The pathophysiology and retention of gadolinium

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Objectives

- ***Elucidation*** *of the mechanisms of gadolinium-based contrast agent-induced toxicity is an* ***active area of investigation***

- *The focus of this presentation is the work in my laboratory concerning the* ***mechanisms*** *of gadolinium-based contrast agent* ***toxicity*** *and how this is* ***manifested systemically***

- *A* ***model*** *has been* ***established*** *in rodents*

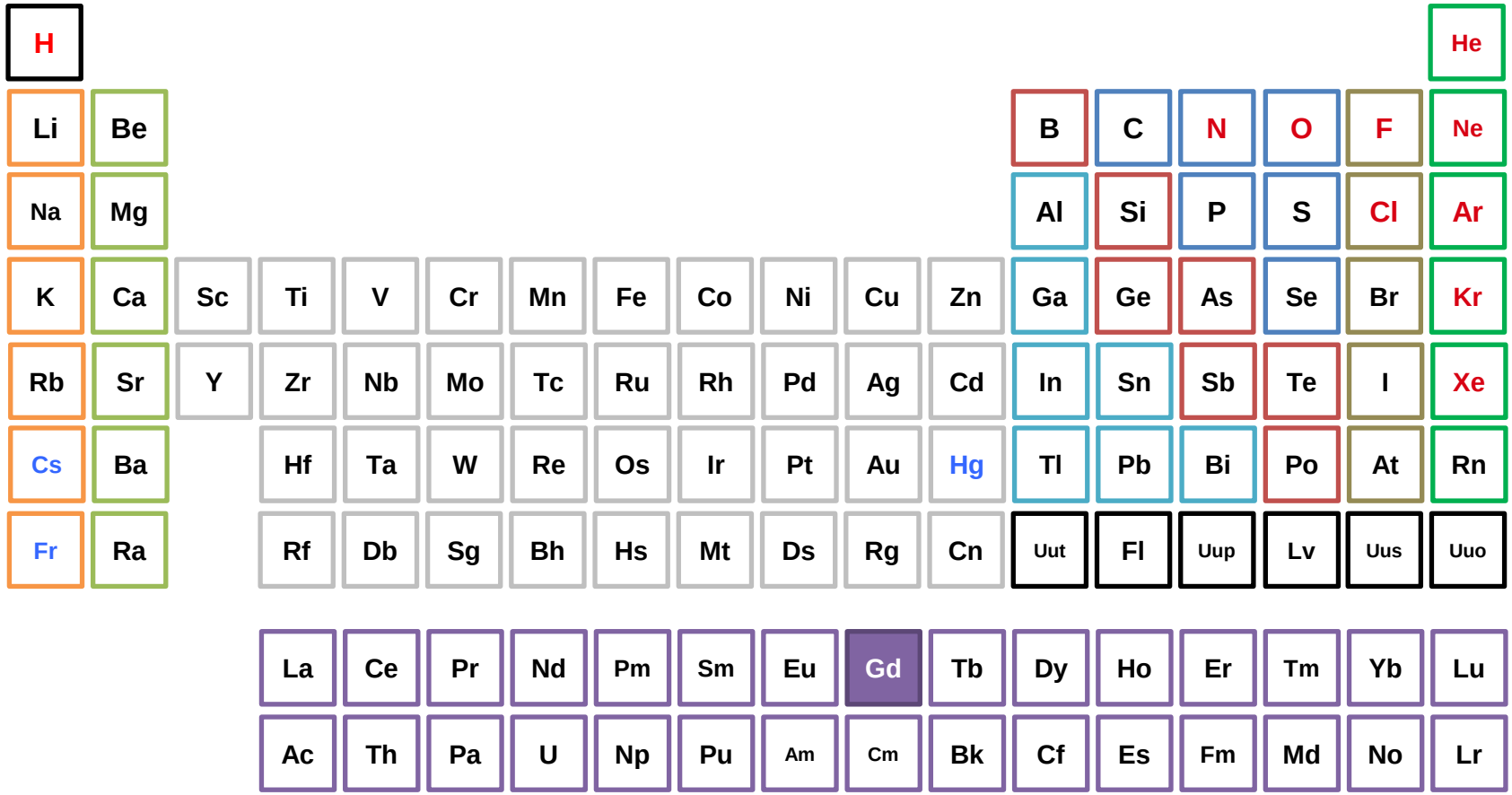
- *One gadolinium-based contrast agent has been used in these experiments, Omniscan (gadodiamide/caldiamide), but the* ***findings*** *may be* ***applicable*** *for the other gadolinium-based contrast agents*

Overview

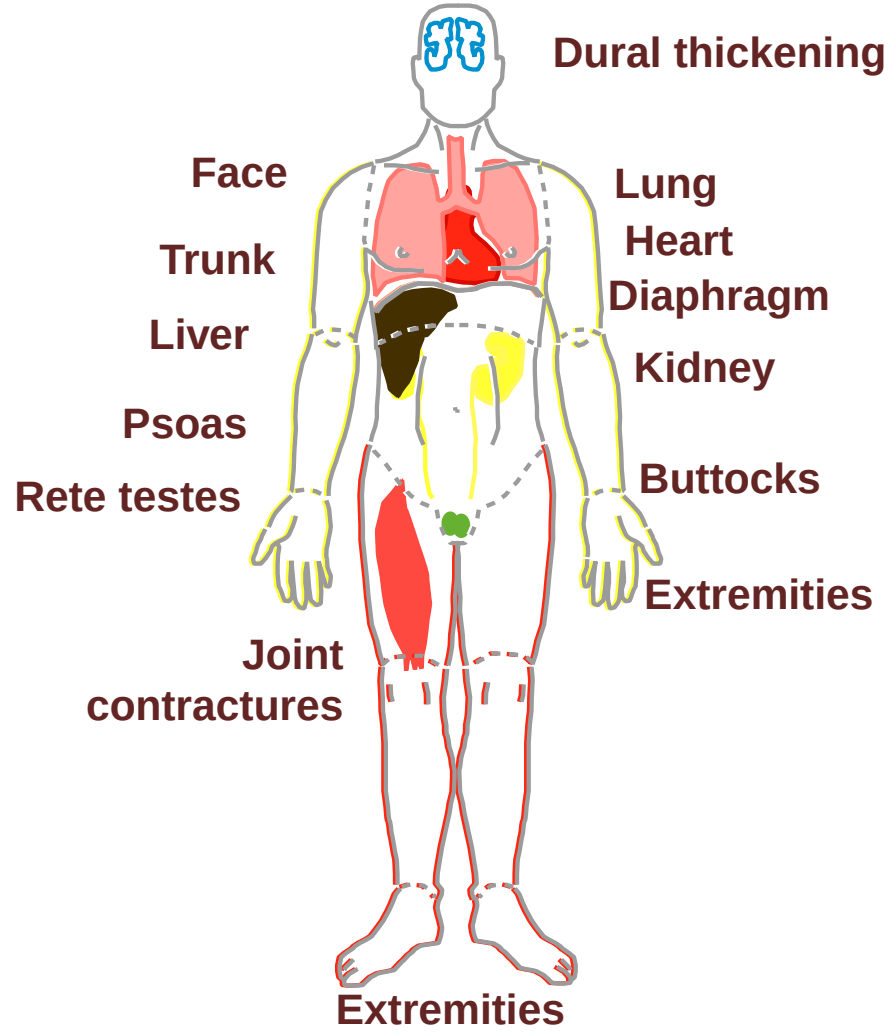
- *There are many different chemical formulations of **gadolinium-based contrast agents** used in **magnetic resonance imaging***
- ***Gadolinium-based contrast agents** have been linked to 'nephrogenic' **systemic fibrosis cases***
- *There is **evidence** that **gadolinium** is **deposited** in the **central nervous system***
- *The central nervous system **toxicity** warrants **more study***
- ***Gadolinium-based contrast agents** are biologically **active***
- ***Little** is known about the **metabolism** of **gadolinium-based contrast agents,** their **biologic effects,** and the **implications** of **retained** gadolinium*
- *The **toxic effects** and mechanisms of **gadolinium-based contrast agents** is a major **gap** in our knowledge*
- ***Understanding** the pathophysiology of **gadolinium-induced systemic fibrosis** will be **critical** for **future discoveries***
- *How gadolinium from **different contrast agents** distributes throughout the body is an **active area** of investigation*

Wagner B et al, *Adv Chronic Kidney Dis*, 2017
Wagner B et al, *Am J Physiol Renal Physiol*, 2016

The periodic table of elements

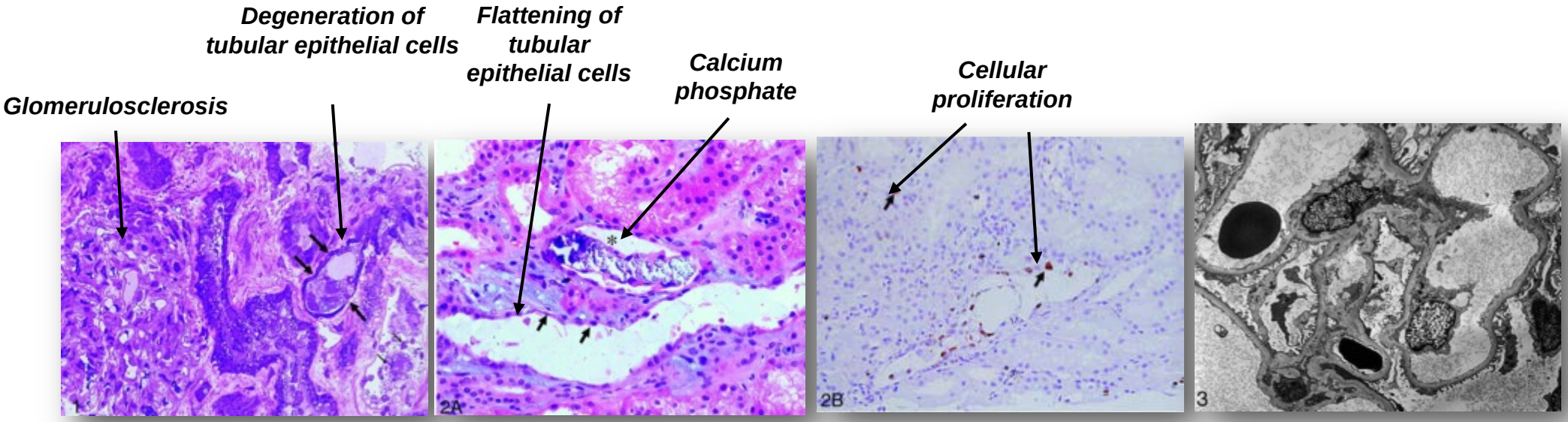


‘Nephrogenic’ systemic fibrosis, a man-made disease caused by magnetic resonance imaging contrast agents



Girardi M et al, *J Am Acad Dermatol*, 2011

Gadolinium-based contrast agents can be acutely nephrotoxic *in humans*



Toluidine blue stain - *Kidney*

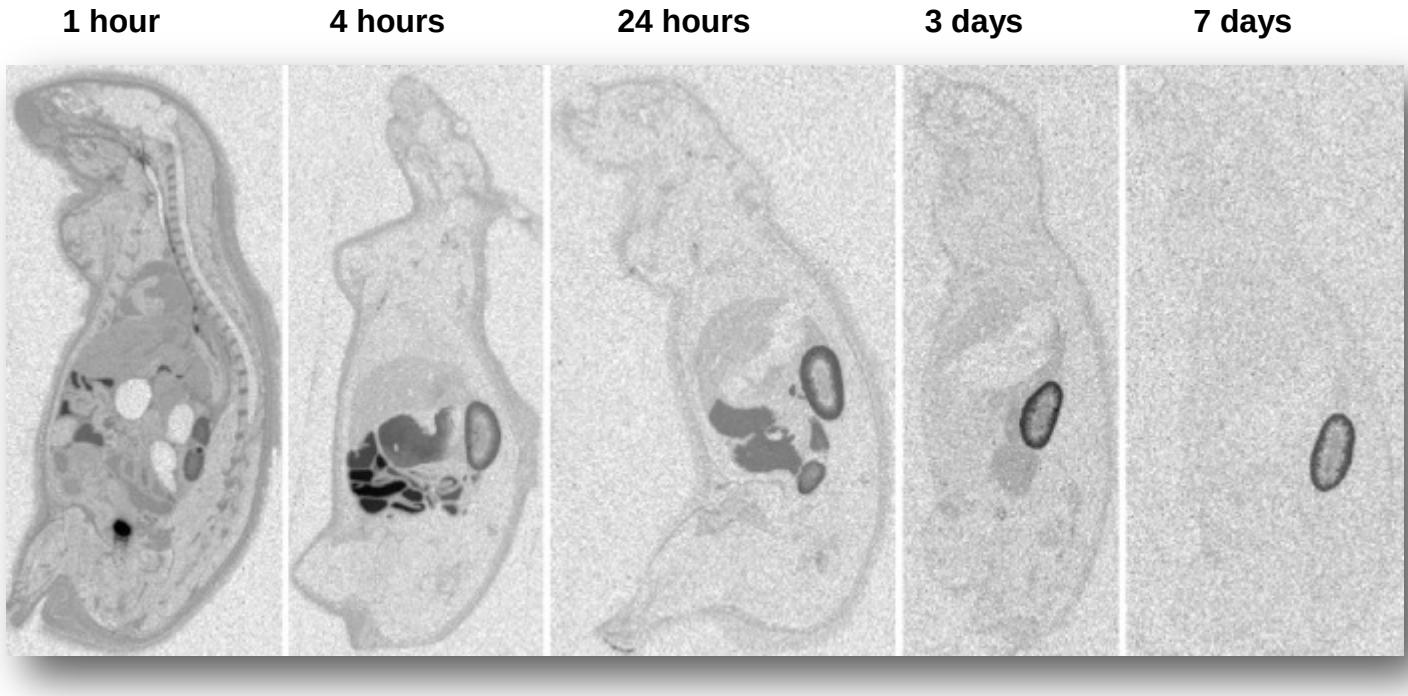
H&E stain - *Kidney*

Immunostain - *Kidney*

Electron microscopy - *Kidney*

Akgun H et al, *Archives of Pathology & Laboratory Medicine*, 2006

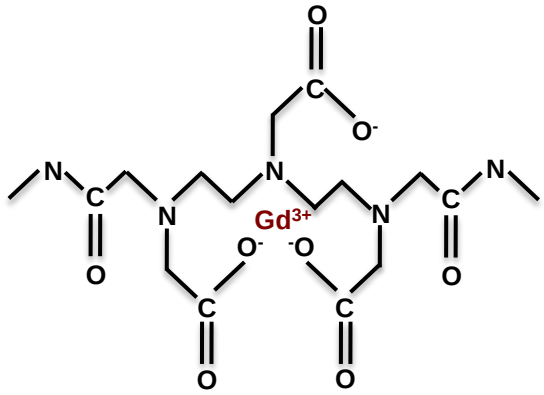
Widespread biodistribution of gadolinium-based contrast; remnants in the kidney cortex up to 7 days after a single, clinically-relevant injection in rat



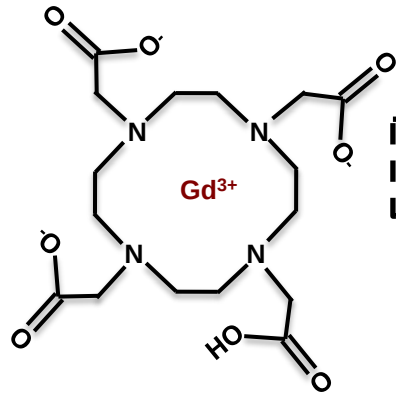
Quantitative whole-body autoradiography

Kindberg GM et al, *Eur Radiol,* 2010

Differential effects of gadolinium-based contrast agents in rats

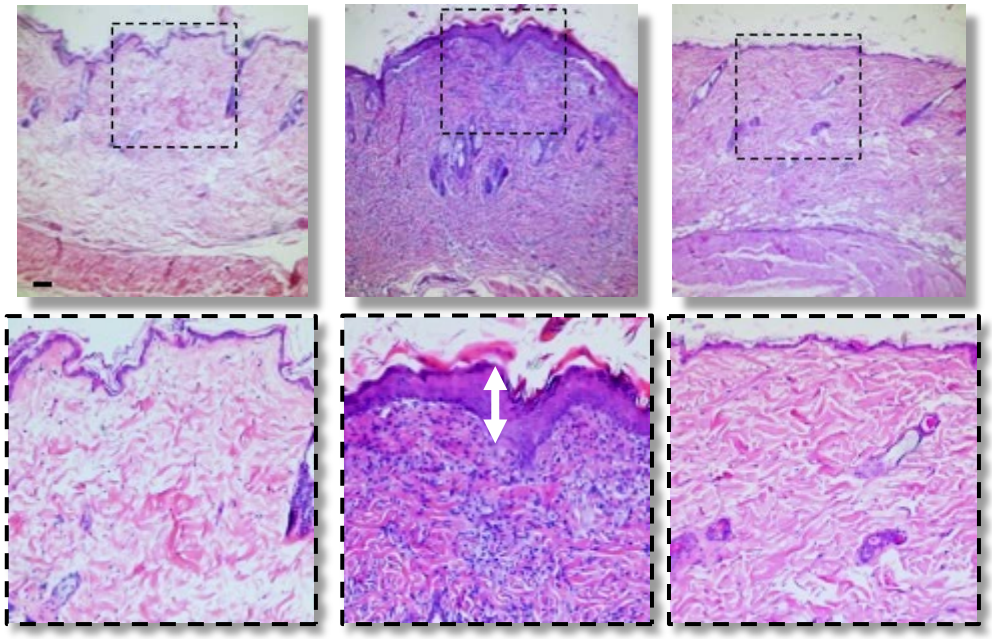


Omniscan ***(gadodiamide >> caldiamide)***



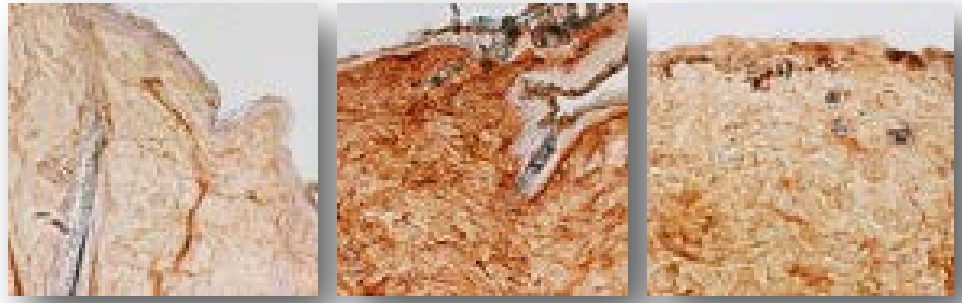
ProHance ***(gadoteridol)***

Control **Gadodiamide** **Gadoteridol**



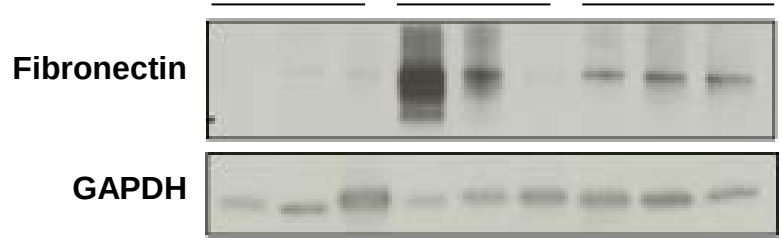
H&E *staining - Skin*

Control **Gadodiamide** **Gadoteridol**



Immunohistochemical *staining – Skin fibronectin (marker of fibrosis)*

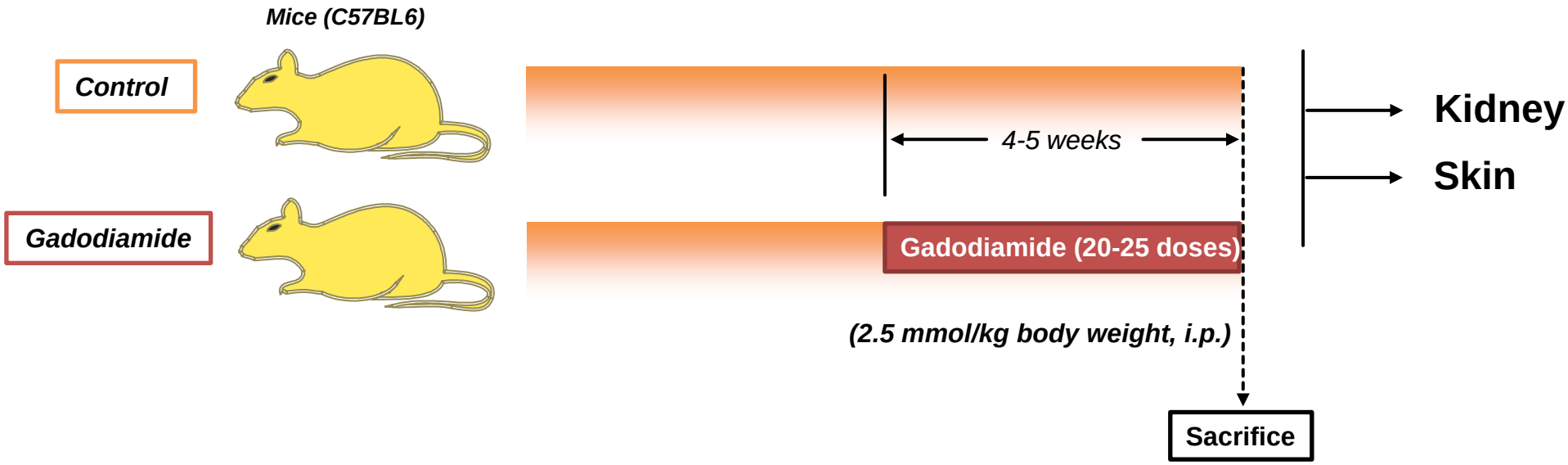
Control **Gadodiamide** **Gadoteridol**

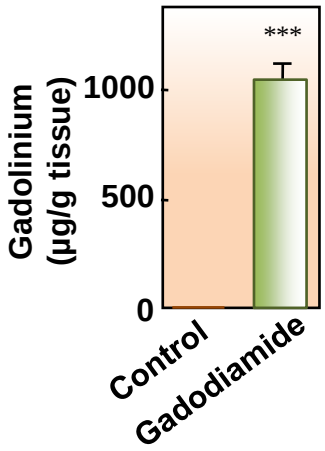


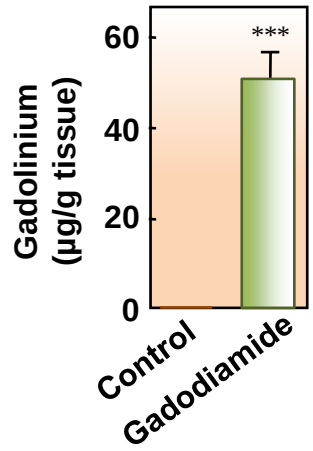
Immunoblot *- Skin*

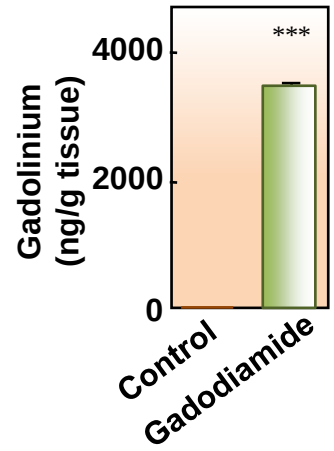
Do C, Barnes JL, Tan C, Wagner B, *Am J Physiol Renal Physiol*, 2014

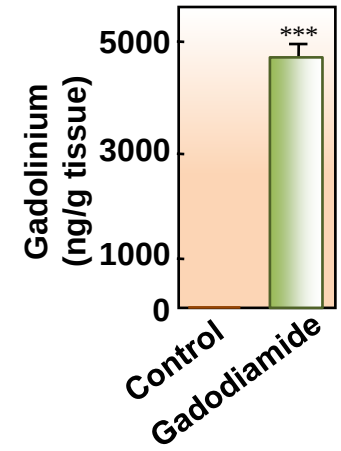
Gadodiamide administration in mice with *normal renal function*



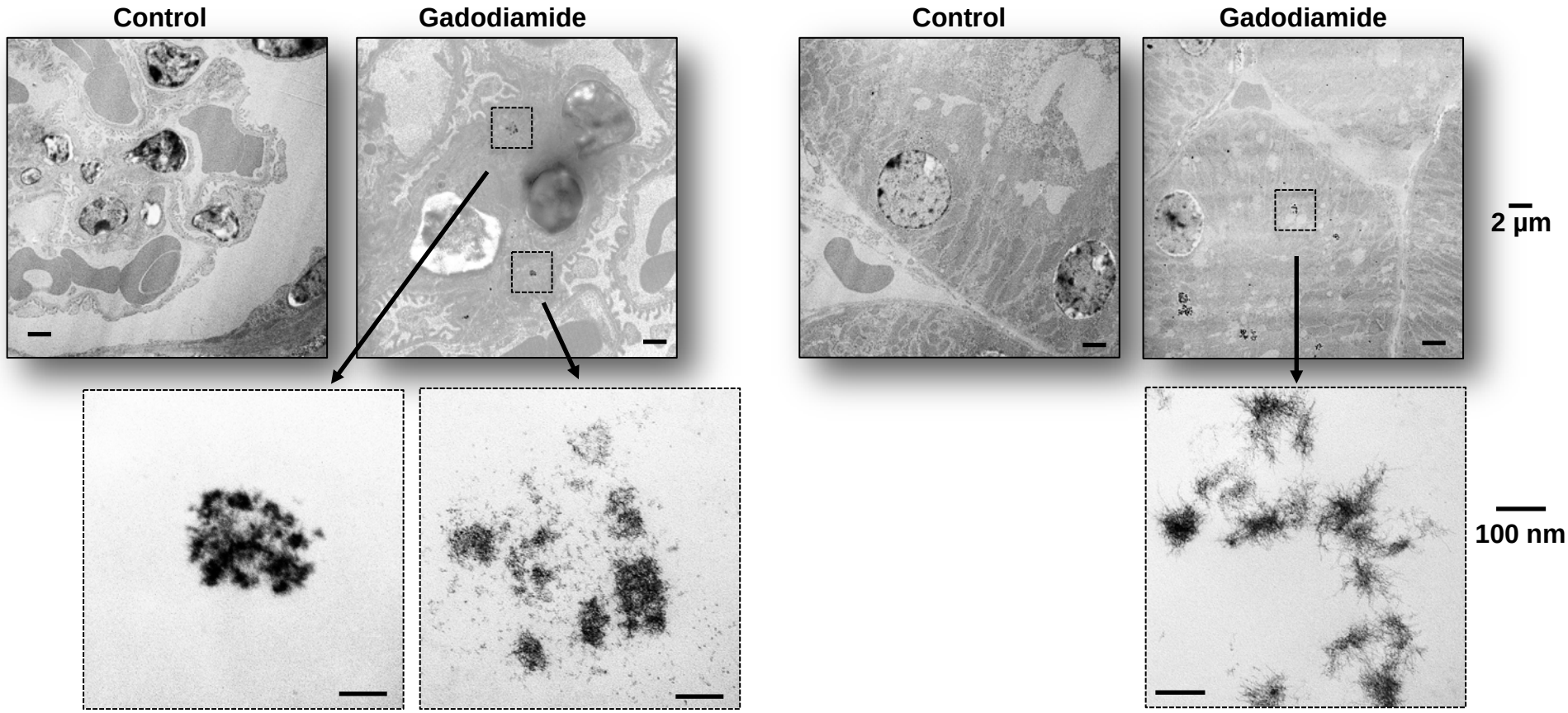








Electron microscopy shows *electron-dense deposits* in the kidneys of gadodiamide-treated mice *with normal renal function*



Transmission electron microscopy *- Glomeruli*

Transmission electron microscopy *- Tubules*

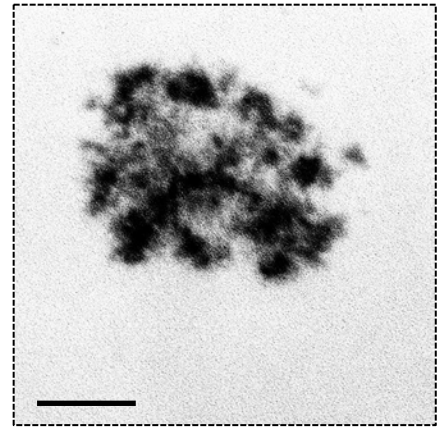
Wagner laboratory, unpublished

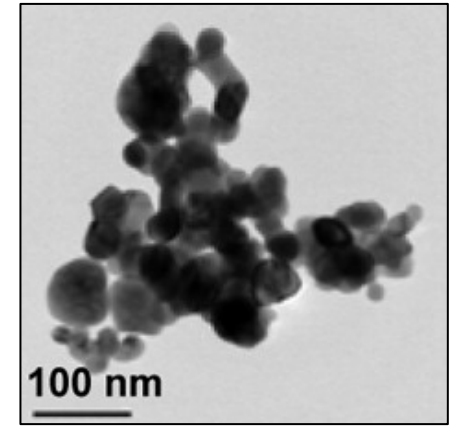
The renal deposits resemble Gd_2O_3 disordered mesh-like nanowire/nanoparticle aggregates *in vitro*

Gadodiamide

Gd_2O_3

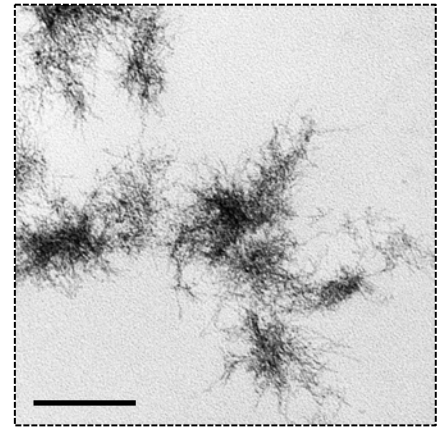
Transmission electron microscopy *- Mesangium*



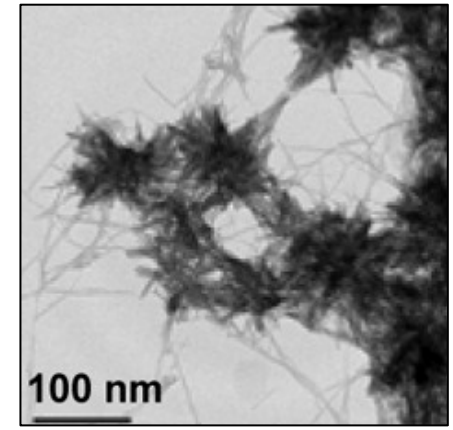


Transmission electron microscopy *- Water*

Transmission electron microscopy *- Tubule*



100 nm

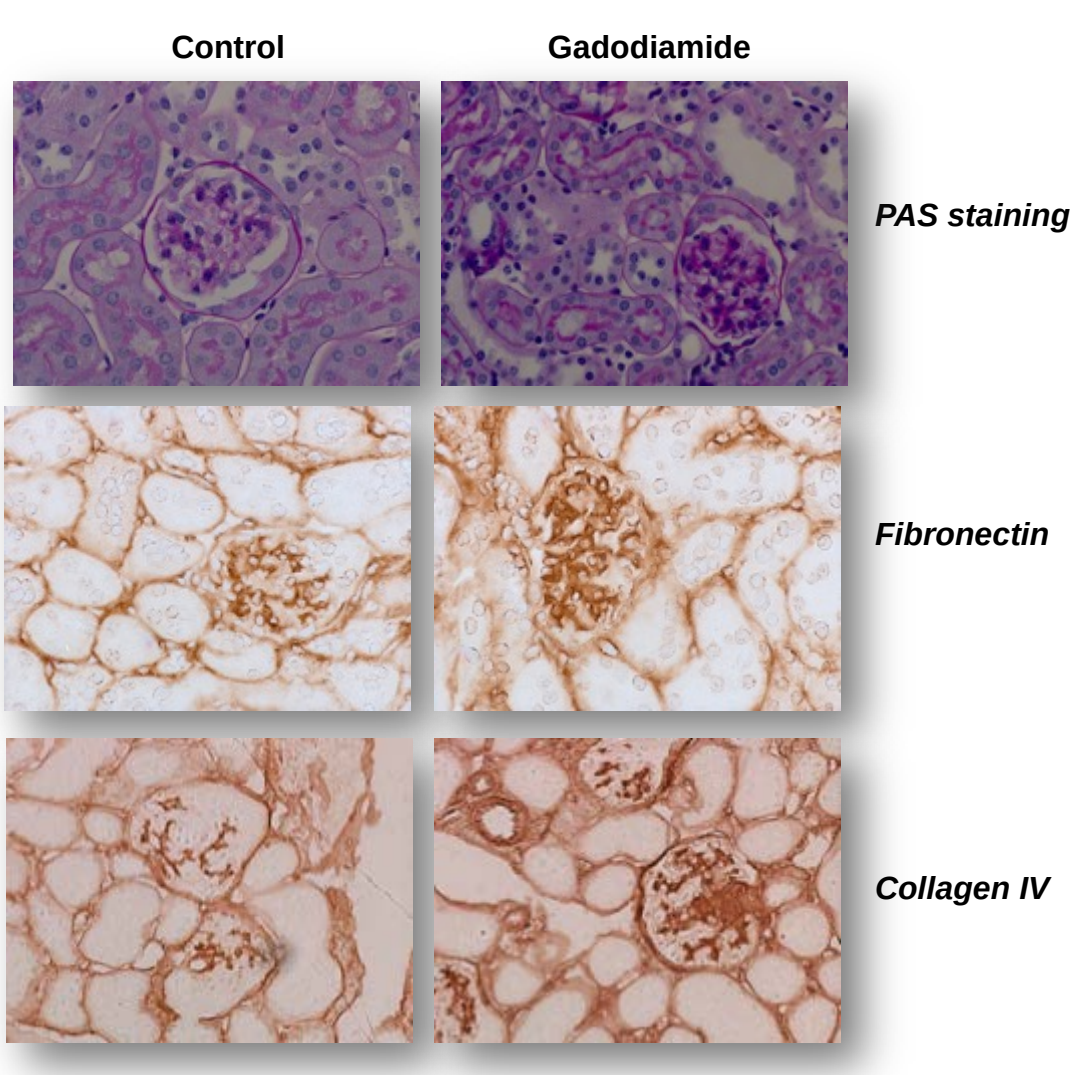


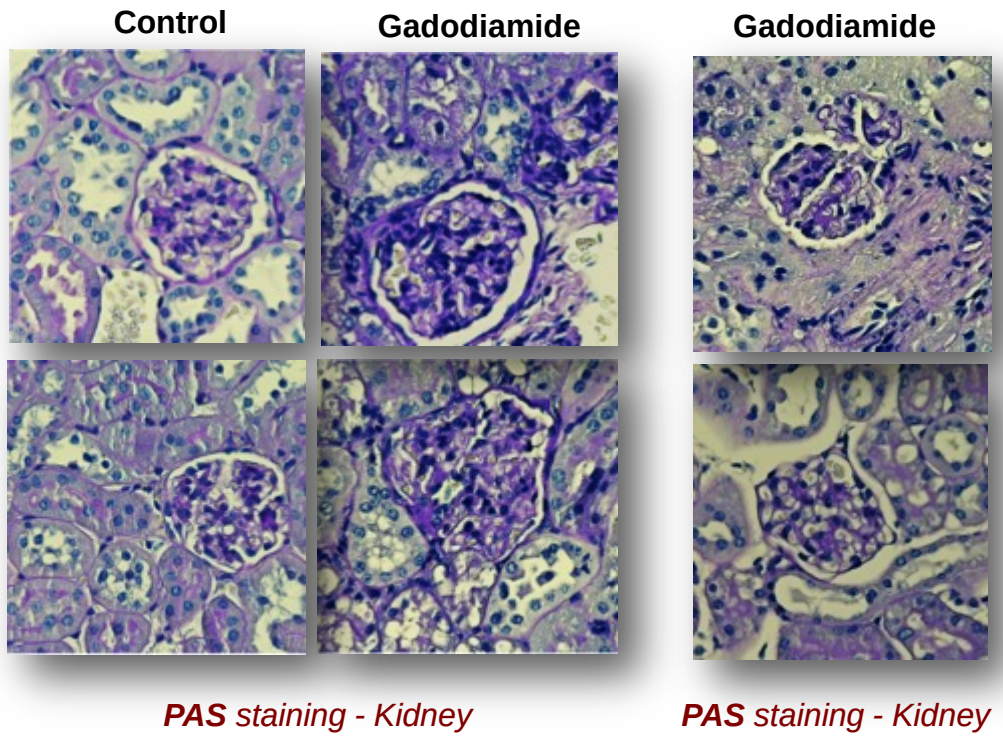
Transmission electron microscopy *– Phagolysosomal-simulated fluid*

Wagner laboratory, unpublished

Li R et al, *ACS Nano*, 2014

Gadodiamide induces renal fibrosis in mice





***PAS** staining - Kidney*

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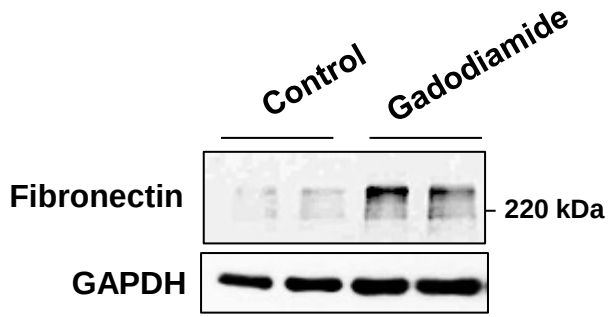
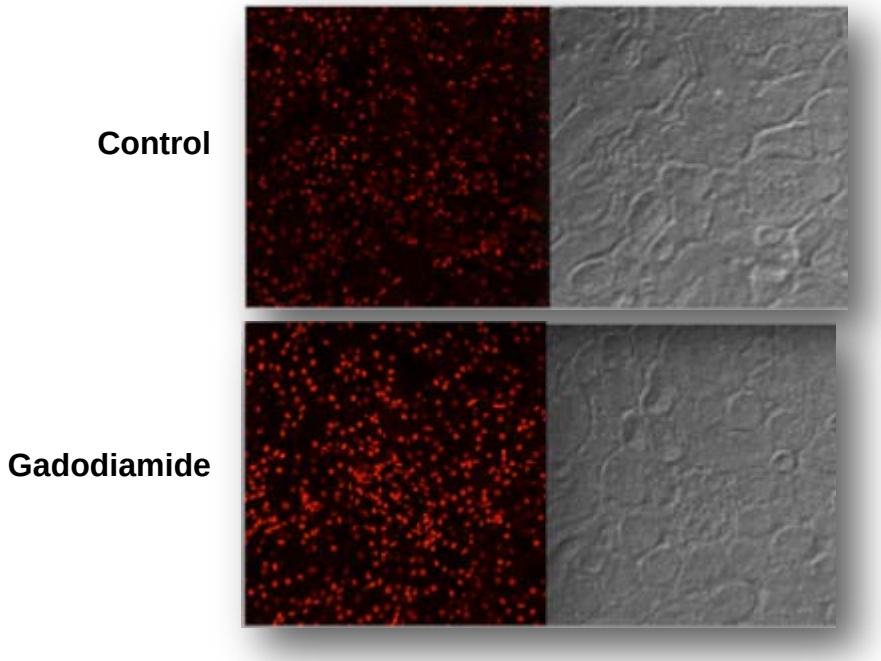


***Immunoblot** - Skin*

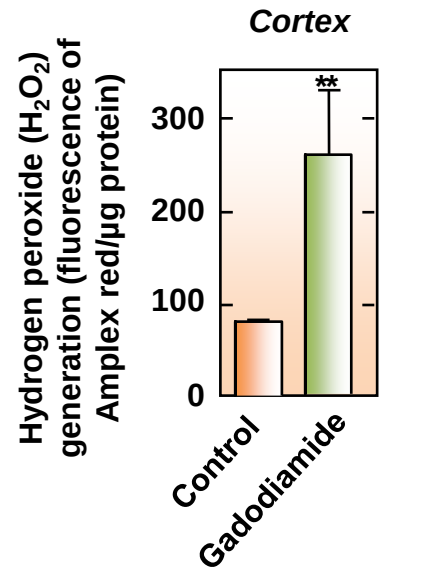
Wagner laboratory, unpublished

Gadodiamide induces oxidative stress in the mouse kidney



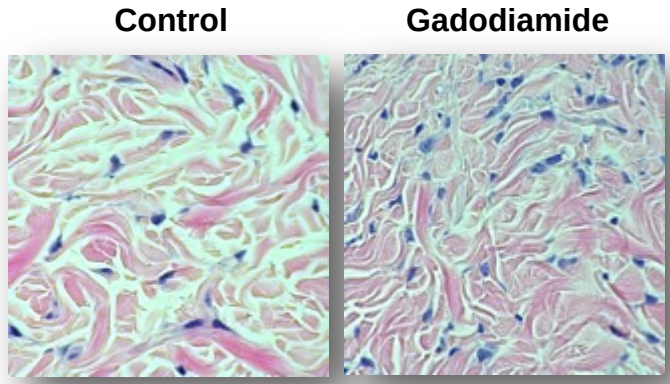
DHE fluorescence with confocal laser scanning microscopy

Amplex red assay

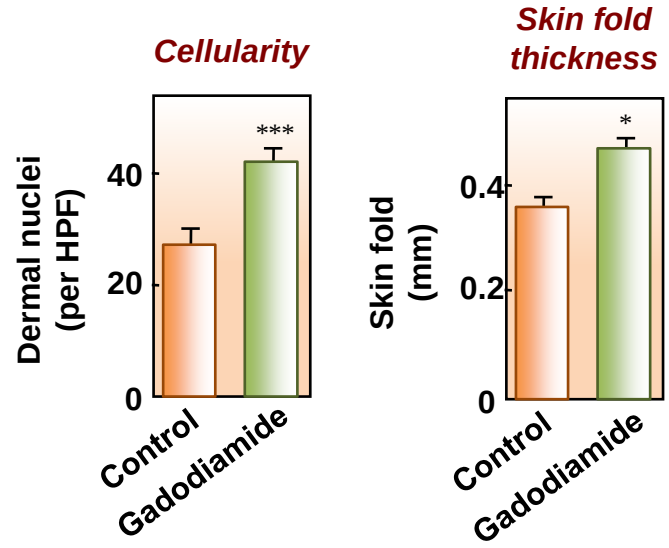


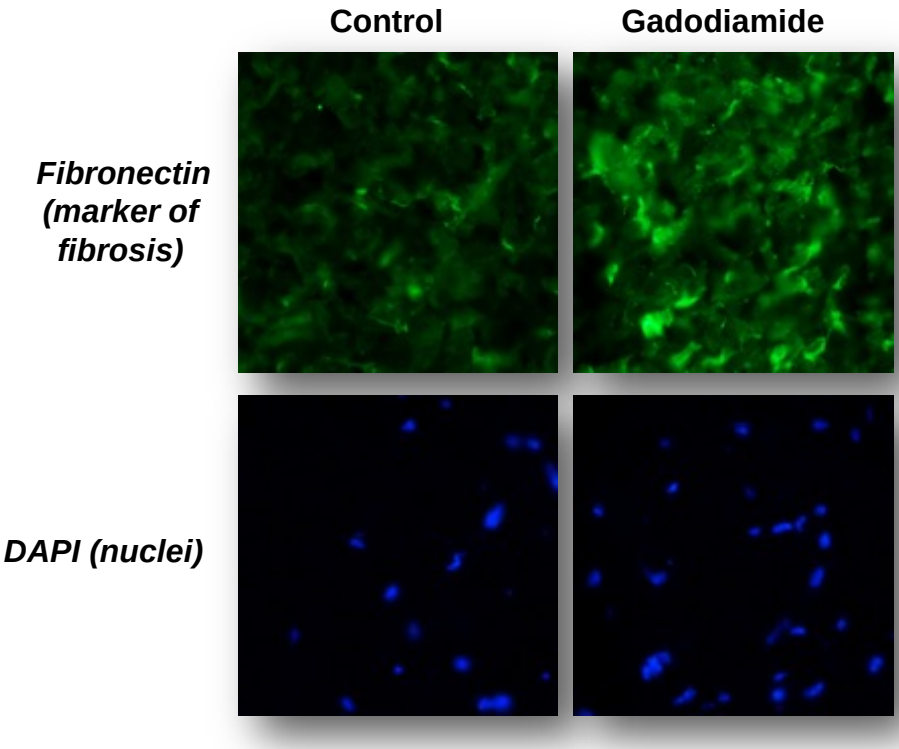
Wagner laboratory, unpublished

Gadodiamide induces skin fibrosis in mice with normal renal function

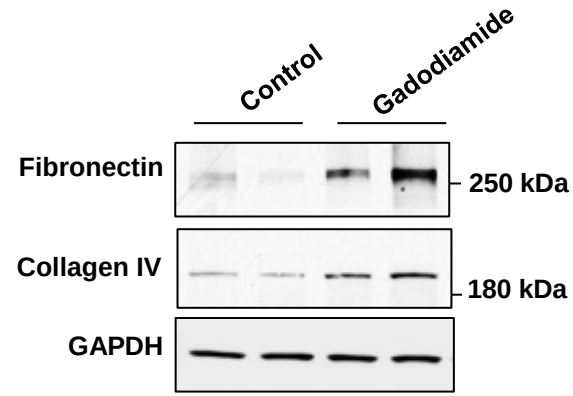


***H&E** staining - Skin*



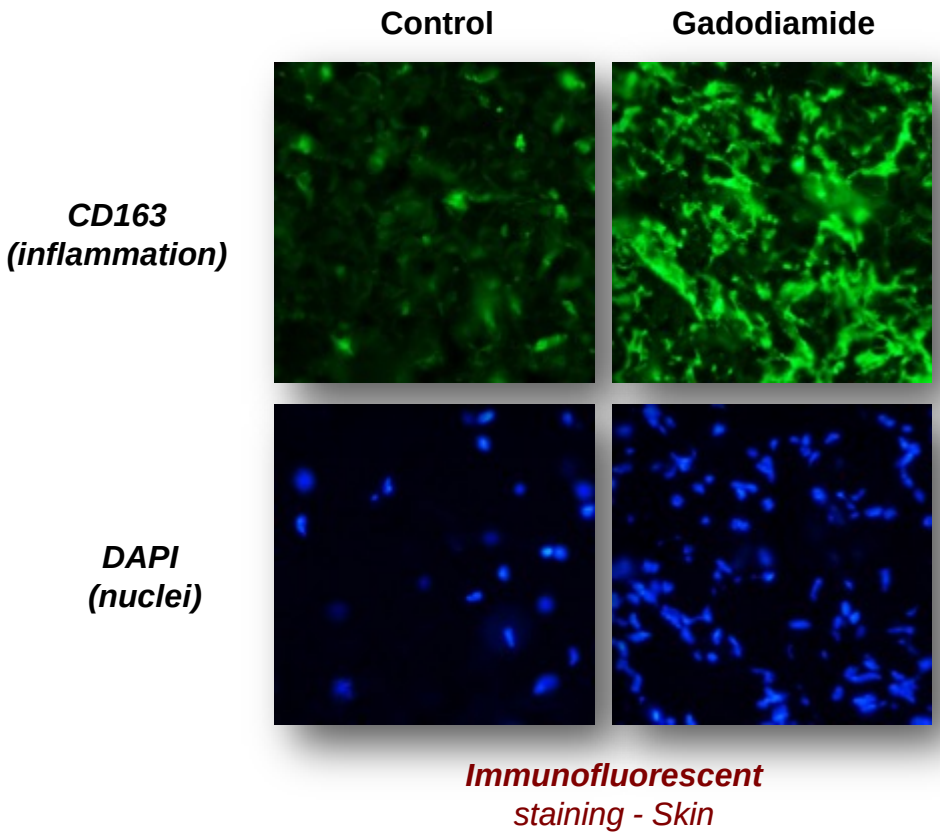


***Immunofluorescent** staining - Skin*

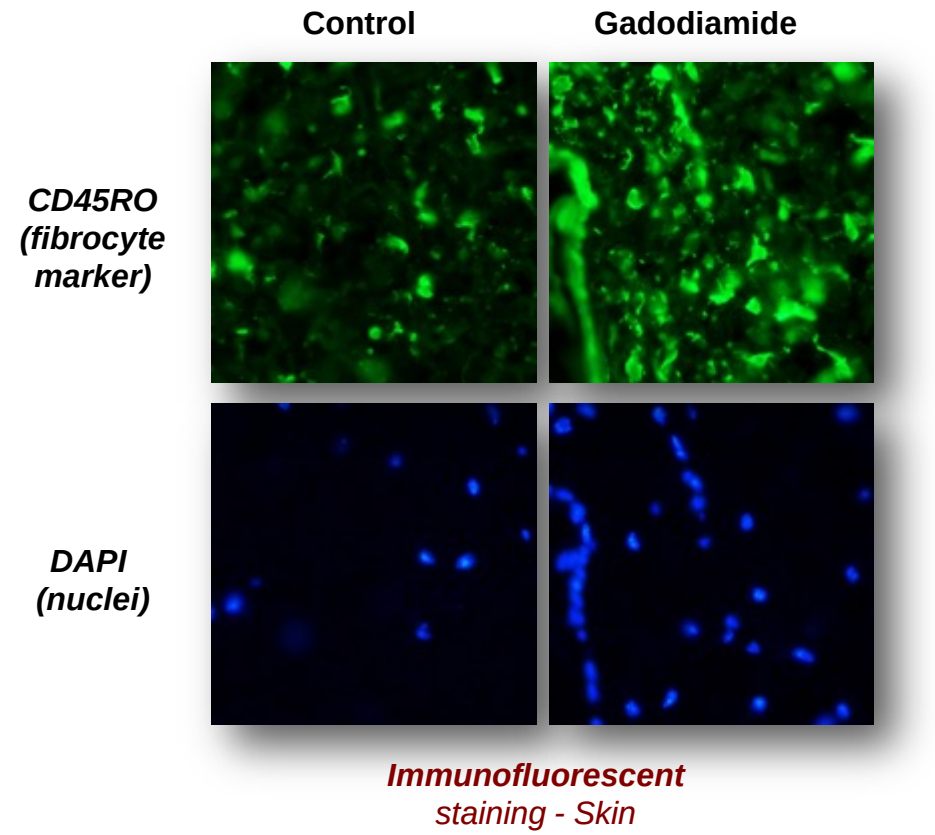


Wagner laboratory, unpublished

Gadodiamide treatment leads to inflammation and bone marrow-derived cells to the dermis in mice with normal renal function



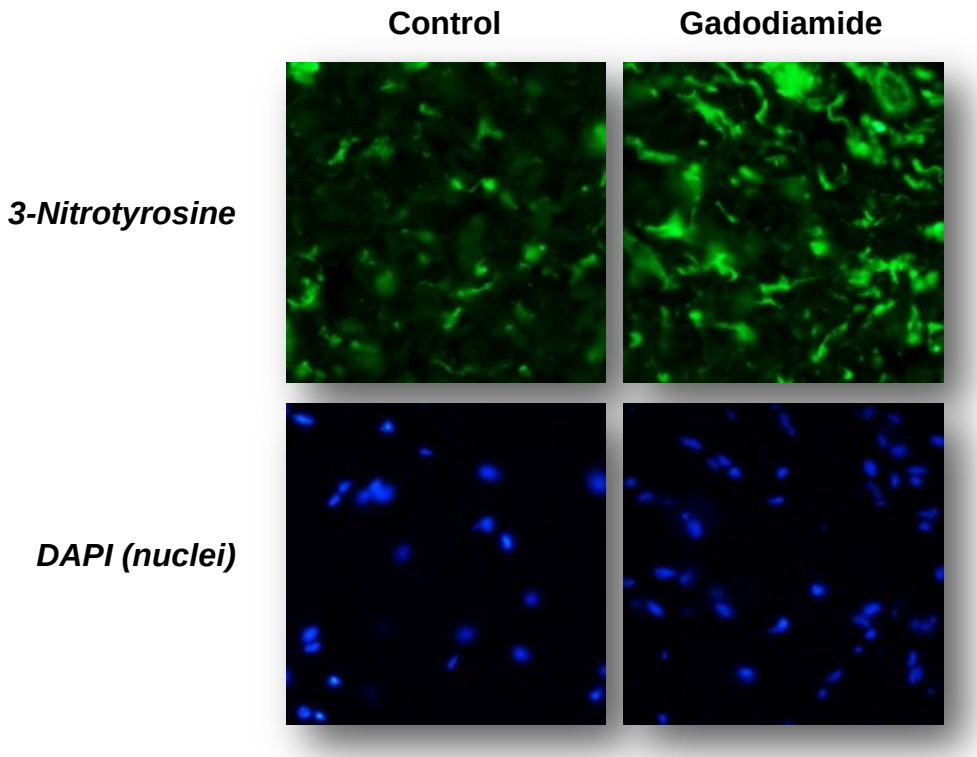
Immunofluorescent
staining - Skin



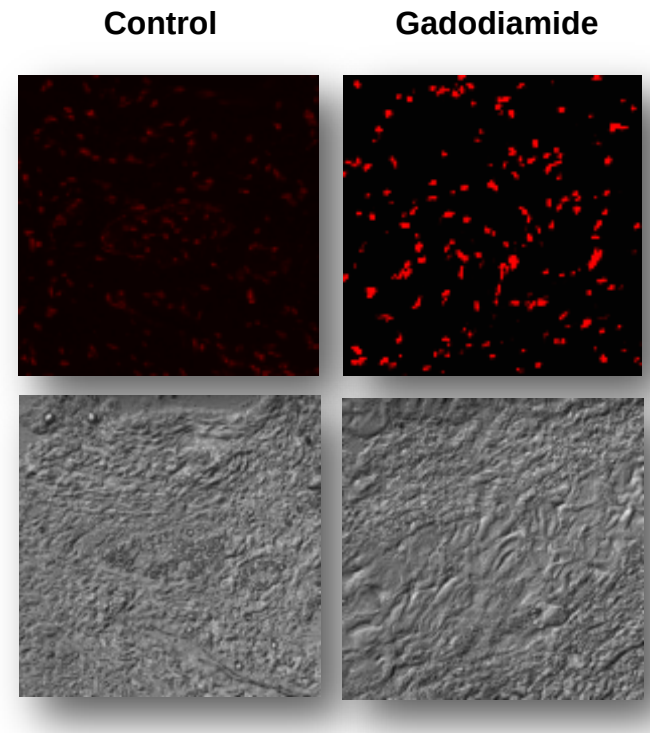
Immunofluorescent
staining - Skin

Wagner laboratory, unpublished

Gadodiamide increases oxidative stress in the skin of mice with normal renal function



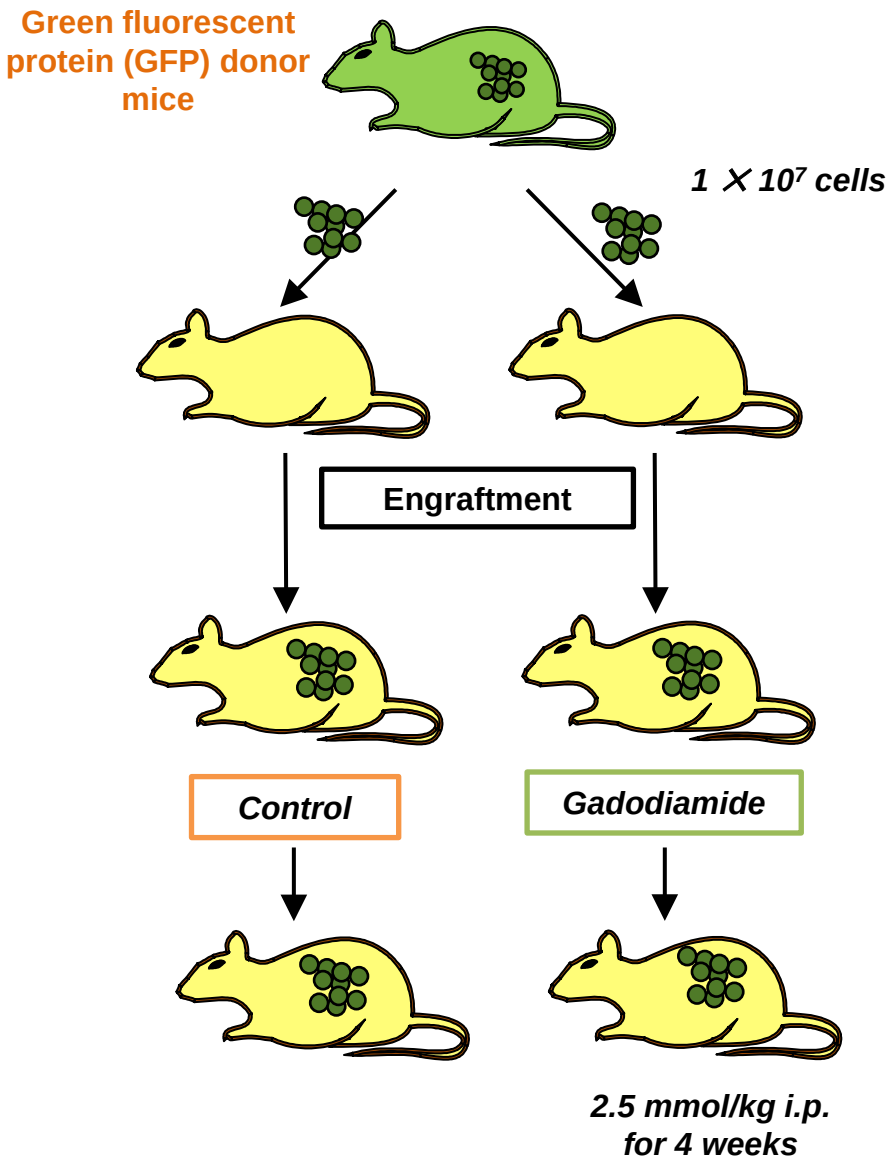
Immunofluorescent *staining - Skin*

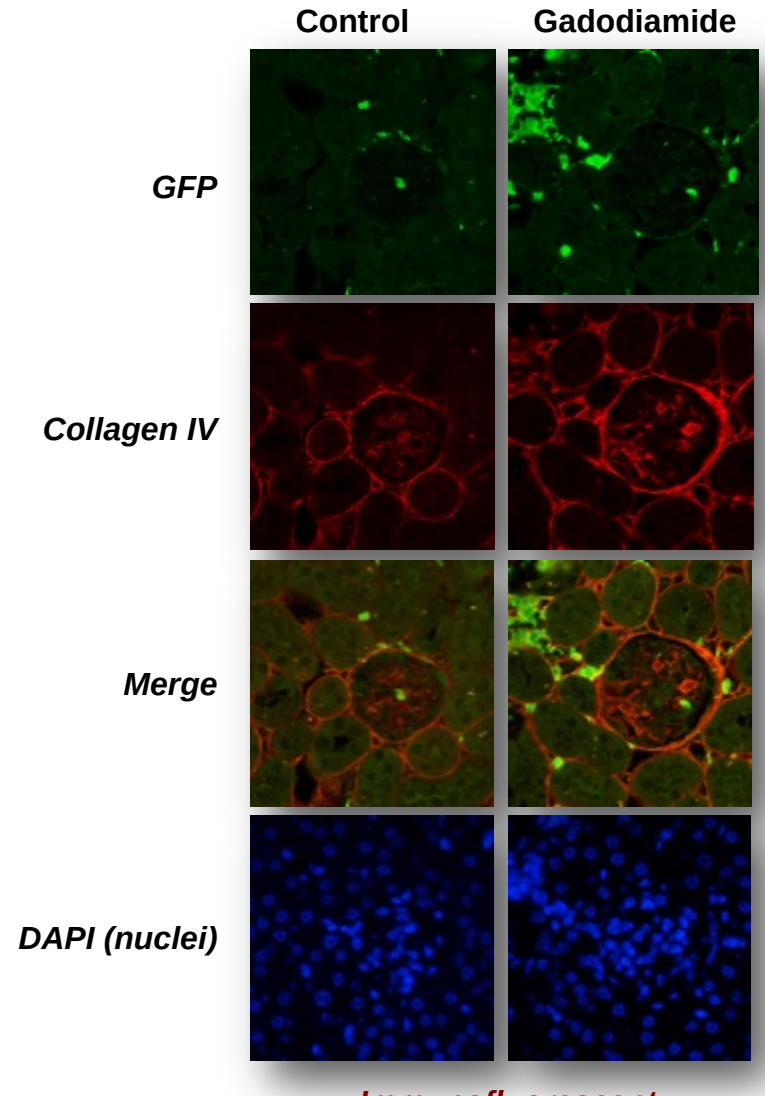


In situ DHE *staining and confocal microscopy - Skin*

Wagner laboratory, unpublished

Experimental design: Tagged bone marrow transplant in mice with *normal renal function*

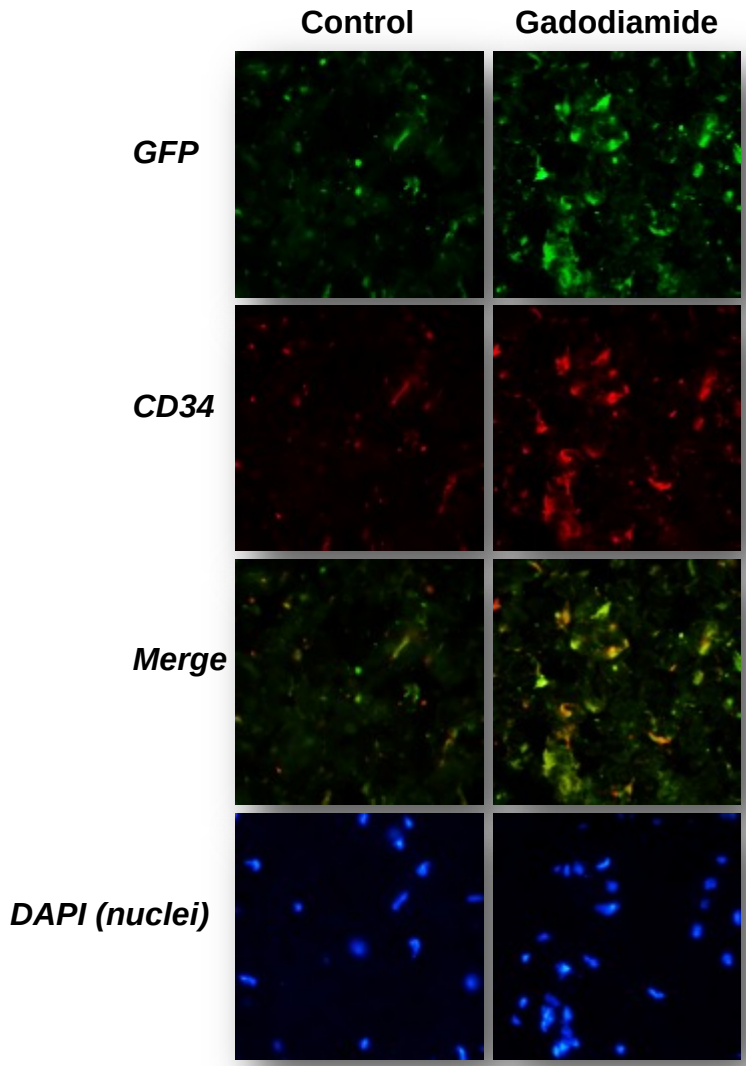




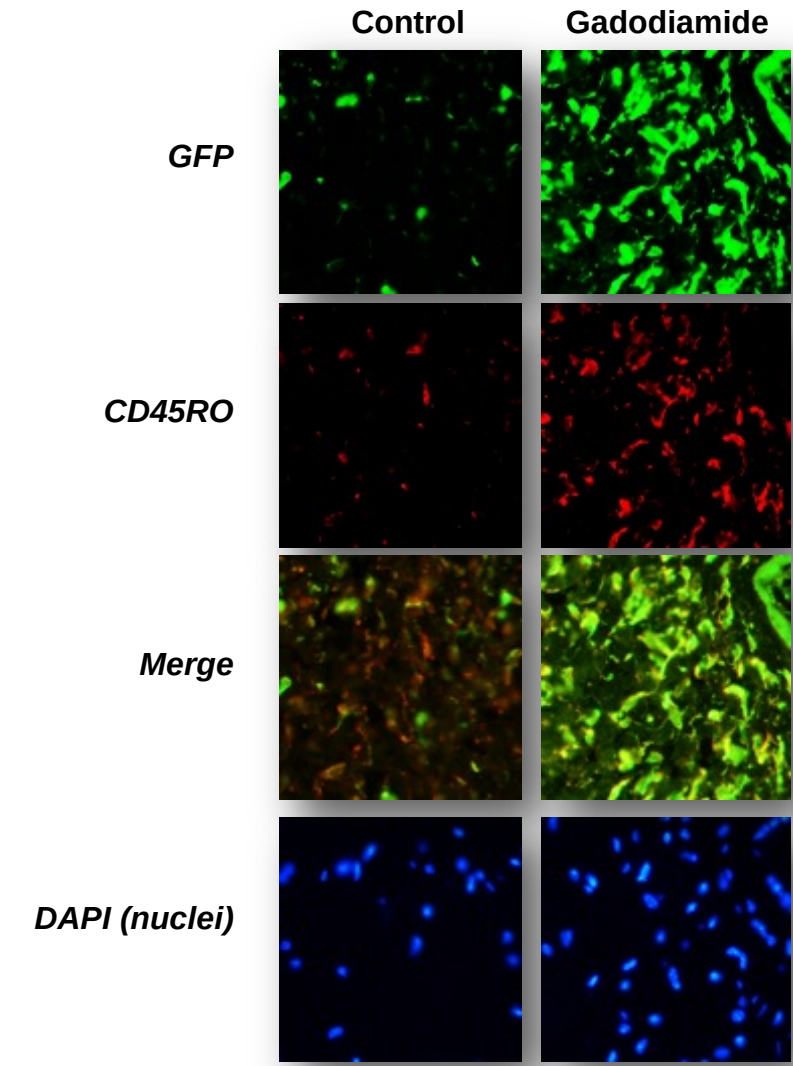
Immunofluorescent *staining – Kidney*

Wagner laboratory, unpublished

Gadodiamide induces the recruitment of bone marrow-derived fibroblasts to the skin in mice



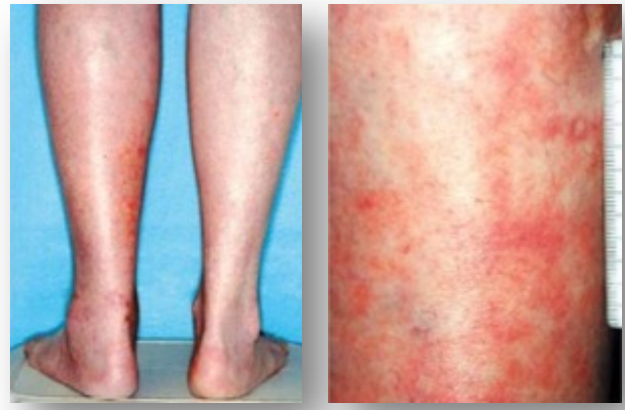
Immunofluorescent *staining - Skin*



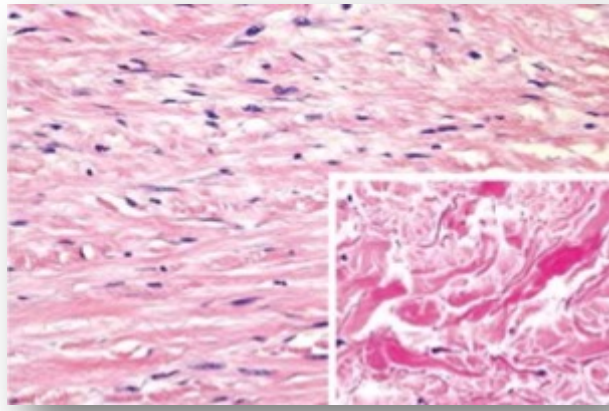
Immunofluorescent *staining - Skin*

Wagner laboratory, unpublished

Biopsies of patients with NSF demonstrate significant expression of the hematopoietic progenitor marker CD34

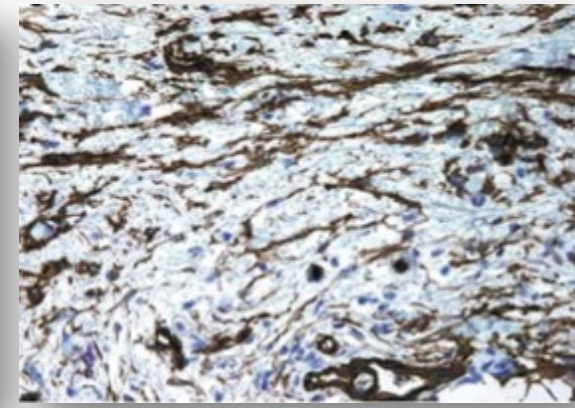


Clinical photographs of a patient showing skin lesions



H&E staining - Skin

Dermal hyper-cellularity



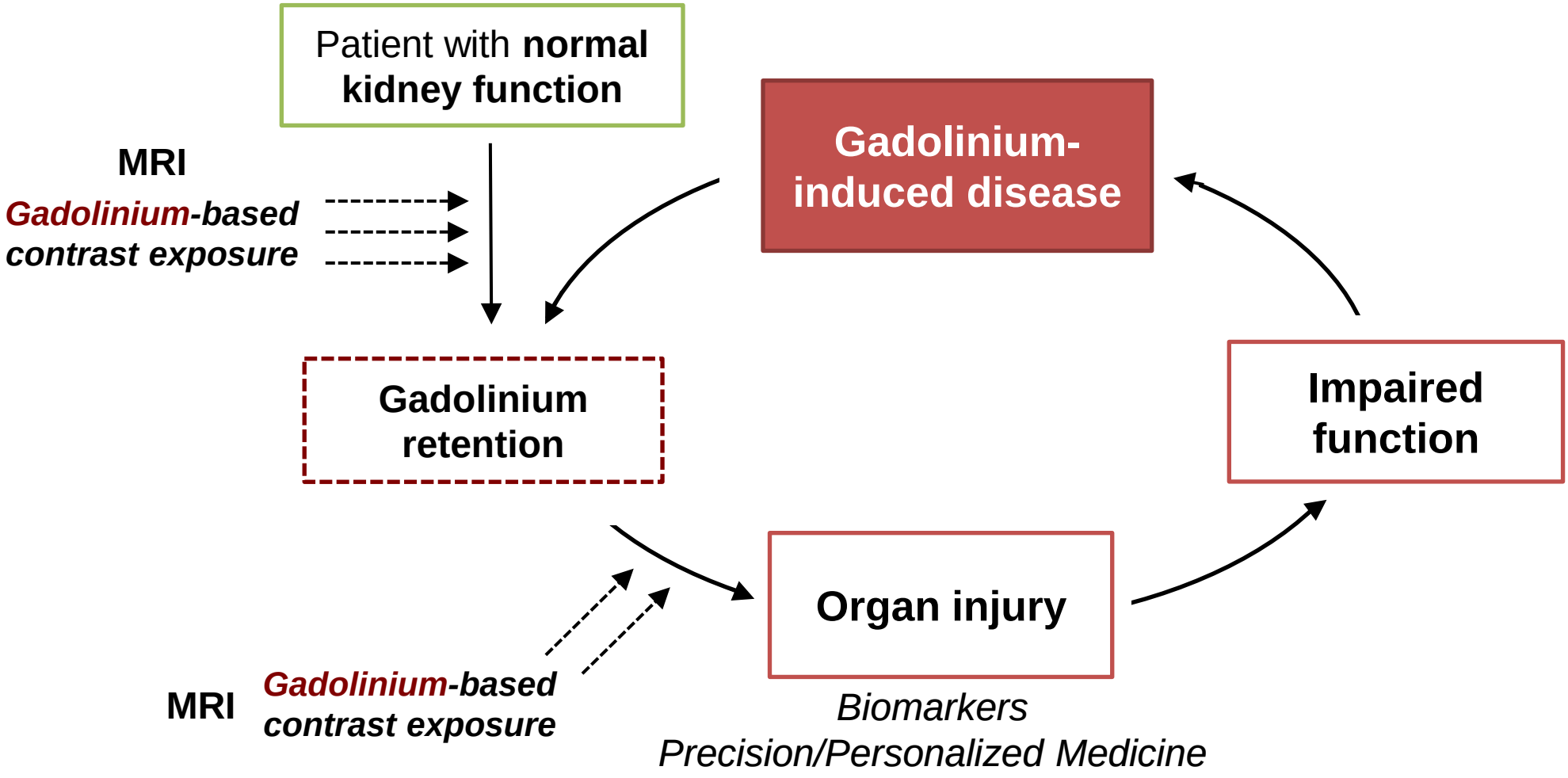
*Immunostaining for **CD34** - Skin*

Kroshinsky D et al, *N Eng J Med*, 2009

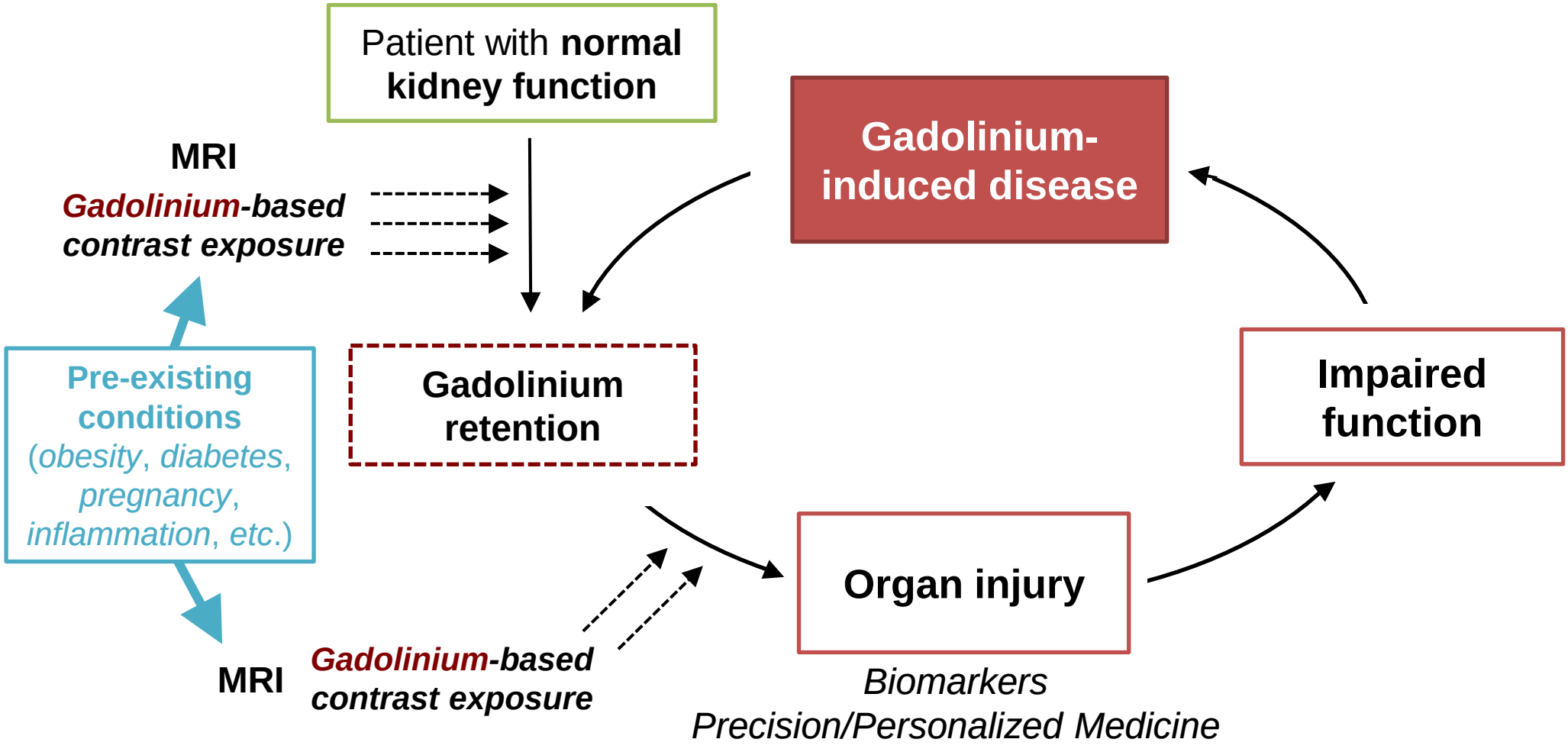
Conclusions

- *Gadolinium **retention** can be detected in **humans** and in **our models**; This allows the **mechanistic** study of gadolinium-induced **organ injury***
- *The pathologic **effects** of gadolinium-based contrast agents are **not well-characterized***
- *Our experiments show that **renal insufficiency** is **not requisite** for fibrosis*
- *Mechanistically, our experiments demonstrate that it is the recruitment of **bone marrow-derived cells** that mediate the **deleterious actions***
- *We provide examples of important avenues to **understanding** the **mechanisms** of **disease** (lending itself to the **discovery** of **biomarkers**)*
- ***Dechelation** of gadolinium is a **hypothetical** pathologic mechanism.*
- *Studies concerning the biologic effects of **rare earth metals** in general and their **retention** in human organs are in the **nascent** stage*
- *The **science** on this topic is at **ground zero***

Working hypothesis



Working hypothesis



Acknowledgments

UTHSCSA
Nephrology

Wagner's Laboratory

- ***Chunyan Tan***
- ***Catherine Do, M.D.***

Viktor Drel, Ph.D.

- **Yves Gorin, Ph.D.**

Denis Féliers, Ph.D.

Jeffrey L. Barnes, Ph.D.

Seema Ahuja, M.D.

Doug-Yoon Lee, Ph.D.

Hanna E. Abboud, M.D.

Rush University Medical Center
Internal Medicine Department

Jochen Reiser, M.D., Ph.D.

RUSH UNIVERSITY MEDICAL CENTER

Northwestern

Keith MacRenaris, Ph.D.

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UTSA

Miguel Yacaman, Ph.D.
Josefina Arellano-Jimenez, Ph.D.

UTSA

UNC

Michael Jay, Ph.D.
John Prybylski, Ph.D.

UNC ESHELMAN SCHOOL OF PHARMACY

Supported by :

- NIDDK

NIH RO1DK102085 (PI)

- **Veterans Administration Merit Award I01BX001958 (PI)**

Veterans Administration Career Development Award (PI)

Veterans Administration VISN 17 New Investigator Award (PI)