Progression and Reversal of Renal Fibrosis: Novel Diagnostic Markers and Possible Targets for Therapy in CKD

Christos Chatziantoniou

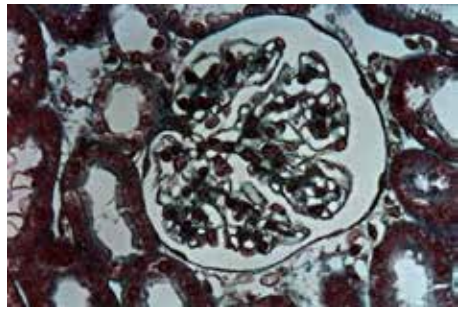
Inserm UMR S 1155, Tenon Hospital, Paris

Tenon Hospital

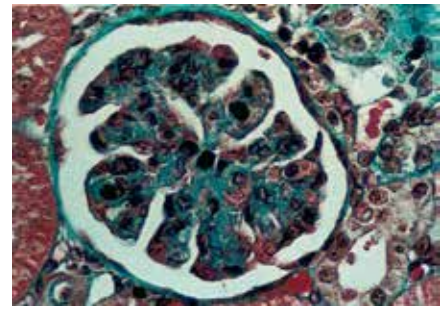
Research Building

CHRONIC KIDNEY DISEASE: IS IT REVERSIBLE?

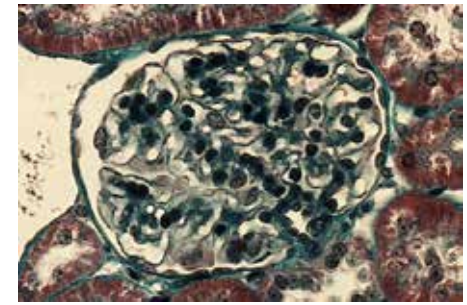
Boffa et al JASN 2003 (Editorial)



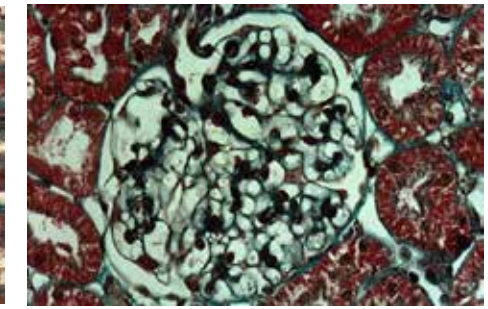
Control



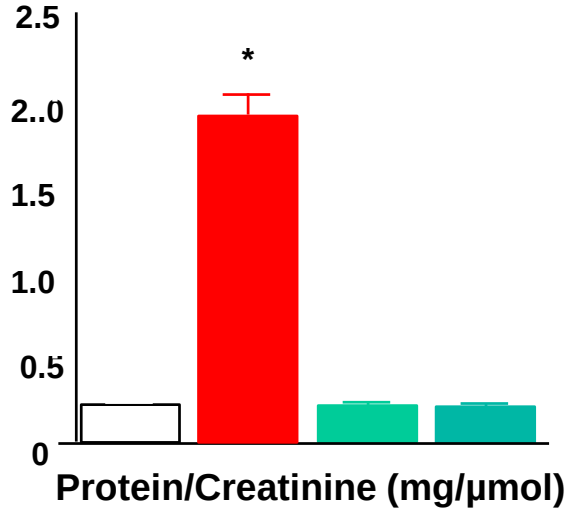
L-NAME 4w

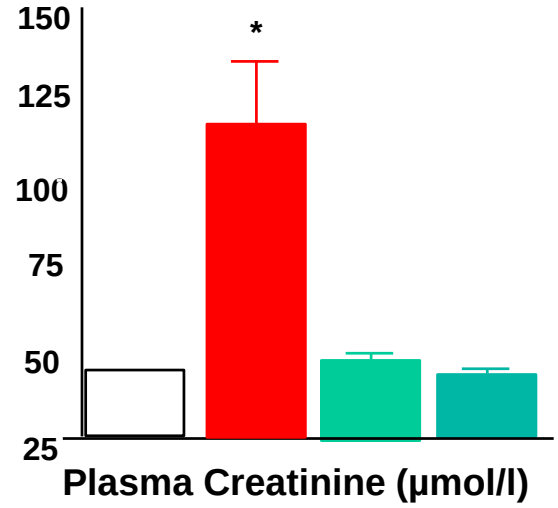


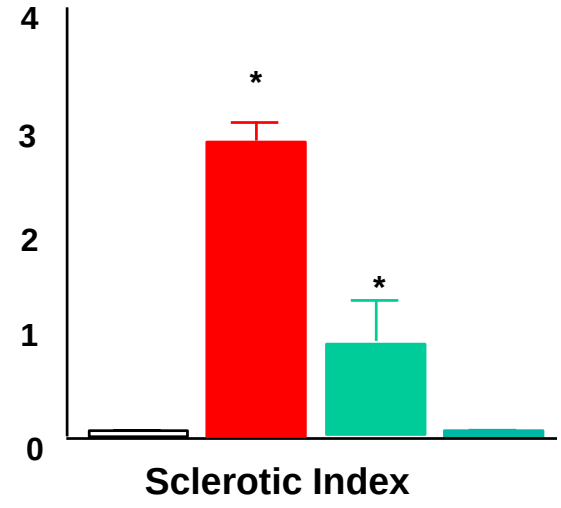
L-NAME 4w +
L-NAME + Los 1w



L-NAME 4w +
L-NAME + Los 4w



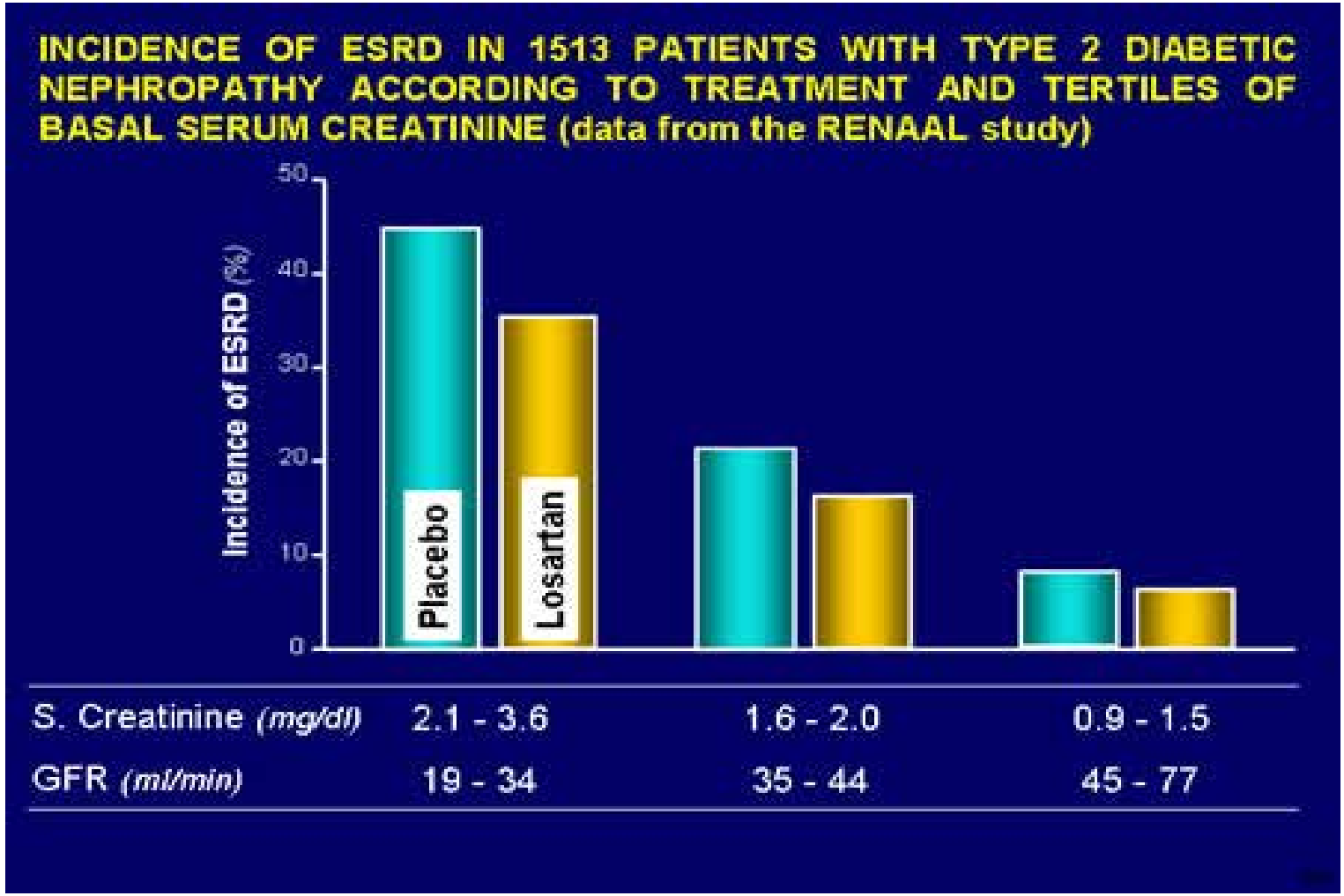




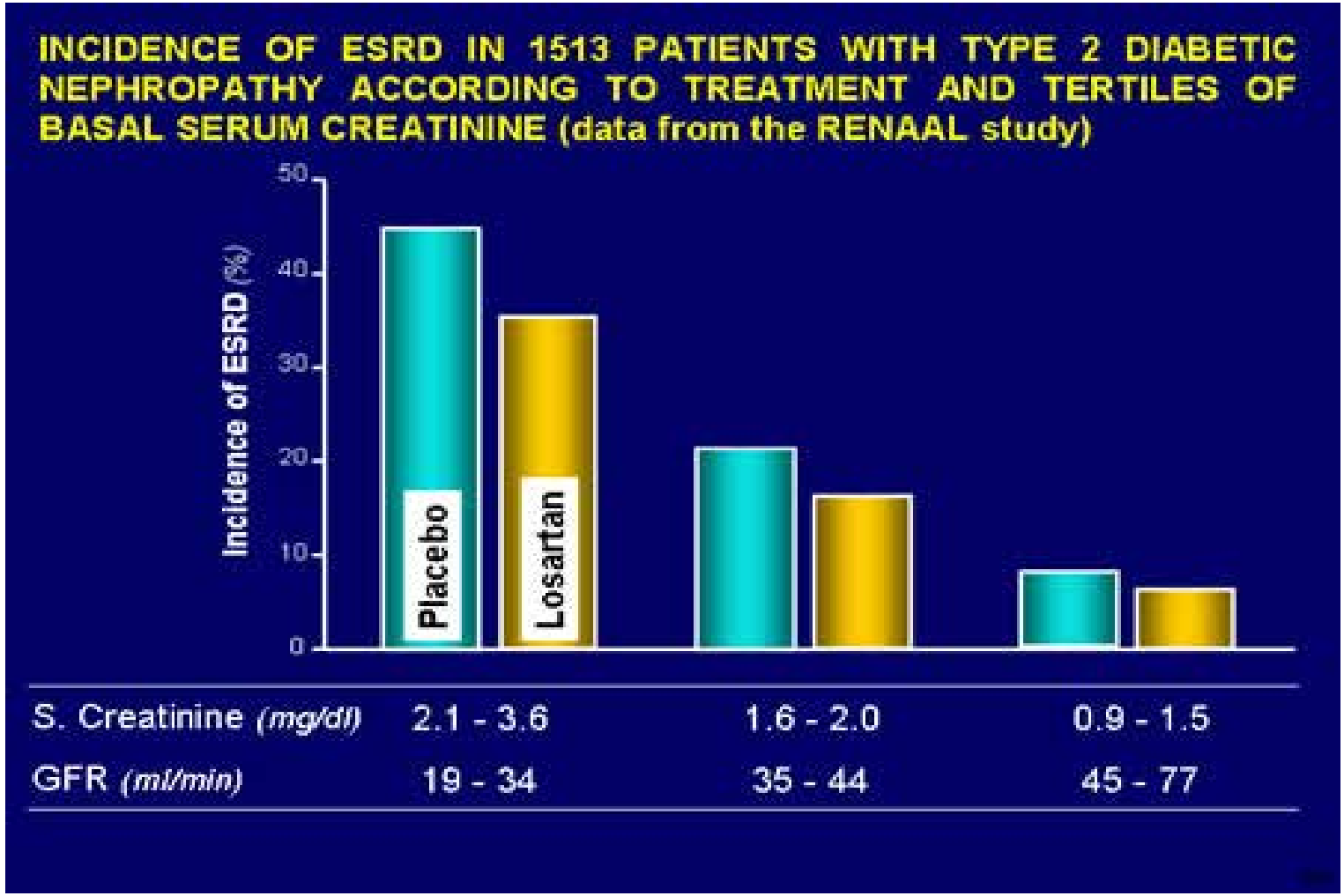
How to Efficiently Treat Experimental CKD: the Ang II Antagonism Option

• Aging	AT1 antagonism	Rat	Kidney Int 58:2425, 2000
• NO inhibition	ET-1 antagonism	Mouse	Hypertension 37:490, 2001
• MWF	ACE in + AT1 ant	Rat	Kidney Int 62:885, 2002
• NO inhibition	AT1 antagonism	Rat	JASN 14:1132, 2003
• UUO	ACE inhibition	Rat	J Nephrol 16:203, 2003
• 5/6 nephrectomy	ACE inhibition	Rat	JASN 14:2833, 2003
• anti-GBM	BMP-7 delivery	Mouse	Nat Med 9:964, 2003
• 5/6 nephrectomy	ACE inhibition	Rat	JASN 15:3063, 2004
• diabetes	ACE inhibition	Rat	Diabetes 53:1119, 2004
• 5/6 nephrectomy	Aldosterone inhib	Rat	JASN 16:3306, 2005
• UUO	R-UUO	Mouse	JASN 16:3623, 2005
• NO inhibition	NO re-activation	Mouse	NDT 21:881, 2006
• Dahl	Kallikrein delivery	Rat	Hum Gene Ther 17:1, 2006
• RenTg	AT1 antagonism	Mouse	PLoS One 4:e6721, 2009

REVERSAL OF RENAL FAILURE BY ANG II ANTAGONISM: IS IT EFFICIENT IN HUMANS? (Remuzzi)



REVERSAL OF RENAL FAILURE BY ANG II ANTAGONISM: IS IT EFFICIENT IN HUMANS? (Remuzzi)



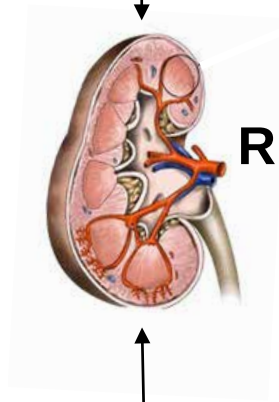
We need early biomarkers and/or additional targets for therapy

The Challenge for a Therapy of CKD: Targeting the Cause?

Paracrine Factors
Angiotensin II
Endothelin
Growth Factors

Metabolic Factors
Proteinuria
Hyperglycemia
Dyslipidemia
Oxidative Stress
Hypoxia

Inflammatory Factors
Cytokines
Chemokines
Toll-like receptors



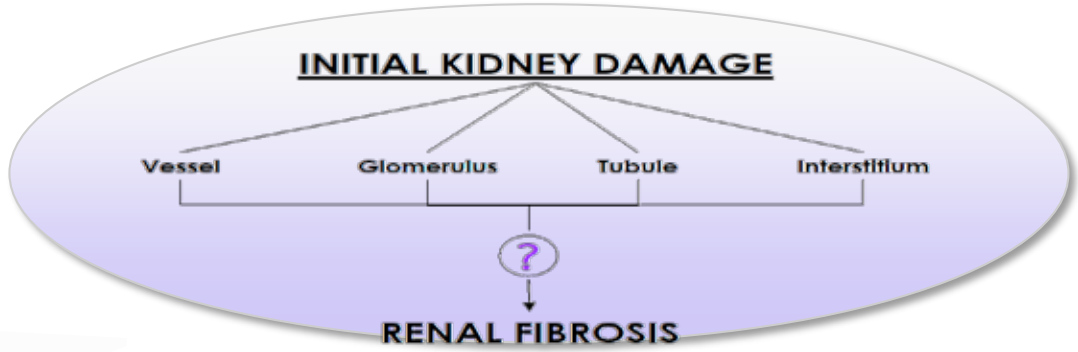
RENAL DISEASE

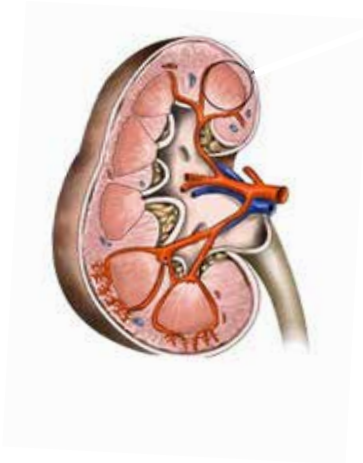
Genetic Factors
ACE
ROP/Os strain

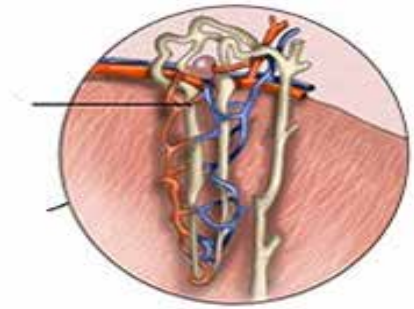
Hemodynamic Factors
Arterial Hypertension
Glomerular Hypertension
Shear stress, stretch stress

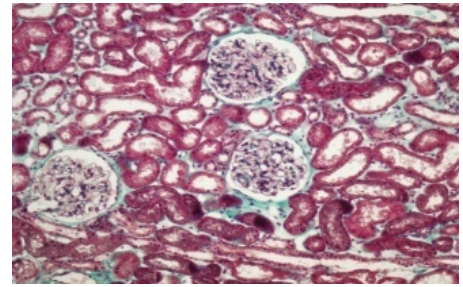
Cellular Factors
Epithelial-mesenchymal transition
Myofibroblasts

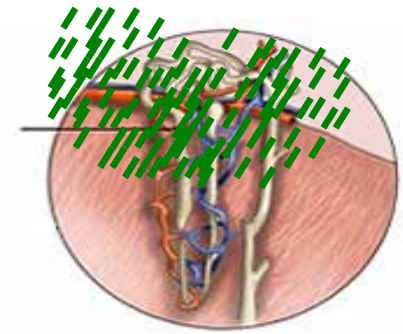
The Challenge for a Therapy of CKD: Targeting the Culprit Cell?

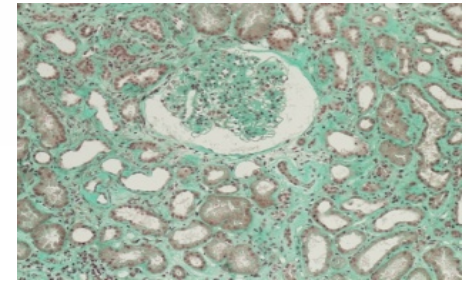




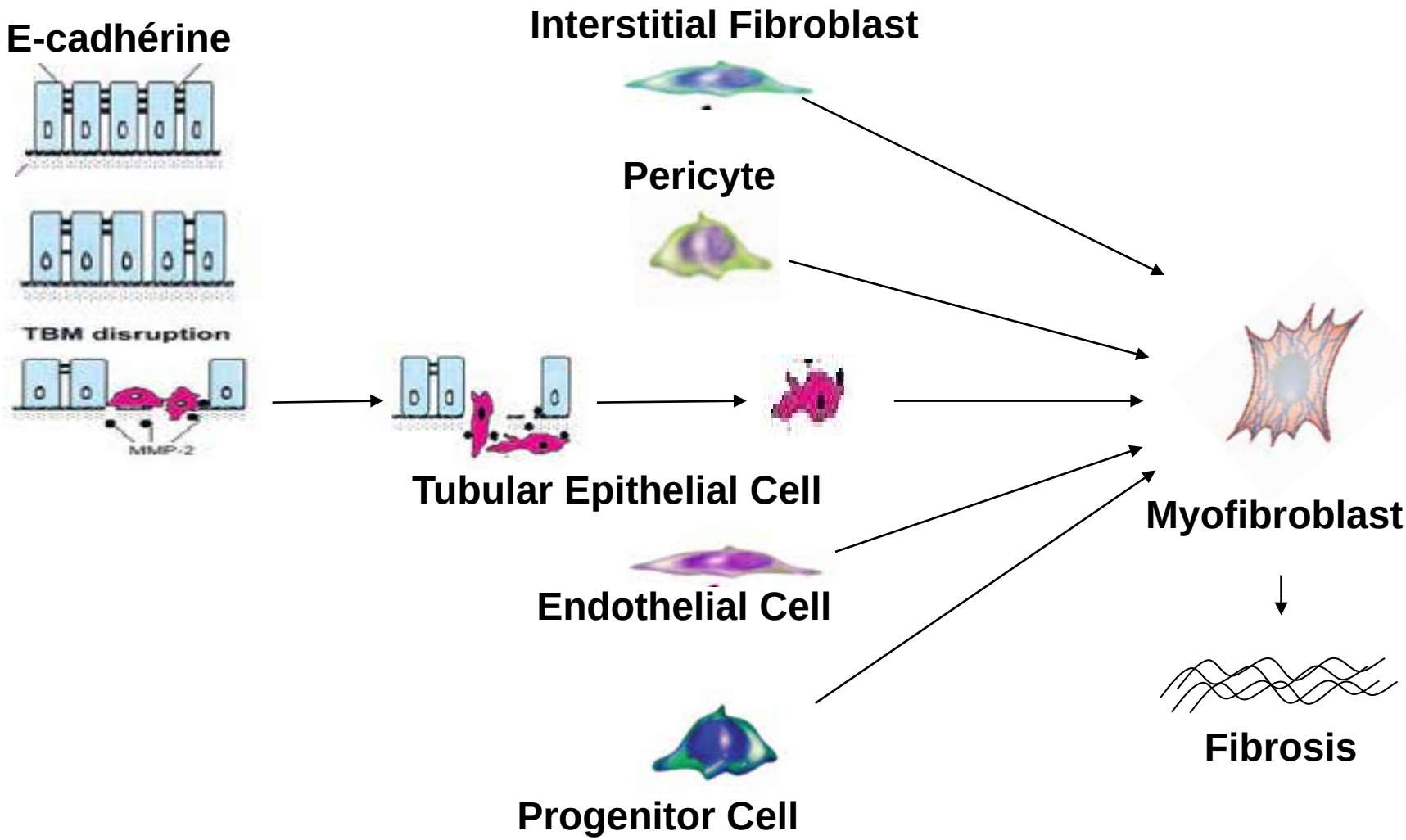




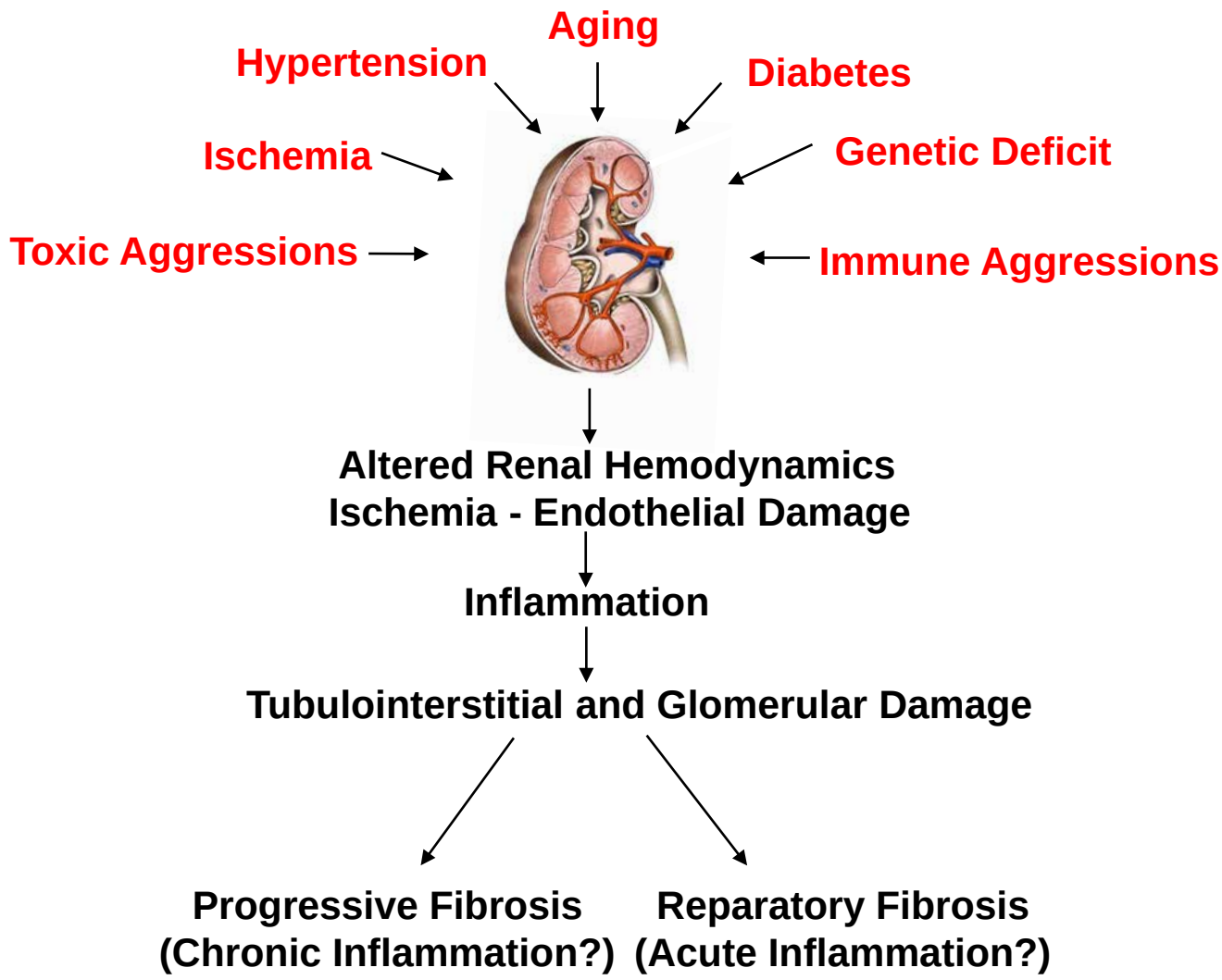




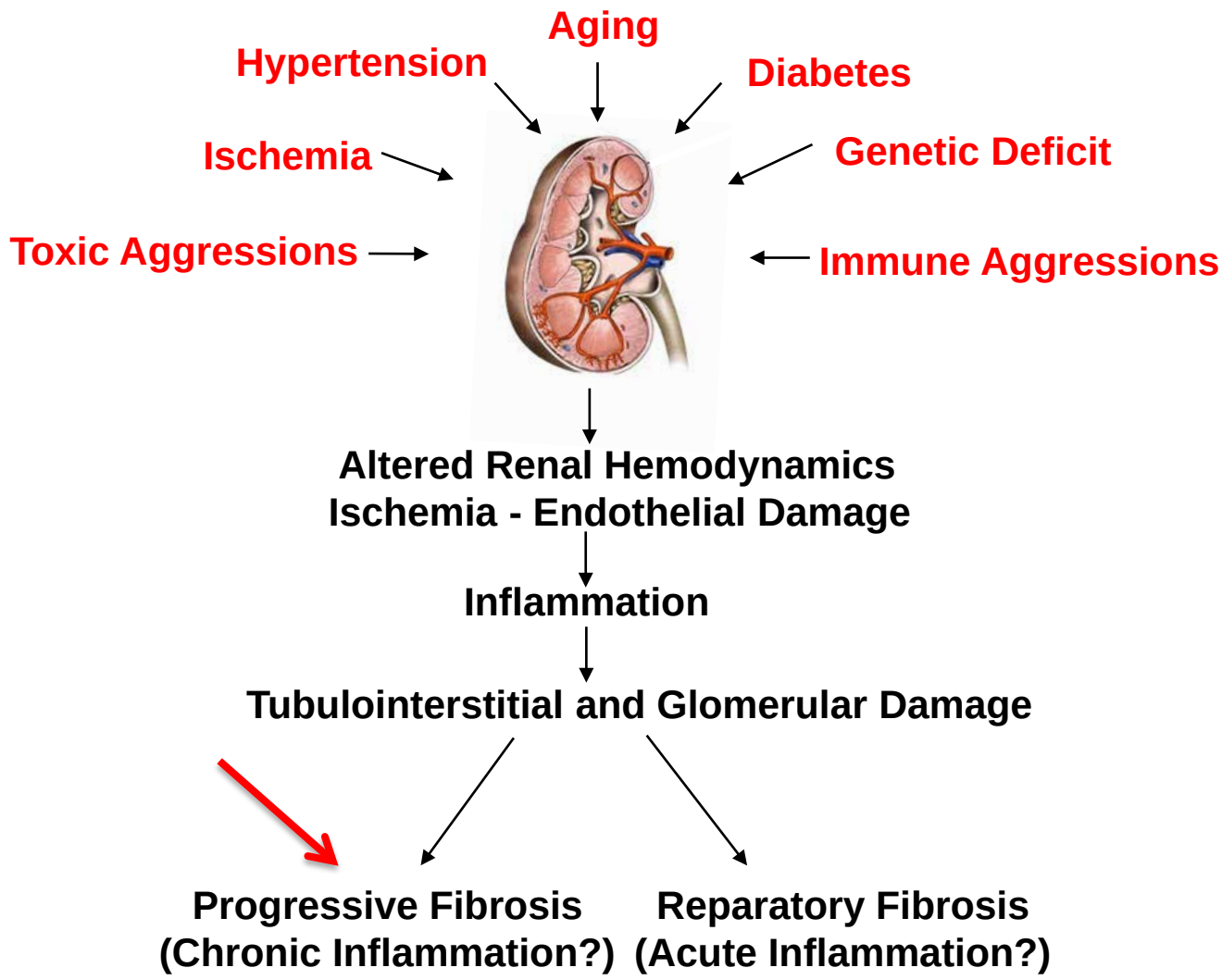
Plasticity of Renal Cells: is any Particular Cell Type Responsible of Renal Fibrosis?



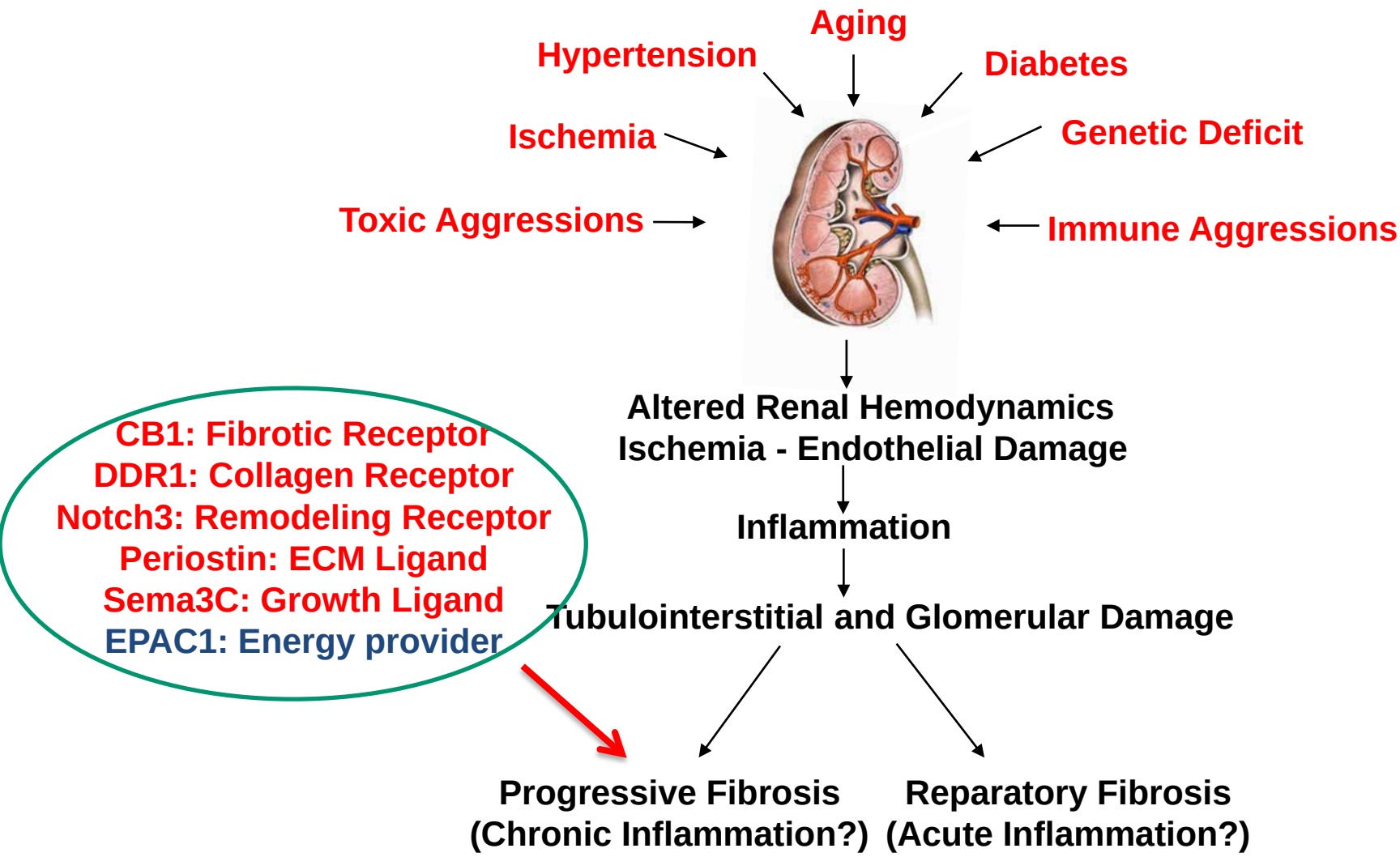
The Challenge for a Therapy of CKD: Finding novel Mediators - What Strategy?



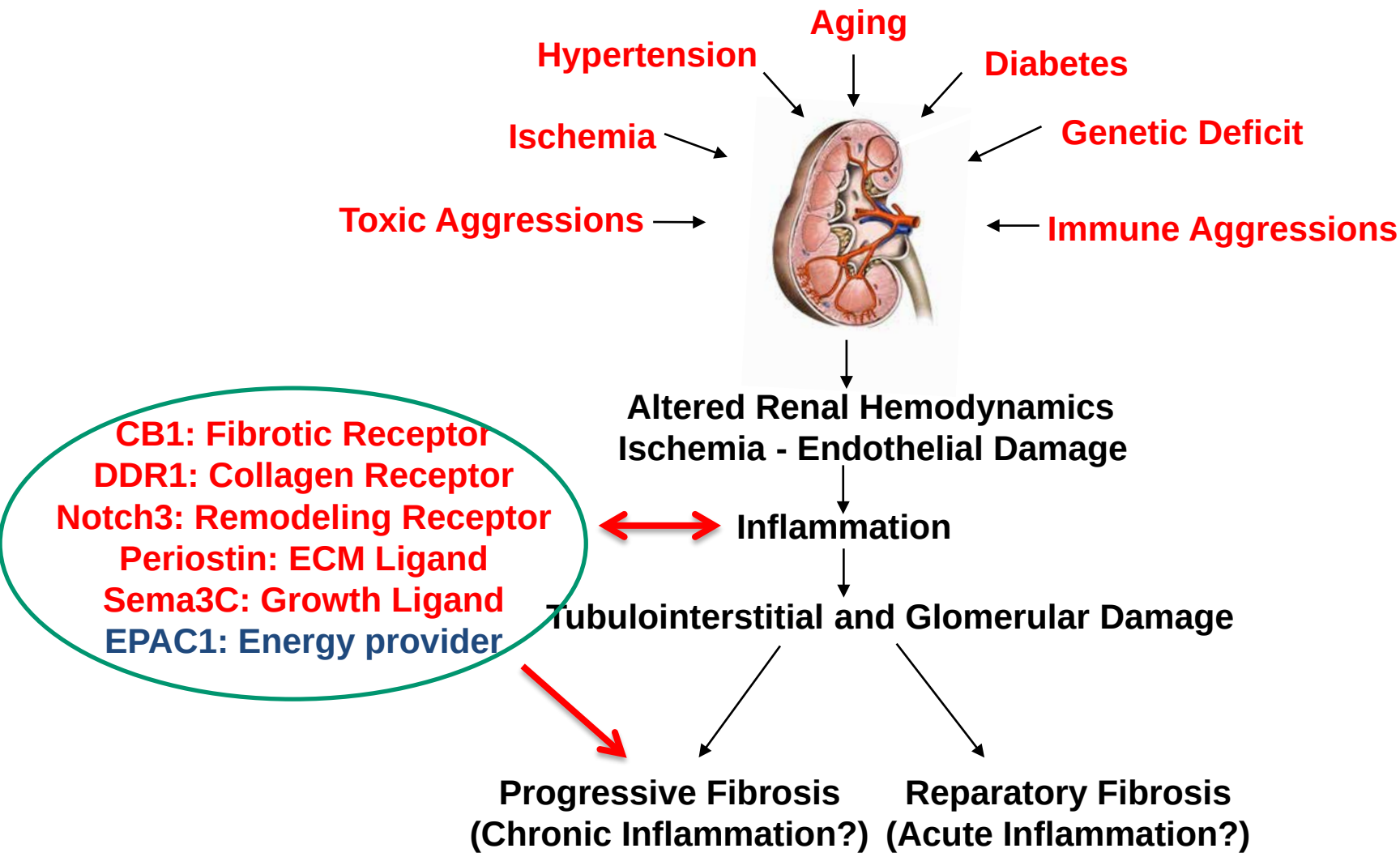
The Challenge for a Therapy of CKD: Finding novel Mediators - What Strategy?



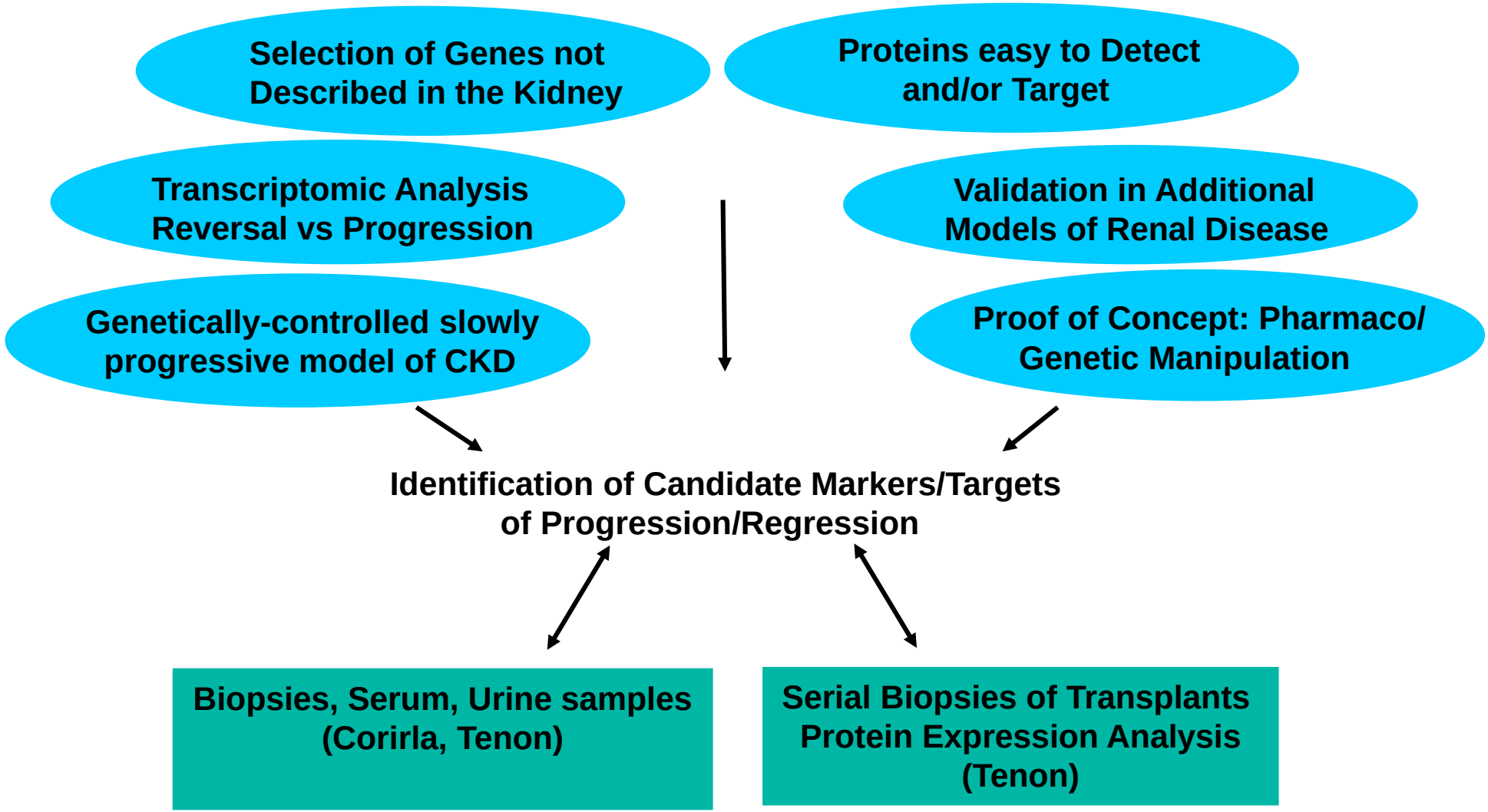
The Challenge for a Therapy of CKD: Finding novel Mediators - What Strategy?



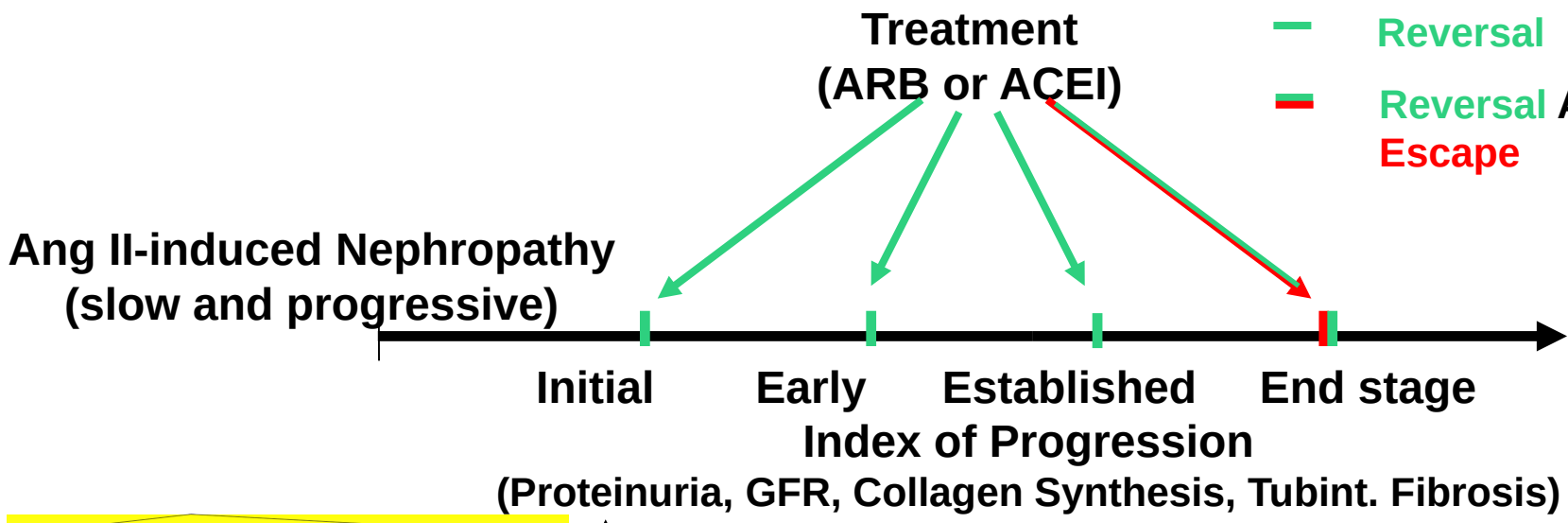
The Challenge for a Therapy of CKD: Finding novel Mediators - What Strategy?

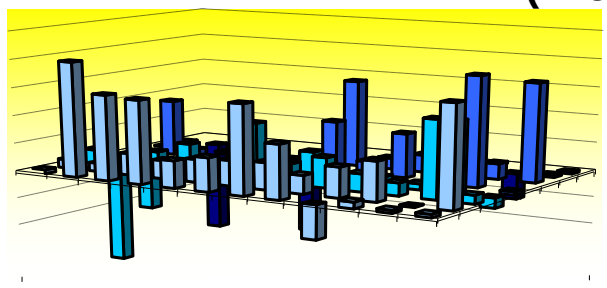


Strategy to Identify Novel Diagnostic Markers and/or Targets of Therapy of CKD



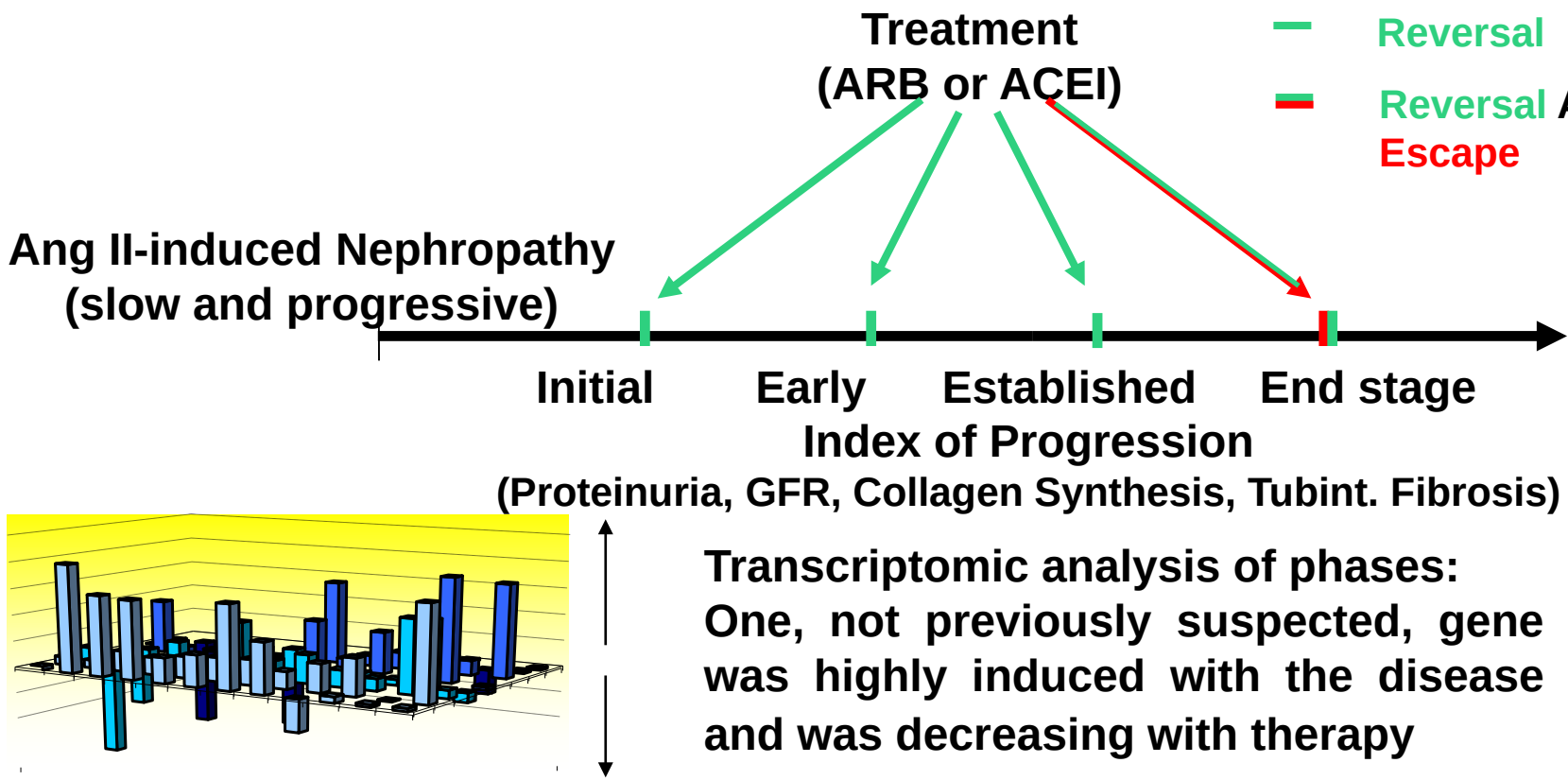
Using a Slowly Progressive Model of CKD (Transgenic Mice Overexpressing Renin) to Identify Novel Markers of Renal Disease





Transcriptomic analysis of phases: One, not previously suspected, gene was highly induced with the disease and was decreasing with therapy

Using a Slowly Progressive Model of CKD (Transgenic Mice Overexpressing Renin) to Identify Novel Markers of Renal Disease



Transcriptomic analysis of phases:
One, not previously suspected, gene was highly induced with the disease and was decreasing with therapy

PERIOSTIN

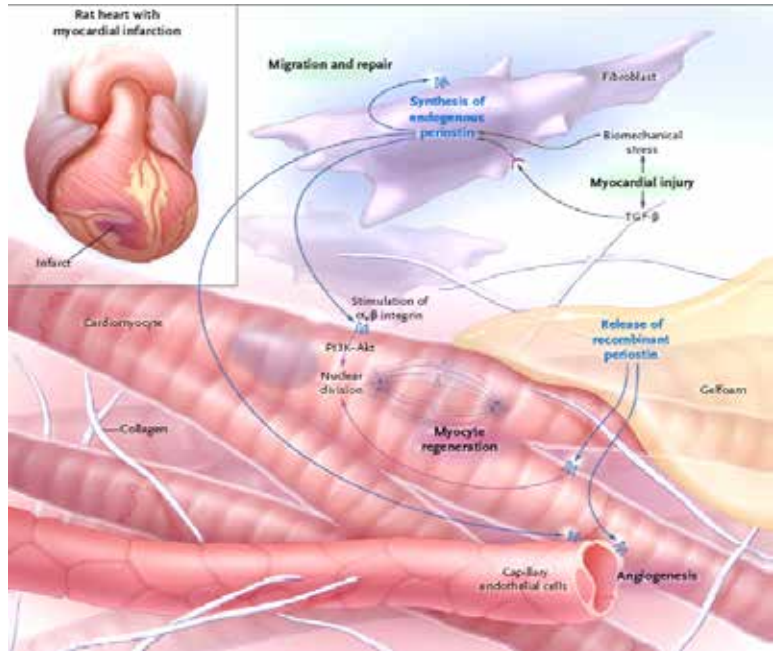
Revisiting Periostin, a Dentist's Protein

Periostin in Physiology

- A 90 kDa protein involved in cell adhesion
- Secreted after synthesis to be deposited within extracellular matrix
- Involved in embryonic and dental development (periosteum, periodental ligament)

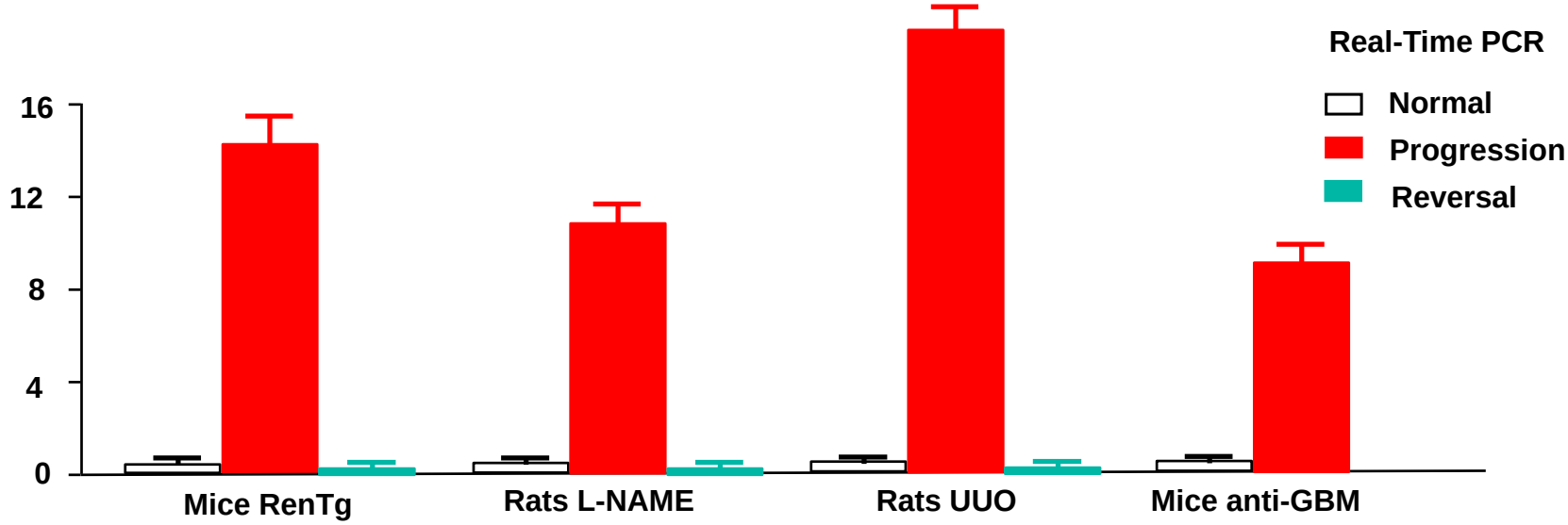
Periostin in Pathophysiology

- Higly induced after myocardial injury
- Interacting with the TGFb signaling
- Involved in cell phenotype alterations

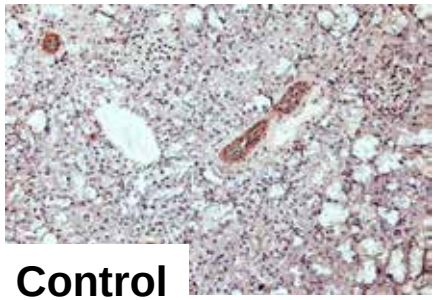


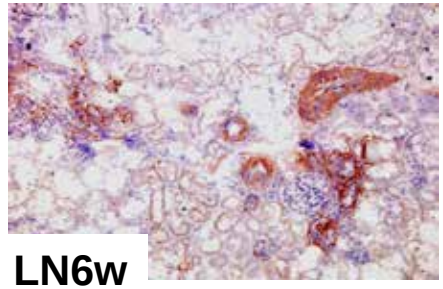
Periostin is highly Induced in All tested Models of CKD

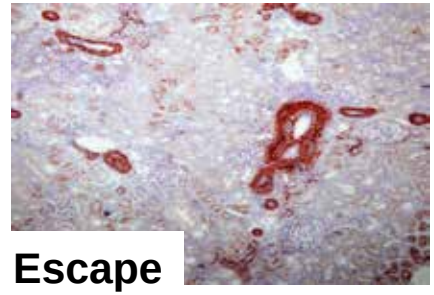
(Mael-Ainin, JASN 2014)

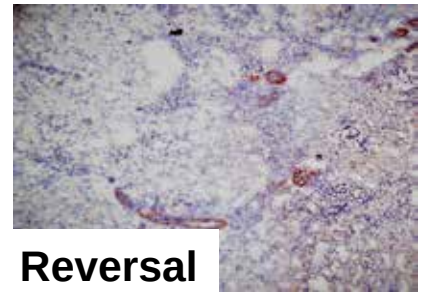


Periostin expression is Focal, around the Damaged Tissue

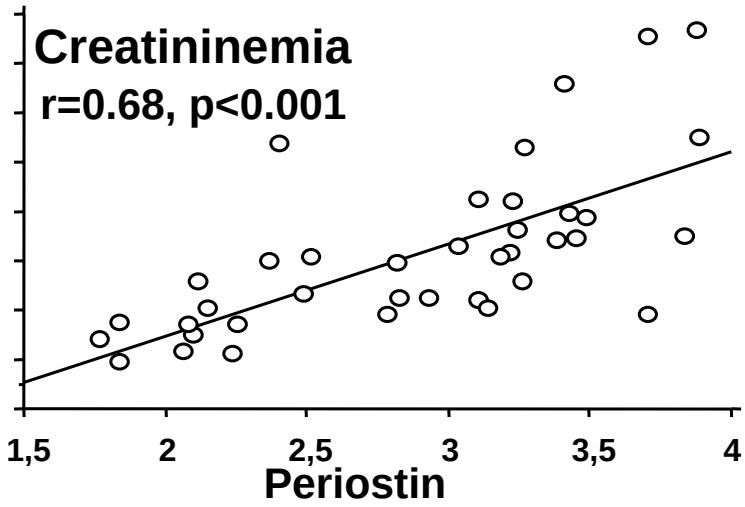

Control

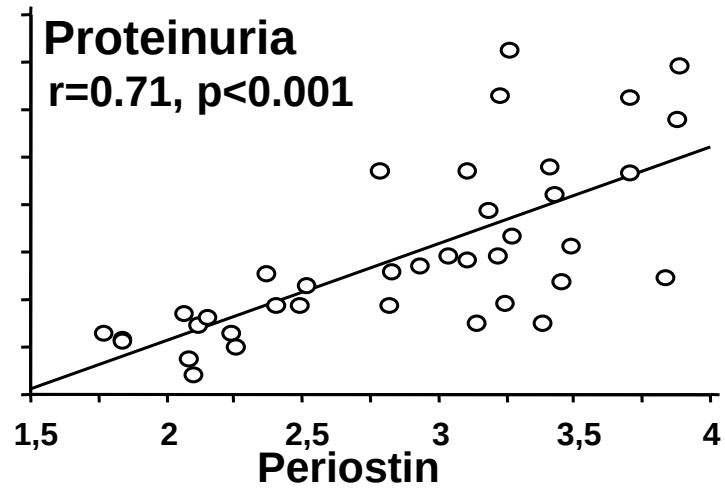

LN6w

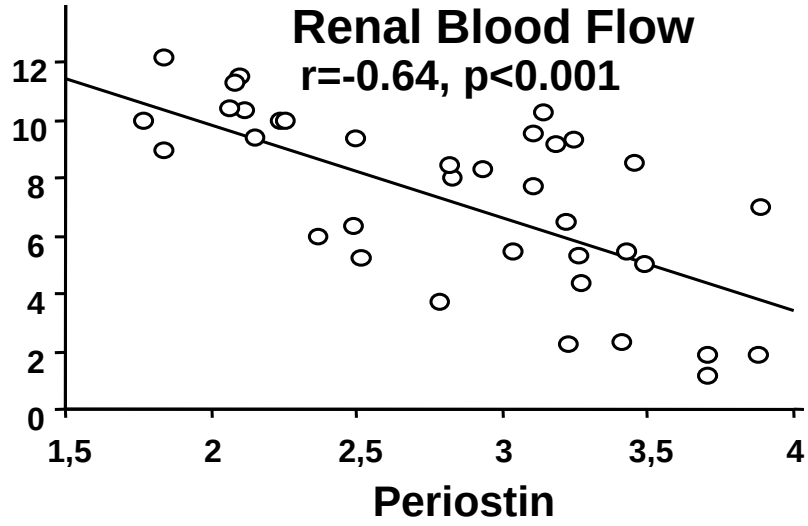

Escape


Reversal

Periostin Correlates Inversely to Renal Function during Progression/Regression of CKD (Guerrot, PLoS 2012)







Can we use Periostin as a Marker of Renal Disease?

- **Which cells are producing periostin following injury?**
- **Is periostin expression relevant to human CKD?**
- **Is periostin a better marker than the already existing?**

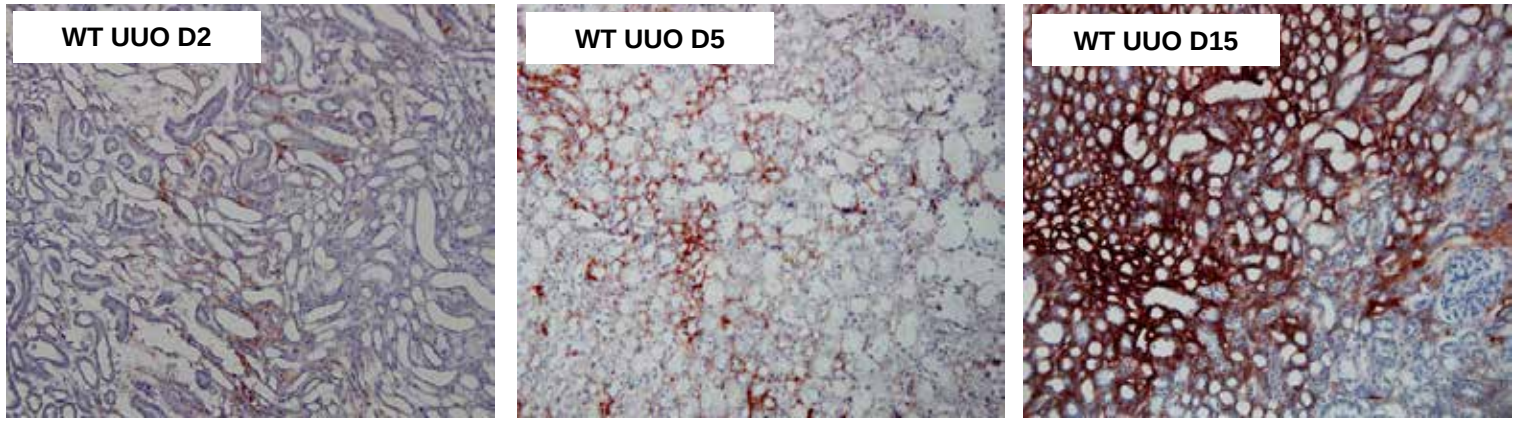
WHICH CELLS ARE PRODUCING PERIOSTIN FOLLOWING INJURY?

(MAEL-AININ JASN 2014, EDITORIAL)

$Postn^{LacZ}$ mice : Periostin cell tracing ⟶ lacZ reporter gene

$Postn^{LacZ}$ mice : LacZ expression following UUO

Postn expression following UUO in WT mice



Is Periostin Relevant to Renal Disease in Humans?

The American Journal of Pathology, Vol. 179, No. 4, October 2011
Copyright © 2011 American Society for Investigative Pathology.
Published by Elsevier Inc. All rights reserved.
DOI: 10.1016/j.ajpath.2011.06.002

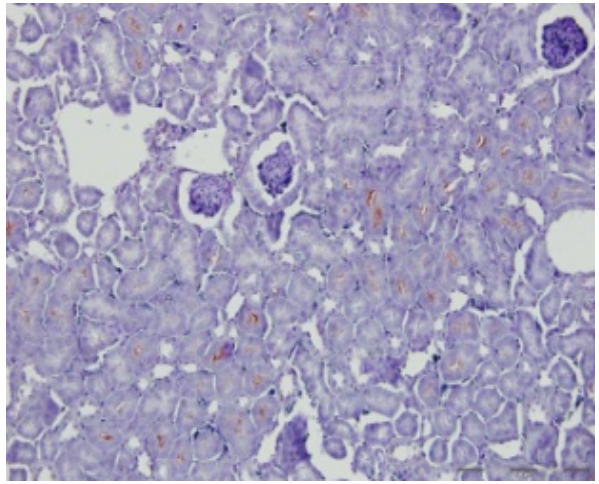
Cardiovascular, Pulmonary, and Renal Pathology

Periostin Is Induced in Glomerular Injury and Expressed *de Novo* in Interstitial Renal Fibrosis

Kontheari Sen,* Maja T. Lindenmeyer,*† Ariana Gaspert,‡ Felix Eichinger,§ Matthias A. Neusser,† Matthias Kretzler,§ Stephan Segerer,†¶ and Clemens D. Cohen*†

From the Institute of Physiology and the Department of Anatomy,¶ University of Zurich, Zurich, Switzerland; the Division of Nephrology† and the Institute of Surgical Pathology,‡ University Hospital Zurich, Zurich, Switzerland; and the Department of Medicine,§ University of Michigan, Ann Arbor, Michigan*

Matricellular proteins are a class of extracellular matrix (ECM)-related molecules defined by their ability to modulate cell matrix interactions through binding cell surface receptors such as integrins, as well as extracellular growth factors and collagens. Beside their role in constant ECM remodeling, matricellular proteins are key regulators of matrix accumulation, cell-matrix interaction, and fibrosis.[1] Thrombospondins (TSPs, protein symbols: THBSs), osteopontin, secreted protein acidic rich in cysteine (SPARC), and members of the CCN family [eg, connective tissue growth factors (CTGF)] are prominent representatives of this group of molecules.[2] These pro-



Normal Human Kidney

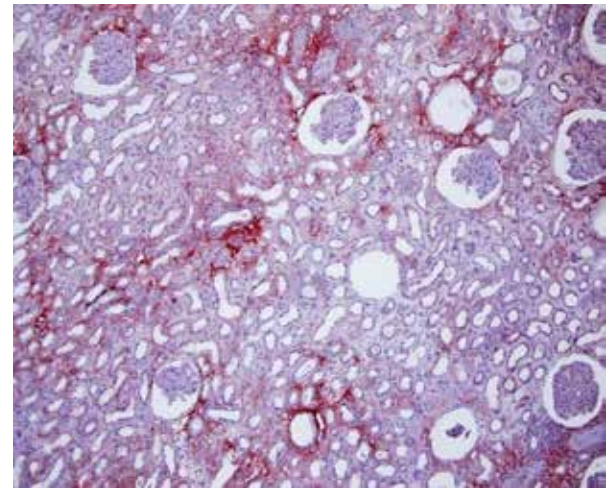
Nephrol Dial Transplant (2012) 27: 2702–2711
doi: 10.1093/ndt/gfr670
Advance Access publication 13 December 2011

Periostin: novel tissue and urinary biomarker of progressive renal injury induces a coordinated mesenchymal phenotype in tubular cells

Bancha Satirapoj[1,2], Ying Wang[1], Mina P. Chamberlin[1], Tiane Dai[1], Janine LaPage[1], Lynetta Phillips[1], Cynthia C. Nast[1,3] and Sharon G. Adler[1]

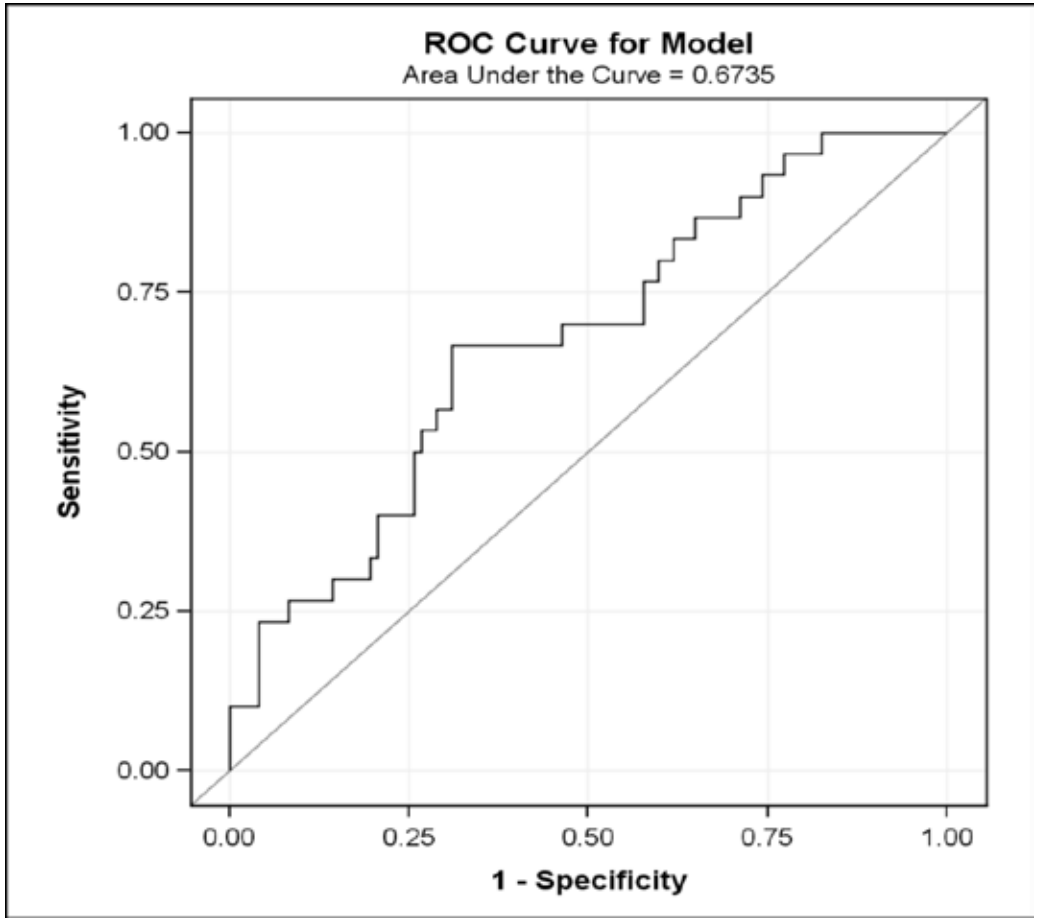
[1]Los Angeles Biomedical Research Institute, Harbor-UCLA, Torrance, CA, USA, [2]Division of Nephrology, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand and [3]Cedars-Sinai Medical Center, Los Angeles, CA, USA

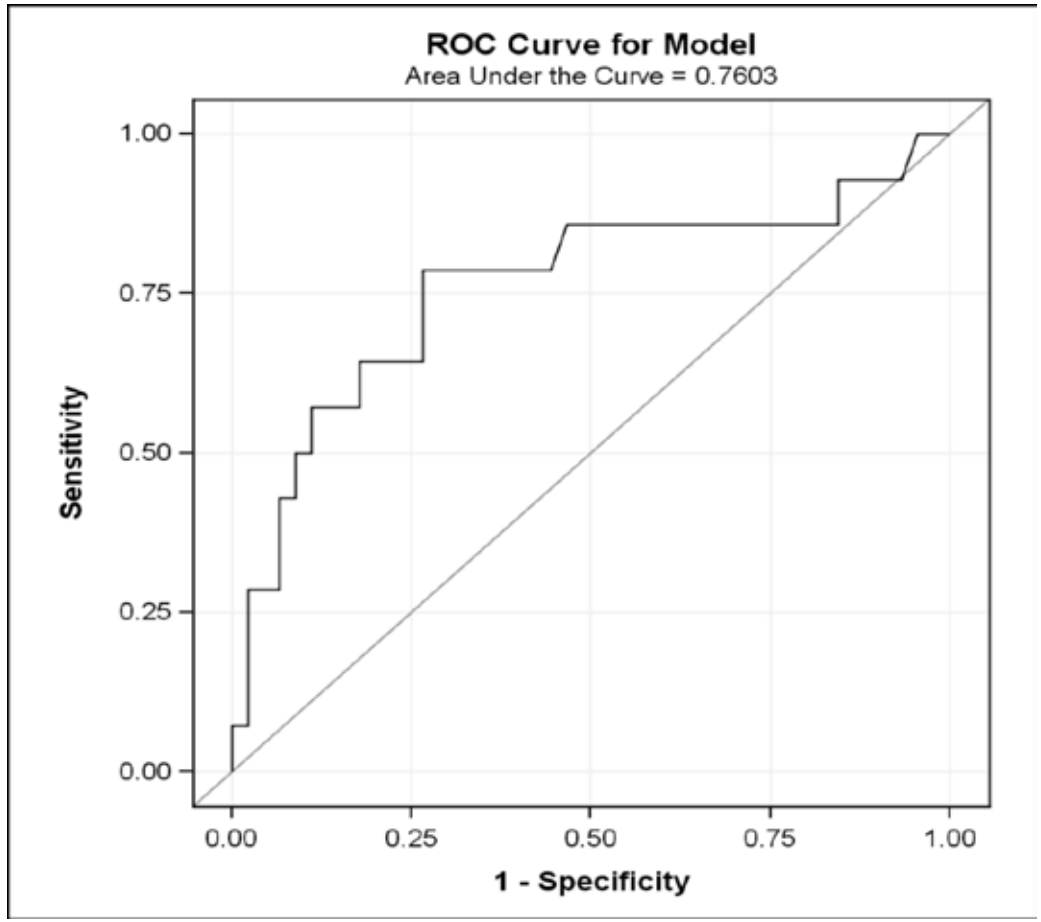
Correspondence and offprint requests to: Sharon G. Adler; E-mail: sadler@labiomed.org



Chronic Allograft Nephropathy

Is Periostin a Better Marker than the Already Existing? to Predict Renal Graft Outcome, possibly Yes (Alfieri, revision)





Vimentin **(n=216)** **Periostin**

Periostin and Inflammation: a Read out Marker of Therapy Efficiency in Asthma

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohen, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.

From the Allergy Medical Clinic, Los Angeles (J.C.), 3-V Biosciences, Menlo Park (M.V.P.), and Genentech, South San Francisco (J.R.A., J.M.H., H.S., L.C.W., Z.S., S.M., M.D.E., S.P.B., J.G.M.) — all in California; University of Wisconsin School of Medicine and Public Health, Madison (R.F.L.); Baylor College of Medicine, Houston (N.A.H.); and the Clinical Research Center, St. Louis (P.E.K.). Address reprint requests to Dr. Matthews at Product Development–Immunology, Genentech, 1 DNA Way, South San Francisco, CA 94080-4990, or at matthews.john@gene.com.

This article (10.1056/NEJMoa1106469) was published on August 3, 2011, at NEJM.org.

N Engl J Med 2011;365:1088-98.

ABSTRACT

BACKGROUND

Many patients with asthma have uncontrolled disease despite treatment with inhaled glucocorticoids. One potential cause of the variability in response to treatment is heterogeneity in the role of interleukin-13 expression in the clinical asthma phenotype. We hypothesized that anti–interleukin-13 therapy would benefit patients with asthma who had a pretreatment profile consistent with interleukin-13 activity.

METHODS

We conducted a randomized, double-blind, placebo-controlled study of lebrikizumab, a monoclonal antibody to interleukin-13, in 219 adults who had asthma that was inadequately controlled despite inhaled glucocorticoid therapy. The primary efficacy outcome was the relative change in prebronchodilator forced expiratory volume in 1 second (FEV_1) from baseline to week 12. Among the secondary outcomes was the rate of asthma exacerbations through 24 weeks. Patient subgroups were prespecified according to baseline type 2 helper T-cell (Th2) status (assessed on the basis of total IgE level and blood eosinophil count) and serum periostin level.

RESULTS

At baseline, patients had a mean FEV_1 that was 65% of the predicted value and were taking a mean dose of inhaled glucocorticoids of 580 μg per day; 80% were also taking a long-acting beta-agonist. At week 12, the mean increase in FEV_1 was 5.5 percentage points higher in the lebrikizumab group than in the placebo group (P=0.02). Among patients in the high-periostin subgroup, the increase from baseline FEV_1 was 8.2 percentage points higher in the lebrikizumab group than in the placebo group (P=0.03). Among patients in the low-periostin subgroup, the increase from baseline FEV_1 was 1.6 percentage points higher in the lebrikizumab group than in the placebo group (P=0.61). Musculoskeletal side effects were more common with lebrikizumab than with placebo (13.2% vs. 5.4%, P=0.045).

CONCLUSIONS

Lebrikizumab treatment was associated with improved lung function. Patients with high pretreatment levels of serum periostin had greater improvement in lung function with lebrikizumab than did patients with low periostin levels. (Funded by Genentech; ClinicalTrials.gov number, NCT00930163.)

Can we use Periostin as a Marker of Renal Disease?

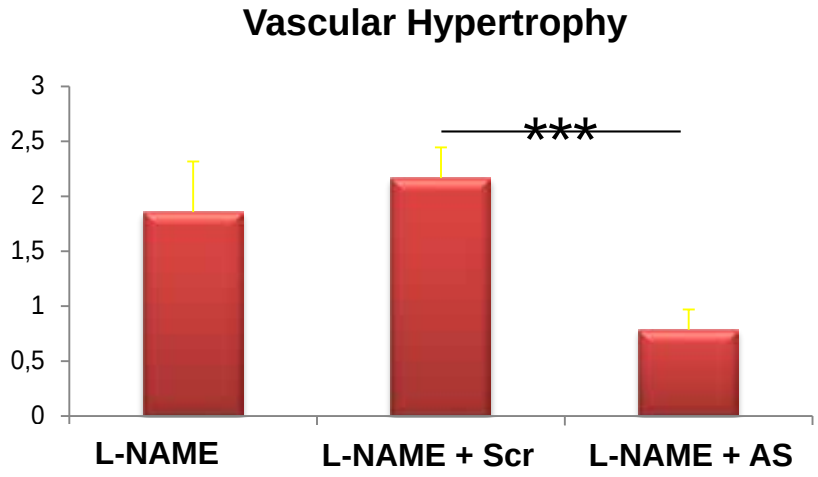
- Which cells are producing periostin following injury?
- Is periostin expression relevant to human CKD?
- Is periostin a better marker than the already existing?

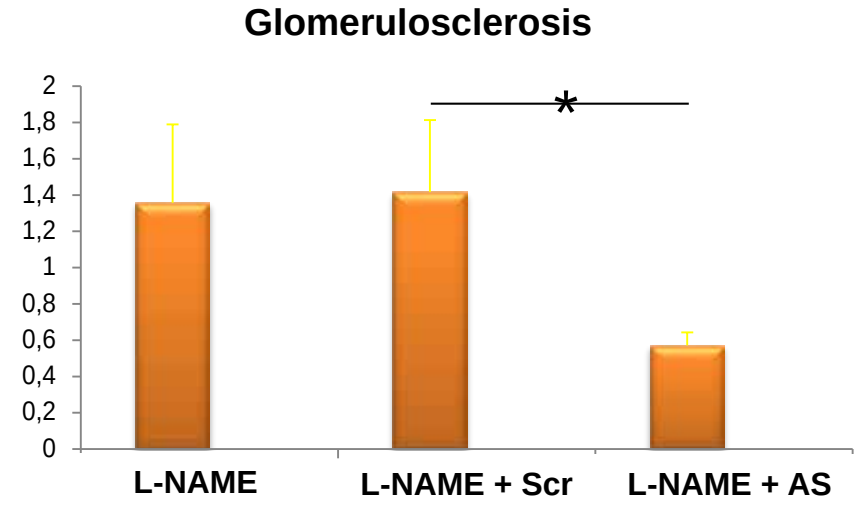
Can Periostin be a Target for Therapy of CKD?

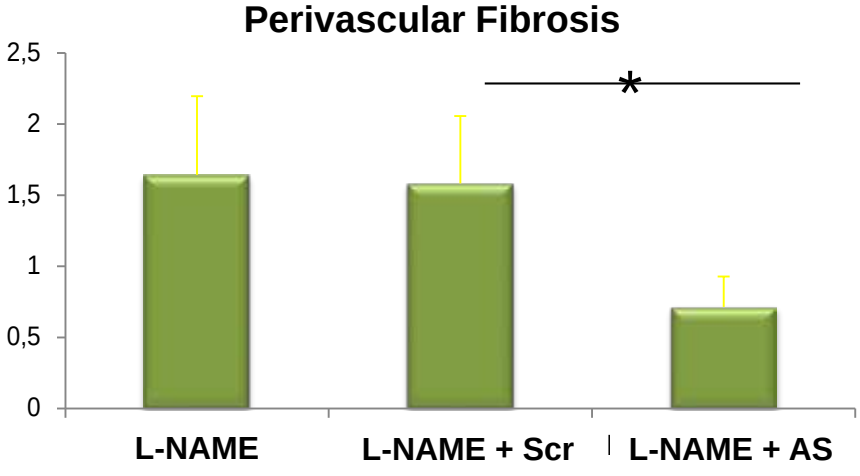
- Does inhibition of periostin expression protect animals against renal disease?
- What are the mechanisms of action of periostin?
- Can we develop a therapy based on periostin inhibition?

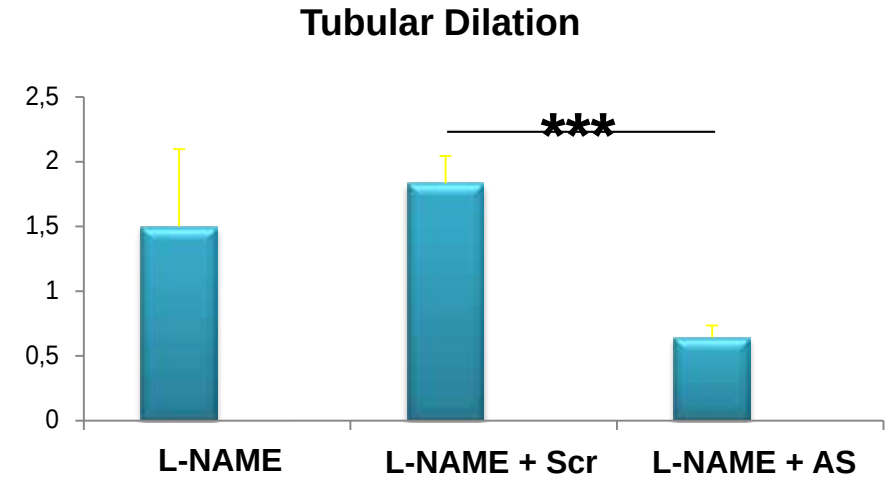
Periostin Silencing by Antisense ODNs Prevented the Progression of L-NAME-induced Renal Injury

(Mael-ainin JASN 2014)

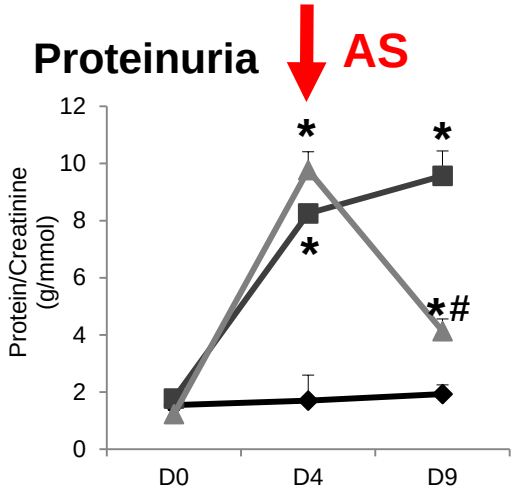


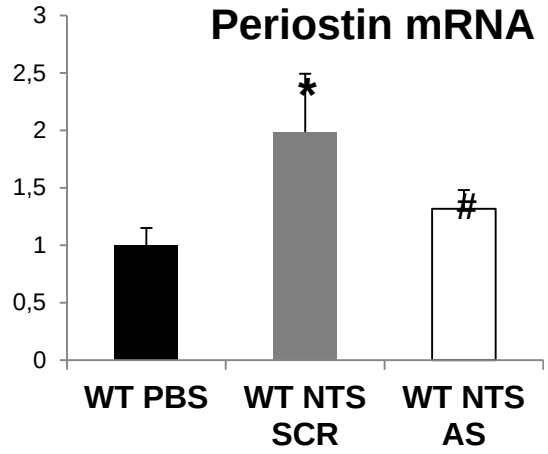


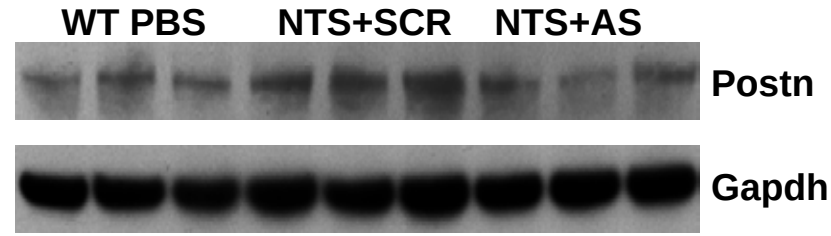




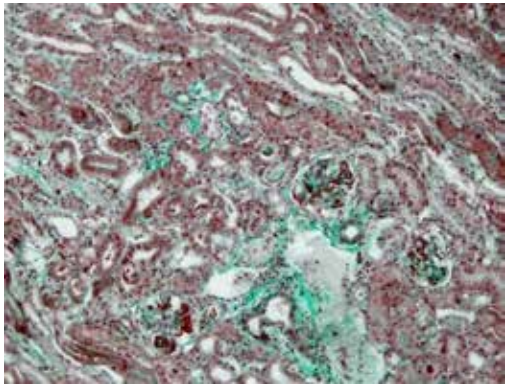
Proof of Concept for Therapy: Periostin Silencing Protects Against NTS-induced CKD (Prakoura JASN 2017)



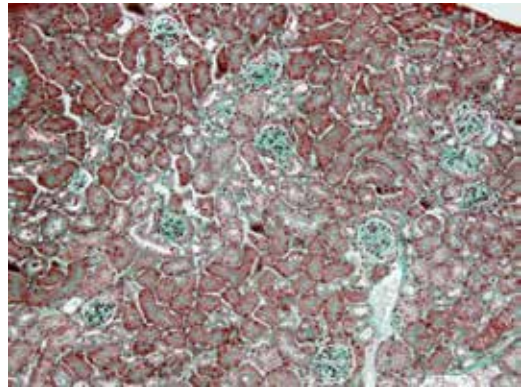




WT NTS SCR

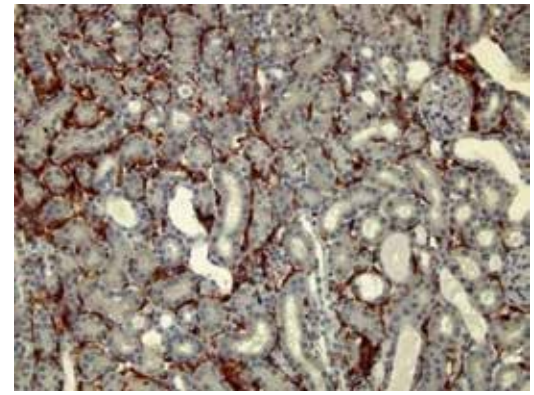


WT NTS AS

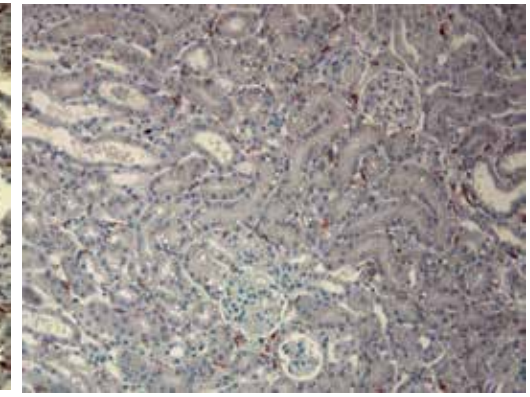


F4/80

WT NTS SCR

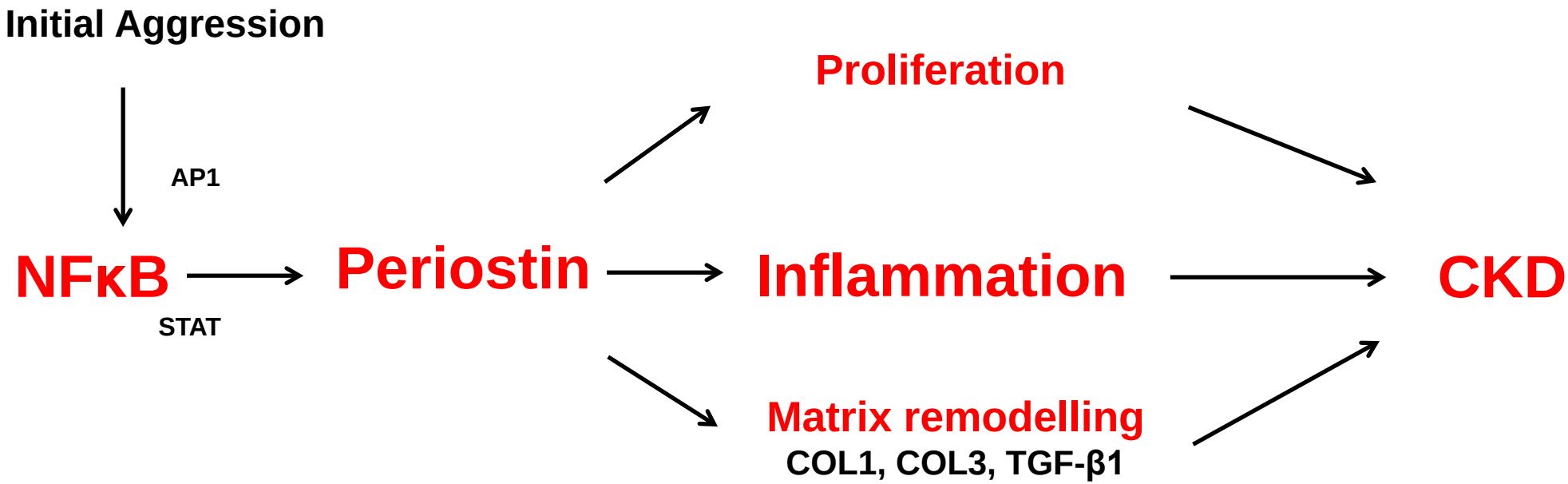


WT NTS AS



Periostin Mechanisms Inducing CKD

(Prakoura JASN 2017)



Periostin Is a Key Player in Phenotype Change of Macrophages to Induce Inflammation, Tumor Growth and Metastasis

Nat Cell Biol, 2015

nature
International weekly journal of science
Full text access provid
Home | News & Comment | Research | Careers & Jobs | Current Issue | Archive | Audio & Video
Research › Letters › Article

NATURE | LETTER
previous article next artic

Interactions between cancer stem cells and their niche govern metastatic colonization

Ilaria Malanchi, Albert Santamaria-Martínez, Evelyn Susanto, Hong Peng, Hans-Anton Lehr, Jea
Francois Delaloye & Joerg Huelsken

Affiliations | Contributions | Corresponding author

Nature (2011) | doi:10.1038/nature10694
Received 26 July 2010 | Accepted 01 November 2011 | Published online 07 December 2011

ARTICLES
nature cell biology

Periostin secreted by glioblastoma stem cells recruits M2 tumour-associated macrophages and promotes malignant growth

Wenchao Zhou[1], Susan Q. Ke[1], Zhi Huang[2], William Flavahan[3], Xiaoguang Fang[1], Jeremy Paul[1], Ling Wu[2], Andrew E. Sloan[5], Roger E. McLendon[4], Xiaoxia Li[2], Jeremy N. Rich[3] and Shideng Bao[1,5]

Tumour-associated macrophages (TAMs) are enriched in glioblastoma multiformes (GBMs) that contain glioma stem cells (GSCs) at the apex of their cellular hierarchy. The correlation between TAM density and glioma grade suggests a supportive role for TAMs in tumour progression. Here we interrogated the molecular link between GSCs and TAM recruitment in GBMs and demonstrated that GSCs secrete periostin (POSTN) to recruit TAMs. TAM density correlates with POSTN levels in human GBMs. Silencing POSTN in GSCs markedly reduced TAM density, inhibited tumour growth, and increased survival of mice bearing GSC-derived xenografts. We found that TAMs in GBMs are not brain-resident microglia, but mainly monocyte-derived macrophages from peripheral blood. Disrupting POSTN specifically attenuated the tumour-supportive M2 type of TAMs in xenografts. POSTN recruits TAMs through the integrin $\alpha_v\beta_3$ as blocking this signalling by an RGD peptide inhibited TAM recruitment. Our findings highlight the possibility of improving GBM treatment by targeting POSTN-mediated TAM recruitment.

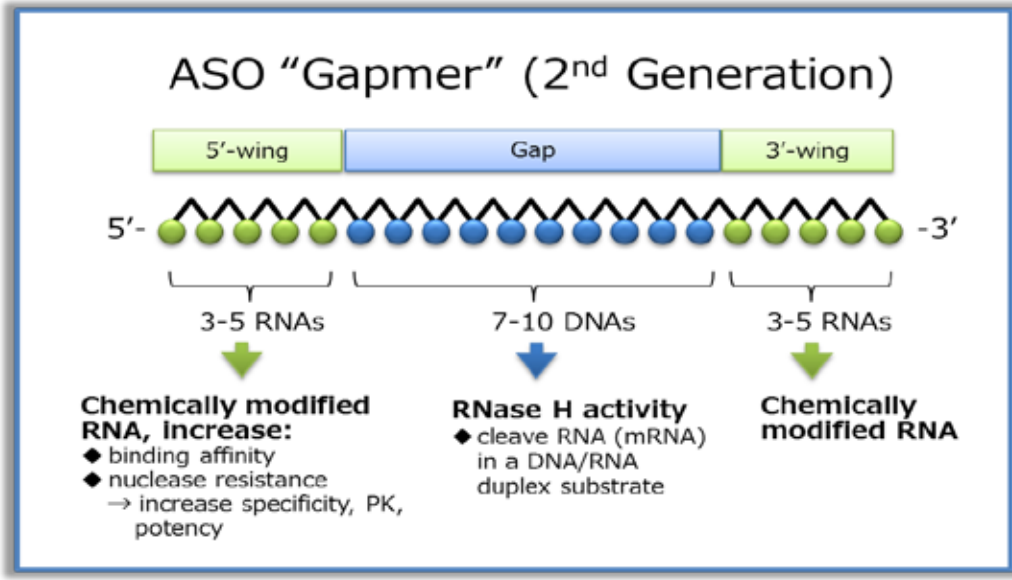
GBM is the most common and lethal type of primary brain tumour[1]. The median survival of GBM patients is less than 16 months despite optimal treatment[2]. Abundant macrophage infiltration is a common feature of GBMs, but these TAMs in GBMs lack apparent phagocytic activity[3]. In addition, an inverse correlation between TAM infiltration and GBM prognosis has been reported[4]. Recent studies suggested that TAMs may promote GBM tumour progression in multiple aspects[5–8]. The TAM secreted cytokines, including IL-6 and IL-10, have been shown to promote cancer cell proliferation in GBMs (ref. 8). TAMs could also facilitate GBM tumour growth by promoting neo-vascularization[5,7]. Moreover, TAMs can interfere with the anti-tumour functions of other immune cells[5], although TAMs do not exhibit traditional immunocyte properties. Thus, TAMs mainly play a tumour-supportive role in GBM progression. As pioneering immunotherapies have shown initial promise for GBM treatment, interrogating immunologic regulation in GBMs may inform therapy[9–11]. In addition, as TAMs in GBM may originate from either monocytes from peripheral blood or resident microglia in brain, identifying the source of TAMs in GBMs will provide critical information to determine the appropriate therapeutic approaches. Therefore, determining the cellular and molecular mechanisms underlying TAM recruitment may facilitate the development of therapeutics to effectively improve GBM treatment.

Macrophages can be categorized into M1 and M2 subtypes based on their polarization status[12]. In tumours, the M1 or M2 subtype TAMs represent tumour-suppressive or tumour-supportive macrophages, respectively[13]. Cell surface markers including Iba1 and CD11b are commonly used to label total TAMs (refs 12,14). Several surface markers such as CD163, Fizz1 and Arg1 have been used to mark M2 subtype TAMs, whereas other surface markers including MHCII, CD11c and iNOS have been suggested for M1 subtype TAMs (refs 15–19). Although TAMs in lower grade astrocytomas were strongly stained with the M1 marker MHCII (ref. 20), TAMs in GBM tumours manifested strong M2 marker staining[17,21]. Such correlation between tumour grades and the M2 TAM abundance further suggests that the M2 type TAMs might play a critical role in GBM progression. However, TAMs in GBMs may be derived from circulating monocytes or resident microglia[15,16]. Despite the fact that these two populations may share some surface markers in brain[15,16], studies using CX3CR1(+/GFP)/CCR2(+/RFP) knock-in

[1]Department of Stem Cell Biology and Regenerative Medicine, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA. [2]Department of Immunology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA. [3]Departments of Neurological Surgery & Pathology, University Hospitals, Case Medical Center & Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA. [4]Department of Pathology, Duke University Medical Center, Durham, North Carolina 27710, USA.
*Correspondence should be addressed to S.B. (e-mail: bao@ccf.org)

Received 23 May 2014; accepted 26 November 2014; published online 12 January 2015; DOI: 10.1038/ncb3090

Novel Approaches for Therapy : Antisense OligoNucleotides



The 2nd Generation ASO "Gapmer"

- Uniformly modified with PS (phosphorothioate) in the backbone
- 2'-deoxyribose gap is essential for recruitment of endonuclease (RNase H), and minimum gap size of 7-10 residues is necessary.
- The gap is flanked by 2'-modified residues, such as 2'-O-Me, 2'-MOE or LNA.
- 2G ASOs are significantly better in their potency, stability and tolerability compared with 1G PS ASO.

(Yogesh S Sanghvi, 2013 Future science)

ASO pharmacokinetic feature

- **Distribute out of plasma and into tissues**
- **Majority of drug localizes within cells in tissues**
- **Multiple routes of delivery**
- **Strong PK/PD correlation demonstrated in tissues** such as:
  - **Kidney**
  - Liver
  - Bone marrow
  - Adipose tissue
  - Spleen, lymph nodes
  - Lung (aerosol)
  - CNS (ICV or IT)
  - Human cancer
  - Sites of inflammation

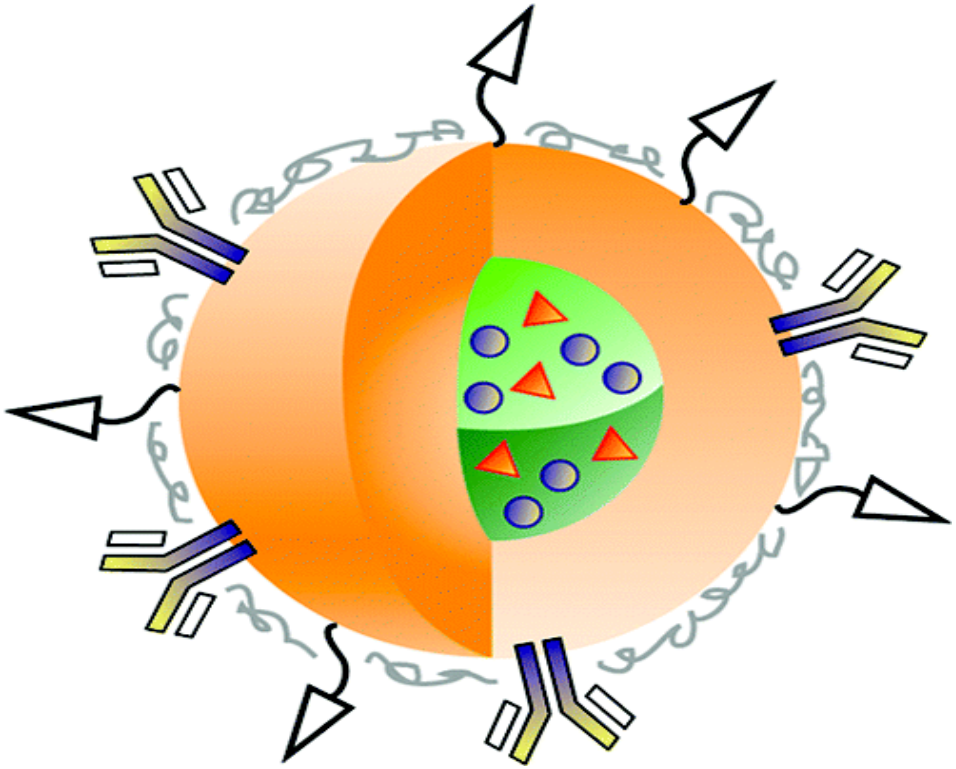
(C. Frank Bennett, Isis Pharm.)

Clinical status of ASOs

- Among all oligo-based technology, ASO has the largest portfolio in active clinical trials.
- Consistent PK PD profiles regardless of size and sequence composition
- Good number of ASOs have sailed through Ph1 safety studies without serious concern.
- Two out of three market approved drugs are ASO, and the most recently approved (mipomersen) is a 2G ASO (Gapmer).

(Yogesh S Sanghvi, 2013 Future science)

Novel Approaches for Precision Medicine : Nanoparticles



40-400 nm

- **Physical properties :**
  - **Biocompatible**
  - **Simple**
  - **Stable**
  - **Big scale use**
  - **Biodegradable**
- **Contrast agent properties :**
  - **Magnetic (NPs Fe_2O_3, Gd, …)**
  - **Optical Imaging**
  - **Electronic Density (I, Gd, …)**
  - **Thermical Imaging**
- **Therapy properties :**
  - **Site specific targeting**
  - **Drug Storage**
  - **Controlled release**
  - **Local Hyperthermia**

Can an Agent like Periostin be a Biomarker and a Target for Therapy of CKD?

Advantages

- It is 'silent' during adulthood under physiological conditions.
- It is highly induced and released early from the suffering cells.
- It is induced by the activation of inflammatory pathways, such as NFkB.
- Its levels are well correlated with the degree of damage.
- Its activation induces phenotype changes further increasing inflammation AND inducing fibrosis.
- Pharmaco-genetic inhibition of its synthesis protects kidneys in experimental models AND does not affect physiological functions.

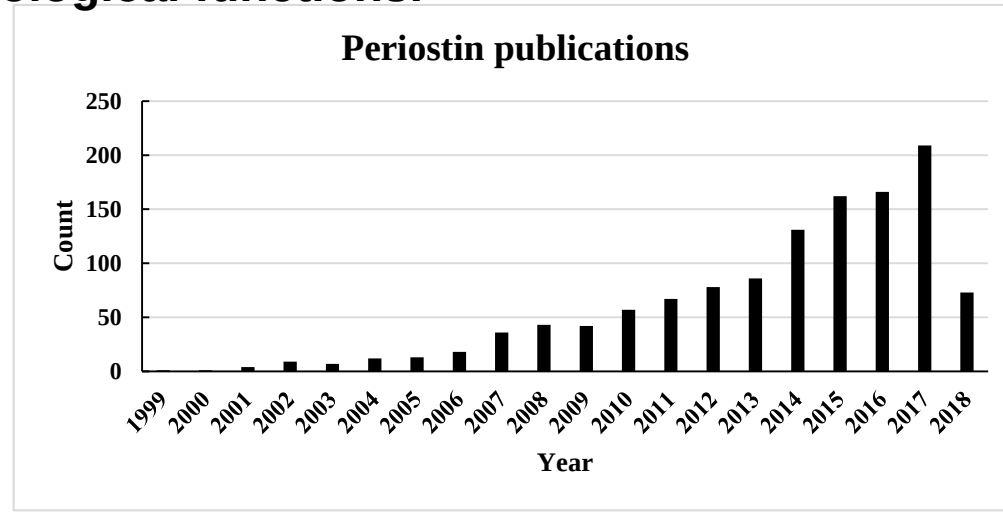
Can an Agent like Periostin be a Biomarker and a Target for Therapy of CKD?

Advantages

- It is 'silent' during adulthood under physiological conditions.
- It is highly induced and released early from the suffering cells.
- It is induced by the activation of inflammatory pathways, such as NFkB.
- Its levels are well correlated with the degree of damage.
- Its activation induces phenotype changes further increasing inflammation AND inducing fibrosis.
- Pharmaco-genetic inhibition of its synthesis protects kidneys in experimental models AND does not affect physiological functions.

Scientific Interest:

- Rapidly expanding field
- Commercially available kits for detection in plasma exist



Next Step (for Nephrology):

- Define the category(ies) of patients to be used.

But, Is the Therapy of CKD a Priority for the Private Sector Today?

2013: Winner “New Therapy Strategies” (for targeting glomerulonephritis)

2015: Winner “Fast Track Drug Discovery” challenge (for targeting CAN)

Last min info: Sanofi Innovation Awards “Periostin as target of Therapy” (June 2018)

But, Is the Therapy of CKD a Priority for the Private Sector Today?

2013: Winner “New Therapy Strategies” (for targeting glomerulonephritis)

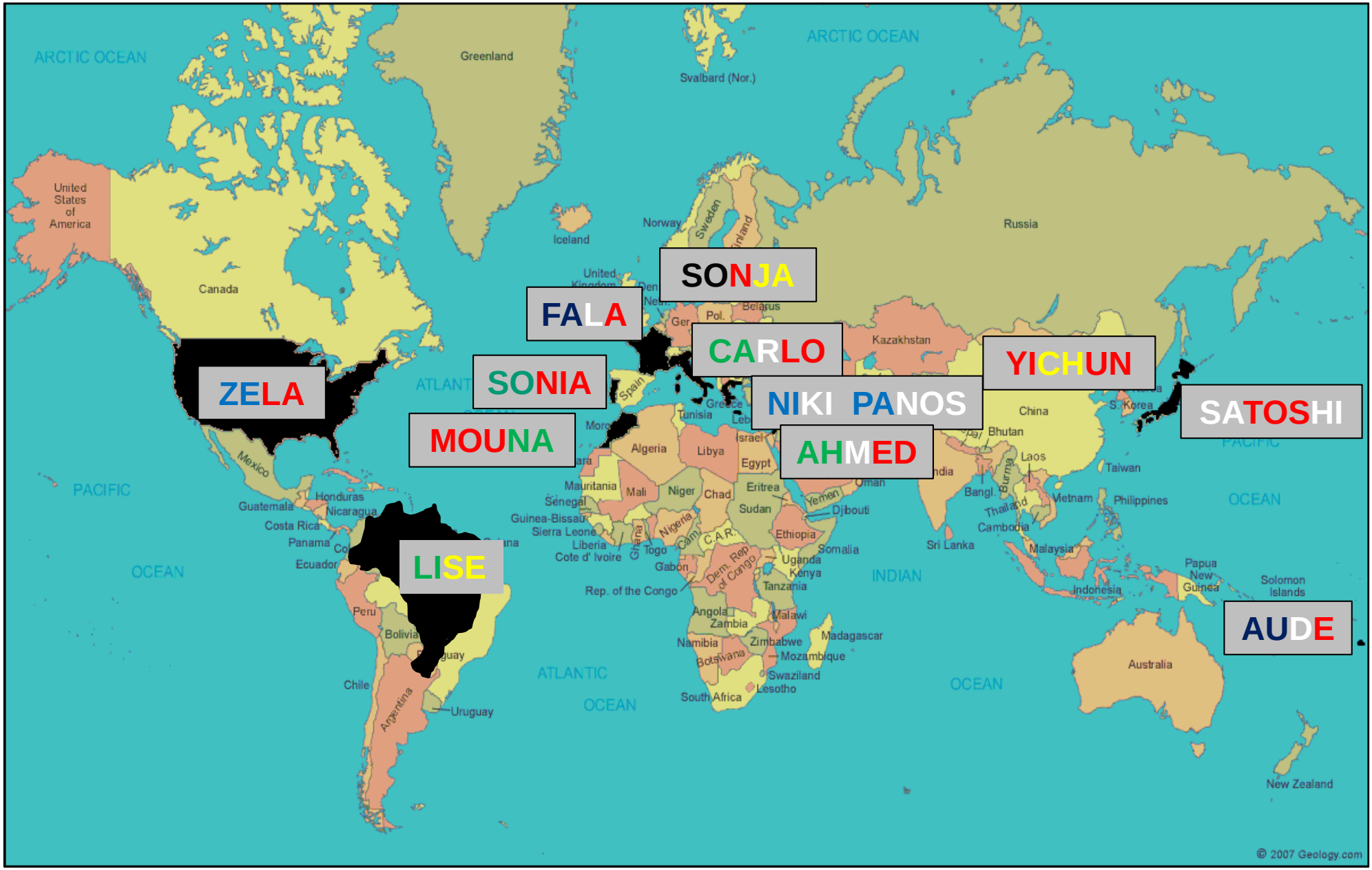
2015: Winner “Fast Track Drug Discovery” challenge (for targeting CAN)

Last min info: Sanofi Innovation Awards “Periostin as target of Therapy” (June 2018)

ΣΥΜΠΕΡΑΣΜΑ ΓΙΑ ΤΗΝ ΑΝΑΠΤΥΞΗ ΝΕΩΝ ΘΕΡΑΠΕΥΤΙΚΩΝ ΑΓΩΓΩΝ:

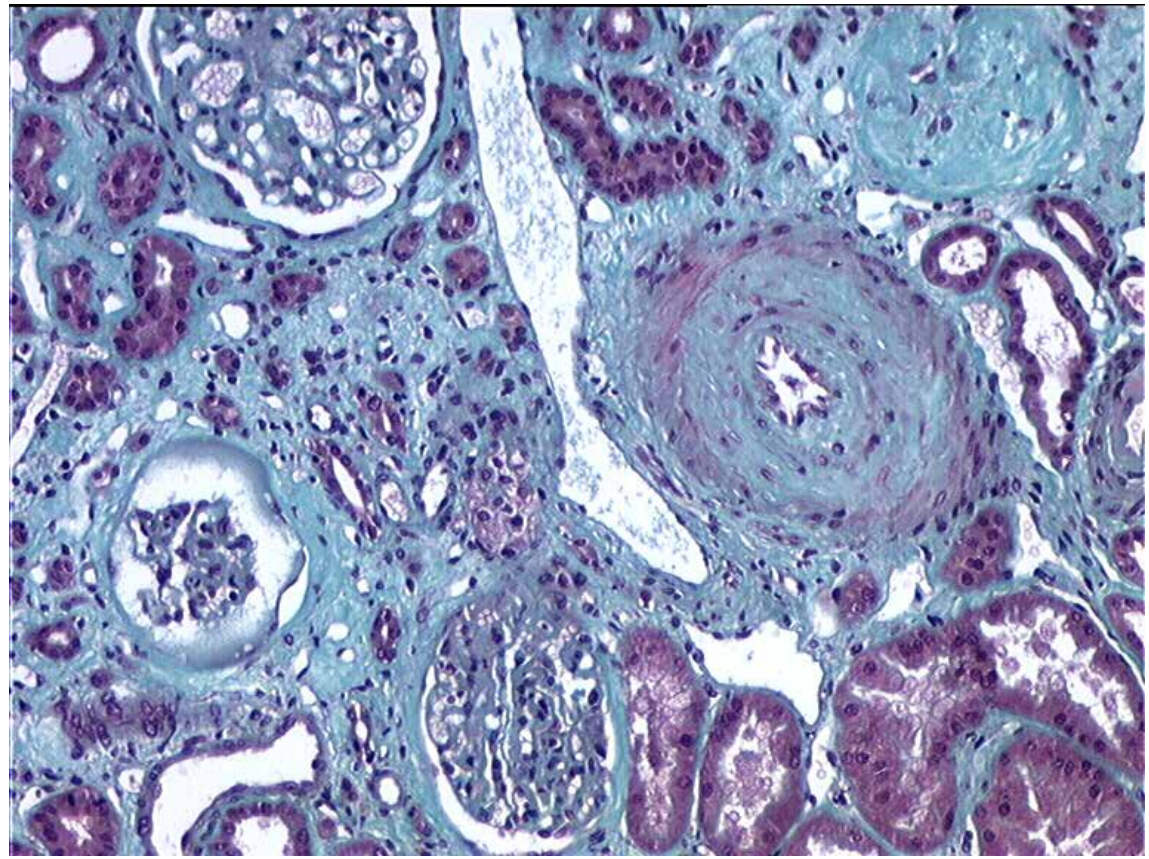
«ΜΑΣ ΕΡΩΤΕΥΟΝΤΑΙ, ΑΛΛΑ ΔΕΝ ΜΑΣ ΝΥΜΦΕΥΟΝΤΑΙ »

The People Behind this Story:



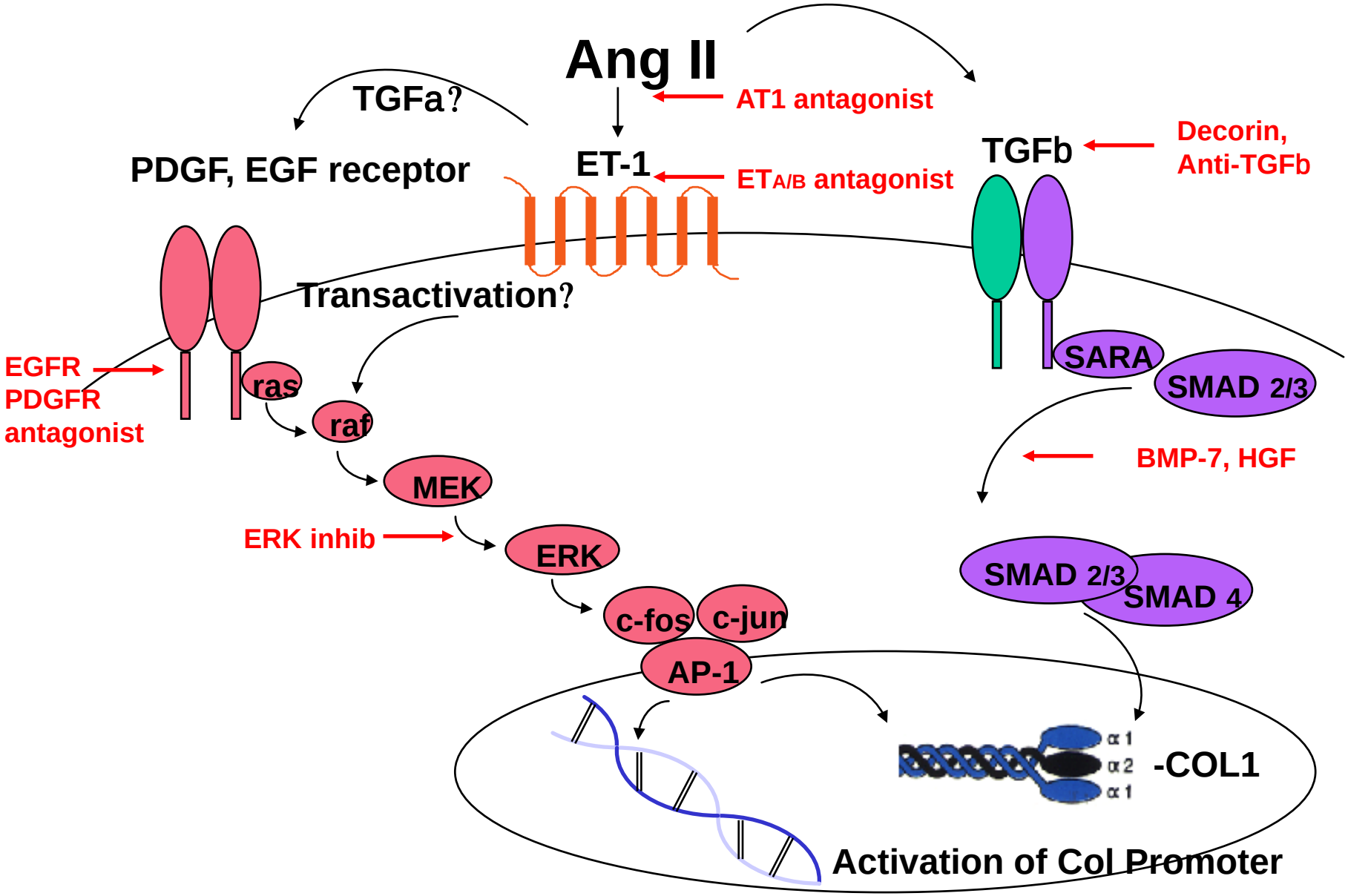
INSERM UMR S 1155, TENON HOSPITAL, PARIS

Chronic Kidney Disease: a Major Public Health Issue

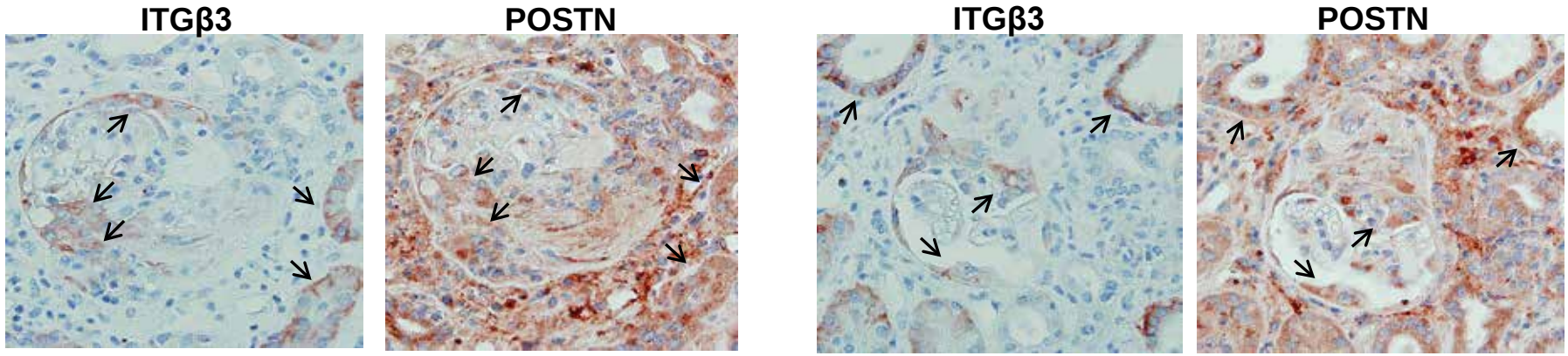


- 3 000 000 people in France with some degree of renal disease
- 80 000 people in France with End Stage Renal Failure (> 350 000 in EU)
- 7-8% annual increase rate (Hypertension, Diabetes, Aging)
- No therapy; available options : Dialysis and/or Transplantation
- 2-3% of Health Budget

Ang II signaling pathways inducing renal fibrosis



Relevance : Periostin and Its Receptor Integrin b3 are Induced and Co-localized in Glomerulonephritis



Periostin Mechanisms Inducing CKD

Initial Aggression

AP1

NFκB

STAT

Periostin

Proliferation

Inflammation

Matrix remodelling

COL1, COL3, TGF-β1

CKD