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

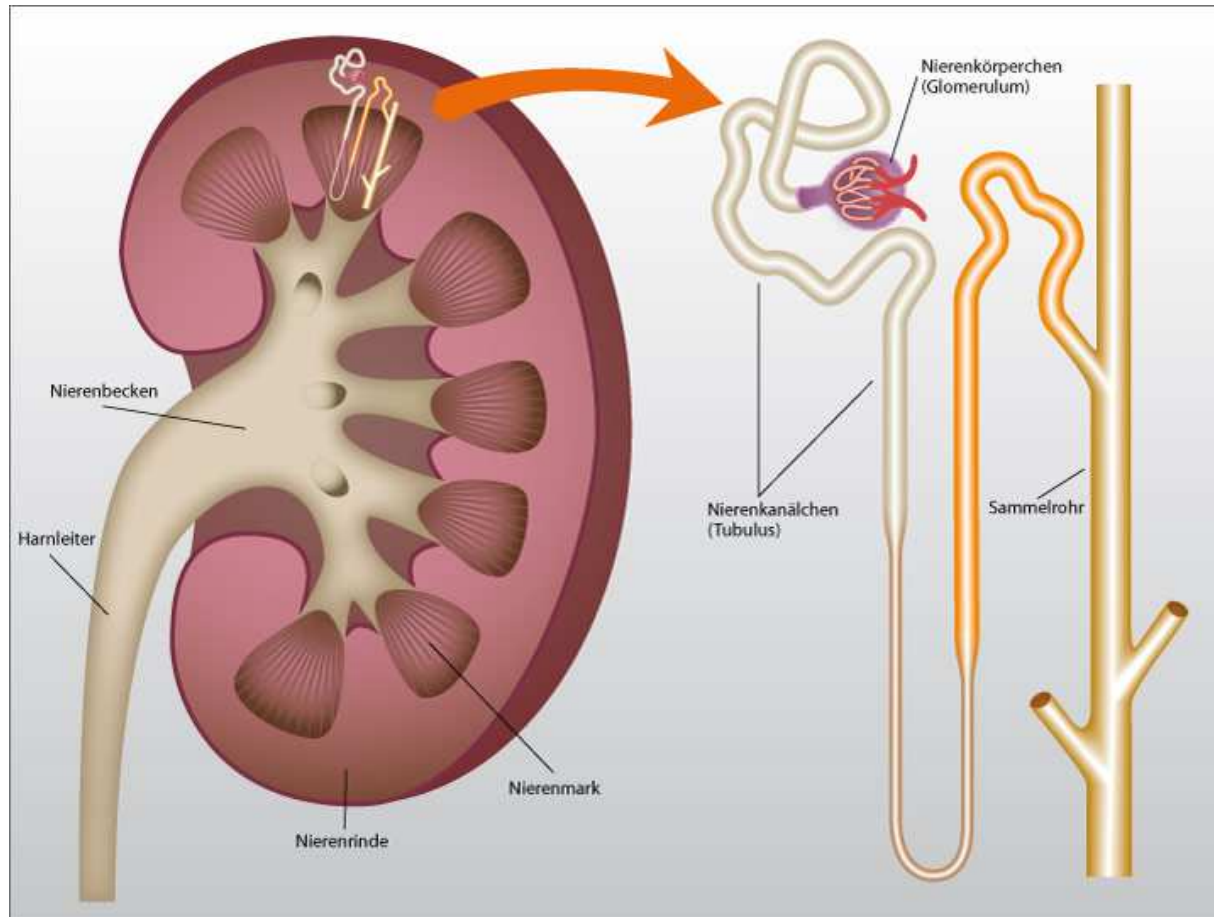
1. Münsteraner Zystentag
PD Dr. Max Liebau

22.09.2018 Liebau | Pädiatrische Nephrologie, iSPZ, Zentrum für Molekulare Medizin Köln

Zystennieren

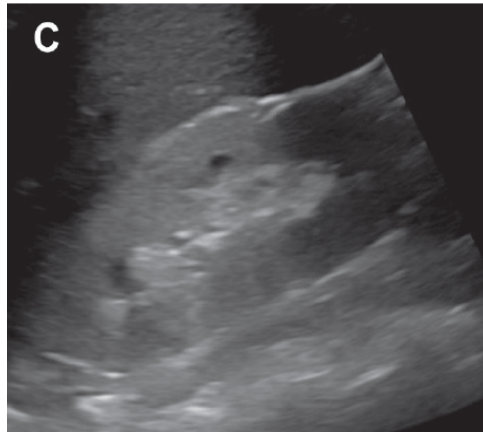


Jede Niere besteht aus ca. 1 Mio Funktionseinheiten

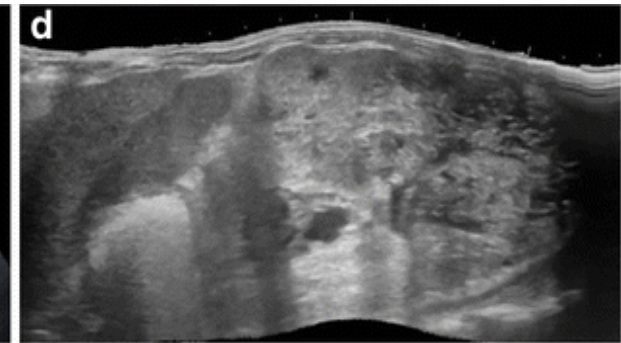


www.nierenforschung.de

Zysten sind flüssigkeitsgefüllte epithelausgekleidete Hohlräume

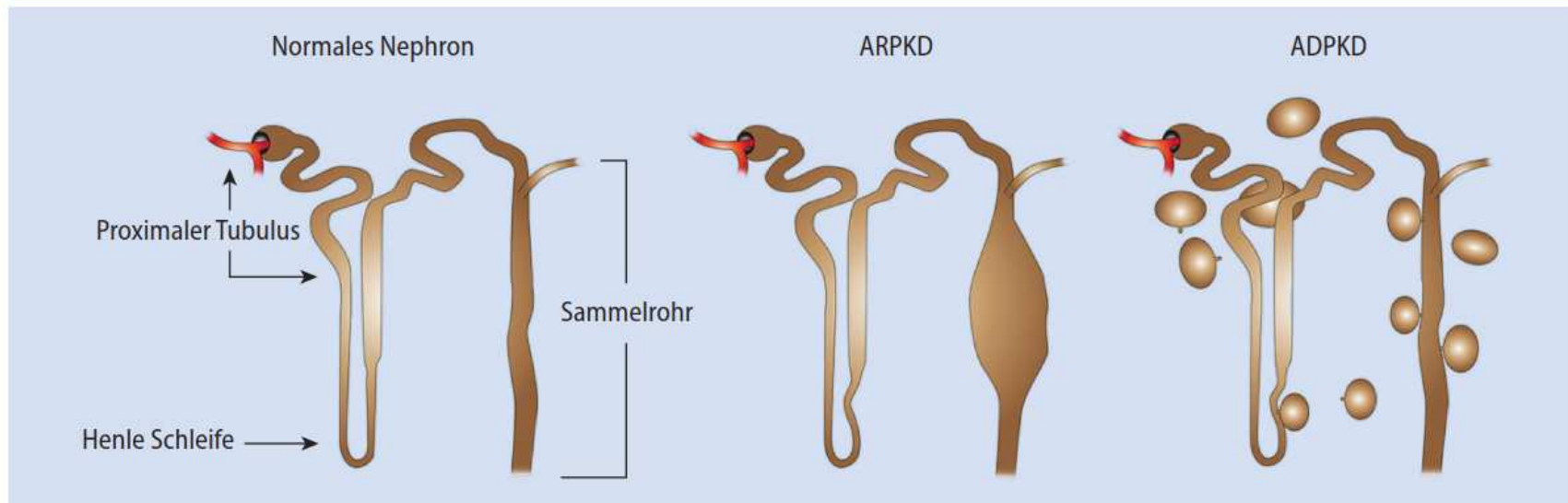


Liebau and Habbig,
DGfN-News 2015



Liebau & Serra
Pediatr Nephrol, 2013

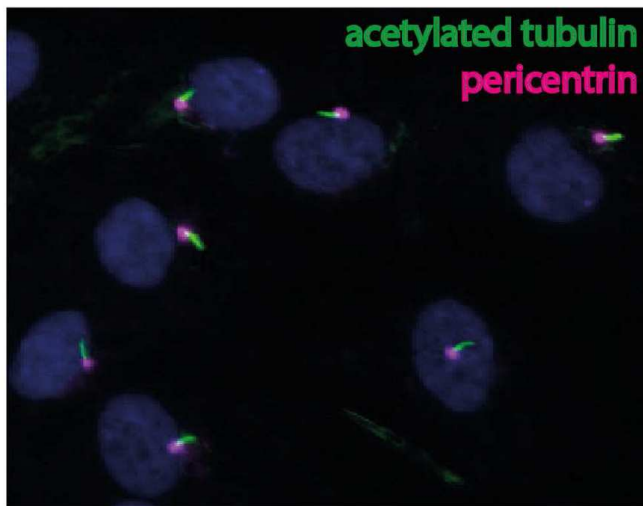
Zysten sind flüssigkeitsgefüllte epithelausgekleidete Hohlräume



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

Wie kommt es zu diesen Erweiterungen?

Zilien



Liebau;
Front Pediatr, 2014



Pazour et al.;
Trends Cell Biol, 2002

.....

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

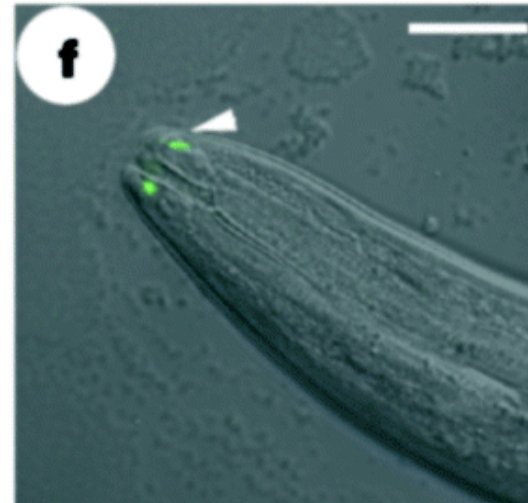
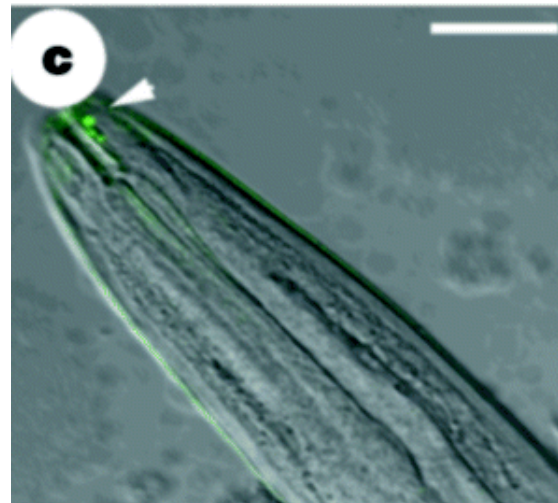
Maureen M. Barr & Paul W. Sternberg

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



www.easterncrct.edu

Nature, 1999



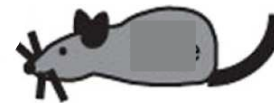
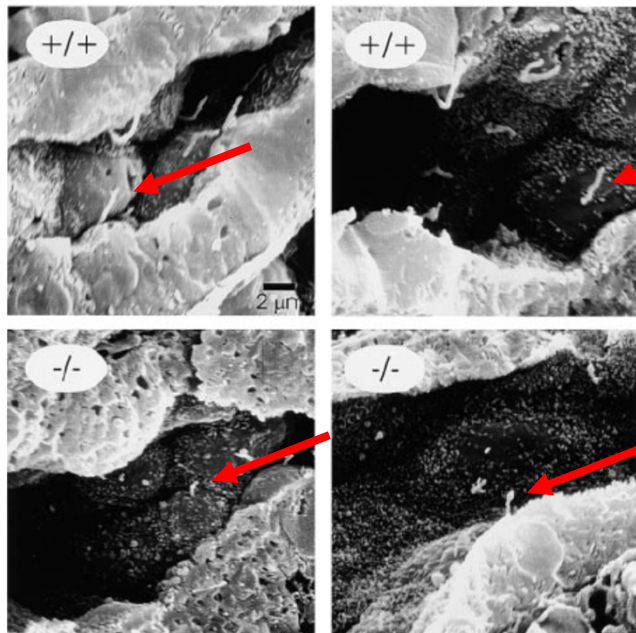
Chlamydomonas IFT88 and Its Mouse Homologue, Polycystic Kidney Disease Gene *Tg737*, Are Required for Assembly of Cilia and Flagella

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;

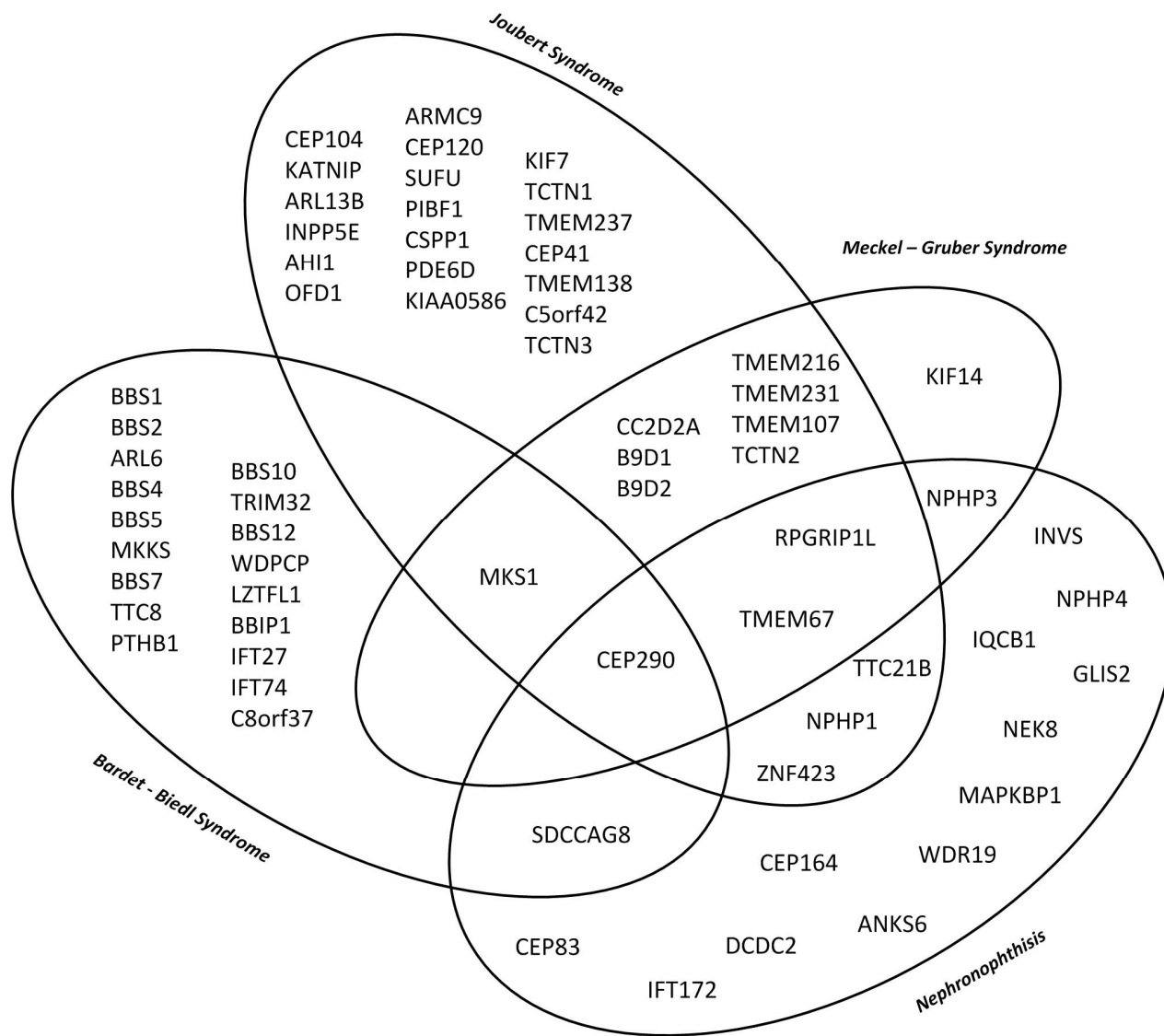
and [§]Department of Microbiology, Molecular Biology, and Biochemistry, University of Idaho, Moscow, Idaho 83844



J Cell Biol, 2000

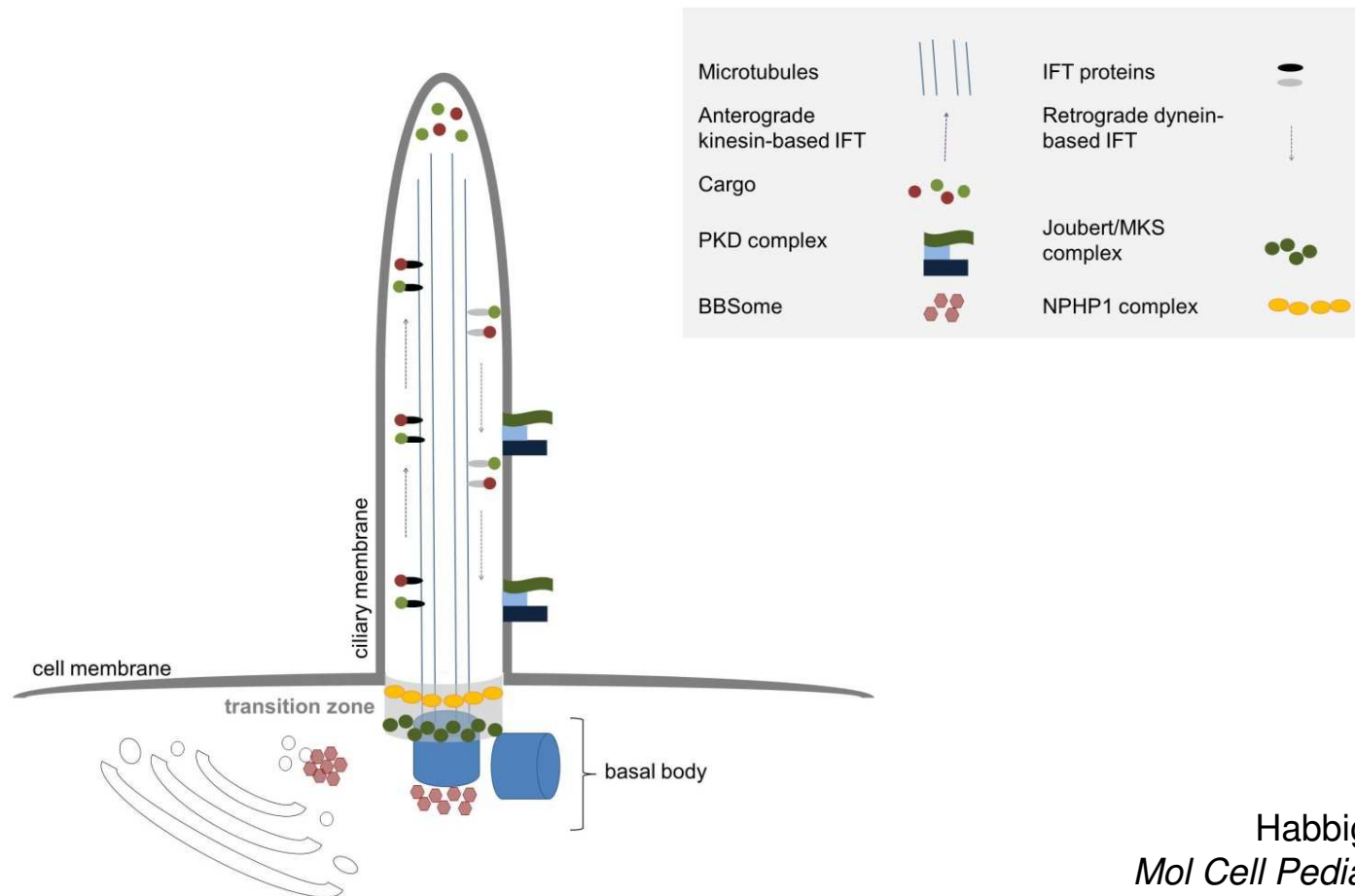


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+ ARPKD
 + ADPKD
 + (...)

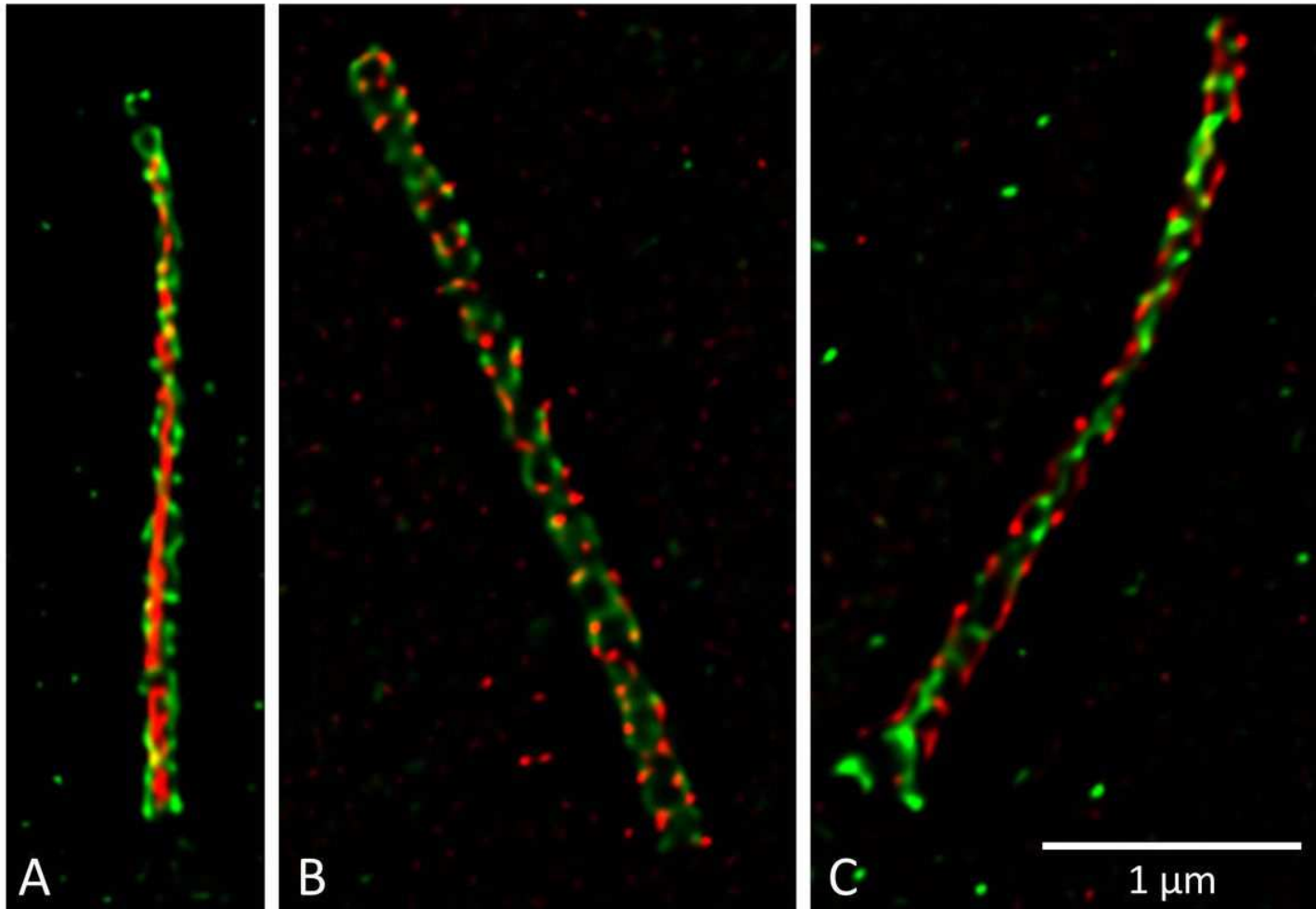
Zystennierengenprodukte am Zilium



Habbig & Liebau,
Mol Cell Pediatrics, 2015



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Bernhard Schermer, www.nierenforschung.de

REVIEW

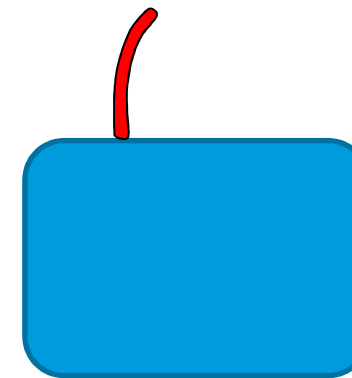
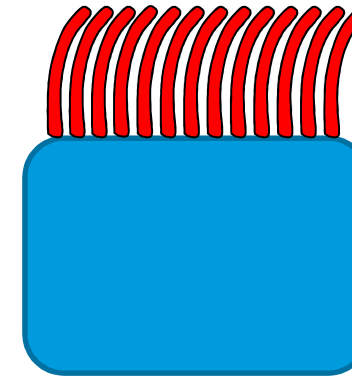
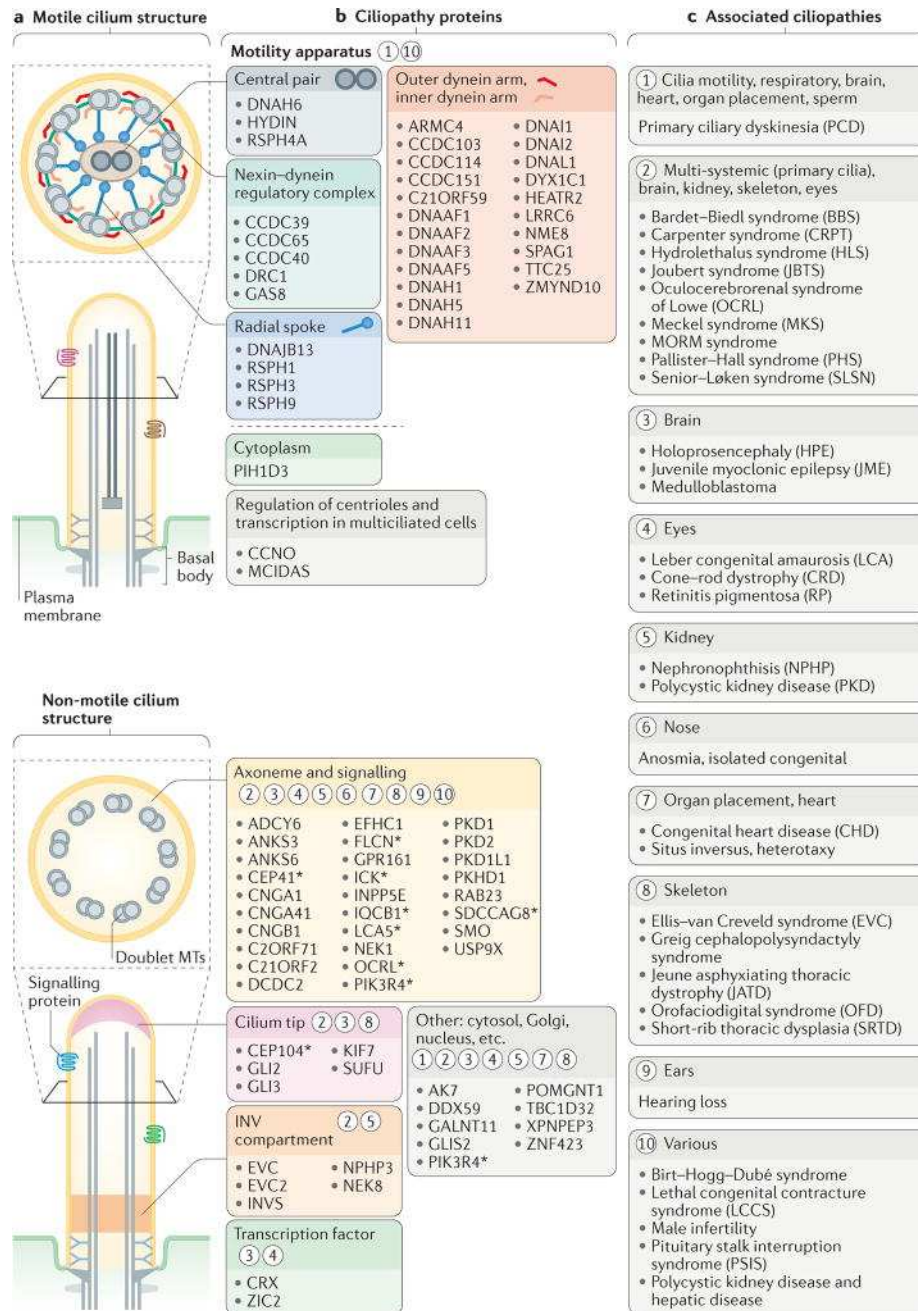
J Am Soc Nephrol 15: 2528–2536, 2004

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

GREGORY J. PAZOUR

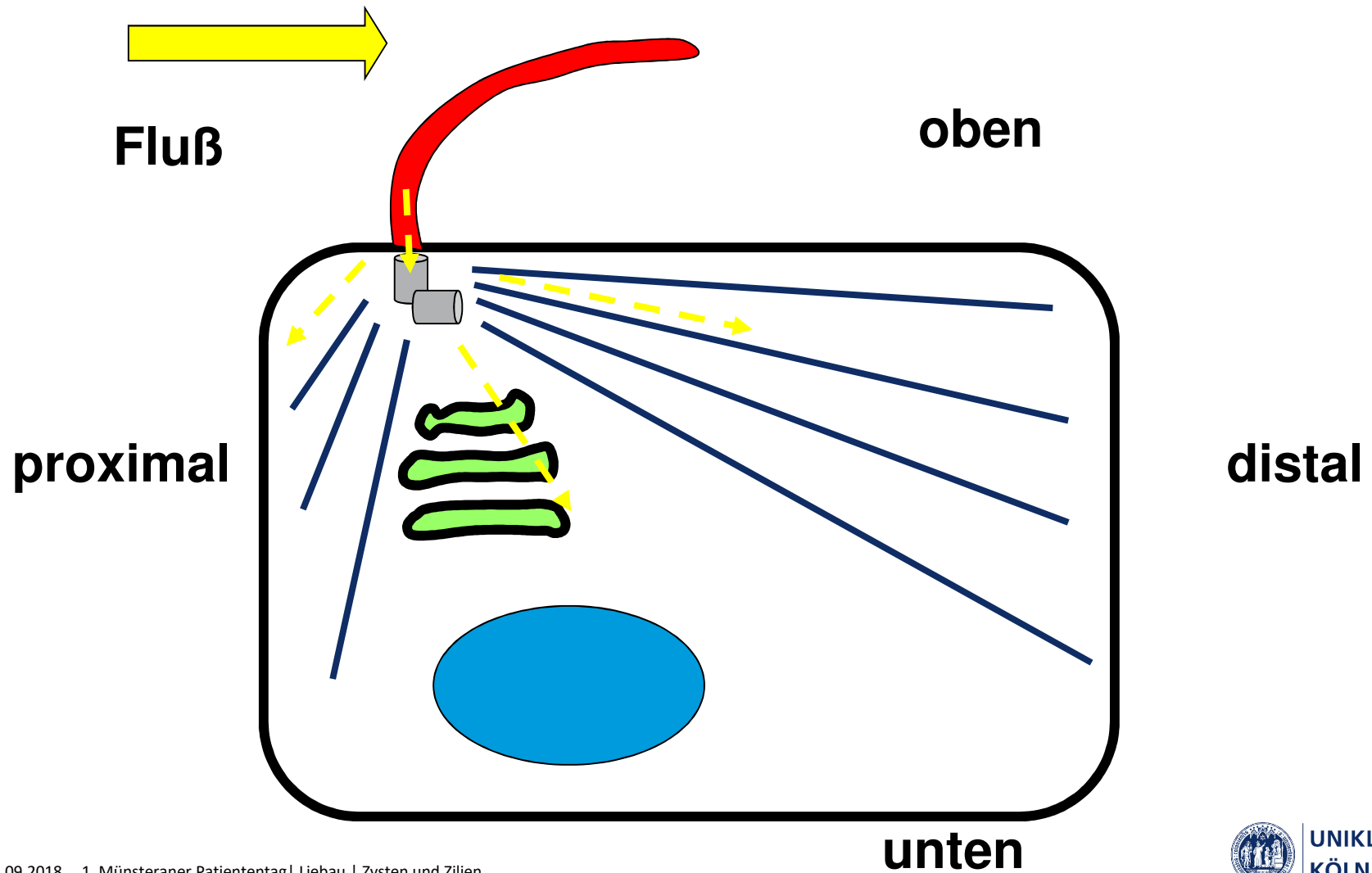
Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, Massachusetts

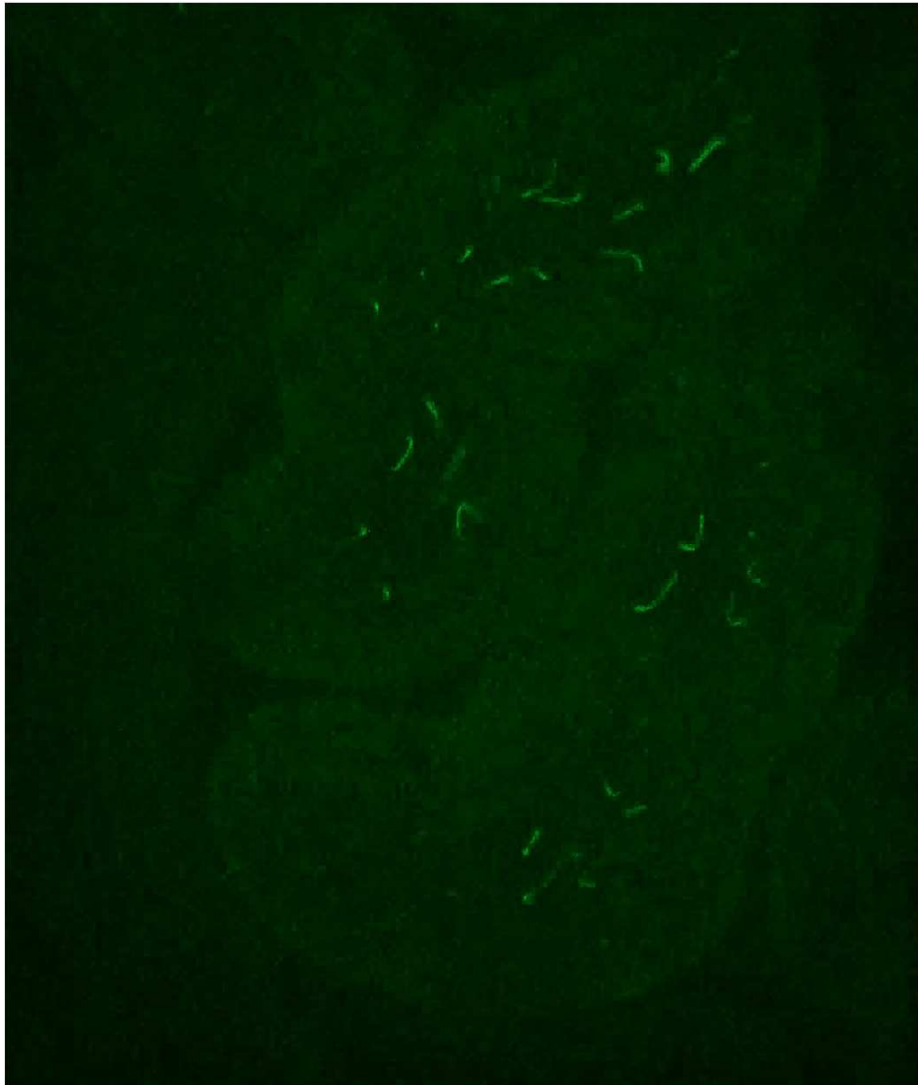




2017: 35 Ziliopathien
187 Ziliopathie-Gene
241 weitere Kandidatengene

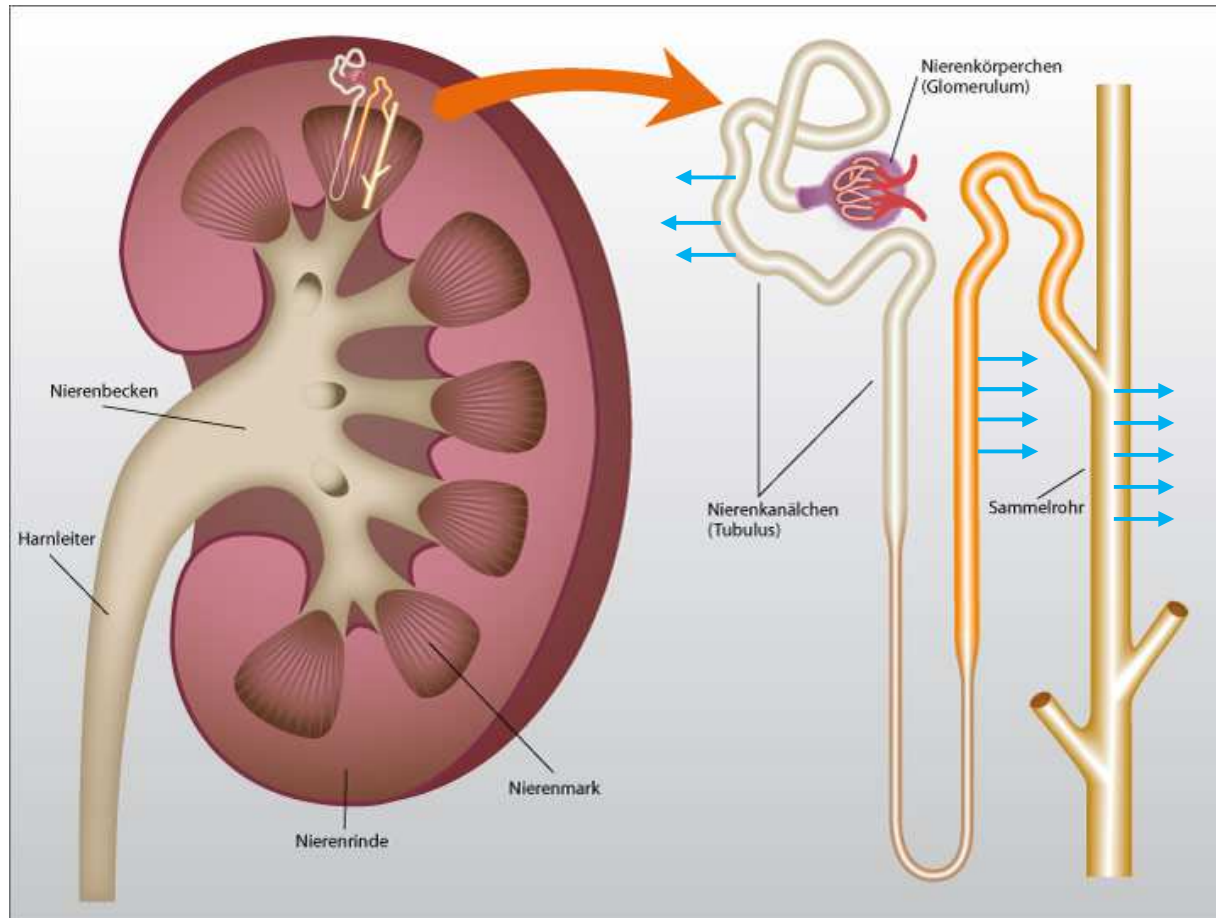
Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017



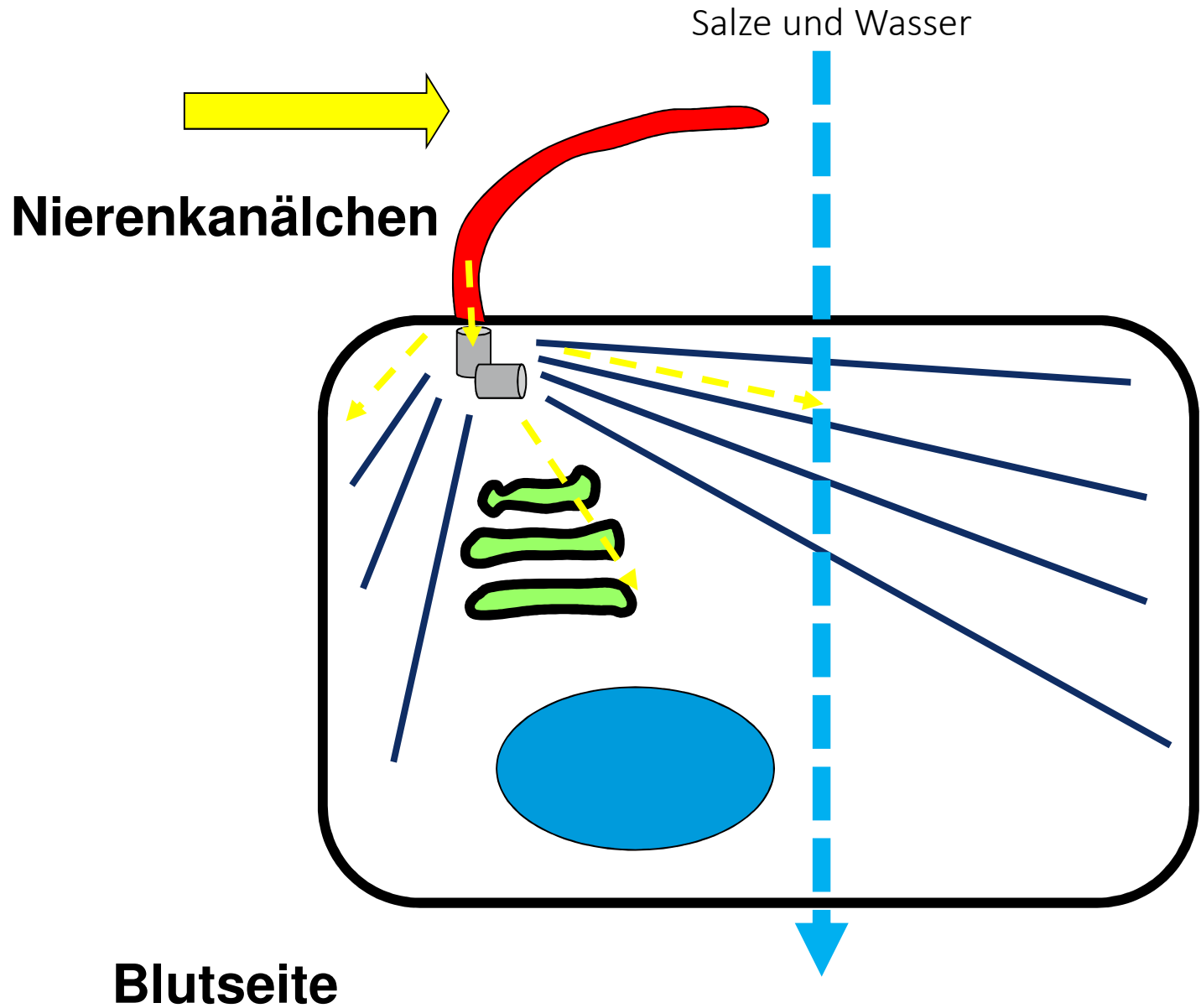


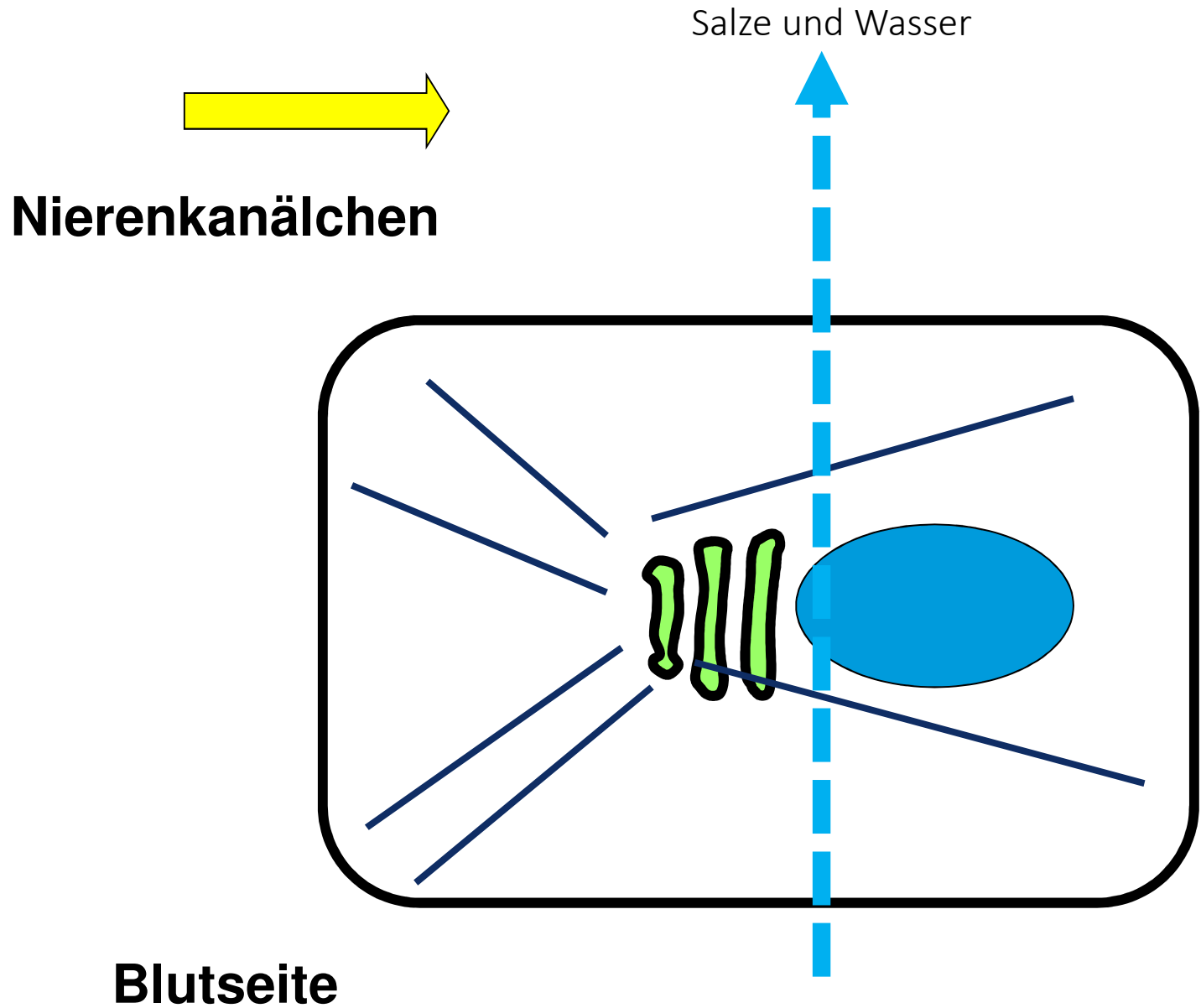
O'Connor et al., *Cilia*, 2013

Im Nierenkanälchen (Tubulus) wird der Urin nachbearbeitet

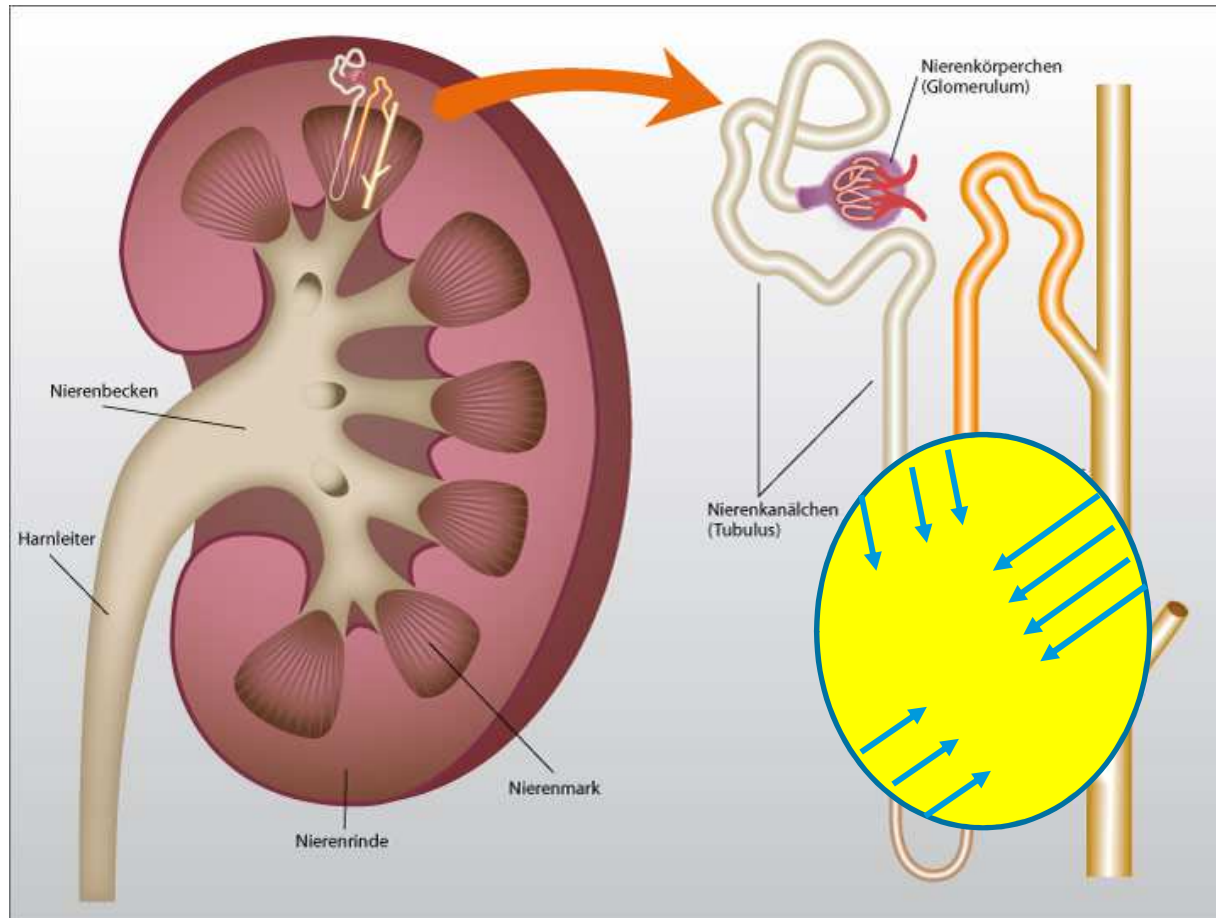


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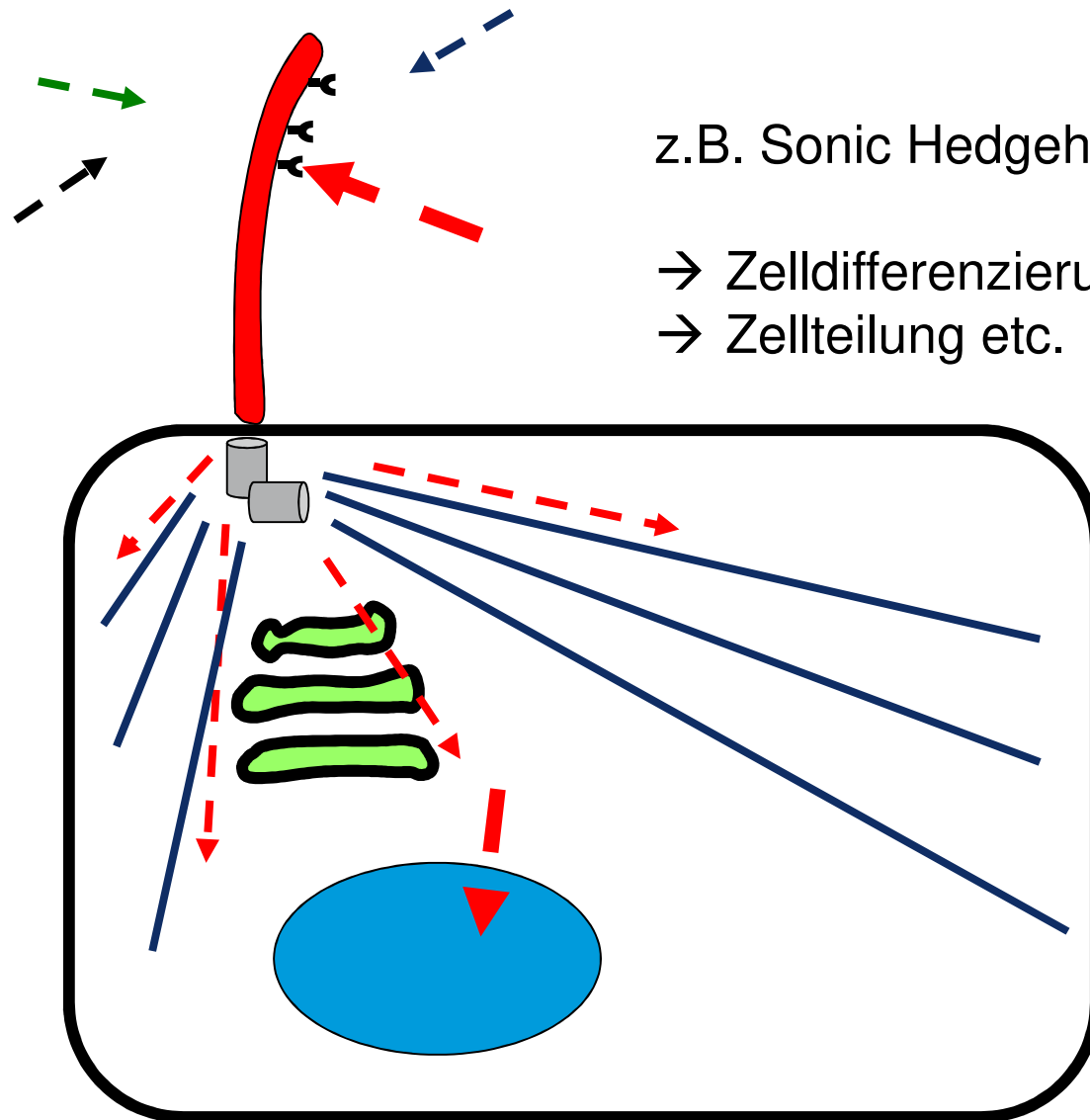




Im Nierenkanälchen (Tubulus) wird der Urin nachbearbeitet



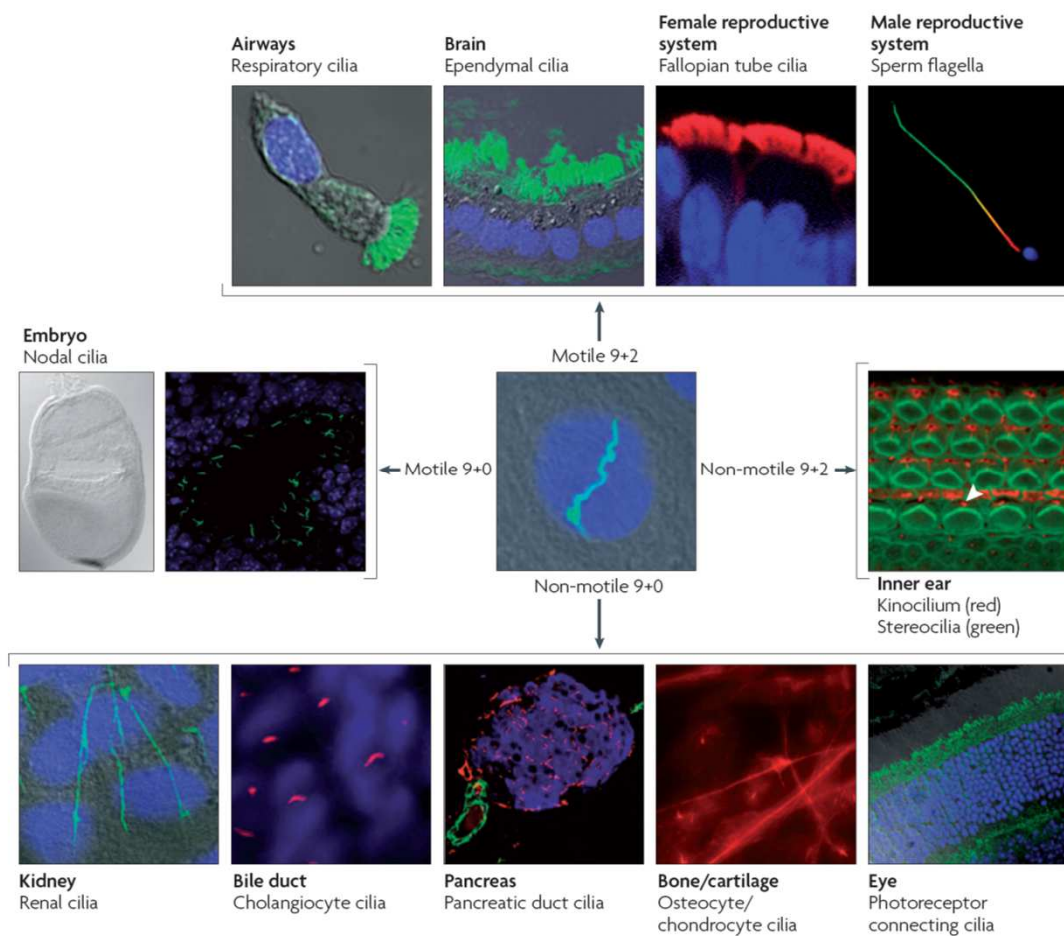
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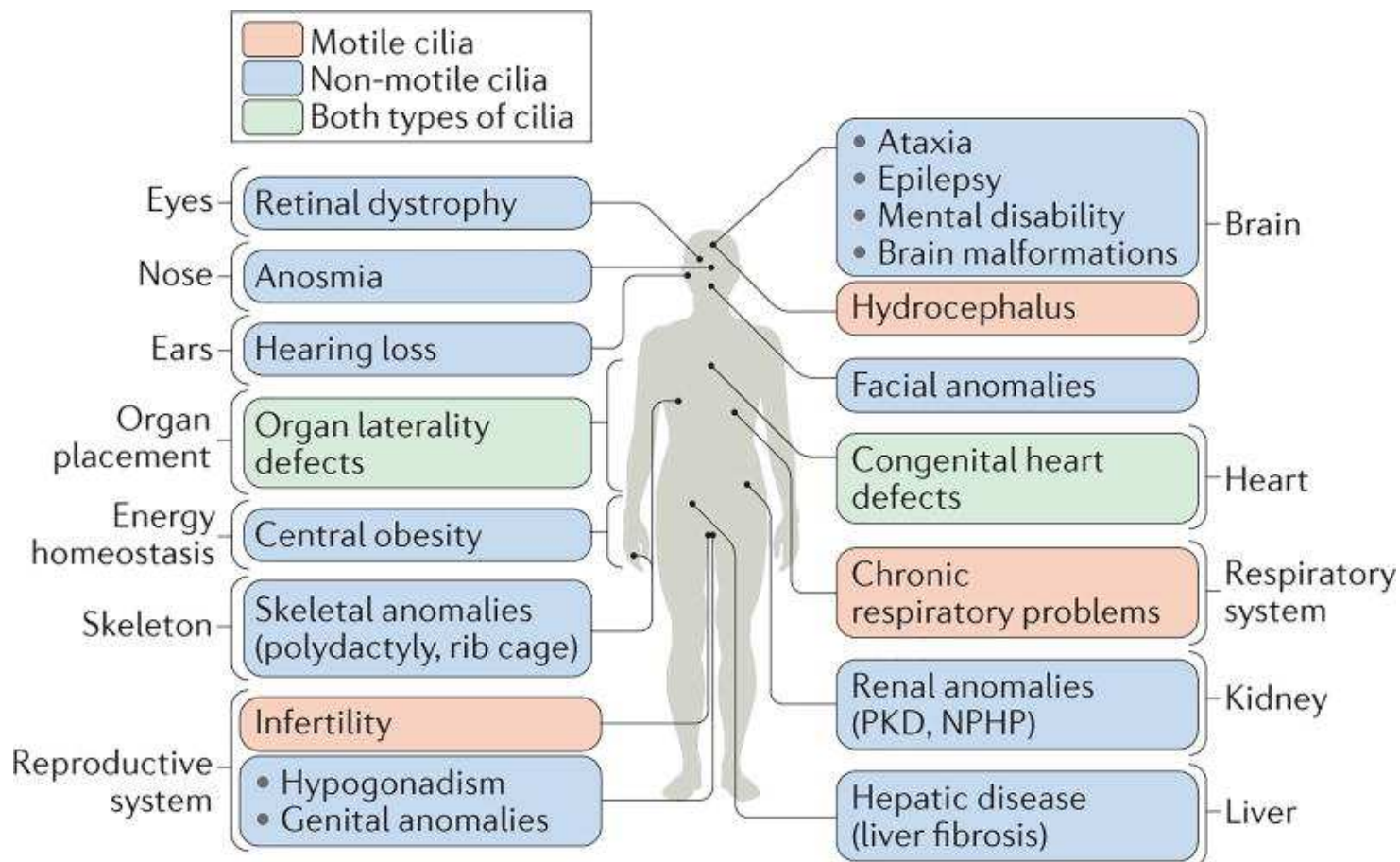
z.B. Sonic Hedgehog Signaling

- Zelldifferenzierung und Funktion
- Zellteilung etc.

Zilien finden sich auf vielen Zellen



Ziliendefekte führen zu vielen Symptomen

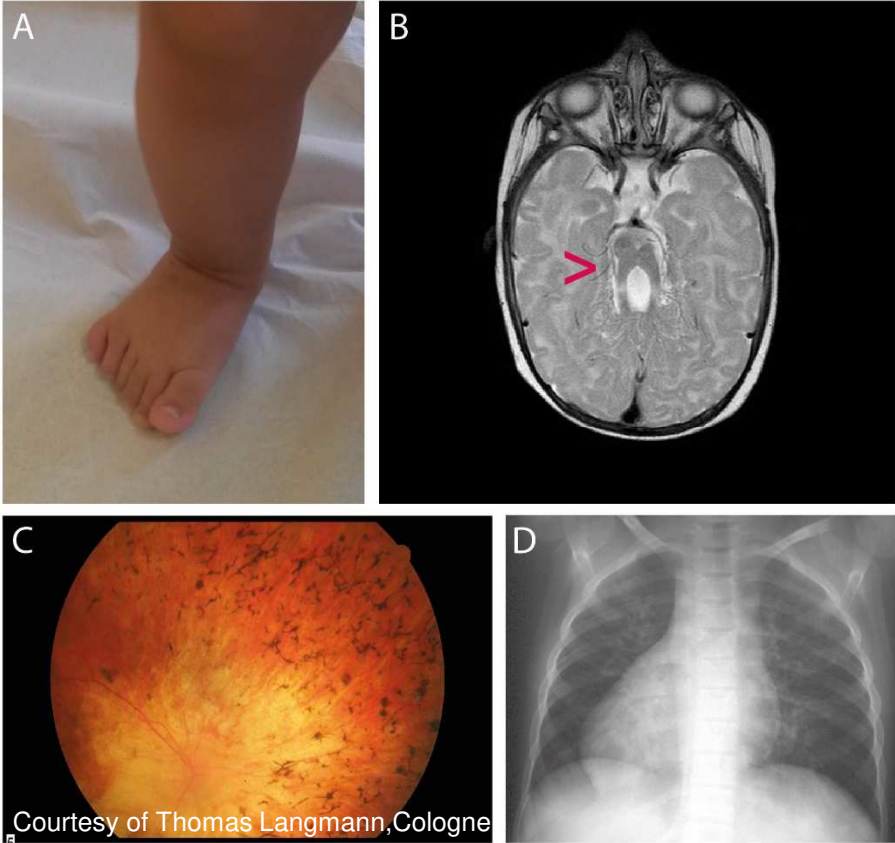


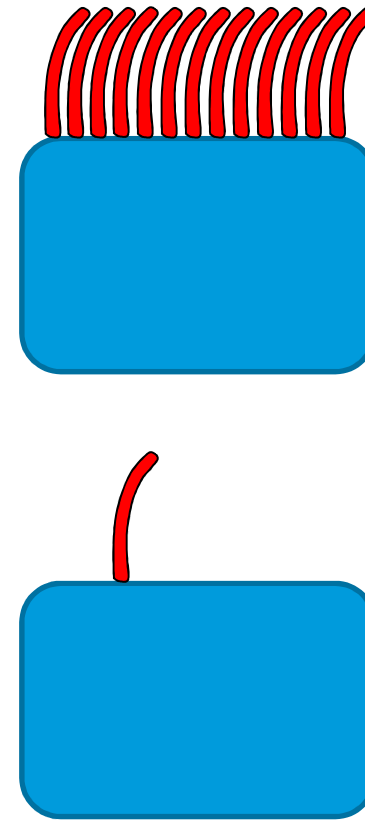
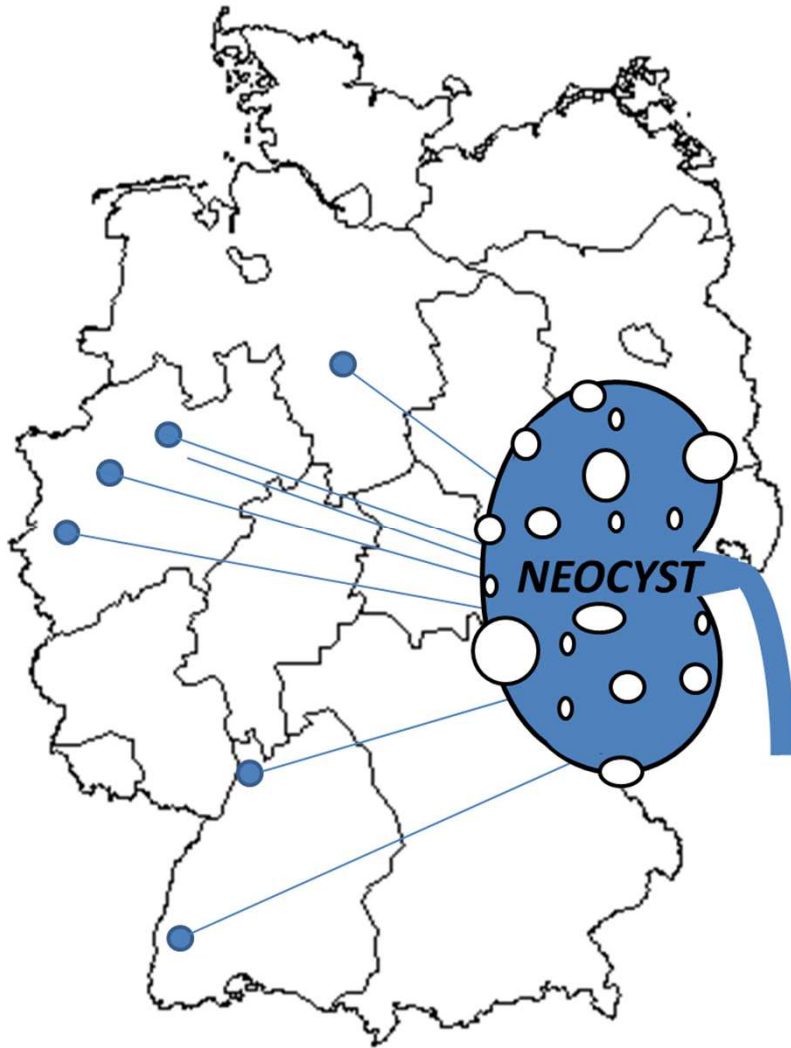
Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017

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

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

Extrarenale Symptome





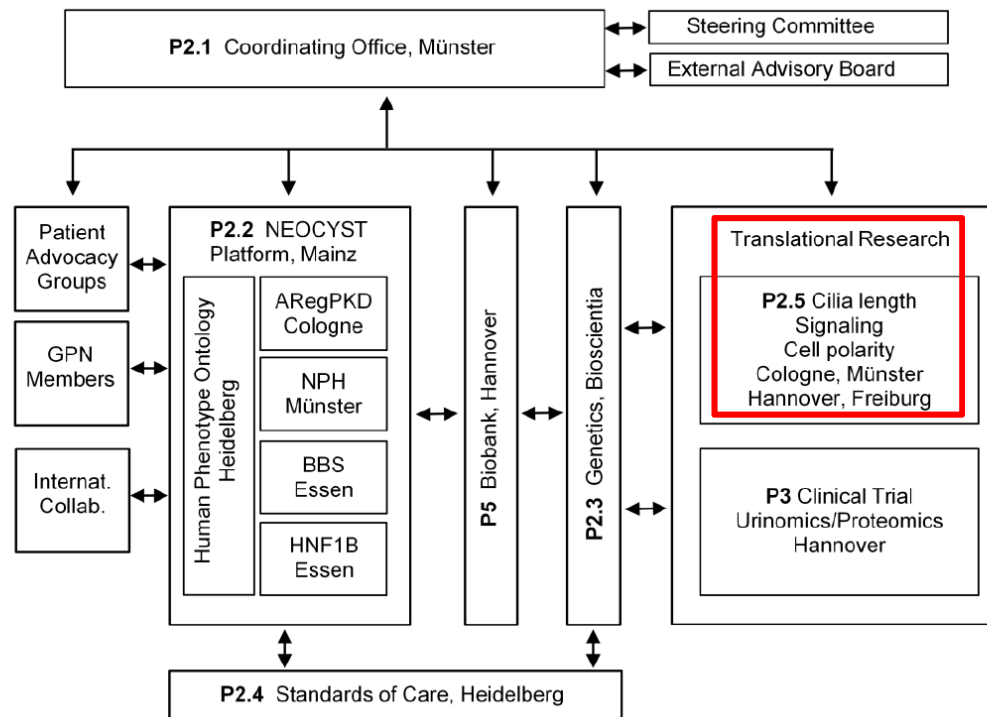
GEFÖRDERT VOM

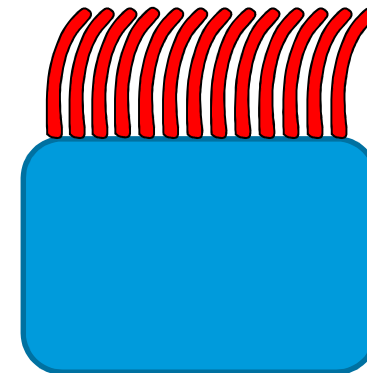
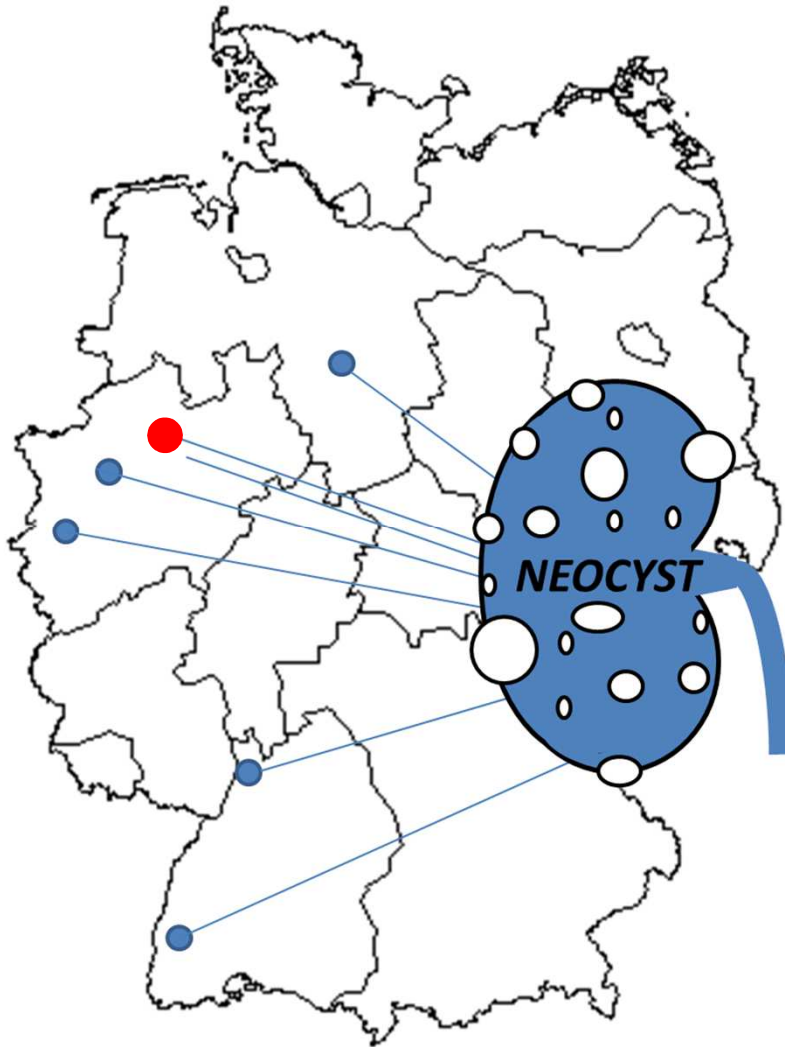


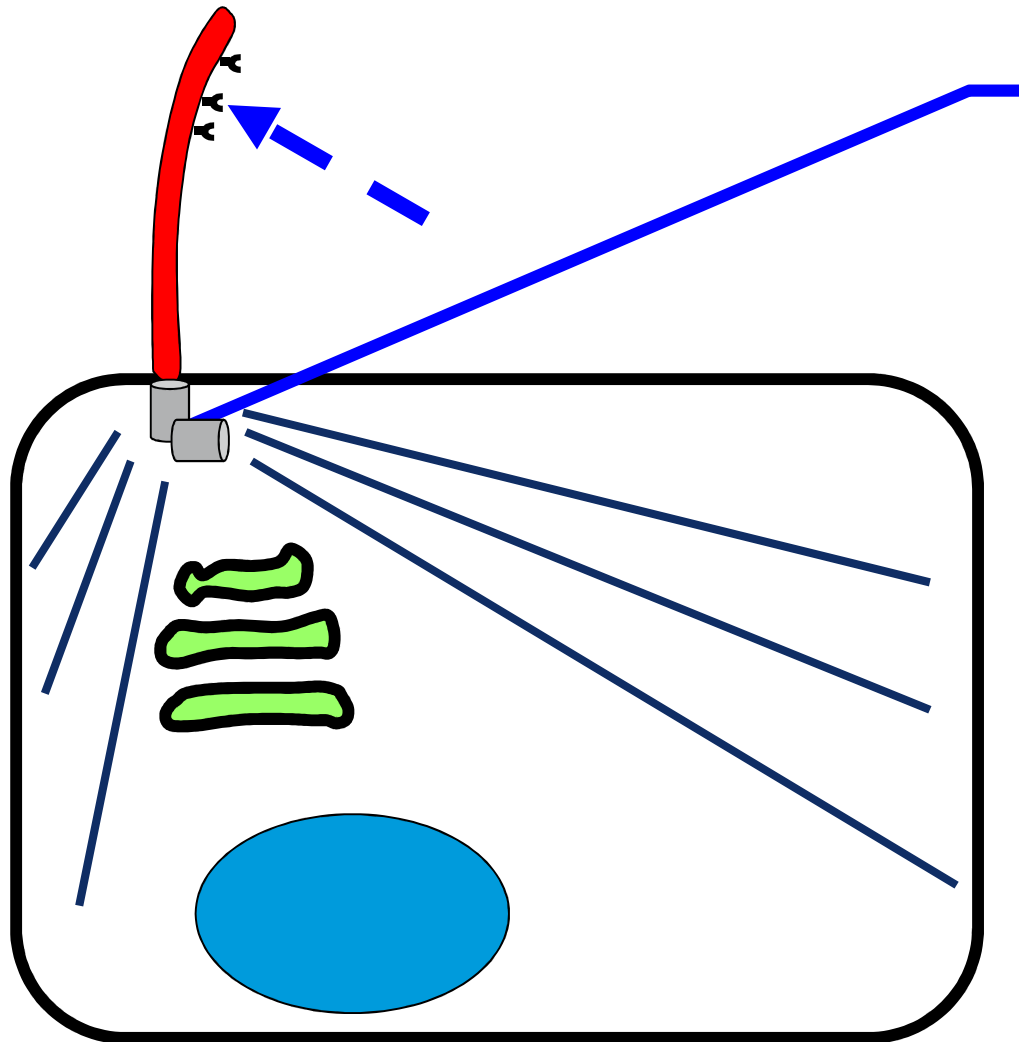
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NEOCYST

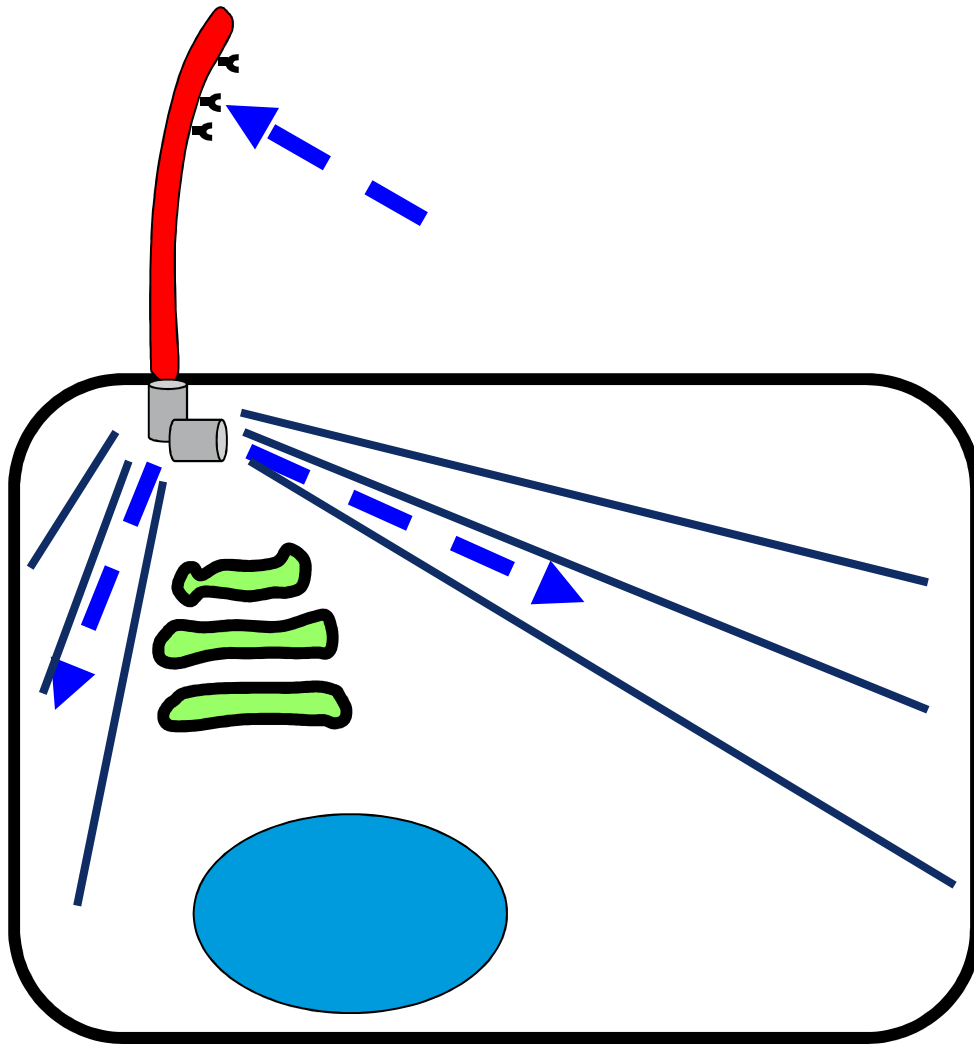
Network for **Early Onset Cystic** Kidney Diseases



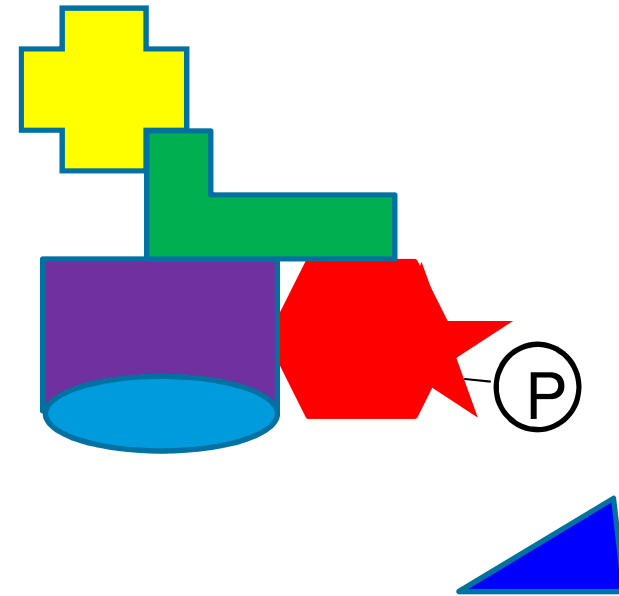




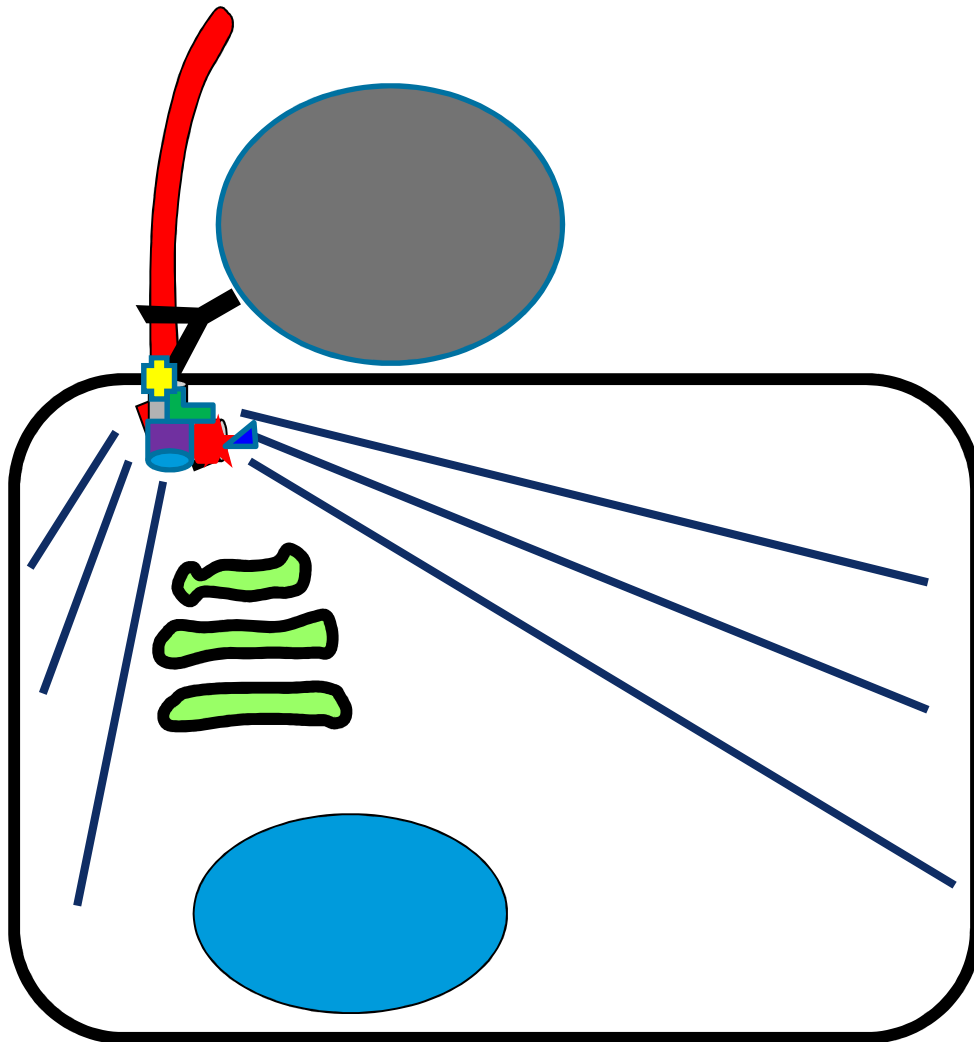
Was passiert bei der
Signalweitergabe
intrazellulär?



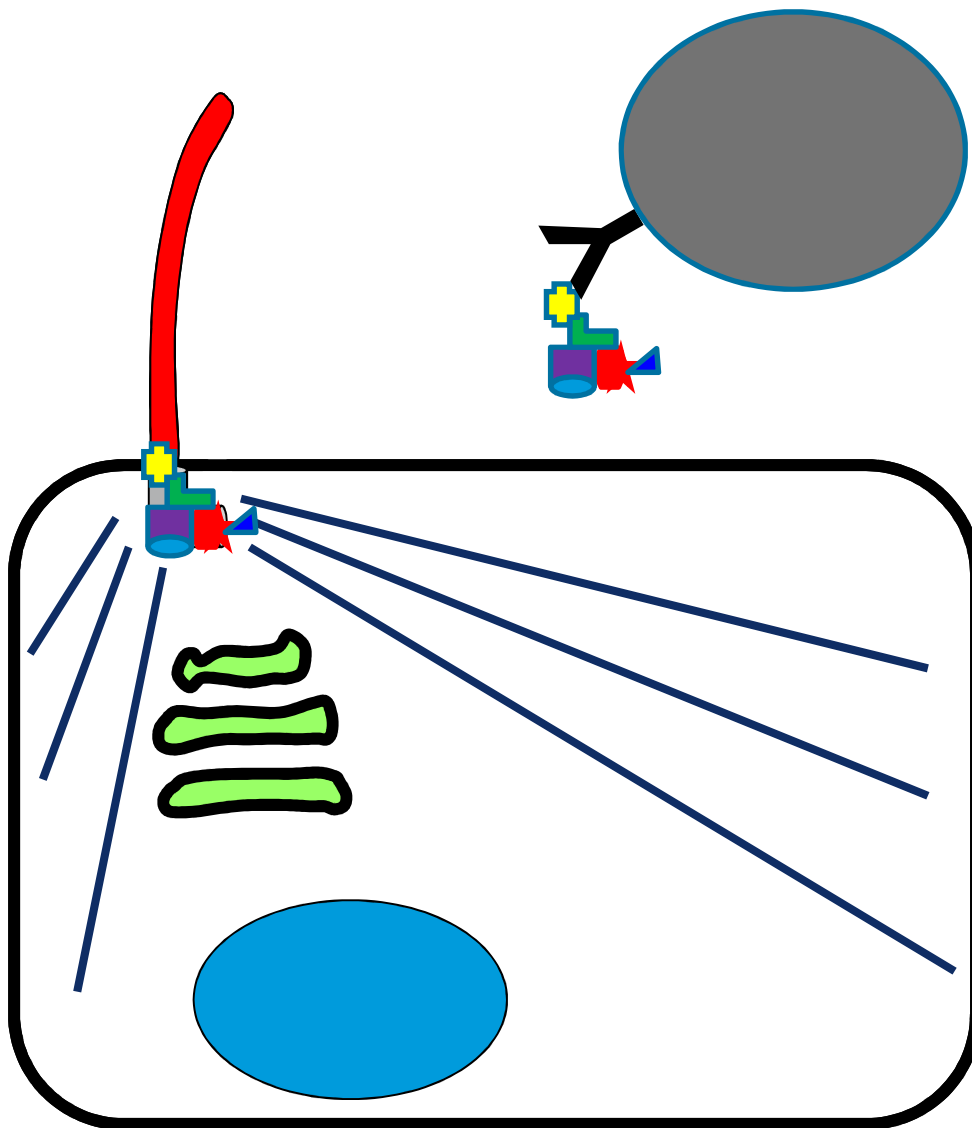
Intrazelluläre Proteinkomplexe



→ Signale:
Zellteilung, Zelltod etc.



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?

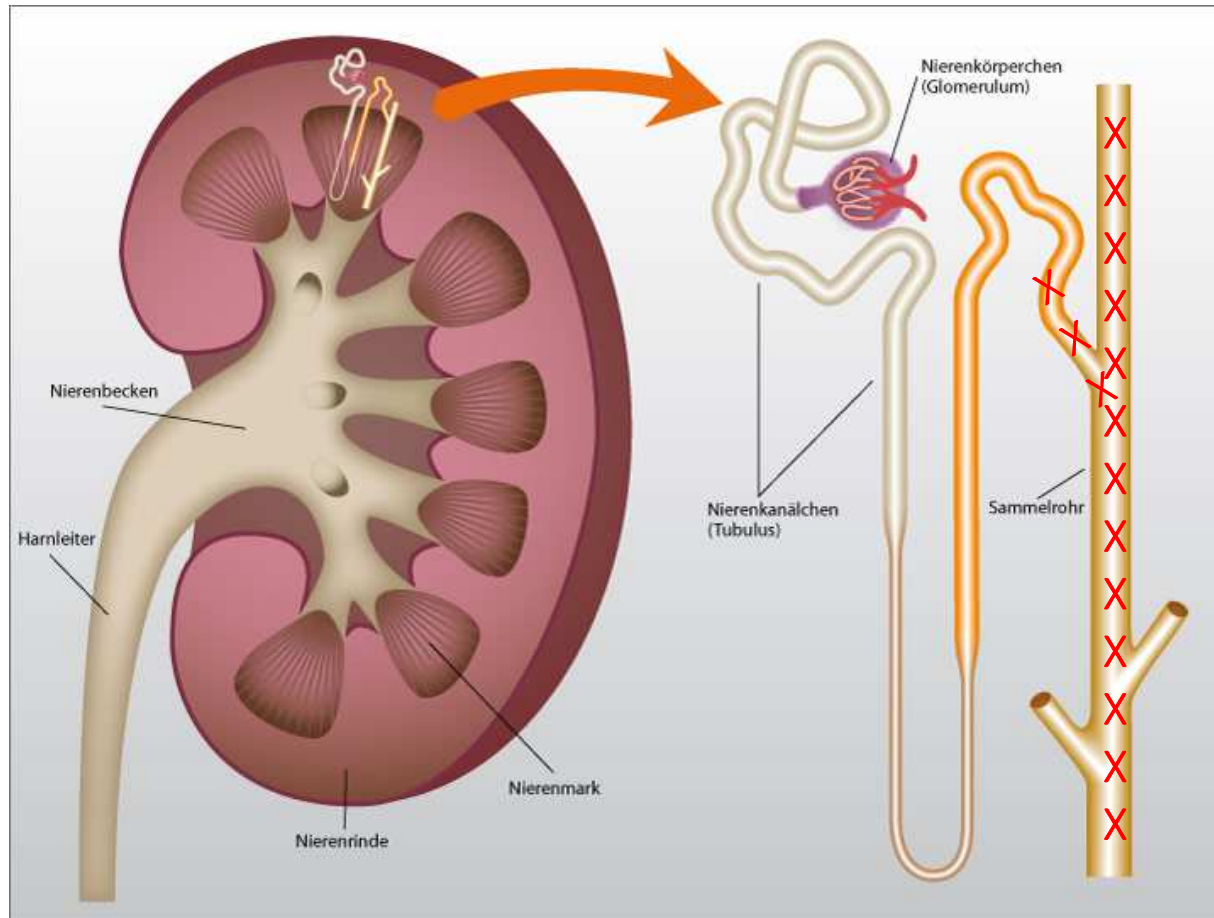
ARTICLE

Open Access

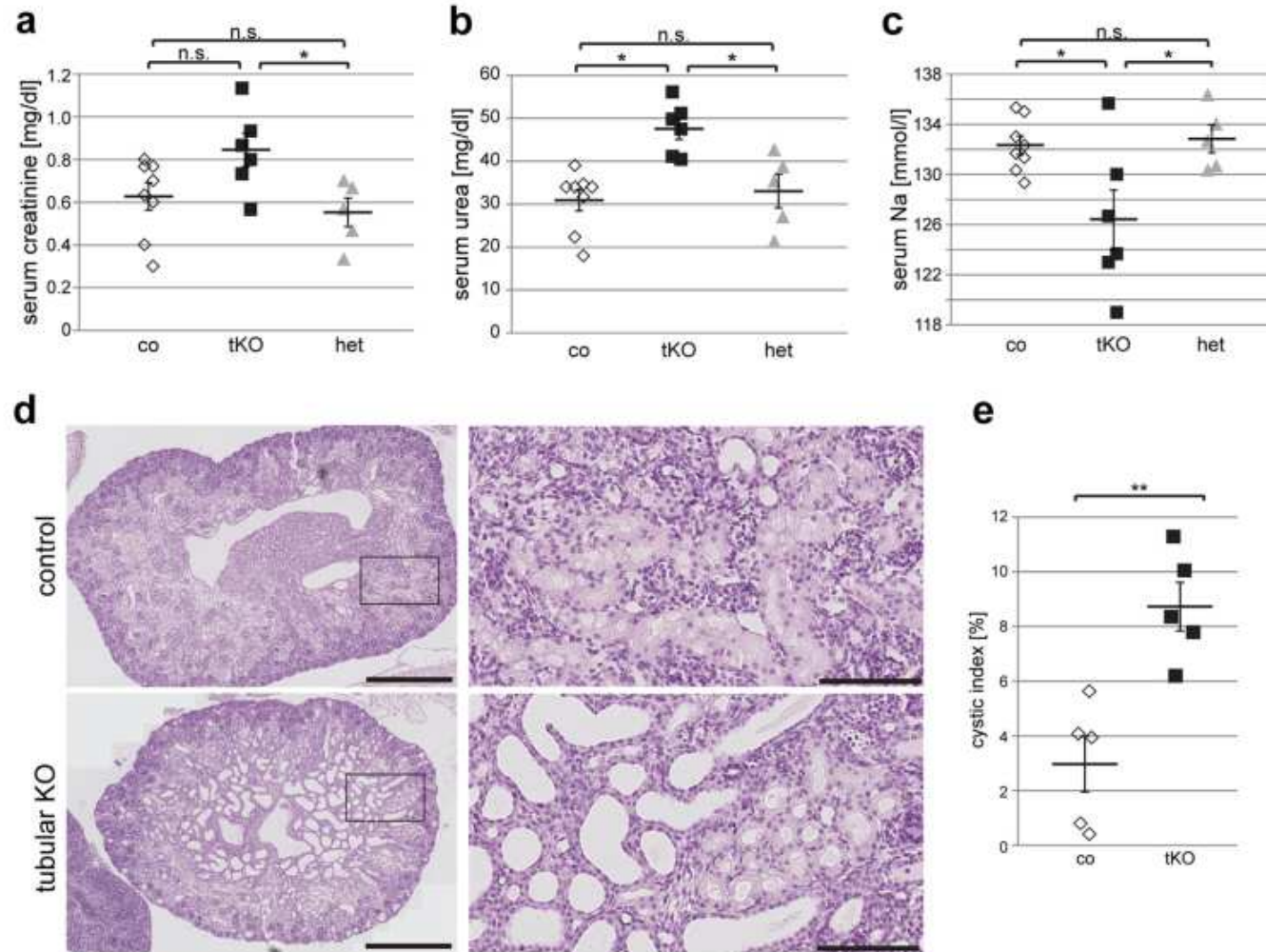
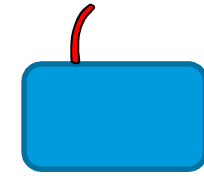
Targeted deletion of the AAA-ATPase Ruvbl1 in mice disrupts ciliary integrity and causes renal disease and hydrocephalus

Claudia Dafinger^{1,2,3}, Markus M. Rinschen^{1,2,4}, Lori Borgal^{1,2}, Carolin Ehrenberg¹, Sander G. Basten⁵, Mareike Franke⁶, Martin Höhne^{1,2,4,7}, Manfred Rauh⁸, Heike Göbel⁹, Wilhelm Bloch¹⁰, F. Thomas Wunderlich^{2,4,11,12}, Dorien J. M. Peters¹³, Dirk Tasche¹, Tripti Mishra^{1,2}, Sandra Habbig^{1,2,3}, Jörg Dötsch³, Roman-Ulrich Müller^{1,2,4}, Jens C. Brüning^{2,4,11,12}, Thorsten Persigehl⁶, Rachel H. Giles⁵, Thomas Benzing^{1,2,4,7}, Bernhard Schermer^{1,2,4,7} and Max C. Liebau^{1,2,3}

Genetische Erkrankungen in verschiedenen Nephronabschnitten



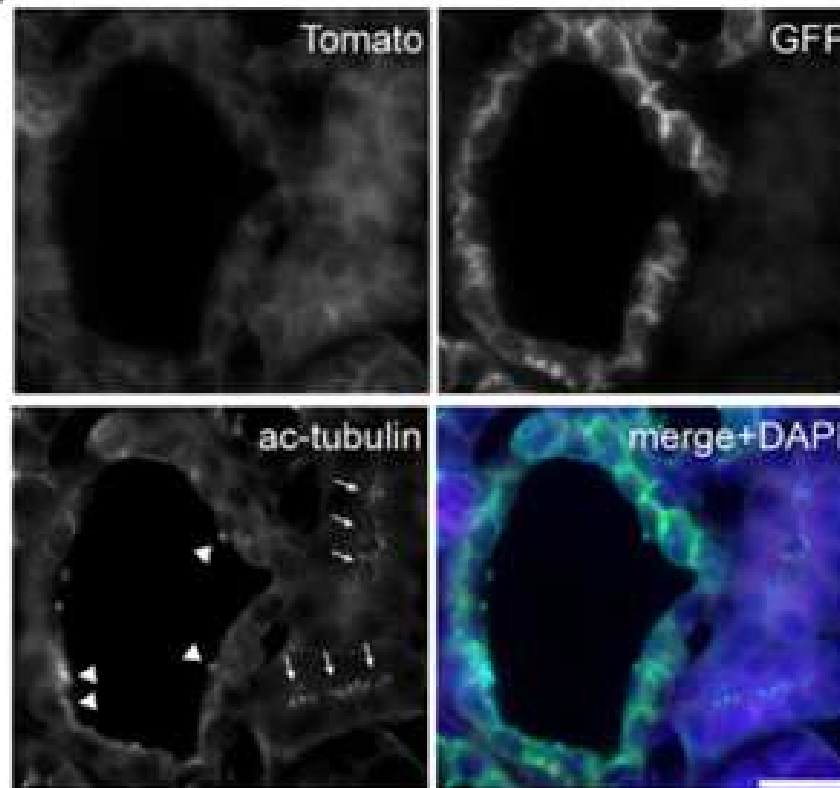
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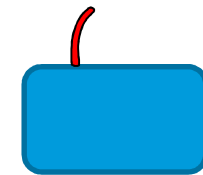
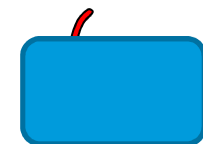
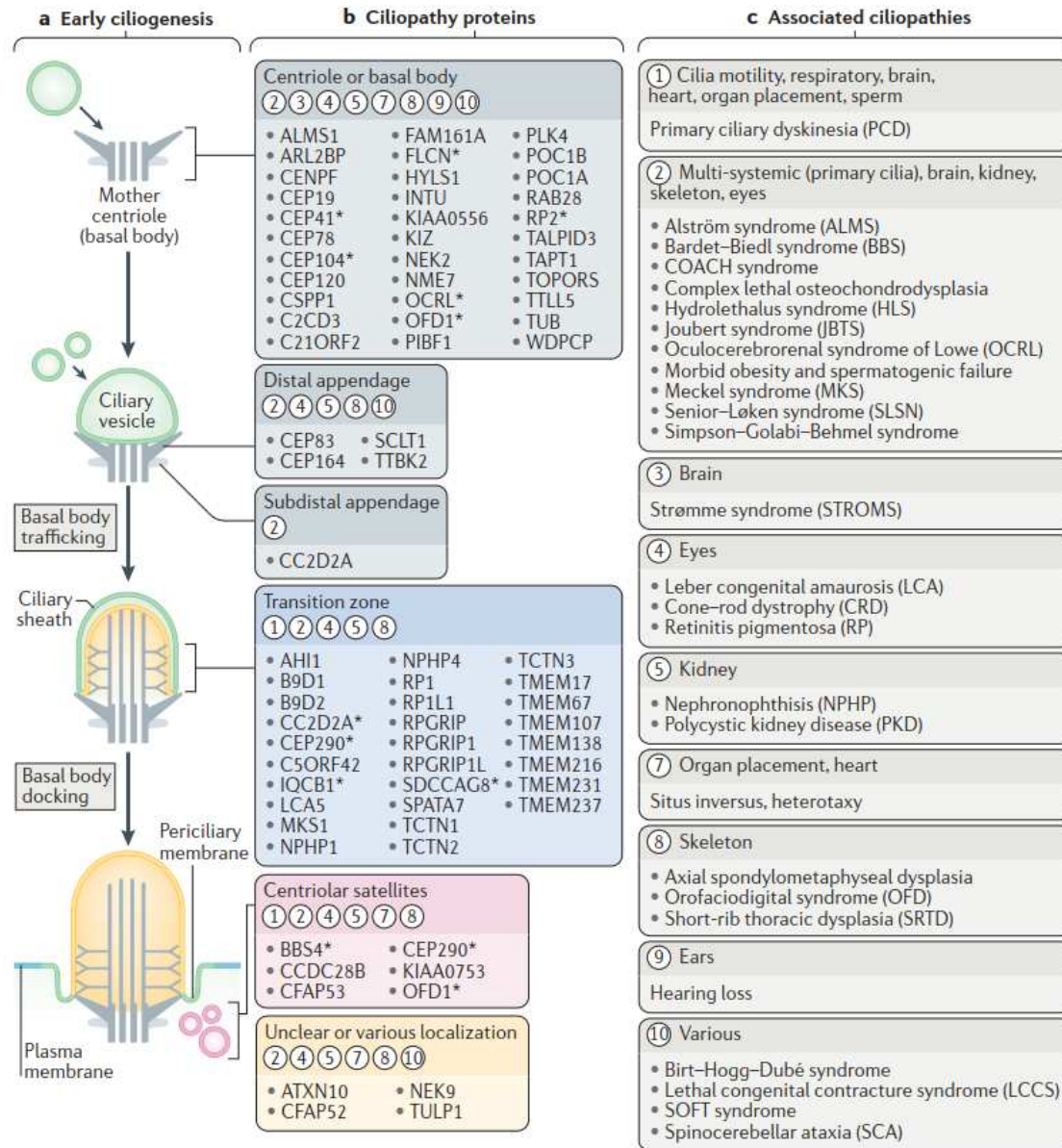


Warum?

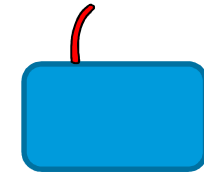


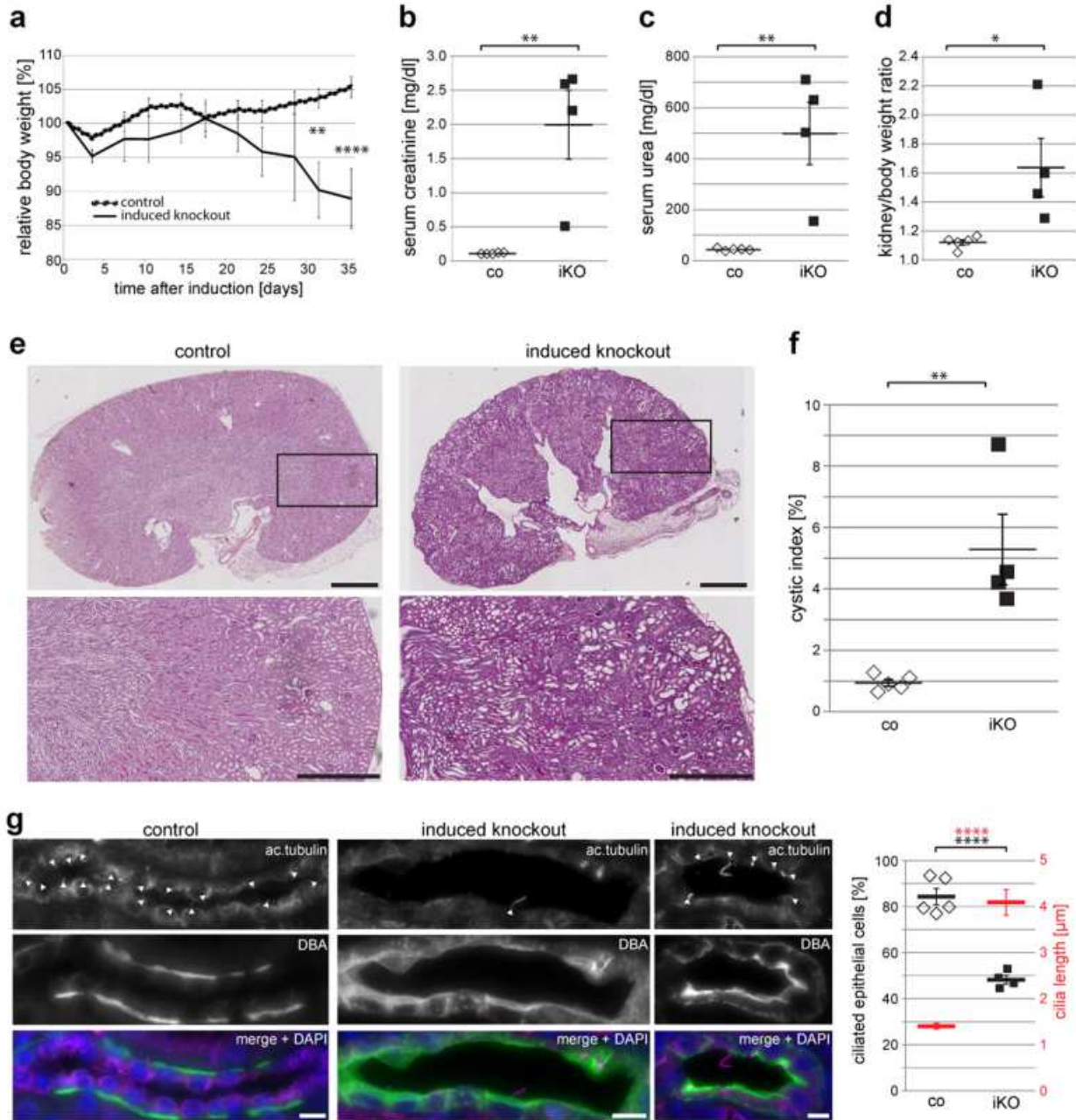
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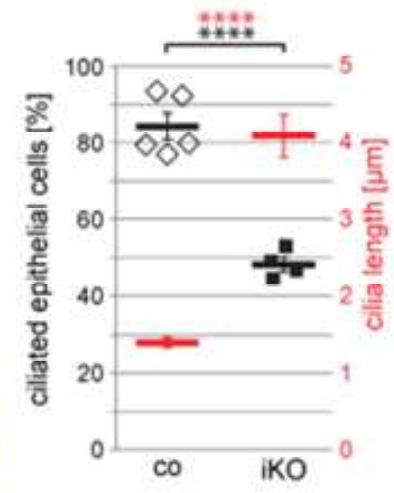
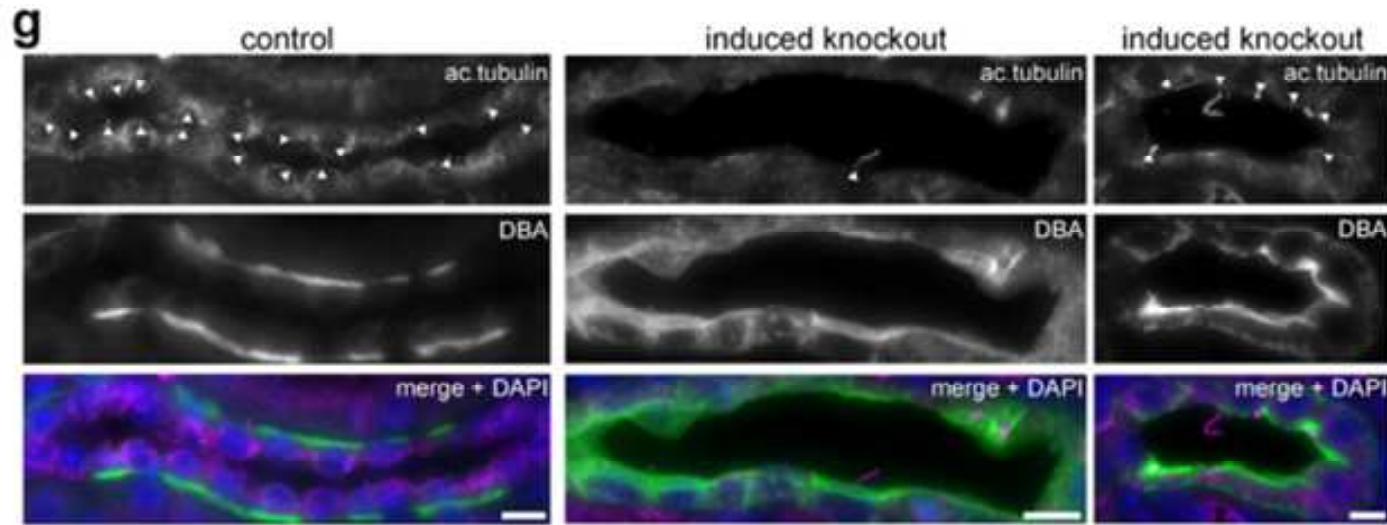
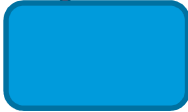


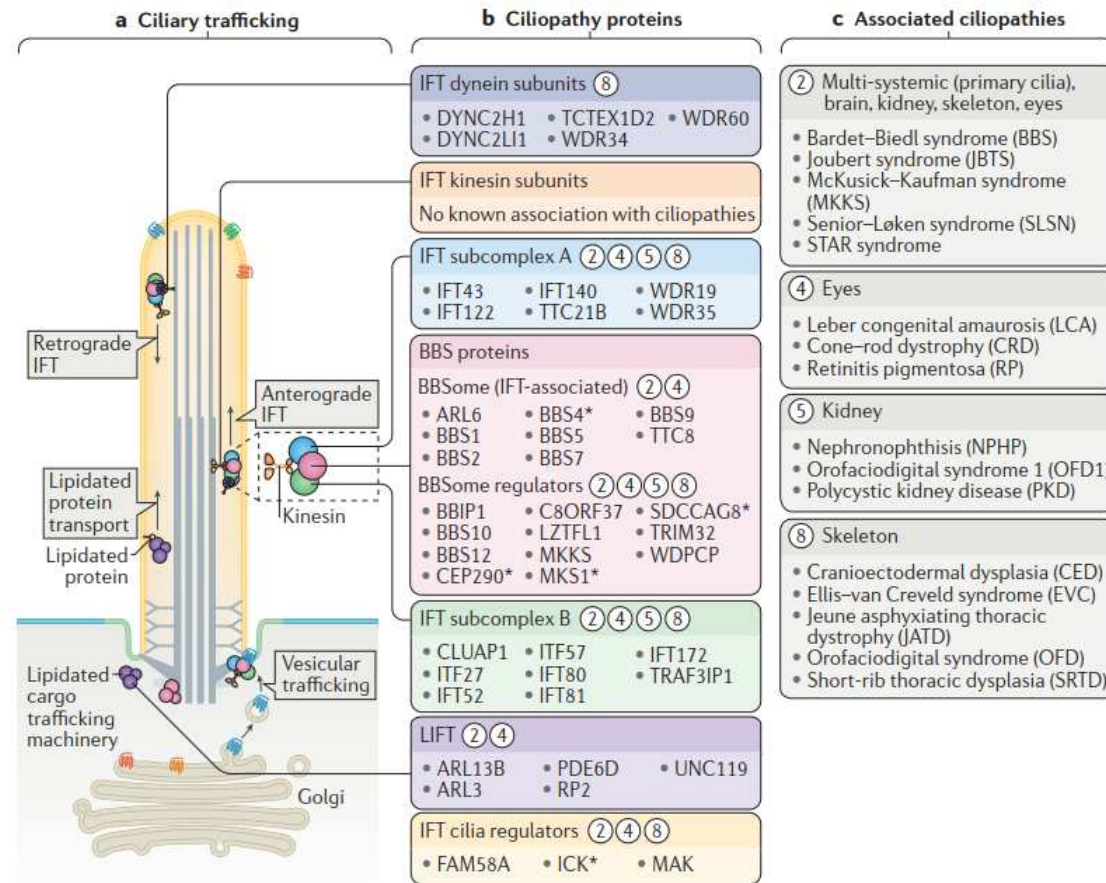
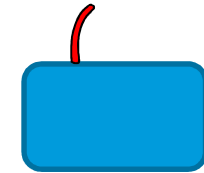


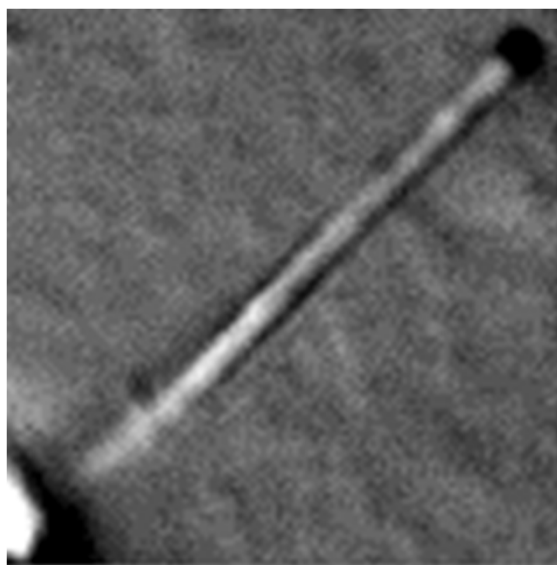
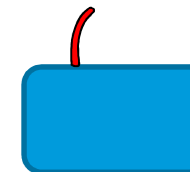
Reiter and Leroux,
Nat Rev Mol Cell Biol, 2017







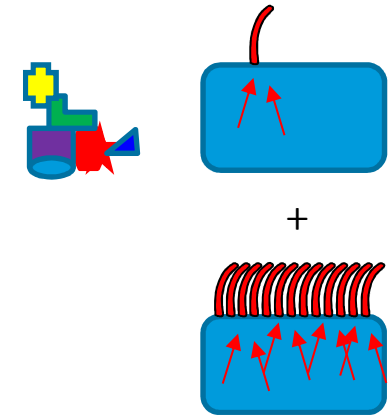
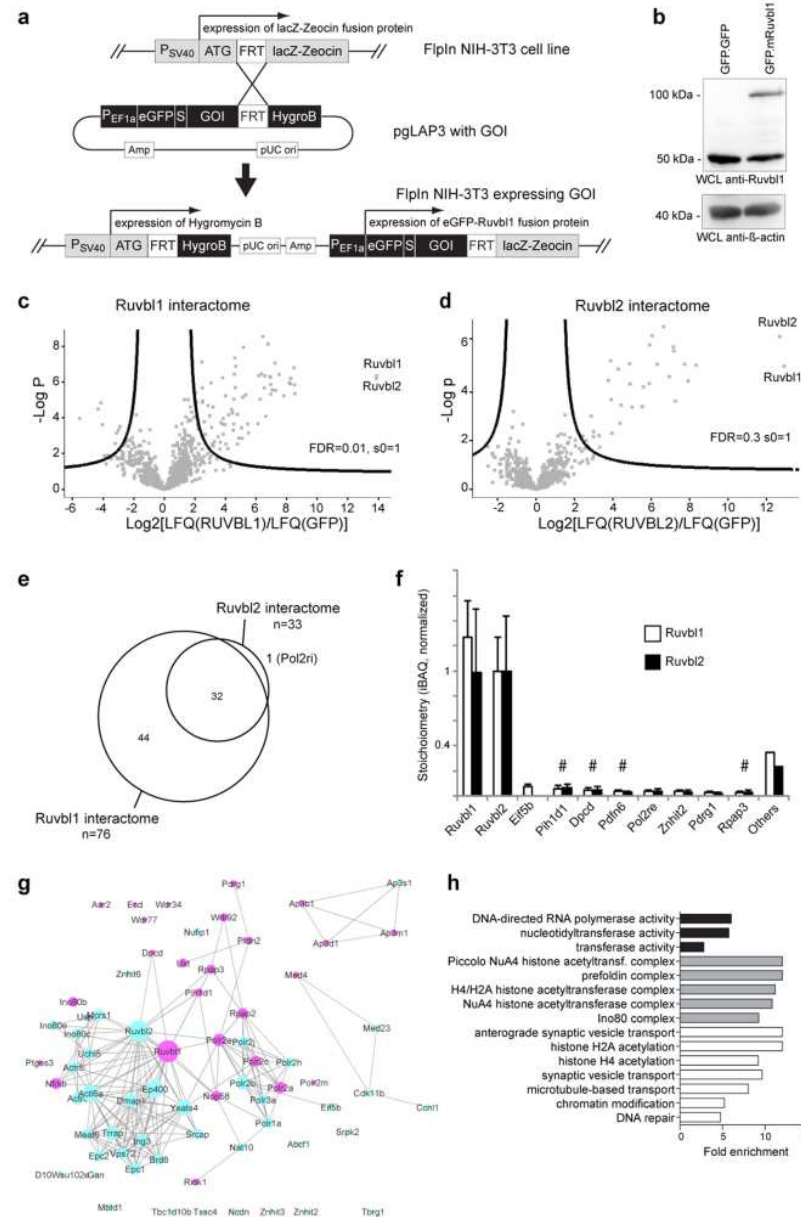


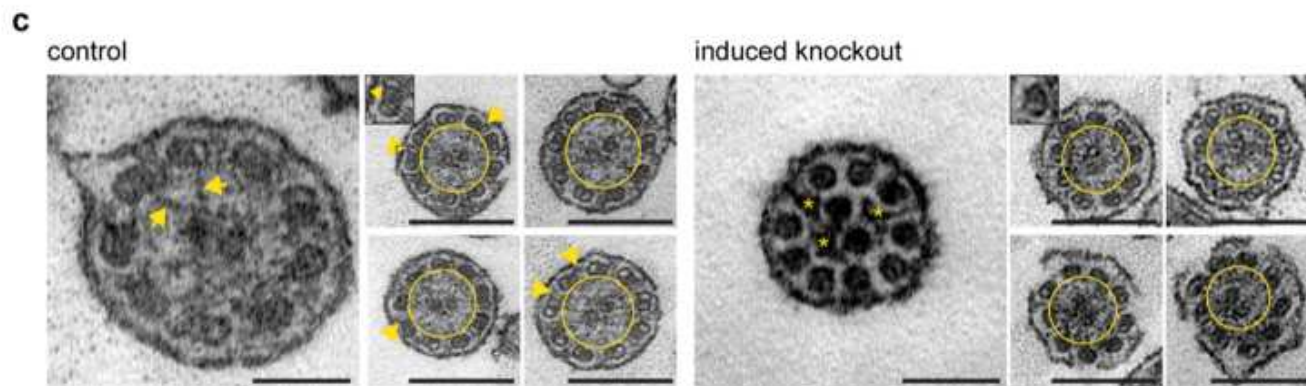
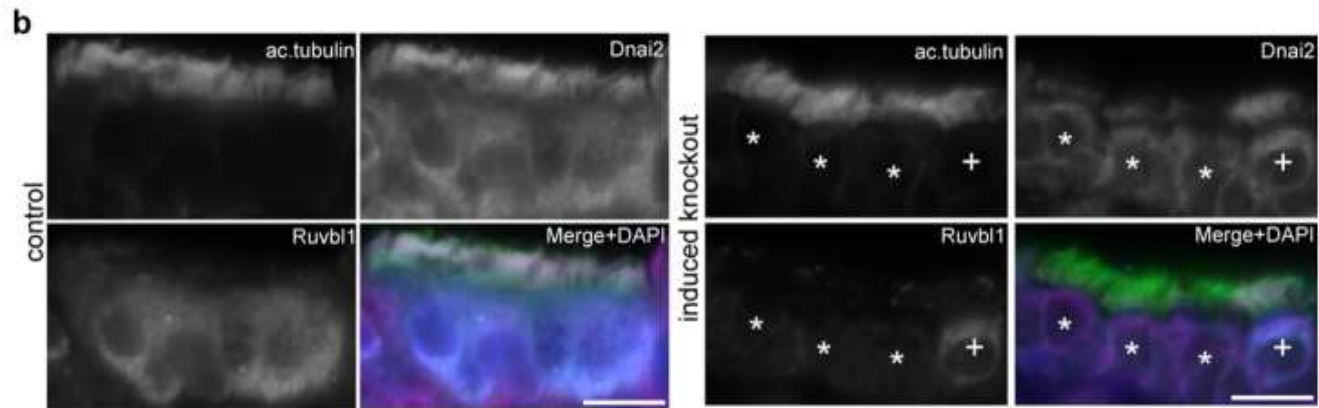
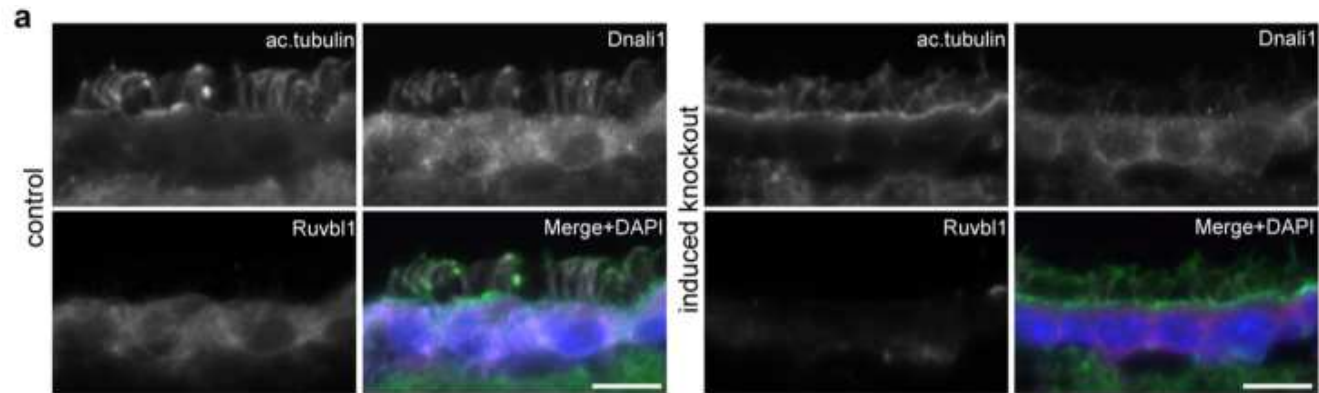
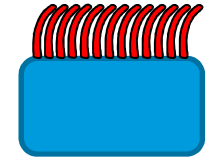


Craig et al.,
JCB, 2010



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Dafinger et al.,
Exp Mol Med, 2018

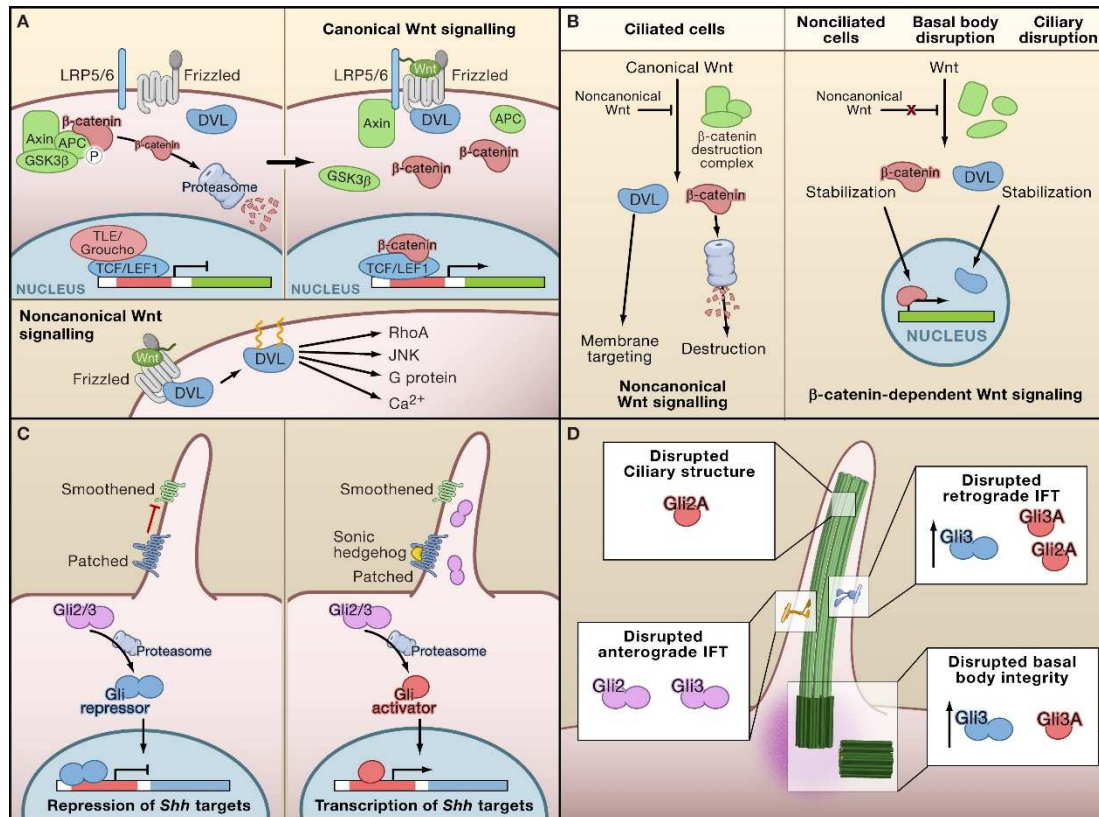
Warum ist solche Forschung wichtig?





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

EMBO Workshop

Cilia 2018

02 – 05 October 2018 | Copenhagen, Denmark

<http://meetings.embo.org/event/18-cilia>

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 University of Copenhagen, DK

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30 June 2018
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30 September 2018
 Abstract submission deadline
20 July 2018

Standard fees
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Bradley K. Yoder
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Monica Bettencourt-Dias
 Instituto Gulbenkian de Ciência, PT

Alessandra Boletta
 San Raffaele Scientific Institute, Milan, IT

Alexander Dammernann
 Max F. Perutz Laboratories, University of Vienna, AT

Bénédictte Durand
 Université Claude Bernard Lyon, FR

Peter K. Jackson
 Stanford University School of Medicine, US

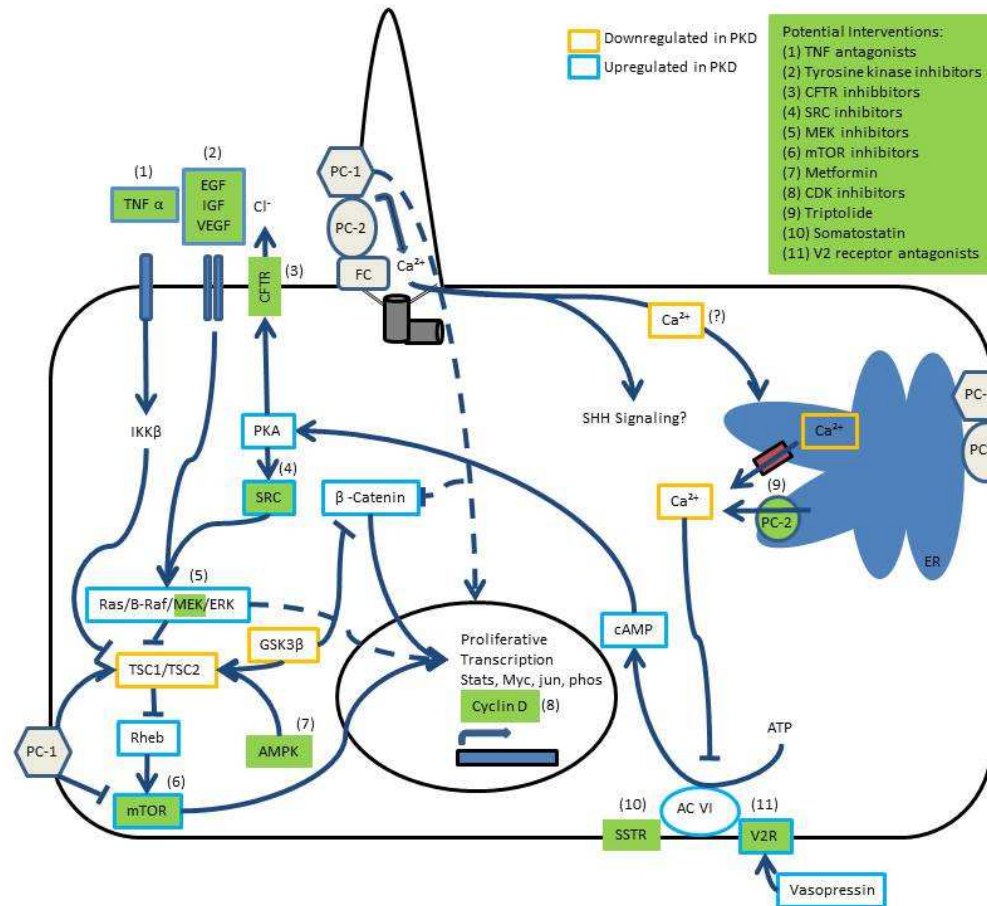
Masahide Kikkawa
 University of Tokyo, JP

Michel Leroux
 Simon Fraser University, CA

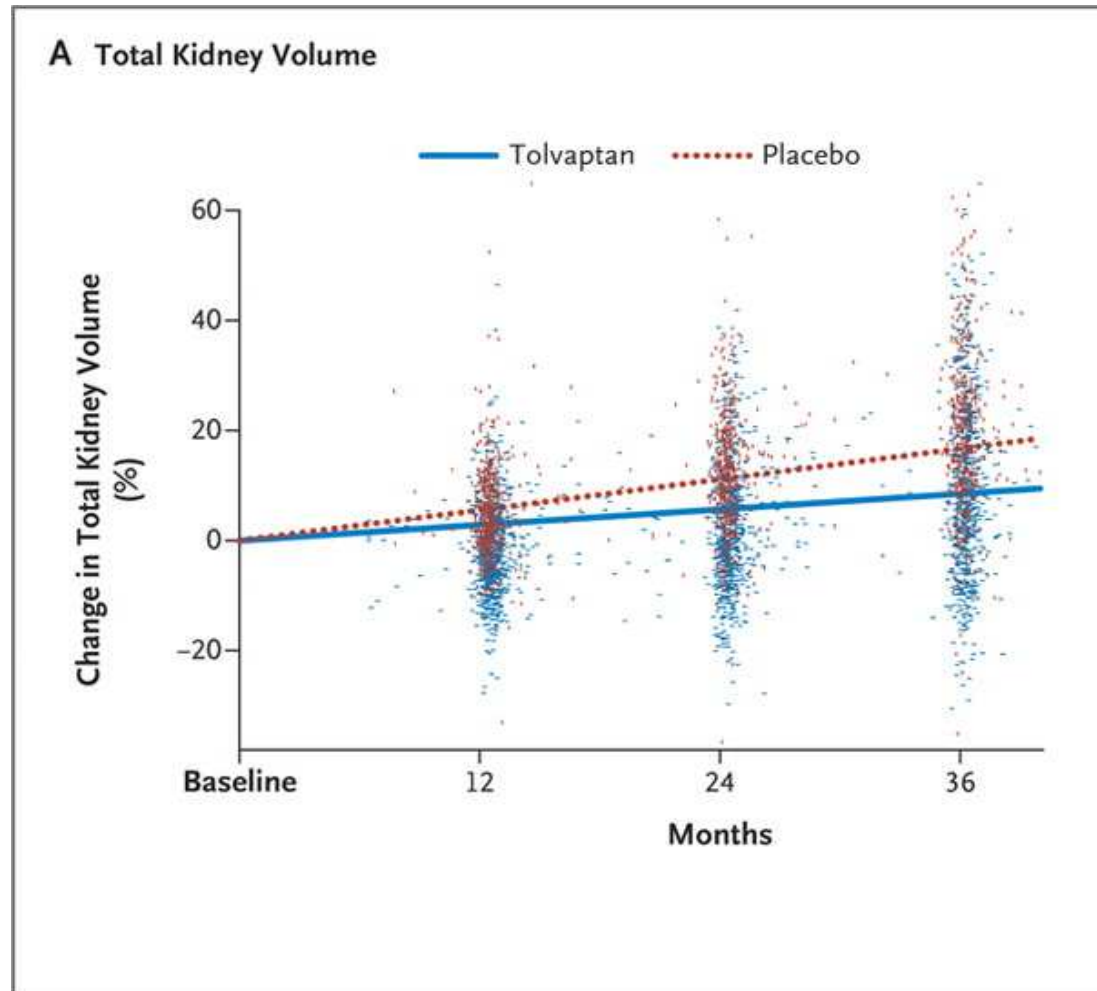
Esbén Lorentzen
 Aarhus University, DK

Jane Lucas
 University of Southampton, UK

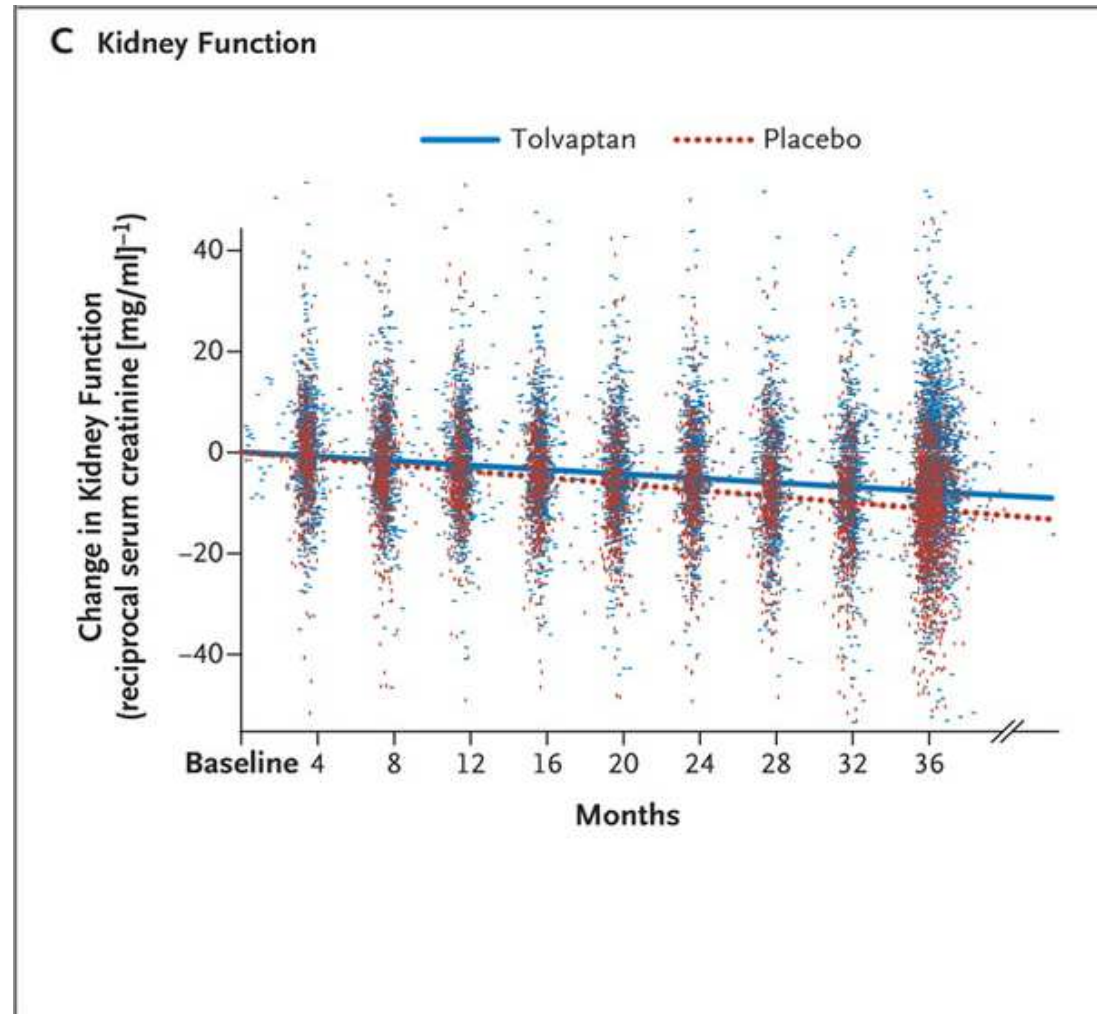
Signalveränderungen bei PKD



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



Torres et al., NEJM 2013



Torres et al., NEJM 2013



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Grundlagenwissenschaft

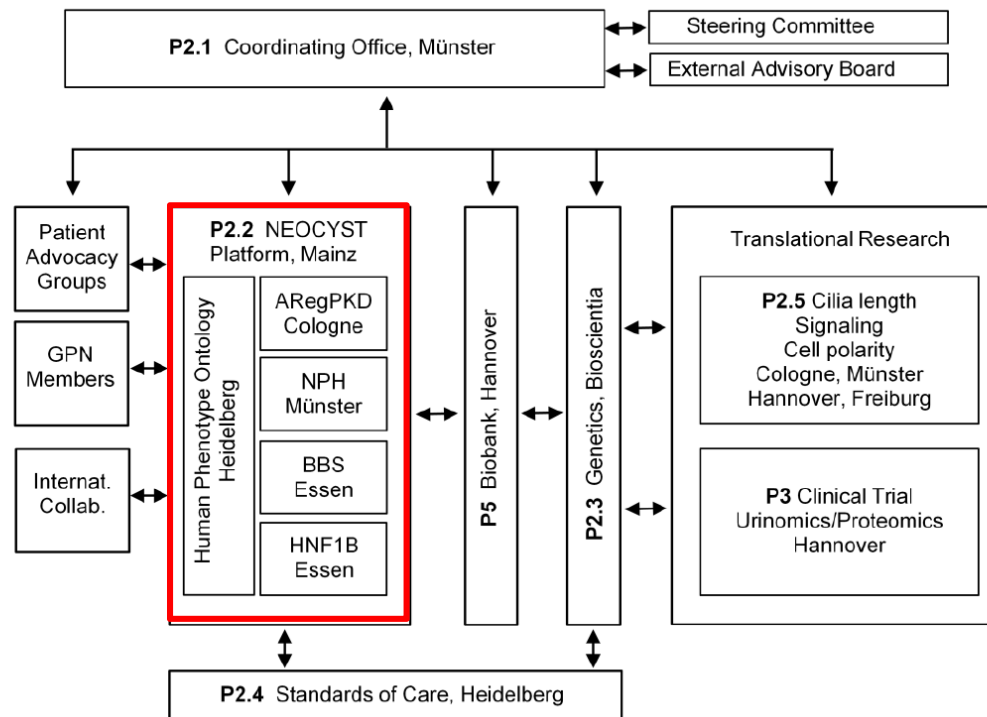
„Translationale
Forschung“



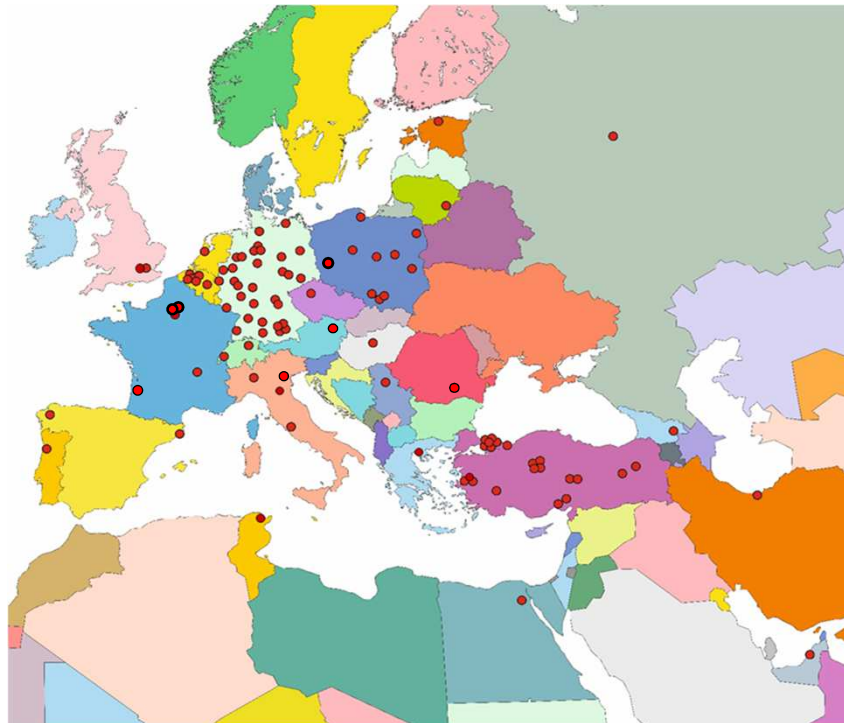
Klinische Beobachtung

NEOCYST

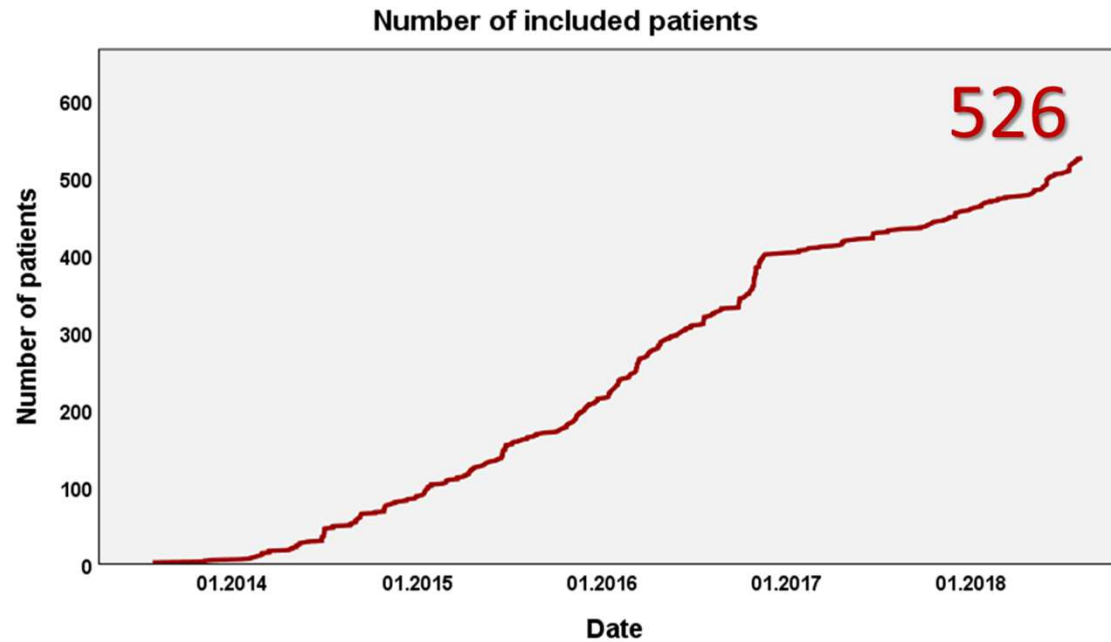
Network for **Early Onset Cystic** Kidney Diseases



ARegPKD – 111 Zentren in 27 Ländern



ARegPKD – 111 Zentren in 27 Ländern



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.



European Society for paediatric nephrology



Leading European Nephrology

GPN

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 **PETER-STIFTUNG**
für die Nierenwissenschaft
Schwerpunkt *Kindernephrologie*

GEFÖRDERT VOM

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 European Reference Networks

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