Molecular background of renal cancer

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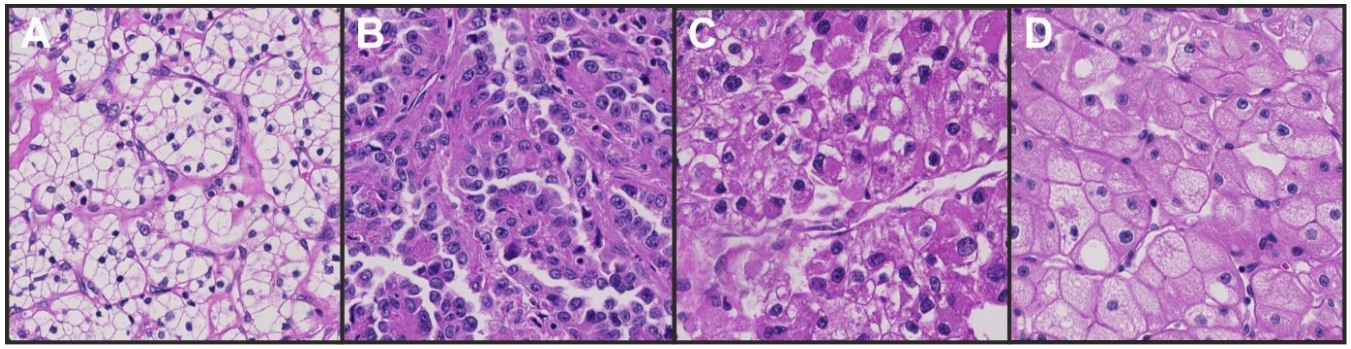
Department Pathology and Molecular Pathology
University Hospital Zurich

International Academy of Pathology, Hong Kong Division

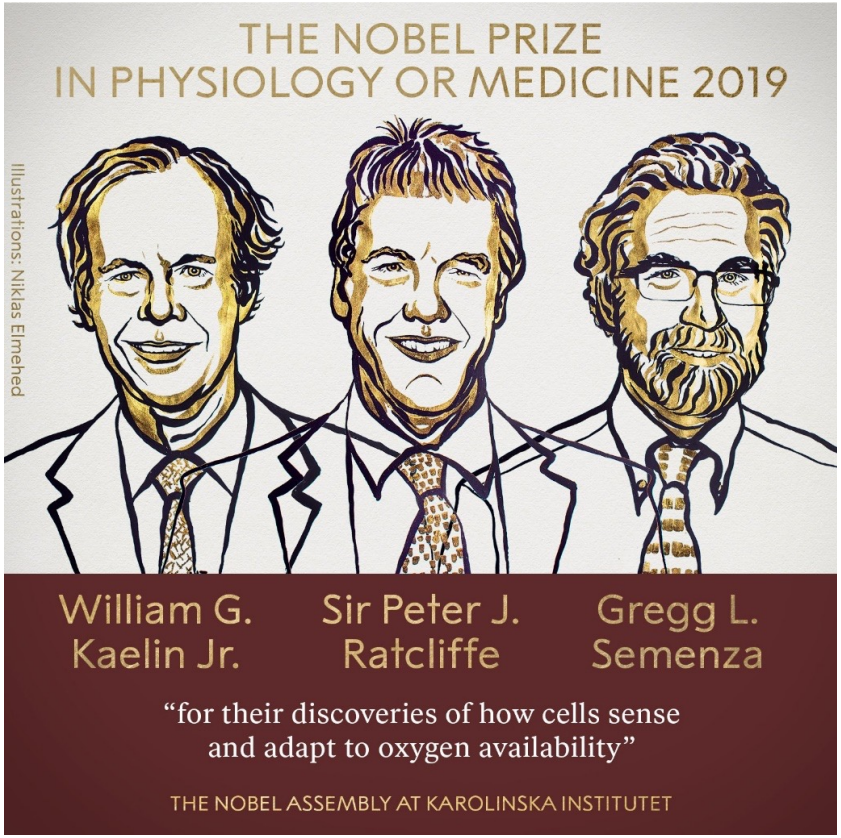
November, 10th 2024

Renal Cell Carcinoma (RCC) subtypes



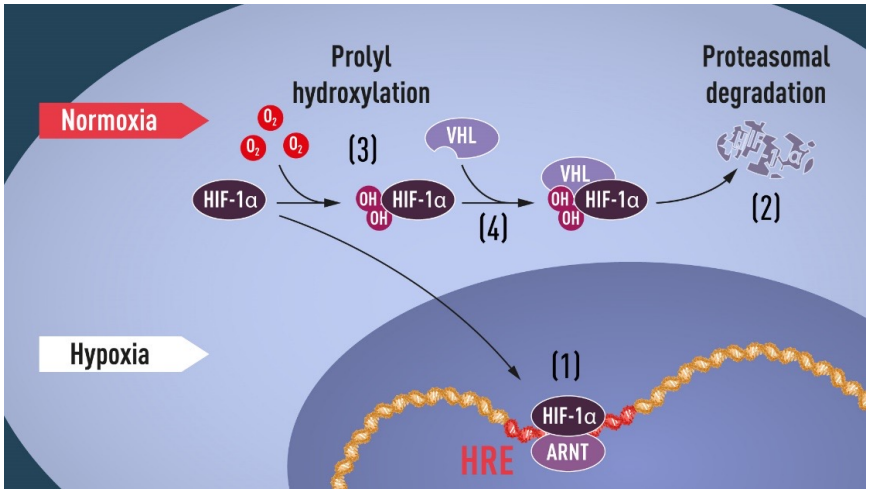
RCC subtype	clear cell	papillary type 1	papillary type 2	chromophobe
Incidence	75 %	15 %		5 %
Genes for familial types	*VHL*	*MET*	*FH*	*BHD (FLCN)*

How cells sense and adapt to oxygen availability



Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

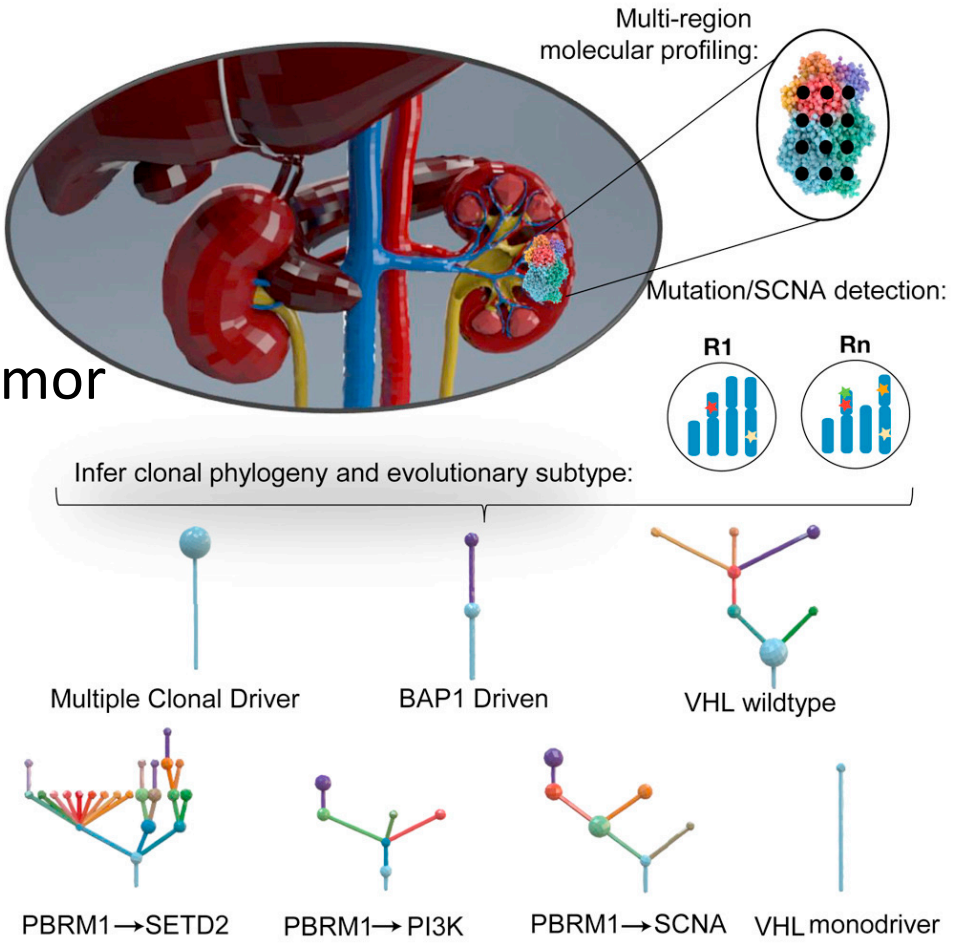
- At normal oxygen levels, HIF is targeted for proteasomal degradation by VHL.
- When oxygen levels are low, the amount of HIF-1alpha increases so that it can bind to and thus regulate genes expression.



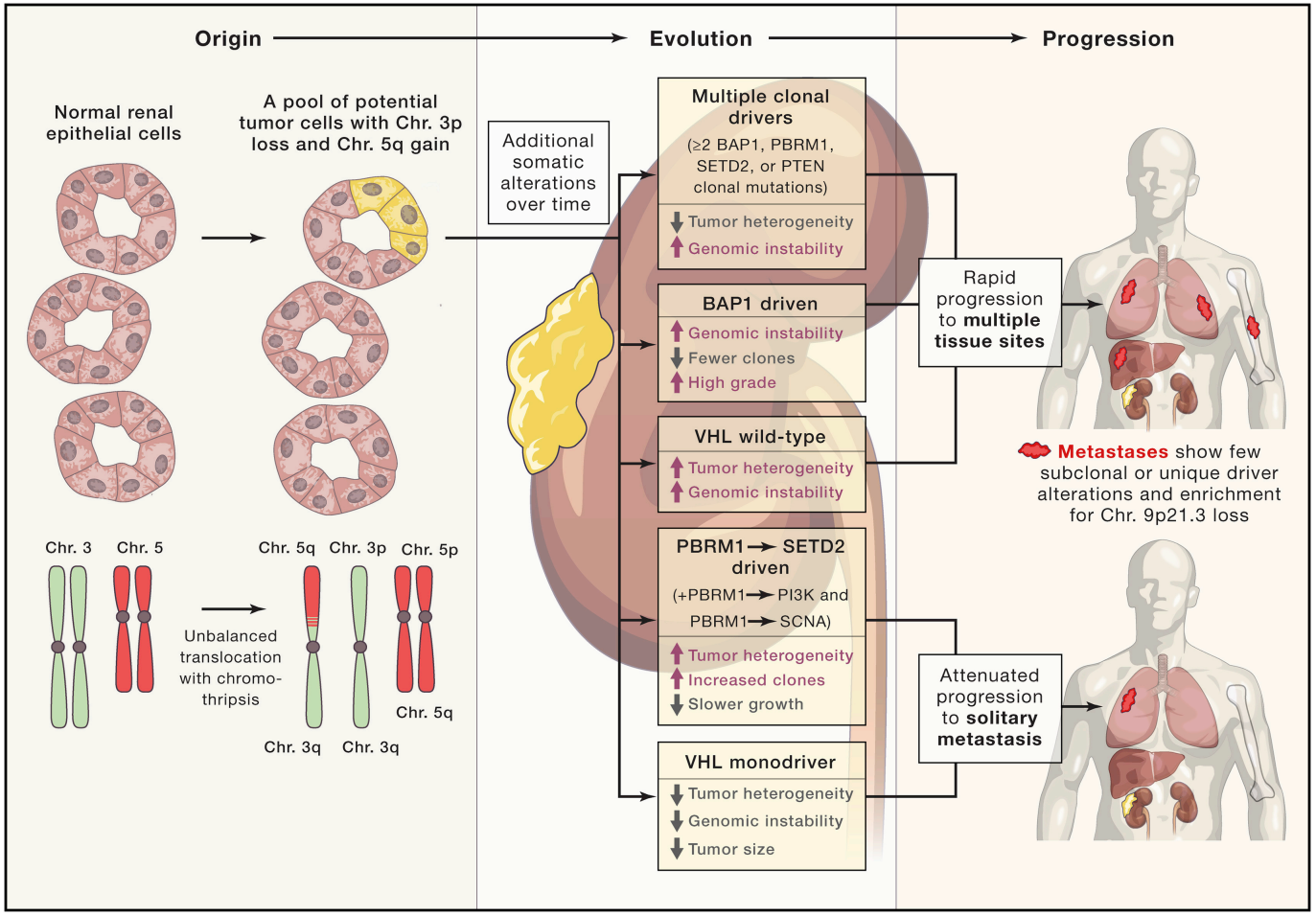
USZ Universitäts Spital Zürich

Samra Turajlic et al., 2018, Cell 173, 595–610
Deterministic Evolutionary Trajectories Influence Primary Tumor Growth: TRACERx Renal

- 101 patients
- prospective study
- up to 30 driver events per tumor
- subclonal diversification
- 7 evolutionary subtypes



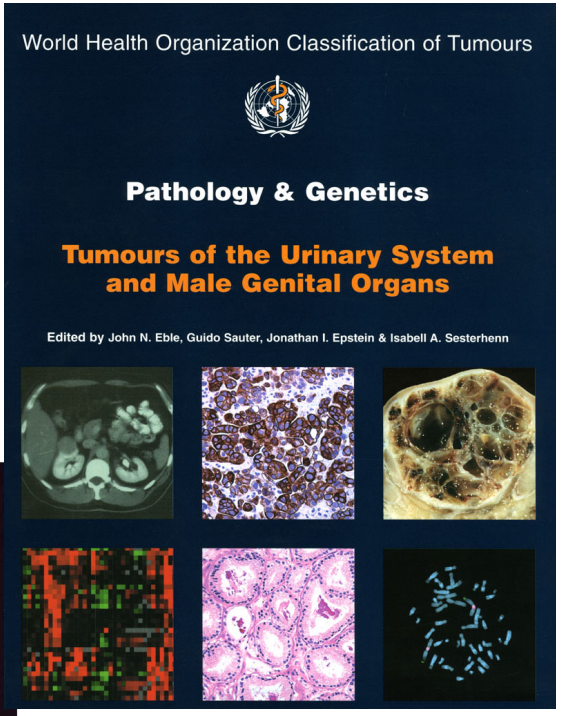
Ricketts, Linehan, Cell *173*, April 19, 2018: Multi-regional Sequencing Elucidates the Evolution of Clear Cell Renal Cell Carcinoma

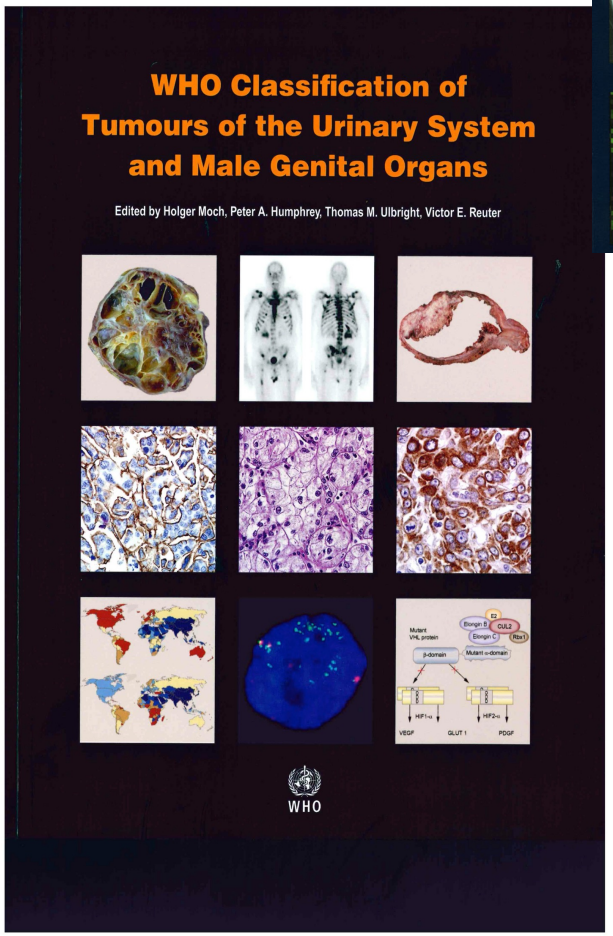


2004: chapter for familial RCC

2016: new entities of familial RCC

2022: chapter „Genetic tumour syndromes of urinary and male genital tract“





REVIEW ARTICLE

Hereditary Syndromes With Associated Renal Neoplasia: A Practical Guide to Histologic Recognition in Renal Tumor Resection Specimens

Christopher G. Przybycin, MD, Cristina Magi-Galluzzi, MD, PhD, and Jesse K. McKenney, MD

Adv Anat Pathol 2013;20:245–263

SPECIAL ARTICLE

Hereditary Renal Cell Carcinoma Syndromes

Clinical, Pathologic, and Genetic Features

Adebowale J. Adeniran, MD, Brian Shuch, MD,† and Peter A. Humphrey, MD, PhD**

Am J Surg Pathol 2015;39:e1–e18

Seminars in Diagnostic Pathology 35 (2018) 184–192

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Morphological clues to the appropriate recognition of hereditary renal neoplasms

Holger Moch[a,*], Riuko Ohashi[b,c], Jatin S. Gandhi[d], Mahul B. Amin[d,e]

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[b] *Histopathology Core Facility, Niigata University Faculty of Medicine, Niigata, Japan*
[c] *Division of Molecular and Diagnostic Pathology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*
[d] *Department of Pathology and Laboratory Medicine, University of Tennessee Health Sciences, Memphis, USA*
[e] *Department of Urology, University of Tennessee Health Sciences, Memphis, USA*

Seminars in Diagnostic Pathology 35 (2018)

Table 1
Hereditary Conditions and Associated renal neoplasms.

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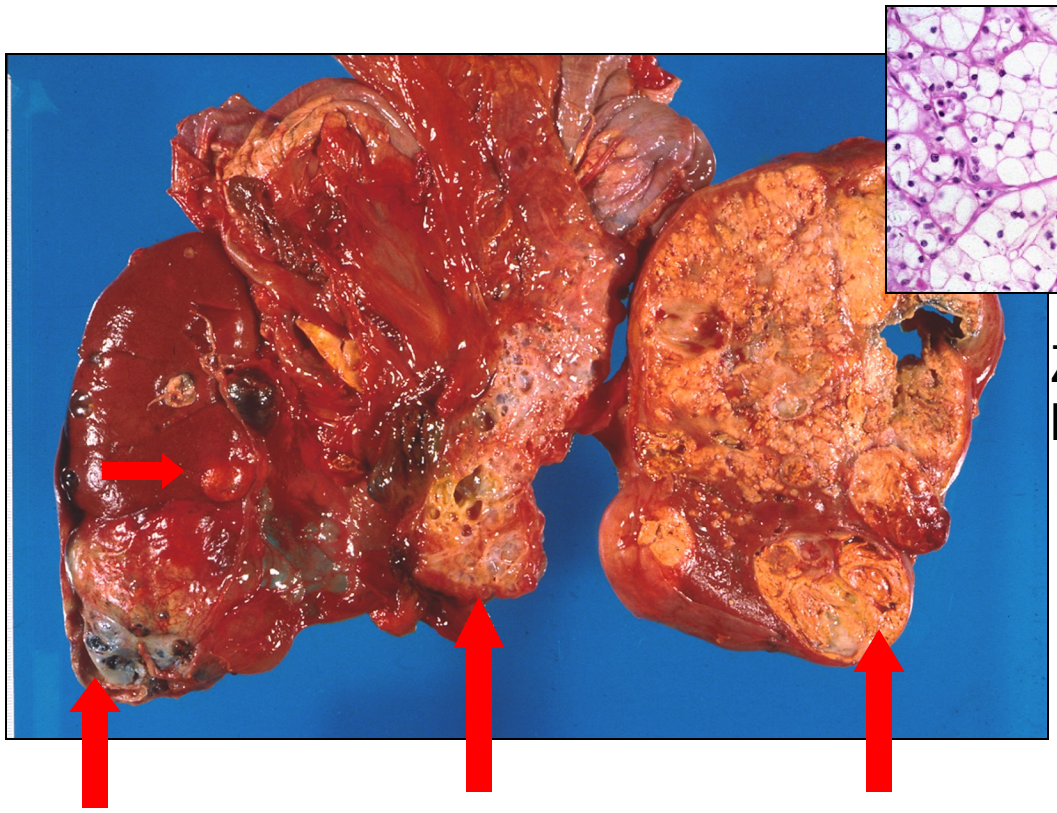
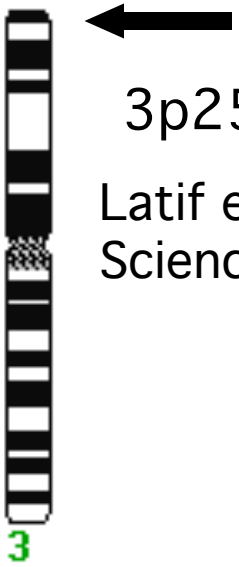
Seminars in Diagnostic Pathology 2018; Moch H et al.

von Hippel-Lindau-Syndrome



Zbar et al.:
Nature 1987



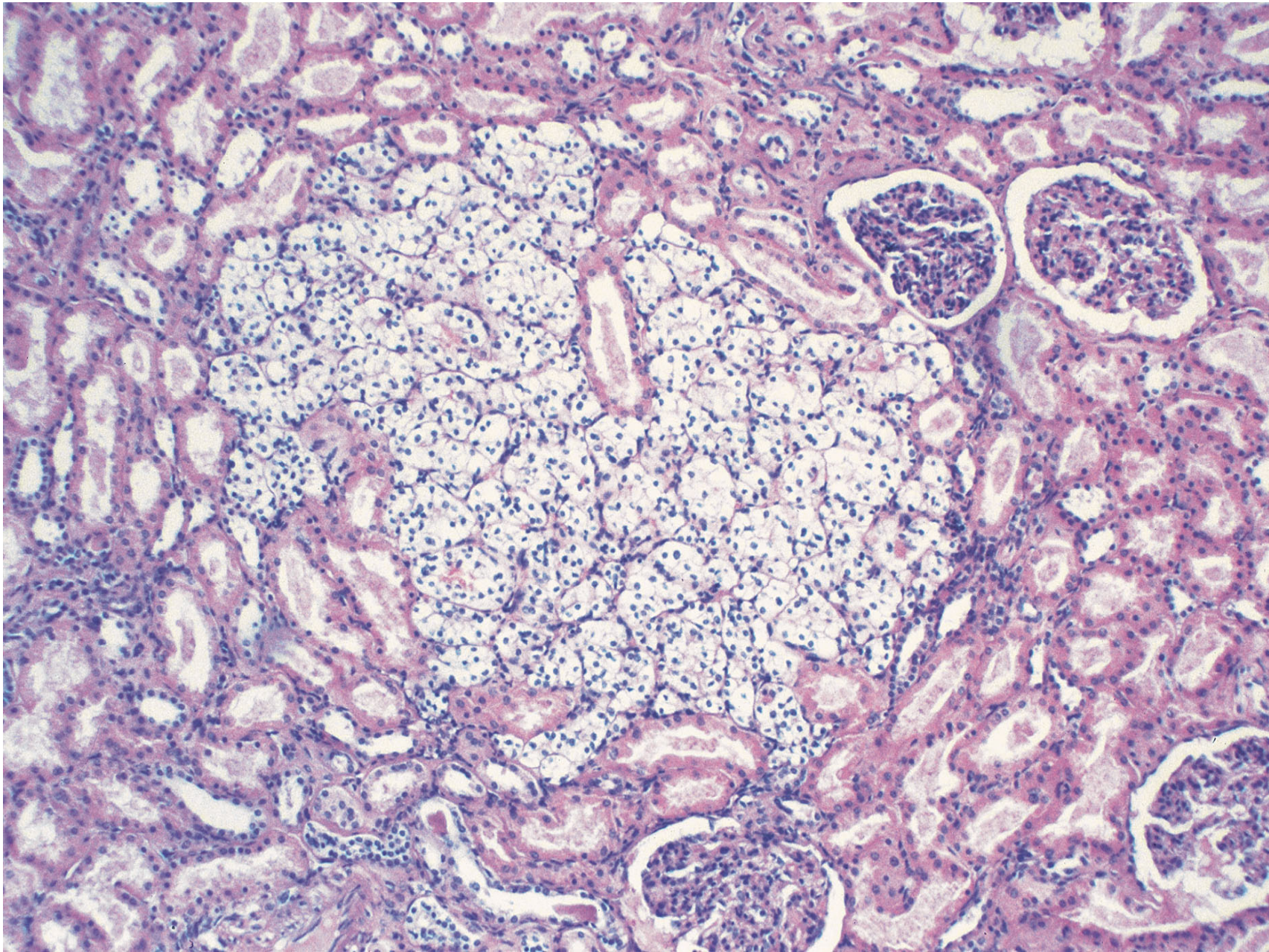
3p25-26

Latif et al.:
Science 1993

Renal cysts **Pancreatic cysts** **bilateral renal carcinoma**

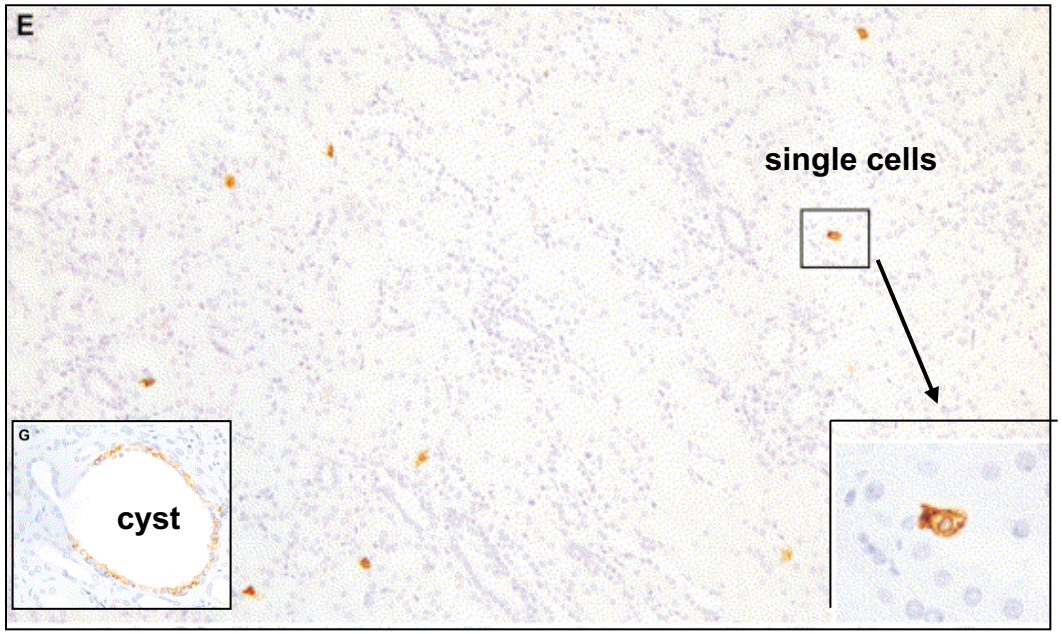
Extrarenal manifestations: Pheochromocytomas, Hemangioblastomas, Angiomas in Retina

Tumorlets

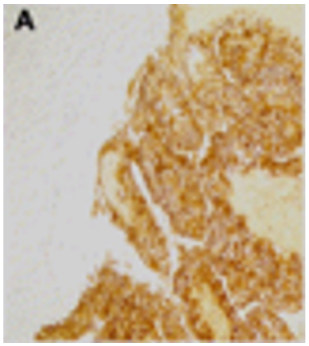


Early on in VHL disease, the vast majority of lesions in kidneys of VHL patients are single cells, cysts occur relatively infrequent and carcinoma less frequently still

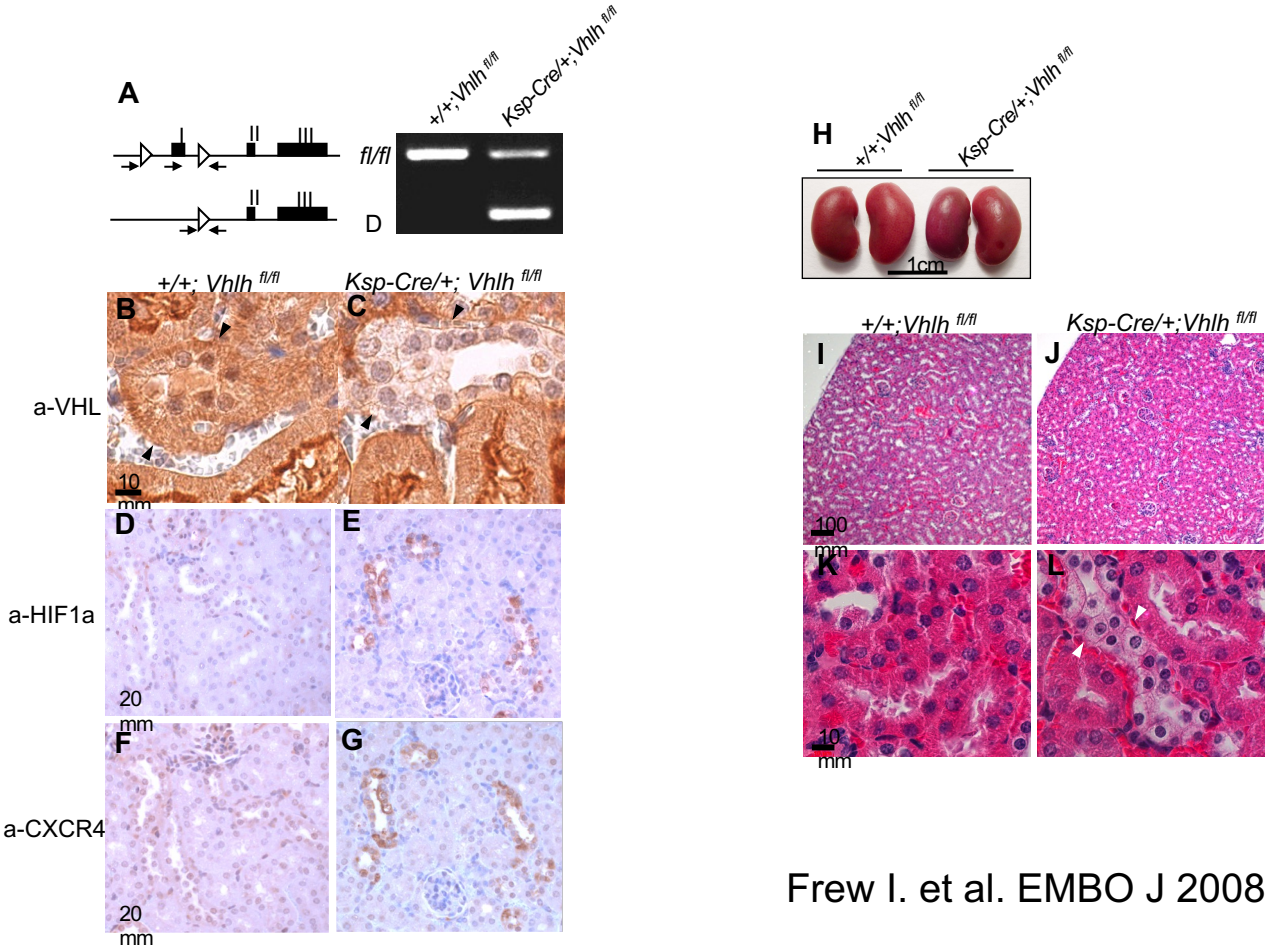
anti-CA9 (HIF target gene)



Mandriota *et al.* 2002
Cancer Cell 1:459-68

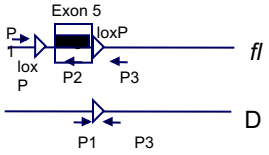


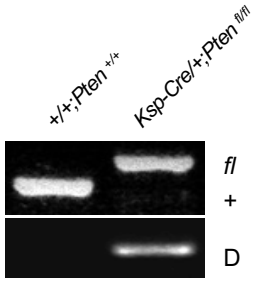
Kidney-specific Vhlh knockout

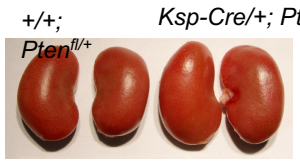


Frew I. et al. EMBO J 2008

Kidney-specific Pten knockout







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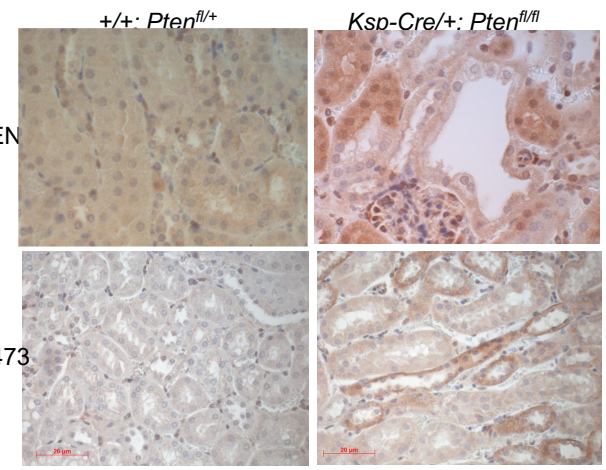
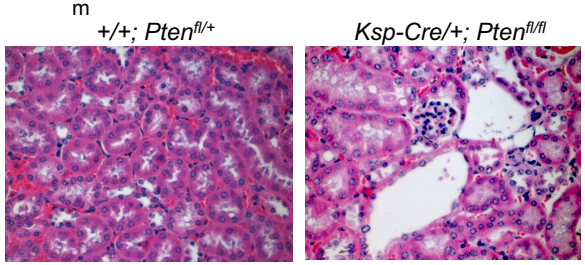
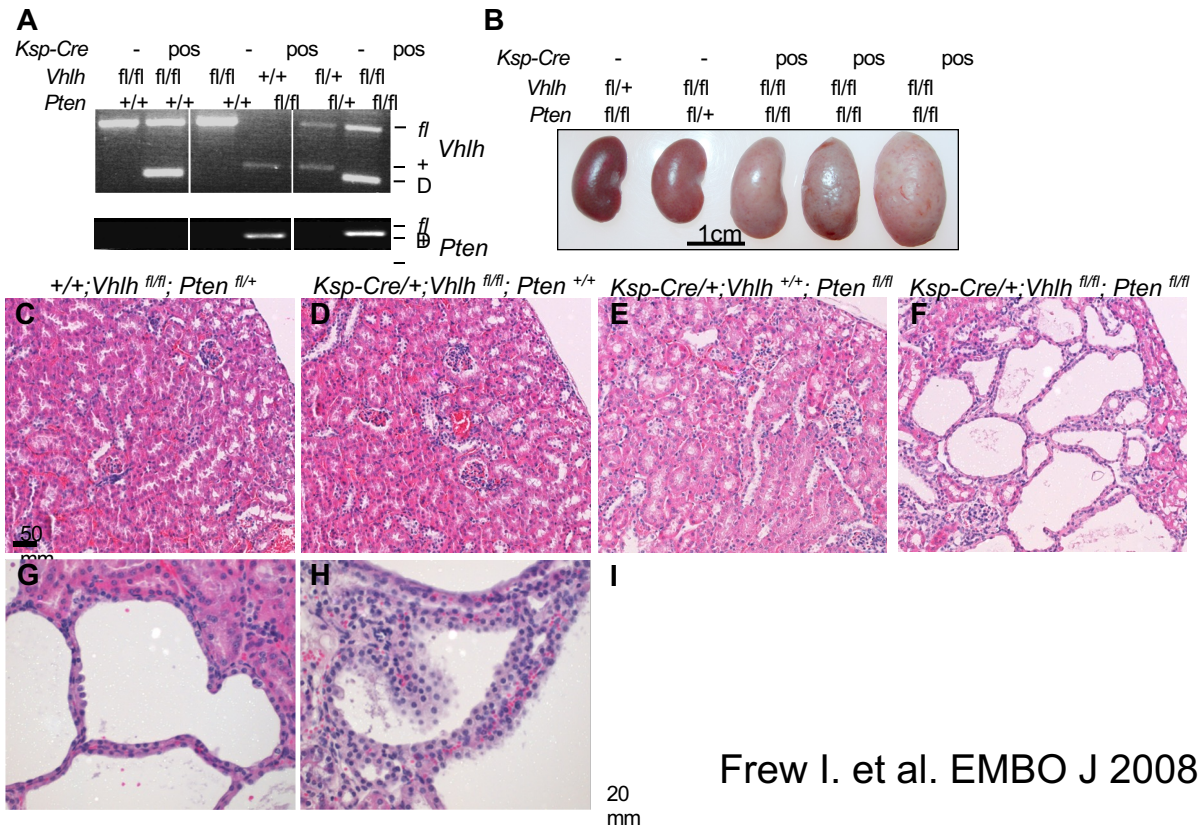




Frew I. et al. EMBO J 2008

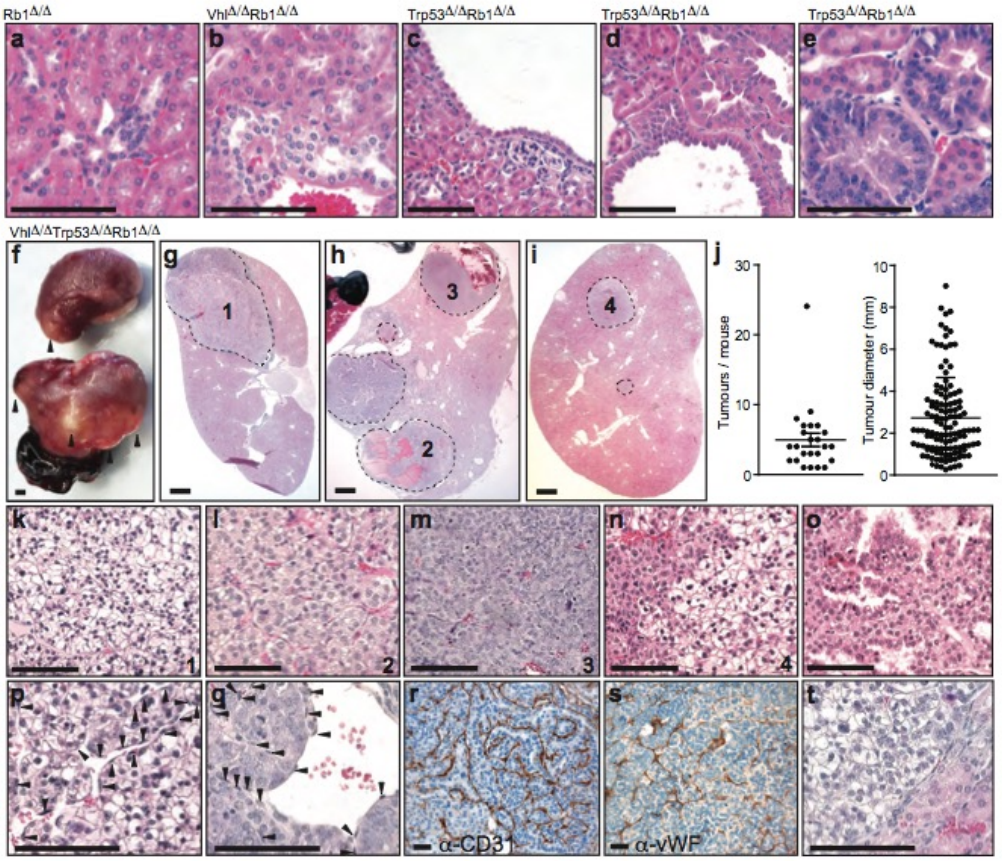
Kidney-specific Vhlh/Pten knockout

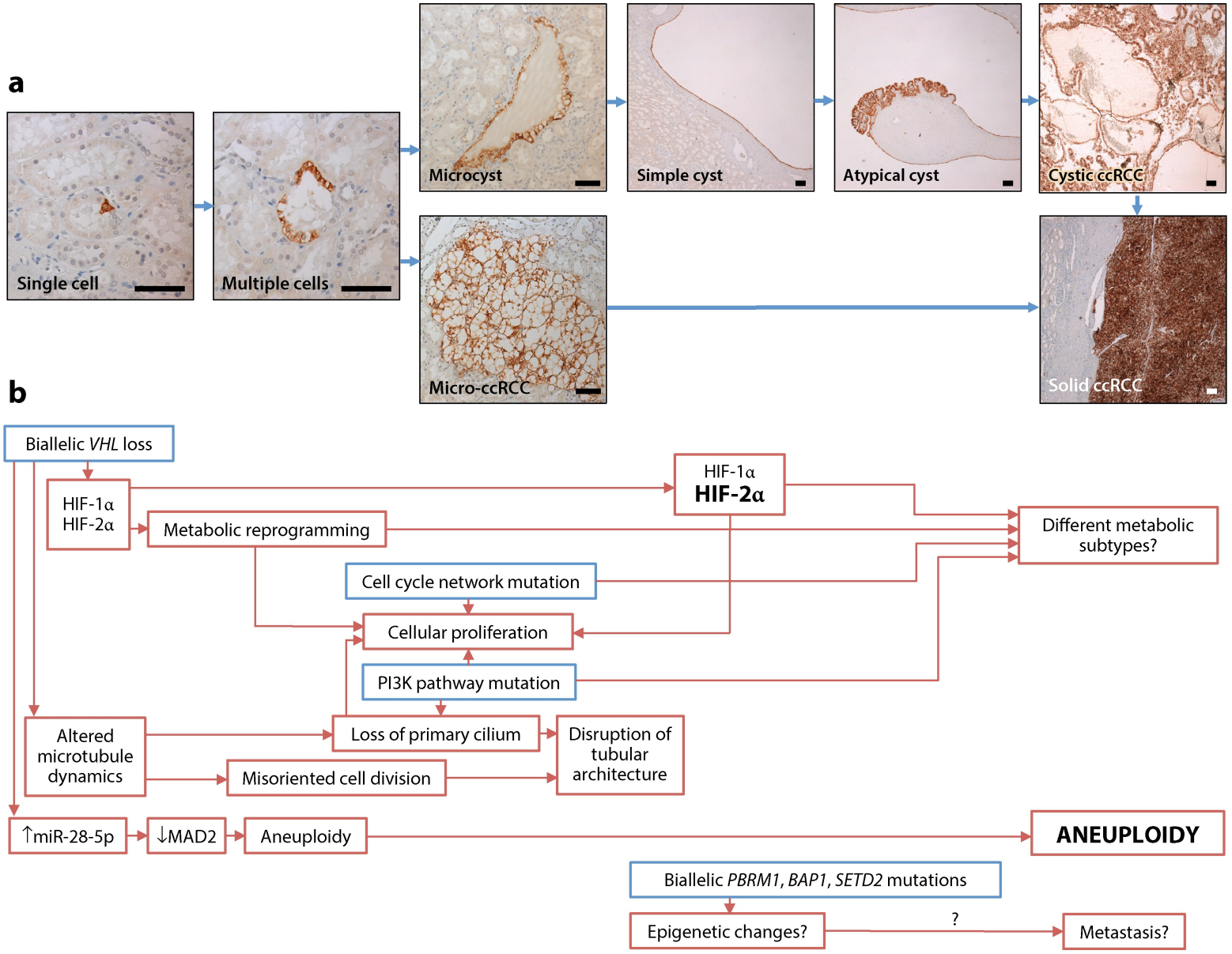


Frew I. et al. EMBO J 2008

Combined *Vhl*, *Trp53* and *Rb1* mutation causes clear cell renal cell carcinoma in mice

Sabine Harlander et al.: Nat Med 2018





Frew IJ, Moch H. 2015.
Annu. Rev. Pathol. Mech. Dis. 10:263–89

VHL-associated RCC

- Incidence 1:36000-1:45000
- Neumann HP et al.: *Prevalence, morphology and biology of renal cell carcinoma in von Hippel-Lindau Disease compared to sporadic renal cell carcinoma.* **J Urol** 16, pp.1248-1254, 1998
- Prevalence: 1.6 % in unselected RCC patients
- occur 25 years earlier
- better 10 years survival ($p<0.001$)
- metastases occur only in tumors larger than 7 cm

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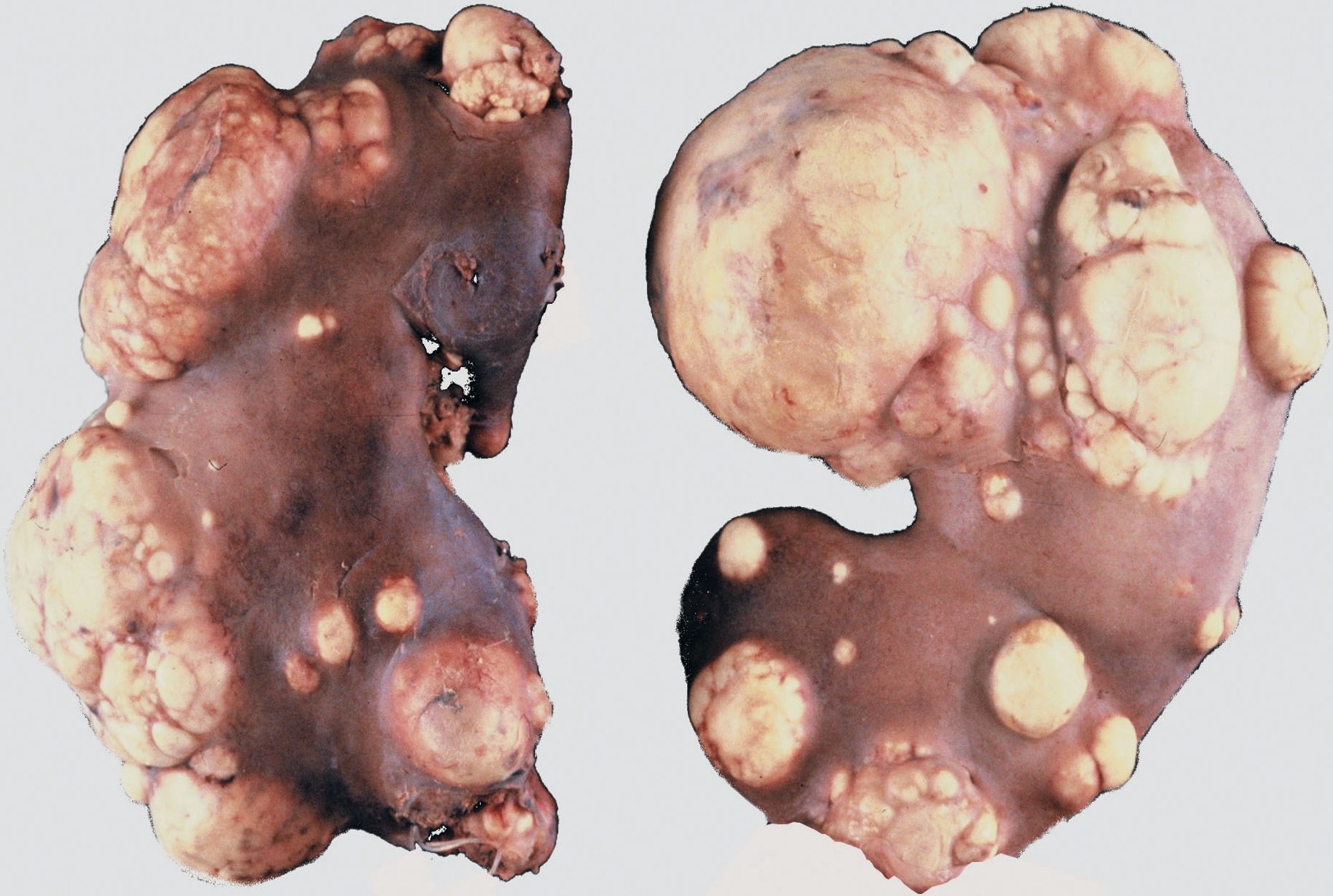
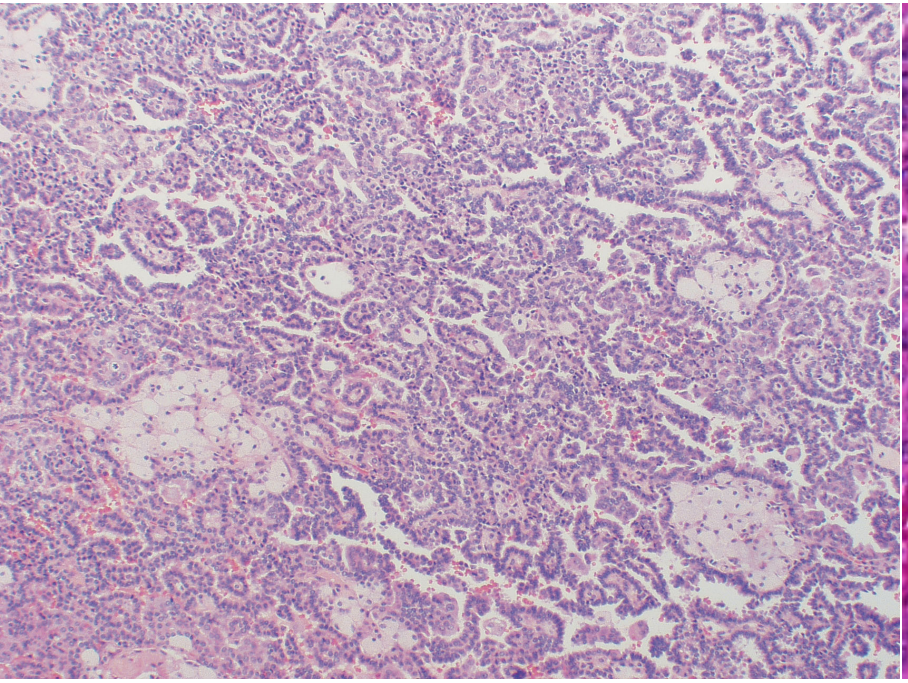
Seminars in Diagnostic Pathology 2018; Moch H et al.

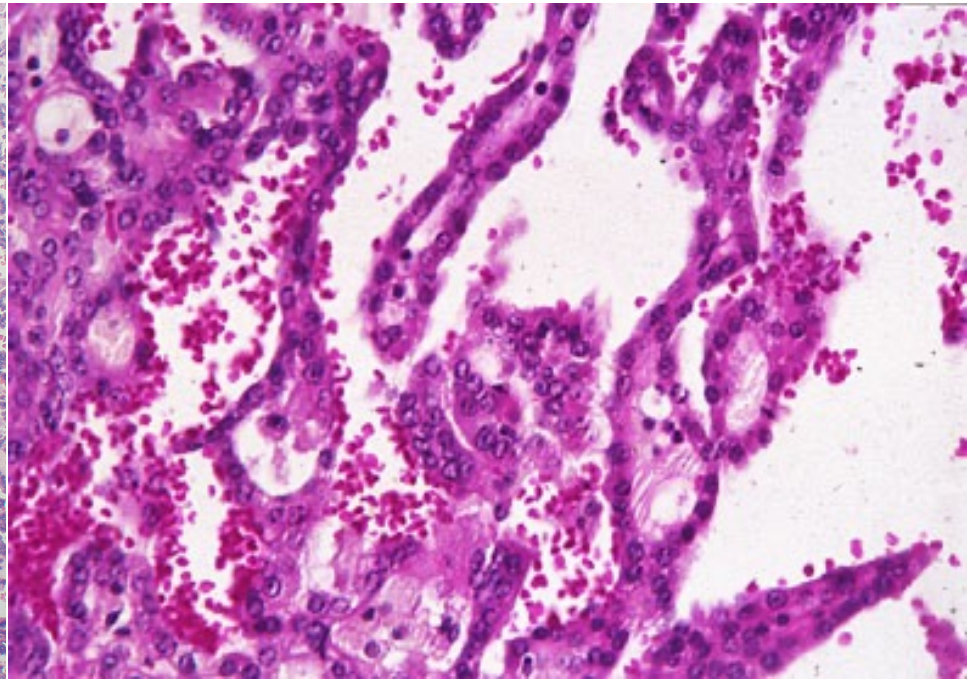


Hereditary Papillary RCC

c-Met Gene on 7q31

Type 1 papillary RCC
no known extrarenal manifestations



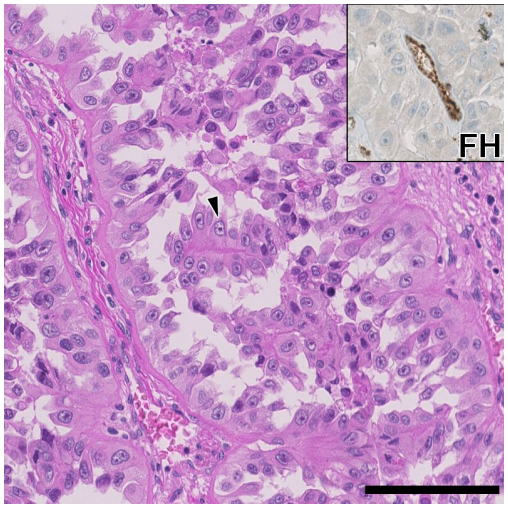


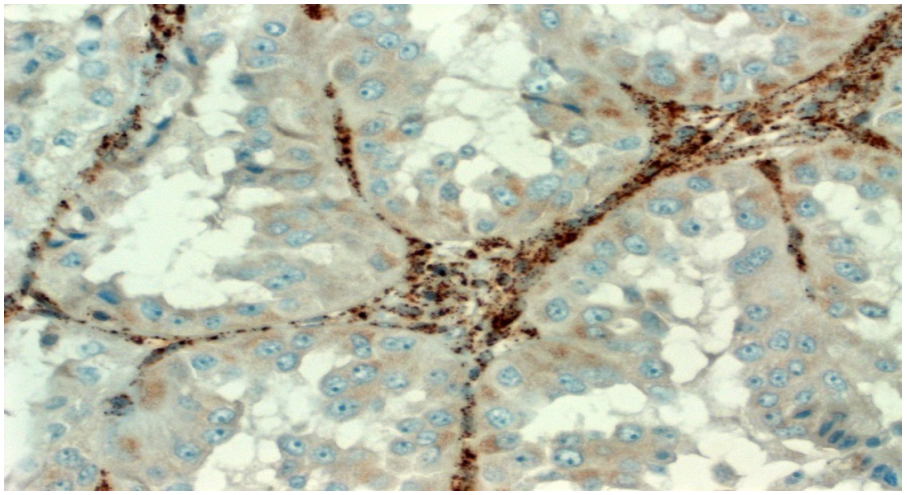
Hereditary Leiomyomatosis and RCC Syndrome (HLRCC)

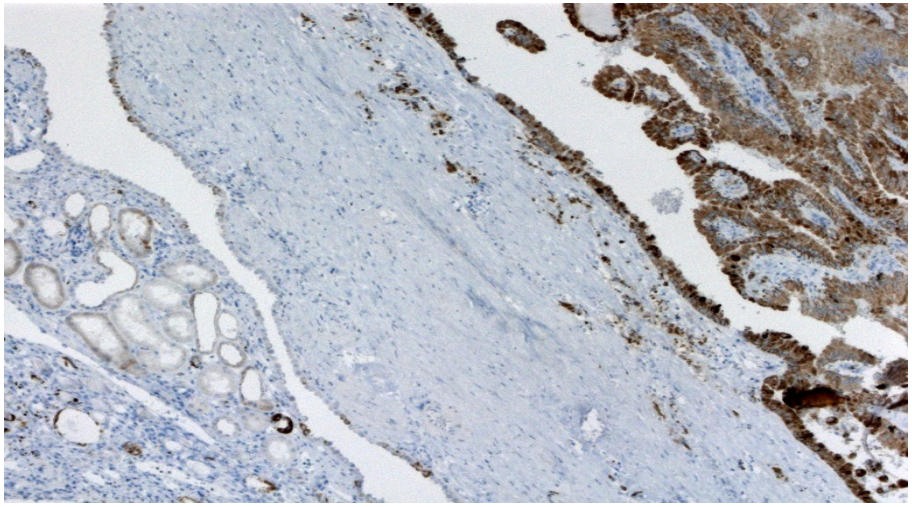
Fumarate Hydratase (*FH*) Gene on 1q42

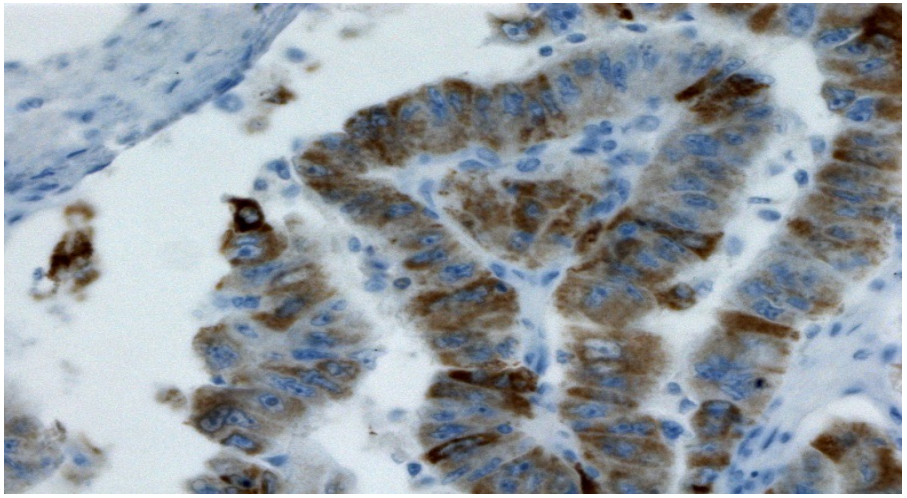
Extrarenal manifestations:
leiomyomas of skin and uterus
leiomyosarcoma

Leiomyomas of the Skin









Overexpression of cysteine-S(2Succino)cysteine

RESEARCH ARTICLE

WILEY

Novel morphological and genetic features of fumarate hydratase deficient renal cell carcinoma in HLRCC syndrome patients with a tailored therapeutic approach

Nicolas Wyvekens[1] | Nadejda Valtcheva[1] | Axel Mischo[2] | Birgit Helmchen[1] | Thomas Hermanns[3] | Matthias Choschzick[1] | Andreas M. Hötker[4] | Anita Rauch[5] | Beda Mühleisen[6] | Dilara Akhoundova[2] | Achim Weber[1,7] | Holger Moch[1] | Niels J. Rupp[1]

Genes Chromosomes Cancer. 2020;1–9

both cases were treated in first line with bevacizumab/erlotinib and showed remarkable and long lasting responses

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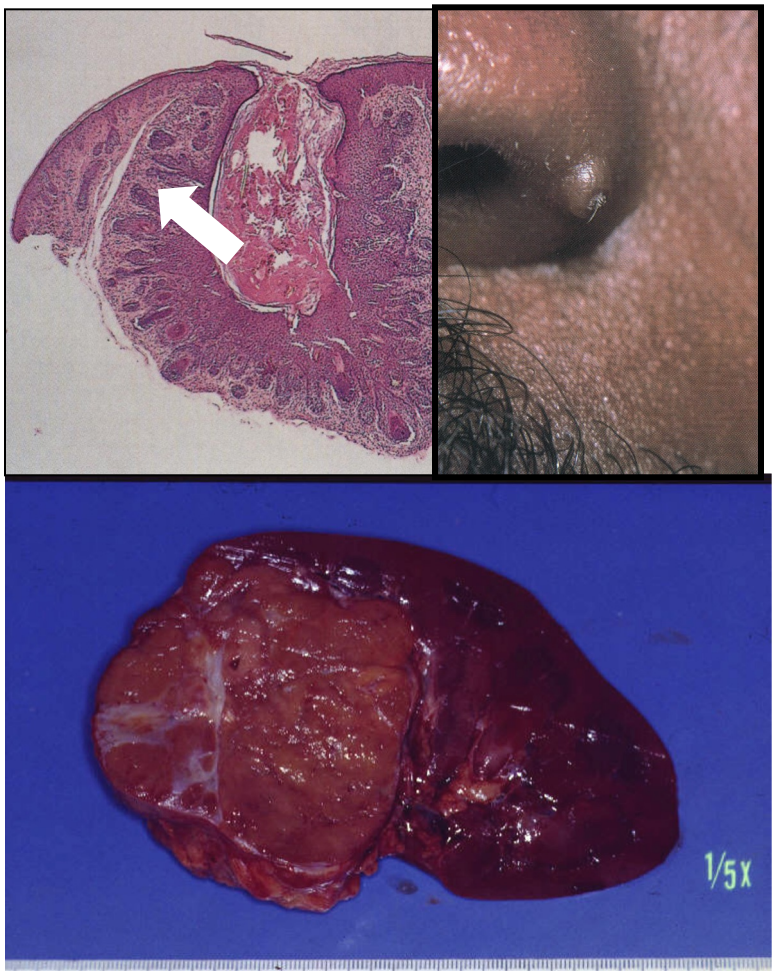
Seminars in Diagnostic Pathology 2018; Moch H et al.

Bird - Hogg - Dubé - Syndrome*

- mutations in human folliculin (BHD) gene on 17p11
- autosomal-dominant



* Toro JR, Glenn G, Duray P et al. : Arch Dermatol 1999; 135: 1195 - 1202

Birt Hogg Dubé syndrome

- Extrarenal manifestations:
  - Facial **fibrofolliculoma** and **trichodiscoma**: multiple, whitish (2-4 mm) smooth papules over the face, neck, oral cavity, and upper trunk, sometimes pedunculated (acrochordons)**.**
  - Lung cysts with risk of spontaneous **pneumothorax**
  - **Colonic polyps**

Renal Tumors in BHD Syndrome

- Oncocytoma
- Chromophobe RCC
- Hybrid oncocytic/chromophobe RCC (HOCT)

HOCT: Hybrid Oncocytic Chromophobe Tumor

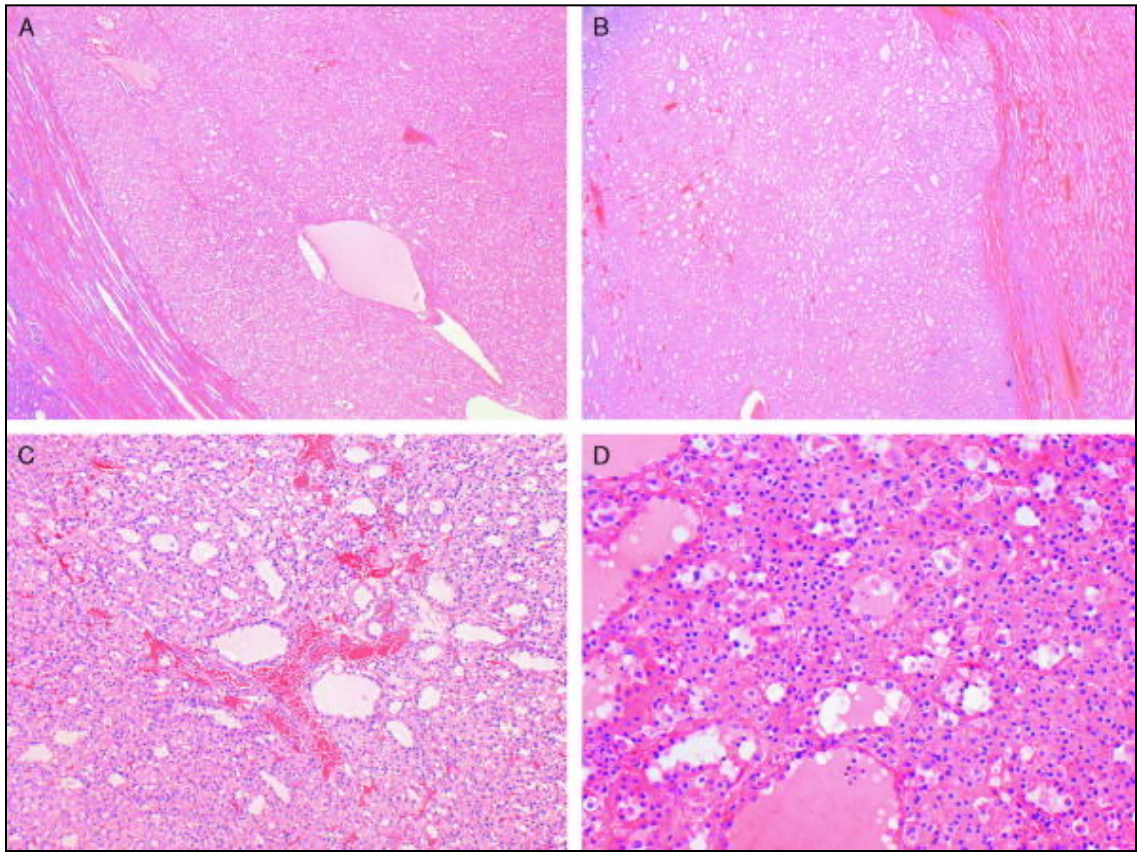
- WHO: Oncocytoma can resemble eosinophilic ChRCC, and a small subset of tumors have overlapping histology between oncocytoma and ChRCC (Hybrid Oncocytic Chromophobe Tumor). These are commonly seen in BHD syndrome and renal oncocytosis. Tumors with this morphology may also occur sporadically.

Hereditary paraganglioma pheochromocytoma syndrome and SDH-deficient renal carcinoma

germline mutation of SDH subunit genes:

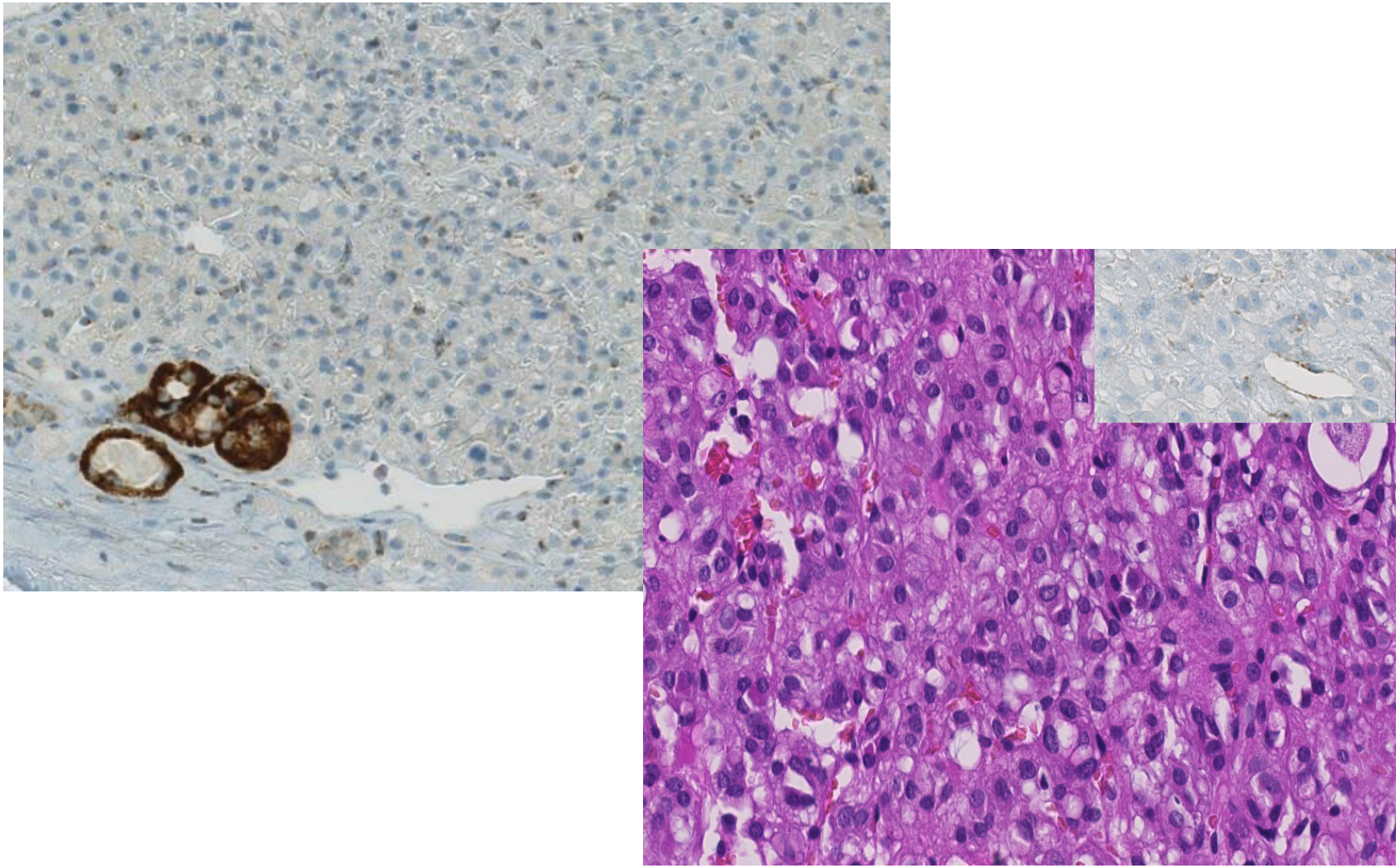
Extrarenal manifestations:

- Pheochromocytomas
- Paragangliomas
- Pituitary adenomas
- GIST



Gill, Anthony
Succinate Dehydrogenase (SDH)-deficient Renal Carcinoma: A Morphologically Distinct Entity: A Clinicopathologic Series of 36 Tumors From 27 Patients.
American Journal of Surgical Pathology. 38(12):1588-1602, 2014.

Williamson SR et al.: Mod Pathol 2015
10 patients



SDH-B (ABCAM ab14714, clone 21A11)

Cowden Syndrome (CS)

PTEN (phosphatase and tensin homologue) hamartoma tumor syndrome germline mutations of the *PTEN* tumor suppressor gene on 10q23.3.

autosomal dominant

Extrarenal manifestations:

trichilemmomas, papillomatous papules, and acral and plantar keratosis

visceral arteriovenous malformations

intestinal and colonic polyps, uterine fibroids, lipomas,

increased susceptibility to thyroid, breast, endometrial, colon and renal cancers

kidney cancer: all the classic histological types

Table 1
Hereditary Conditions and Associated renal neoplasms.

Syndrome	Gene Protein	Chromosome	Kidney	Skin	Other Tissue	Syndrome	Gene Protein	Chromosome
von Hippel-Lindau	*VHL* pVHL	3p25	Multiple, bilateral clear-cell renal cell carcinoma (CCRCC), renal cysts	–	Retinal and CNS haemangioblastomas, phaechromocytoma, pancreatic cysts	von Hippel-Lindau	*VHL* pVHL	3p25
Hereditary papillary renal cancer	*c-MET* HGF-R	7q31	Multiple, bilateral papillary renal cell carcinomas (PRCC), Type 1	–		Hereditary papillary renal cancer	*c-MET* HGF-R	7q31
Hereditary leiomyomatosis and RCC	FH *FH*	1q42–43	Papillary renal cell carcinoma (PRCC), non-Type 1	Nodules (leiomyomas)	Uterine leiomyomas and leiomyosarcomas	Hereditary leiomyomatosis and RCC	FH *FH*	1q42–43
Birt-Hogg-Dubé	*BHD* Folliculin	17p11.2	Multiple chromophobe RCC, conventional RCC, hybrid oncocytoma, papillary RCC, oncocytic tumors	Facial fibrofolliculomas	Lung cysts, spontaneous pneumothorax	Birt-Hogg-Dubé	*BHD* Folliculin	17p11.2
Constitutional chromosome 3 translocation	unknown		Multiple, bilateral clear-cell renal cell carcinomas (CCRCC)	–	–	Constitutional chromosome 3 translocation	unknown	
Hyperparathyroidism-jaw tumor (HP-JT)	*HRTP2*	1q25–32	Mixed epithelial and stromal tumors, papillary RCC: cysts	–	Parathyroid tumors, fibro-osseous mandibular and maxillary tumors	Hyperparathyroidism-jaw tumor (HP-JT)	*HRTP2*	1q25–32
Familial papillary thyroid cancer (FPTC)	Unknown gene	1q21	Papillary RCC, oncocytoma	–	Papillary thyroid cancer, nodular thyroid disease	Familial papillary thyroid cancer (FPTC)	Unknown gene	1q21
Tuberous sclerosis	*TSC1* Hamartin*TSC2*Tuberin	9q34 16p13	Multiple, bilateral angiomyolipomas, lymphangioleiomyomatosis	Cutaneous angiofibroma ('adenoma sebaceum') *peau chagrin*, subungual fibromas	Cardiac rhabdomyomas, adenomatous polyps of the duodenum and the small intestine, lung and kidney cysts, cortical tubers and subependymal giant cell astrocytomas (SEGA)	Tuberous sclerosis	*TSC1* Hamartin*TSC2*Tuberin	9q34 16p13
BAP1 inactivated RCC	BAP1 proteins	3p21	clear cell RCC	uveal melanoma, cutaneous melanoma, and melanocytic BAP1-mutated atypical intradermal tumors	*meso*thelioma,	BAP1 inactivated RCC	BAP1 proteins	3p21

Seminars in Diagnostic Pathology 2018; Moch H et al.

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Seminars in Diagnostic Pathology 2018; Moch H et al.

Hyperparathyroidism-jaw tumor (HP-JT) syndrome

Extrarenal manifestations:

- Hyperparathyroidism secondary to parathyroid adenoma or carcinoma
- Fibroosseous lesions of mandible and maxilla (ossifying fibroma)

Oncogene (2006), 1–10

www.nature.com/onc

ONCOGENOMICS

Sporadic human renal tumors display frequent allelic imbalances and novel mutations of the *HRPT2* gene

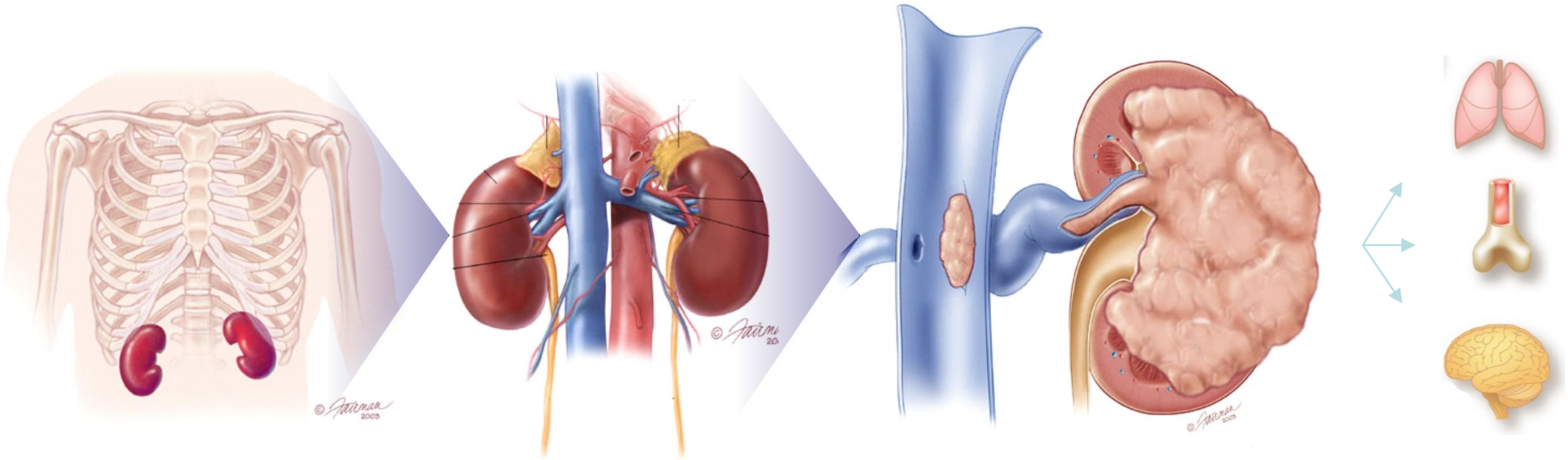
J Zhao[1], A Yart[2], S Frigerio[1], A Perren[1], P Schraml[1], C Weisstanner[1], T Stallmach[1], W Krek[2] and H Moch[1]

[1]Department of Pathology, Institute of Surgical Pathology, University Hospital Zurich, Zurich, Switzerland and [2]Institute of Cell Biology, Swiss Federal Institute of Technology Zurich, Zurich, Switzerland

Take Home Messages

- Correct renal tumor classification allows to identify hereditary tumor syndromes!
- Definitive confirmation by testing patient for germline mutation
- don’t forget (!): Lynch-Syndrome with *upper tract urothelial cancer*

Molecular background of ccRCC and treatment

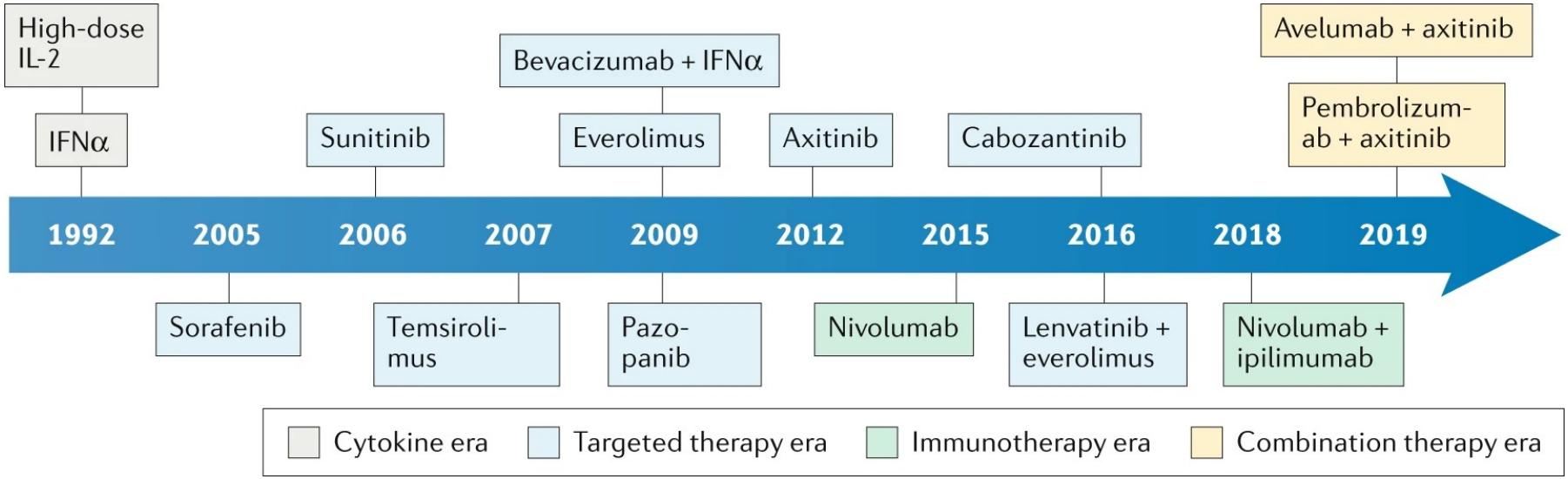


Hypervascular → Anti-VEGFR-TKIs

Immunogenic → Immune checkpoint inhibitors

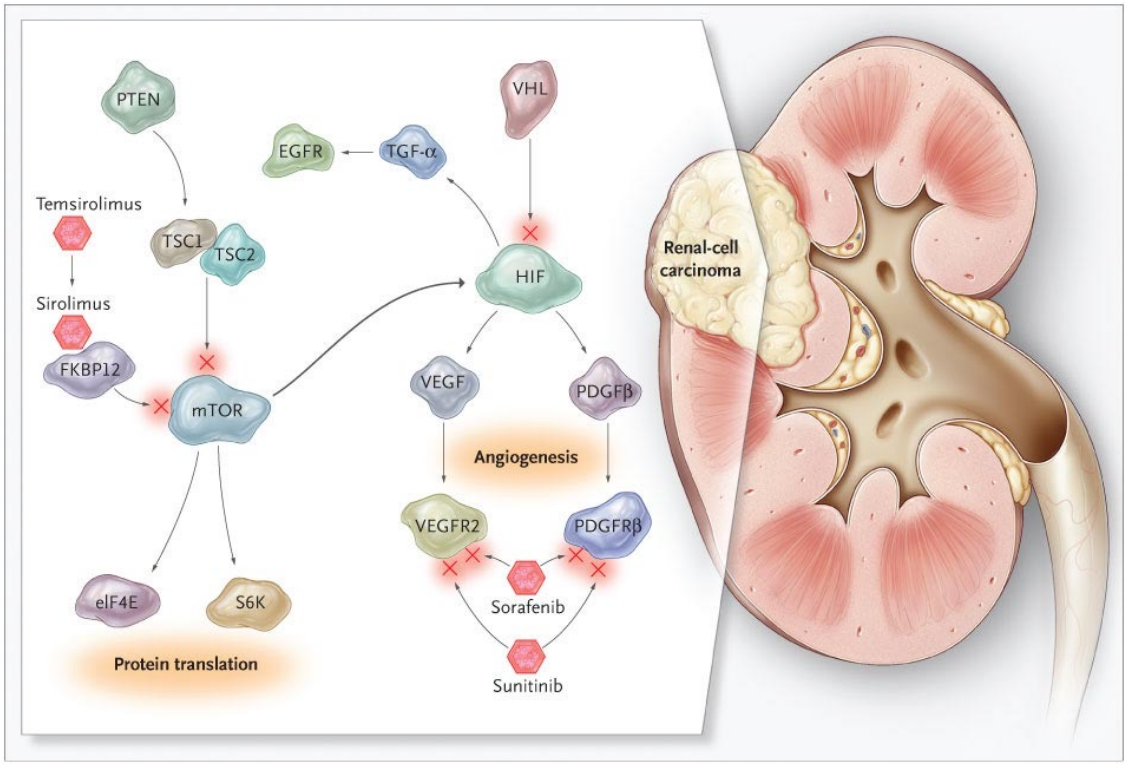
Metabolic → m-TOR-inhibitors

Molecular background of ccRCC and treatment



Clear cell versus „non-clear cell RCC“?!

Molecular background of ccRCC and treatment



Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma

Brugarolas J.: N Engl J Med 2007; 356: 185-187

Molecular background of ccRCC and treatment

Search for a predictive biomarker!

2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Eric Jonasch, M.D., Frede Donskov, M.D., Ph.D., Othon Iliopoulos, M.D., W. Kimryn Rathmell, M.D., Ph.D., Vivek K. Narayan, M.D., Benjamin L. Maughan, M.D., Stephane Oudard, M.D., Tobias Else, M.D., Jodi K. Maranchie, M.D., Sarah J. Welsh, M.D., Sanjay Thamake, Ph.D., Eric K. Park, M.D., Rodolfo F. Perini, M.D., W. Marston Linehan, M.D., and Ramaprasad Srinivasan, M.D., Ph.D., for the MK-6482-004 Investigators*

LETTERS
https://doi.org/10.1038/s41591-021-01324-7
nature medicine
Check for updates

Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis

Toni K. Choueiri[1]✉, Todd M. Bauer[2], Kyriakos P. Papadopoulos[3], Elizabeth R. Plimack[4], Jaime R. Merchan[5], David F. McDermott[6], M. Dror Michaelson[7], Leonard J. Appleman[8], Sanjay Thamake[9], Rodolfo F. Perini[9], Naseem J. Zojwalla[9] and Eric Jonasch[10]✉

Molecular background of ccRCC and treatment

Molecular and Cellular Pathobiology

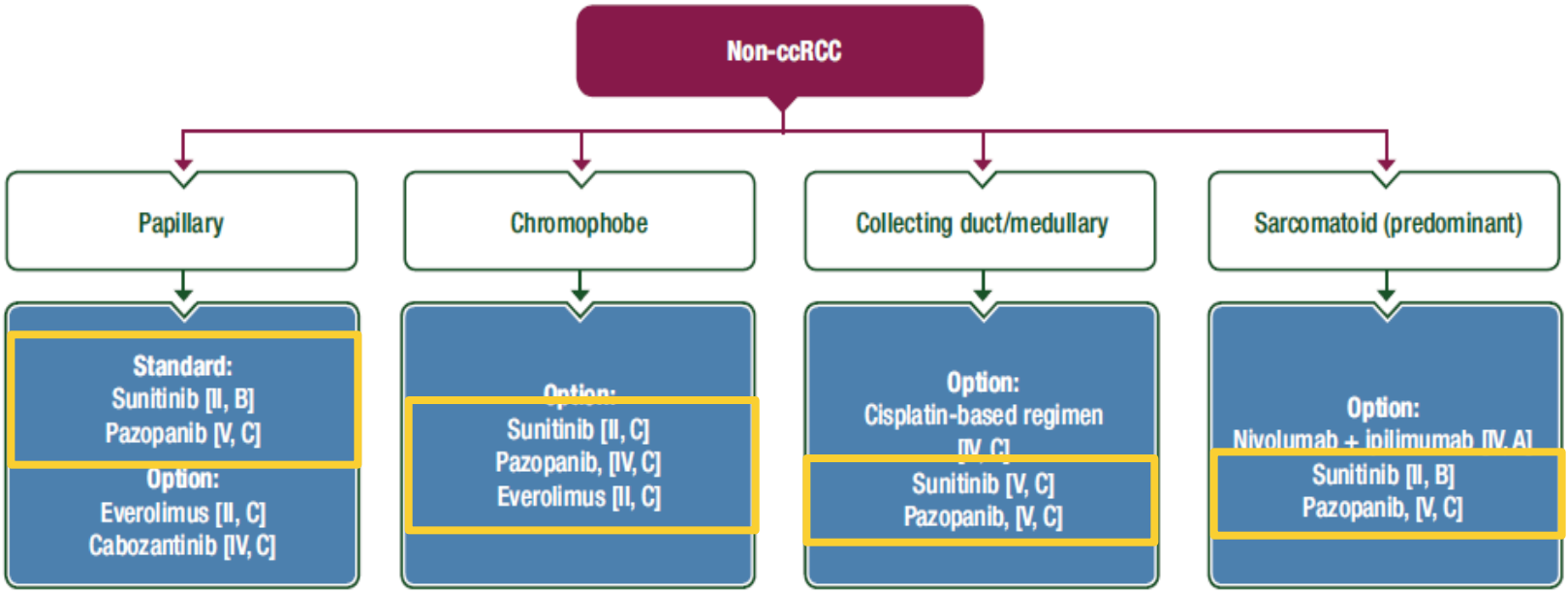
Cancer Research

VHL Gene Mutations and Their Effects on Hypoxia Inducible Factor HIFα: Identification of Potential Driver and Passenger Mutations

Markus P. Rechsteiner[1], Adriana von Teichman[1], Anna Nowicka[1], Tullio Sulser[2], Peter Schraml[1], and Holger Moch[1]

with HIFα, elongin B, and elongin C; and a third with pVHL functions comparable with wild type. We therefore conclude that the specific impact of missense mutations may help to distinguish between driver and passenger mutations and may explain responses of ccRCC patients to HIF-targeted therapies. *Cancer Res; 71(16); 5500–11.*

No effective targeted treatment exists for advanced non-ccRCC tumours



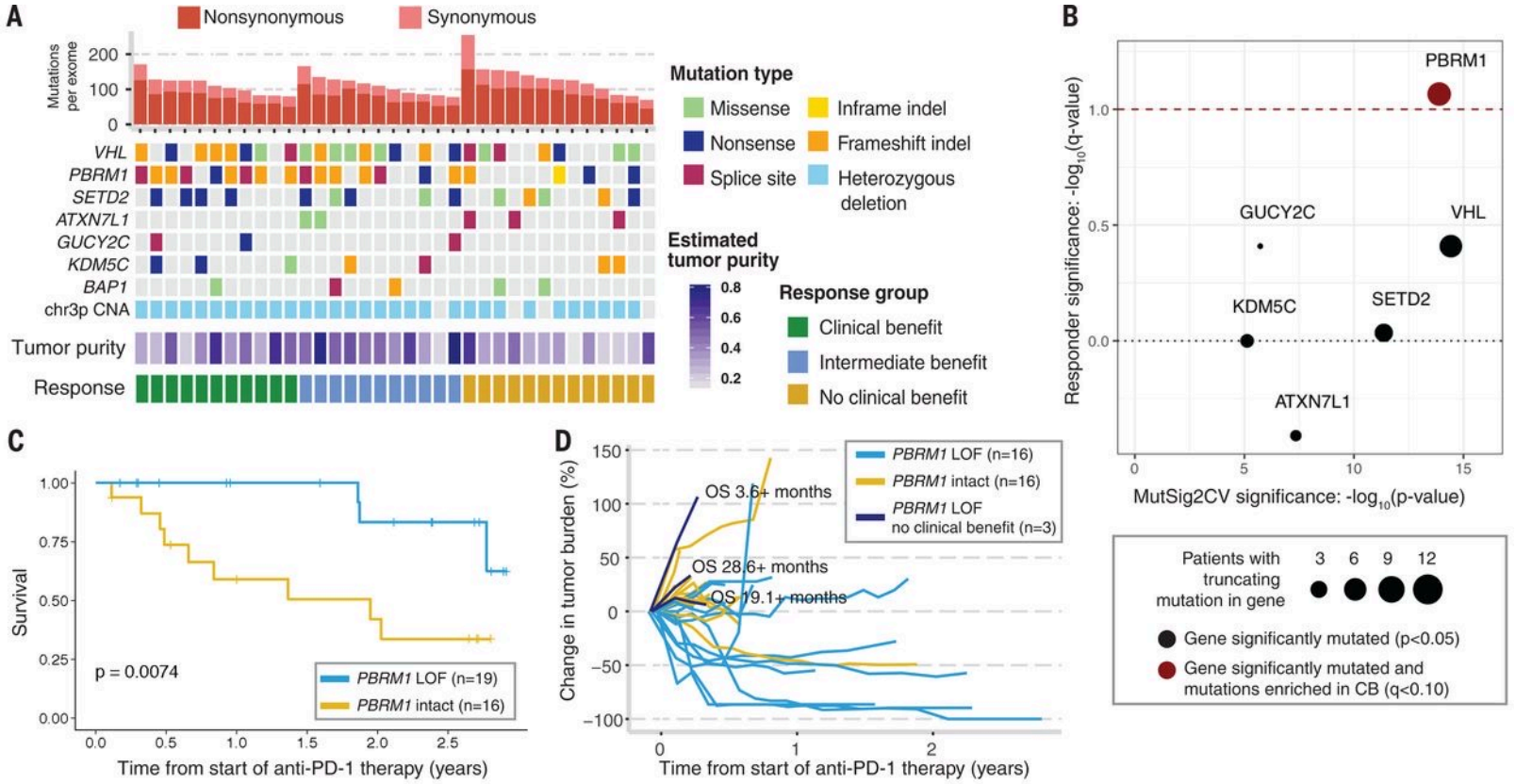
Escudier et al., Ann Oncol, 2019

Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

by Diana Miao, Claire A. Margolis, Wenhua Gao, Martin H. Voss, Wei Li, Dylan J. Martini, Craig Norton, Dominick Bossé, Stephanie M. Wankowicz, Dana Cullen, Christine Horak, Megan Wind-Rotolo, Adam Tracy, Marios Giannakis, Frank Stephen Hodi, Charles G. Drake, Mark W. Ball, Mohamad E. Allaf, Alexandra Snyder, Matthew D. Hellmann, Thai Ho, Robert J. Motzer, Sabina Signoretti, William G. Kaelin, Toni K. Choueiri, and Eliezer M. Van Allen

Science
Volume 359(6377):801-806
February 16, 2018

Analysis of tumor-genome features *in discovery cohort* reveals a correlation between PBRM1 LOF mutations and clinical benefit from anti–PD-1 therapy.



Diana Miao et al. Science 2018;359:801-806

Sarcomatoid differentiation and immune checkpoint blockade

Cancer Treatment and Research Communications 33 (2022) 100640

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

The significance of sarcomatoid and rhabdoid dedifferentiation in renal cell carcinoma

Andrew W. Hahn [a,*], Justin Lebenthal [b], Giannicola Genovese [a,c], Kanishka Sircar [d,e], Nizar M. Tannir [a], Pavlos Msaouel [a,d,**]

[a] Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America
[b] Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America
[c] Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America
[d] Department of Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America
[e] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States of America

Table 4 | **Prospective data assessing response of sRCC to immune checkpoint blockade**

Clinical trial	Phase	*N*	ORR	PR	CR	Median PFS	Median OS	Intervention arm (*n*)	Standard of care arm (*n*)
Atezolizumab[171]	I	18[a]	33%	–	–	4.2 months	26.2 months	Atezolizumab (18*)	–
CheckMate-214[173]	III	139	60.8%	41.9%	18.9%	26.5 months	NR	Ipilimumab + nivolumab (74)	Sunitinib (65)
Keynote-426[177]	III	105	58.80%	47%	11.8%	NR	NR	Pembrolizumab + axitinib (51)	Sunitinib (54)
Javelin Renal-101[180]	III	108	46.8%	42.6%	4.3%	7.0 months	–	Avelumab + axitinib (47)	Sunitinib (61)
IMmotion151[181]	III	142	49%	39%	10%	8.3 months	21.7 months	Atezolizumab + Bevacizumab (68)	Sunitinib (74)

–, not specified; CR, complete response; NR, not reached; OS, overall survival; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Includes sRCCs and grade 4 RCCs. ORR, PFS and OS values presented in this table are based on results from the intervention arm.

Media Release

Roche

Basel, 11 December 2017

Phase III IMmotion151 study showed Roche's Tecentriq (atezolizumab) and Avastin (bevacizumab) reduced the risk of disease worsening or death for the initial treatment of certain people with advanced kidney cancer

- **Tecentriq and Avastin showed improvement in investigator-assessed progression-free survival (PFS) compared with sunitinib for people whose disease expressed PD-L1**
- **Data will be discussed with health authorities globally, including the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)**

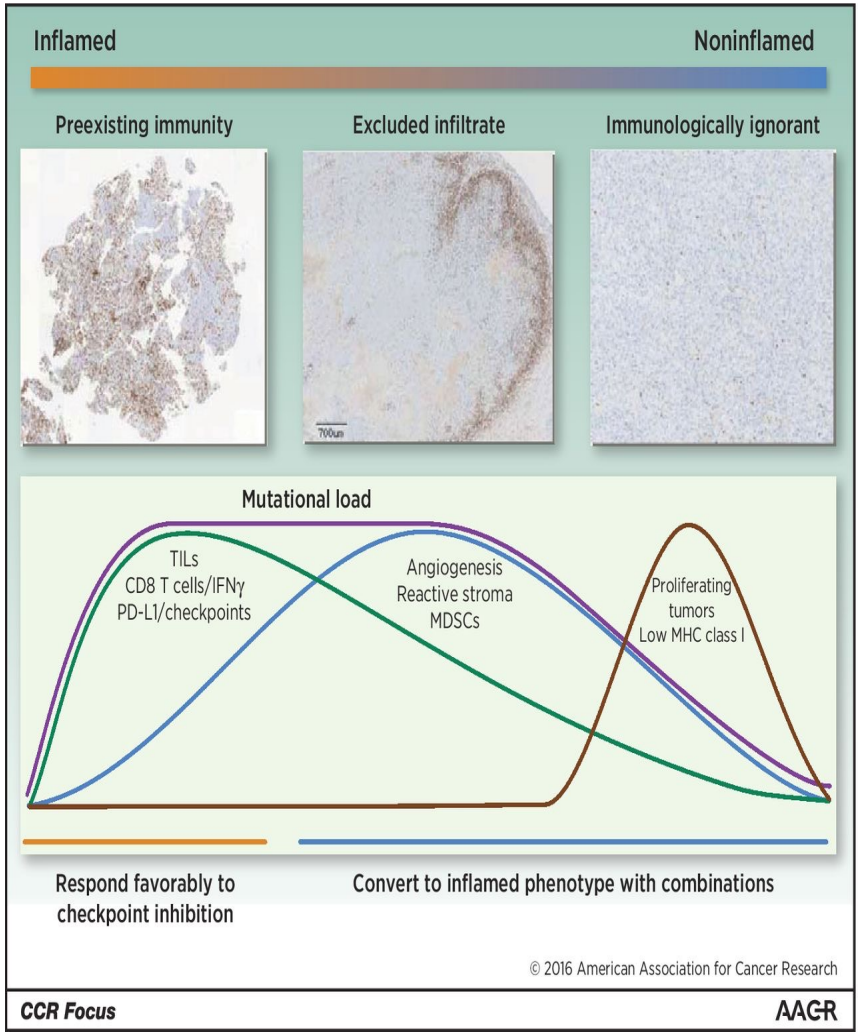
The proposed mechanism of action for the combination, suggested by biomarker data, is that bevacizumab rescues innate resistance to atezolizumab via effects on the tumor microenvironment.

How can we stratify patients who will benefit from novel immunotherapeutic agents?

tumor immunity continuum

and

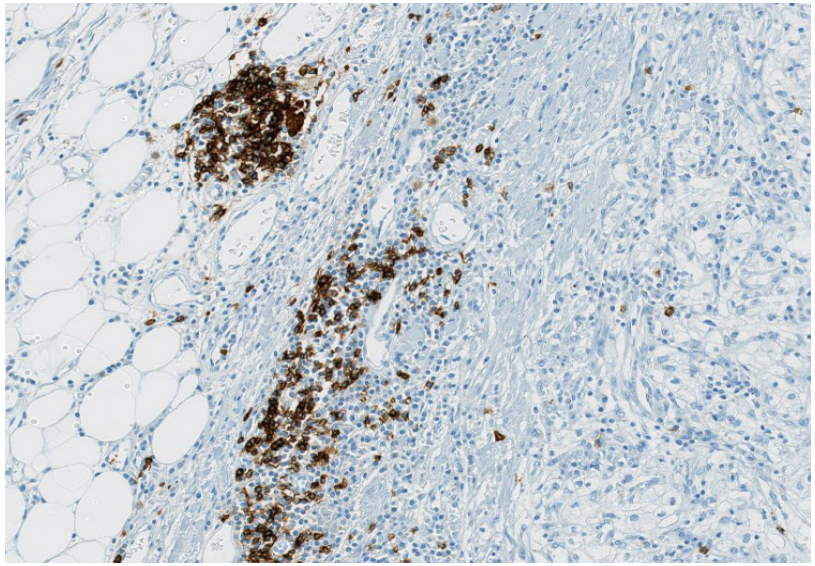
tumor microenvironment



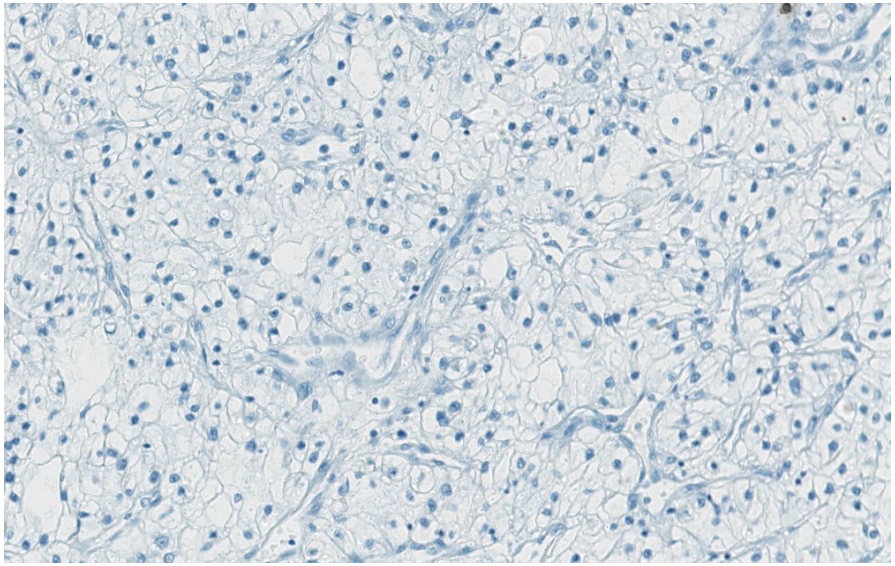
Priti S. Hegde et al. Clin Cancer Res 2016;22:1865-1874

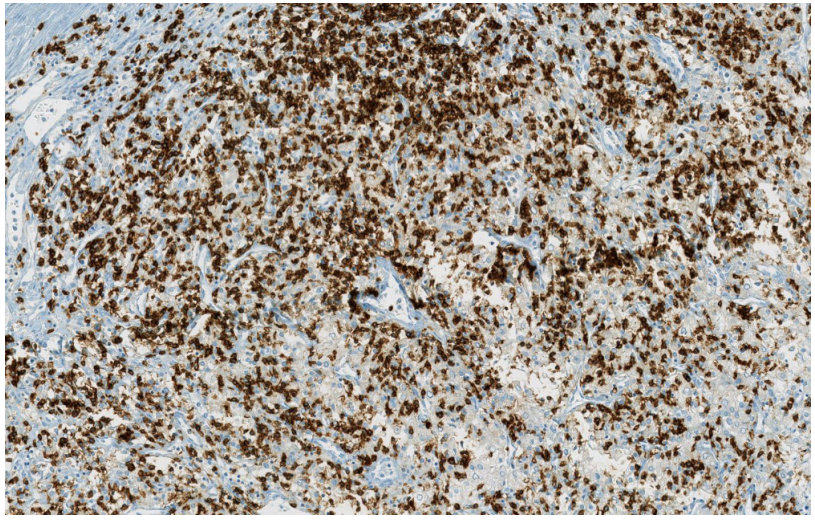
Cancer Immunophenotypes in ccRCC

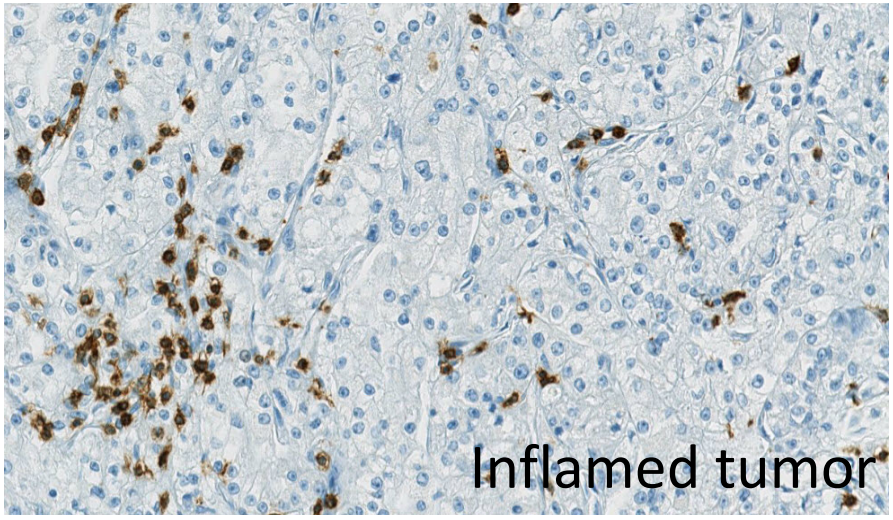
Immune-excluded tumor



Immune-desert tumor

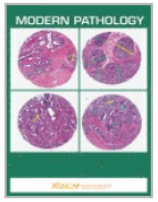






Inflamed tumor

Modern Pathology
Volume 32, Issue 7, July 2019, Pages 1042-1052

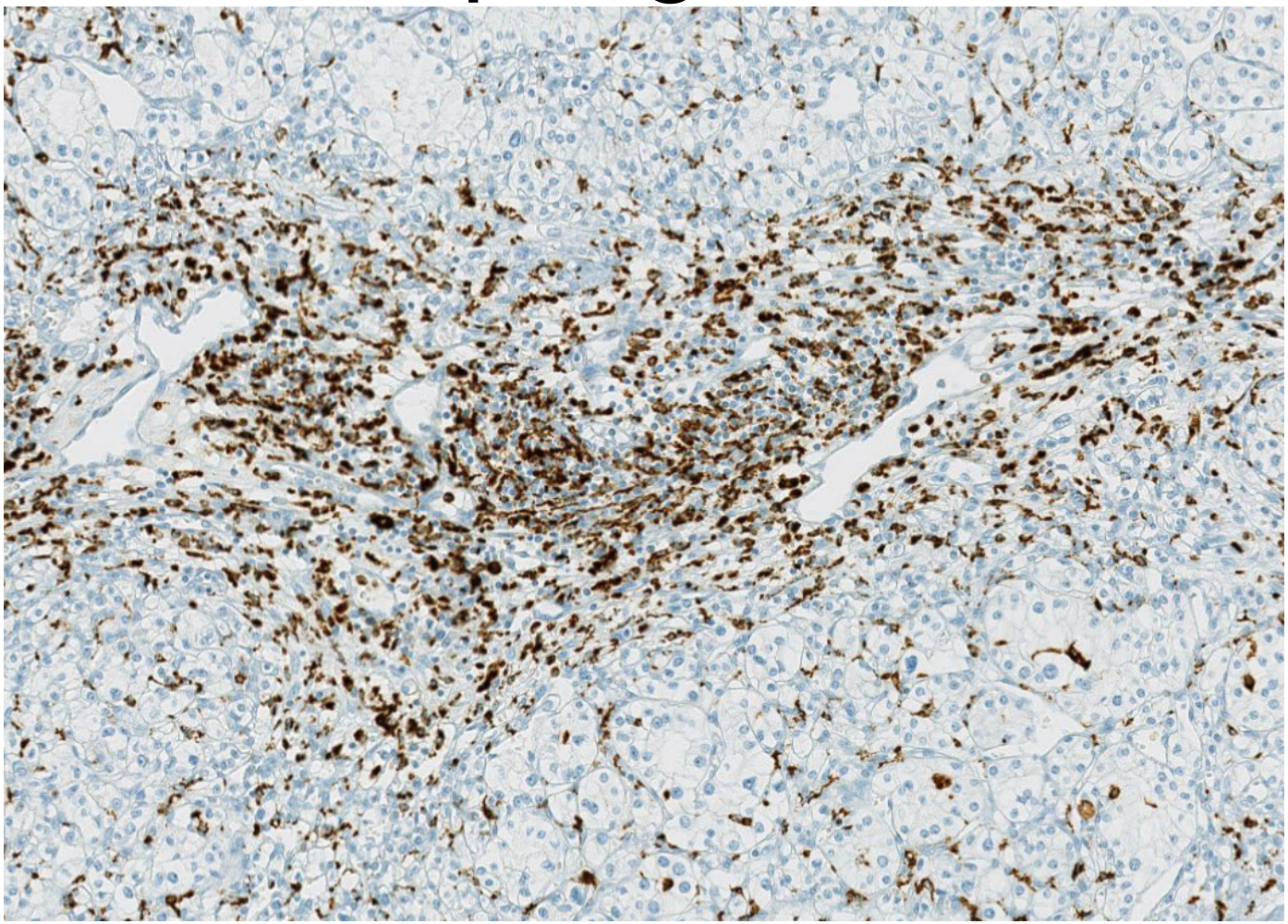


Article

Specific immune cell and lymphatic vessel signatures identified by image analysis in renal cancer

Peter Schraml [1], Maria Athelogou [2], Thomas Hermanns [3], Ralf Huss [2], Holger Moch [1]

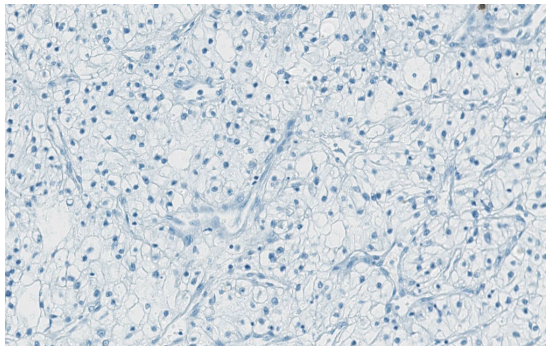
Macrophages in ccRCC

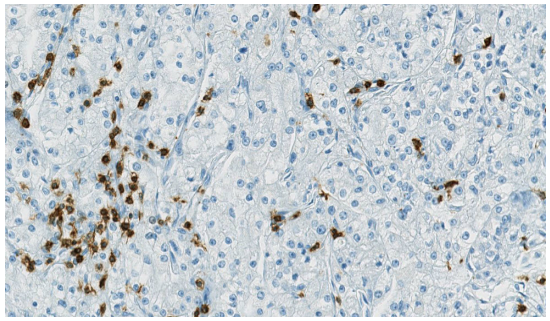


CD68

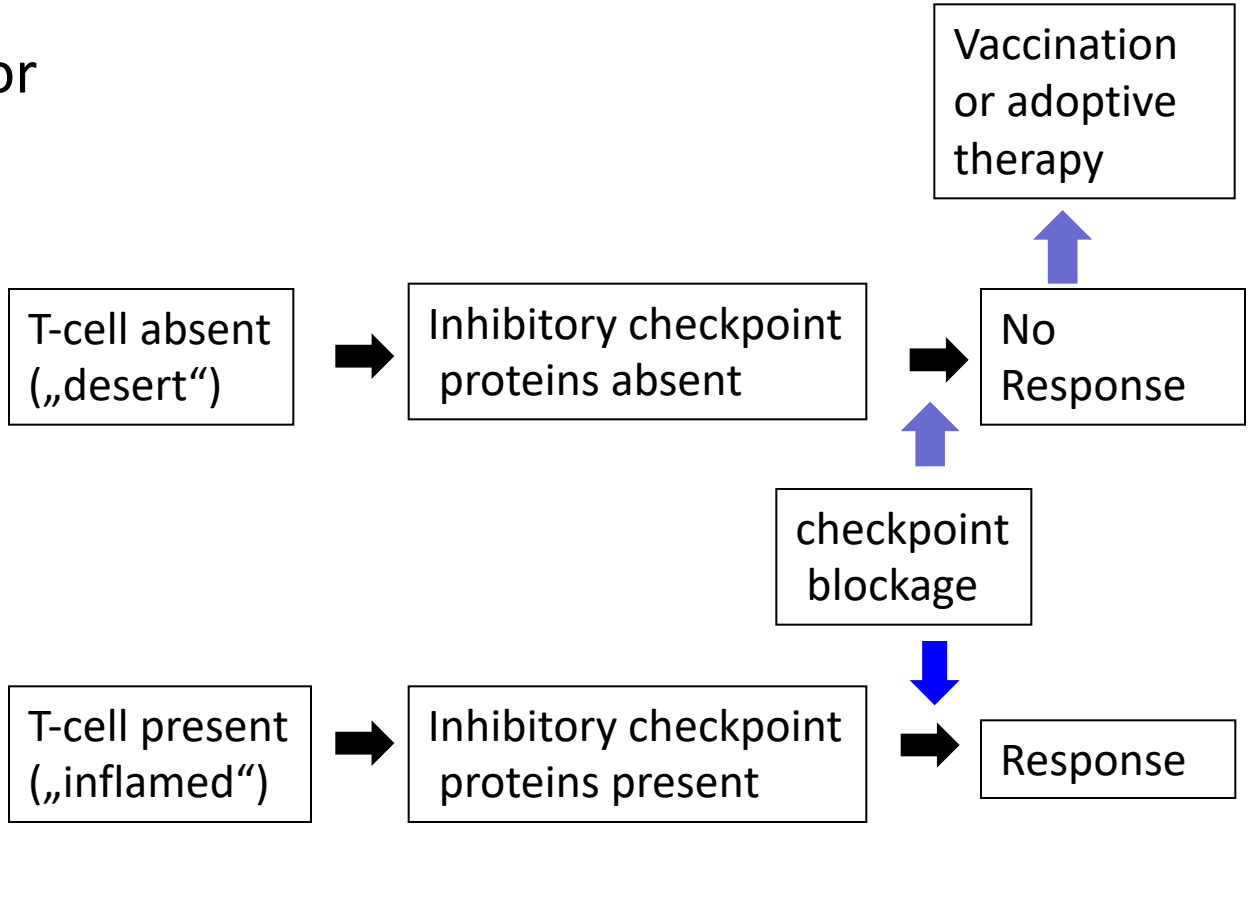
No benefit of checkpoint blockage therapy expected for „Non-inflamed“ tumors

Immune-desert tumor

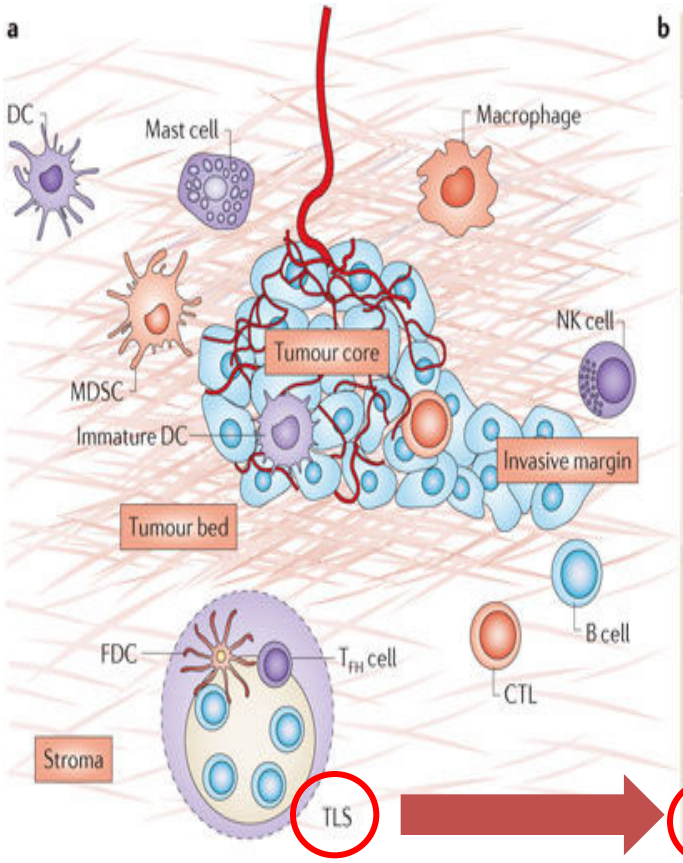




Inflamed tumor



Digital Pathology: Immune Contexture in ccRCC



b

Immune contexture	Parameters: positive association with survival
Type	CTLs ($CD3^+CD8^+$)
	Memory T cells ($CD45RO^+$)
Location	Core of the tumour
	Invasive margin
Density	Number of cells per mm^2: 1, 10, 100, 1,000, 10,000 — $CD3^+_{CT}$, $CD3^+_{IM}$, $CD8^+_{CT}$, $CD8^+_{IM}$, $CD45RO^+_{CT}$, $CD45RO^+_{IM}$
Functional orientation	T_H1 cell-associated factors (IFNγ, IL-12, T-bet and IRF1)
	Cytotoxic factors (granzymes, perforin and granulysin)
	Chemokines (CX3CL1, CXCL9, CXCL10, CCL5 and CCL2)
	T_H17 cells, T_{Reg} cells and T_H2 cells have a variable effect on survival, depending on tumour type
TLS	Presence and quality

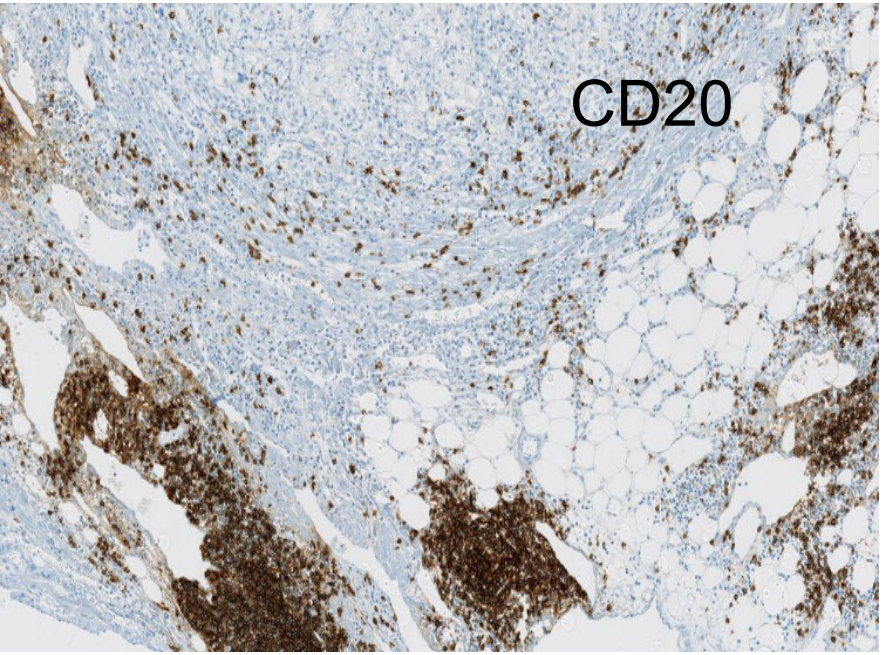
CTL: Cytotoxic T-cells (TILs)

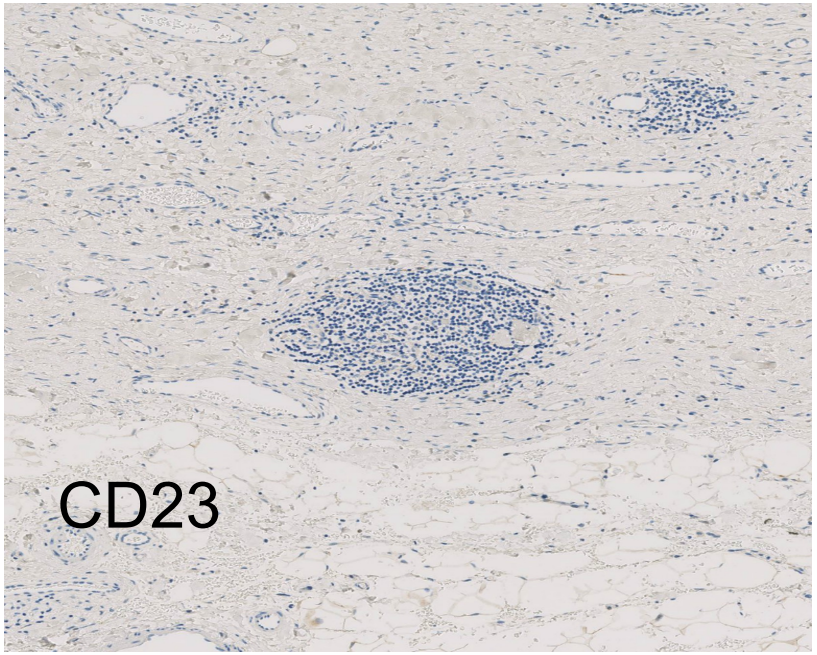
TLS: Ectopic lymphoid aggregates that are generated during the process of chronic immune stimulation and that exhibit the structural characteristics of secondary lymphoid organs.

Nature Reviews | Cancer

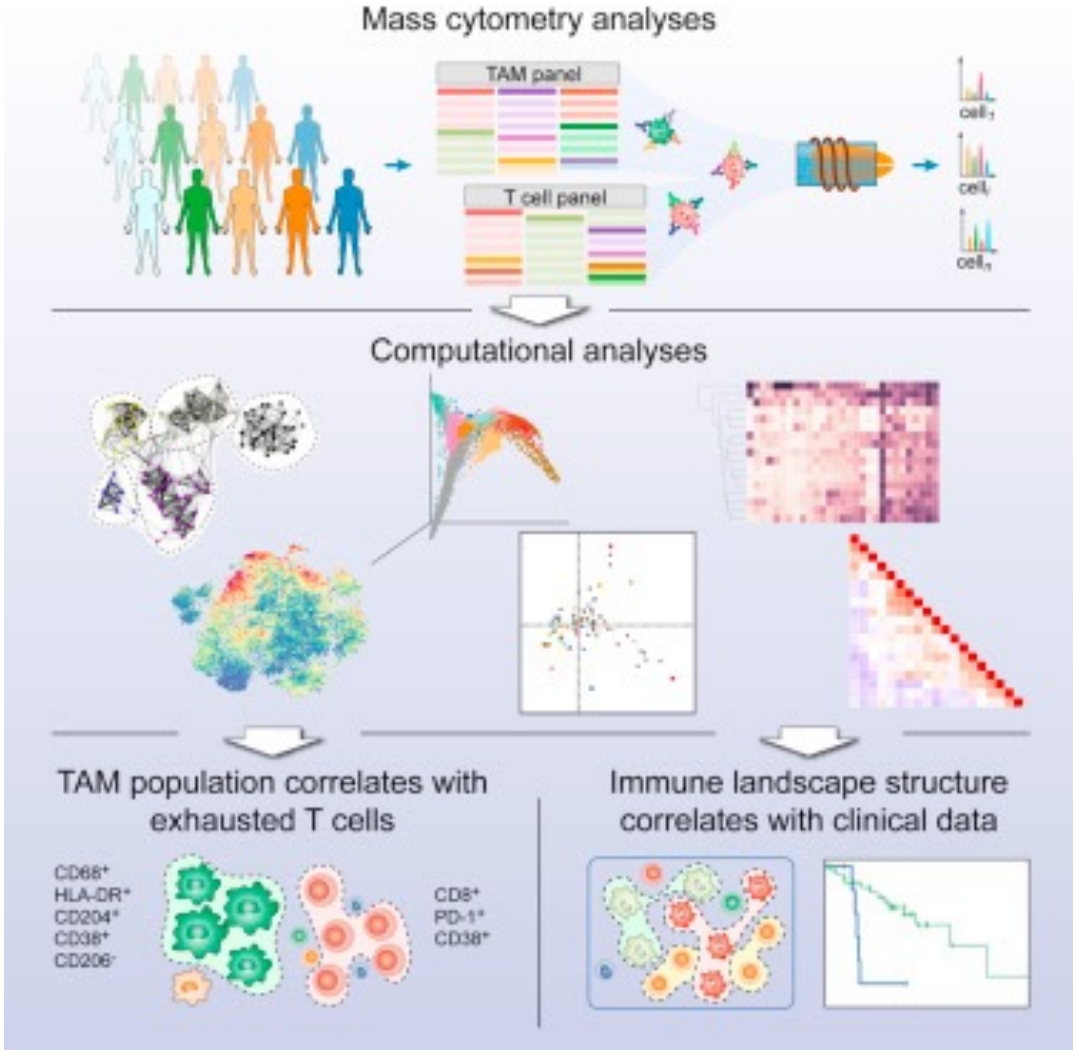
TLS and Immunotherapy

- TLS are not associated with poor prognosis (due to absent maturation?)
- Digital Pathology: TLS size plays a role (Sobottka et al., J Immunother 2022)



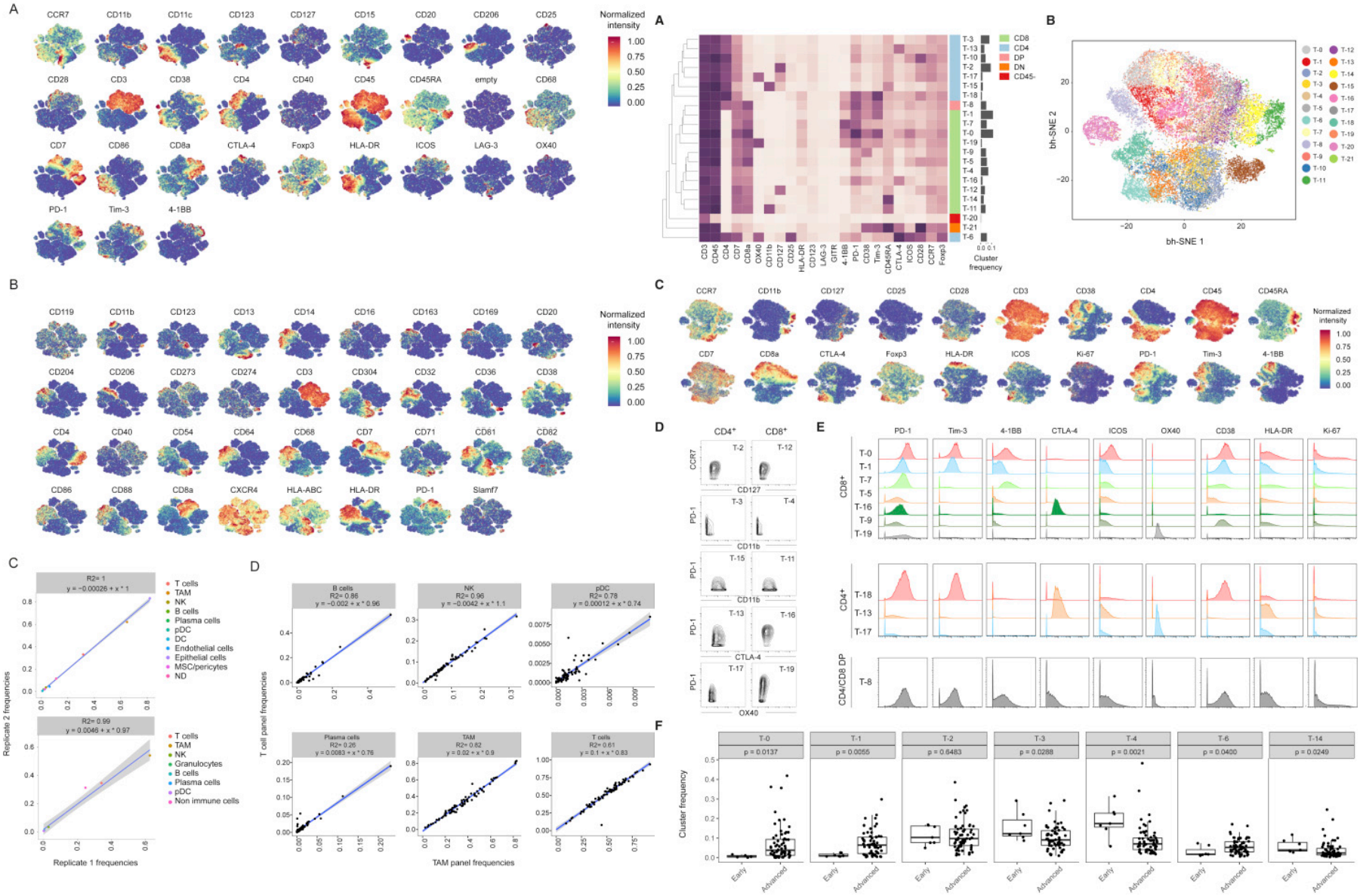


Imaging Mass Cytometry to Characterize Tumor Microenvironment



S. Chevrier, M. Alexander, S. Jewett, H. Moch,…B. Bodenmiller

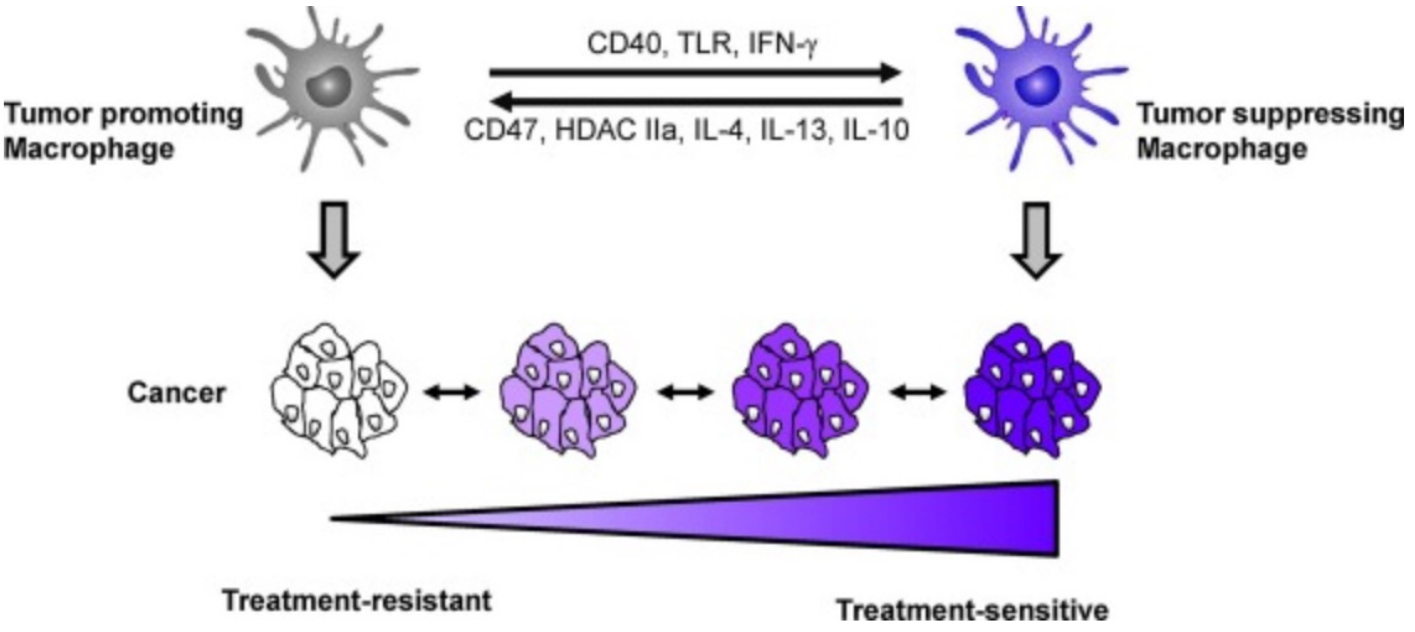
An Immune Atlas of Clear Cell Renal Cell Carcinoma Cell 169, 2017



S. Chevrier, M. Alexander, S. Jewett, H. Moch,…B. Bodenmiller

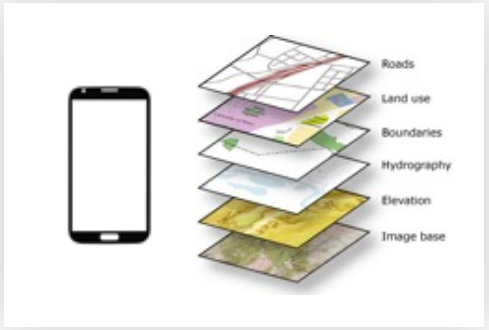
An Immune Atlas of Clear Cell Renal Cell Carcinoma Cell 169, 2017

Macrophages and treatment response



The role of a pathologist is evolving

Molecular testing is evolving towards precision medicine



Classic
- IHC
- FISH
- PCR

Comprehensive molecular profiling
- Next-generation DNA sequencing
- Protein analysis
- Immune signature analysis
- Liquid biopsy (cancer DNA detection from blood)

Classification based on molecular profiling?

Adapted from Toward precision medicine, NAS 2013.

Future of RCC classification?

Multispeciality approach to RCC management

Challenges:

- Morphology-based
- Genomics-based
- -omics technologies
- Clinical relevance


UniversitätsSpital
Zürich
Departement
Pathologie