, [3]Medicine and Oncology, McGill University, Montréal, Canada

POSTER: 2

Abstract:
We generated an adipose-specific *Flcn* knockout (adipo-FLCN KO) mouse model to investigate the role of FLCN in energy metabolism. Here we show that the absence of FLCN leads to a complete metabolic reprogramming of white adipocytes. Adipo-FLCN KO mice exhibit increased energy expenditure that protects from high fat diet (HFD)-induced obesity. Importantly, FLCN ablation leads to a hyper-activation of AMPK, which in turns induces and activates two key transcriptional regulators of cell metabolism, PGC-1α and ERRα resulting in upregulation of nuclear-encoded mitochondrial genes to promote mitochondrial activity in lipid metabolism. Accordingly, levels of mitochondrial uncoupling proteins are upregulated in FLCN KO white adipose tissue. As a consequence, the FLCN KO mice are more resistant to cold exposure associated with increased browning of inguinal fat depots. These results show new role for FLCN in metabolic control and identify a novel molecular pathway involved in browning of fat.

Notes:

T5 – FLCN and AMPK confer resistance to hyperosmotic stress via remodeling of glycogen stores

Elite Possik[1,2], Andrew Ajisebutu[1,2], Sanaz Manteghi[1,2], Mathieu Flamand[1], Barry Coull[3], Kathrin Schmeisser[1,2], Tarika Vijayaraghavan[1,2], Thomas Duchaine[1,2], Maurice van Steensel[3], David H. Hall[4] and Arnim Pause[1,2]

[1]Goodman Cancer Research Center, McGill University, Montréal, Québec, H3A 1A3, Canada.
[2]Department of Biochemistry, McGill University, Montréal, Québec, H3G 1Y6, Canada.
[3]College of Life Sciences, University of Dundee, Dundee, DD1 4HN, UK.
[4]Department of Neuroscience, Albert Einstein College of Medicine, NY10461, New York, USA.

POSTER:3

Abstract:
Here we identify a novel osmotic stress resistance pathway in *Caenorhabditis elegans (C. elegans),* which is dependent on the metabolic master regulator 5'-AMP-activated protein kinase (AMPK) and its negative regulator Folliculin (FLCN). *flcn-1* mutants exhibit increased resistance to hyperosmotic stress via constitutive AMPK-dependent accumulation of glycogen reserves. Upon hyperosmotic stress exposure, glycogen stores are rapidly degraded, leading to a significant accumulation of the organic osmolyte glycerol through transcriptional upregulation of glycerol-3-phosphate dehydrogenase enzymes (gpdh). Importantly, the hyperosmotic stress resistance in *flcn-1* mutant and wild type animals is strongly suppressed by loss of AMPK, glycogen synthase, glycogen phosphorylase, or simultaneous loss of *gpdh* enzymes. Importantly, we show that glycogen accumulates in kidneys from mice lacking FLCN and in renal tumors from a BHD patient. Our findings suggest a dual role for glycogen, acting as a reservoir for energy supply and osmolyte production, and both processes might be supporting tumorigenesis.

Notes:

T6 – Tumor suppressor folliculin regulates mTORC1 through primary cilia

Xuwen Zhao, Mingming Zhong, and Yu Jiang
Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA.

Abstract:
Folliculin (FLCN) is the tumor suppressor associated with the Birt–Hogg–Dubé (BHD) syndrome that predisposes patients to incident of hamartomas and cysts in multiple organs. Its inactivation causes deregulation in the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway. However, the underlying mechanism is poorly defined. In this study, we show that FLCN is a ciliary protein that functions through primary cilia to regulate mTORC1. In response to flow stress, FLCN interacts with LKB1 and recruits the kinase to primary cilia for activation of AMPK resided at the basal body, which causes mTORC1 downregulation. In cells depleted of FLCN, LKB1 fails to accumulate in primary cilia and AMPK at the basal body remains inactive, thus nullifying the inhibitory effect of flow stress on mTORC1 activity. Our results demonstrate that FLCN is part of a flow sensory mechanism that regulates mTORC1 through primary cilia.

Notes:

T7 – Role of the folliculin interacting protein Plakophilin 4/p0071 in cell adhesion and metabolism

Damir Khabibullin[1], Carmen Priolo [1], John Asara [2], Elizabeth Henske[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA,
[2]Beth Israel Deaconess Medical

POSTER: 4

Abstract:
The armadillo-repeat containing protein plakophilin 4 (PKP4, p0071) physically interacts with folliculin (FLCN). Low p0071 expression is specifically associated with chromophobe RCC (Walter, Histopathology 2009), which also occur in BHD. The role of p0071 in tumorigenesis is not well understood. We reported that downregulation of either p0071 or FLCN enhances cell-cell adhesion in multiple cellular lineages (Medvetz, PLoS One 2012; Khabibullin Physiol Rep 2014). In unpublished data, we found that p0071 downregulation leads to significant transcriptional (Lincscloud database) and metabolomic changes in HeLa cells, including an increase in intracellular lactate and changes in metabolites of the TCA cycle. Oxygen consumption rate (Seahorse analyzer) was also impacted by inhibition of p0071. Transcriptionally, downregulation of p0071 induced a signature similar to regulators of mRNA processing and transcription. These data suggest that p0071 is a novel regulator of cell metabolism, adhesion, and transcription with relevance to the pathogenesis of BHD and chromophobe RCC.

Notes:

T8 – Xp11.2 translocation RCC mouse model

Masaya Baba[1,2], Ying Huang[1], Hisashi Hasumi[1,3], Mitsuko Furuya[1,4], Yukiko Hasumi[1], Masahiro Yao[1,3], Laura S. Schmidt[1,5], W. Marston Linehan[1]

[1]Urologic Oncology Branch, NCI/NIH,USA, [2]International Research Center for Medical Sciences, Kumamoto University, Japan, [3]Department of Urology, Yokohama City University, Japan, [4]Department of Molecular Pathology, Yokohama City University, Japan, [5]Basic Science Program, Leidos Biomedical Research, Inc., Frederick National Lab, USA

POSTER: 5

Abstract:
TFE3 is a basic helix-loop-helix leucine zipper (bHLH-Zip) transcription factor, whose nuclear translocation and transcriptional activity is regulated by FLCN. Since TFE3 is known to form a variety of chimeric genes which retain their bHLH-Zip structures including PRCC-TFE3, PSF-TFE3, and NONO-TFE3, which are found in Xp11.2 translocation RCC, aberrant transcriptional activity of TFE3 most likely plays an important role in BHD RCC development. Although these chimeric TFE3 genes seem to work as oncogenes, their precise molecular function remains to be clarified. To address this point, we have generated an Xp11.2 translocation RCC mouse model, in which a floxed Neomycin cassette followed by a PRCC-TFE3 cDNA are inserted in the Rosa26 locus. By crossing these mice with cadherin 16-Cre transgenic mice, we can induce kidney specific PRCC-TFE3 expression resulting in RCC development. This model will be useful to clarify the molecular mechanisms of both Xp11.2 translocation RCC and BHD-associated RCC development.
Funded in part by FNLCR Contract HHSN261200800001E to LSS.

Notes:

T9 – Metabolic Regulation of the Kidney Cancer Epigenome

Sunil Sudashan

Department of Urology, The University of Alabama at Birmingham, 1720 2nd Ave South, Birmingham, AL 35294

Notes:

T10 – Functional analysis of PBRM1 in ccRCC

Lili Liao[1], Wei Jiang [1], Essel Dulamir [2], Theodore Parsons [1], Kathik Devarajan [2], Qiong Wang [1], Raymond O'Neill [1] Haifeng Yang[1]

Thomas Jefferson University[1].; Fox Chase Cancer Center[2],

Abstract:
Recently inactivating mutations in polybromo-1 (PBRM1) were iscovered in about 40% of sporadic ccRCC. Mulitple lines of evidence suggest that it is another essential tumor suppressor gene like VHL. As the second most mutated gene in ccRCC, it is not known how the tumor-derived mutations disrupt its tumor suppressor functions and how to curb tumor growth of PBRM1-deficient cancer cells. We found that the vast majority of tumor-derived mutations disrupted PBRM1's ability to bind to the rest of PBAF chromatin-remodeling complex. We identified a 25aa sequence on PBRM1 that was necessary and sufficient for PBAF binding, and identified lysine acetylation on PBRM1 as critical PBAF binding signal. In an IHC study of ccRCC TMA derived from Fox Chase Cancer Center, we found that the loss of PBRM1 associated with worse prognosis to the patients while the losses of BRM or BRG1, the enzymatic subunits of PBAF, were associated with better prognosis. Consistent with BRM loss having protective effect, BRM suppression in ccRCC cancer cells significantly retarded accelerated tumor growth elicited by PBRM1 loss. Thus BRM might be a critical drug target for PBRM1-deficient ccRCC cancer cells.

Notes:

T11 – Germline FLCN mutation spectrum and phenotype analysis of 226 families with Birt-Hogg-Dube´syndrome: the NCI experience

Laura S. Schmidt, Lambros Stamatakis, Lindsay A. Middelton, James Peterson, Cathy D.Vocke, Catherine A. Stolle, Edward W. Cowen, Maria J. Merino, Berton Zbar, Adam R. Metwalli, W. Marston Linehan

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Abstract:
Germline FLCN mutations are responsible for Birt-Hogg-Dubé syndrome(BHD) characterized by fibrofolliculomas, lung cysts, spontaneous pneumothoraces and renal neoplasia. To date 226 families clinically diagnosed with BHD have been evaluated at the National Cancer Institute. FLCN mutations were confirmed in 194 of 203 genetically evaluated BHD families (95.6%). Seventy-one unique mutations including frameshift (63.6%), nonsense (9.7%), missense (2.4%), amino acid deletion (2.4%) and splice site (11.6%) mutations, and 11 (5.4%) intragenic duplications/deletions were identified. Three FLCN mutations, including the exon 11 c.1285dup/delC mutation, each occurred in >5% of BHD families. Fibrofolliculomas and lung cysts were the most penetrant clinical manifestations(>80%). Renal manifestations, most frequently hybrid oncocytic tumors, developed in half of all BHD families. Although no clear genotype-phenotype correlations were observed, no renal neoplasia was reported in 3 families harboring large gene deletions encompassing the putative exon1 promoter region. This study contributes 16 novel mutations to the reported FLCN mutation spectrum.

Funded in part by NCI Contract HHSN261200800001E.

Notes:

T12 – Current and Emerging Techniques for Detection of FLCN Mutations

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National Cancer Institute[1], Maryland, MD, Dermatology, Department of Veterans Affairs USA [2]; GeneDx, BioReference Laboratories, Inc., Gaithersburg, MD Maryland, USA [3]

POSTER: 6

Abstract:
Birt-Hogg-Dubé syndrome (BHDS) (MIM 135150) is an autosomal dominant predisposition to the development of follicular hamartomas (fibrofolliculomas), lung cysts, spontaneous pneumothorax, and kidney neoplasms. Germline mutations in FLCN are associated with the susceptibility for BHDS. To date 162 FLCN germline mutations have been reported in the literature. Objective: To characterize methods for FLCN mutation detection. Methods: Initial screening was conducted with direct bidirectional DNA sequencing of the coding regions and splice sites of exons 4-14 of FLCN. If no mutation was identified by sequencing analysis, large intragenic insertion and deletion mutations were screened by RQ-PCR and targeted arrays comparative genomic hybridization with exon-level resolution. Results: The FLCN mutation detection rate by direct sequencing was 88 percent. We detected 87 unique novel FLCN germline mutations: 40 deletions, 15 insertions, 14 missense,12 nonsense, 4 splice site and 2 deletion/insertion. We identified one whole gene FLCN deletion and 12 unique large FLCN intragenic deletions.. Including this report, to date there are 249 unique FLCN mutations identified. Exome sequencing results of BHDS families will be discussed. A worldwide review of published FLCN mutations will be discussed, A combination of methods are efficacious in detecting FLCN mutations.

Notes:

T13 – LONGINg to broaDENN our understanding of the Folliculin/Fnip complex through its yeast orthologue Lst7/Lst4

Angela Pacitto[1], David B. Ascher[1], Louise H Wong[2], Beata K Blaszczyk[1], Ravi K Nookala[1], Nianshu Zhang[1], Svetlana Dokudovskaya[3], Timothy P Levine[2] and Tom L Blundell[1]

Department of Biochemistry; University of Cambridge; Cambridge, UK [1] , Department of Cell Biology; UCL Institute of Ophthalmology; London, UK [2], CNRS UMR 8126; Université Paris-Sud 11; Institut Gustave Roussy; Villejuif, France [3]

POSTER: 7

Abstract:
The FLCN gene, which encodes the protein folliculin, is mutated in Birt-Hogg-Dubé syndrome. Lst7 is the known Saccharomyces cerevisiae orthologue of folliculin. We present here experimental evidence that Lst4 is the yeast folliculin interacting partner (Fnip1/2) orthologue and exists in complex with Lst7. In yeast, the Lst7/Lst4 complex dynamically associates with the vacuolar membrane under nutrient stress conditions. Further studies of the Lst7/Lst4 complex from Kluyveromyces lactis showed that Lst7/Lst4 exists as a 1:1 heterodimer and identified important interacting regions. Additionally, we determined the crystal structure of the N-terminal region of Lst4 from K. lactis to 2.14 Å resolution and show it contains a longin domain. Folliculin and Fnip1/2 have been proposed to be members of the DENN-family of proteins, and the longin domain is the first domain of this protein fold. This work expands our understanding of the structural organisation of the Flcn/Fnip complex and its role in disease.

Notes:

T14 – Zinc Metallochaperone ZMC1 demonstrates a new drug mechanism for p53 reactivation and personalized chemotherapy

Adam R. Blanden[1], Xin Yu[2], Isabel Utschig[1], Darren R. Carpizo2, Stewart N. Loh[1]

[1]Biochemistry and Molecular Biology, Upstate Medical University, Syracuse NY and [2]Rutgers Cancer Institute of New Jersey, New Brunswick, NY

POSTER :8

Abstract:
p53 is a Zn2+-dependent tumor suppressor found mutated in ~50% of cancers. Data from the WHO demonstrate that ~9% of kidney cancers and ~25% of urological cancers harbor mutations in p53. One of the most common ways p53 becomes inactivated is by mutational disruption of binding interactions with Zn2+, causing the metal to be released and DNA binding activity to be lost. We describe a new class of experimental cancer drugs that reactivate mutant p53 by restoring proper zinc binding to several zinc-impaired mutants. Our primary lead compound, ZMC1, reactivates p53 by delivering Zn2+ across the plasma membrane and buffering intracellular Zn2+ to a level that the compromised binding site can bind, thus restoring p53's structure and function. ZMC1 shows excellent selectivity for mutant cancer cells in culture and a wide therapeutic index in vivo. We conservatively estimate the pool of patients that can potentially be treated by zinc metallochaperones to be ~70,000 cases per year in the U.S.

Notes:

T15 – c-Abl Mediated Tyrosine Phosphorylation of Aha1 Activates its Co-chaperone Function in Renal Cell Carcinoma

Diana M. Dunn[1,2,3], Mark R. Woodford[1,3], Andrew W. Truman[4,5], Sandra M. Jensen[6], Jacqualyn Schulman[1,3], Tiffany Caza[7], Taylor C. Remillard[1,3], David Loiselle[8], Donald Wolfgeher[5], Brian S. J. Blagg[9], Lucas Franco[9], Timothy A. Haystead[8], Soumya Daturpalli[10], Matthias P. Mayer[10], Jane B. Trepel[11], Rhodri M. L. Morgan[12], Chrisostomos Prodromou[12], Stephen J. Kron[5], Barry Panaretou[13], William G. Stetler-Stevenson[6], Steve Landas[7], Len Neckers[14], Gennady Bratslavsky[1,3], Dimitra Bourboulia[1,2,3], Mehdi Mollapour[1,2,3]

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POSTER: 9

Abstract:
The ability of Heat Shock Protein 90 (Hsp90) to hydrolyze ATP is essential for its chaperone function. The co-chaperone Aha1 stimulates Hsp90 ATPase activity tailoring the chaperone function to specific "client" proteins. The intracellular signaling mechanisms directly regulating Aha1 association with Hsp90 remain unknown. Here we show that c-Abl kinase phosphorylates Y223 in human Aha1 (hAha1) promoting its interaction with Hsp90. This, consequently, results in an increased Hsp90 ATPase activity, enhances Hsp90 interaction with kinase clients, and compromises the chaperoning of non-kinase clients such as glucocorticoid receptor and CFTR. Suggesting a regulatory paradigm, we also find that Y223 phosphorylation leads to ubiquitination and degradation of hAha1 in the proteasome. Finally pharmacologic inhibition of c-Abl prevents hAha1 interaction with Hsp90 thereby, hypersensitizing renal cell carcinoma (RCC) to Hsp90 inhibitors both *in vitro a*nd *ex vivo.*

Notes:

T16 – The FNIP co-chaperones inhibit Hsp90 molecular chaperone ATPase activity

Mark R. Woodford[1,2,3], Diana Dunn[1,2,3], Adam R. Blanden[2,3], Taylor C Remillard[1,3], Sarina Bottone[1,2,3], Rhodri M. L. Morgan[4], Steve Landas[3,5], Chrisostomos Prodromou[6], Laura S. Schmidt[7,8], Stewart N. Loh[2,3], Dimitra Bourboulia[1,2,3], W. Marston Linehan[8], Gennady Bratslavsky[1,3] and Mehdi Mollapour[1,2,3]

[1] Department of Urology, [2] Department of Biochemistry and Molecular Biology,
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Poster 10

Abstract:
Heat shock protein-90 (Hsp90) is an essential molecular chaperone in eukaryotes and it is involved in maintaining the stability and activity of numerous proteins, also known as clients, involved in signaling pathways. Hsp90 ATPase activity is essential for its chaperone function and it is tightly regulated by co-chaperones. Here, we show that the tumor suppressor Folliculin (FLCN) is an Hsp90 client protein and its binding partners FNIP1/FNIP2 function as co-chaperones. FNIPs also decelerate the chaperone cycle, therefore facilitating FLCN interaction with Hsp90, consequently ensuring FLCN stability. We also show that FNIPs compete with the activating co-chaperone Aha1 for binding to Hsp90, therefore providing a reciprocal regulatory mechanism for chaperoning of kinase and non-kinase clients. Finally, we have shown that over-expression of FNIPs enhance Hsp90 binding to its inhibitors, suggesting that FNIPs expression level can potentially serve as a predictive indicator of tumors response to Hsp90 inhibitors.

Notes:

Loss of respiratory chain complex I activity in renal oncocytomas without FLCN mutation

Martin Lang[1], Cathy D. Vocke[1], Maria J. Merino[2], Laura S. Schmidt[1], W. Marston Linehan[1]

[1]Urologic Oncology Branch and [2]Laboratory of Pathology, Center for Cancer Research, National Cancer Institute,

POSTER: 14

Abstract:
Renal oncocytomas (RO) are benign tumors characterized by a prominent accumulation of defective mitochondria. They can present as part of the kidney phenotype in Birt-Hogg-Dubé (BHD) syndrome, as sporadic unifocal tumors, or as bilateral and multifocal (BMF) lesions. Sporadic RO have been shown to frequently carry pathogenic mutations in the mitochondrial genome (mtDNA). We sequenced the entire mtDNA in a total of 55 samples including BHD-associated RO and BMF oncocytomas. While BHD tumors did not show pathogenic mtDNA mutations, all BMF oncocytomas carried disruptive mtDNA mutations affecting genes assembled into complex I of the respiratory chain. Kidneys from each BMF patient displayed oncocytosis and carried the same mutation in all tumors, suggesting that the mutations arose during early embryonic kidney development. Immunohistochemistry as well as in vitro and in situ enzyme activity assays confirmed the specific loss of NADH:ubiquinone oxidoreductase enzyme activity in BMF oncocytomas, but not in BHD tumors.

Notes:

T17 – Cancer in Our Genes International Patient Databank (CGIP)

Ilene Sussman and Suzanne Nylander

VHL Alliance - 2001 Beacon St #208, Boston, MA 02135, USA

Abstract:
In March 2014, the VHL Alliance (VHLA) in collaboration with the National Organization of Rare Disease (NORD) launched successfully an online research study, Cancer in Our Genes International Patient Databank (CGIP, https://databank.vhl.org). CGIP, now outside of its pilot phase and into a stable platform, is designed as a longitudinal registry and data collection tool to measure the impact of modifiable lifestyle factors on tumor development of new VHL lesions and other related rare diseases including Hereditary Leiomyomatosis and Renal Cell Cancer, Birt-Hogg-Dubé, and Succinate Dehydrogenase Complex Subunit B).

CGIP is the first of its kind comprehensive patient-entered registry and already represents the largest study for VHL. This FDA-acknowledged databank has already shown utility and value by providing novel information, including a new possible marker of disease. With 400 participants already accrued, CGIP has demonstrating the feasibility of collecting data from this patient population.

A progress update will be presented.

Notes:

T18 – Oncogenetic testing, diagnosis and follow-up in Birt-Hogg-Dubé syndrome, development of a guideline in Belgium.

Jo Robays (KCE), Sabine Stordeur (KCE), Frank Hulstaert (KCE), Jean-François Baurain (Cliniques universitaires St-Luc), Teofila Caplanusi (UZ Brussel), Kathleen Claes (UZ Gent), Eric Legius (UZ Leuven), Sylvie Rottey (UZ Gent), Dirk Schrijvers (ZNA), Urielle Ullman (Institut de Pathologie, Gosselies), Tom Van Maerken (UZ Gent), Bruce Poppe (UZ Gent)
1. KCE - Federaal Kenniscentrum - Centre fédéral d'expertise

Abstract:
This clinical practice guideline is based on the collaborative efforts of the Belgian Health Care Knowledge Centre (KCE), the College of Human Genetics and the College of Oncology, using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Results:
We only found case reports and descriptions of data from registries of limited size with clinical descriptions and inventories of different mutations found on BHD patients, who were included from various sources and using variable inclusion criteria, clinical implications are therefore unclear. We did not find studies on follow-up. Therefore, recommendations are largely consensus-based. KCE recommendations are based on the recommendations of the BHD consortium. The recommendations were slightly modified by the GDG at points where the GDG considered that the recommendations were not sufficiently clear, based on their expert opinion.

- Referral to a specialist genetics clinic for counseling and testing should be considered based on family or personal history, whether the individual is affected or not.
- If possible, genetic testing for a family should usually start with the testing of an affected individual (mutation searching/screening) to try to identify a mutation in the appropriate gene.
- Patients should be considered as a case of Birt-Hogg-Dubé syndrome if they fulfill one major or two minor criteria for diagnosis:

  Major criteria
  - At least five fibrofolliculomas or trichodiscomas, at least one histologically confirmed, of adult onset
  - Pathogenic FLCN germline mutation

  Minor criteria
  - Multiple lung cysts: bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
  - Renal cancer: early onset (<50 years) or multifocal or bilateral renal cancer, or renal cancer of mixed chromophobe and oncocytic histology
  - A first-degree relative with BHD

- Following patients should be referred for genetic testing and counseling:
    - o Patients fulfilling the criteria for Birt-Hogg-Dubé syndrome mentioned above
    - o Multifocal or bilateral renal cancer
    - o Renal cancer of mixed chromophobe and oncocytic histology
    - o Renal cancer onset below 40 with oncocytic histology
    - o Patients with unexplained cystic lung disease, and if the lung cysts are bilateral and basally located
    - o Patients who have familial cystic lung disease, familial pneumothorax, familial renal cancer, or any combination of spontaneous pneumothorax and kidney cancer in an individual or family
    - o A first-degree relative with BHD.

Early detection of at-risk individuals affects medical management. However, in the absence of an increased risk of developing childhood malignancy, it is recommended to delay genetic testing in at-risk individuals until they reach age 18 years and are able to make informed decisions regarding genetic testing. For patients with confirmed BHD syndrome:

- Consider a yearly ultrasound or MRI scan of the kidney starting at age 20 to 25 years.
- Consider a thoracic high resolution CT scan before surgery that requires general anaesthesia.
- Discourage scuba diving.

Notes:

T19 – A Clinicopathological Study of 264 Individuals in 102 Japanese BHD Families

Mitsuko Furuya[1], Reiko Tanaka[2], Masahiro Yao[3], Hisashi Hasumi[3], Naoto Kuroda[4], Yoji Nagashima[5], Yasuhiro Iribe[1] and Yukio Nakatani[6]

Departments of Molecular Pathology[1] and Urology[3], Yokohama City University, Yokohama Japan. Medical Mycology Research Center[2], Chiba University, Chiba, Japan
Department of Diagnostic Pathology[4], Kochi Red-cross Hospital, Kochi, Japan
Department of Surgical Pathology[5], Tokyo Women's Medical University, Tokyo, Japan.
Department of Diagnostic Pathology[6], Chiba University Graduate School of Medicine, Chiba, Japan

POSTER: 11

Abstract:
We investigated clinicopathological features of 264 individuals from 102 Japanese Birt-Hogg-Dubé syndrome (BHD) families. Genetic testing revealed 25 different mutation patterns including several unreported mutations. Among 264 individuals who had BHD-associated symptoms, 53 (20.0%) had renal cell carcinomas (RCCs), and 24 patients (45.3%) with RCCs belonged to the families with cytosine duplication (c.1285dupC) in the C8 tract of exon 11. The most frequent histological types were hybrid oncocytic/chromophobe tumor (HOCT) (41.5%) and chromophobe RCC (37.7%). We performed copy number variation analysis in 10 tumors. Most of chromophobe RCCs and HOCTs showed balanced genomic profiles. There were copious numbers of uniparental disomy (UPD). The common UPD regions were chromosomes 8q11, 16q11, Xp22-21, Xp11, Xq11, Xq13 and Xq23. Collective data supported a genetic distinction between RCCs in BHD and sporadic histological counterparts. Common UPD in chromophobe RCCs and HOCTs indicated that these 2 types were relatively similar rather than distinctively different in genetic events.

Notes:

T20 – Cost-Effectiveness of HRCT Screening for Birt-Hogg-Dubé syndrome in Patients Presenting with Spontaneous Pneumothorax

Nishant Gupta[1], Dale Langenderfer[2], Francis X. McCormack[1], Daniel P. Schauer[3], and Mark H. Eckman[3]

[1] Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine University of Cincinnati, Cincinnati, OH, [2] Department of Environmental Heath, University of Cincinnati, Cincinnati, OH, [3] Division of General Internal Medicine, Department of Internal Medicine, University of Cincinnati, Cincinnati, OH

Abstract:
Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant tumor suppressor syndrome associated with renal neoplasms, pulmonary cysts and recurrent pneumothorax. The diagnosis of BHD is often delayed, often occurring after the second pneumothorax. The objective of our study was to evaluate the cost-effectiveness of high-resolution computed tomography (HRCT) of chest to facilitate early diagnosis and intervention.

Methods:
We constructed a Markov state-transition model to assess the cost-effectiveness of HRCT screening for spontaneous pneumothorax patients to facilitate early identification and pleurodesis for BHD. Baseline data for prevalence of BHD, and rates of recurrent pneumothoraces were derived from the literature. Costs were extracted from 2014 Medicare data. The strategy of HRCT screening followed by pleurodesis in patients with BHD was compared to no HRCT screening.

Results:
The prevalence of BHD in this patient population varies between 5-10%. In our base case analysis, screening for BHD by HRCT was less costly and more effective than not screening. HRCT screening remained cost-effective for BHD prevalence as low as 0.72%.

Conclusions:
Screening for BHD with HRCT in patients presenting with spontaneous pneumothorax is cost-effective.

Notes:

T21 – Pulmonary manifestations in Birt-Hogg-Dubé syndrome; An overview of results in the VU University Medical Center.

Johannesma PC[1], Houweling AC[2], van Beek I2, Paul MA[3], van Waesberghe JHTM[4], Reinhard R[4], Starink ThM[5], Menko FH[6], van Moorselaar RJA[7], Postmus PE[8]

Department of Pulmonary Diseases[1],Clinical Genetics2, Thoracic Surgery[3], Radiology[4], Urology, VU University Medical Center, Amsterdam, The Netherlands[7].
Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands[5]
Family Cancer Clinic, The Netherlands Cancer Institute, Amsterdam, The Netherlands[6].
Department of Molecular and Clinical Cancer Medicine, Clatterbridge Cancer Centre, Liverpool Heart & Chest Hospital, University of Liverpool, Liverpool, United Kingdom [8].

POSTER: 12

Abstract:
PSP remains a significant problem, especially in those with a pathogenic FLCN mutation (7.5%-10% of all PSP). The characteristic pulmonary cysts are not visible on standard X-ray, and may therefore be missed in the standard diagnostic work up for SP cases. On thoracic CT >90% of BHD patients have one or more lung cysts, mainly in the lower parts of the lung; BHD patients had significantly more lung cysts ($p<0.001$), differed significantly in size (<1cm and >2cm, ($p<0.001$)), distributed significantly more often below the level of the main carina ($p<0.001$), and distributed significantly more diffuse in the lung ($p<0.001$) compared to PSP patients without a pathogenic FLCN mutation. The number of lung cysts in BHD patients with a history of (recurrent) pneumothorax is significantly higher ($p<0.008$) compared to that in BHD patients without a history of pneumothorax. The size of lung cysts is not a benchmark for occurrence or recurrence rate of SP in BHD patients. We found a significant higher recurrence rate among BHD patients with SP after conservative treatment compared to invasive treatment. In our opinion treatment should aim at completely obliterating the pleural cavity, for instance through VATS including total pleurectomy and pleurodesis. Based on these results, we conclude that current guidelines are not sufficient for the diagnosis and treatment of Birt-Hogg-Dubé patients who present with their first spontaneous pneumothorax. Including chest CT in guidelines for first time PSP improves detection of BHD. This leads to earlier detection of BHD associated RCC and more adequate treatment of SP with a lower recurrence rate.

Notes:

T22 – Renal imaging, follow-up and tumour characteristics in 164 patients with Birt-Hogg-Dubé syndrome.

Johannesma PC[1], van de Beek I2, Reinhard R[3] van der Wel JWT[1], Rozendaal L[4], Starink ThM[5], Waesberghe JHTM[3], Horenblas S[6], Postmus PE[7], Houweling AC[2], van Moorselaar RJ[8].

Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, the Netherlands[1], Department of Clinical Genetics, VU University Medical Center, Amsterdam, the Netherlands[2] Department of Radiology, VU University Medical Center, Amsterdam, the Netherlands[3] Department of Pathology, VU University Medical Center, Amsterdam, the Netherlands[4] Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands[5] Department of Urologic Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands[6] Department of Molecular and Clinical Cancer Medicine, Clatterbridge Cancer Centre, Liverpool Heart& Chest Hospital, University of Liverpool, Liverpool, United Kingdom[7]. Department of Urology, VU University Medical Center, Amsterdam, the Netherlands[8]

POSTER: 13

Abstract:
Renal cell cancer (RCC) is part of the Birt-Hogg-Dubé syndrome (BHD), an autosomal dominant inherited disorder caused by mutations in the FLCN gene. Renal surveillance in BHD is warranted but the optimal imaging method and interval remain to be defined.

Aim of the study:
To retrospectively evaluate the compliance to the current advised frequency of surveillance and the outcomes of this in patients diagnosed with BHD in two Dutch specialized centers.

Methods:
Informed consent was obtained from 164 out of 200 patients diagnosed with BHD since 2004. We collected all available renal imaging follow up data. In addition, we collected the medical records of 22 patients treated for RCC.

Results:
In 118/164 cases (72%) initial imaging consisted of both a renal MRI and ultrasound. Follow up in 135 cases (82%) consisted of annual renal ultrasound. The total follow-up period was calculated to be 485 patient years. Full compliance with the surveillance was recorded for 108/135 cases (80%). Sixteen patients were diagnosed with RCC at initial screening. Six of them were symptomatic, 10 were asymptomatic. At follow up, renal cell cancer was found in six patients without a renal tumour at initial screening and in one patient who was also diagnosed with RCC at initial screening. In total, 35 RCC were detected in these 22 patients. The number of tumours found per patient during the observation period was: 1 in 14 patients, 2 in 4 patients, 3 in 3 patients, 4 in 1 patient. In 5 of the 9 patients with multiple tumours these were bilateral. Both MRI and ultrasound were performed in 20/35 tumours. Four tumours were visible only on MRI, all four were <3cm.

Conclusions:
Our data indicate that compliance to advised screening for RCC is high and that ultrasound might be a sensitive and widely available imaging modality for detecting clinically relevant renal tumours in BHD patients. Follow up studies in BHD patient cohorts are required to further determine the optimal screening method and interval in BHD patients.

Notes:

T23 – Surgical and functional outcomes of patients with multifocal RCC

Adam Metwalli

Urologic Oncology Branch, National Cancer Institute, National Institutes of Health
CRC 2W-5740, 9000 Rockville Pike Bethesda MD 20892

Notes:

T24 – What is new in non-clear RCC.

Brian Shuch

Yale Cancer Center, Yale School of Medicine, New Haven, 35 Park Street, Ste 4th Floor, New Haven, CT 06511

Notes:

T 25 – Role of a surgeon in management of metastatic RCC

Gennady Bratslavsky[1,2,3]

[1] Department of Urology, [2] Department of Biochemistry and Molecular Biology,
[3] Cancer Research Institute[5], Department of Pathology, SUNY Upstate Medical University, 750 E. Adams St., Syracuse, NY 13210, USA

Notes:

T26 – Bolstering Anti-Tumor Immunity to Kidney Cancer with Current Clinical Approaches

Jason Muhitch

Department of Urology, Roswell Park Cancer Institute, Buffalo, NY

Abstract:
Metastatic Renal Cell Carcinoma (RCC) is a lethal disease and the only curative approaches involve anti-tumor immune responses. For anti-tumor immunotherapy to be effective, activated tumor-specific CD8 T cells must detect tumor-associated antigens (TAA) presented on tumor cells to initiate contact-dependent cell lysis. Radiation has been shown to induce TAA expression in a variety of malignancies and is generally well-tolerated. However, RCC has been historically classified as a radiation resistant tumor type. This presentation will present recent findings in a first-of-its-kind clinical trial that treated RCC patients with high-dose radiation and later evaluated TAA expression in surgically resected patient RCC lesions. Additionally we will discuss how immunotherapy via dendritic cell vaccination can promote tumor-specific T cell responses that, in a subset of RCC patients, can result in complete, durable responses.

Notes:

T27 – Systemic therapy for advanced and metastatic non-clear RCC

Namitha Chittoria

VA Medical Center Syracuse, Hematology and Oncology, 800 Irving Ave Ste 111-H
Syracuse, NY 13210

Notes:

T28 – Updates on the Classification of Renal Cell Carcinoma

Fang-Ming Deng
Department of Pathology, NYU School of Medicine, TH-432, 560 First Avenue, New York, NY 10016

Abstract:
Classification of renal tumors has been rapidly evolving in the last decade. Many new tumor entities have been discovered. This is a brief review of pathologic features of the new tumor types that did not exist in the 2004 classification and will be added to the 2016 classification. These include hybrid oncocytic chromophobe tumor, Tubulocystic renal cell carcinoma, Hereditary leiomyomatosis renal cell carcinoma syndrome-associated RCC, SDH deficient renal cell carcinoma and several other types.

Notes:

BHD Patient and Family member session Saturday morning

Lindsay Middelton, RN, CGC
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Abstract:
Due to the rarity of Birt Hogg Dube and Hereditary Leiomyomatosis and Renal Cell cancer, people affected by these conditions often have questions and concerns which cannot be answered by their local health care providers, and they do not know anyone else who has their condition to discuss their concerns. Patients and their family members will have an opportunity to ask general questions of BHD & HLRCC experts in an informal Q & A setting. A short presentation will be made about the ABC's of clinical trials- what are they about – what does the terminology mean? Moreover, people who have BHD or HLRCC will meet one another and discuss a variety of issues and concerns with a clinician with extensive clinical experience with these conditions.

Notes:

POSTERS

POSTER: 1 Adam Price (see abstract page 17)
VHL and FLCN kidney tumor suppressors are positive regulators of autophagic program targeting midbodies for lysosomal degradation.

POSTER: 2 Arnim Pause PhD (see abstract page 19)
FLCN Repression Induces Metabolic Reprogramming of White Adipose Tissue Through the AMPK/PGC-1α/ERRα Axis

POSTER:3 Arnim Pause (see abstract page 20)
FLCN and AMPK confer resistance to hyperosmotic stress via remodeling of glycogen stores

POSTER: 4 Damir Khabibullin PhD (see abstract page 22)
Role of the folliculin interacting protein Plakophilin 4/p0071 in cell adhesion and metabolism

POSTER: 5 Masaya Baba MD, PhD (see abstract page 23)
Xp11.2 translocation RCC mouse model

POSTER: 6 Jorge R. Toro (see abstract page 27)
Current and Emerging Techniques for Detection of FLCN Mutations

POSTER: 7 Angela Pacitto PhD (see abstract page 28)
LONGINg to broaDENN our understanding of the Folliculin/Fnip complex through its yeast orthologue Lst7/Lst4

POSTER :8 Adam R. Blanden (see abstract page 29)
Zinc Metallochaperone ZMC1 demonstrates a new drug mechanism for p53 reactivation and personalized chemotherapy

POSTER: 9 Diane Dunn (see abstract page 30)
c-Abl Mediated Tyrosine Phosphorylation of Aha1 Activates its Co-chaperone Function in Renal Cell Carcinoma

POSTER: 10 Mark Woodford (see abstract page 31)
The FNIP co-chaperones inhibit Hsp90 molecular chaperone ATPase activity

POSTER: 11 Mitsuko Furuya (see abstract page 36)
A Clinicopathological Study of 264 Individuals in 102 Japanese BHD Families

POSTER: 12 Paul C. Johannesma MD (see abstract page 38)
Pulmonary manifestations in Birt-Hogg-Dubé syndrome; An overview of results in the VU University Medical Center

POSTER: 13 Paul C. Johannesma MD (see abstract page 39)
Renal imaging, follow-up and tumour characteristics in 164 patients with Birt-Hogg-Dubé syndrome.

POSTER: 14 Martin Lang MD (see abstract page 32)
Loss of respiratory chain complex I activity in renal oncocytomas without FLCN mutation

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