How does alpha galactosidase deficiency lead to cell damage & how can it be repaired?

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Disclosure of Interests

- Genzyme, a Sanofi company: consultancy, honoraria
- Shire, honoraria

A **rational** therapeutic **approach** requires a good grasp of the **pathogenesis**

The **problems** in Fabry nephropathy:

a) **No** satisfactory animal model

b) **Rare** disease

c) **Very long** natural history

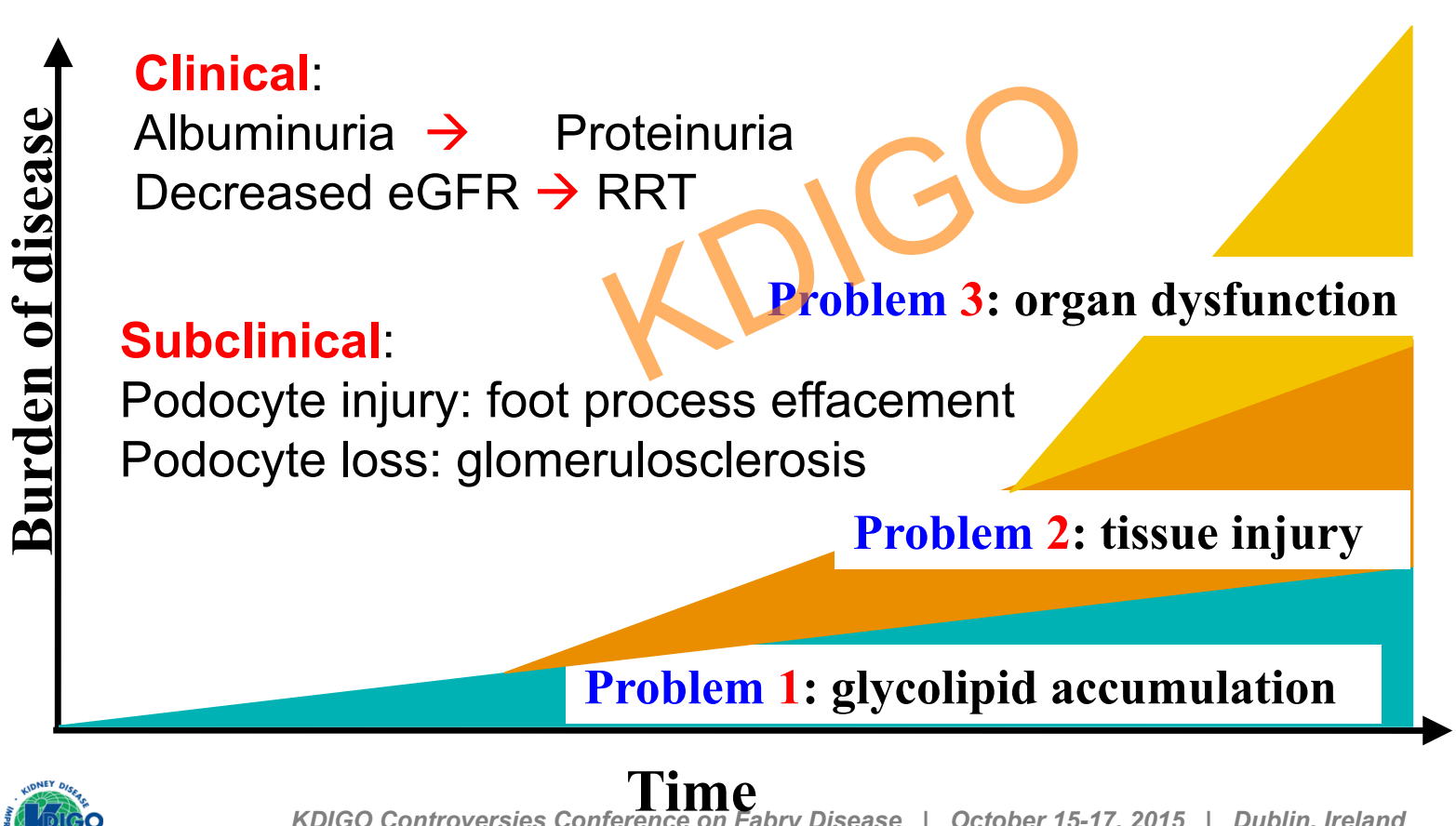
Compromised ability to
- **Generate** hypothesis
- **Test** hypothesis in adequately powered RCT

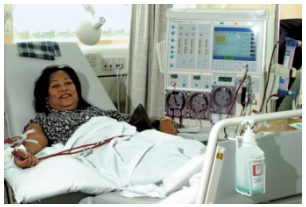
Pathogenesis of Fabry nephropathy: 3 sequential problems, each requiring a specific therapeutic approach

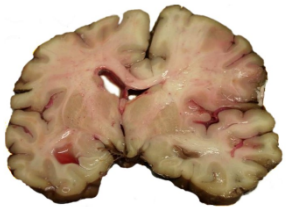
Enzymatic defect → Glycolipid accumulation → **Black box** → Tissue injury

Clinical:
Albuminuria → Proteinuria
Decreased eGFR → RRT

Subclinical:
Podocyte injury: foot process effacement
Podocyte loss: glomerulosclerosis





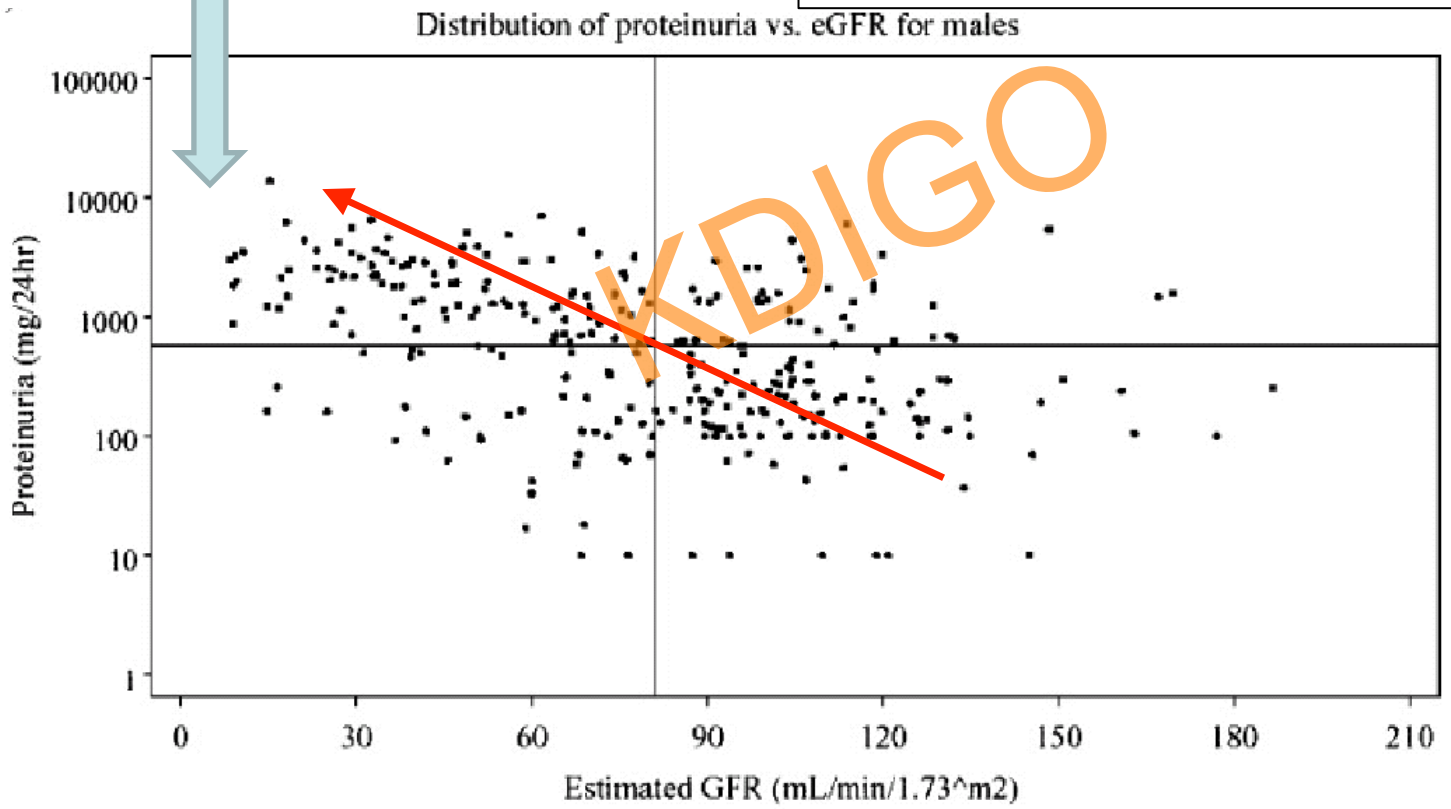


Eng CM et al. J Inherit Metab Dis 2007;30:184-92.

Fabry nephropathy is a progressive proteinuric chronic kidney disease of metabolic origin

RRT Mean age 40 years

Natural history: 40 years: implications for clinical trials assessing **hard end-points**



Ortiz A et al. NDT 2008

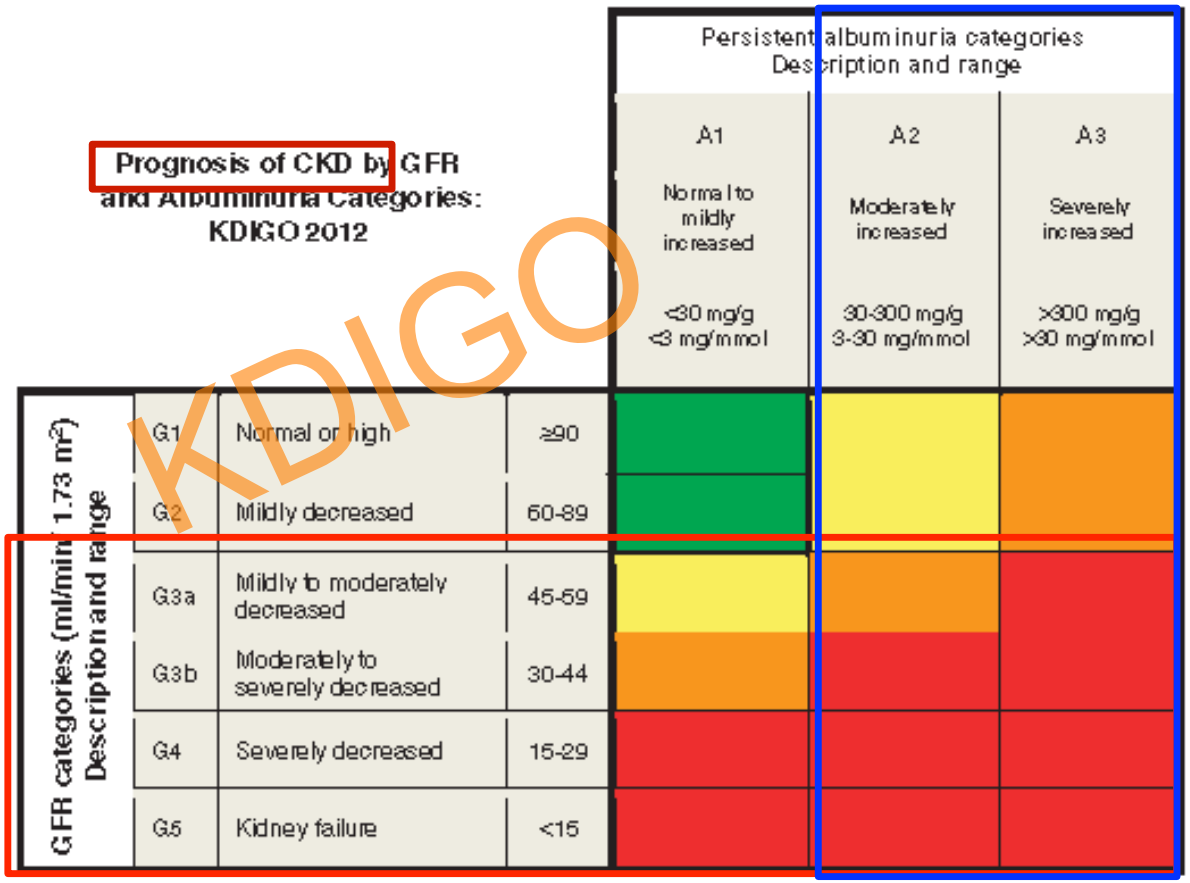
What basic concepts did we learn from chronic kidney disease?

Albuminuria (not exactly proteinuria)

Current KDIGO CGA classification of CKD

Albuminuria and CKD progression

GFR



no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red,

Unless proven otherwise, these general concepts apply to Fabry nephropathy

KDIGO CKD 2012. Kidney Int Suppl 2013.

What basic concepts did we learn from chronic kidney disease?

Current KDIGO CGA classification of CKD

Albuminuria and survival
- **All cause**
- **CV**

Albuminuria (not exactly proteinuria)

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ≥300
eGFR >105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

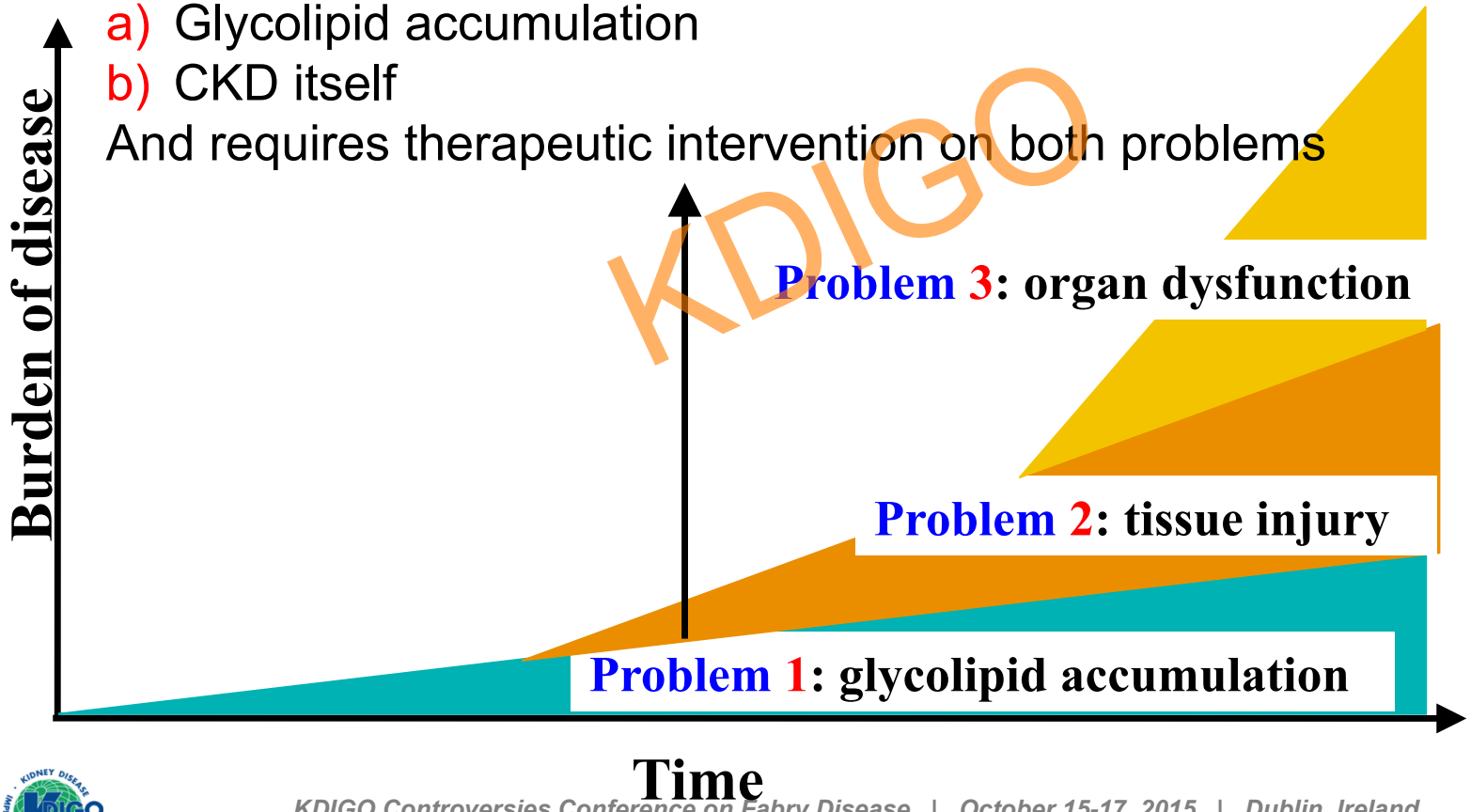
GFR

Unless proven otherwise, these general concepts apply to Fabry nephropathy

KDIGO CKD 2012. Kidney Int Suppl 2013.

Pathogenesis of Fabry nephropathy: 3 sequential problems, each requiring a specific therapeutic approach

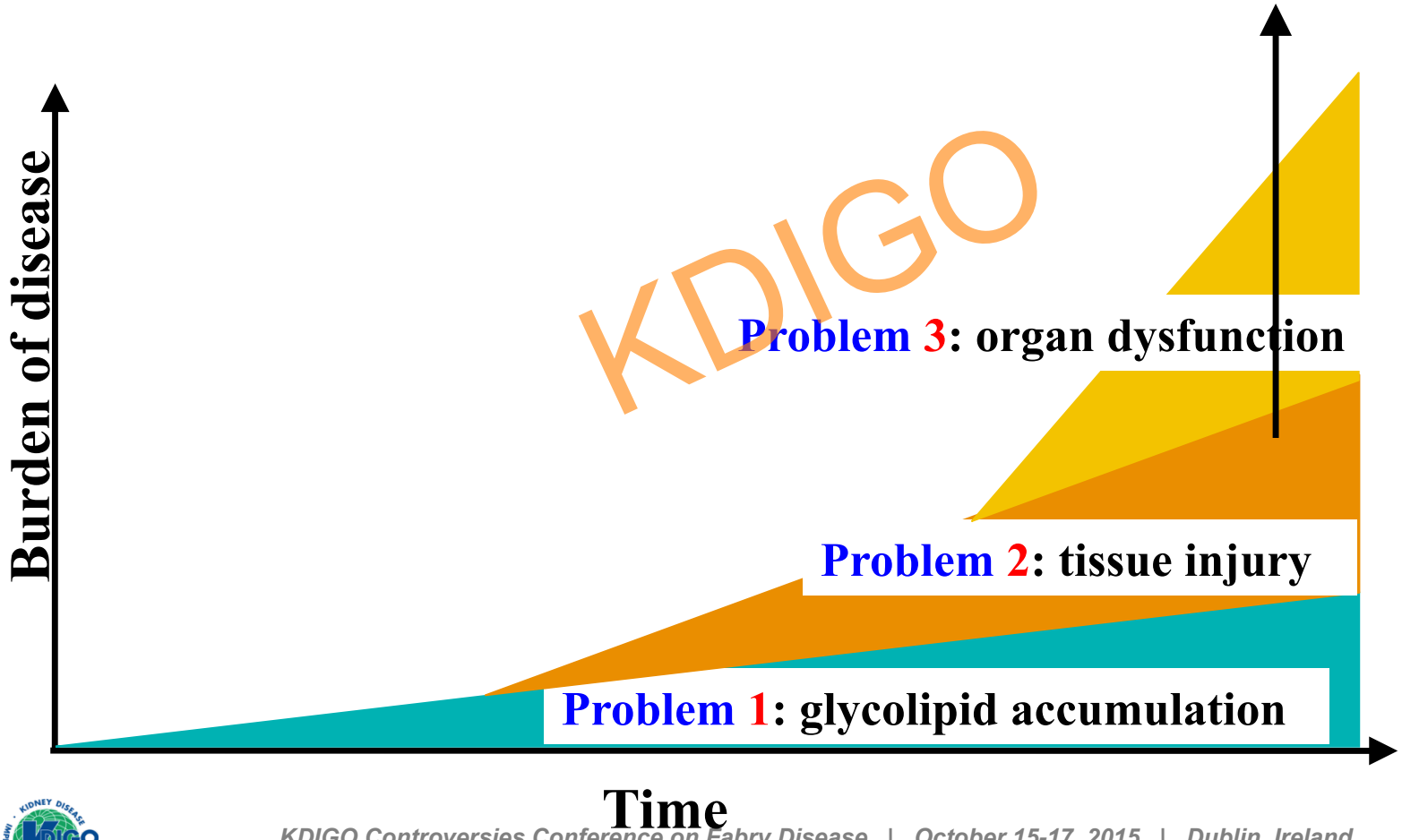
A Fabry patient with UACR 40 mg/day with normal GFR,
That is, having **problem 1** + **problem 2**
May have cell and tissue injury resulting from both
a) Glycolipid accumulation
b) CKD itself
And requires therapeutic intervention on both problems



Eng CM et al. J Inherit Metab Dis 2007;30:184-92.

Pathogenesis of Fabry nephropathy: 3 sequential problems, each requiring a specific therapeutic approach

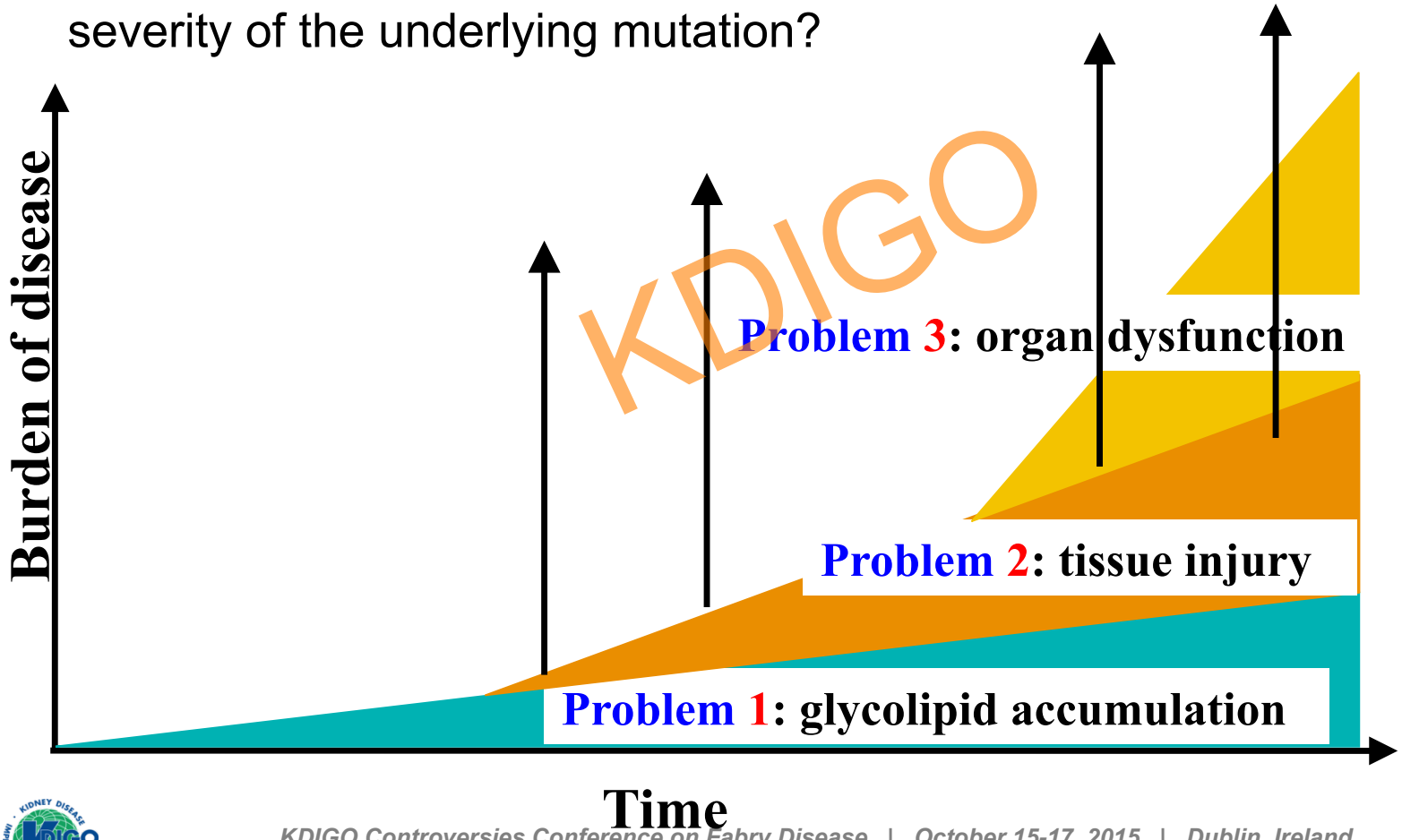
What are the expectations for ERT **alone** when started at this stage?



Eng CM et al. J Inherit Metab Dis 2007;30:184-92.

Pathogenesis of Fabry nephropathy: 3 sequential problems, each requiring a specific therapeutic approach

What conclusions can be drawn from studies of ERT **alone** enrolling patients at different stages of the disease? And even with different severity of the underlying mutation?



Eng CM et al. J Inherit Metab Dis 2007;30:184-92.

What CKD guidelines apply to Fabry patients?

- In adults aged **≥50** years with CKD, we **recommend** treatment with a **statin** (1B)

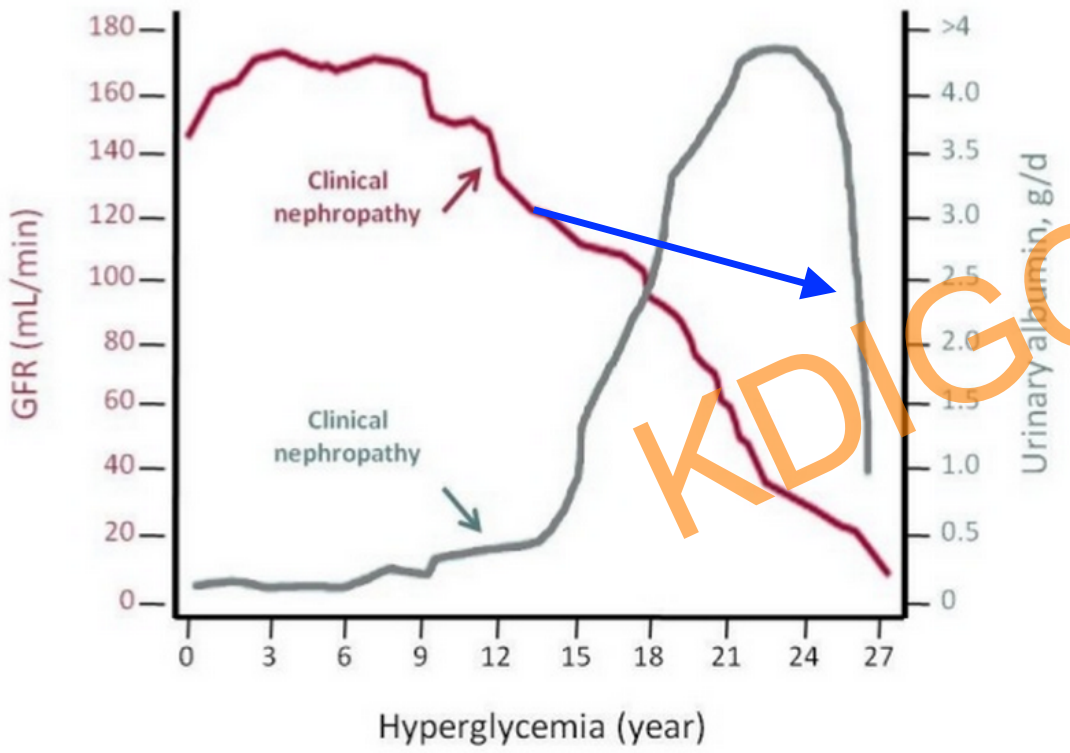
- In adults aged **18–49** years with **CKD**, we **suggest** **statin** treatment in people with **DM** (2A)

Fabry not mentioned….. Should it be considered "**general**" CKD or "**DM-equivalent**" CKD?

SHARP key RCT
Randomized nearly 10,000 patients, 5 year follow-up
Events placebo **13.4**%, statins **11.3**% (17% decrease)

These recommendations do to refer to patients treated with chronic dialysis or kidney transplantation

What basic concepts did we learn from diabetic nephropathy?



1. May lead to **ESRD despite** treating the metabolic defect

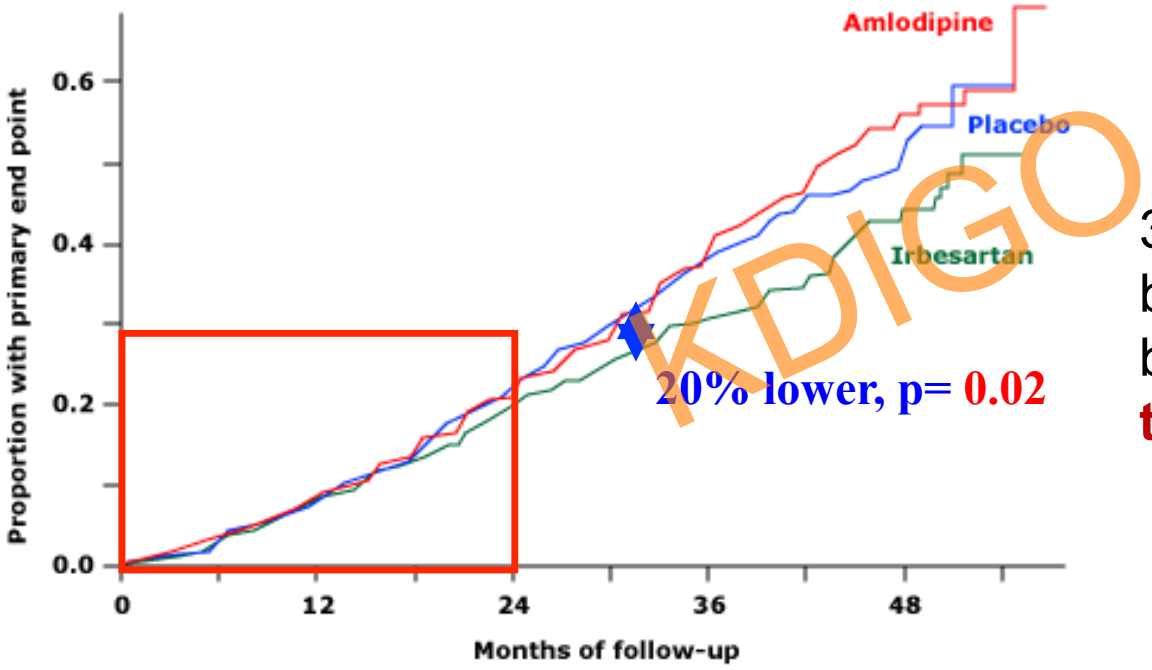
2. **Nephroprotection** slows the loss of GFR

NKDEP National Kidney Disease Education Program

Reference: Adapted from Friedman, 1999

What basic concepts did we learn from diabetic nephropathy?

Irbesartan Diabetic Nephropathy Trial (IDNT): 1715 T2DM hypertensive patients with DN (mean sCr 1.7 mg/dL)



3. But RCTs showing the beneficial effects of RAS blockade enrolled **thousands** of patients!

At **2.6 years**, irbesartan was associated with a 20% lower risk of the primary end point (doubling of sCr, ESRD or death than placebo.

Up-to-date 2014. *Adapted from Lewis EJ, et al. N Engl J Med 2001; 345:851*

Therapy for Fabry nephropathy: 3 sequential approaches

Problem 1: **clear** glycolipids

Decrease synthesis, increase clearance **ERT**

Problem 2: provide add-on tissue protection (**nephroprotection**)

Borrow concepts from diabetic nephropathy

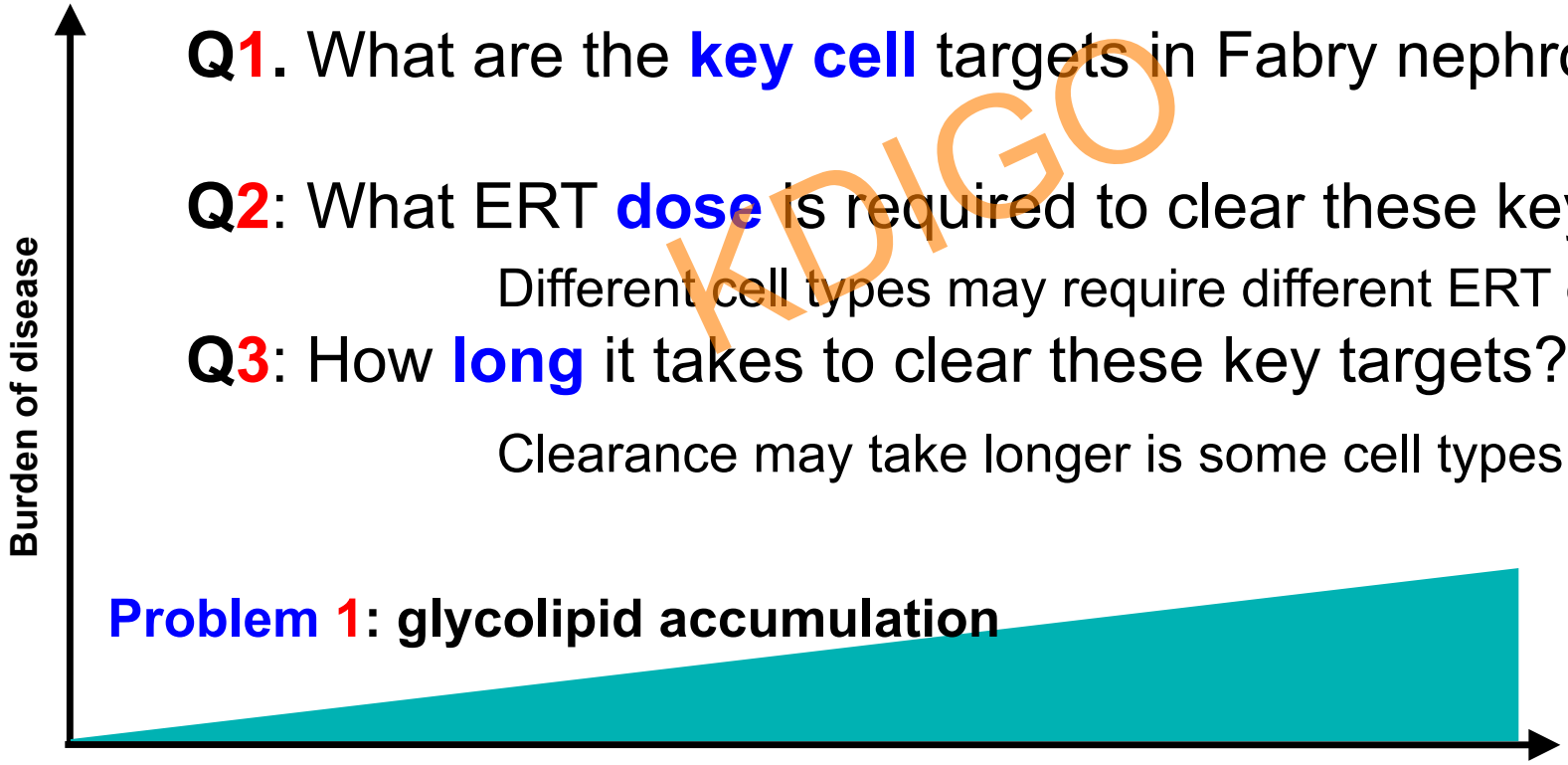
Unravel the **black box** in Fabry nephropathy

Problem 3: **replace** organ function

Therapy for Fabry nephropathy: 3 sequential approaches

Enzymatic defect → Glycolipid accumulation

1. ERT



Q1. What are the **key cell** targets in Fabry nephropathy?

Q2: What ERT **dose** is required to clear these key targets?

Different cell types may require different ERT doses

Q3: How **long** it takes to clear these key targets?

Clearance may take longer is some cell types

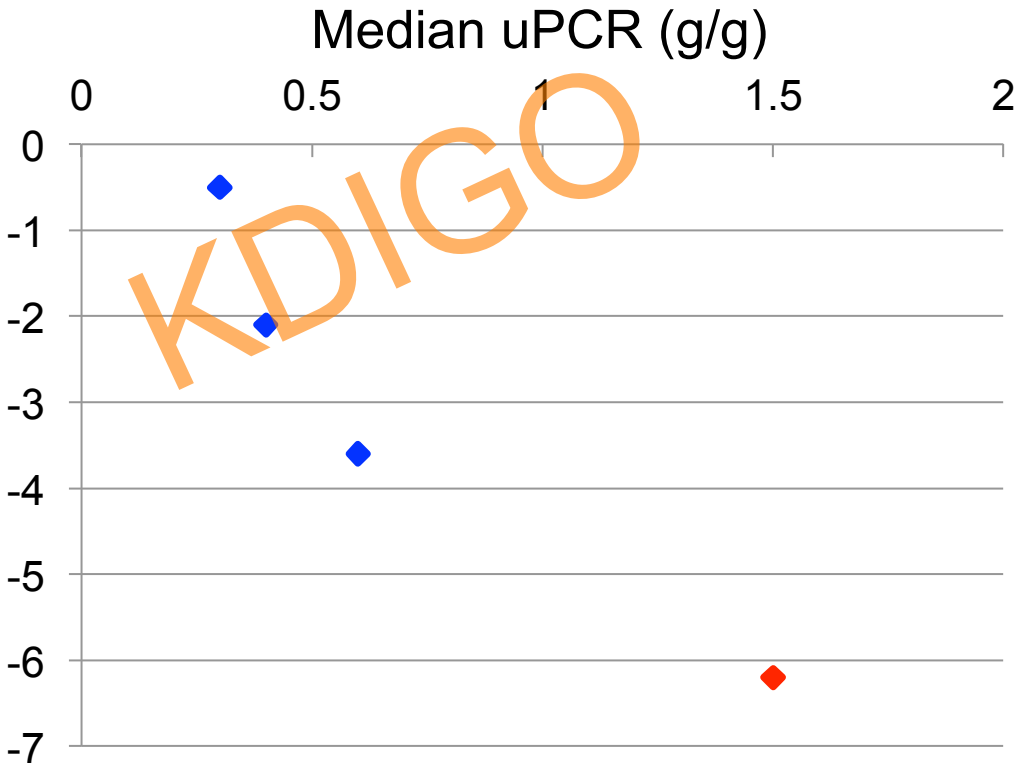
Eng CM et al. J Inherit Metab Dis 2007;30:184-92.

What is the role of albuminuria in Fabry nephropathy?

- Albuminuria (proteinuria ≈ albuminuria x 2) is a major **risk factor** for **progression** of CKD in Fabry disease

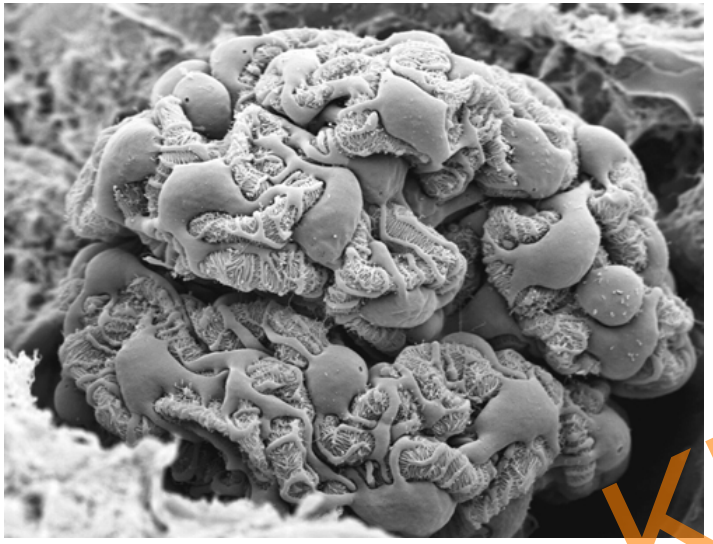
Nat history data

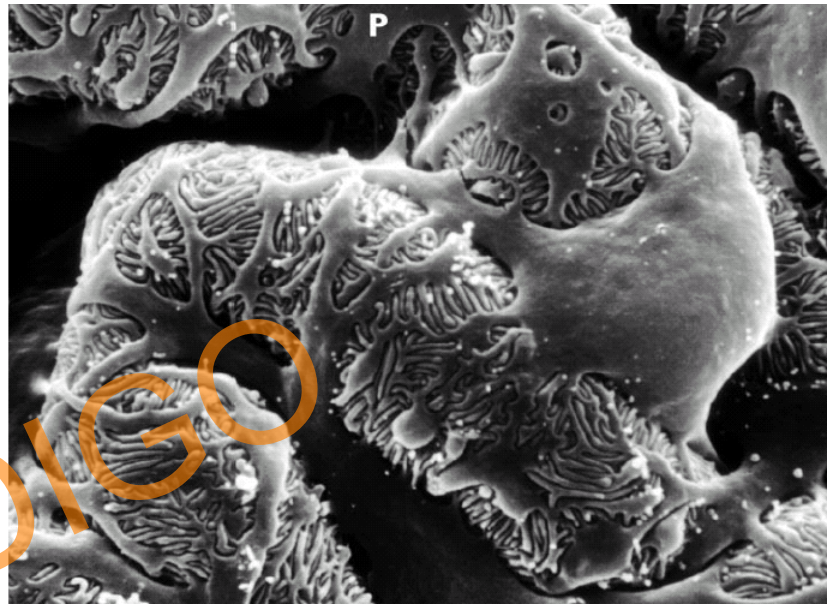
Median eGFR slope (ml/min/year)

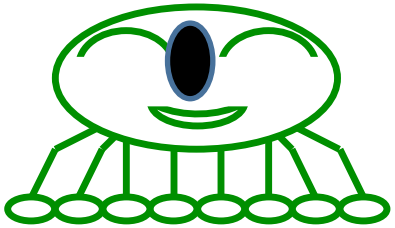


Warnock NDT 2012, Wanner CJASN 2010

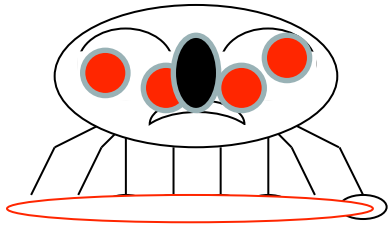
What is the meaning of albuminuria in Fabry nephropathy?





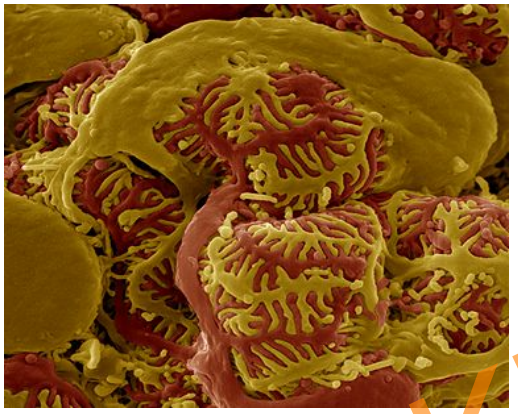


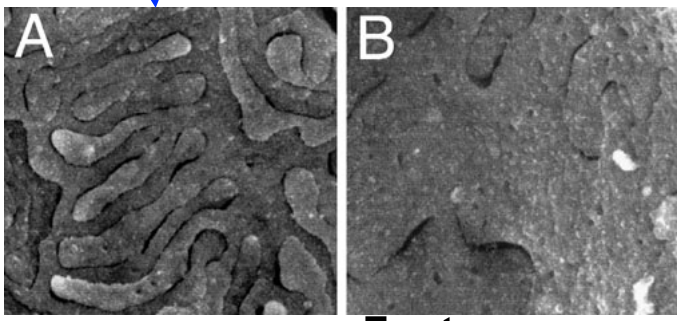
Happy, healthy podocyte



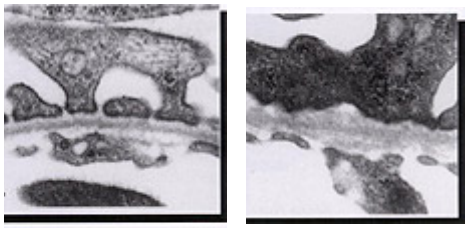
Not-so-happy Fabry podocyte full of deposits

Albuminuria usually indicates podocyte injury





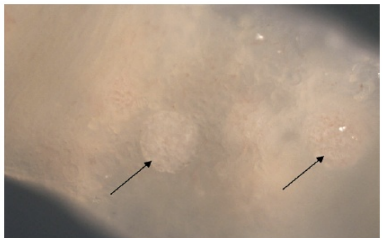
Foot process
effacement



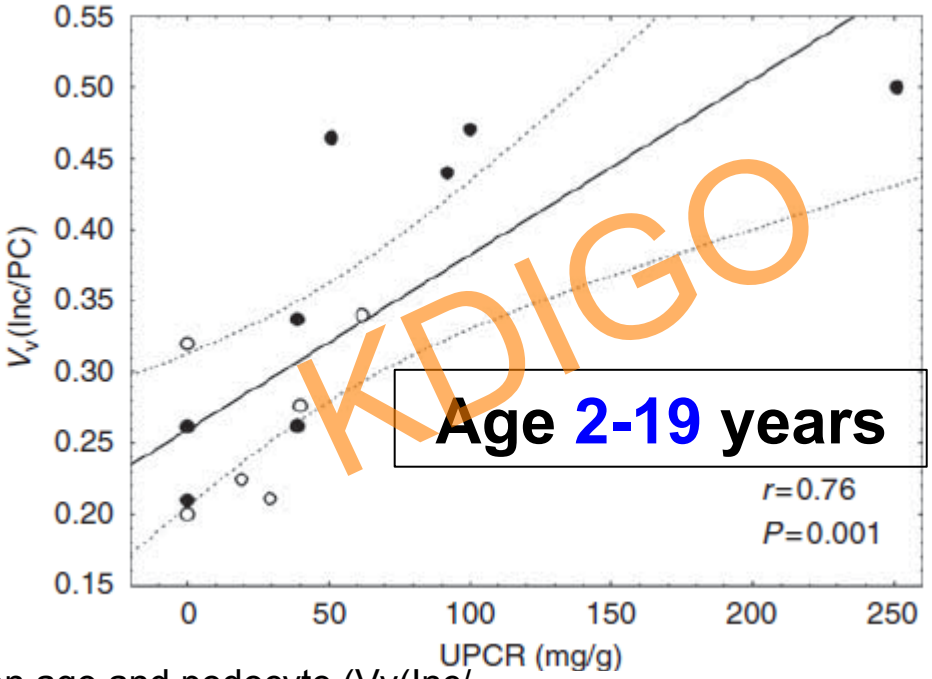
Foot process
effacement

Ramson et al. U Michigan www-scf.usc.edu/~thecc/ImageStorage/podocyte.jpg

Podocyte inclusions and albuminuria in Fabry



Podocyte inclusions vs proteinuria



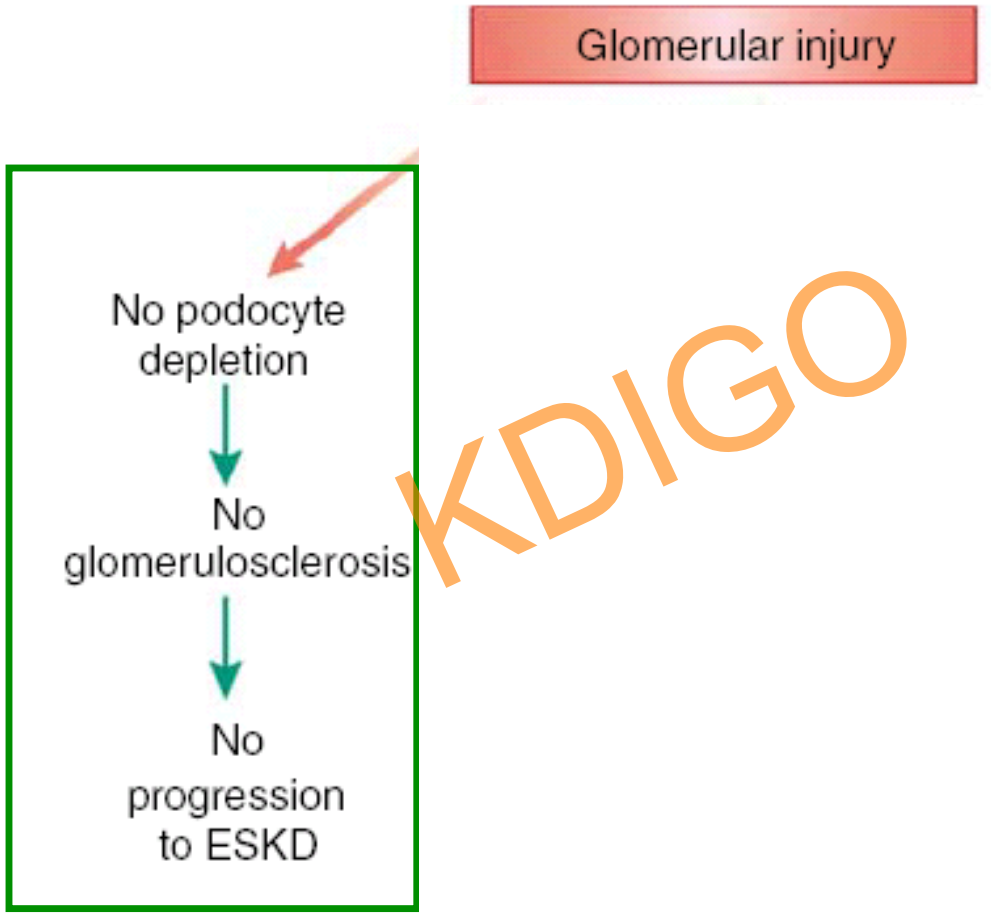
No relationship between v(Inc/Endo) and proteinuria

Relationship between age and podocyte (Vv(Inc/PC)), and endothelial cell (Vv(Inc/Endo)) GL-3 fractional volume of inclusions per cytoplasm

Segmental foot process effacement in **all glomeruli**

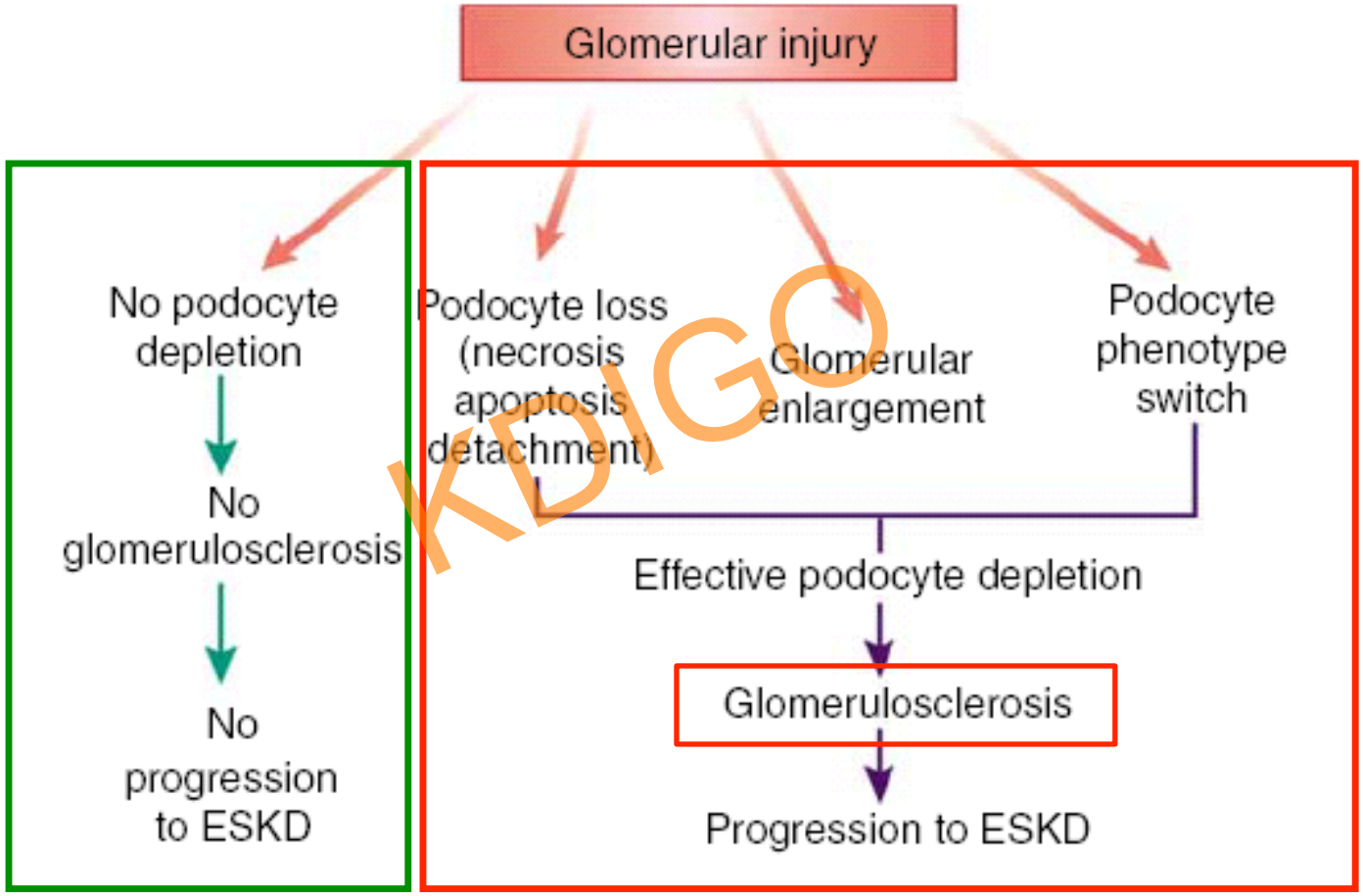
Tondel et al. AKD 2009. Najafian et al. KI 2010

The podocyte depletion hypothesis



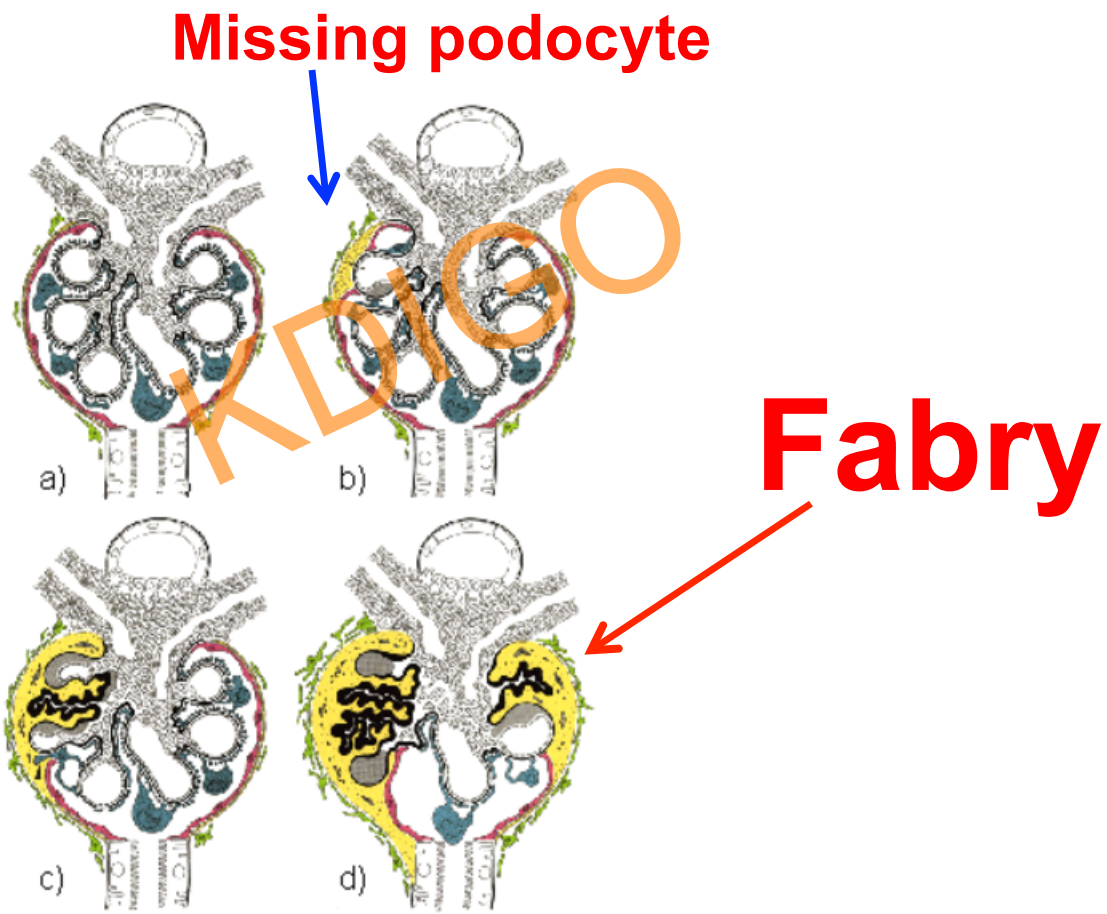
Wiggins 2007

The podocyte depletion hypothesis



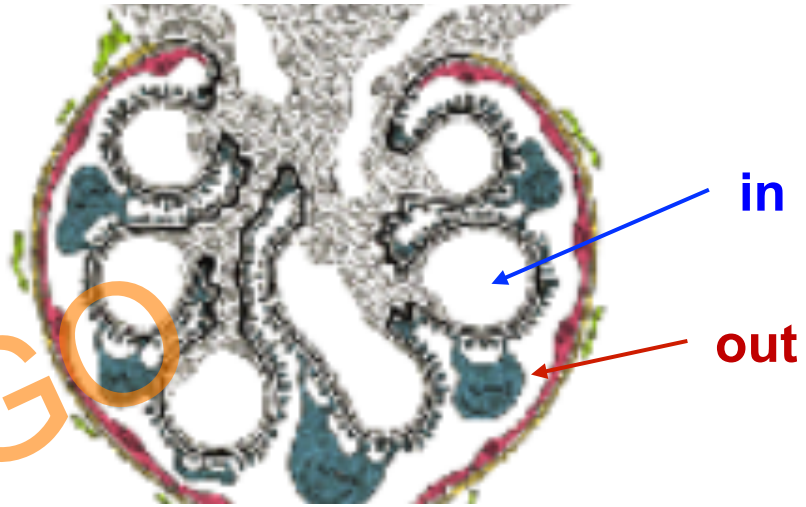
Wiggins 2007

Podocyte loss is known to result in glomerulosclerosis (glomerular fibrosis)

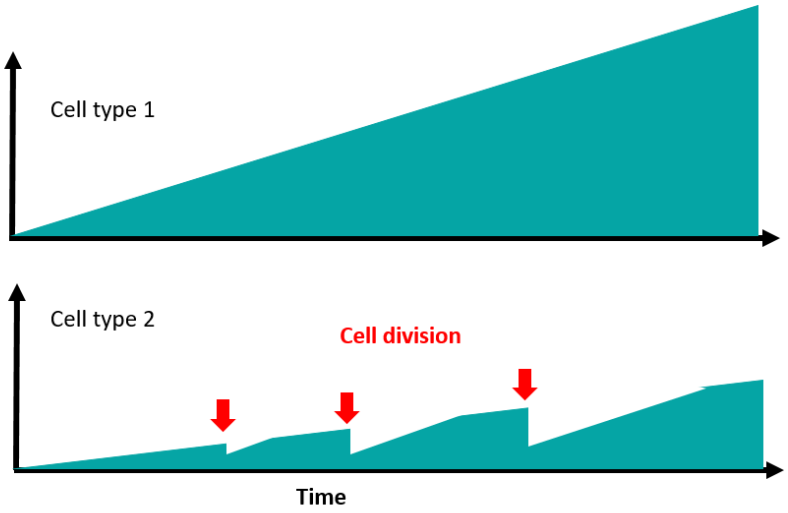


The two problems with podocyte clearance in Fabry nephropathy

1. They are **outside** the vessels



2. They are very **long-lived** cells, with little if any turnover

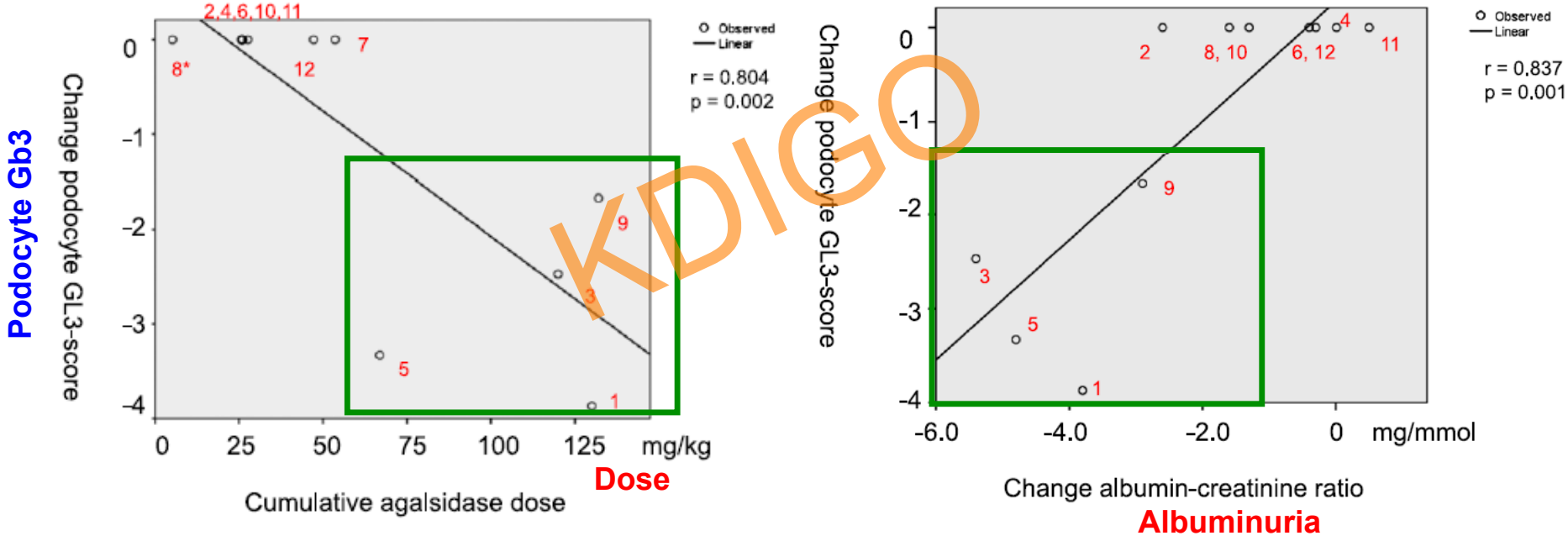


ERT response of podocytes and albuminuria

renal biopsy befrore and after 5 years of ERT in young patients on agalsidase alpha or beta

The **higher the cumulative dose**, the **better the podocyte clearance**

The **better the podocyte clearance**, the **more reduction in albuminuria**



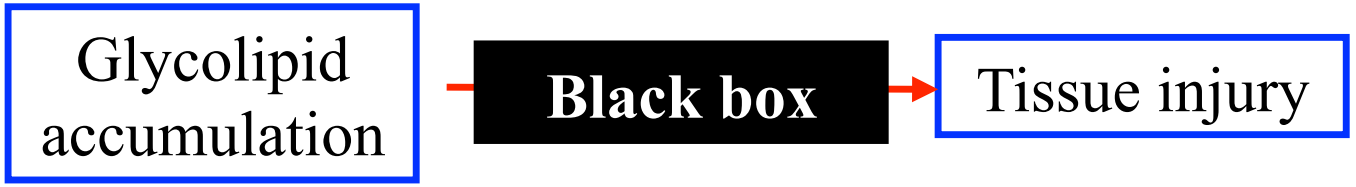
highly significant correlation between **podocyte clearance and cumulative agalsidase dose** (r=0.804; **P=0.002**)

Tøndel C, J Am Soc Nephrol. **2013** Jan;24(1):137-48.

Summary so far

- While it is relatively easy to clear endothelial cells, it may take years and high doses of ERT to clear podocytes
- Clearance of podocytes was associated with improved albuminuria
- Since albuminuria is a marker for disease progression, podocytes appear to be key target cells in the kidney

Let´s try to fill the black box for podocytes!

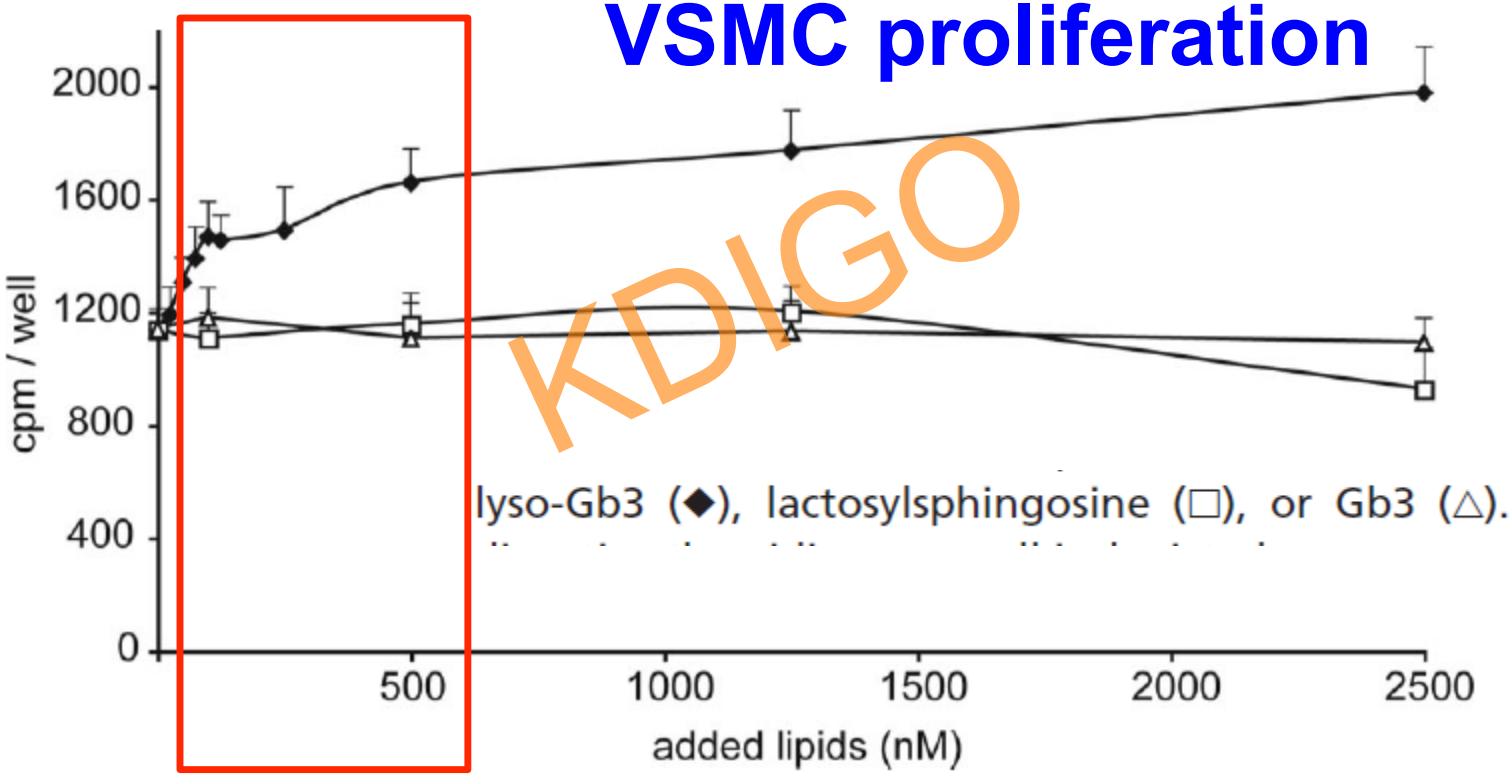


The molecule: Lyso-Gb3

Elevated globotriaosylsphingosine is a hallmark of Fabry disease

Johannes M. Aerts*†, Johanna E. Groener*, Sijmen Kuiper*, Wilma E. Donker-Koopman*,

VSMC proliferation



Fabry disease circulating lyso-Gb3 concentration range

PNAS 2008

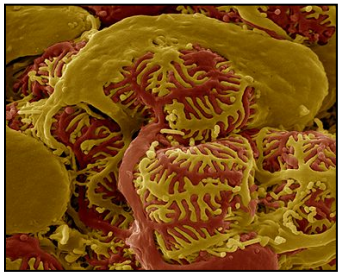
The cell type: cultured human podocytes

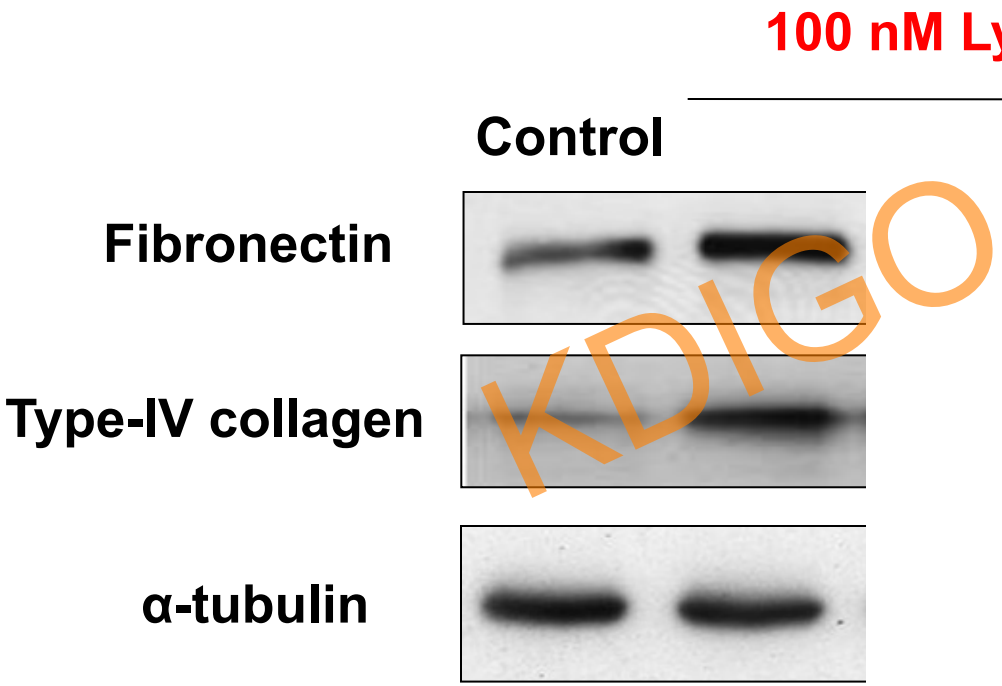
The results: At concentrations found in the circulation of Fabry patients, lyso-Gb3 reproduces some of the effects of high glucose in podocytes

- Secretion of **TGF-β1** leading to autocrine stimulation of **extracellular matrix** secretion
- Activation of **Notch1** leading to **inflammatory** and **pro-fibrotic** responses

Sanchez-Niño et al NDT 2011 and Hum Mol Genet.2015

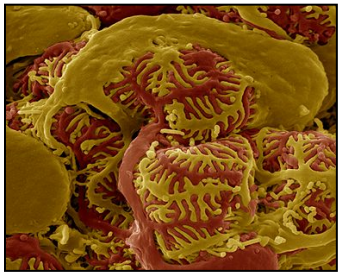
Vitamin D receptor activators downregulate fibrosis mediators induced by lyso-Gb3 in cultured podocytes

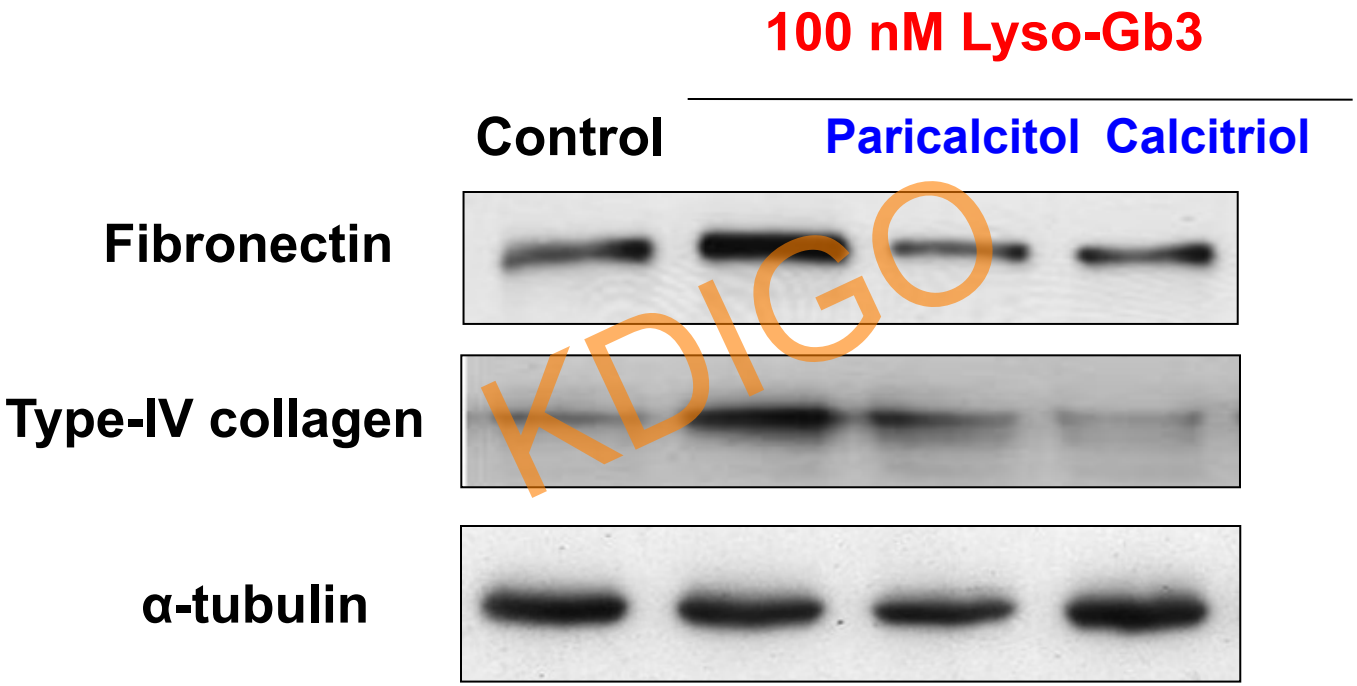




Sanchez-Niño et al, NDT 2011

Vitamin D receptor activators downregulate fibrosis mediators induced by lyso-Gb3 in cultured podocytes



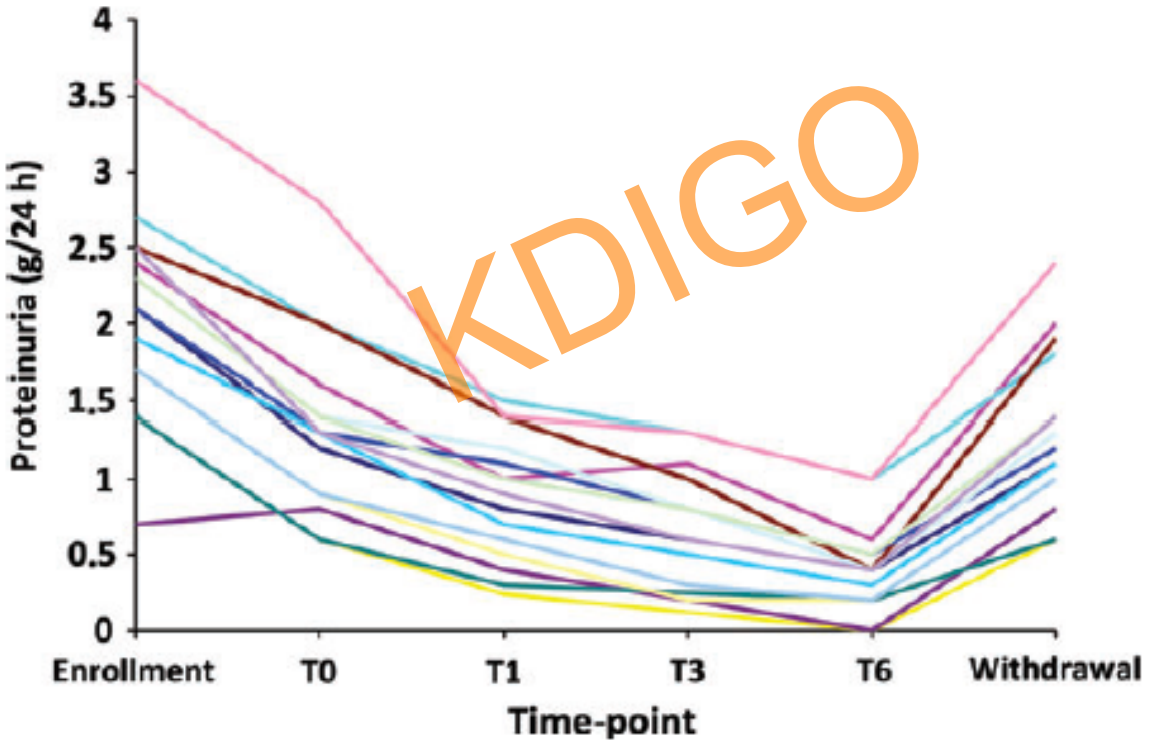


Sanchez-Niño et al, NDT 2011

May this help Fabry patients?

Paricalcitol antiproteinuric in Fabry nephropathy

25-OH-Vitamin D (ng/mL) 22.17 ± 11.2
RAS targeting: 0.7/patient
Paricalcitol 1 μg/d



Pisani et al. NDT 2014

Evolving paradigm of Fabry disease

The clean-up the pipes paradigm

Problem

Glycolipids **obstruct** pipes (arteries)

Solution

ERT **cleans** pipes

Result

Problem solved

The leaking pipe paradigm

Glycolipids lead to **obstructed and leaking** pipes (albuminuria)

ERT **cleans** pipes

Pipes clean but s… broken!!!

Take home message

- The issue in Fabry disease is **not just glycolipid accumulation**... At least for the majority of patients currently on ERT throughout the world (mean age at start of ERT 40 years in Fabry Registry)
- While clinical trials showed that ERT efficienty clears endotheial cells, clearance of additional cell types, such as **podocytes** may be required for organ protection... And this may require **higher ERT** doses
- Different forms of tissue injury may require differet **add-on** therapeutic approaches
- The fact that **lyso-Gb3**, which is usually not normalized by ERT, elicits adverse cellular responses in podocytes suggests that normalization of lyso-Gb3 may be **a therapeutic target** and that as long as that is not achieved, patients may require add-on tissue protective therapy

The bathtub paradigm of glycolipd accumulation

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Lyso-Gb3 and other cell types

- lysoFb3
- Complete replacement: insulin vs pancreas tx
- Ckd: dialysis and uremia

- Open the drainage
  - Replace the enzyme
  - “repair” the enzyme
- Close the tap

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