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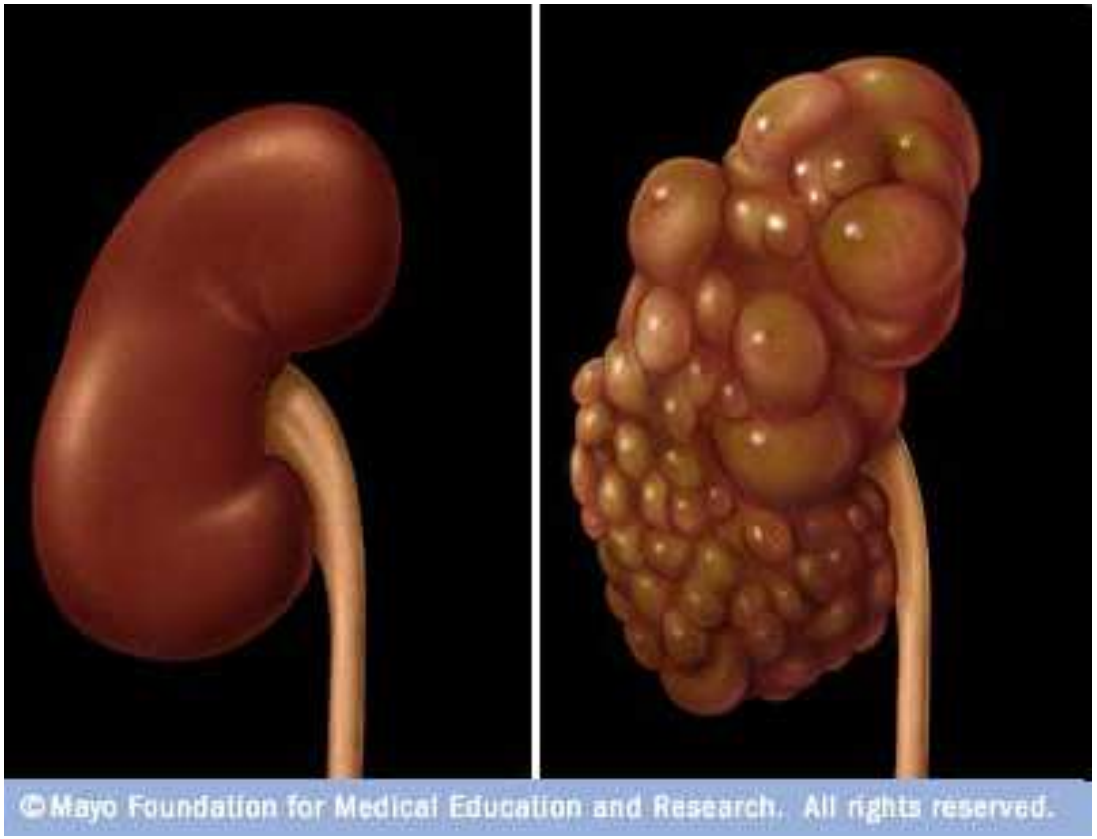
Von Zysten und Zilien – „Wenn die Antenne nicht mehr funkt“

1. Münsteraner Zystentag

PD Dr. Max Liebau

Zystennieren



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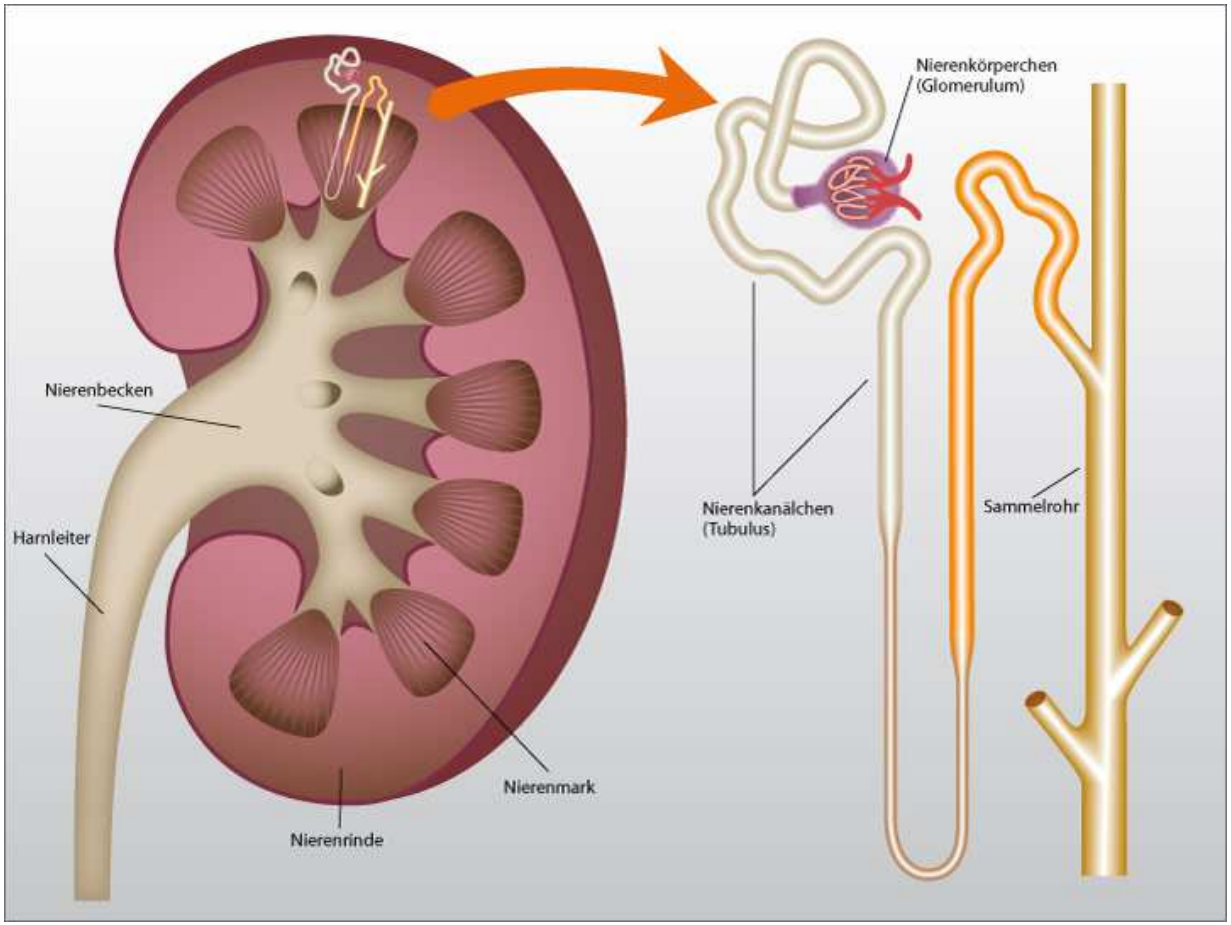
Jede Niere besteht aus ca. 1 Mio Funktionseinheiten



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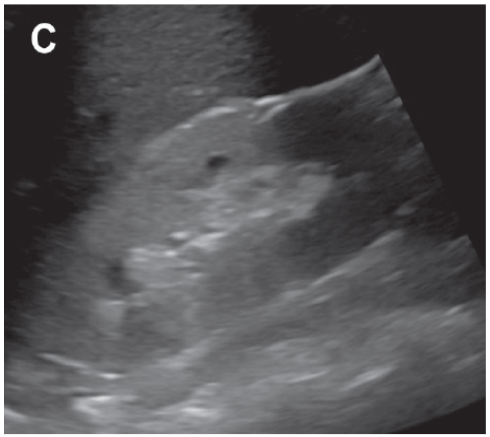
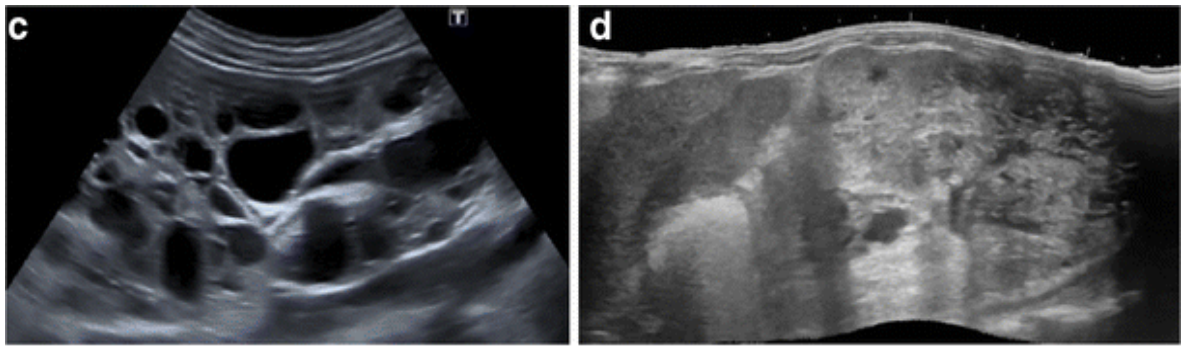
Zysten sind flüssigkeitsgefüllte epithelausgekleidete Hohlräume



Liebau and Habbig,
DGfN-News 2015



Liebau & Serra
Pediatr Nephrol, 2013

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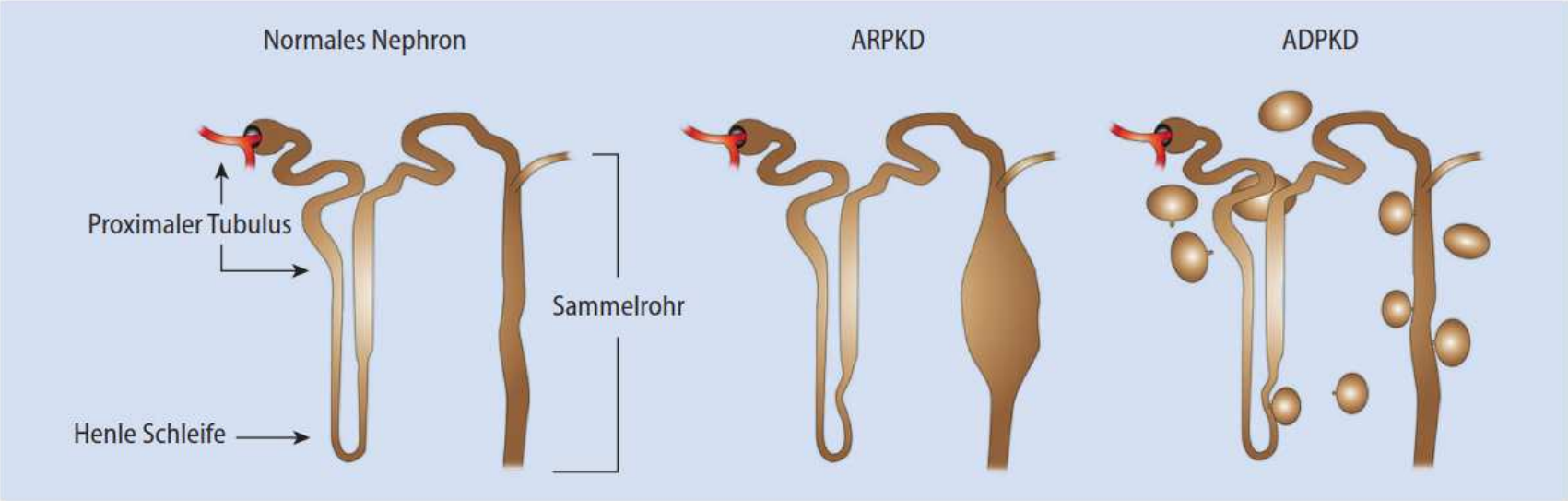
Zysten sind flüssigkeitsgefüllte epithelausgekleidete Hohlräume



Müller und Liebau,
in „Nierenerkrankungen des Kindes- und Jugendalters“ (Dötsch/Weber Hrsg), 2017

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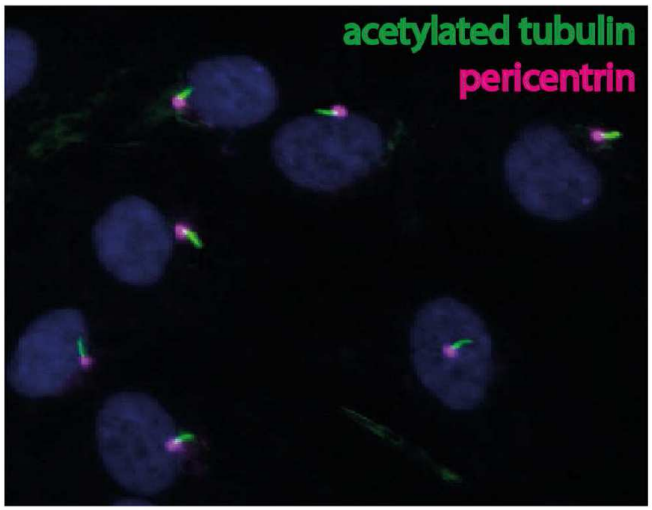
Wie kommt es zu diesen Erweiterungen?

Zilien



Liebau;
Front Pediatr, 2014

Pazour et al.;
Trends Cell Biol, 2002

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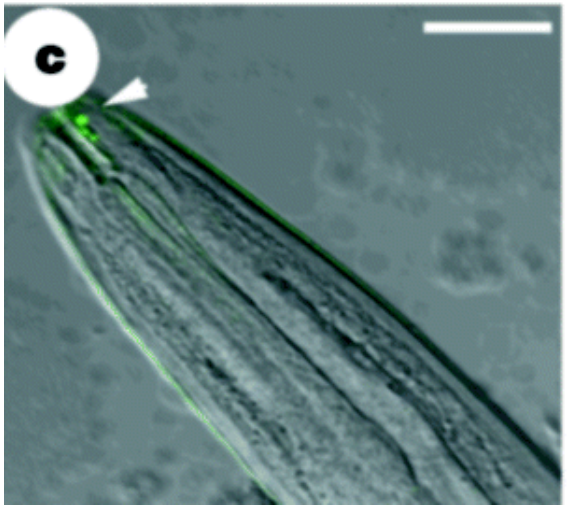
A polycystic kidney-disease gene homologue required for male mating behaviour in *C. elegans*

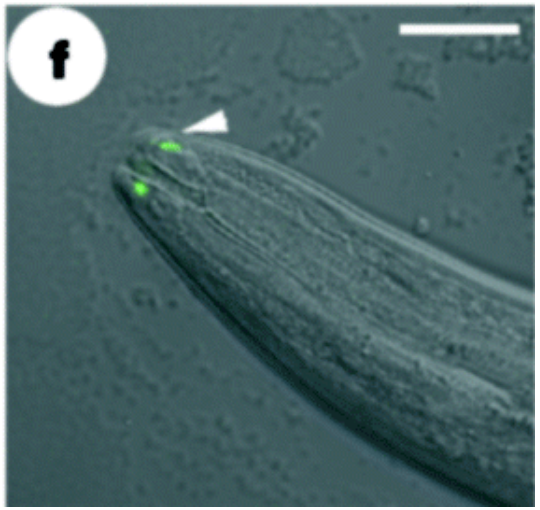
Maureen M. Barr & Paul W. Sternberg

Howard Hughes Medical Institute and Division of Biology, California Institute of Technology, Pasadena, California 91125, USA

Nature, 1999

www.easternct.edu





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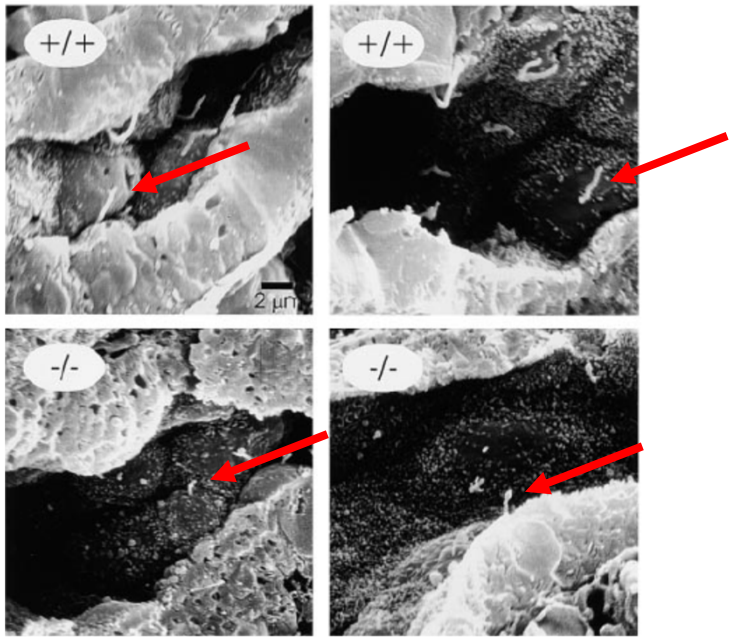
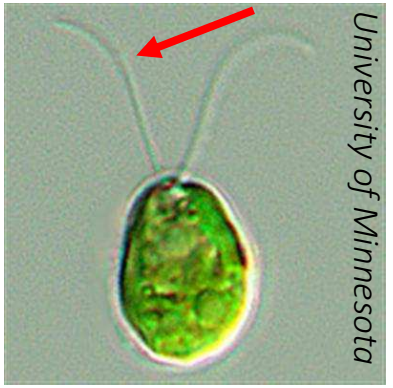
Published October 30, 2000

*Chlamydomonas IFT*88 and Its Mouse Homologue, Polycystic Kidney Disease Gene *Tg*737, Are Required for Assembly of Cilia and Flagella

Gregory J. Pazour,* Bethany L. Dickert,* Yvonne Vucica,‡ E. Scott Seeley,‡ Joel L. Rosenbaum,‡ George B. Witman,* and Douglas G. Cole§

*Department of Cell Biology, University of Massachusetts Medical School, Worcester, Massachusetts 01655; ‡Department of Molecular, Cellular, and Developmental Biology, Yale University, New Haven, Connecticut 06520; and §Department of Microbiology, Molecular Biology, and Biochemistry, University of Idaho, Moscow, Idaho 83844





J Cell Biol, 2000

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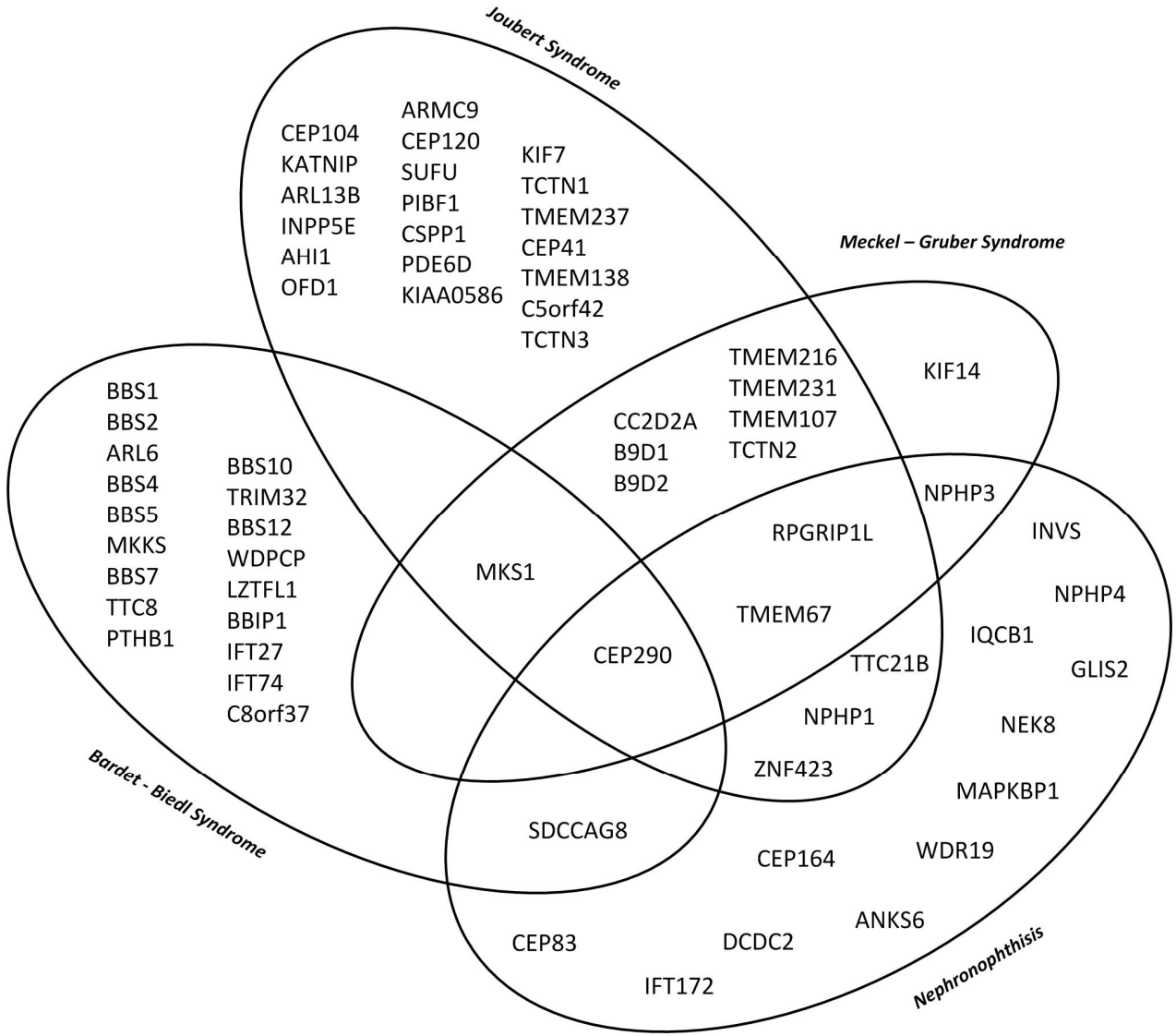
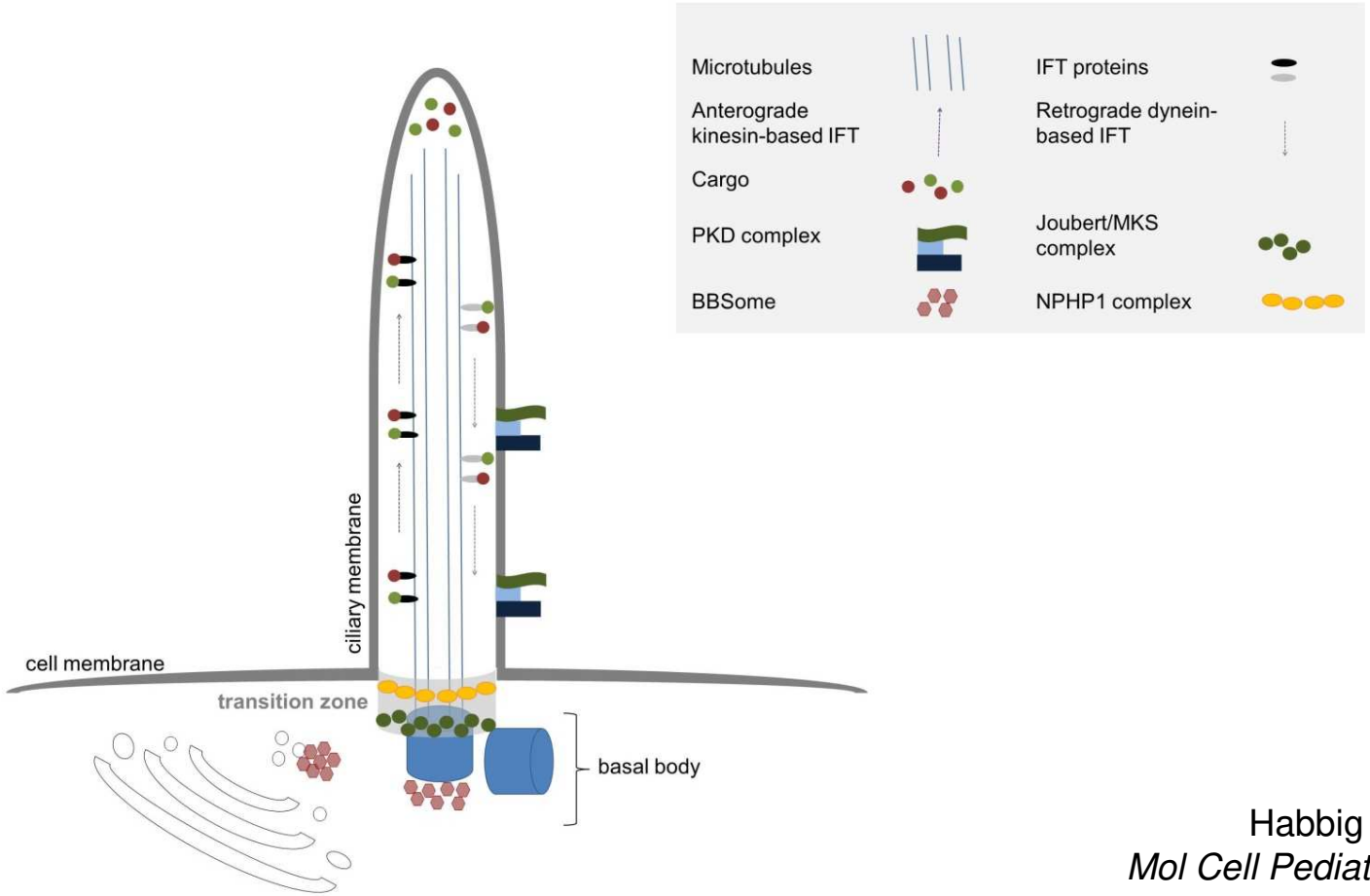


+ ARPKD
+ ADPKD
+ (...)

König et al.,
Frontiers in Peds, 2018

Zystennierengenprodukte am Zilium



Habbig & Liebau,
Mol Cell Pediatrics, 2015

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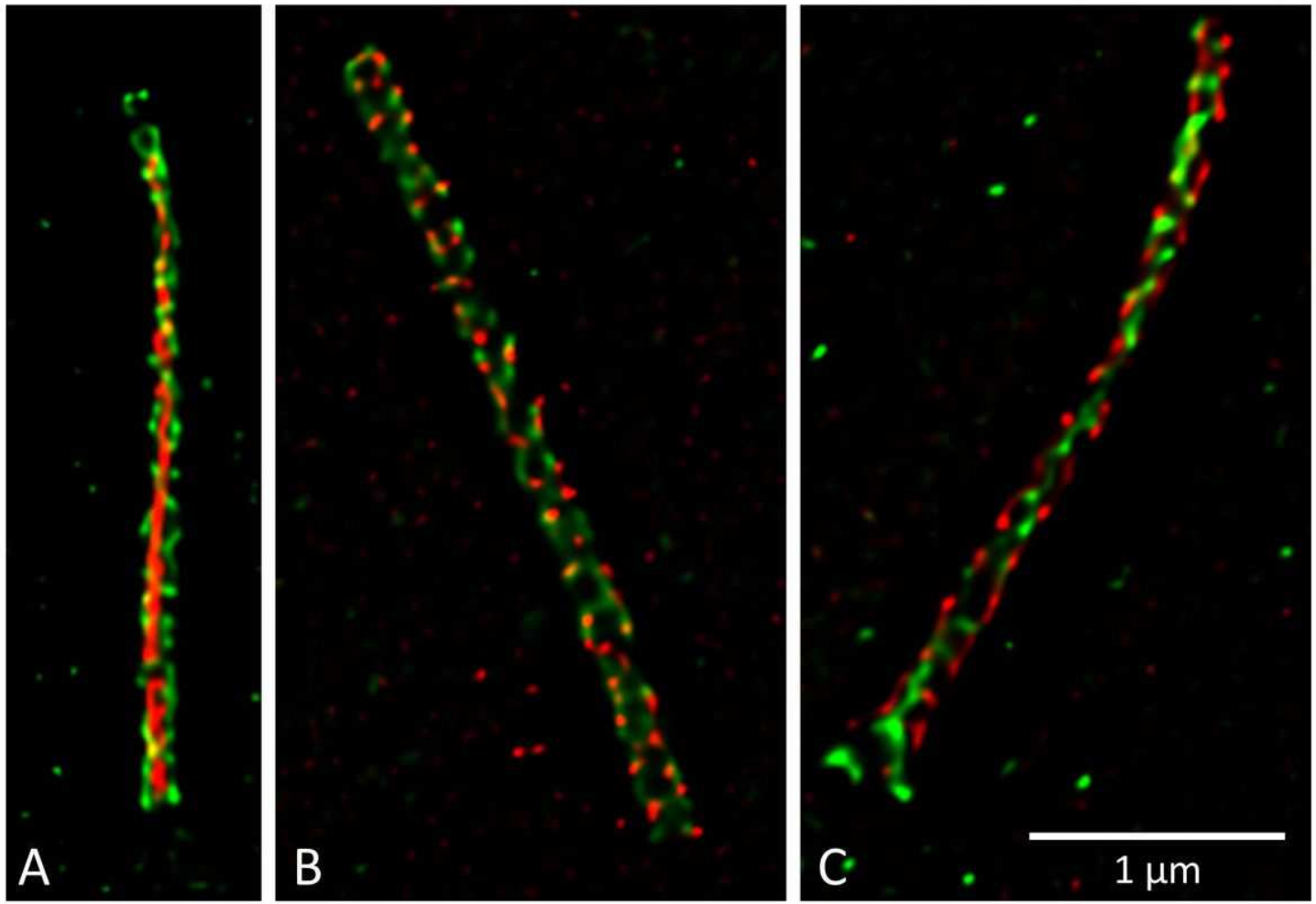

Bernhard Schermer, www.nierenforschung.de

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REVIEW

J Am Soc Nephrol 15: 2528–2536, 2004

Intraflagellar Transport and Cilia-Dependent Renal Disease: The Ciliary Hypothesis of Polycystic Kidney Disease

GREGORY J. PAZOUR
Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

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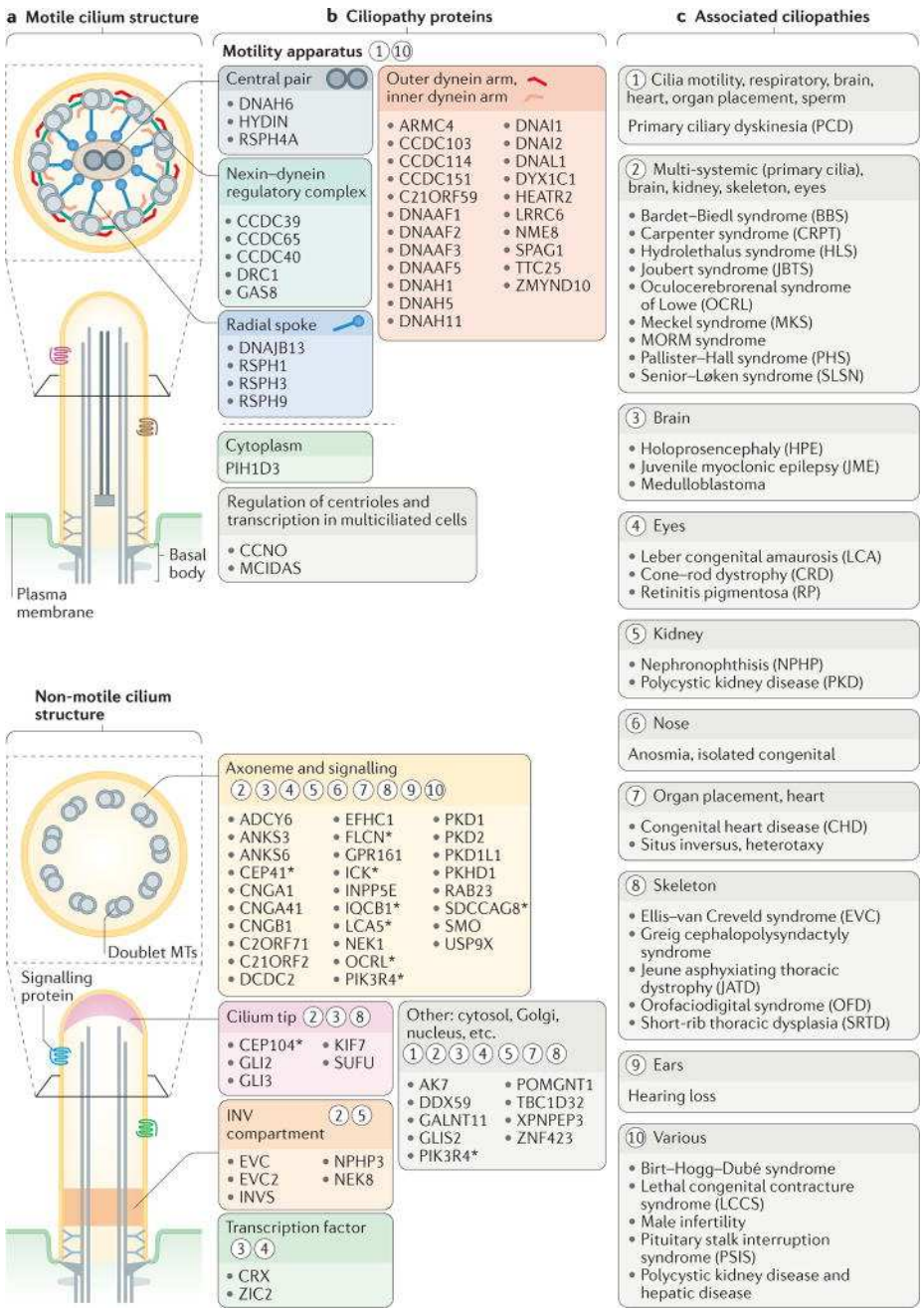
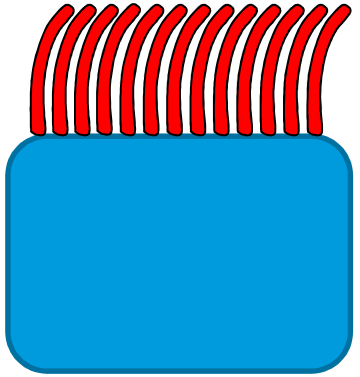
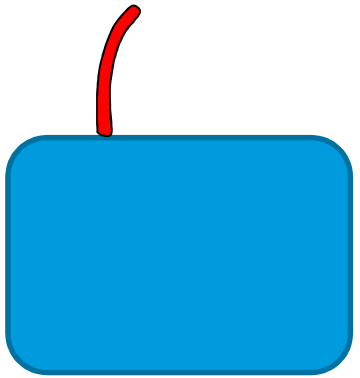
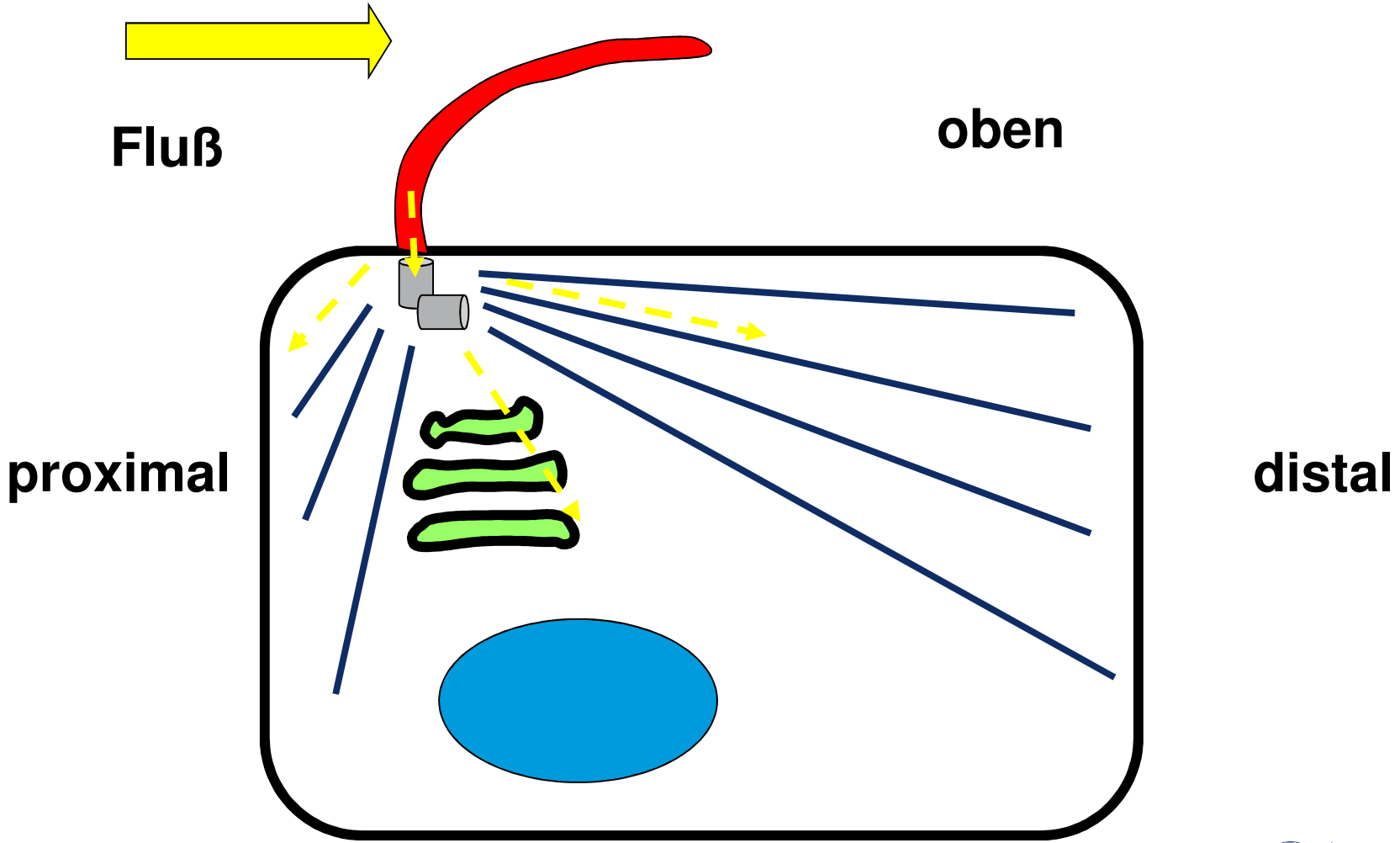


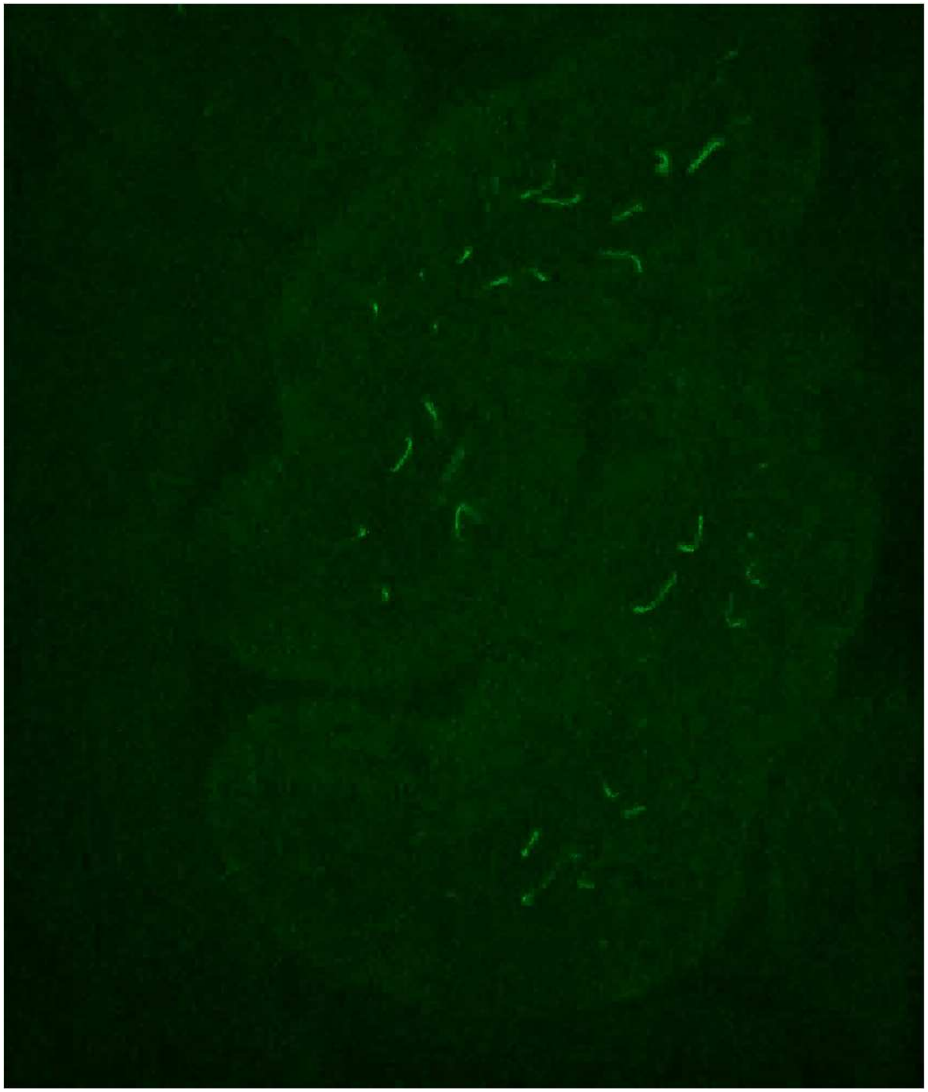




2017: 35 Ziliopathien
187 Ziliopathie-Gene
241 weitere Kandidatengene

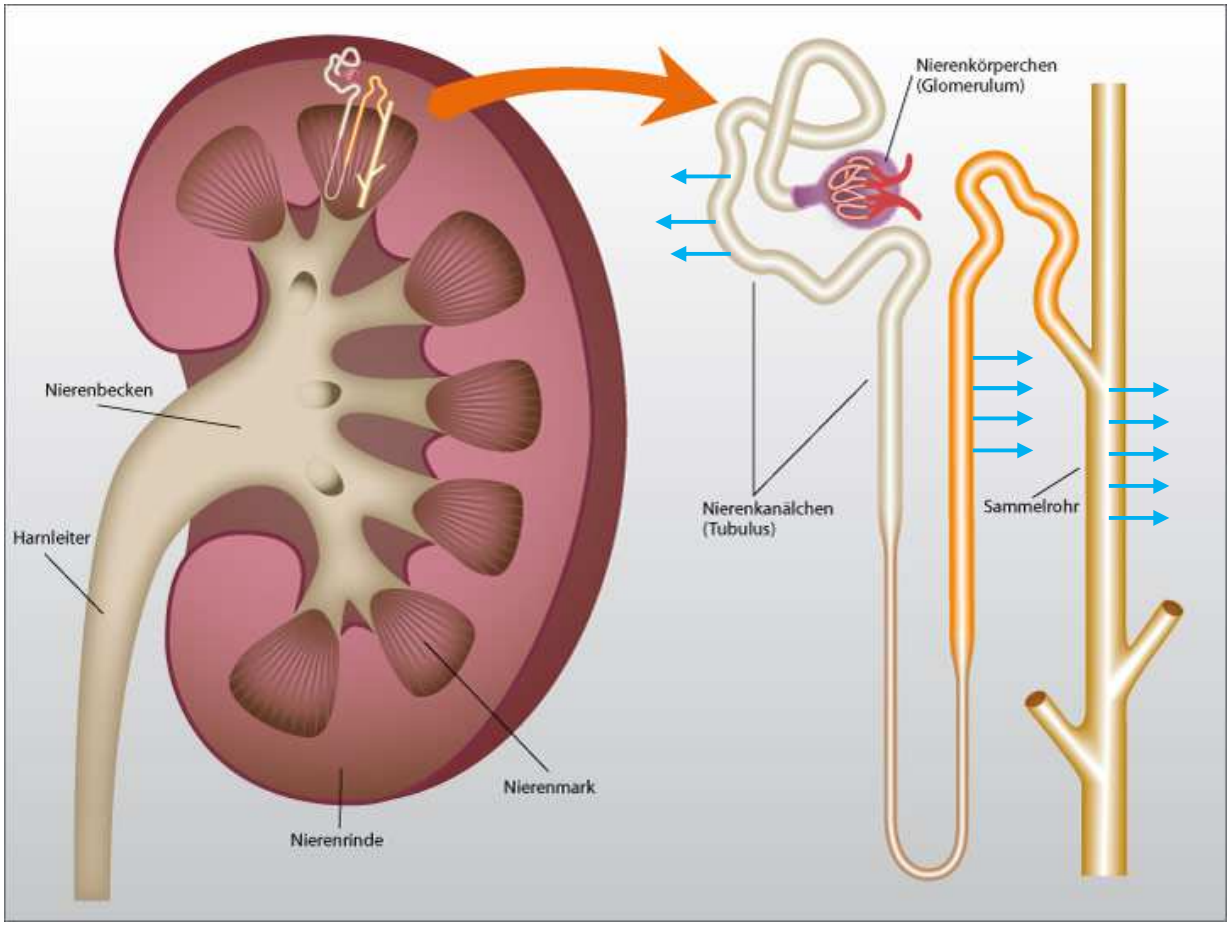
Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017





O‘Connor et al., *Cilia,* 2013

Im Nierenkanälchen (Tubulus) wird der Urin nachbearbeitet



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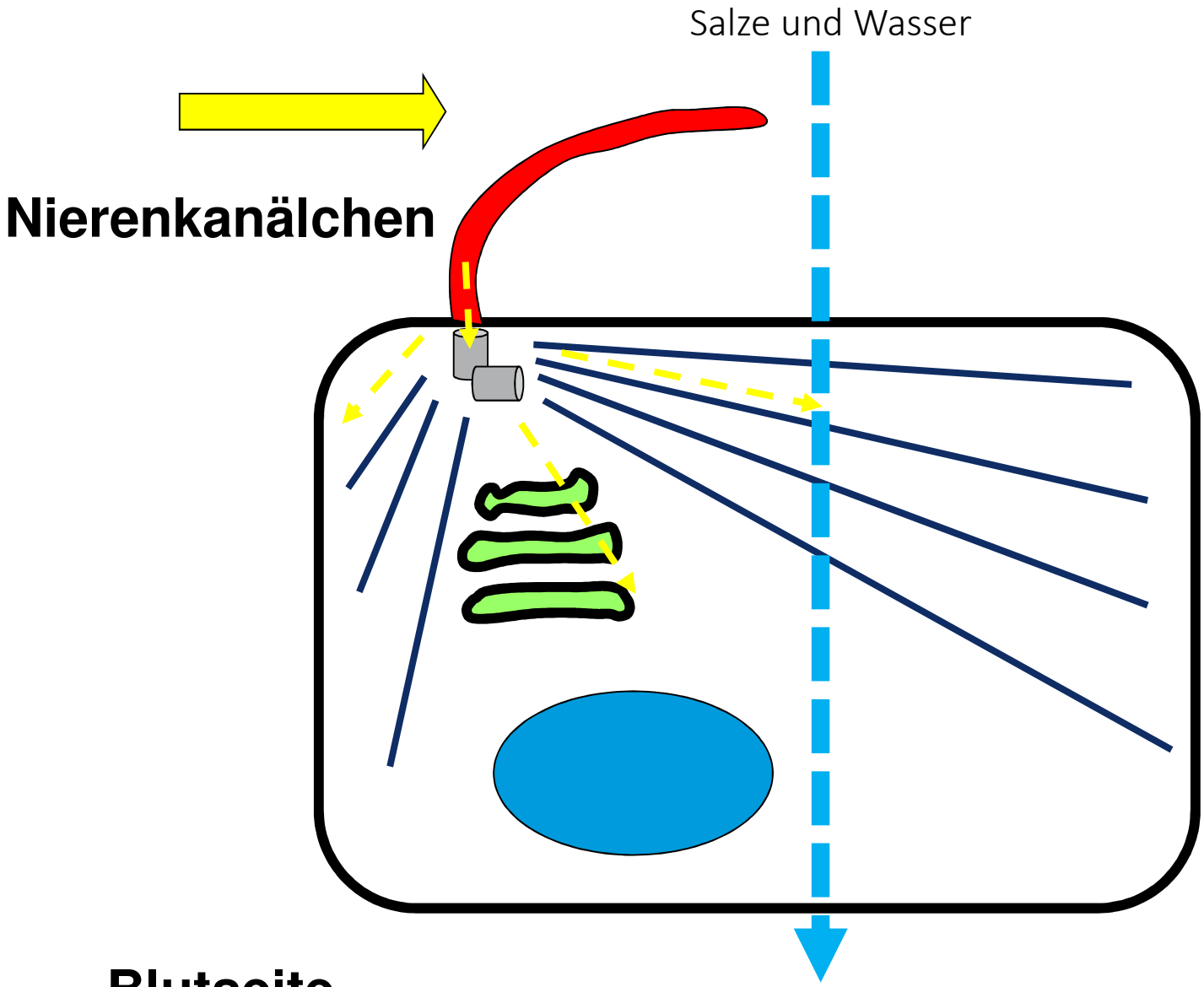
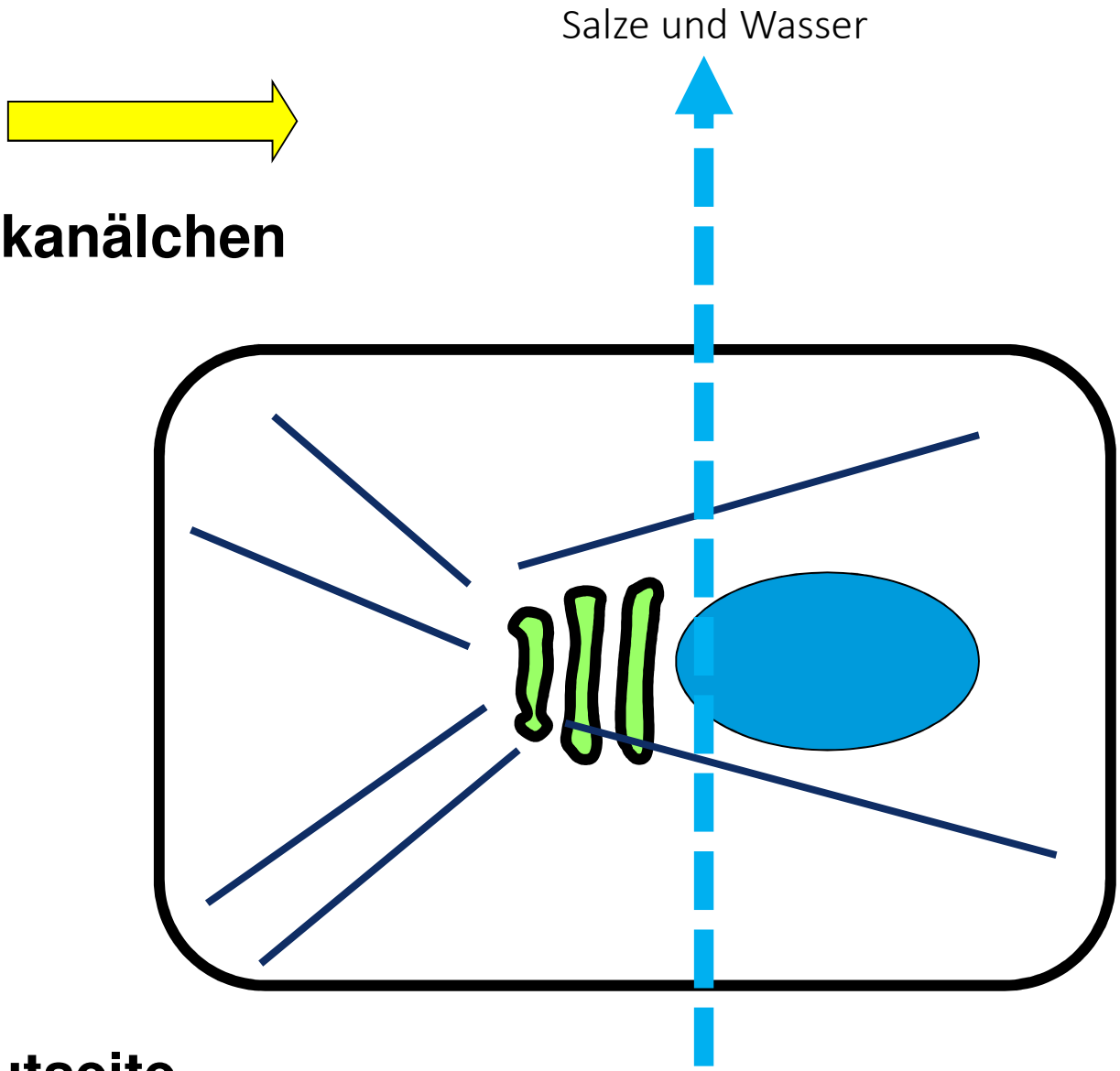
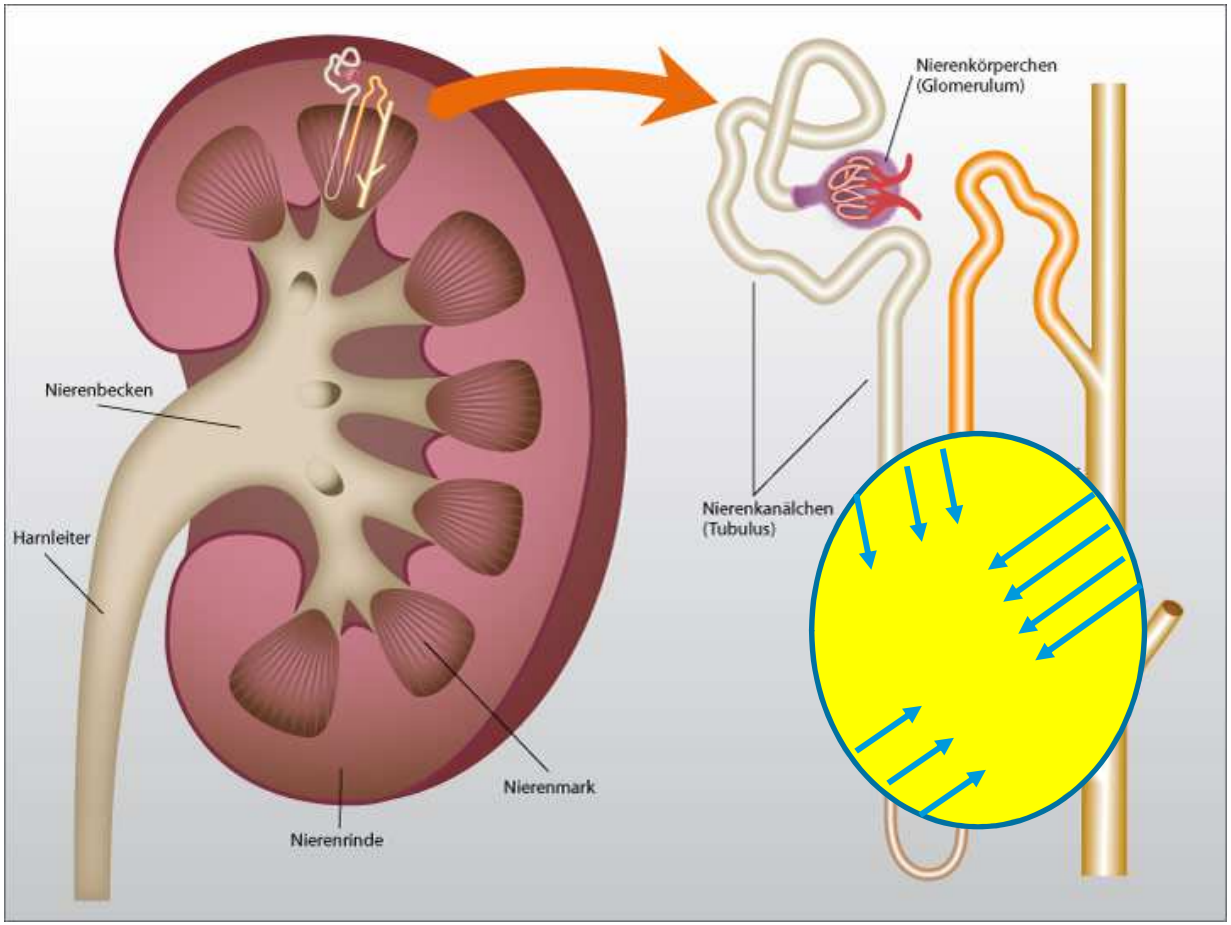



Salze und Wasser
Nierenkanälchen
Blutseite

Im Nierenkanälchen (Tubulus) wird der Urin nachbearbeitet



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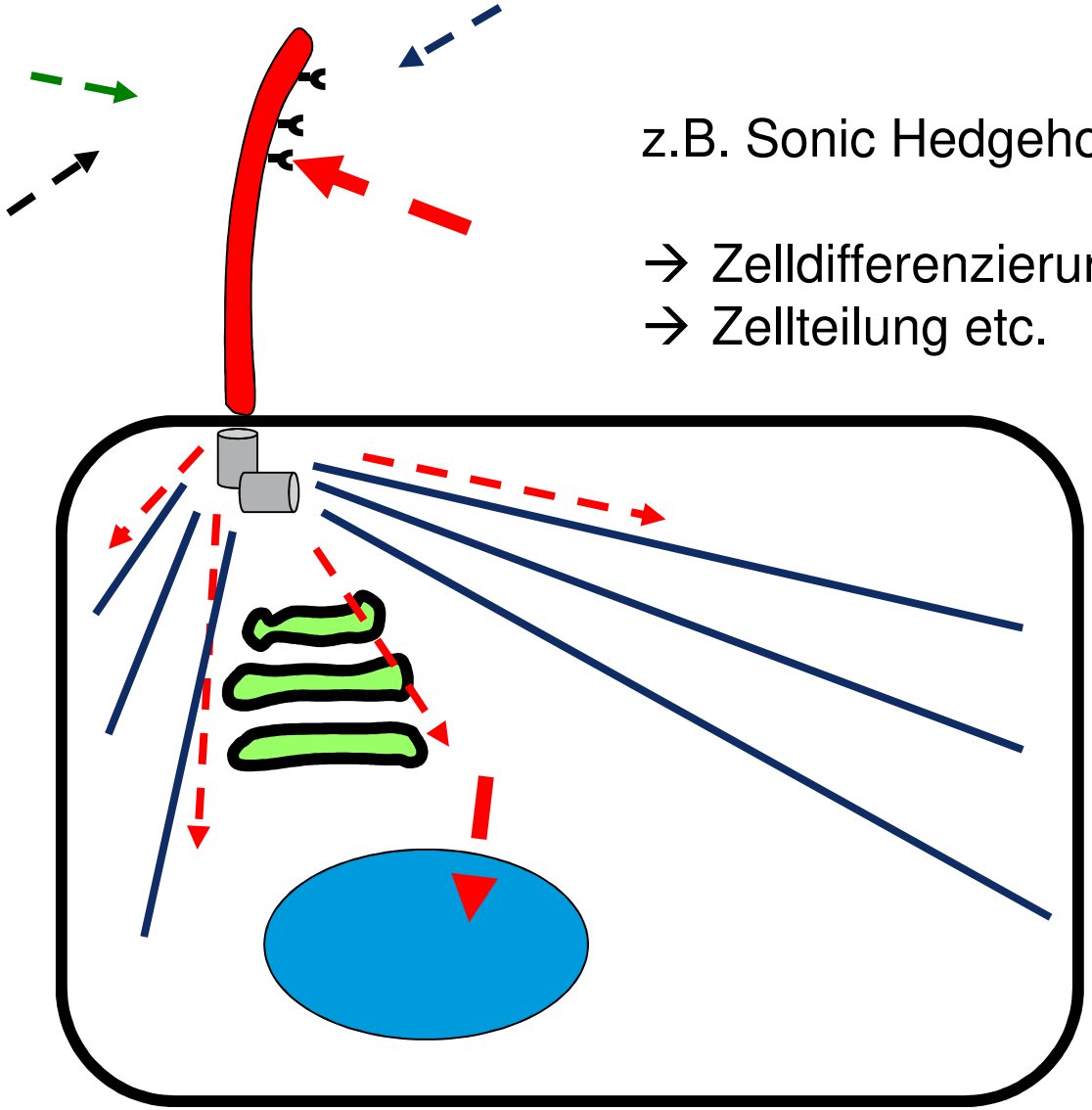
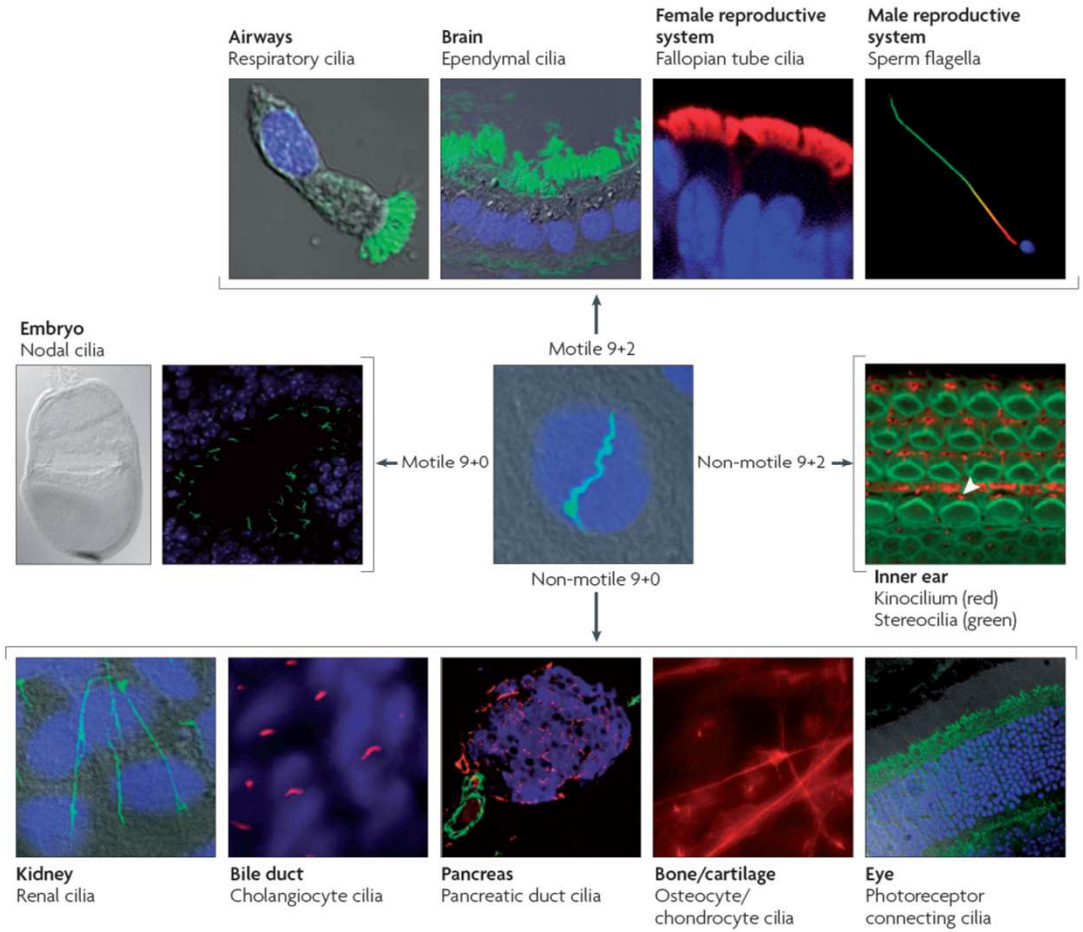


z.B. Sonic Hedgehog Signaling

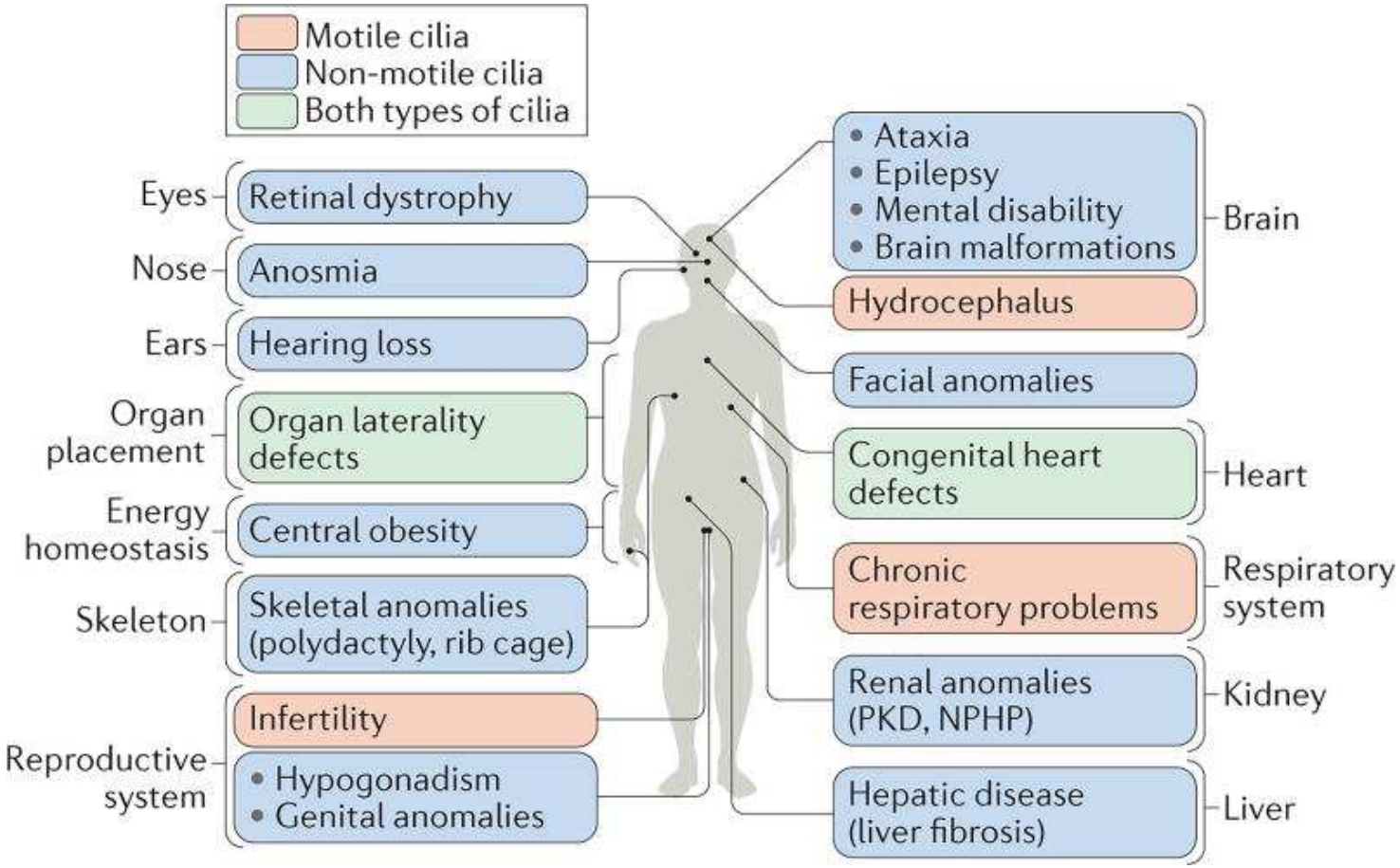
→ Zelldifferenzierung und Funktion
→ Zellteilung etc.

Zilien finden sich auf vielen Zellen

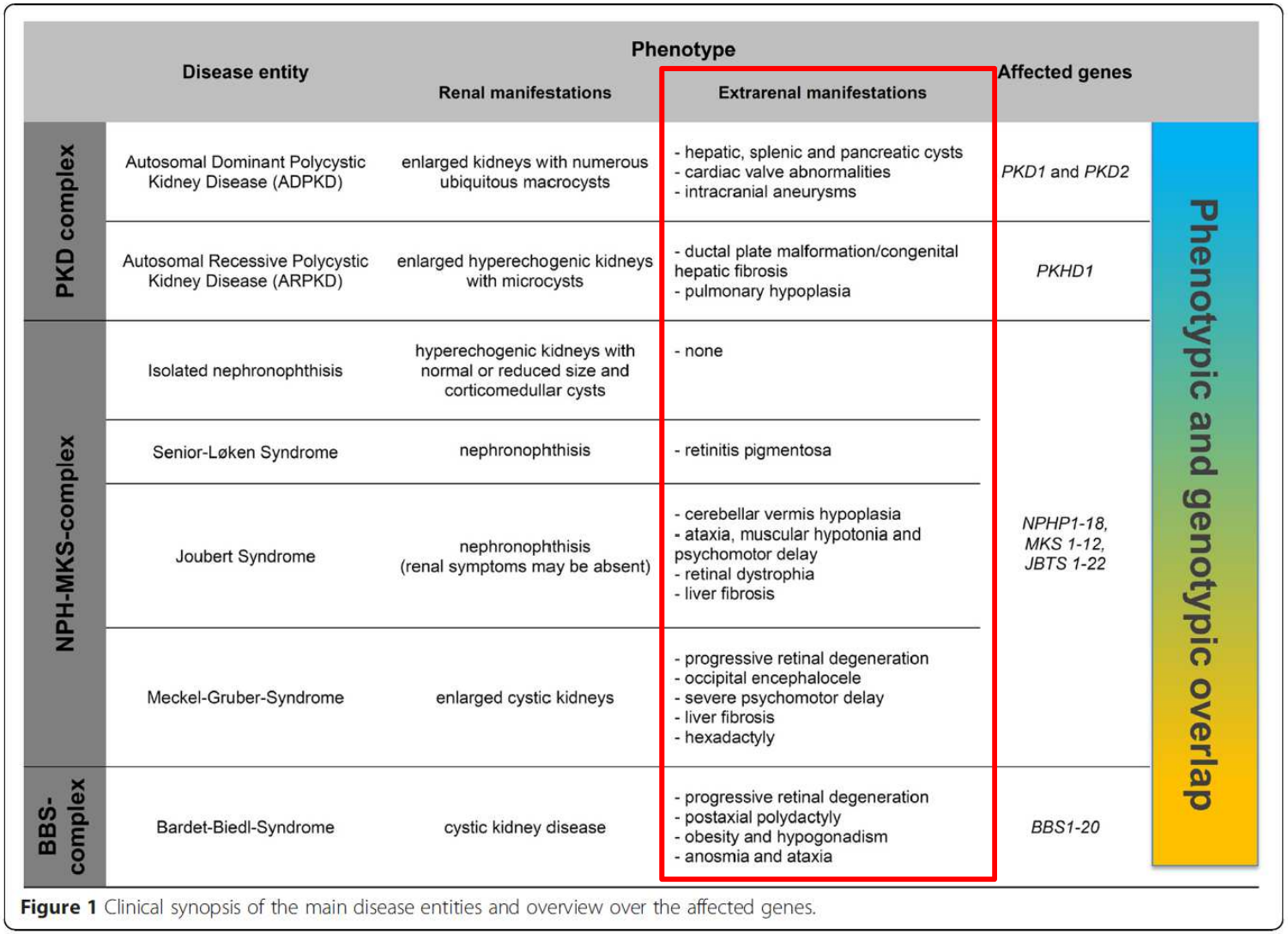


Fliegauf, Benzing, Omran,
Nat Rev Mol Cell Biol, 2007

Ziliendefekte führen zu vielen Symptomen



Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017

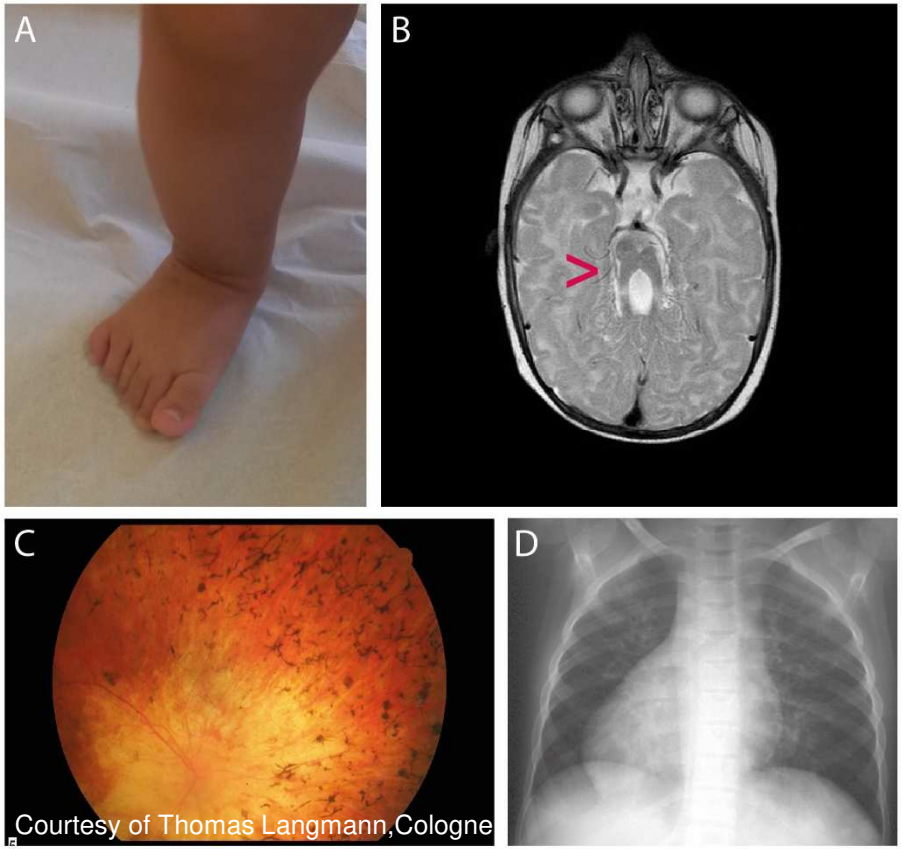


	Disease entity	Phenotype: Renal manifestations	Phenotype: Extrarenal manifestations	Affected genes	
PKD complex	Autosomal Dominant Polycystic Kidney Disease (ADPKD)	enlarged kidneys with numerous ubiquitous macrocysts	- hepatic, splenic and pancreatic cysts - cardiac valve abnormalities - intracranial aneurysms	*PKD1* and *PKD2*	Phenotypic and genotypic overlap
PKD complex	Autosomal Recessive Polycystic Kidney Disease (ARPKD)	enlarged hyperechogenic kidneys with microcysts	- ductal plate malformation/congenital hepatic fibrosis - pulmonary hypoplasia	*PKHD1*	
NPH-MKS-complex	Isolated nephronophthisis	hyperechogenic kidneys with normal or reduced size and corticomedullar cysts	- none	*NPHP1-18, MKS 1-12, JBTS 1-22*	
NPH-MKS-complex	Senior-Løken Syndrome	nephronophthisis	- retinitis pigmentosa		
NPH-MKS-complex	Joubert Syndrome	nephronophthisis (renal symptoms may be absent)	- cerebellar vermis hypoplasia - ataxia, muscular hypotonia and psychomotor delay - retinal dystrophia - liver fibrosis		
NPH-MKS-complex	Meckel-Gruber-Syndrome	enlarged cystic kidneys	- progressive retinal degeneration - occipital encephalocele - severe psychomotor delay - liver fibrosis - hexadactyly		
BBS-complex	Bardet-Biedl-Syndrome	cystic kidney disease	- progressive retinal degeneration - postaxial polydactyly - obesity and hypogonadism - anosmia and ataxia	*BBS1-20*	

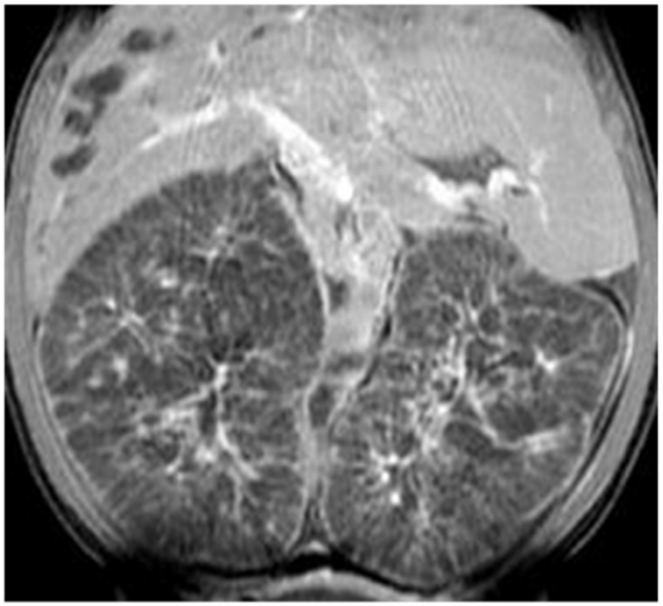
Figure 1 Clinical synopsis of the main disease entities and overview over the affected genes.

Habbig und Liebau,
Mol Cell Pediatrics, 2015

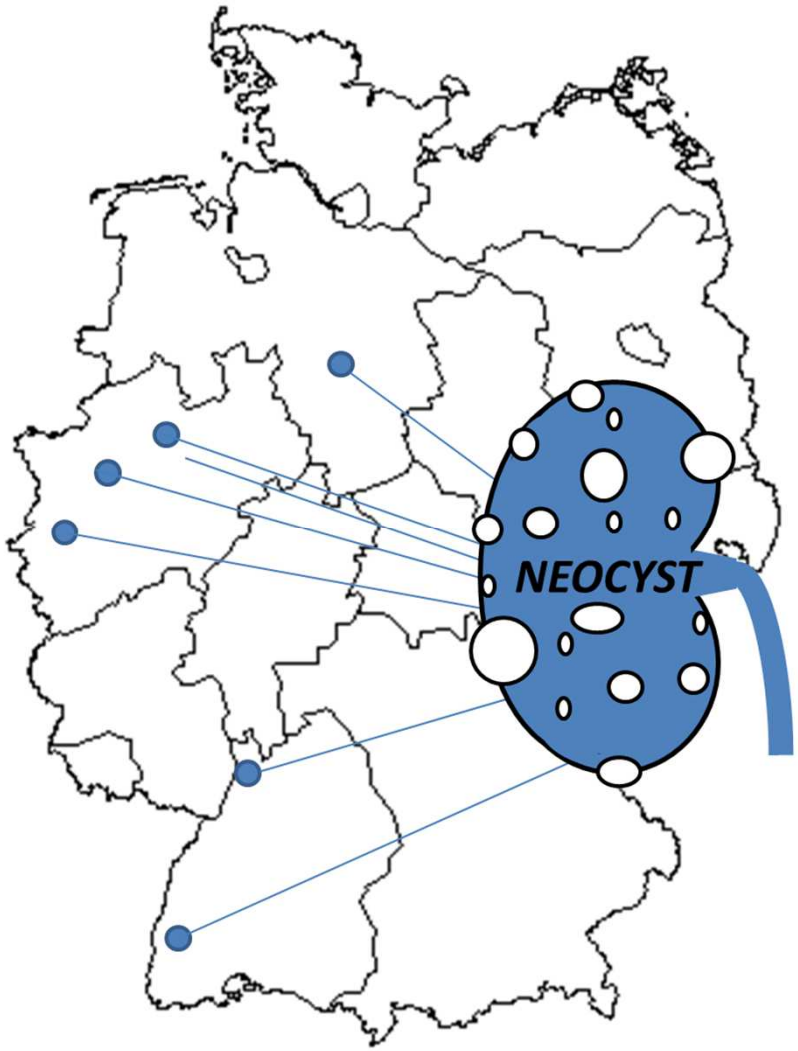
Extrarenale Symptome

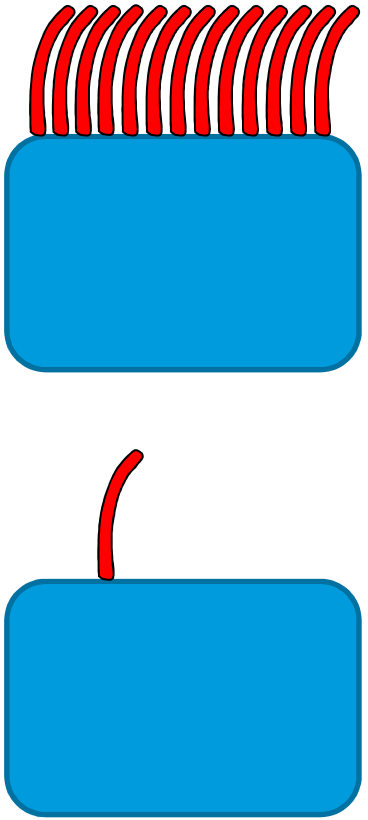


Müller und Liebau,
in „Nierenerkrankungen des Kindes- und Jugendalters“ (Dötsch/Weber Hrsg), 2017



Ebner et al.,
Pediatric Nephrology, 2017





NEOCYST
Network for Early Onset
Cystic Kidney Diseases

GEFÖRDERT VOM
Bundesministerium
für Bildung
und Forschung

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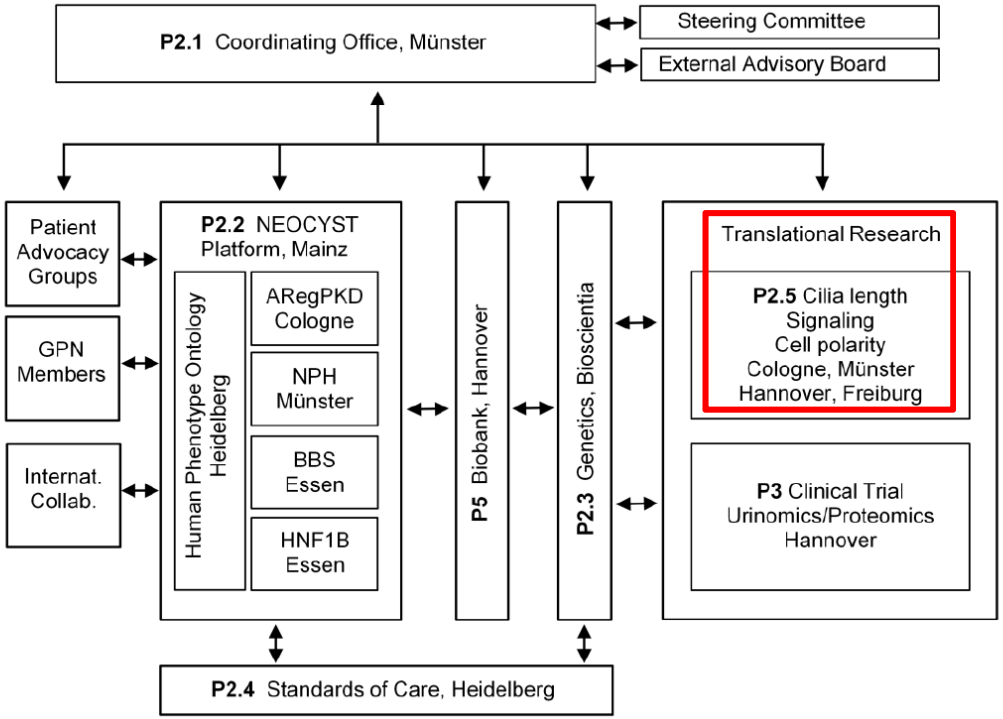
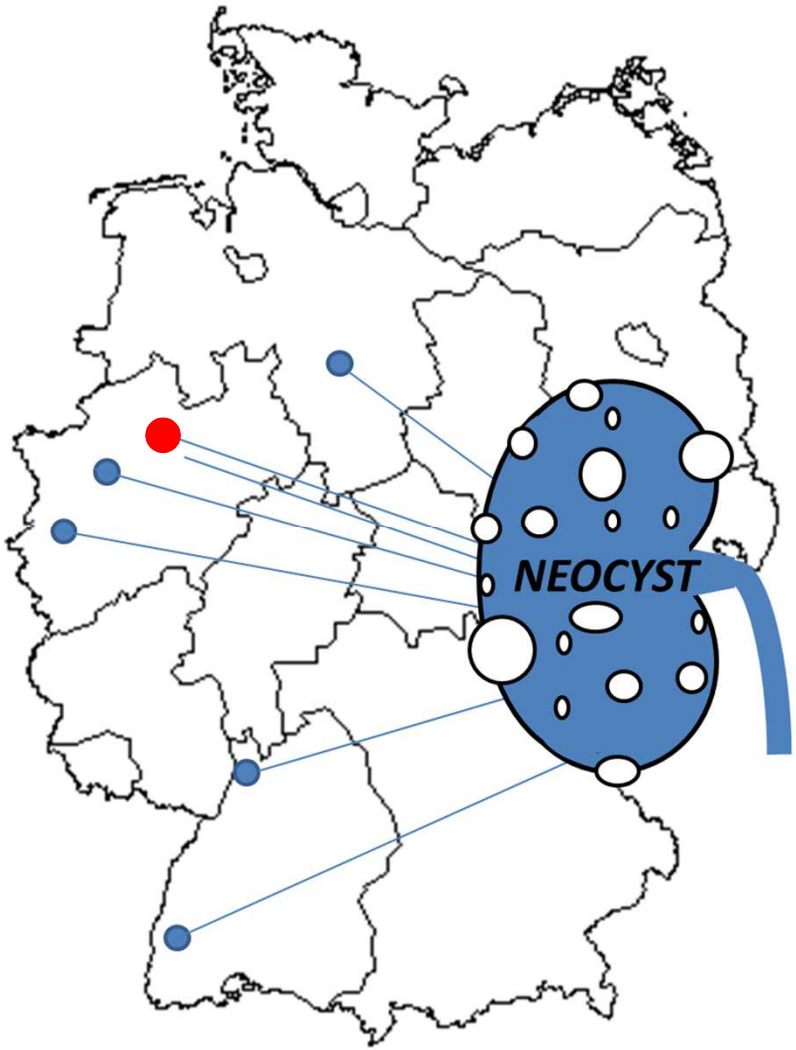
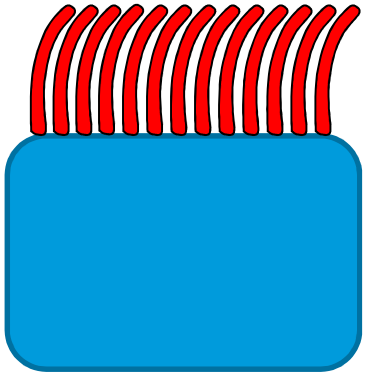
NEOCYST

Network for **E**arly **O**nset **Cyst**ic Kidney Diseases



PKD Familiäre Zystennieren e.V.
NEOCYST
GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung
GPN Gesellschaft für Pädiatrische Nephrologie





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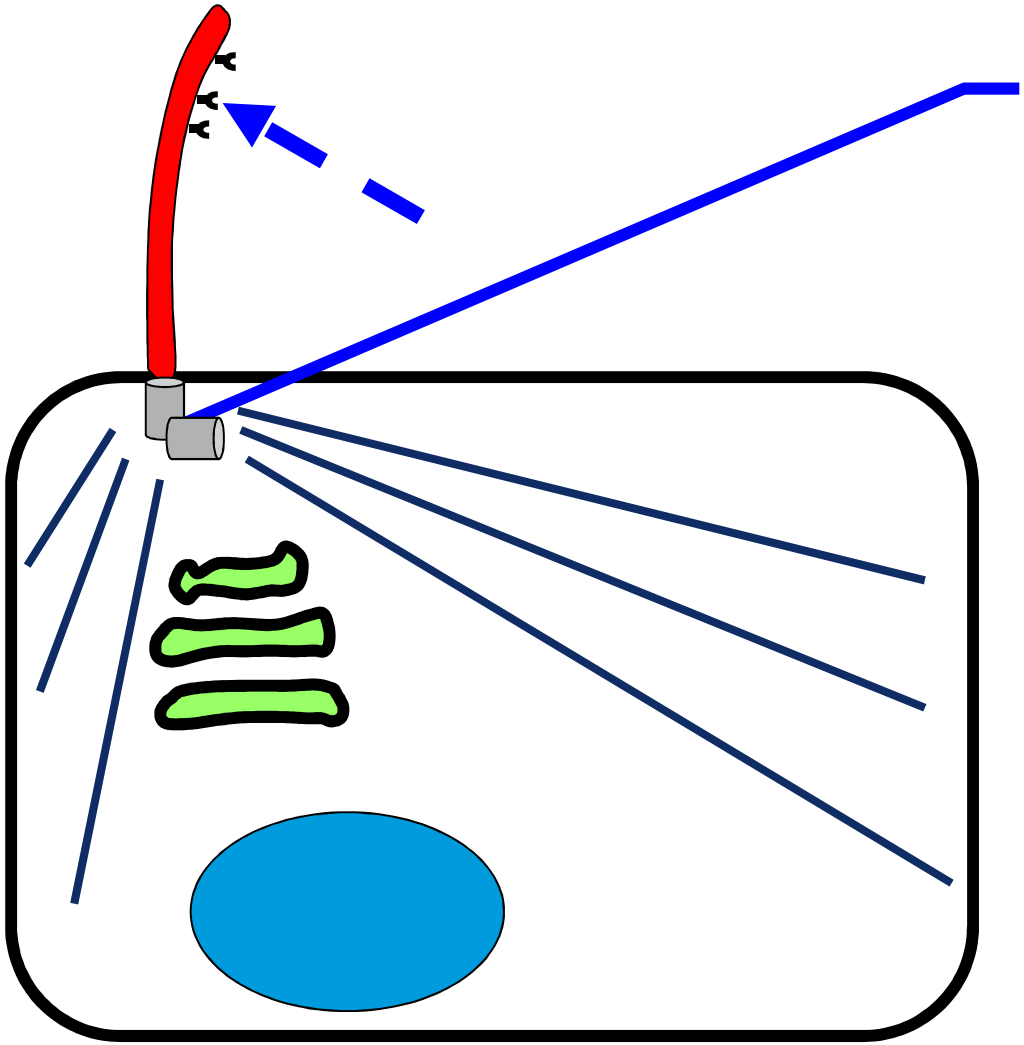
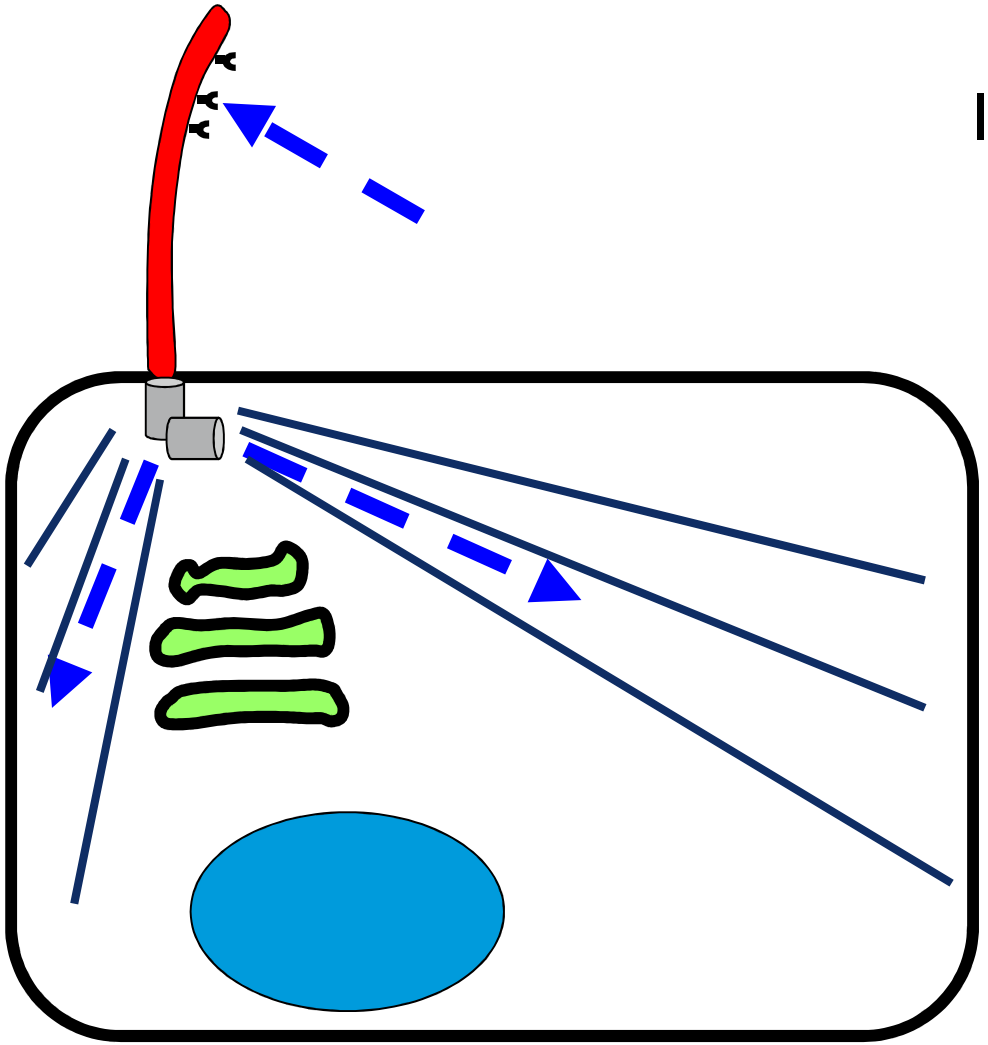
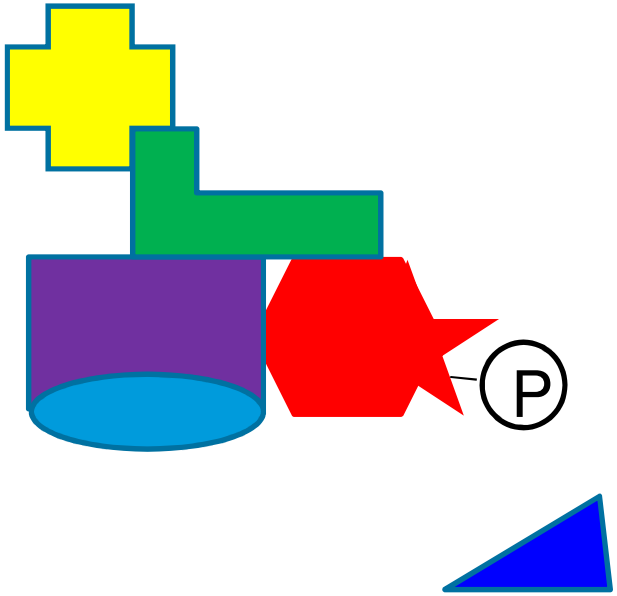


Was passiert bei der Signalweitergabe intrazellulär?



Intrazelluläre Proteinkomplexe



→ Signale:
Zellteilung, Zelltod etc.

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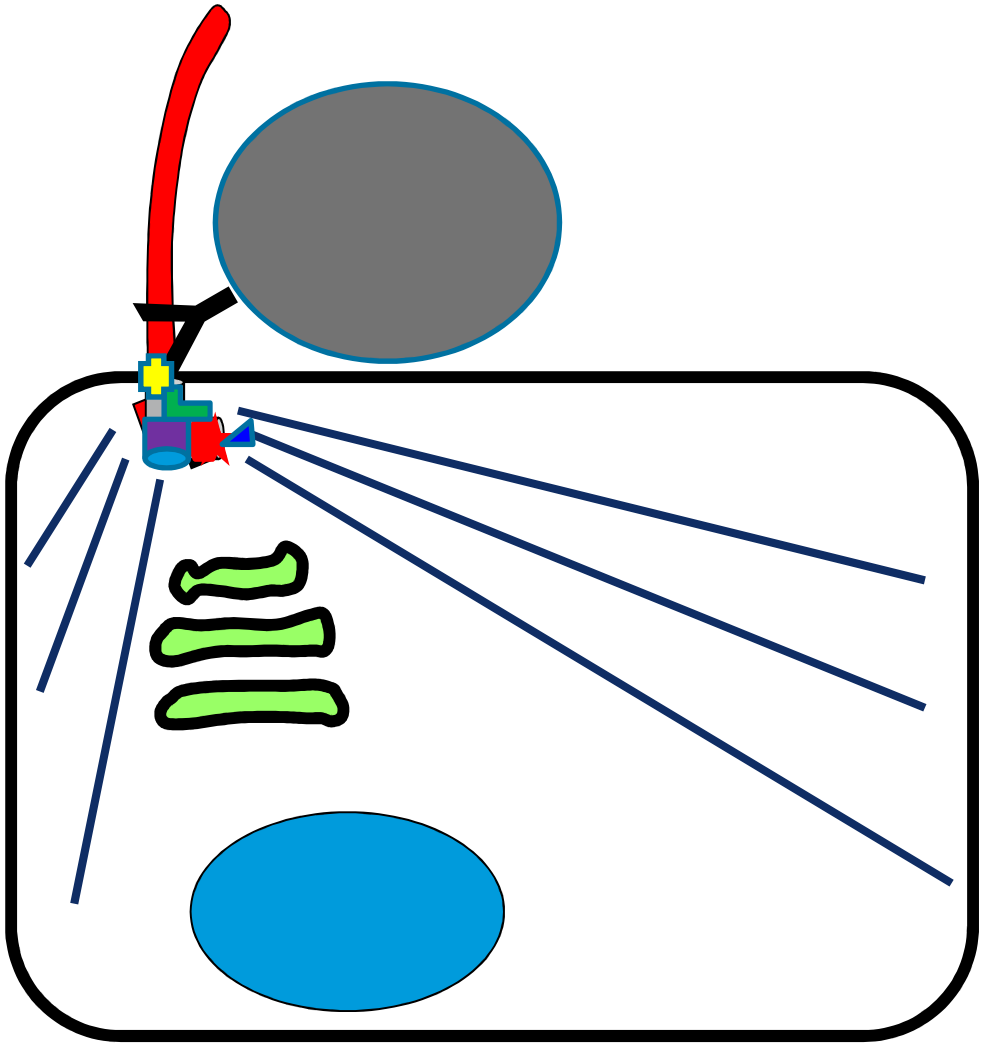
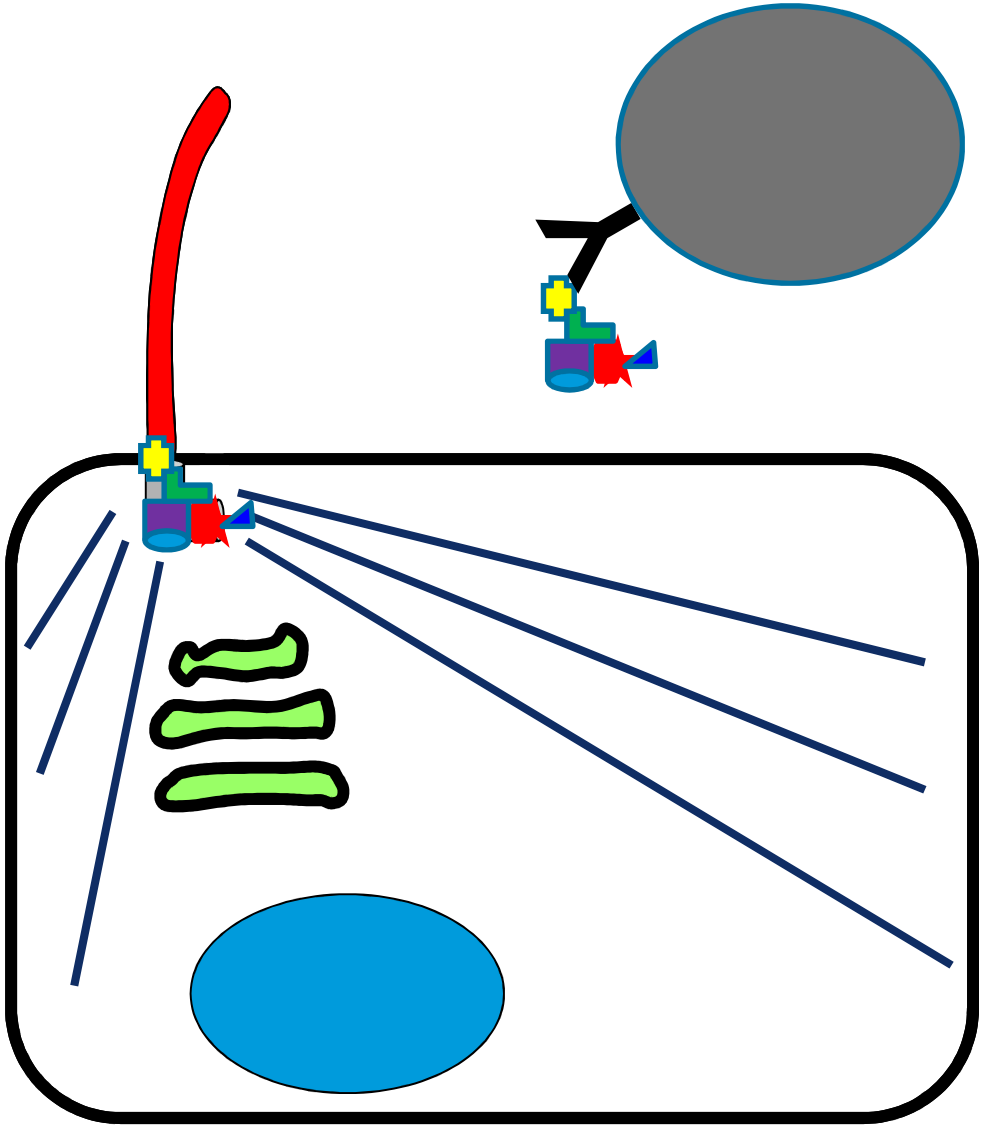


Isolierung und MS-Charakterisierung ziliärer Proteinkomplexe:



Isolierung und MS-Charakterisierung ziliärer Proteinkomplexe:

Mit welchen anderen Proteinen liegt ein krankheitsassoziiertes Zilienprotein in einem Komplex vor?

Welche intrazellulären Signalwege könnten beeinflusst werden?

Dafinger et al. *Experimental & Molecular Medicine* (2018)50:75
DOI 10.1038/s12276-018-0108-z

Experimental & Molecular Medicine

ARTICLE Open Access

Targeted deletion of the AAA-ATPase Ruvbl1 in mice disrupts ciliary integrity and causes renal disease and hydrocephalus

Claudia Dafinger[1,2,3], Markus M. Rinschen[1,2,4], Lori Borgal[1,2], Carolin Ehrenberg[1], Sander G. Basten[5], Mareike Franke[6], Martin Höhne[1,2,4,7], Manfred Rauh[8], Heike Göbel[9], Wilhelm Bloch[10], F. Thomas Wunderlich[2,4,11,12], Dorien J. M. Peters[13], Dirk Tasche[1], Tripti Mishra[1,2], Sandra Habbig[1,2,3], Jörg Dötsch[3], Roman-Ulrich Müller[1,2,4], Jens C. Brüning[2,4,11,12], Thorsten Persigehl[6], Rachel H. Giles[5], Thomas Benzing[1,2,4,7], Bernhard Schermer[1,2,4,7] and Max C. Liebau[1,2,3]

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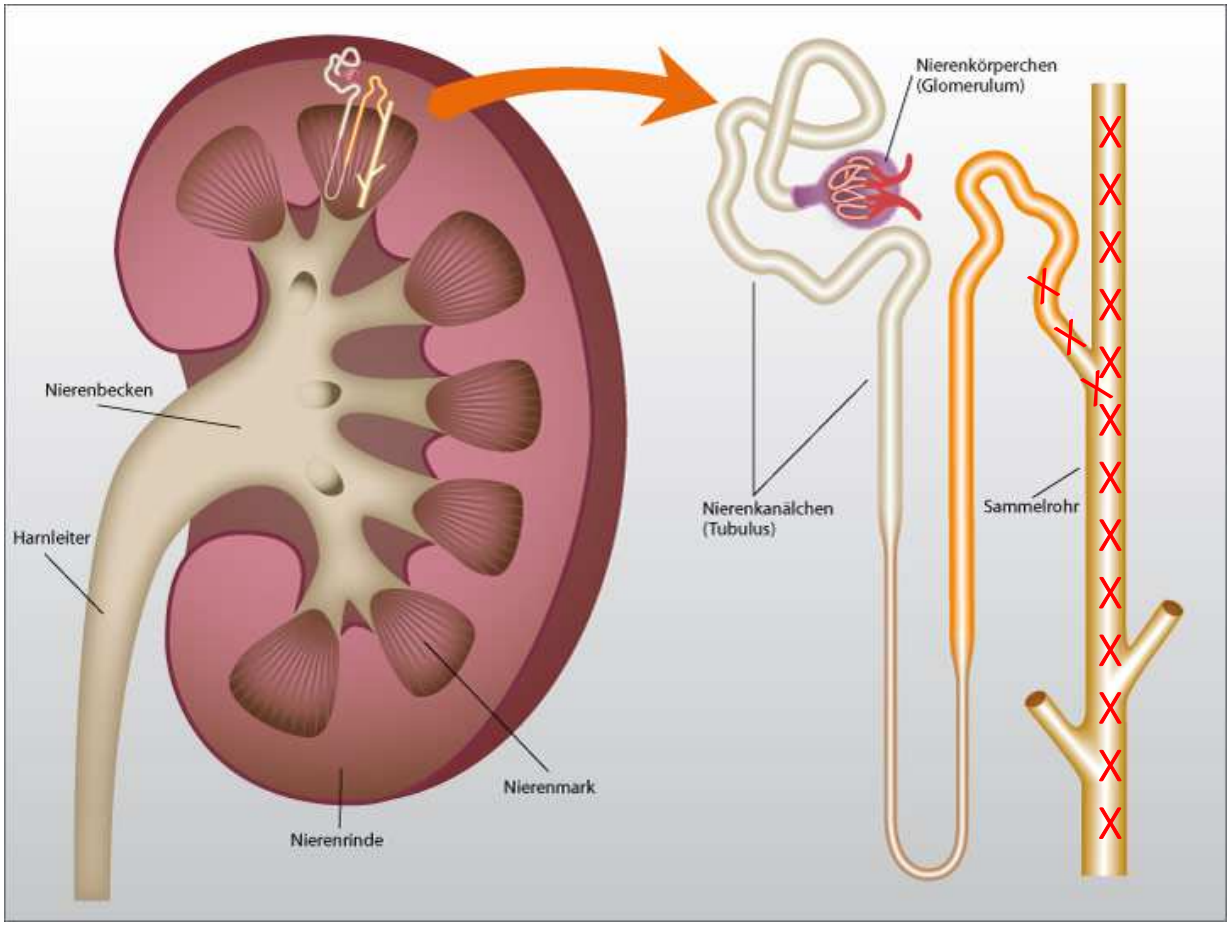
Genetische Erkrankungen in verschiedenen Nephronabschnitten



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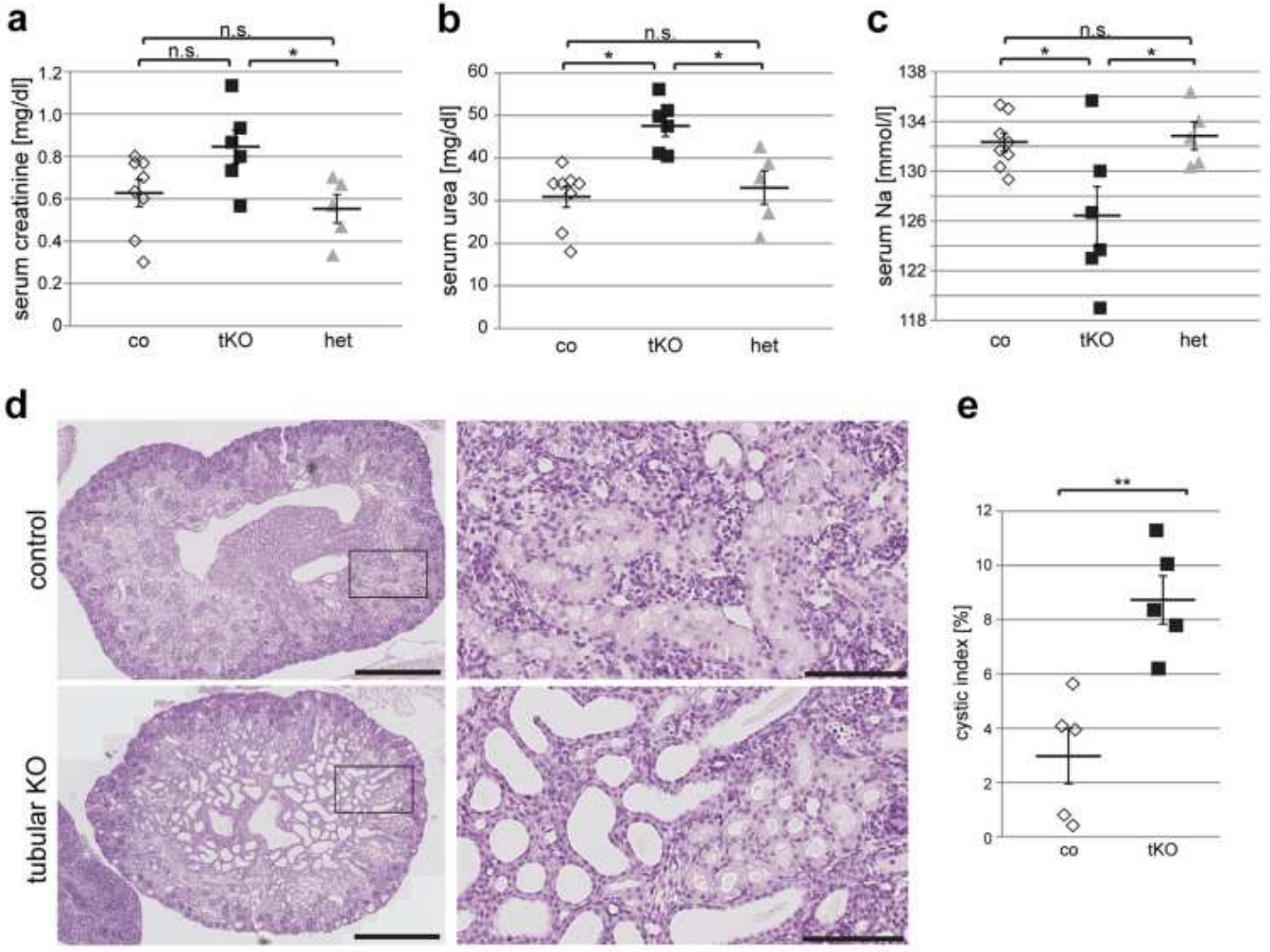
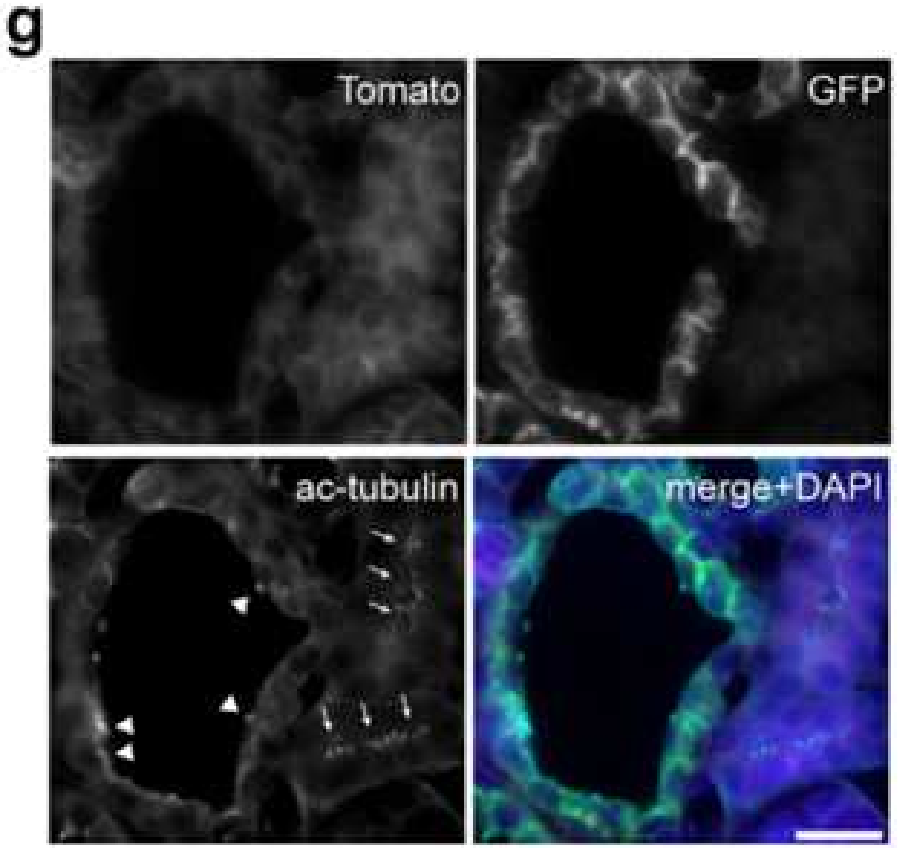
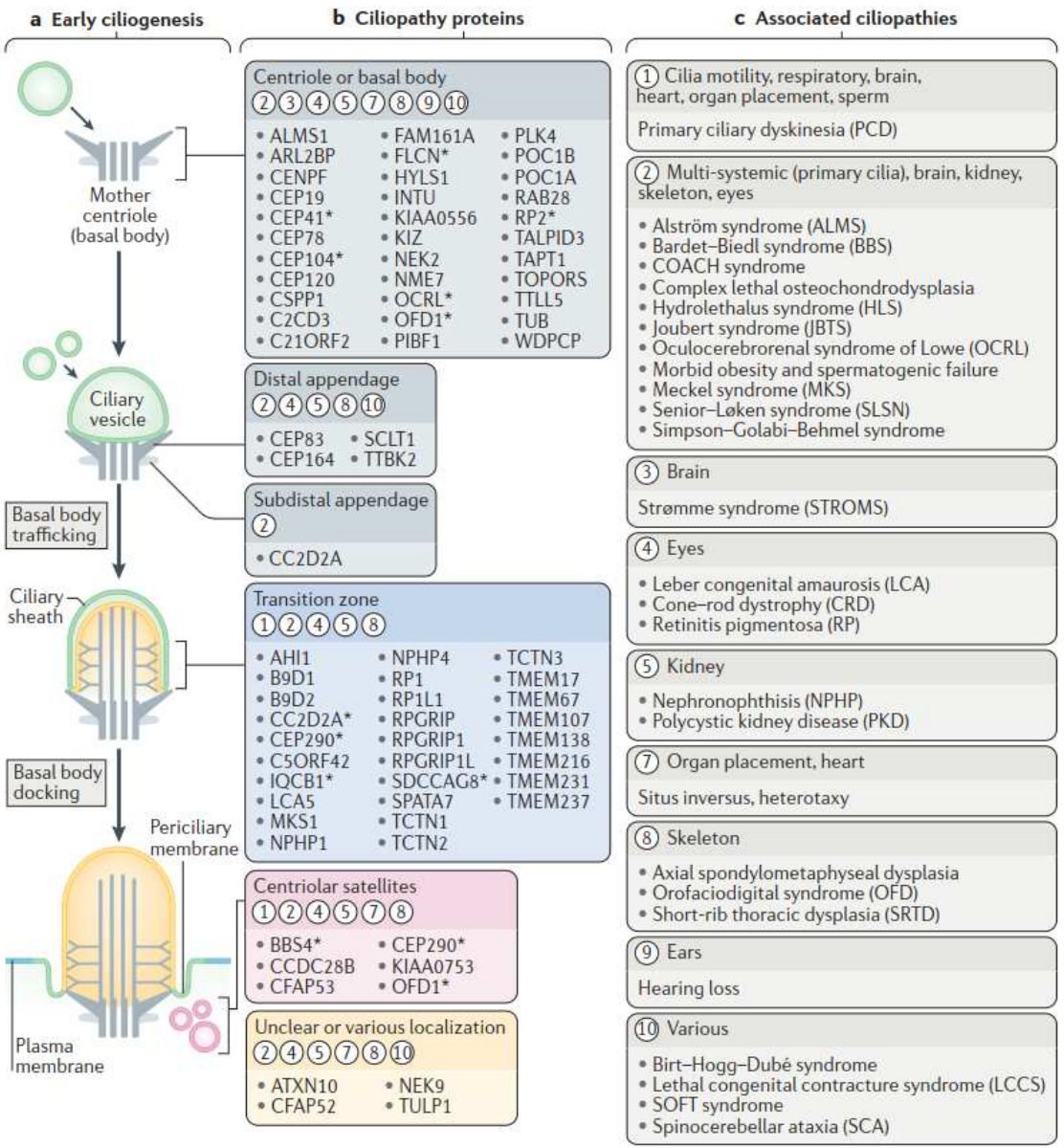


Dafinger et al.,
Exp Mol Med, 2018

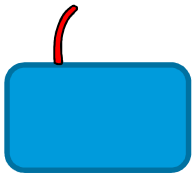
Warum?



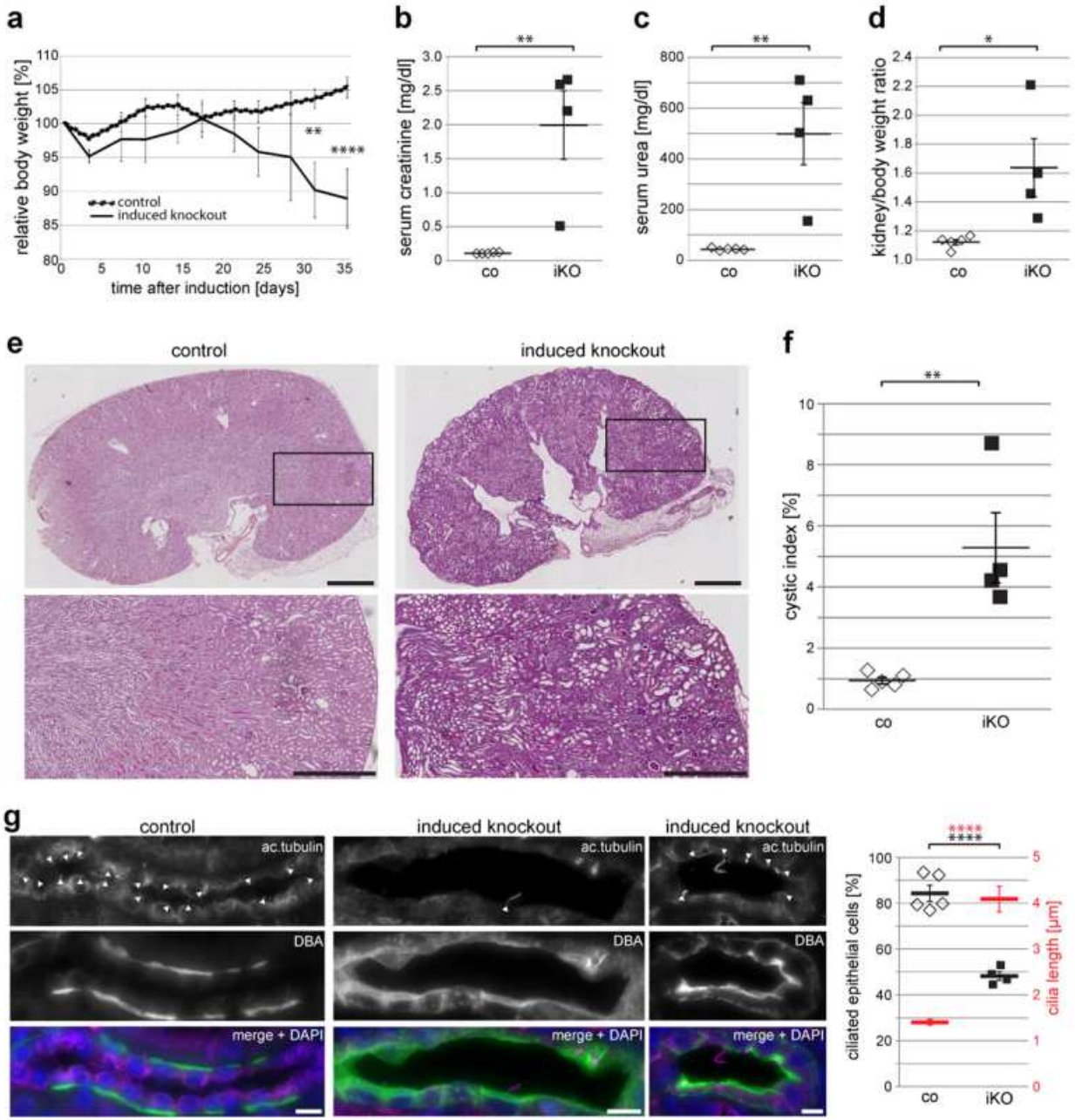
Dafinger et al.,
Exp Mol Med, 2018



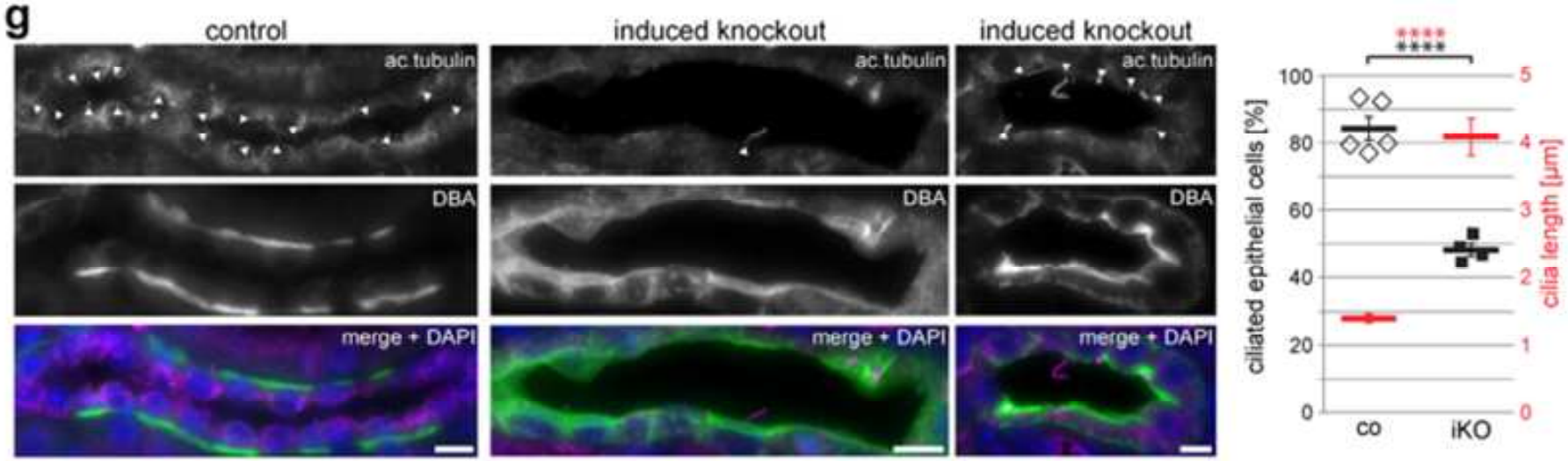
Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017




Genverlust
nach 6 Wochen
Geburt



Dafinger et al.,
Exp Mol Med, 2018



Dafinger et al.,
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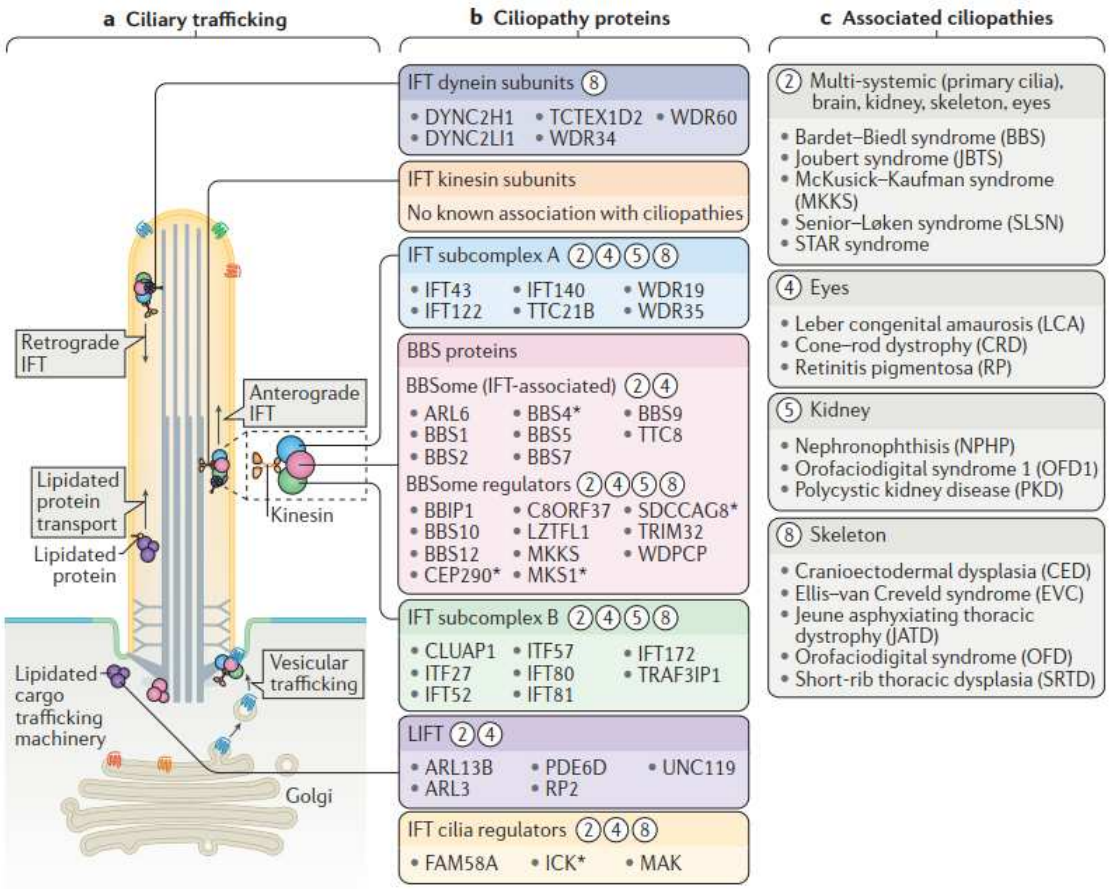
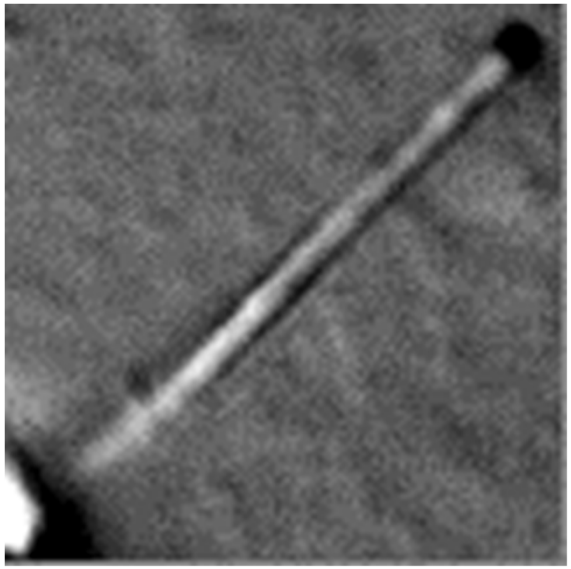


Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017



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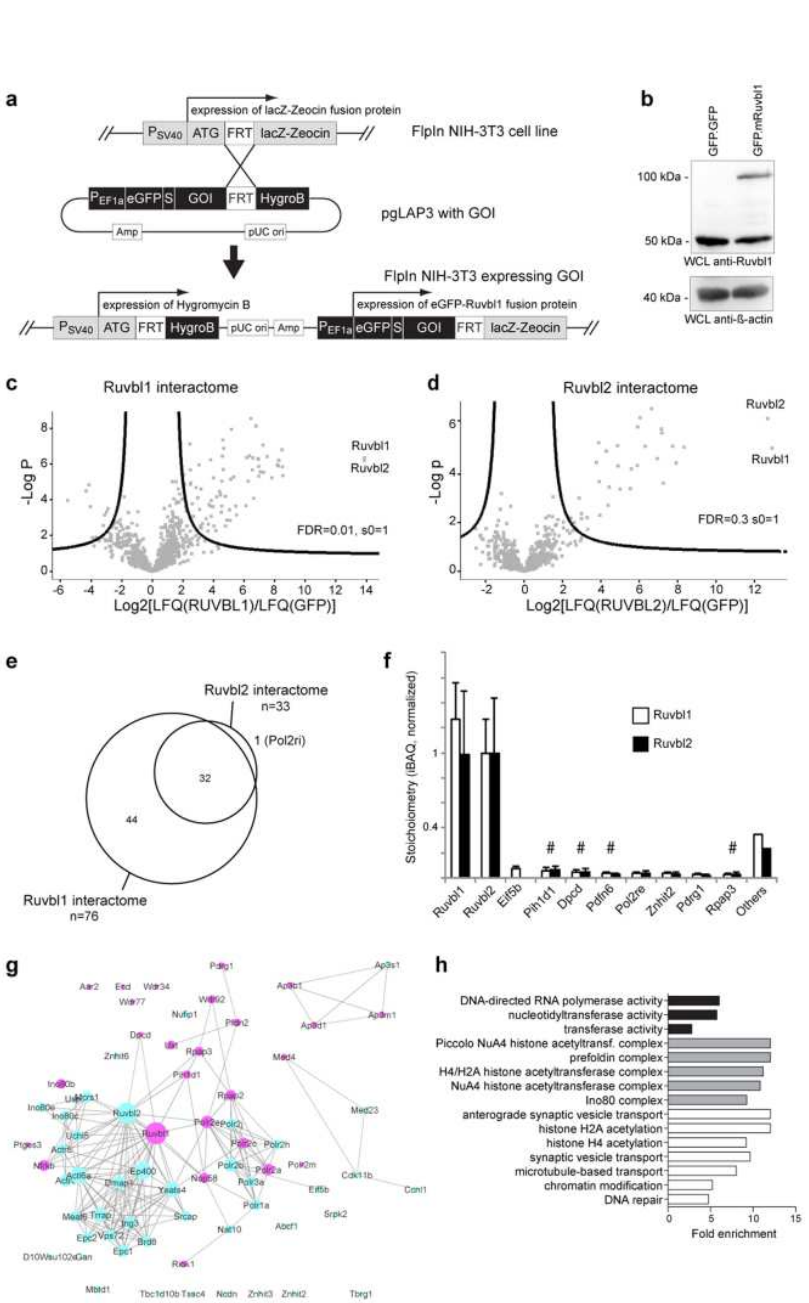

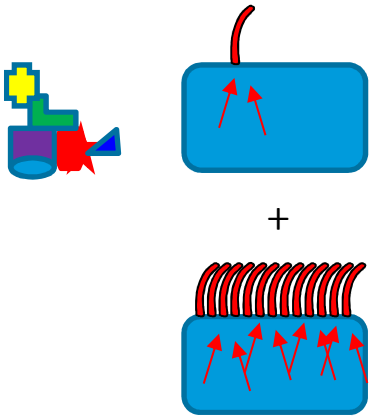

Dafinger et al.,
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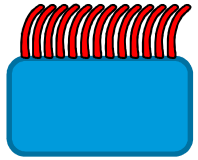
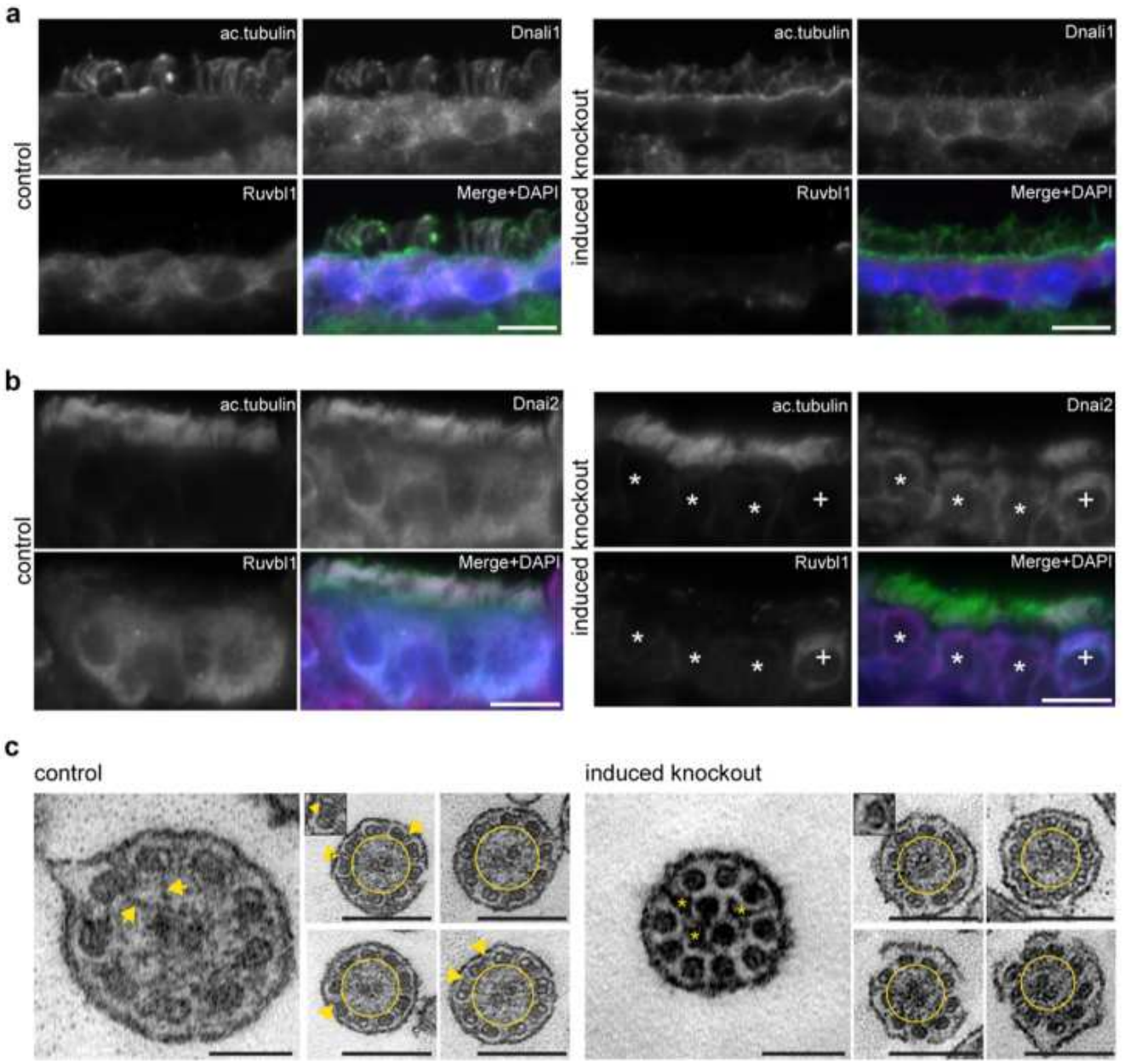




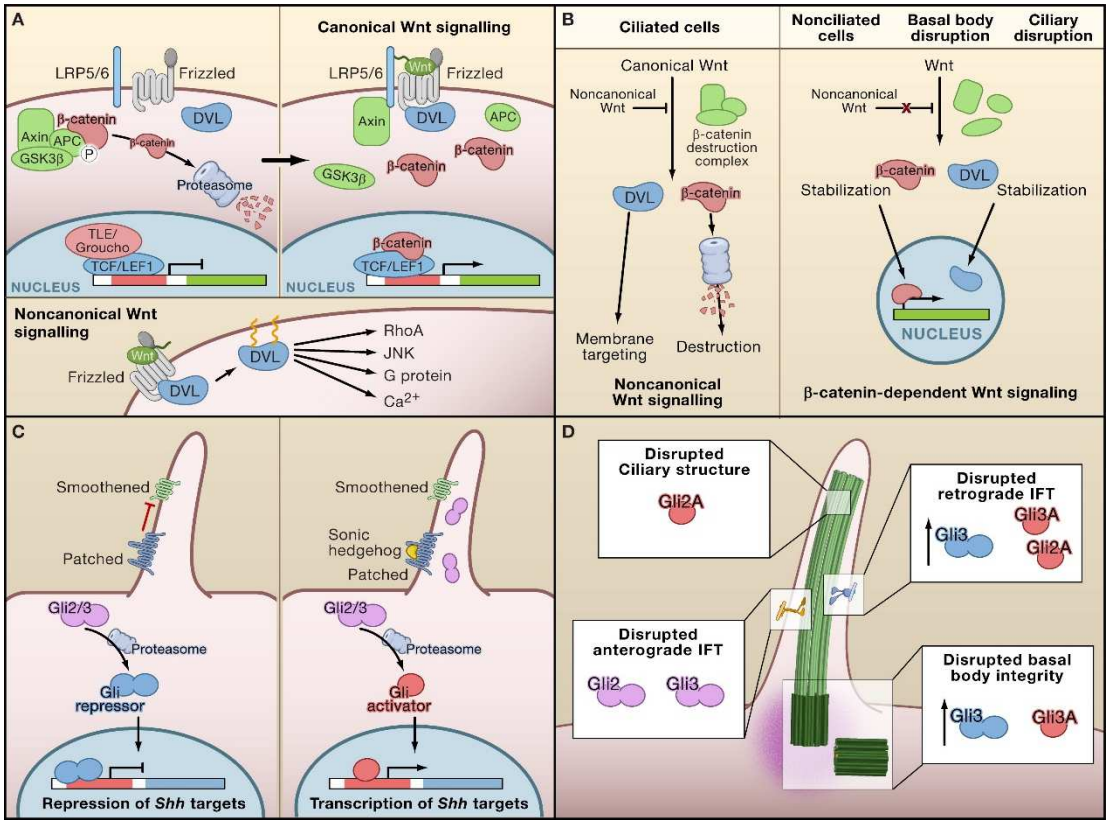
Dafinger et al.,
Exp Mol Med, 2018

Warum ist solche Forschung wichtig?

MINI REVIEW Open Access

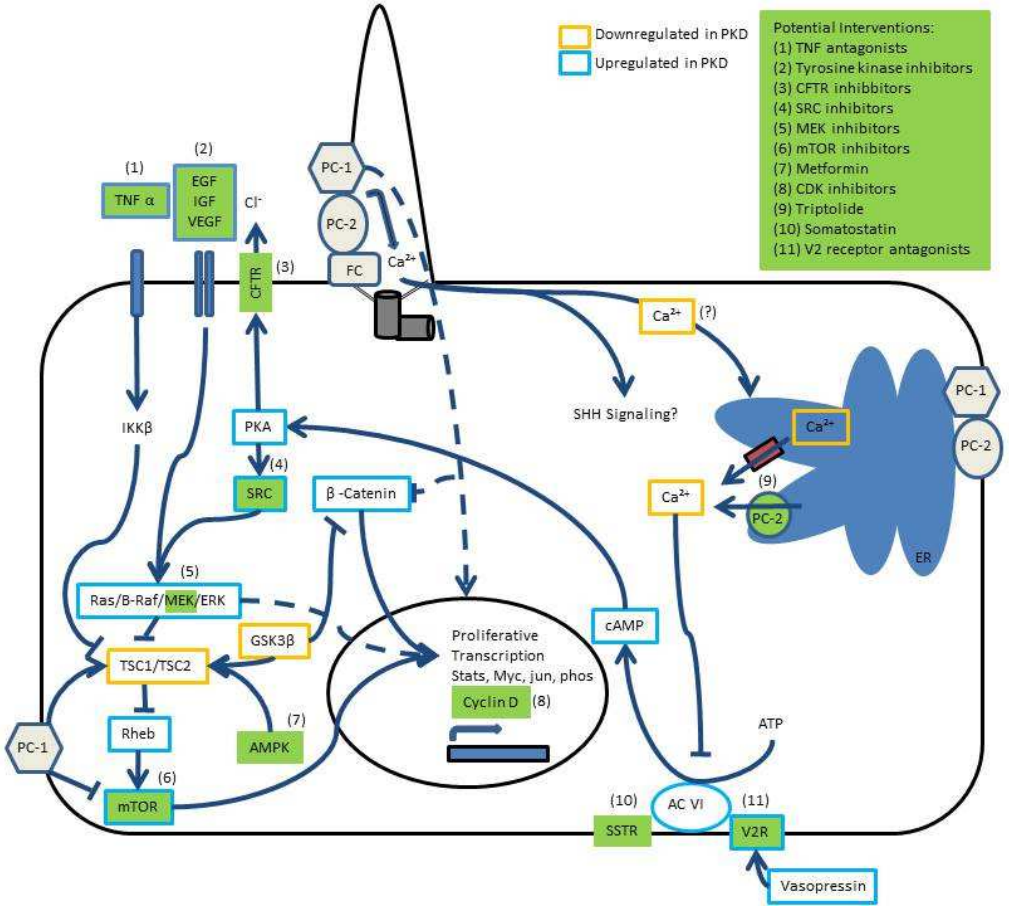
Ciliopathies - from rare inherited cystic kidney diseases to basic cellular function

Sandra Habbig[1,2] and Max Christoph Liebau[1,2*]

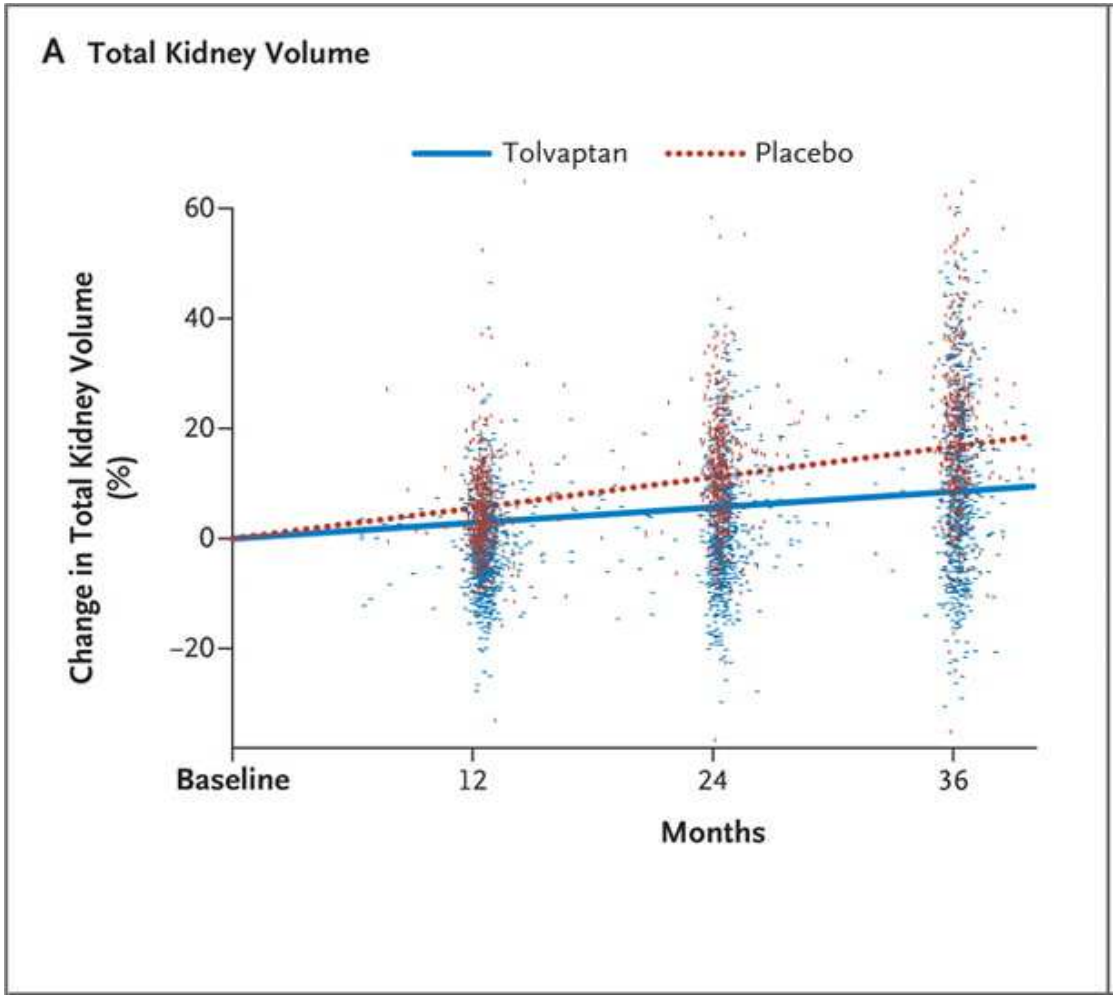


Gerdes et al., *Cell*, 2009

Signalveränderungen bei PKD



Liebau und Bergmann,
in “Pediatric Kidney Disease”, 2nd edition,
Schaefer, Geary (Edrs); 2017



Torres et al., NEJM 2013

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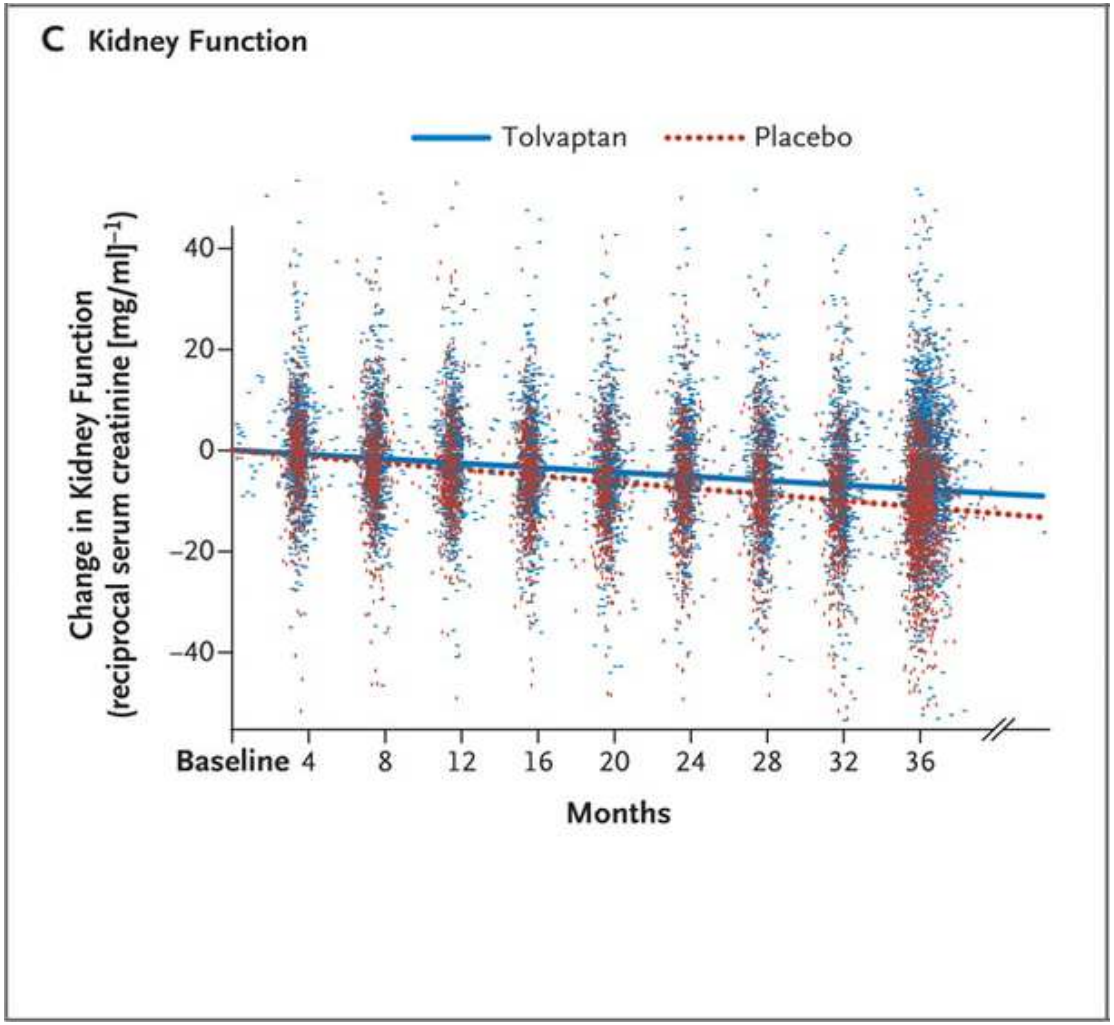

Torres et al., NEJM 2013

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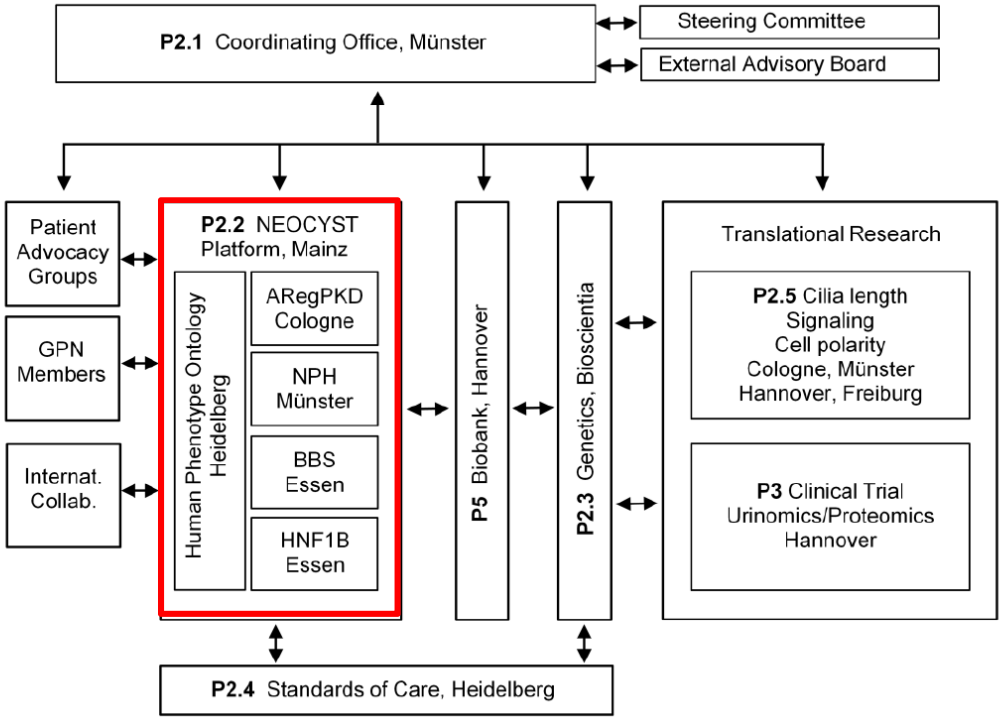
„Translationale Forschung“

Grundlagenwissenschaft ⟷ Klinische Beobachtung

NEOCYST

Network for **E**arly **O**nset **Cyst**ic Kidney Diseases



PKD Familiäre Zystennieren e.V.
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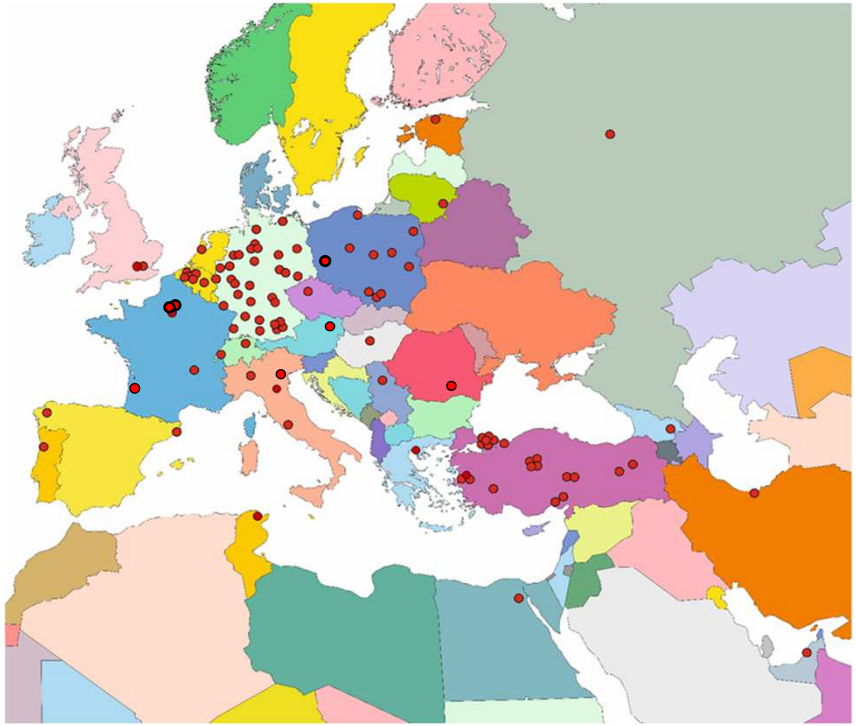
GEFÖRDERT VOM Bundesministerium für Bildung und Forschung
GPN Gesellschaft für Pädiatrische Nephrologie

ARegPKD – 111 Zentren in 27 Ländern



PKD Familiäre Zystennieren e.V.

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european society for paediatric nephrology

GPN Gesellschaft für Pädiatrische Nephrologie

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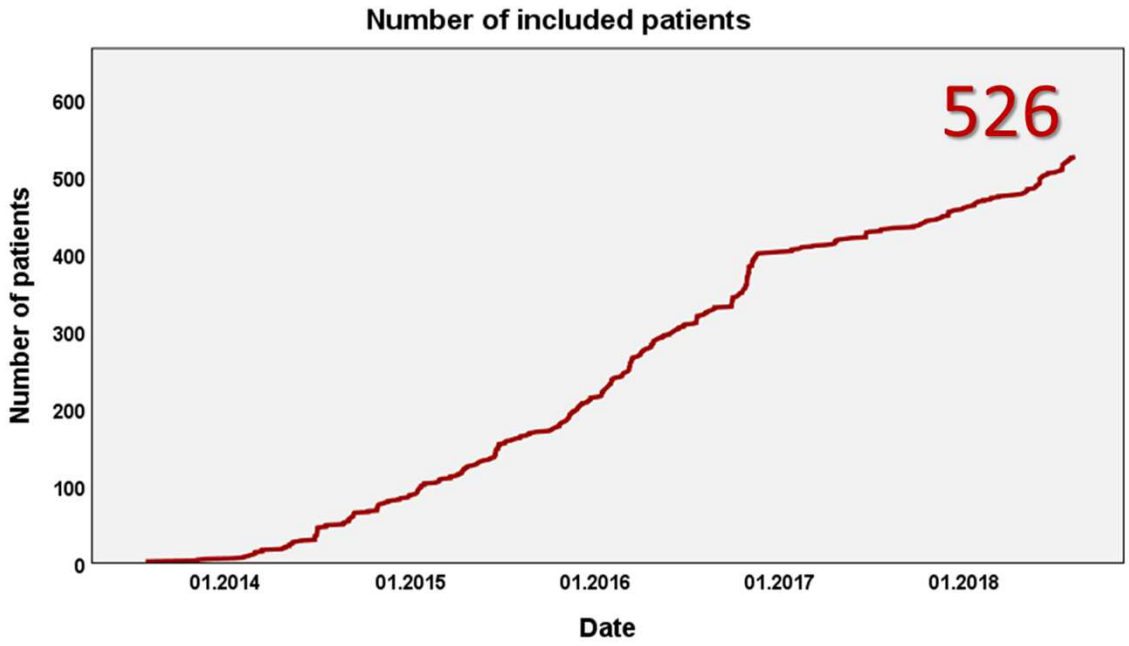

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Zusammenfassung

- Zystennierenerkrankungen sind komplexe Erkrankungen, die mit einer Fehlfunktion von Zilien in Verbindung stehen.
- Zilien regulieren verschiedenen Prozesse in Zellen. Da Zilien nicht nur in der Niere vorkommen, zeigen vielen Patienten mit Zilienerkrankungen Symptome in unterschiedlichen Organen.
- Grundlagenwissenschaftliche Ansätze können beim Verständnis der biologischen Prozesse helfen, die z.B. seltenen Erkrankungen zu Grunde liegen. Grundlagenwissenschaftliche Forschung kann so z.B. wichtige Anstöße bei der Entwicklung neuer Therapieoptionen geben.

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and many more…

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Roman Müller
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Thomas Weimbs

Zentren der GPN und des ESCAPE Netzwerks

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