

Gadolinium Deposition in the Brain: Parallels between Patient-, Animal- and In Vitro-Studies

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IN THE HELMHOLTZ ASSOCIATION

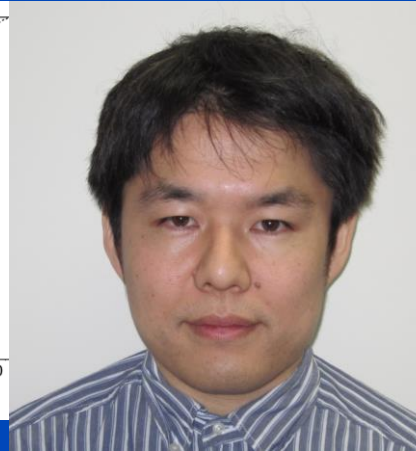
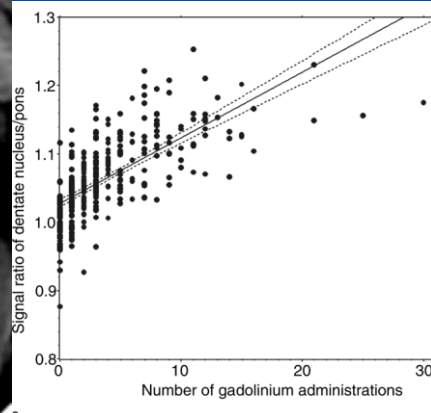
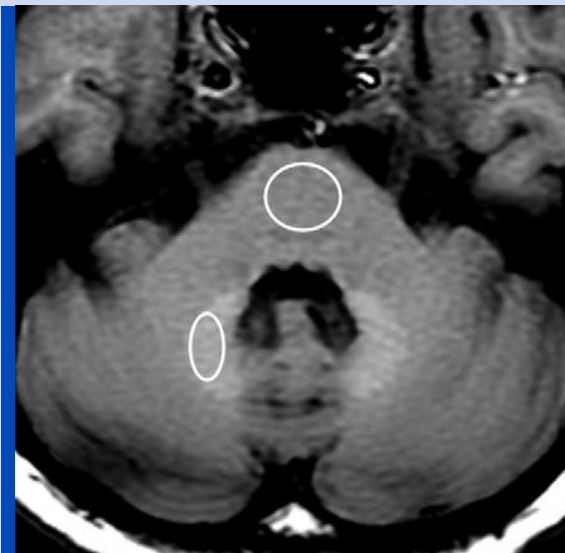


50 Years – Research for
A Life Without Cancer

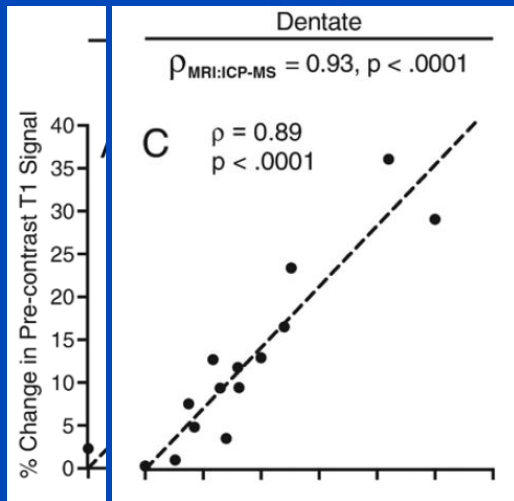
Conflicts of Interest

Guerbet (consultant, financial study support, advisory boards, lectures); Bayer (consultant, financial study support, advisory boards, lectures); GE (advisory board, expert opinion); Bracco (advisory board); Siemens (lectures); Prime Oncology (lectures); AbbVie (advisory board).

Gadolinium Retention in the Brain



Kanda et al, Radiology 2014



McDonald et al, Radiology 2015



Risk-Benefit Evaluation prior to Injection of a GBCA

1. Side Effects of the GBCA

2. Efficacy of the GBCA

3. „Gadolinium Deposition Risk“

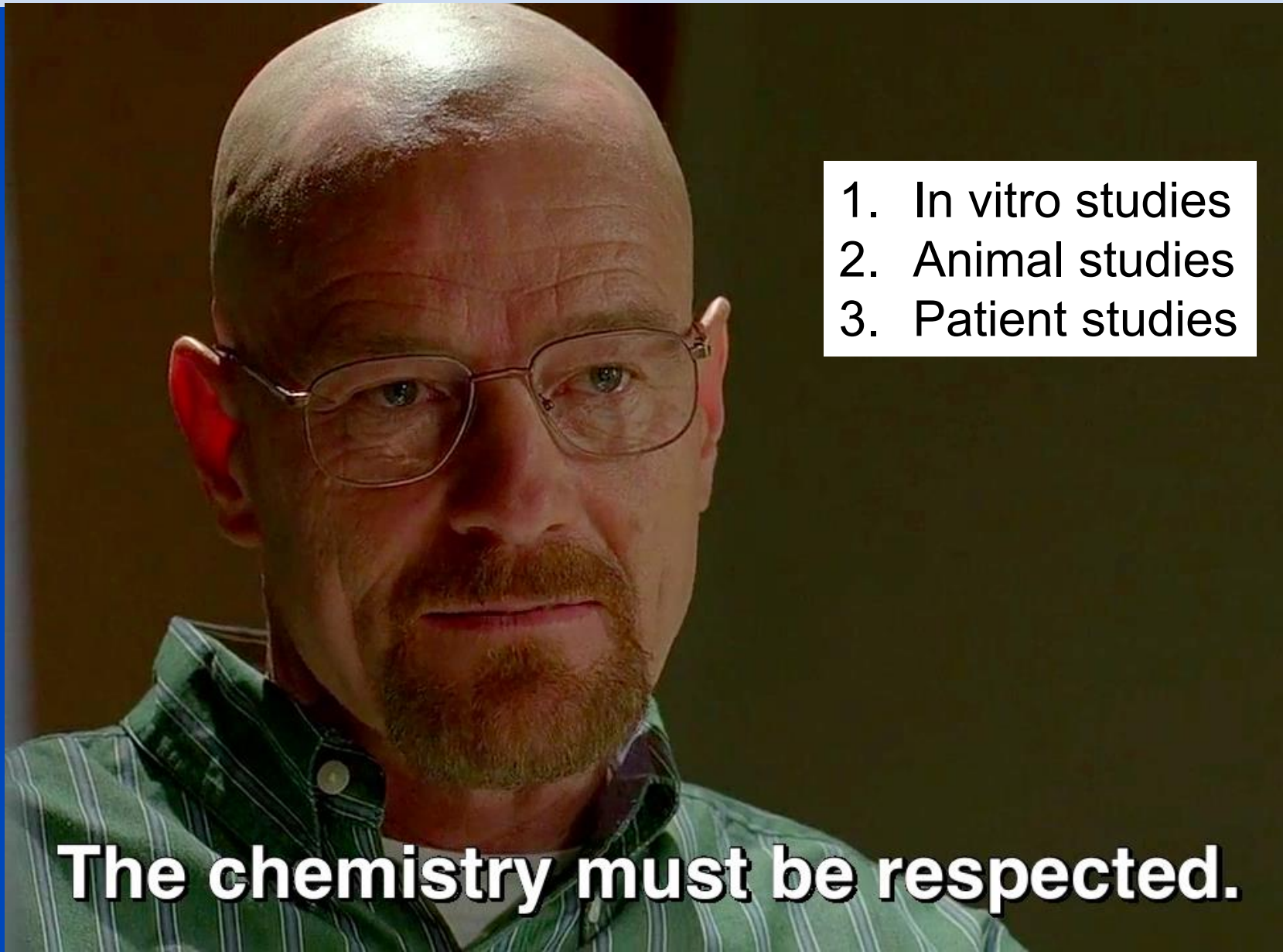
1. What is the Mechanism of Gadolinium-Deposition

2. Are there any clinical correlates?

Question 1: What is the mechanism of Gadolinium Deposition?

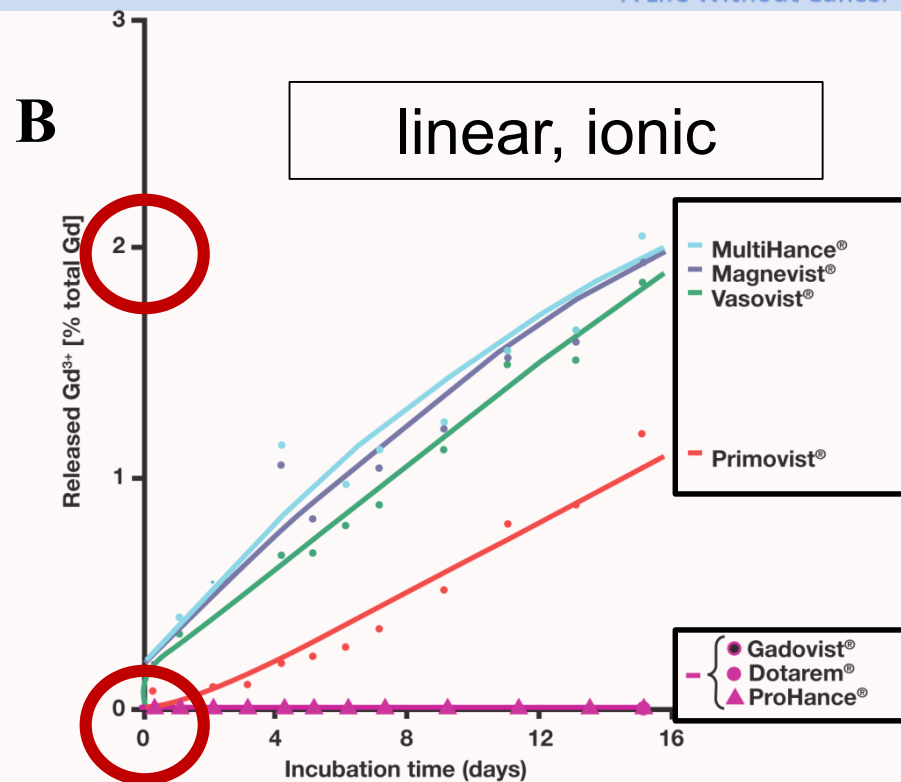
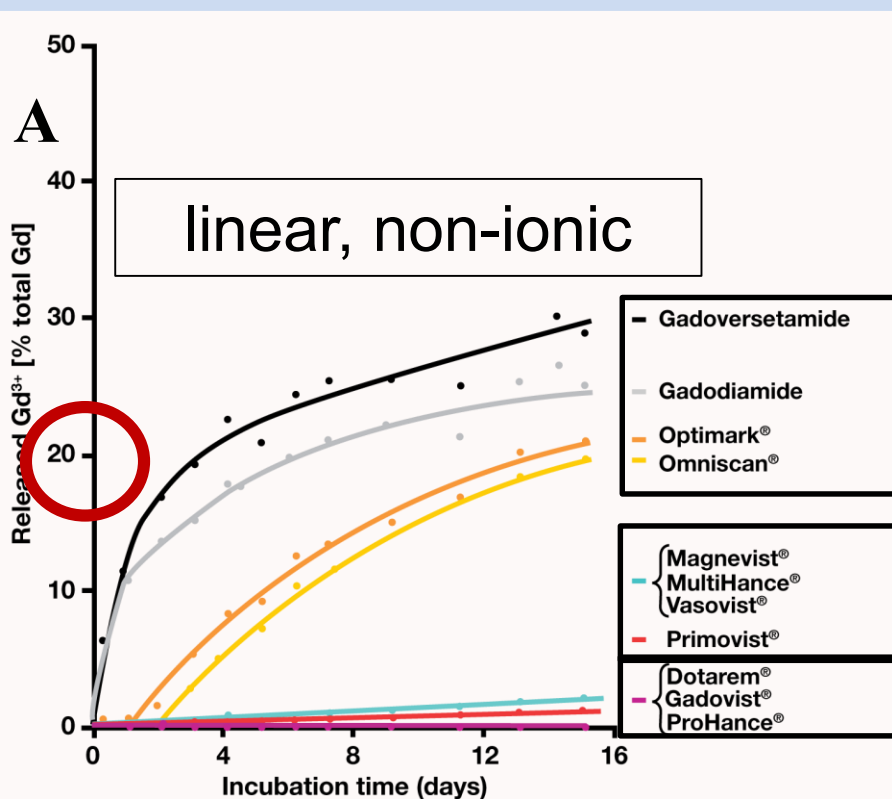
1. In vitro studies
2. Animal studies
3. Patient studies

The chemistry must be respected.



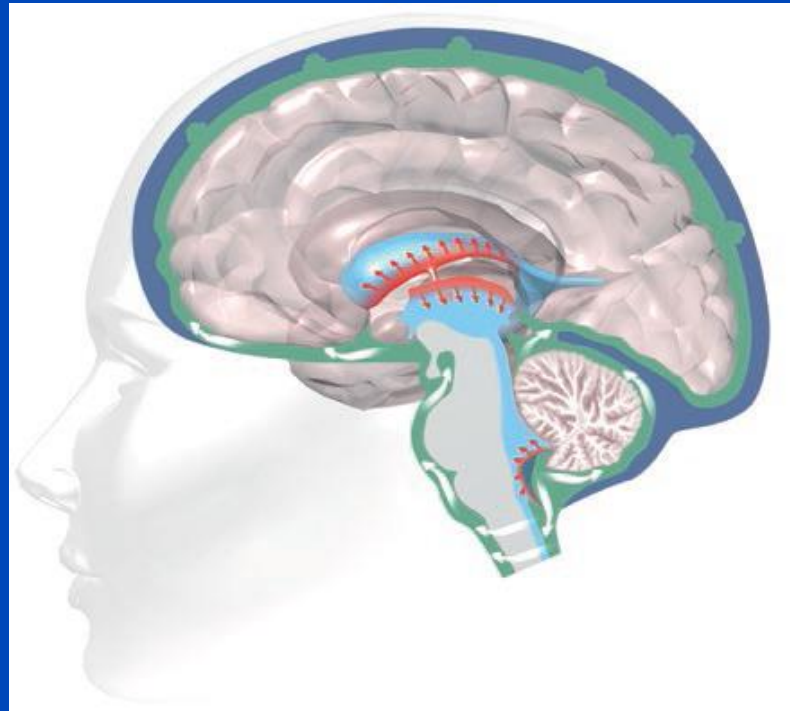
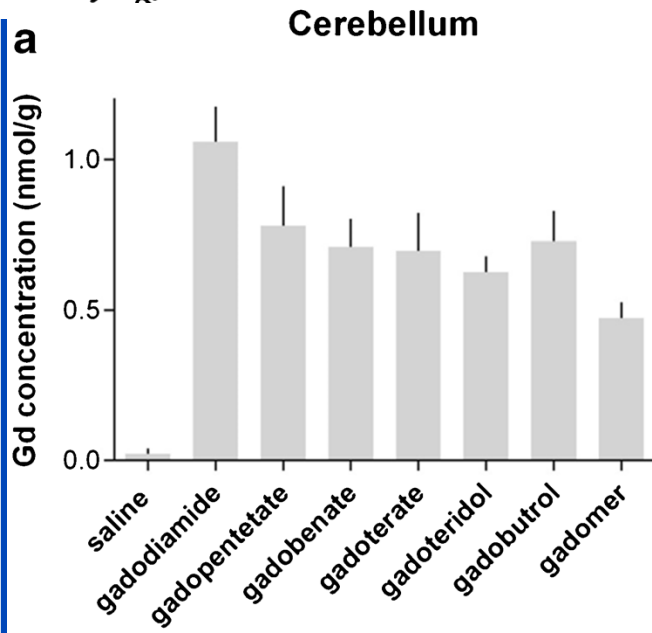
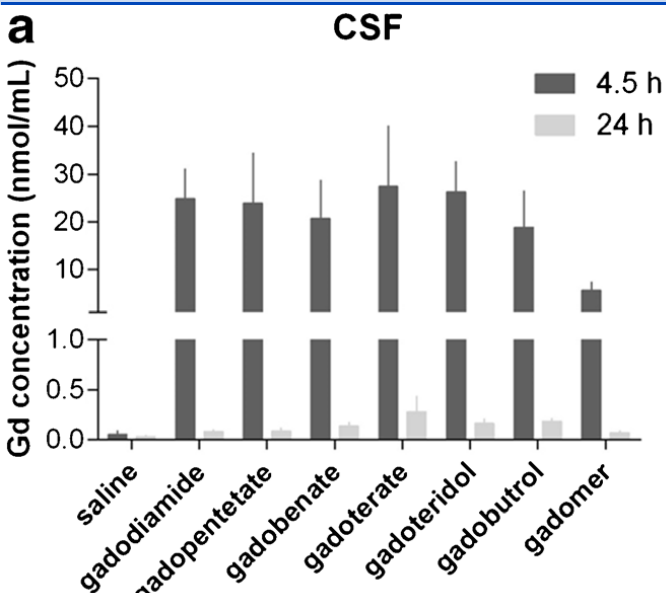
In vitro experiments

incubation in serum at 37 C for 2 weeks



Gadolinium release for macrocyclic GBCAs below the limit of detection

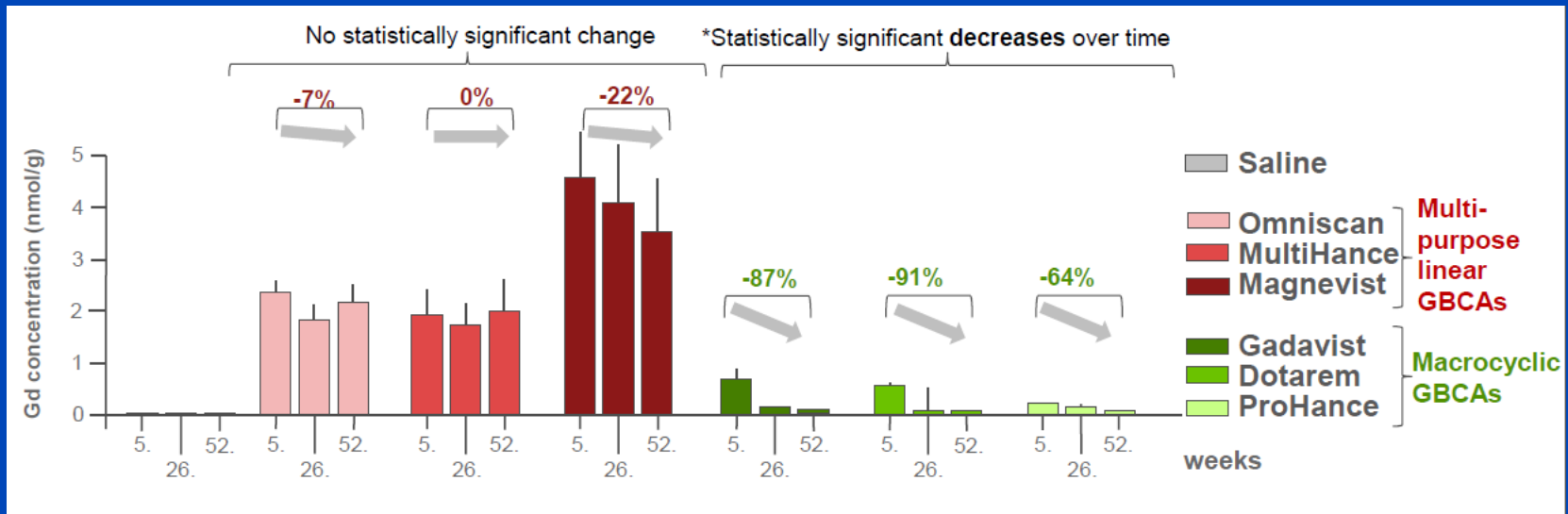
How does the gadolinium get in the brain?



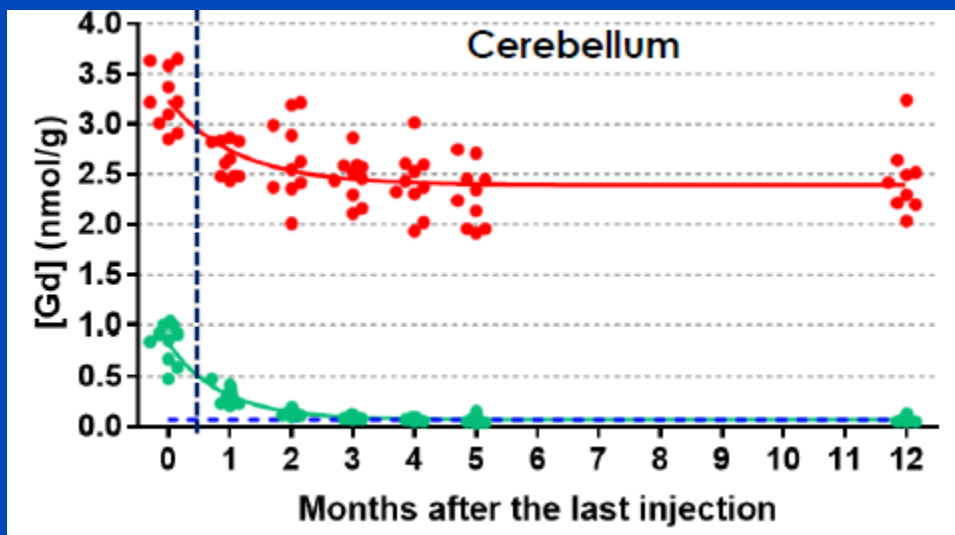
The same amount of all GBCAs can be found in the brain 24 h after injection.

Jost et al, Penetration and distribution of gadolinium-based contrast agents, European Radiology 2016, Image from Bayer-Brochure „Gadolinium Presence in the Brain“

Long Term Results: How much gadolinium does stay in the Brain?

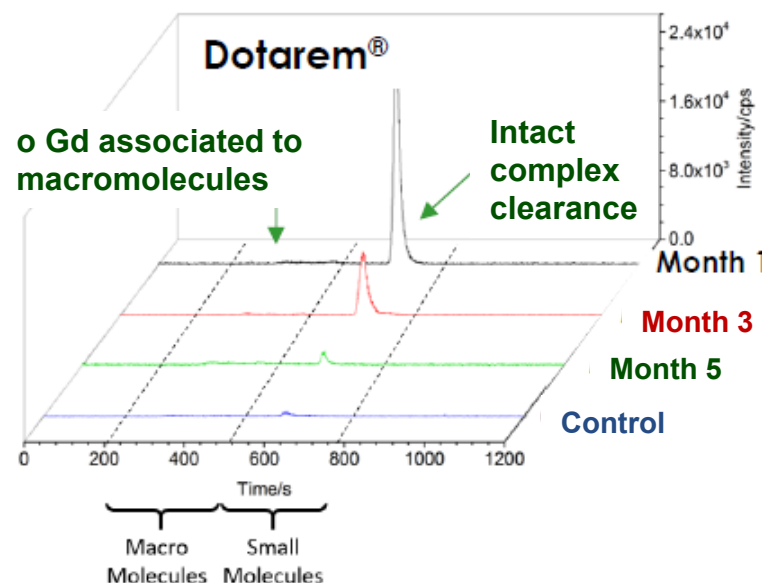
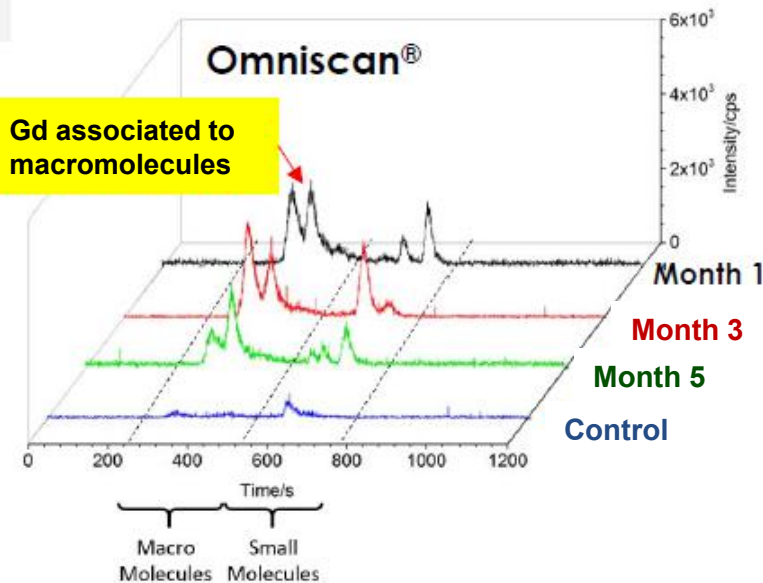
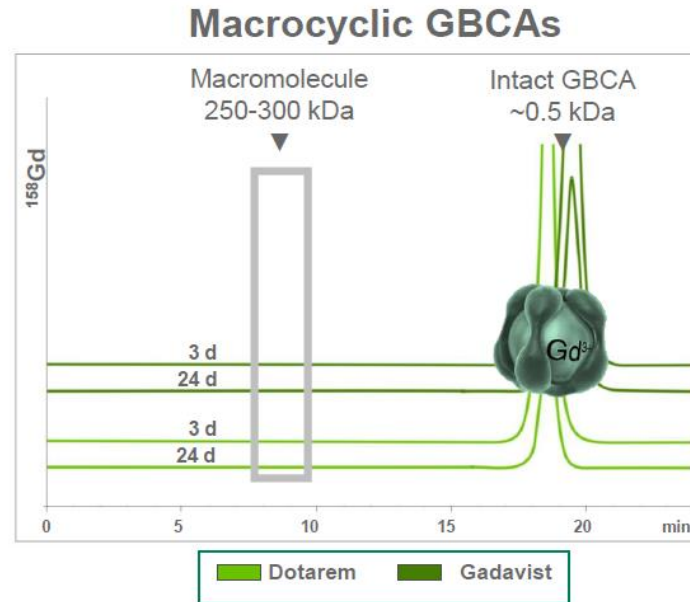
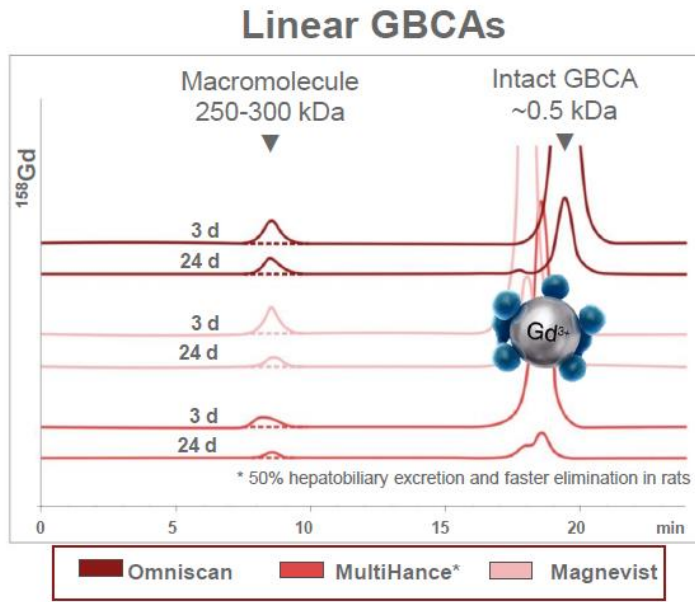


Presented at the FDA MIDAC meeting by Bayer – material from FDA www.fda.gov



Presented at the FDA MIDAC meeting by Guerbet – material from FDA www.fda.gov

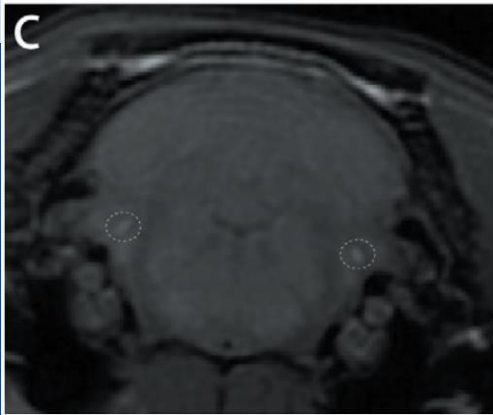
Explanation for Discrepancy: Partly Dechelation of linear GBCAs



Frenzel et al,
Investigative
Radiology
2016

Presented
at the
FDA
MIDAC
meeting
by
Guerbet –
material
from FDA
www.fda.gov
OV

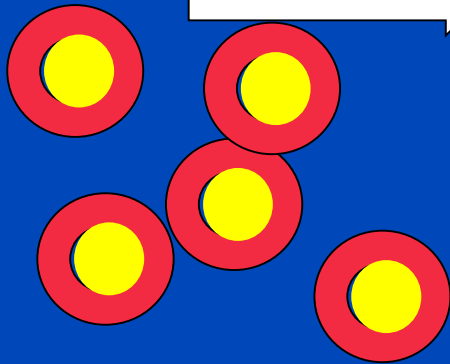
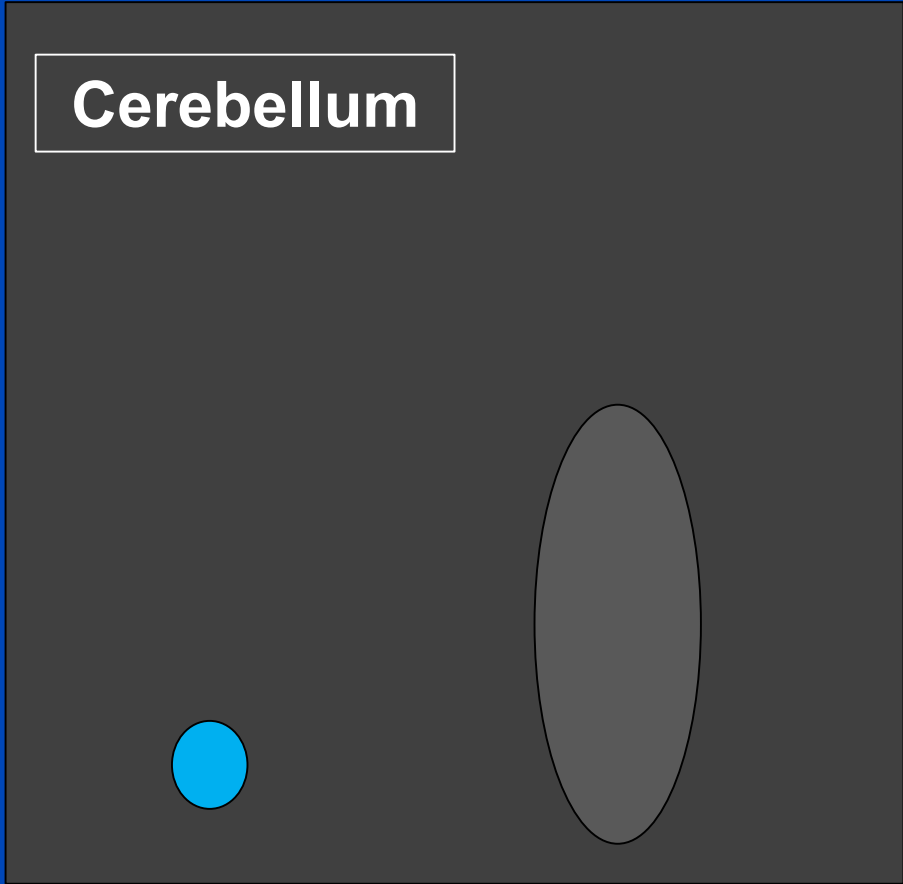
Pathomechanism Macrocyclic GBCAs



McDonald et al, Radiology
2017

CSF, Choroid Plexus

Cerebellum



Gadolinium

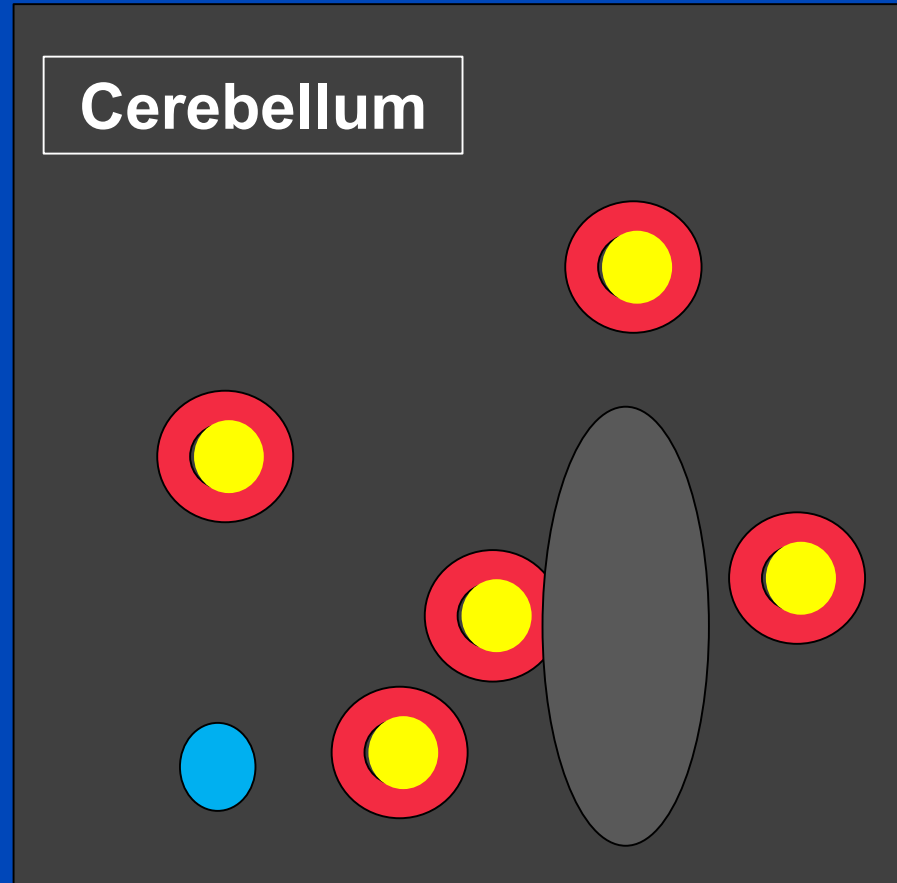
Lin. GBCA

Macr. GBCA

Phosphate


Wash out
over time

Cerebellum



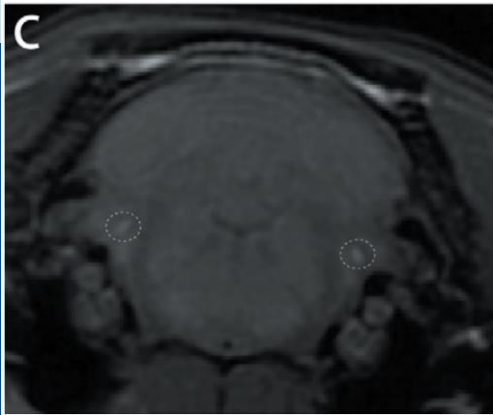
 Gadolinium

 Lin. GBCA

 Macr. GBCA

 Phosphate

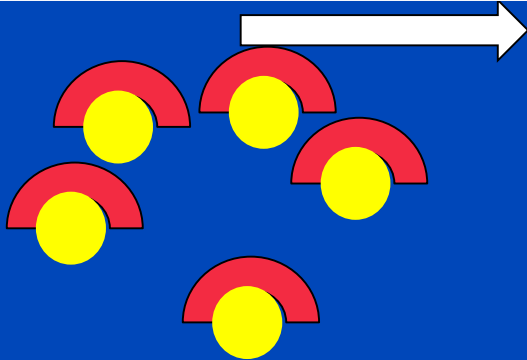
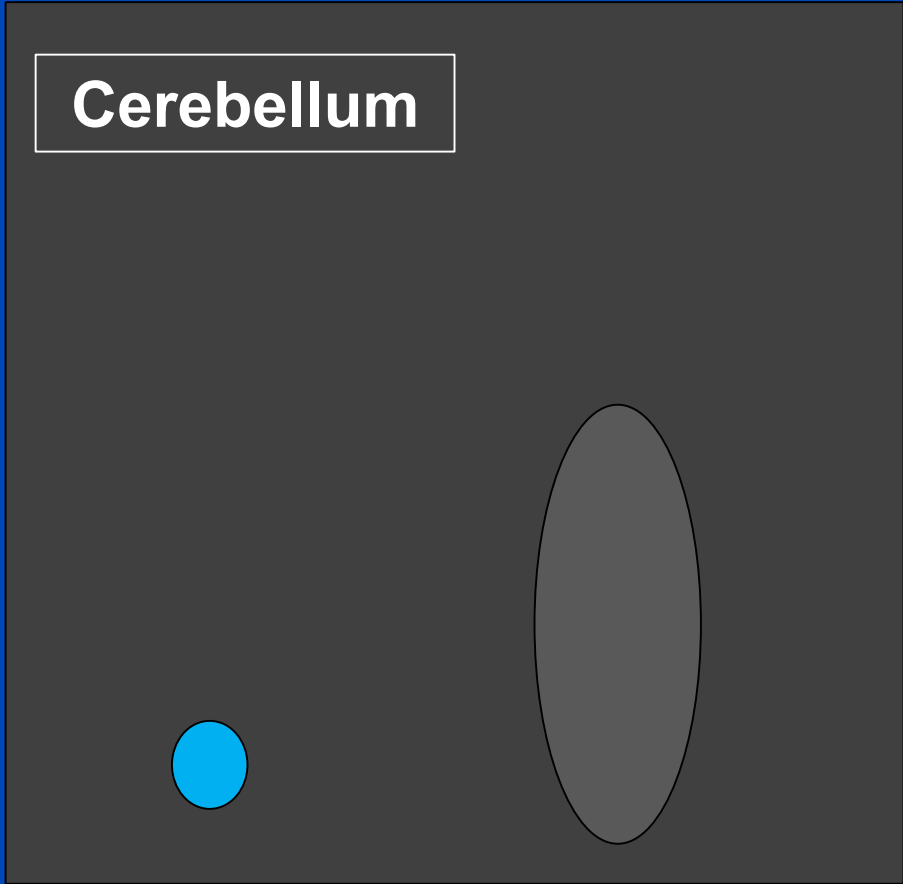
Pathomechanism Linear GBCAs



McDonald et al, Radiology
2017

CSF, Choroid Plexus

Cerebellum



Gadolinium

Lin. GBCA

Macr. GBCA

Phosphate

Pathomechanism Linear GBCAs

Hypothesis 1:

Gad-Deposition depends on specific stability of GBCA

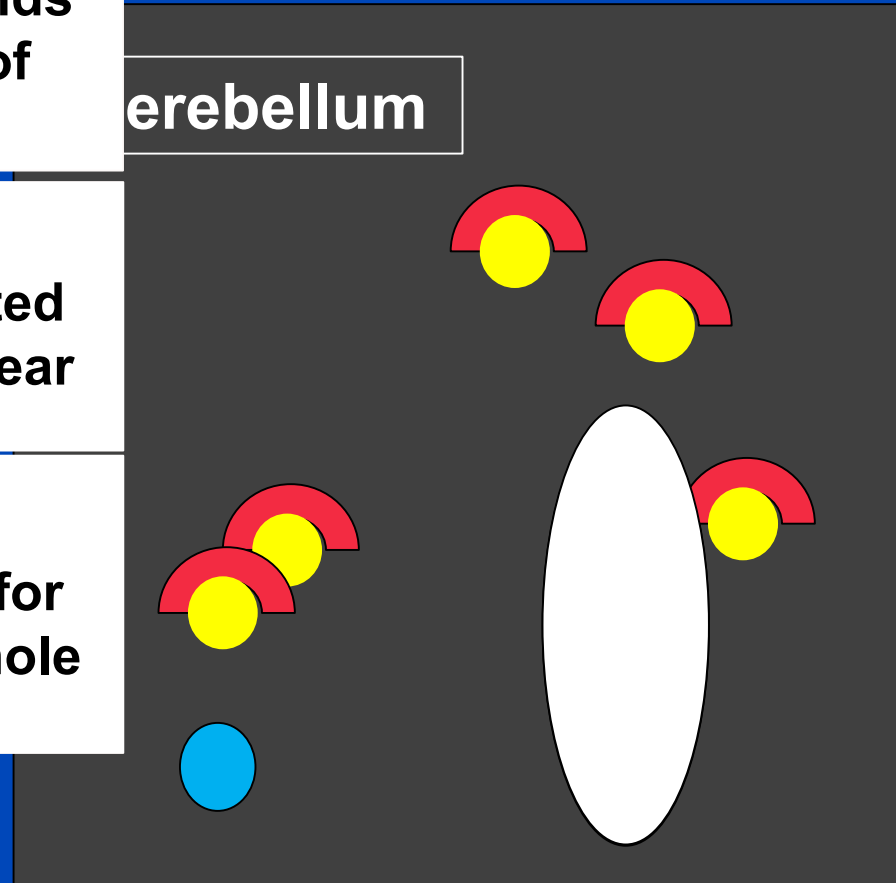
Hypothesis 2:

“Invisible” – precipitated Gad exclusively for linear GBCAs

Hypothesis 3:

SI Increase: *Indicator* for Gad.-Release in the whole body

erebellum



Gadolinium



Lin. GBCA



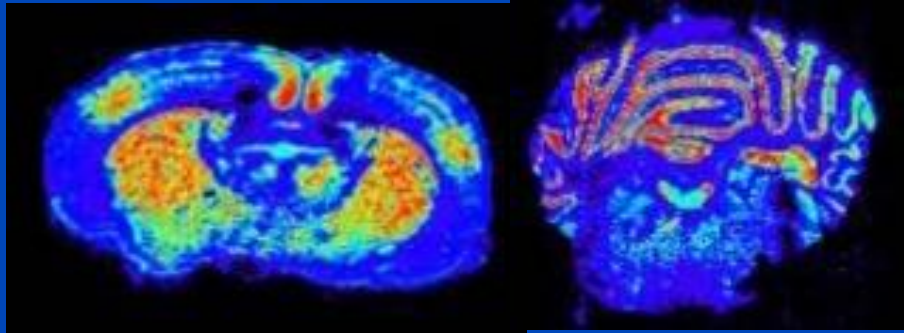
Macr. GBCA



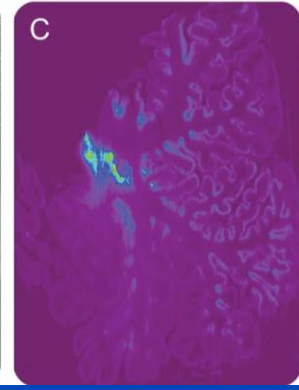
Phosphate

Gadolinium Accumulation in the Brain

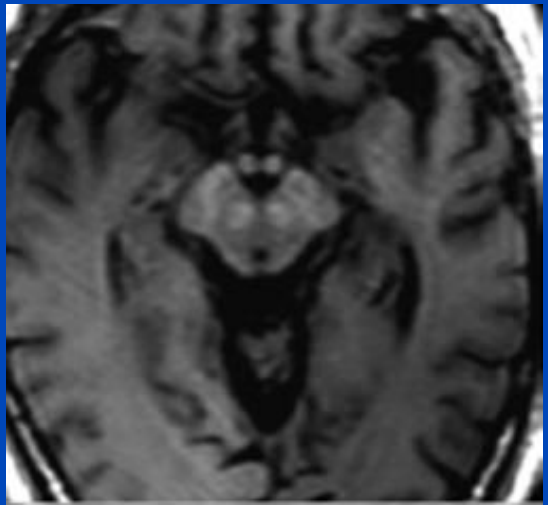
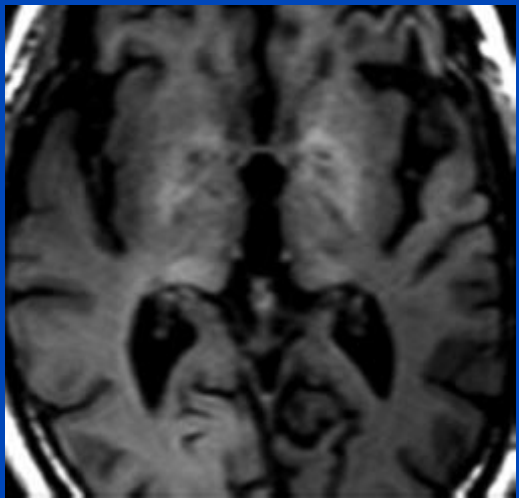
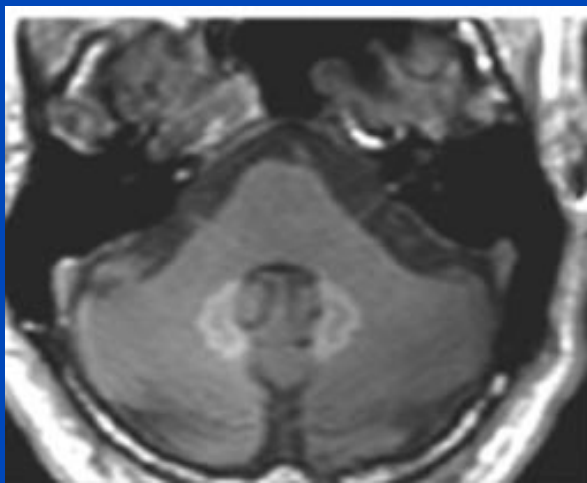
pre contrast T1 vs Laser ICP-MS: LINEAR GBCAs



Lohrke et al,
Invest
Radiol
2017



Roberts et
al,
Neurology
2017



Zhang et
al,
Radiology
2016

Hyperintense regions following 35 injections of lin. GBCAs: DN, Substantia Nigra..

Correlation between Gad accumulation displaying on ICP-MS and hyperintensities on MRI

Patient Studies: Hyperintensities in the Brain

Trade Name	Macrocylic GBCAs			Linear GBCAs		
	Gadovist	Dotarem	Prohance	Omniscan	Magnevist	Multihance
Kanda et al				Yellow	Yellow	
Errante et al				Red	Red	
Kanda II et al			Green	Red	Red	
Quattrocchi et al				Red	Red	
Radbruch I et al		Green		Red	Red	
McDonald et al				Red	Red	
Cao et al	Green			Red	Red	
Ramalho I et al				Red		Red
Stojanov et al	Red			Red		Red
Adin et al	Yellow		Yellow	Yellow	Red	Yellow
Weberling et al						Red
Radbruch II et al	Green					
Ramalho II et al				Red		Yellow
Tedeschi et al	Yellow	Yellow				
Ramalho III et al				Red		
Tanaka et al				Yellow	Yellow	
Cao et al II				Yellow	Yellow	Yellow
Hu et al					Red	
Flood et al					Red	
Roberts et al					Red	
Radbruch III et al	Green	Green				
Zhang et al				Yellow	Yellow	Yellow
Eisele et al		Green				
Schlemm et al	Yellow					
Radbruch IV et al	Green	Green				
Kuno et al					Red	
Bae et al	Green	Green				
Radbruch V et al	Green	Green				
Langner et al	Green	Green				
Ichikawa et al				Red		
Rossi-Espagnet et al		Red		Red		
Forslin et al		Yellow		Yellow	Yellow	
Schneider et al						Green
Müller et al	Green					
Yoo et al	Green					
Tibussek et al		Green	Green			
Lee et al		Green				
Renz et al	Green	Green		Red		
Eisele II et al		Green				
Bjomerud et al	Red					
Spendian et al	Yellow	Yellow				

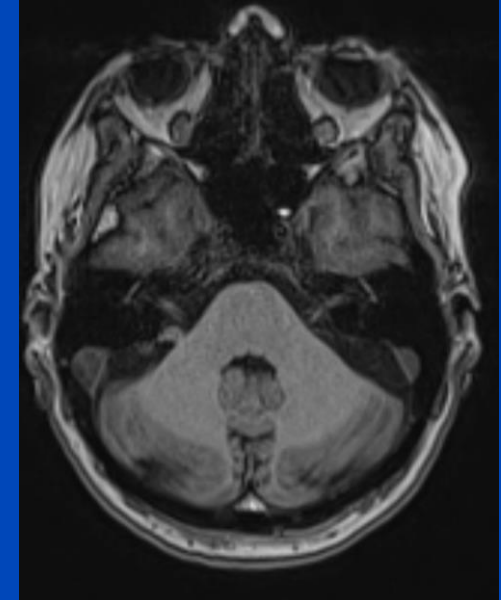
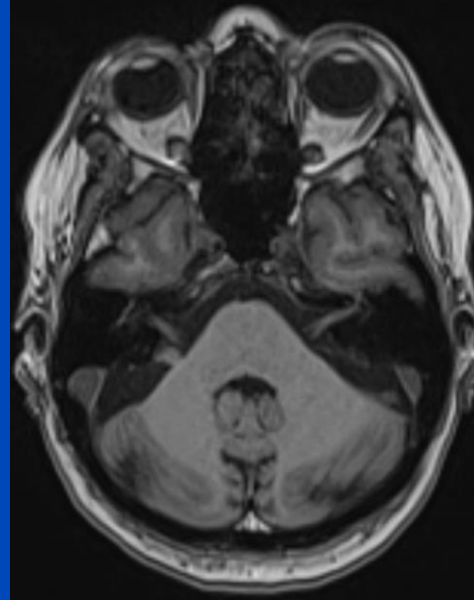
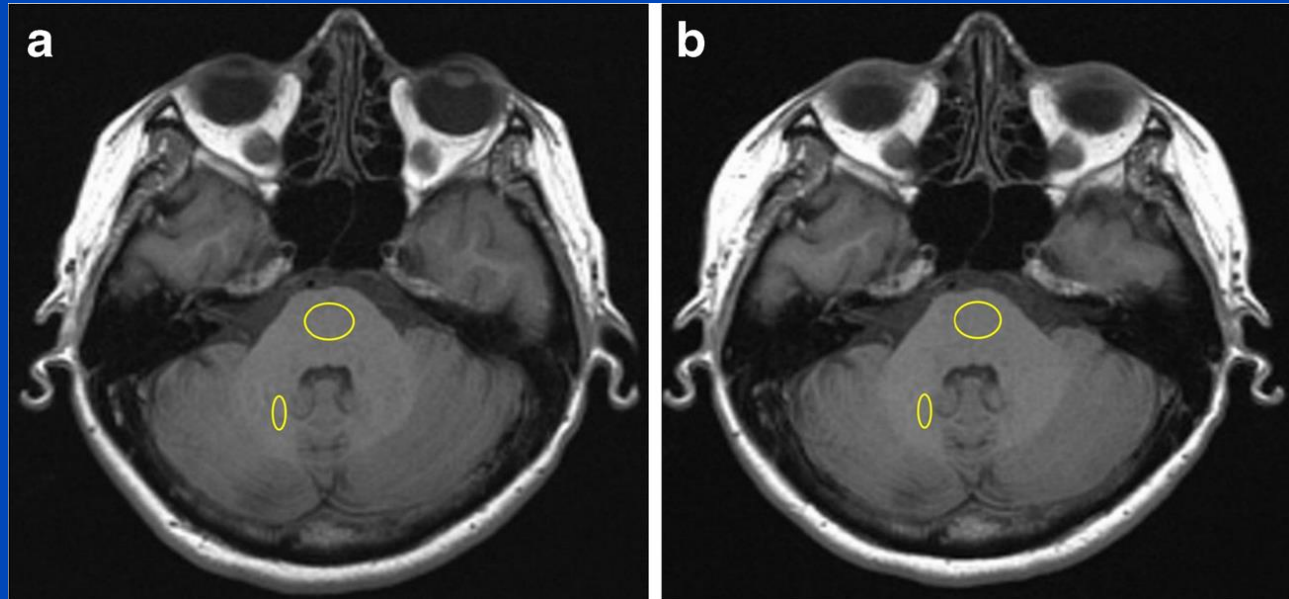
Quality of studies varies highly!

Stojanov 2015

Gadovist (macrocyelic)

- 4.74 ± 0.72 injections of Gadovist
- Significant SI increase DN - Pons ($p < 0.001$)

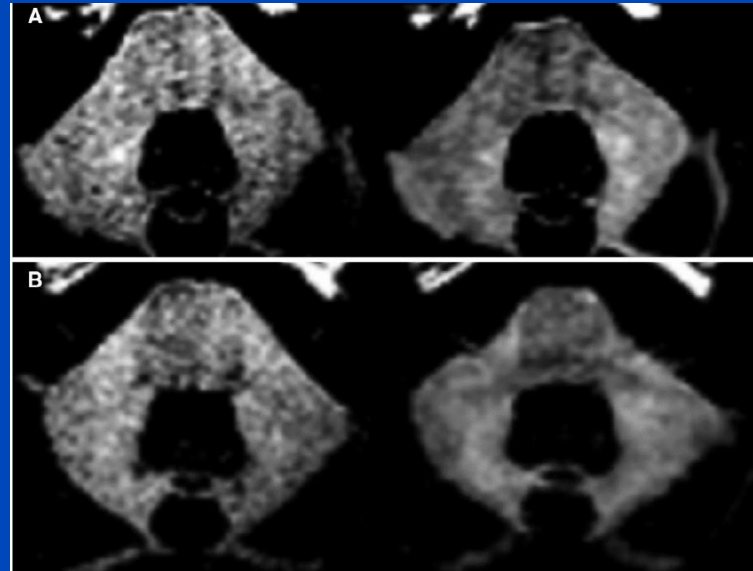
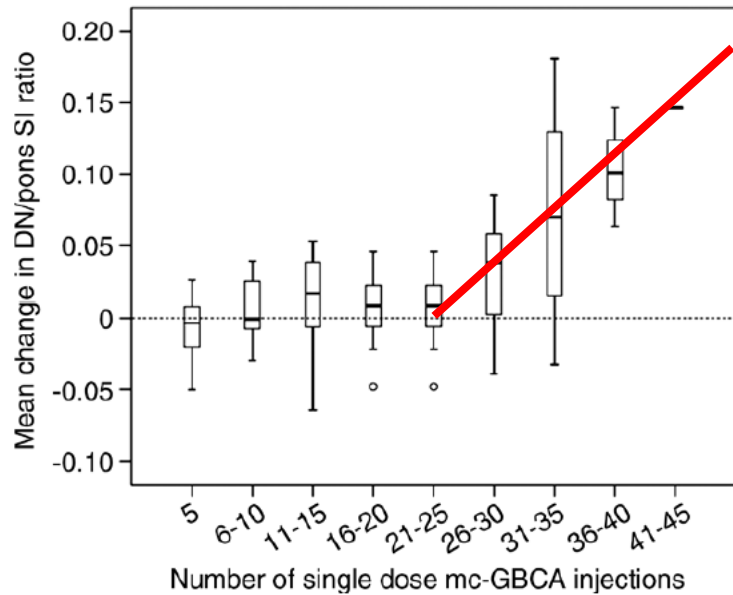
Stojanov et al Euro. Radiology 2015



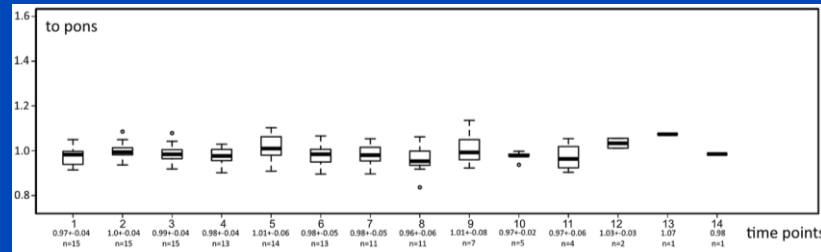
Example
(Radbruch et al,
unpublished):
Pre and after 29
injections of
Gadovist

Bjornerud 2017

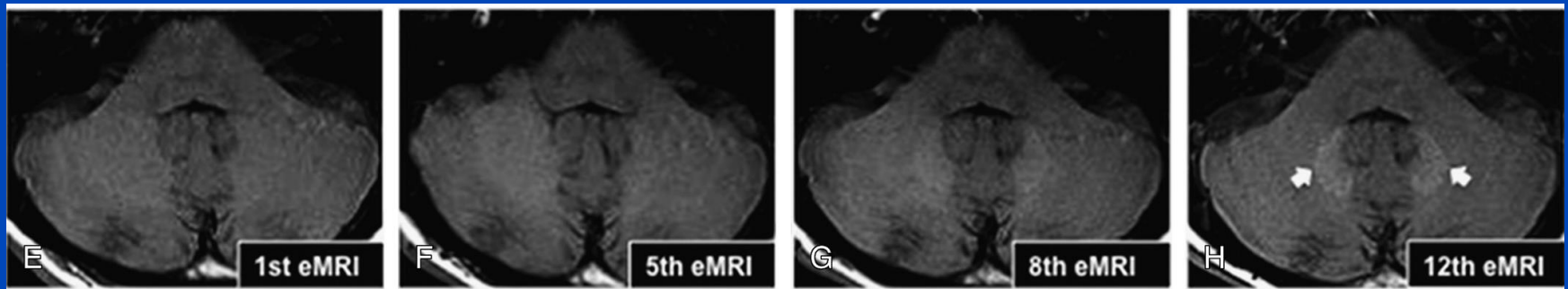
Gadovist (macrocyyclic)



- 17 Patients
- Abrupt increase after 26 injections (6 patients)
- Only in two patients „visible SI increase“

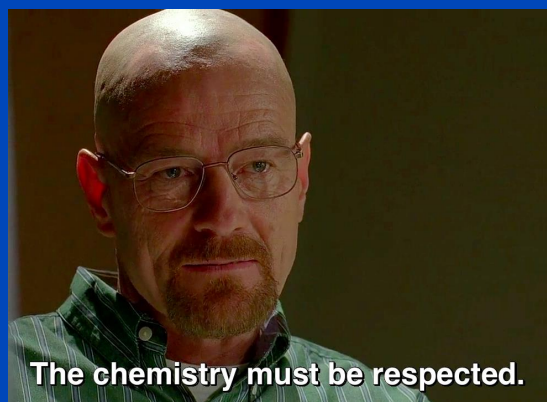


Müller et al,
Clinical
Neuroradiology
2017



Summary Gadolinium Deposition

Type	Linear GBCAs	Macrocyclic
1. In Vitro Experiments	Dechelation	Below the limit of detection
2. Animal Experiments	Dechelation and subsequent binding to Macromolecules or Precipitation	Below the limit of detection
3. Patient Studies	Majority of studies: Hyperintensities	Majority of studies: No Hyperintensities



The chemistry must be respected.

Chelated or dechelated gadolinium deposition

Although Vikas Gulani and colleagues¹ cite most of the recent literature

Letter to the ISMRM
Recommendation by Gulani et al

Radbruch et al, Lancet Neurology 2017

„All GBCAs deposit“ Misleading!

What should we do?

- Avoid studies that obviously cannot be finalized in reasonable time!
- Re-evaluate controversial studies!
- End the debate on hyperintensities!
- Comprehensive study in sheep starting in march 2018
- Establishing of a human tissue bank for all tissues
- It is not possible to prove the null hypothesis!