What can we learn from NSF about broader potential toxicity?

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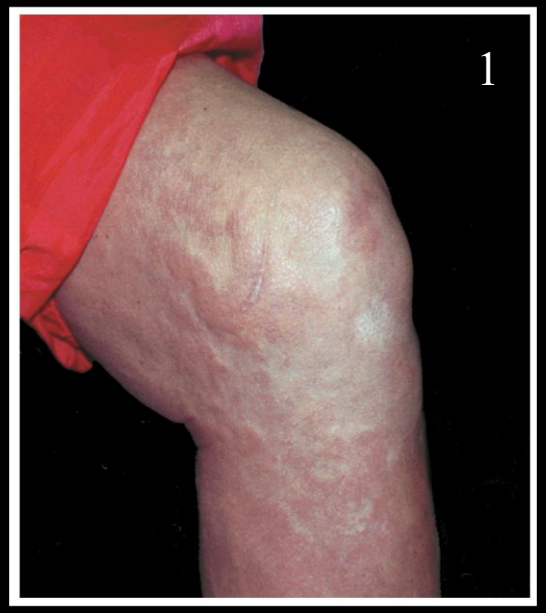
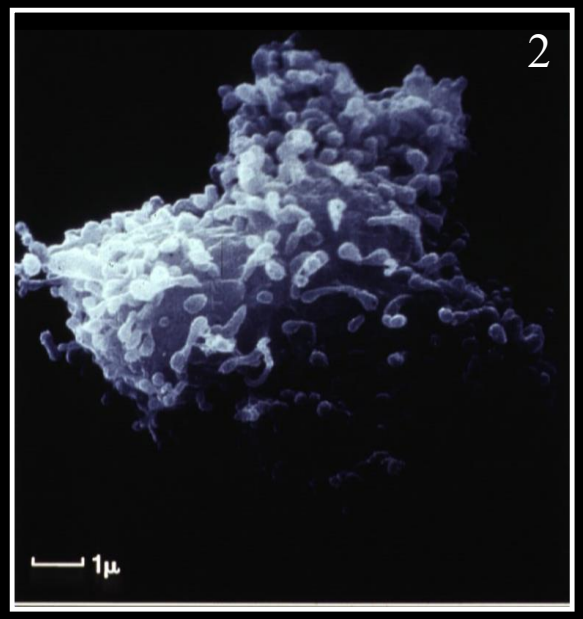
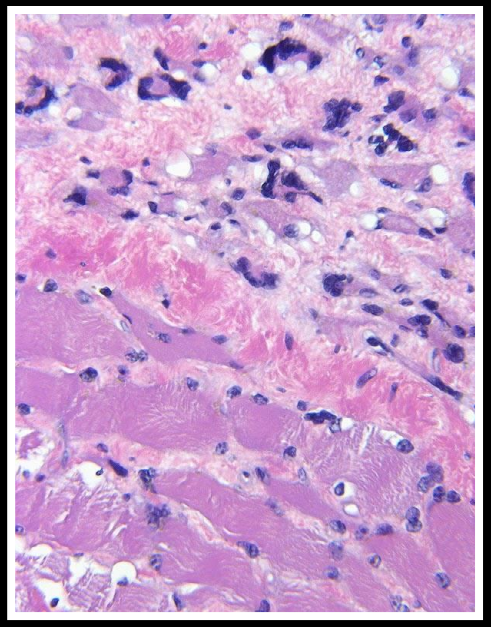
Conflicts of Interest

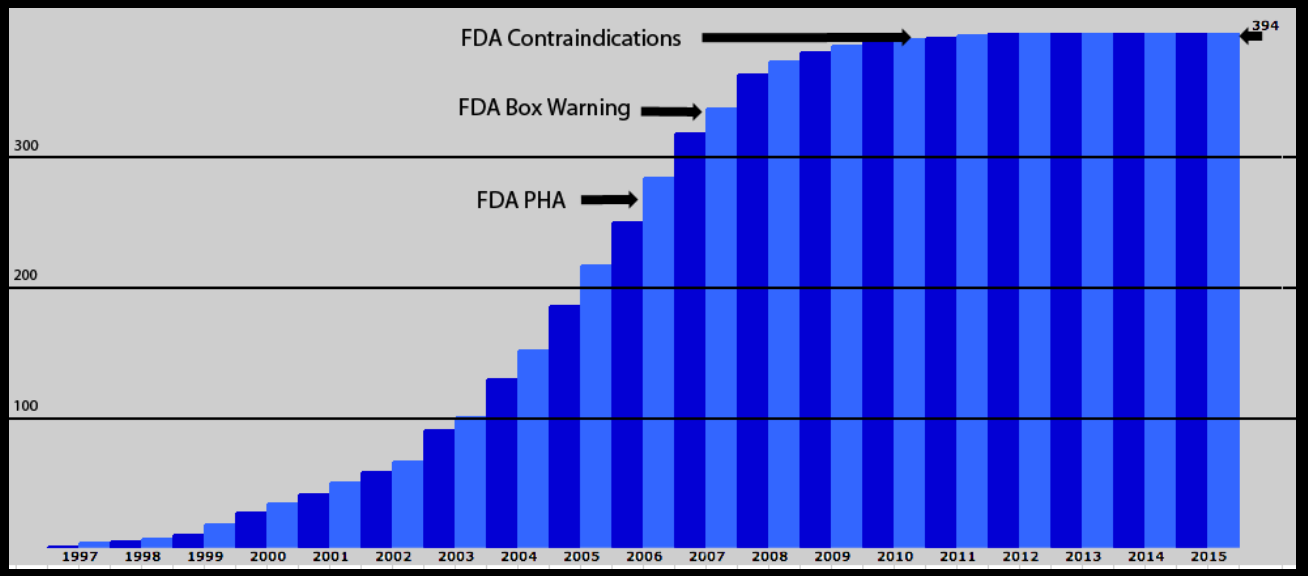
Contracted Research: Bracco and Navitas Life Sciences GmbH.

What did we learn from NSF about GCCA toxicity?









What did we learn from NSF about GCCA toxicity?

- We proved what Carr, et al. warned against in 1984 (1)
  - "…care should obviously be taken in patients with impaired renal function where high in vivo concentrations of Gd-DTPA may occur for prolonged periods."
- We probably explained why Wedeking, et al. (2) found the best correlation of long term deposition of Gd in mice with GCCA dissociation rates at pH 1 (acidic) rather than pH 7.4 (physiologic)
  - Lysosomal pH = 4.5-5 (Mindell (3))
  - Gd detected in lysosomes of macrophages (Mizgerd (4))
- An experimental model of fibrosis triggered by lysosome-processed Gd nanoparticles acting through NLRP3 inflammasome release has been developed by Li, et al. (5)

1. AJR Am J Roentgenol. 1984 Aug;143(2):215-24.
2. Magn Reson Imaging. 1992;10(4):641-8.
3. Annu Rev Physiol. 2012;74:69-86
4. J Leukoc Biol. 1996 Feb;59(2):189-95.
5. ACS Nano. 2014 Feb 25; 8(2): 1771–1783.

Image credits from preceding slide

1. Lancet. 2000 Sep 16;356(9234):1000-1.
2. Mol Med. 1994 Nov;1(1):71-81.
3. With permission, SE Cowper.
4. With permission, SE Cowper.

What do we still need to know?

- How does one define gadolinium toxicity?
  - What is a normal gadolinium level? (inputs: dose, EGFR, agent, etc.)
  - Are there other objective measures? (labs, clinical exam, imaging)
  - Is depression a component of the syndrome?
  - Do some patients with NSF have superimposed gadolinium toxicity?
    - What is different about those with NSF who do not have gadolinium toxicity?
- Are symptoms of gadolinium toxicity reproducible?
  - Can they be measured quantitatively and objectively?
  - Are they self-limited or progressive?
  - Are deposited foci predictive of symptoms/signs?
- Is dechelation required to produce symptoms?
  - If so, in the absence of increased dwell time, is this a dose effect?
  - Is incidence equal among available agents?
- What are the stabilities of GCCA at lysosomal pH?
  - Can they be made more stable?