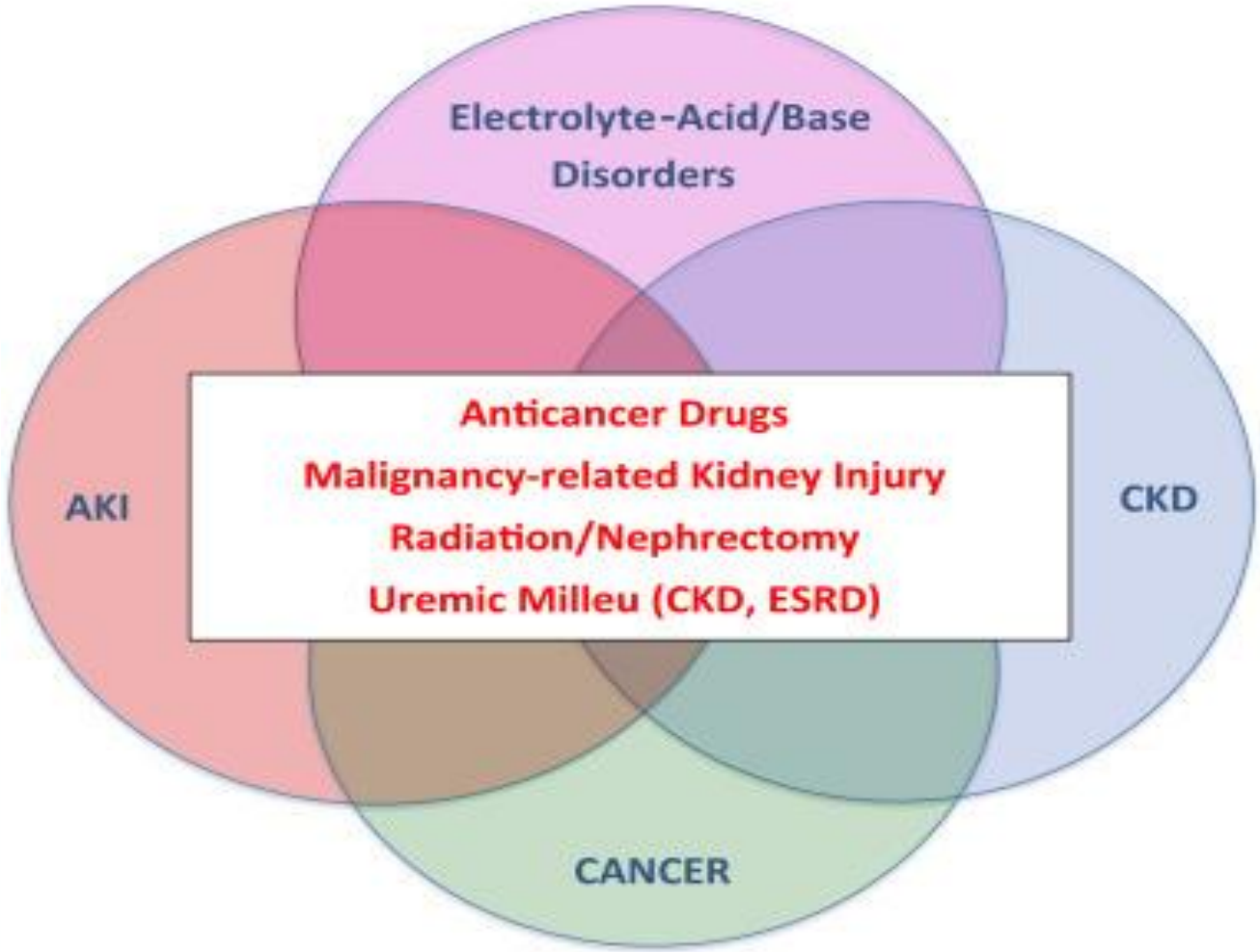
Κοινοί παράγοντες κινδύνου για νεοπλασίες και ΧΝΝ

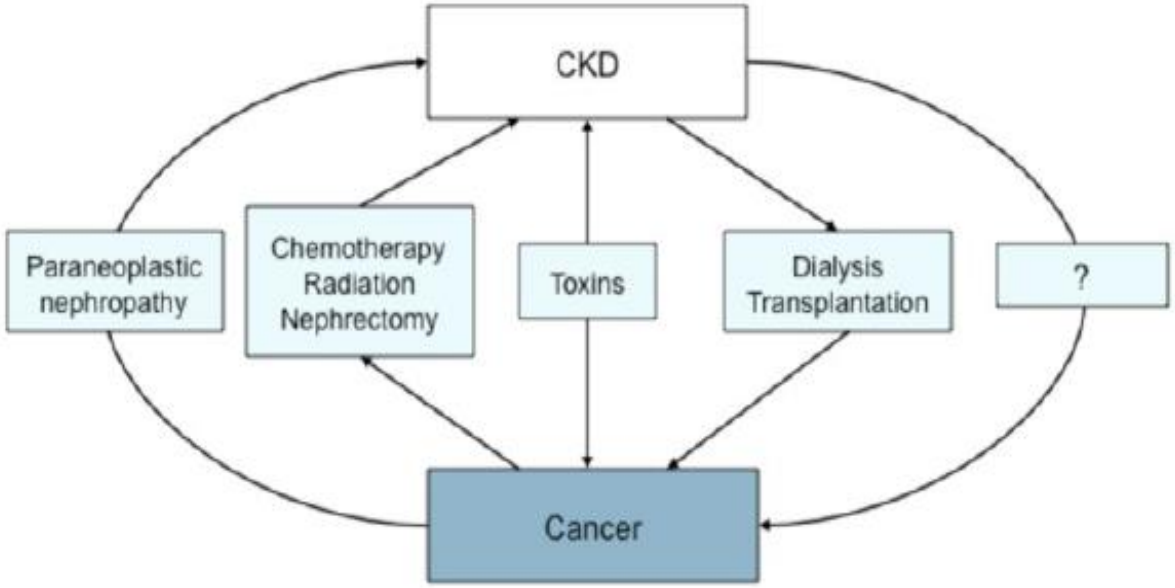
Ιωάννης Γ. Γριβέας, MD,PhD

Νεφρολόγος

athens-NEPHROLOGY

Onco-Nephrology



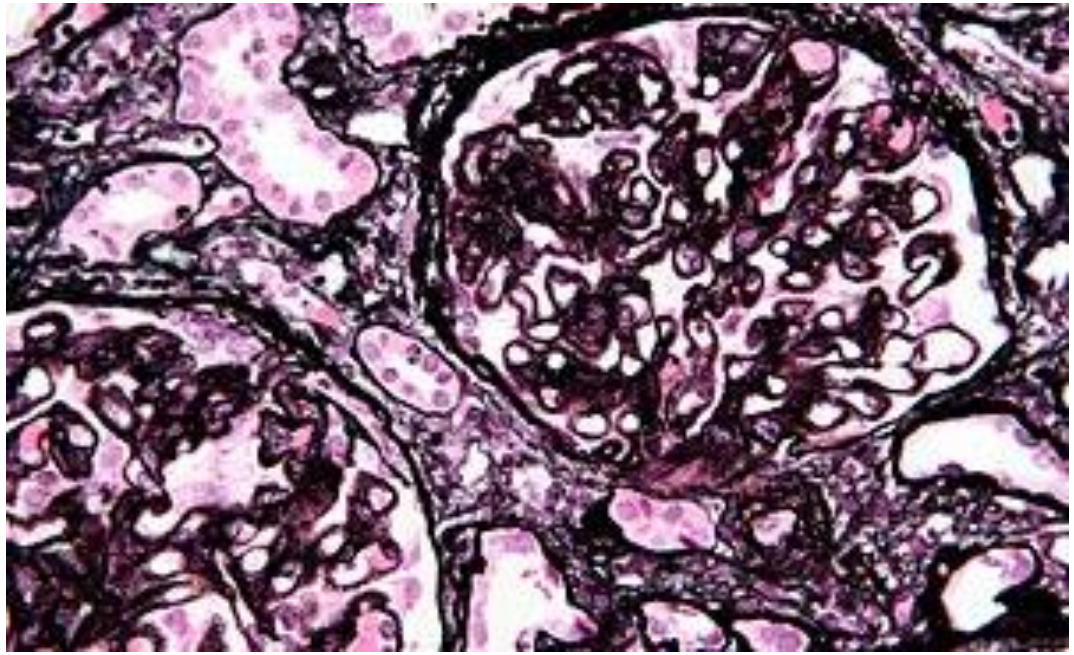


Chronic kidney disease and cancer: a troubling connection

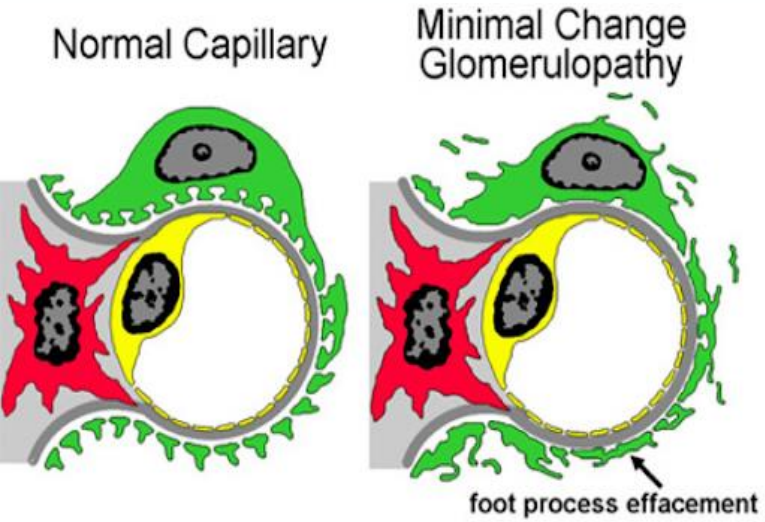
Bénédicte Stengel[1,*]

J Nephrol. 2010; 23(3): 253–262.

- Paraneoplasmatic nephropathies
- CKD chemotherapy and/or radiotherapy
- ESRD high risk for cancer –early stages
- Toxins



Cancer as a cause or a risk factor for chronic kidney disease



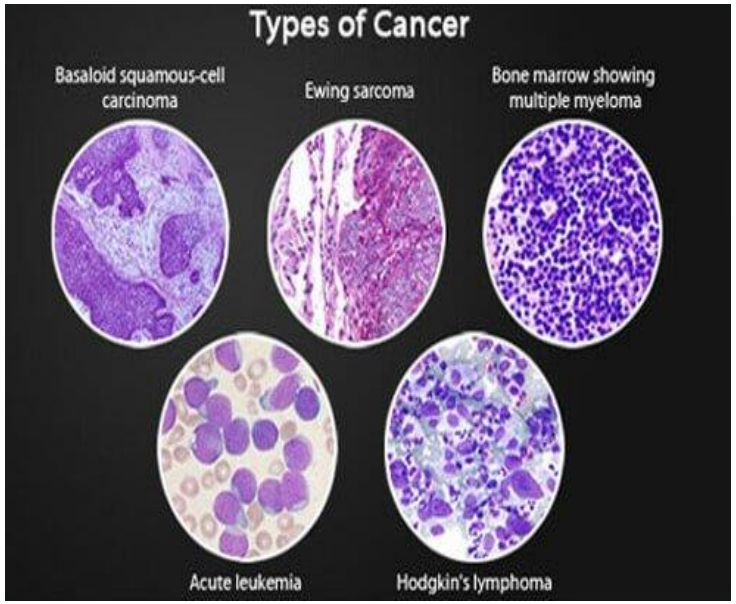
The most frequent situation in which nephrologists have to face CKD in patients with cancer is that following the assessment of kidney function for dosage adjustment before chemotherapy.
Because CKD, defined by an estimated glomerular filtration rate (eGFR) < 60 ml.min/1.73 m , is common, with a prevalence of **about 4% in the adult population aged 20 years and older**, reaching **30% or more in the elderly**, it is expected to be also common in patients with any type of cancer.

In the Renal Insufficiency and Anticancer Medications (IRMA) Study, Launay-Vacher at al showed that among 4,684 participants with cancer, aged an average of 58 yrs, 12% had an eGFR < 60 ml.min/1.73 m using the abbreviated MDRD equation, and 20% with the Cockcroft-Gault formula.

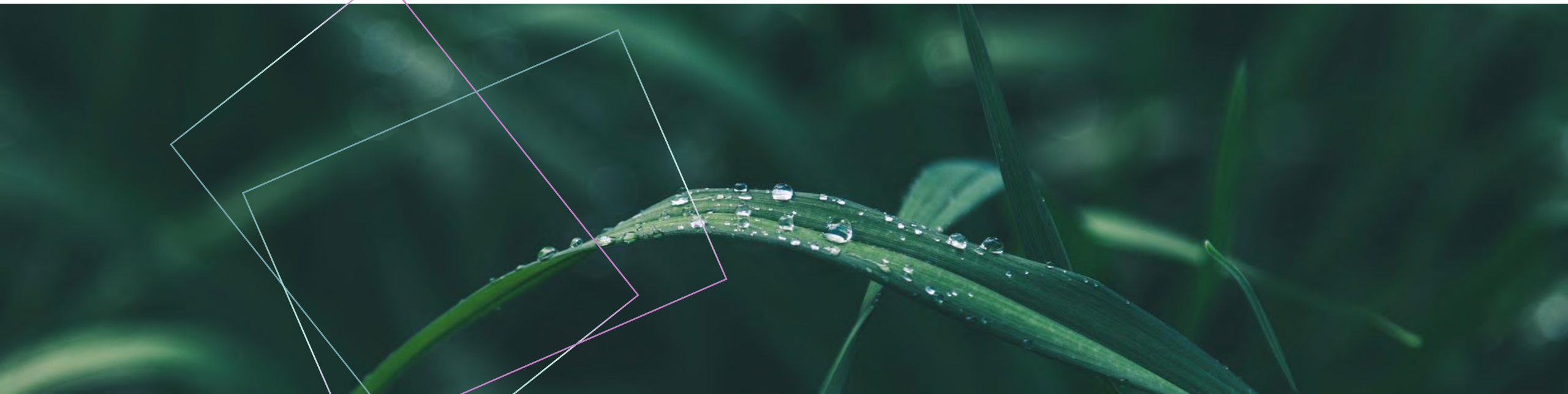
Association, however, does not mean causation, and the cure of most cancers is unlikely to improve the course of CKD. The issue here is that of the prevention of adverse drug effect from overdosage due to renal mpairment

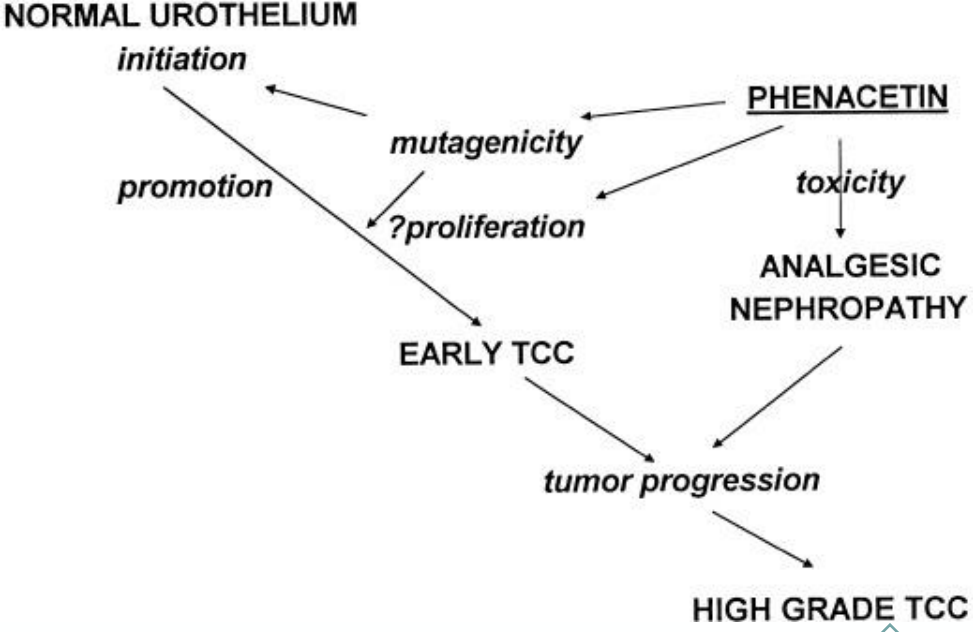
- Interestingly, renal biopsies revealed 92% of patients with cancer-associated MN had more than eight inflammatory cells infiltrating the glomeruli as compared with only 25% of those with idiopathic MN. The determination of leukocyte number was proposed as a mean to identify MN patients who may need cancer screening.

- Regarding the pathophysiology of these paraneoplastic nephropathies, whereas it remains obscure for solid tumor-associated glomerulopathies, a molecular link, and even specific molecular abnormalities, can be demonstrated for lymphoplasmacytic disorders.

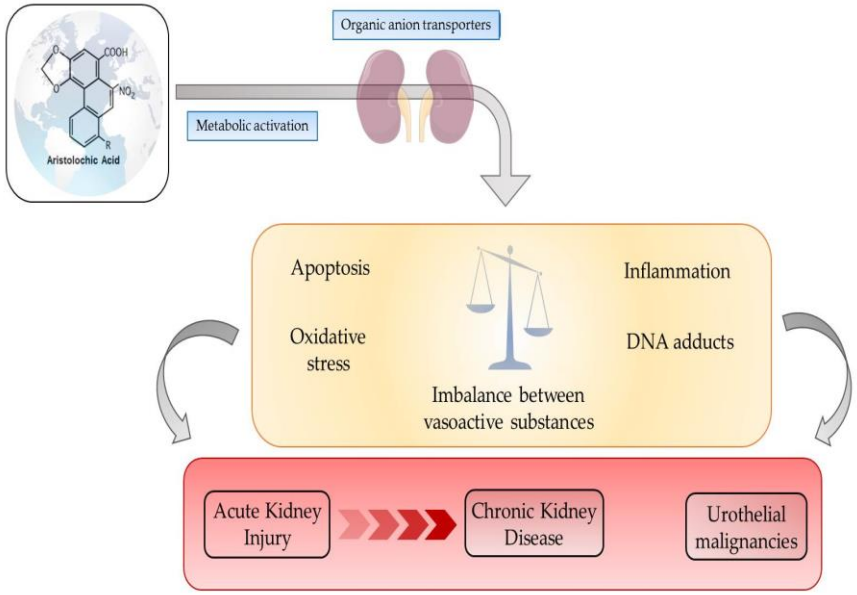


Ronco PM. Paraneoplastic glomerulopathies: new insights into an old entity. Kidney Int.1999;56:355–377.

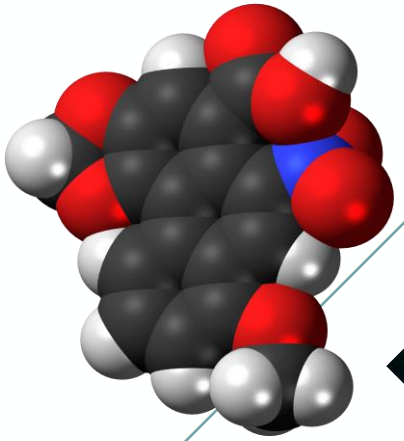


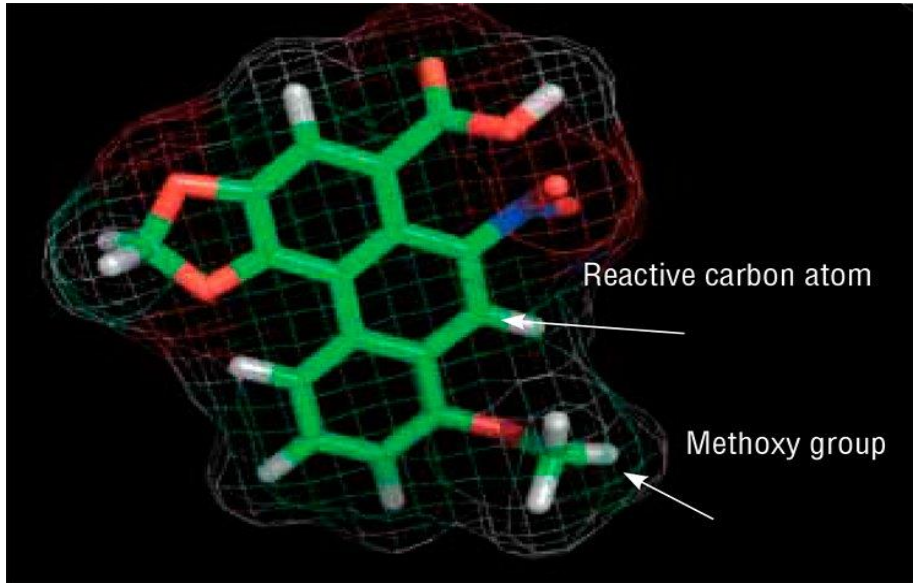


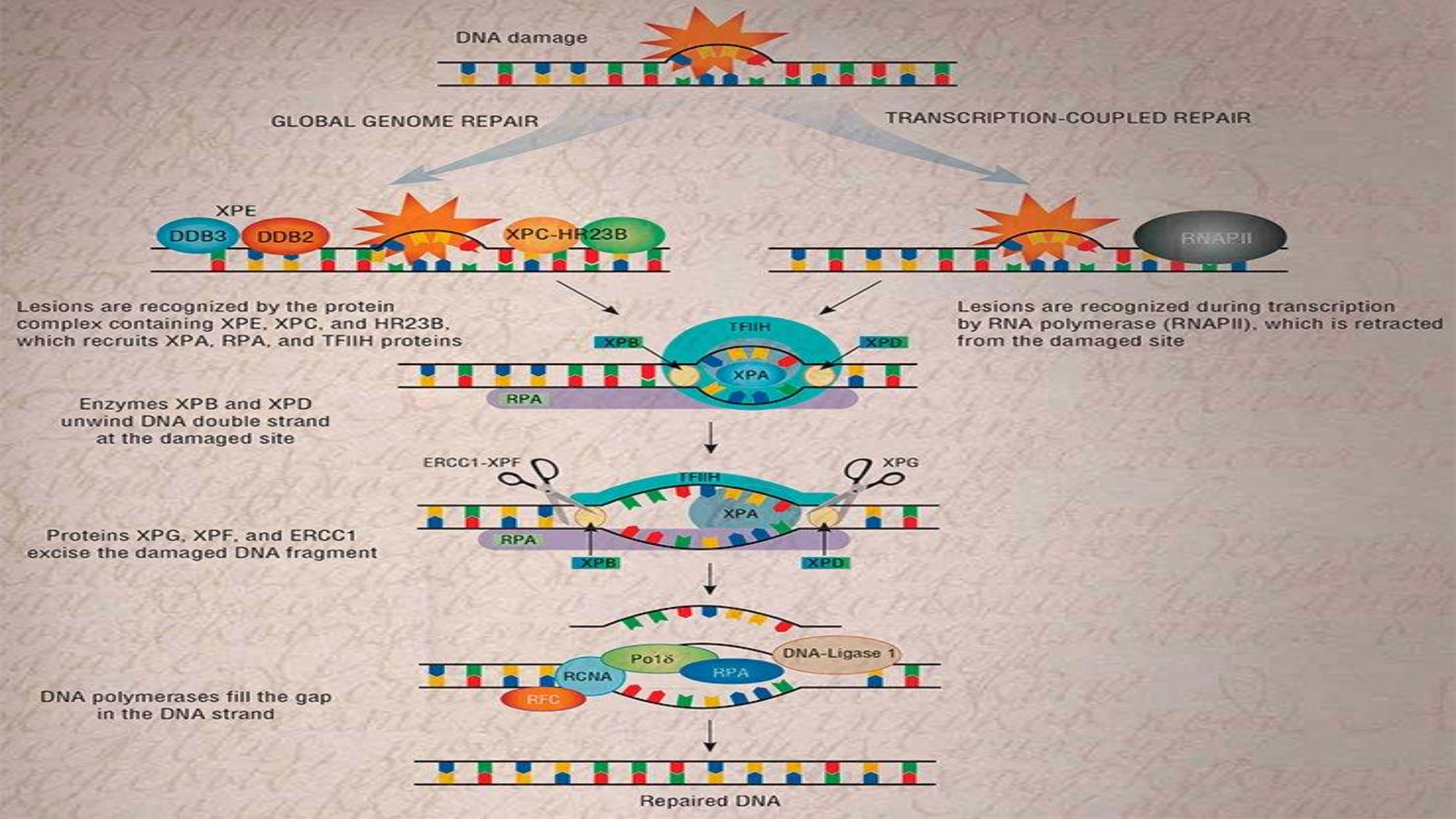
Toxin-related CKD and cancers


Aristolochic Acid
Organic anion transporters
Metabolic activation
Apoptosis
Inflammation
Oxidative stress
DNA adducts
Imbalance between vasoactive substances
Acute Kidney Injury
Chronic Kidney Disease
Urothelial malignancies


SLOVENIA
HUNGARY
Drava River
Danube River
Zagreb
Timişoara
Serbia
Croatia
Sava River
ROMANIA
Belgrade
BOSNIA AND HERZEGOVINA
Sarajevo
Morava River
Danube River
Vratsa
Nis
MONTENEGRO
Podgorica
Pristina
Sofia
Adriatic Sea
ALBANIA
BULGARIA



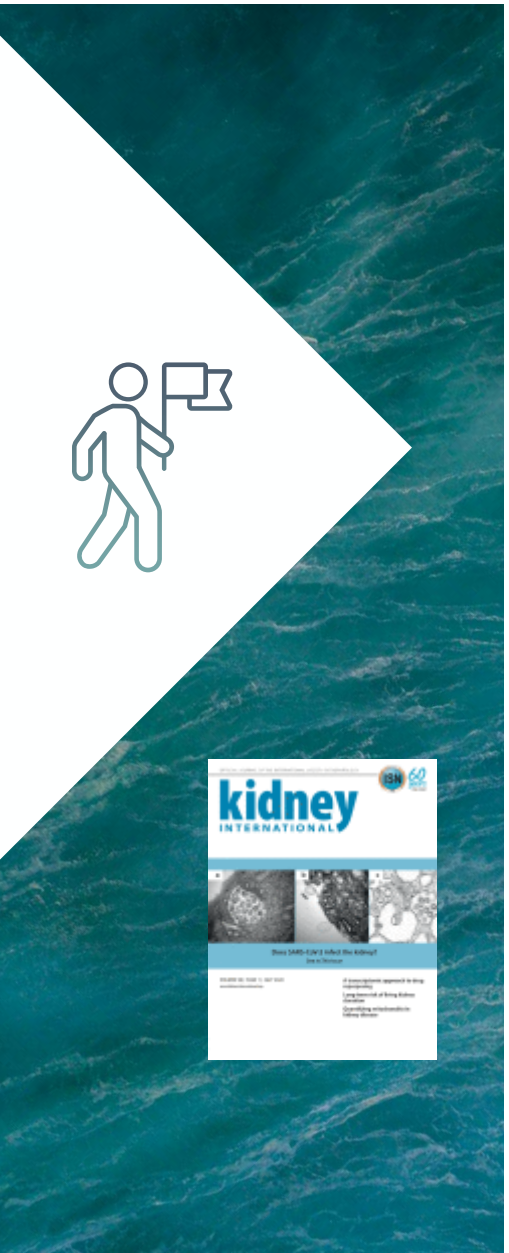

Reactive carbon atom
Methoxy group


DNA damage
GLOBAL GENOME REPAIR
TRANSCRIPTION-COUPLED REPAIR
XPE
DDB3
DDB2
XPC-HR23B
RNAPII
Lesions are recognized by the protein complex containing XPE, XPC, and HR23B, which recruits XPA, RPA, and TFIIH proteins
Lesions are recognized during transcription by RNA polymerase (RNAPII), which is retracted from the damaged site
TFIIH
XPB
XPD
XPA
RPA
Enzymes XPB and XPD unwind DNA double strand at the damaged site
ERCC1-XPF
XPG
TFIIH
XPA
RPA
XPB
XPD
Proteins XPG, XPF, and ERCC1 excise the damaged DNA fragment
Polδ
DNA-Ligase 1
RCNA
RPA
RFC
DNA polymerases fill the gap in the DNA strand
Repaired DNA

New drug toxicities in the onco-nephrology world

Mark A. Perazella[1] and Hassan Izzedine[2,3]

Kidney International (2015) **87**, 909-917



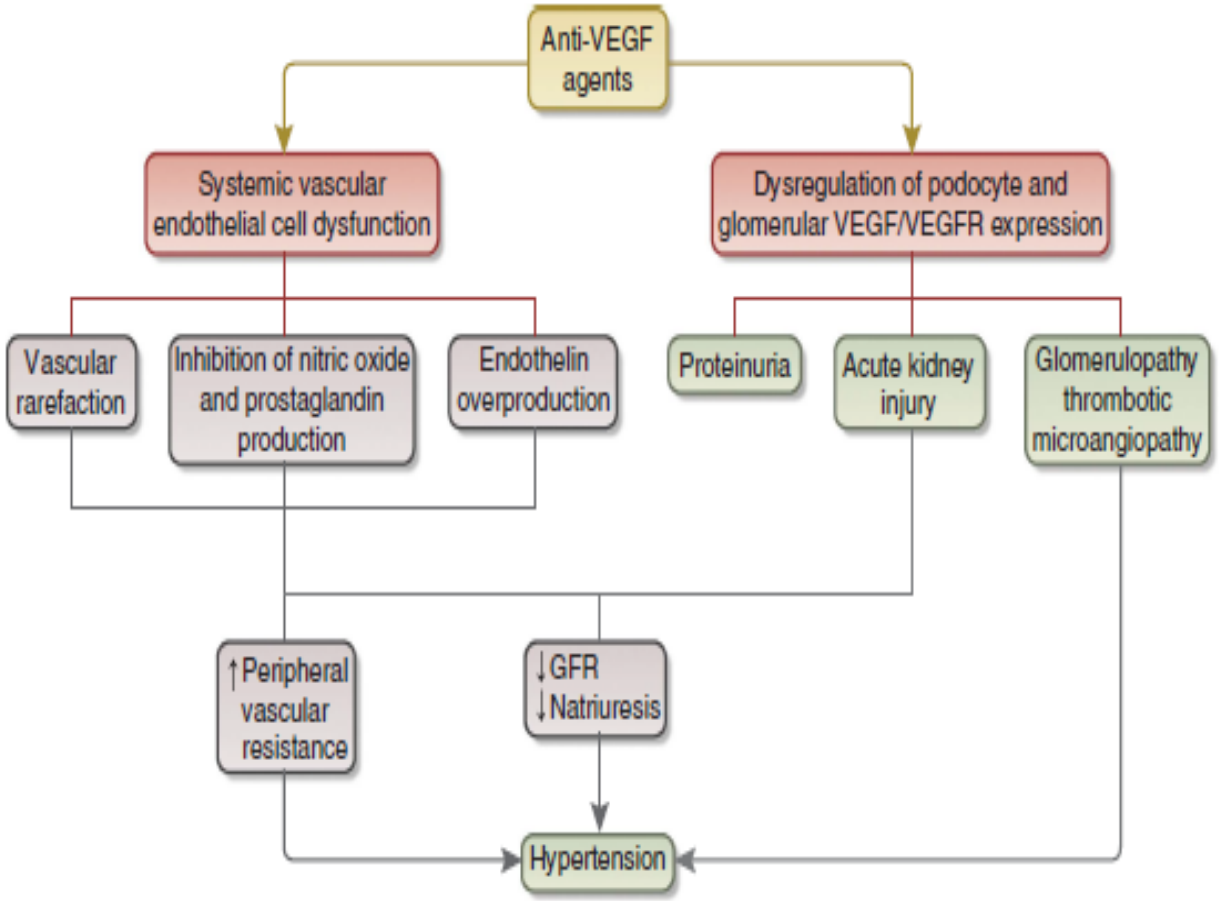


Figure 1 | Potential mechanisms of renal injury and hypertension induced by anti-angiogenic treatment. Systemic vascular endothelial cell dysfunction and localized kidney effects (glomerular endothelial cells and podocytes) of anti-angiogenesis drugs lead to clinical renal syndromes. Hypertension results from both systemic effects and renal effects (acute kidney injury reduces glomerular filtration rate (GFR) and natriuresis, thereby contributing to hypertension). VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

VEGF .... ????????

Vascular Endothelial Growth Factor

Originally described as endothelial **cell-specific mitogen** (Abraham and Schilling, 1989);
Now as VEGF and also known as **vascular permeability factor (VPF).**

VEGF is a sub-family of growth factors, to be specific, **the platelet-derived growth factor family of cystine-knot growth factors.**

Native VEGF is **a basic,** heparin-binding, homodimeric **glycoprotein of 45 kDa** (Ferrara, 1992).

Important signalling protein .

Mainly involved in **angiogenesis** and **vasculogenesis** .

Tumor cells , macrophages, platelets, keratinocytes, and renal mesangial cells etc .

VEGF plays a role in normal physiological functions such **as bone formation, hematopoiesis, wound healing, and development**. (Tischer and Vaisman 1990).

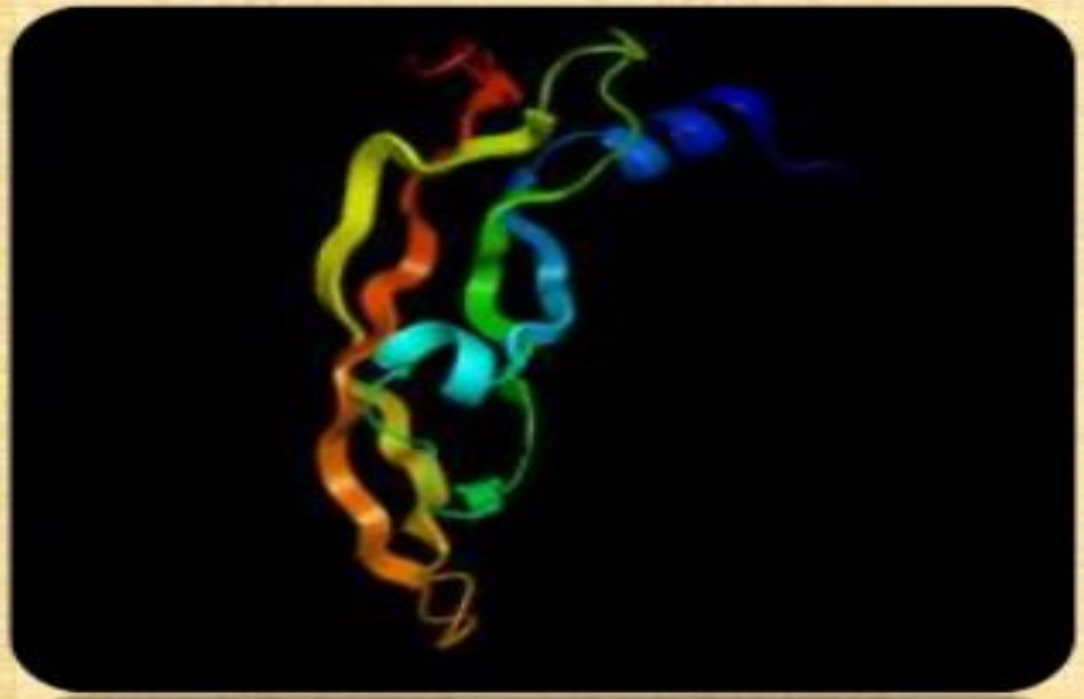
Classification of VEGF

Mammals – Five classes

- VEGF-A
- VEGF-B
- VEGF-C
- VEGF-D
- PGF

Viruses - VEGF-E

Snake venom - VEGF-F



Crystal structure of Vammin, a VEGF-F from a snake venom

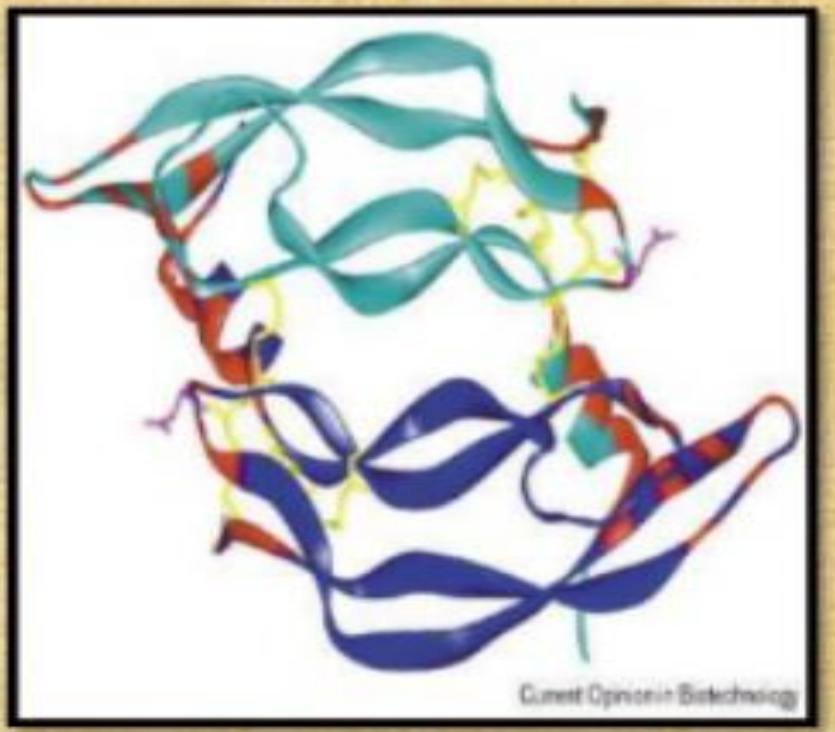
VEGF – A (Senger *et al.*, 1983)

Consist of **121, 165, 189** and **206** peptides in humans.

Main **isoforms**- 121 &165.

Found in chromosome **6** in **human** and **11** in **rats.**

Up regulate -**nitric oxide** production.



Oloffson et al., 2000

VEGF and the diabetic kidney: More than too much of a good thing

Syamantak Majumder, Andrew Advani *

Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada

Journal of Diabetes and Its Complications 31 (2017) 273–279

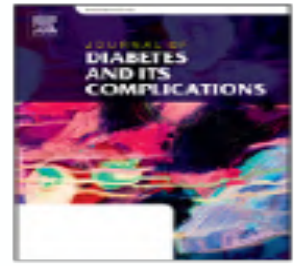
VEGF was "up" in diabetic rats and blockade of its actions attenuated albuminuria:
VEGF was "bad" in diabetic nephropathy.

Since that time, our understanding of the complex paracrine signaling cascades that are mediated by the VEGF family has expanded.
It has be come apparent that it is not simply the amount of "VEGF" that is important, but also

the type of VEGF,

the sites of VEGF action and the

context in which VEGF-mediated signaling occurs.



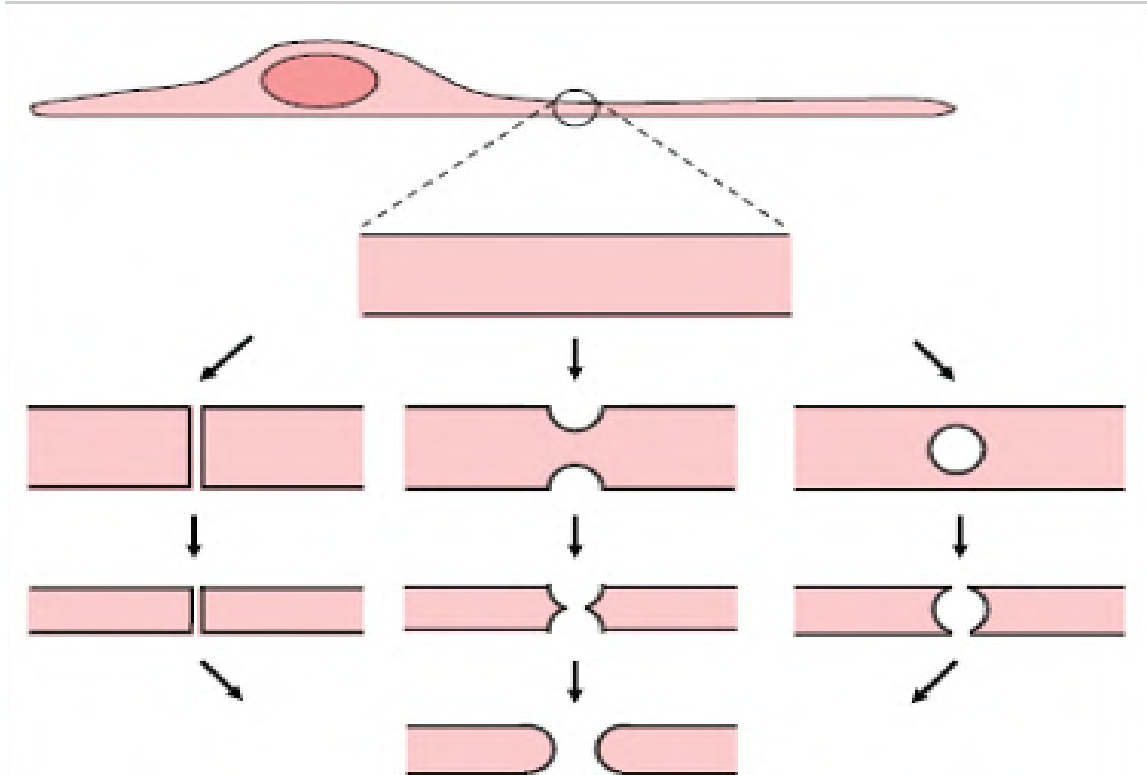
Am J Physiol Renal Physiol 296: F947–F956, 2009.
First published January 7, 2009; doi:10.1152/ajprenal.90601.2008.

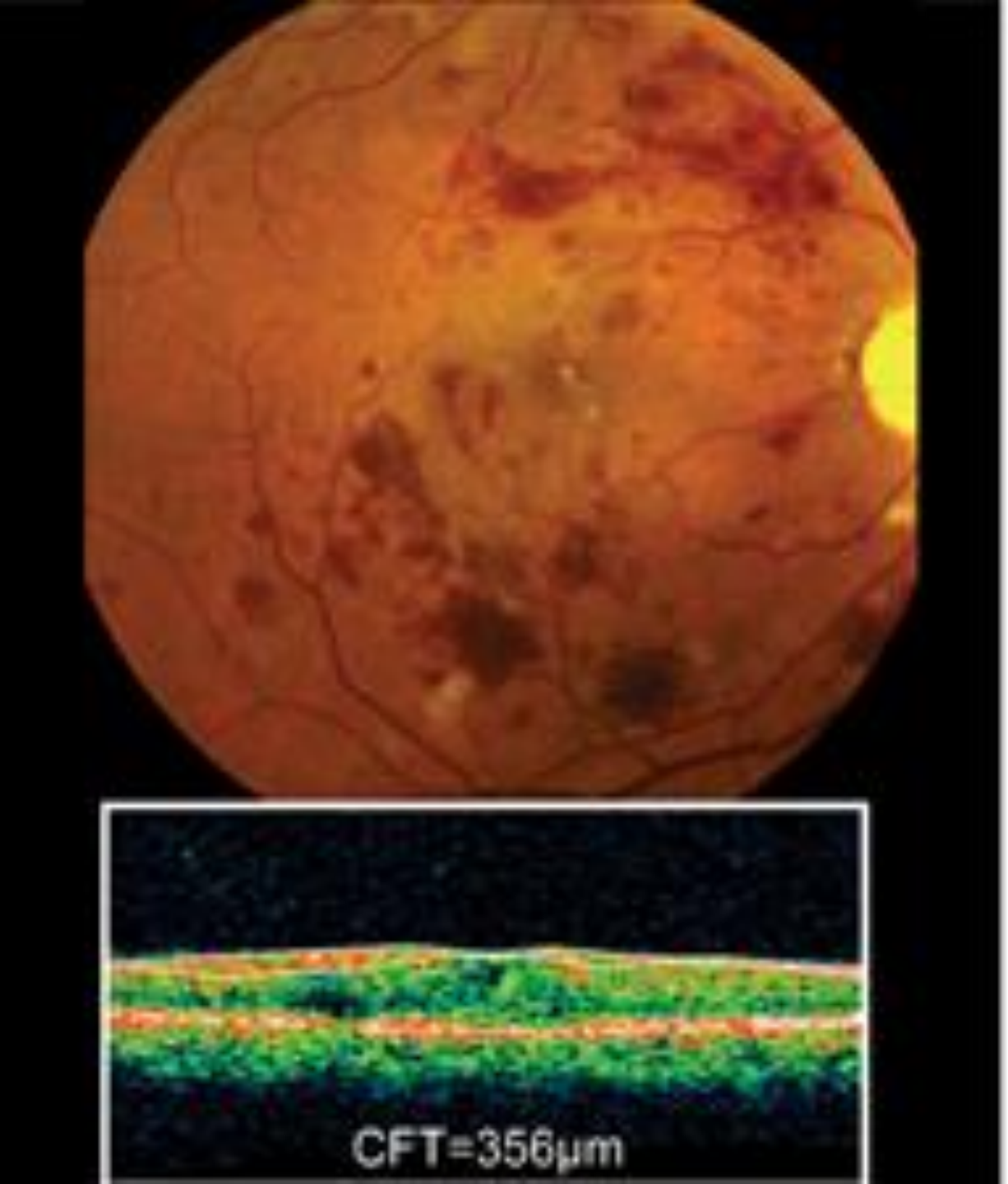
Review

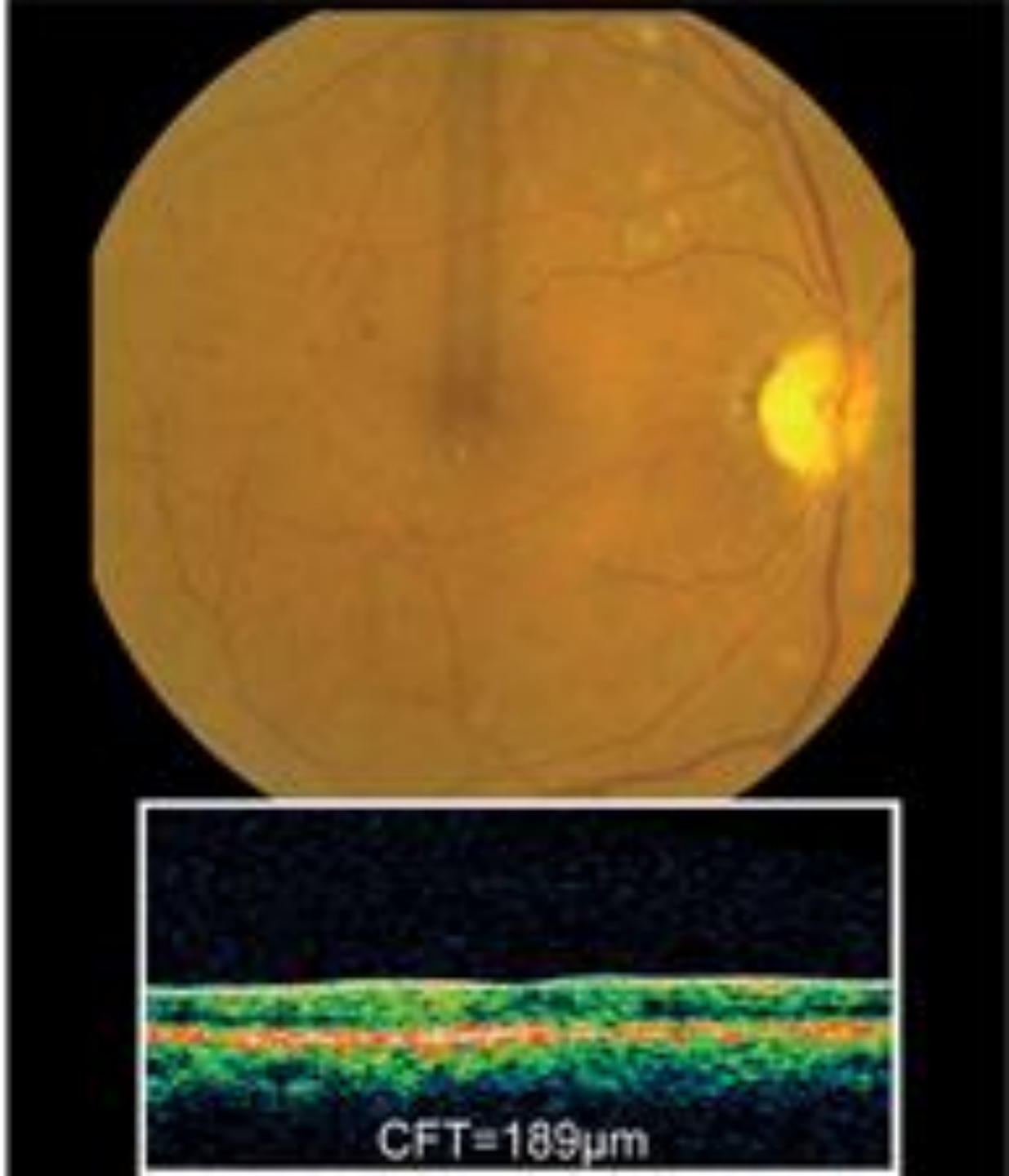
Glomerular endothelial cell fenestrations: an integral component of the glomerular filtration barrier

Simon C. Satchell[1] and Filip Braet[2]

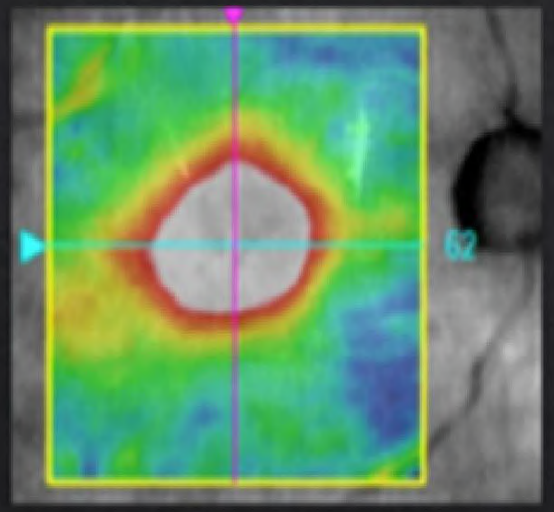
[1]Academic Renal Unit, University of Bristol, Southmead Hospital, Bristol, United Kingdom; and [2]Australian Key Centre for Microscopy and Microanalysis, The University of Sydney, New South Wales, Australia

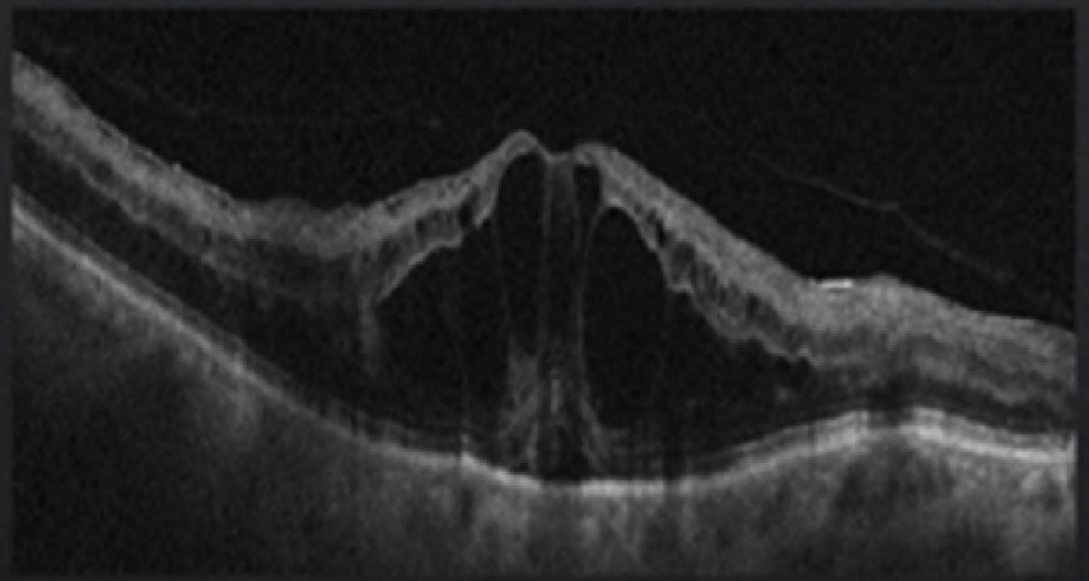


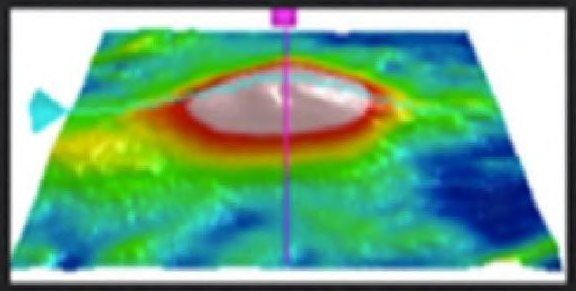

CFT=356μm


CFT=189μm

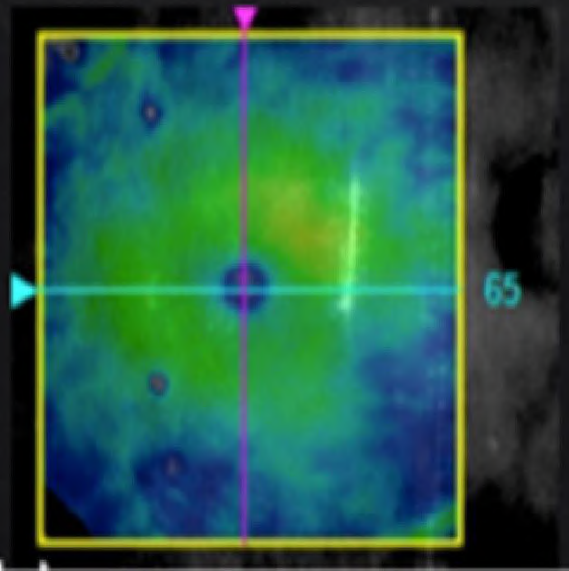
Pre ranibizumab

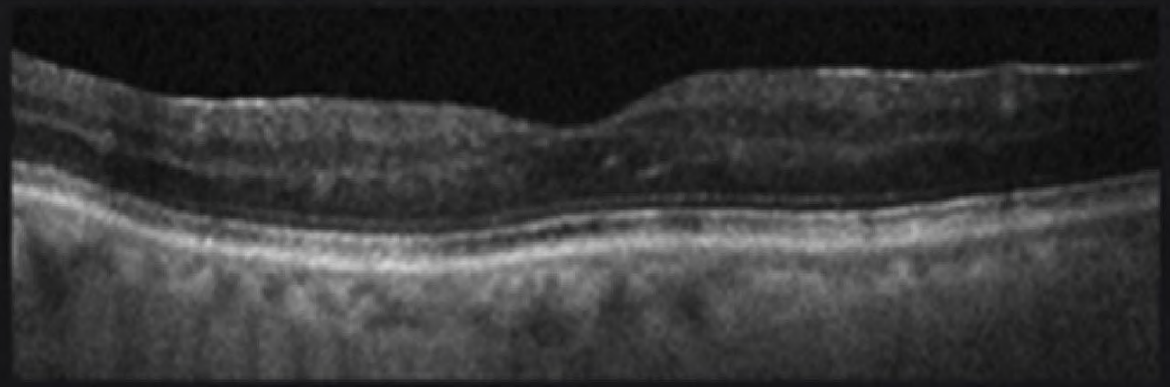


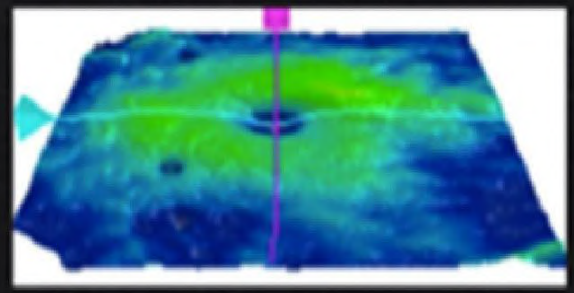




Post 2 aplicaciones ranibizumab







REVIEW ARTICLE

Molecular mechanisms of diabetic vascular complications

Munehiro Kitada, Zhaoyun Zhang, Akira Mima, George L King*

Journal of Diabetes Investigation Volume 1 Issue 3 June 2010

Vascular Endothelial Growth Factor A

VEGF includes a family of growth factors that act on endothelial cells regulated by hypoxia and promote angiogenesis, increase permeability in vasculature, and is also known as a major regulator of endothelial proliferation, migration, and survival[144].

In early stage diabetic nephropathy, many reports have shown that the expression of VEGF-A is increased in glomeruli of diabetic animals[46,149,150] and proposed that inhibition of VEGF-A might have beneficial effects against diabetic renal injuries.

pole[154,155]. At the late stage of nephropathy, the expression of VEGF-A is decreased. Baelde *et al.* showed that the glomerular

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What is the physiological role of VEGF-A in the kidney, especially glomeruli? It is reported that treatment with anti-VEGF antibodies to patients with cancers[160] or within patients with preeclampasia[161] causes proteinuria and endothelial damage, suggesting that VEGF-A plays an important role in maintaining endothelial cell function and the glomerular filtration barrier. Supporting this, detailed reports by Quaggin *et al.* clearly show that VEGF-A is necessary for forming and maintaining the glomerular filtration barrier[162,163]. In their reports, using a condi-

Molecular mechanisms of diabetic vascular complications

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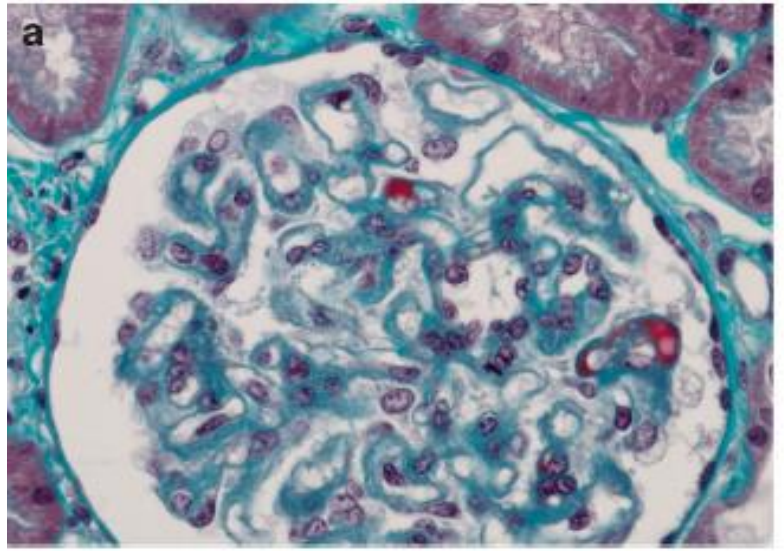
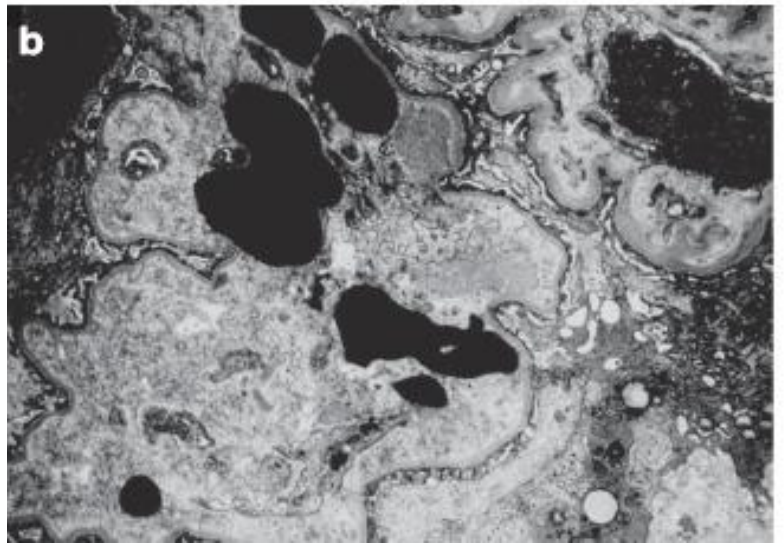
Is VEGF-A a bad or good player for the progression of diabetic nephropathy? Hohenstein *et al.* determined VEGF expression and its bioactivity in glomeruli of type 2 diabetic patients using specific antibodies for VEGF-A and VEGF-VEGFR complex[154]. Although VEGF expression of glomeruli is upregulated during all stages (mild, moderate and severe) of nephropathy, VEGF bioactivity in endothelial cells is only increased in mildly injured glomeruli and decreased in moderate or severe lesions. Furthermore, they showed that glomerular capillary rarefaction was linked to the degree of glomerulosclerosis and endothelial cell proliferation, showing capillary repair was markedly increased only in mildly/moderately injured glomeruli, even if apoptosis was detected in all stages. They suggest that diabetic nephropathy is associated with glomerular capillary rarefaction by an imbalance of endothelial cell proliferation, repair and apoptosis, and injury; and reduced VEGF activity might be an indicator of an insufficient capillary repair reaction[154]. Therefore, if increased VEGF expression occurs as a reaction of compensation for the damage of glomerular endothelial cells, inhibition of VEGF should not be given as a treatment for diabetic nephropathy. However, further studies are needed to conclude whether VEGF-A is or is not an endogenous protective factor for diabetic nephropathy.

New drug toxicities in the onco-nephrology world

Mark A. Perazella[1] and Hassan Izzedine[2,3]

Kidney International (2015) **87**, 909-917





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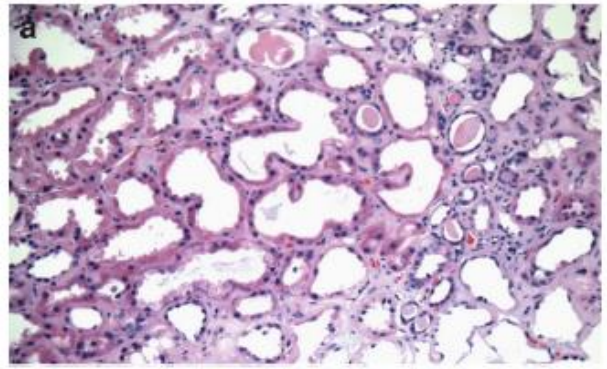

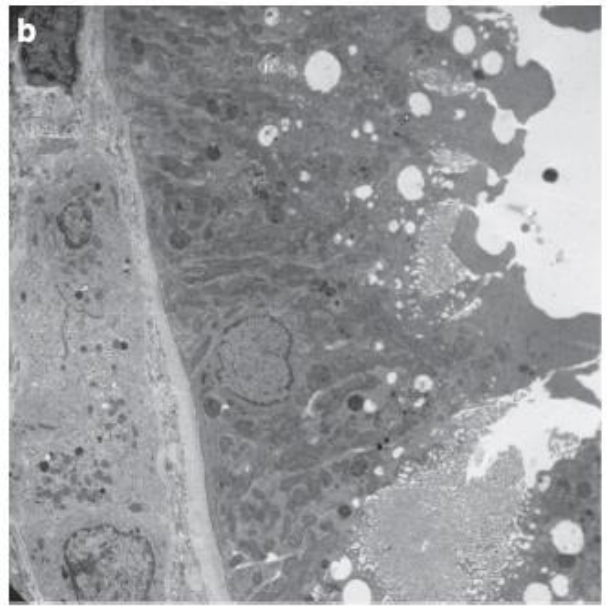

Figure 3 | (a and b) Acute tubular injury/necrosis associated with crizotinib. (**a**) Light microscopy demonstrates tubular cell injury with dilatation, apical blebbing, and loss of brush border (hematoxylin and eosin; original magnification ×400). (**b**) Electron microscopy reveals tubular cell injury with blebbing and loss of brush border (original magnification ×5000).

Table 3 | AKI cases reported in the literature associated with pemetrexed

Author	Age (yrs) /sex	Tumor site	Pemetrexed cycles before AKI	Prior/concomitant nephrotoxic drugs	Kidney injury			Outcome after drug withdrawal
					SCr (mg/dl)		Kidney biopsy	
					Before therapy	At diagnosis		
Michels *et al.*[45]	65/M	Unknown	6	Platin Gemcitabine	1.13	4.54	ATN Interstitial fibrosis	Stable CKD (SCr, 3.62 mg/dl) at 6 months' follow-up
Vootukuru *et al.*[46]	53/F	Lung	2	Carboplatin Gemcitabine Zoledronic acid Contrast media	0.79	4.09	NA	NDI and dRTA despite recovery of renal function (SCr, 1.7 mg/dl) at 1-month follow-up
Stavroulopoulos *et al.*[47]	57/M	Lung	4	Carboplatin Vandetanib	0.94	3.40	ATN Interstitial nephritis Interstitial fibrosis 25%	Renal function deteriorated requiring dialysis at 1-month follow-up despite corticosteroid
Chauvet *et al.*[48]	59/F	Lung	6	Platin Gemcitabine NSAIDs	0.95	4.51	ATN Interstitial fibrosis 60%	Stable CKD (SCr, 2.5 mg/dl) at 10 months follow-up
	60/F	Lung	4	Cysplatin	1.02	4.06	ATN Interstitial fibrosis 30%	Stable CKD at 15 months follow-up
Castro *et al.*[49]	60/M	Pleural	6	Cisplatin	NA	3.07	NA	One hemodialysis session at admission
Glezerman *et al.*[50]	67/M	Lung	54	Carboplatin Quinapril	0.9	2.1	Diffuse ATN Interstitial fibrosis with patchy inflammatory infiltrate	Stable CKD at 10 months follow-up
	77/M	Lung	21	Carboplatin Bevacizumab Losartan	1.1	1.5	Sub ATN mild with interstitial inflammation	Stable CKD at 9 months follow-up
	57/F	Lung	13	Bevacizumab Lisinopril	0.8	1.5	Sub ATN with mild chronic interstitial inflammation	Stable CKD at 4 months follow-up
Personally communicated, unpublished case 1	72/F	Lung	4	Cisplatin	0.71	2.64	ATN Interstitial fibrosis 30%	Stable CKD (SCr, 2.71 mg/dl) at 1-month follow-up
Personally communicated, unpublished case 2	64/M	Lung	6	Oxaliplatin Bevacizumab	0.76	1.60	ATN Interstitial fibrosis 30%	NDI. Stable CKD (SCr, 1.60 mg/dl) at 1-month follow-up

Abbreviations: AKI, acute kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; dRTA, distal renal tubular acidosis; NA, not available; NDI, nephrogenic diabetes insipidus; NSAIDs, non steroidal antiinflammatory drugs; SCr, serum creatinine.

Table 4 | Anticancer drugs and potential nephrotoxicity

Medication	Mechanism of Action	Nephrotoxicity
Anti-angiogenesis drugs	Anti-VEGF Ab, sVEGFR, tyrosine kinase inhibitors	HTN, proteinuria, AKI (TMA, AIN, FSGS)
Androgen deprivation therapy	Testosterone reduction	AKI (no renal histology)
Crizotinib	ALK, MET, and ROS1 tyrosine kinase inhibitor	AKI (ATI/ATN, AIN?)
Clofarabine	Purine nucleoside analog (inhibits DNA synthesis and ribonucleotide reductase; inhibits activation of the mitochondrial repair process)	AKI (ATI/ATN, TMA?)
Pemetrexed	Folate analog that inhibits purine and thymidine nucleotide and protein synthesis	AKI (ATI/ATN) Electrolyte abnormalities
LY2181308	mRNA-targeted anti-sense oligonucleotide (downregulates survivin messenger RNA/protein expression)	AKI (ATI/ATN)
Carfilzomib	Epoxy-ketone proteasome inhibitor	AKI (no renal histology)
Ipilimumab	Monoclonal CTLA-4-blocking antibody	AKI (AIN, GN?)

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; CTLA-4, cytotoxic T-lymphocyte antigen-4; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HTN, hypertension; mRNA, messenger RNA; sVEGFR, soluble vascular endothelial growth factor receptor; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.

Table 1

Description of main cohort studies investigating cancer incidence in patients with CKD before and after dialysis or transplantation for end-stage CKD

	Author, year [Ref] Country	Population	Sample size	Follow- up (yrs)	n observed cancers	Age* (yrs)	Sex ratio
Non end-stage CKD	Wong, 2009 [17] Australia	Population-based cohort of predominantly white Australians	3,049	10.1	711	49–97	0.74
	Jorgensen, 2008 [16] Norway	Population-based cohort of Tromso inhabitants	5,425	10.3	590	24–74	1.13
	Vajdic, 2006 [13] Australia	ANZDATA registry Patients with ESRD studied up to 5 yrs before starting RRT	25,685	4.6	689[a]	50	1.32
Dialysis	Maisonneuve, 1999 [9] Australia, New Zealand	ANZDATA registry	13,497	2.6	500	49	1.26
	Europe	ERA-EDTA registry	296,903	2.9	6,849	52	1.40
	USA	USRDS	521,404	2.2	17,695	58	1.15
	Vajdic, 2006 [13] Australia	ANZDATA registry	24,926	2.7	870[a]	54	1.31
Kidney Transplant	Adami, 2003 [11] Sweden	Transplant patients from in-patient registry	5,004	7.4	639	46	1.53
	Kasiske, 2004 [12]	Record linkage of USRDS with Medicare	35,765	3.0	14.9%[b]	46%	1.50

Open in a separate window

CKD : chronic kidney disease; ANZDATA : Australian and New Zealand Dialysis and Transplant Registry; ERA-EDTA : European Renal Association and European Dialysis and Transplant Association Registry; USRDS : US Renal Data System; CORR : Canadian Organ Replacement register

*Mean or median age or % of patients aged > 50 yrs or min-max in years

[a]excluding nonmelanoma skin cancer

[b]cumulative incidence at 3 yrs after transplantation (number of cancers not available)

Table 2

Relative risk of cancer in patients with non end-stage CKD and in those on dialysis or with a kidney transplant for end-stage CKD

	Non end-stage CKD			Dialysis			Kidney Transplant		
Cancer site	**[Ref]**	**n**	**RR or HR (95%CI)[a],[b] or SIR (95%CI)[c]**	**[Ref]**	**n**	**SIR (95%CI)**	**[Ref]**	**n**	**SIR (95%CI) or RR (95%CI)[d]**
All cancer	[17]	M : 245	1.3 (1.1,1.5)[a]	[9] ANZ	500	1.8 (1.7,2.0)	[11]	639	3.9 (3.6,4.2)
		W : 237	1.0 (0.9,1.2)[a]	[9] Euro	6,849	1.1 (1.0,1.1)	[12][d]	-	-
	[16]	590	1.2 (p<0.001)[b]	[9] USA	17,695	1.2 (1.2,1.2)	[14]	778	2.5 (2.3,2.7)[e]
	[13]	689	1.2 (1.1,1.3)[c]	[13]	870	1.4 (1.3,1.5)	[13]	1,236	3.3 (3.1,3.5)[e]
Genitourinary									
Kidney	[16]	17	1.4 (1.0,2.1)[b]	[9] ANZ	70	9.8 (7.7,12.3)	[11]	28	5.2 (3.4,7.5)
	[13]	193	13.2 (11.4,15.1)[c]	[9] Euro	680	3.3 (3.1,3.6)	[12][d]	-	14.6
				[9] USA	1,303	3.7 (3.5,3.9)	[14]	71	7.3 (5.7,9.2)

Open in a separate window

N : number of observed cancers; SIR : standardized incidence ratio; RR : relative risk or rate ratio; HR : hazard ratio; 95% CI : 95% confidence interval; NS : non significant; NA : not available because of insufficient number of cancer cases; M : men; W : women

eGFR : estimated GFR with the abbreviated MDRD equation in ml/min/1.73 m^2;

[a]Per 10 ml/min/1.73 m^2 decrease in eGFR;
[a†]HR for an eGFR < 40 as compared to > 40 ml/min/1.73 m^2, adjusted for age, smoking, sun-related skin damage and blood pressure
[b]HR of cancer per 1-SD increase of log ACR,
[c]SIR of cancer up to 5 yrs before RRT as compared to the general population
[d]Age-adjusted rate ratio (n cases and CI not available) for cancer in women (except for prostate) 3 years after kidney transplantation
[e]Excluding nonmelanoma skin cancer

Chronic kidney disease and cancer: a troubling connection

Bénédicte Stengel[1,*]

J Nephrol. 2010; 23(3): 253–262.

(Aus der Universitäts-Augenklinik zu Heidelberg.)

Über eine sehr seltene Erkrankung der Netzhaut.

Klinische Beobachtungen.

Von

Prof. Eugen v. Hippel
in Heidelberg.

Mit Tafel III—VI, Fig. 1—5.

Im Jahre 1895 stellte ich in der Demonstrationssitzung des Heidelberger Kongresses einen Patienten mit einer sehr ungewöhnlichen Erkrankung der Netzhaut vor, in der Hoffnung eine Belehrung darüber zu erhalten, wie der Fall zu deuten sei. Von den zahlreichen Untersuchern schien niemand einen analogen gesehen zu haben, eine Ansicht über das Wesen der Sache wurde nur von v. Michel geäussert, der sich zuerst für die Annahme eines Tumors, dann für Tuberkulose aussprach. Der Fall wurde von mir verfolgt, bis das Auftreten von Katarakt eine weitere ophthalmoskopische Beobachtung unmöglich machte. Am 15. VIII. 1896 sah ich einen zweiten vollkommen analogen Fall; ich konnte damals nur ein paar kurze Notizen machen, da der Patient, den ich zum Zeichnen des Befundes bestellt hatte, ausblieb und erst fünf Jahre später wieder erschien.

Die beiden Beobachtungen betreffen ein offenbar sehr seltenes Krankheitsbild, ich fand zunächst in der Literatur nur einen analogen Fall. Als ich beim vorjährigen Heidelberger Kongress meine Abbildungen zeigte und kurz erläuterte, wurde ich noch auf drei Veröffentlichungen [1]) aufmerksam gemacht, in welchen ähnliche Beobachtungen mitgeteilt wurden, ausserdem führten Sattler, Wagenmann und Herzog je einen derartigen Fall an, den sie zu untersuchen und behandeln Gelegenheit hatten.

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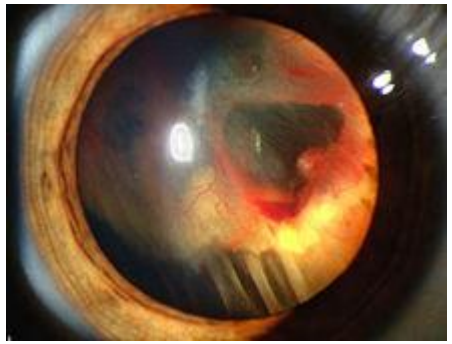
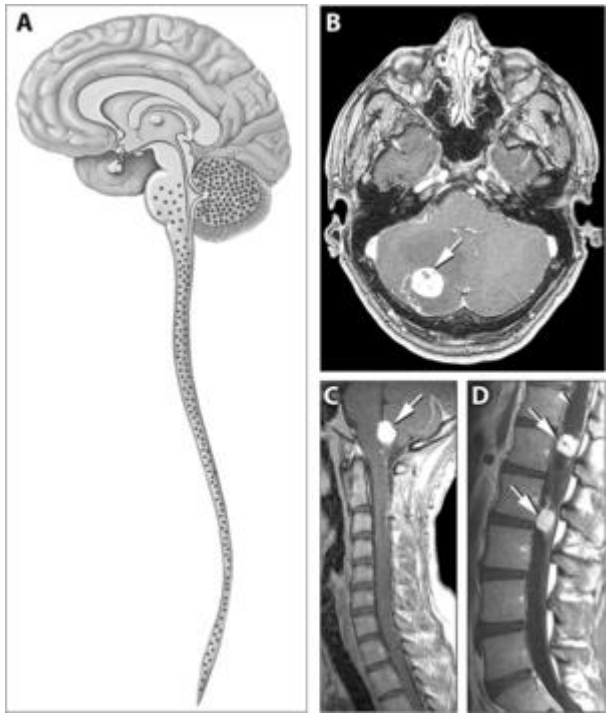
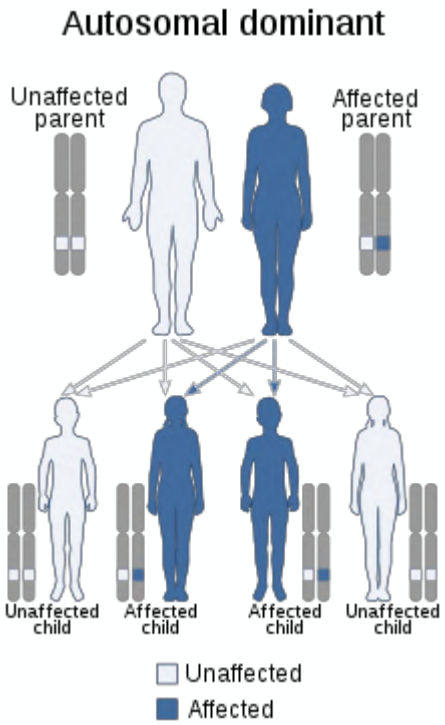
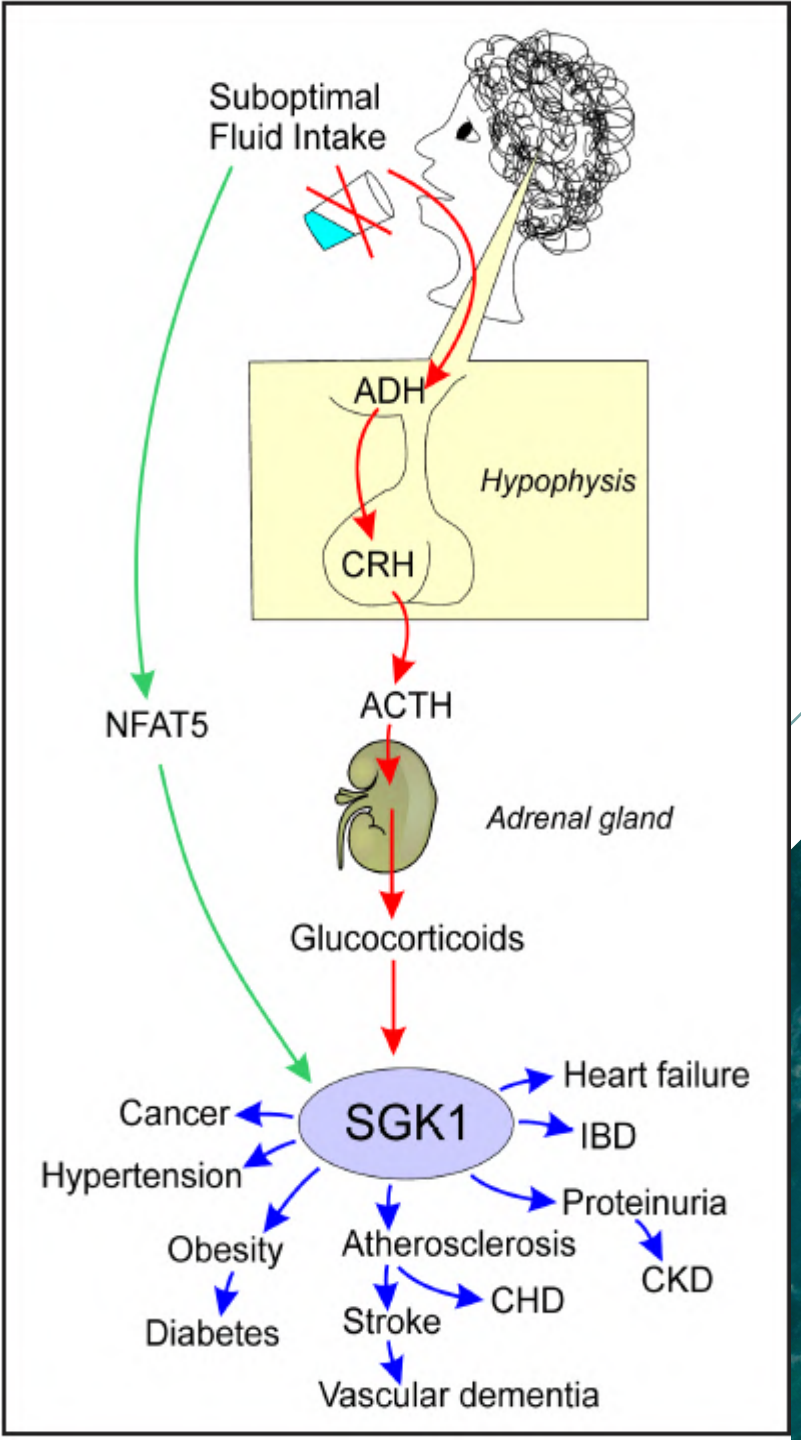
[1]) Fall Leplat, v. Dzialowski und Goldzieher. (Vgl. die spätern epikritischen Bemerkungen.)




A
B
C
D


Autosomal dominant
Unaffected parent
Affected parent
Unaffected child
Affected child
Affected child
Unaffected child
Unaffected
Affected



Kidney and
Blood Pressure
Research

RESEARCH

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Two Liters a Day Keep the Doctor Away? Considerations on the Pathophysiology of Suboptimal Fluid Intake in the Common Population

Florian Lang[a] Isabelle Guelinckx[b] Guillaume Lemetais[b] Olle Melander[c]

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Kidney Blood Press Res 2017;42:483-494

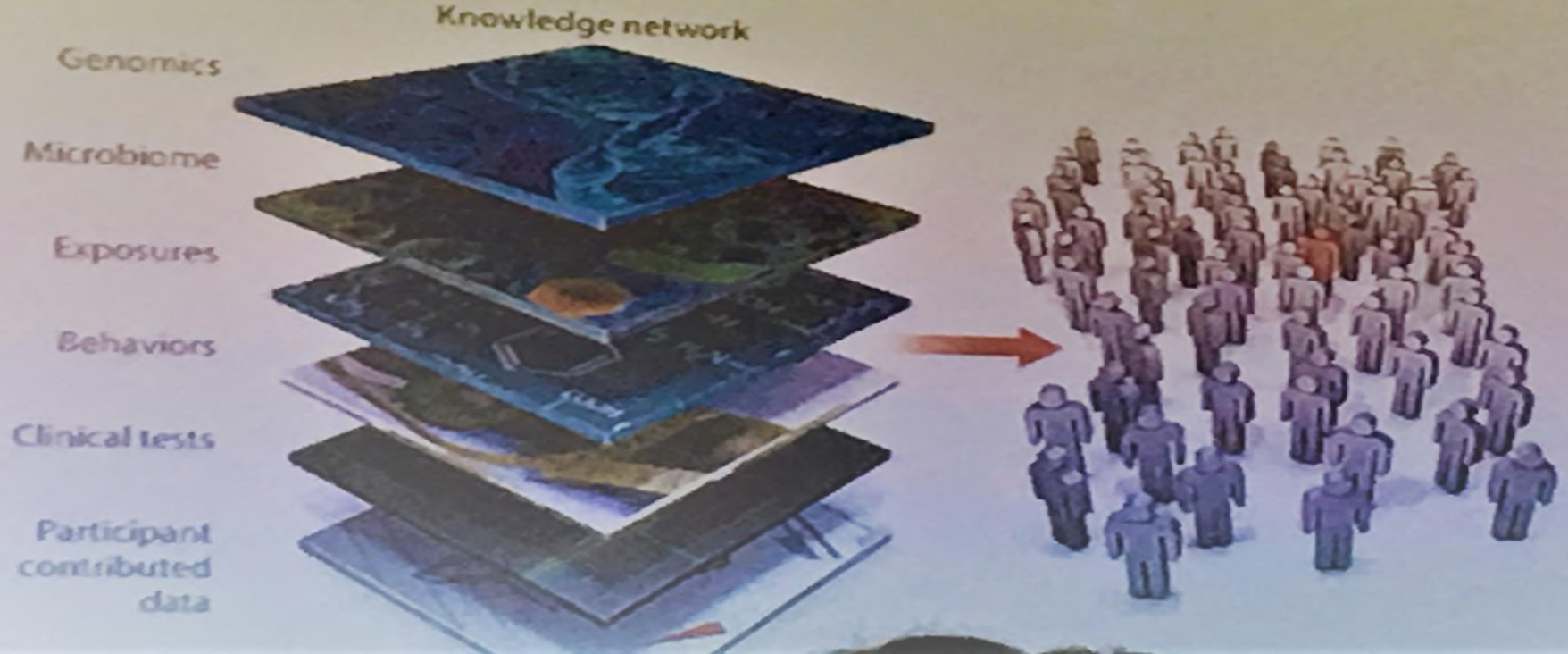
Table 1. Comparison of clinical conditions correlated with enhanced copeptin levels and the respective disorders shown or expected following SGK1 excess. Among the clinical conditions associated with high copeptin levels only cognitive impairment [27, 29] may be related to mechanisms other than increased SGK1 expression. The other clinical disordes are presumably at least in part due to enhanced SGK1 expression and activity. This does, however, not rule out the involvement of further mechanisms and additional experimental effort is needed to define the pathophysiological role of SGK1 in individuals with suboptimal fluid intake.

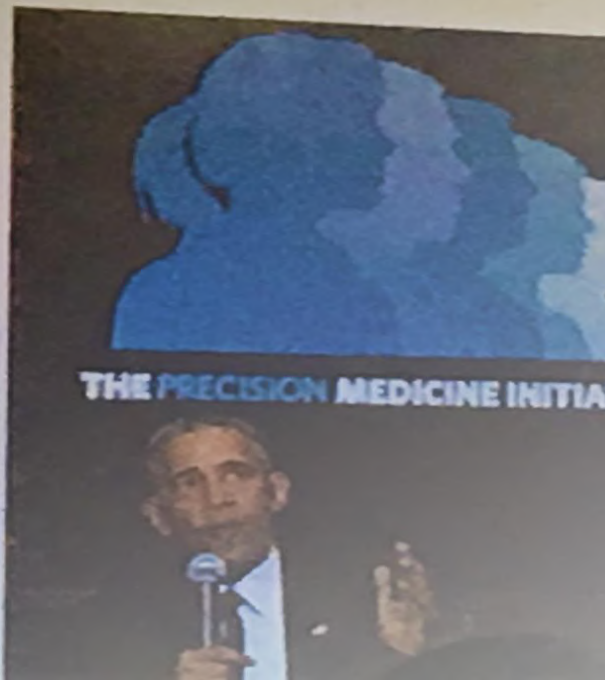
Enhanced Copeptin levels are associated with	References	Enhanced SGK1 activity may contribute to	References
Hypertension	[23, 24]	Hypertension	[37, 43, 50, 56, 58-63]
Obesity	[23-26]	Obesity	[37, 43]
Type 2 diabetes	[18-20]	Type 2 diabetes	[37]
Coronary artery disease vascular dementia	[24, 27]	Atherosclerosis, stroke	[59, 68, 71, 107-109]
Heart failure	[28]	Cardiac remodeling/fibrosis	[7, 103-106, 110]
Microalbuminuria	[25]	Proteinuria	[101, 111]
Chronic kidney disease	[17, 30]	Renal fibrosis	[101]
Inflammatory bowel disease	[31]	Inflammatory bowel disease	[87, 88]
Cancer	[32]	Cancer	[7, 37, 39, 40, 43, 72-80]

The Promise of Precision Medicine

Conventional medical practice is primarily based on "standards of care" as determined by averaging responses across large cohorts.

Personalized (or Precision) Medicine is an emerging healthcare model that takes into account individual variability in genes, environment, and **lifestyle** to guide clinical care to improve prevention, diagnosis, and treatment of disease.






Thank You