

Magnetic Resonance Imaging



- Instrumentation and Facilities
- Sequences
- Relaxation
- MRI contrast agents
- Protein MRI Contrast agents (PRoCAs)

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The Nobel Prize in Physiology or Medicine 2003

"for their discoveries concerning magnetic resonance imaging"

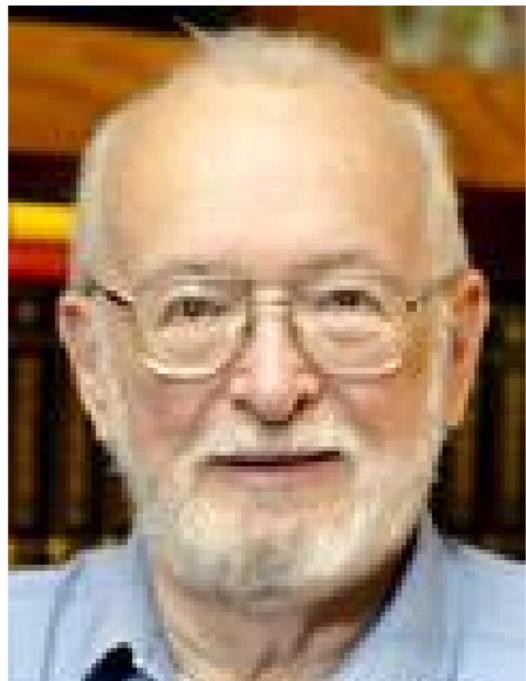


photo University of Illinois



photo PRB

Paul C. Lauterbur

Sir Peter Mansfield

Imaging System: 7T-210 mm

Imaging methods include

1. Relaxometric measurements (T1, T2 and T2* mapping)
2. Quantitative diffusion mapping (DWI) and diffusion tensor imaging (DTI)
3. Quantization of vascular leakiness and permeability of tumor tissue
4. Spectroscopic imaging of 1H metabolites to monitor cellular response to therapy
5. Blood flow measurements using ASL (arterial spin labeling)
6. BOLD (blood oxygen level dependent contrast) for fMRI studies



Bruker - AVANCE III 7T-30cm MRI/MRS Biospec®



- Is capable of executing a variety of high resolution & sensitive MRI and MRS ,
- For different types of animal models including mice, rats, hamsters, voles and marmosets.
- Biospec® is equipped per standards with the actively shielded B-GA 12S HP main gradient and shim set system (up to 440 mT/m)
- B-GA6S-100 gradient/shim insert set (to allow optimum gradient/shim performance for mouse experiments with higher gradient strength up to 1000 mT/m to achieve better contrast with higher resolution.
- A high power version providing 300 A / 500 V output for higher resolution to specifically perform mouse experiments, a high power shim amplifier (8 channels, max. 5 A / 18 V per channel),
- The BGA-26 gradient coil is the high performance, actively shielded alternative with unsurpassed slew rates up to 3440 T/m/s and gradient strengths up to 450 mT/m. Integrated shim coils deliver optimal field homogeneity for EPI, spectroscopy, and spectroscopic imaging applications.
- Volume resonators at a range of 35 mm, up to 72 mm inner diameters, ensure the maximum signal-to-noise ratio and RF-homogeneity. Active RF decoupling allows the flexible operation of independent transmit and receive coils. Multi-channel array coils enable parallel imaging applications and integrated preamplifiers guarantee the optimal sensitivity over a large dynamic range. Hardware recognition of RF coils automatically configures all relevant parameters.
- The ParaVision® 6.0 acquisition workplace

info@bruker-biospin.com

www.bruker.com/paravision

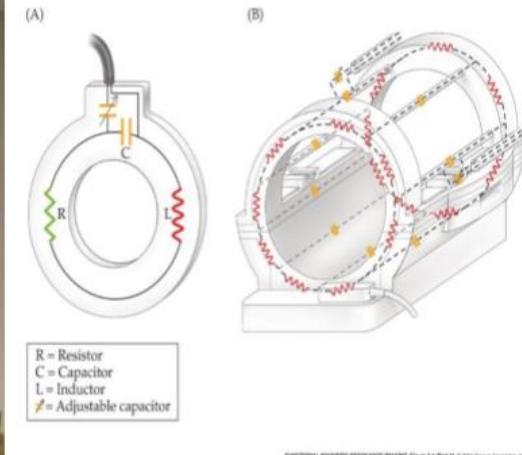


Welcome to CABI!

The Georgia State / Georgia Tech Center for Advanced Brain Imaging is located in midtown Atlanta. Our 3-Tesla Siemens Trio Magnetic Resonance Imaging system allows us to investigate brain function and structure.



Human MRI 3T: 60cm



Surface or volume coil

UGA 3 Tesla magnet

RF coils are quite varied

- Transmit coils and gradient coils are often fixed in the bore much like a high resolution system
- Observe coils may be localized on animal like these surface coils



From Doty Scientific

Emory /GT Biomedical Imaging Technology Center (BITC)

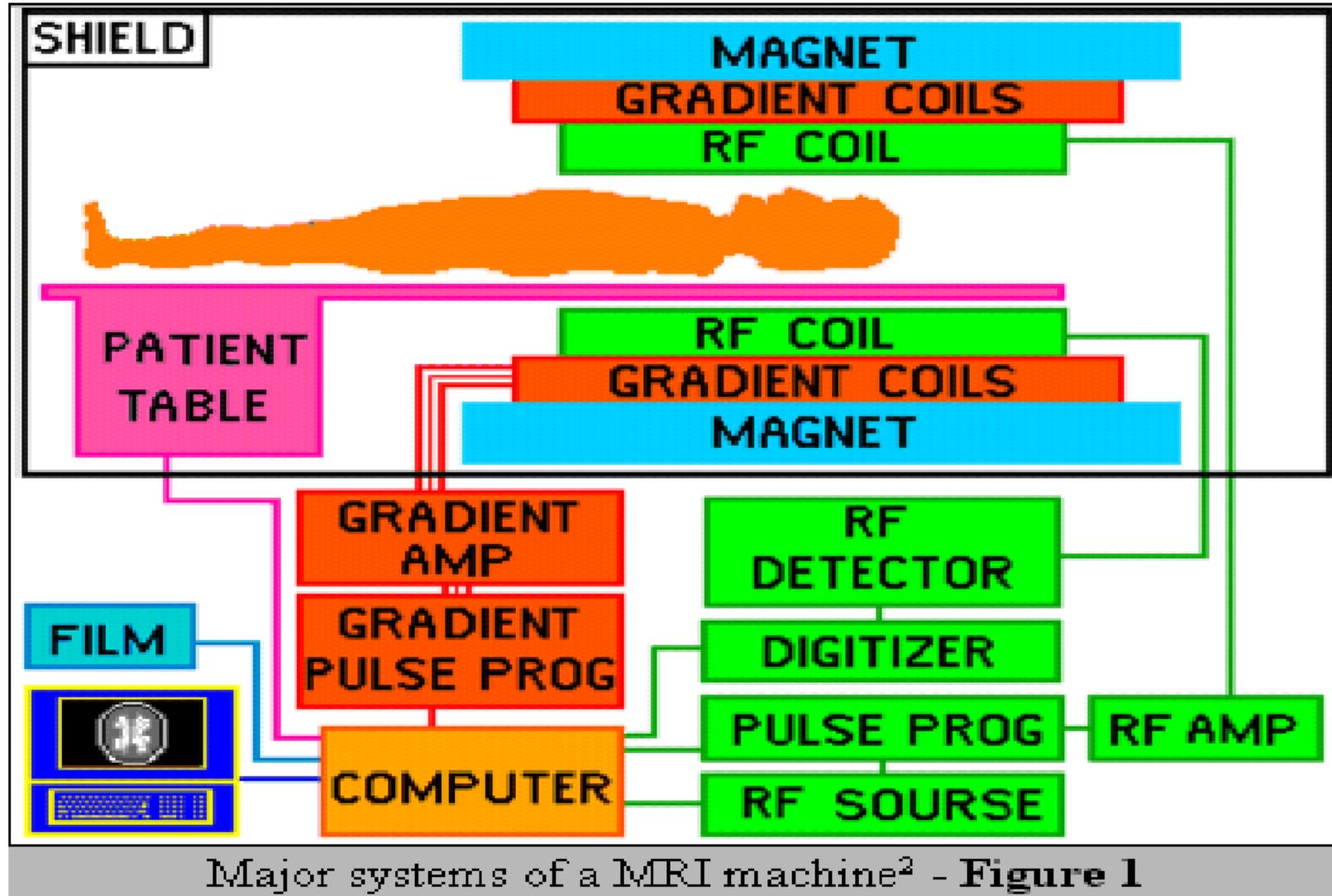
- **3 T Siemens Magnetom Prisma™ whole-body MRI** with 5-10% increase in sensitivity, doubling of the gradient strength, which will allow us to go to a higher resolution and/or shorter TE than currently available
- **9.4T/20-cm Bruker animal MR imaging/MRS**
- **RF coils:**
 - 64, 24 channel Head-Neck array coil [Siemens]
 - Spinal Matrix coil [Siemens]
 - Flexible Body Matrix coil [Siemens]
 - CP Extremity Coil (Knee coil) [Siemens]
 - CP Wrist Coil [Siemens]
- **Managed Peripheral Equipments**
 - [Invivo](#) Vital Sign Monitor (MRI compatible) -- ECG, SpO₂, EtCO₂, and HR (heart bit rate); external trigger signal and synchronized vital signal digital recording. Home-made visual stimulation setup.
 - [Avotec RE-5721](#) Eye Tracker. [Current Designs, Inc.](#) optical button box -- non-audio patient response.
 - Home-made single large button -- simple response. Home-made buzzer -- tactile stimulation.



Georgia Tech NMRI-MR core facility

- Bruker Pharmascan 7T -160 mm
- Gradient system (i.d. 90 mm).
- The maximum Gradient strength is 300 mT/m. RF resonator (i.d. 38 mm) optimized for the study of small rodents.
- * RF resonator (i.d. 60 mm) for the study of larger objects. *
- Transmit/Receive Surface coil (16 mm) for the study of small areas on large objects. *
- Animal beds and anesthesia unit. * Animal monitoring system.

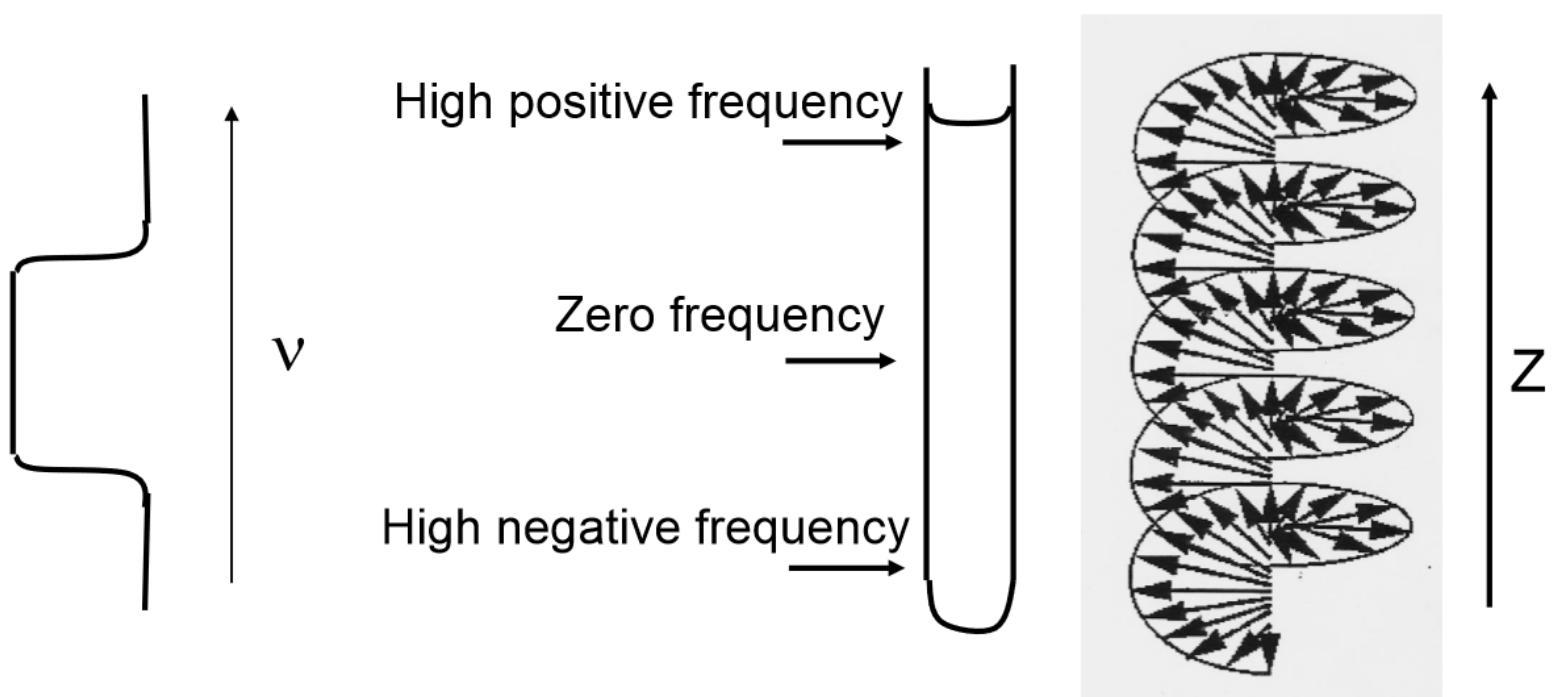
General Imaging System Components



(From Joy Hirsh, Columbia University)

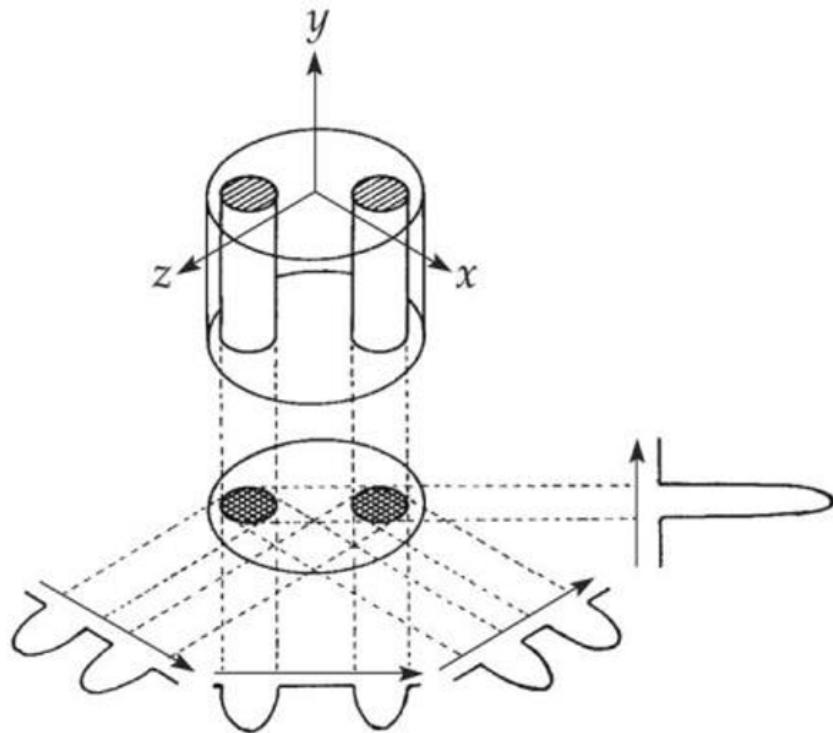
Simple Imaging Strategy

- During gradient spins in each volume element have their own precession frequency
- Can get a 1D image of sample – used in gradient shimming

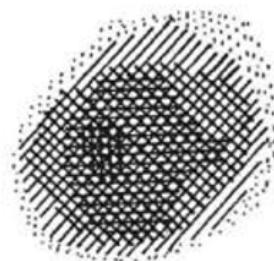


Early Images Were Based on Tomography

(A)



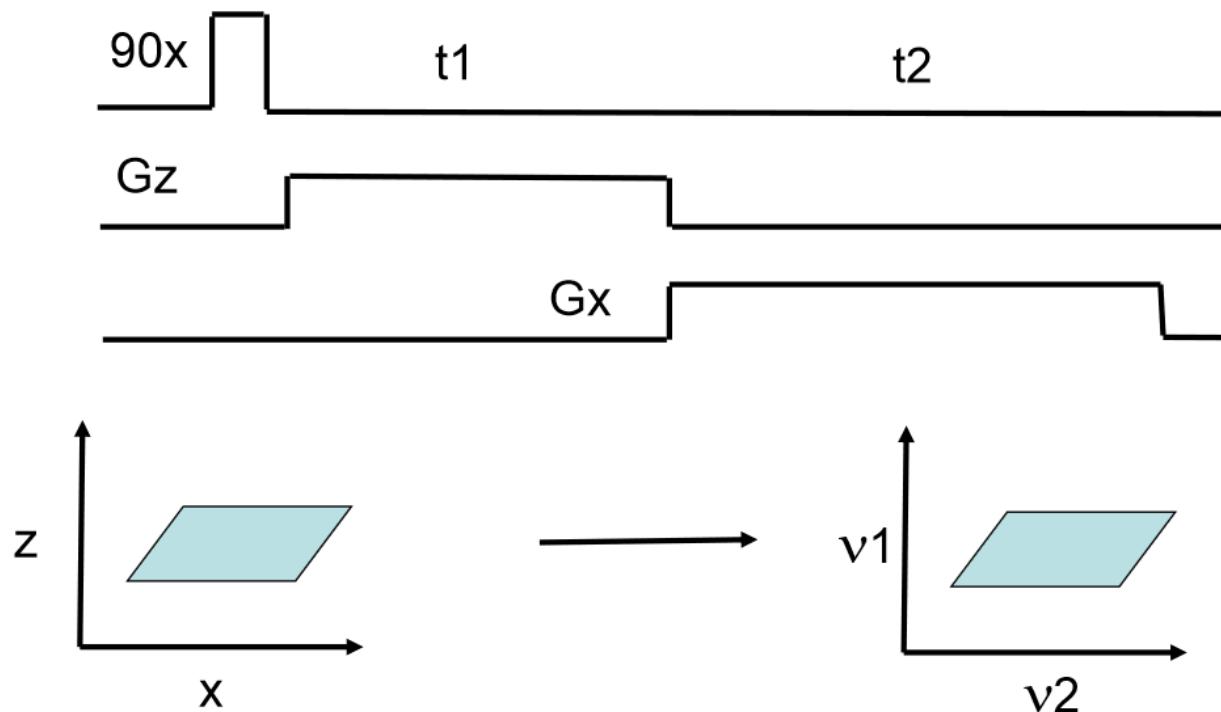
(B)



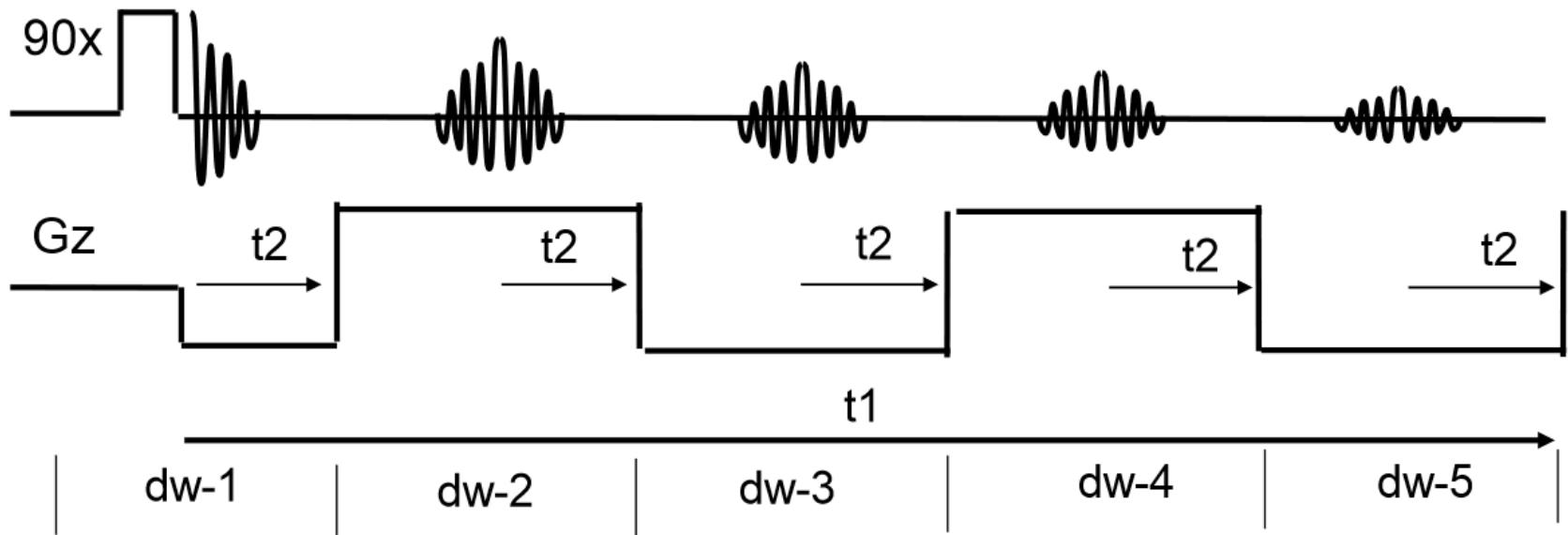
Phantoms at particular regions of space give only signals at frequencies corresponding to those regions. Gradients applied in different directions can be combined for a 2(or 3)D image.

Simple 2D Image

- For 2D imaging use gradients in different directions (x, z) in different evolution periods (t_1, t_2)



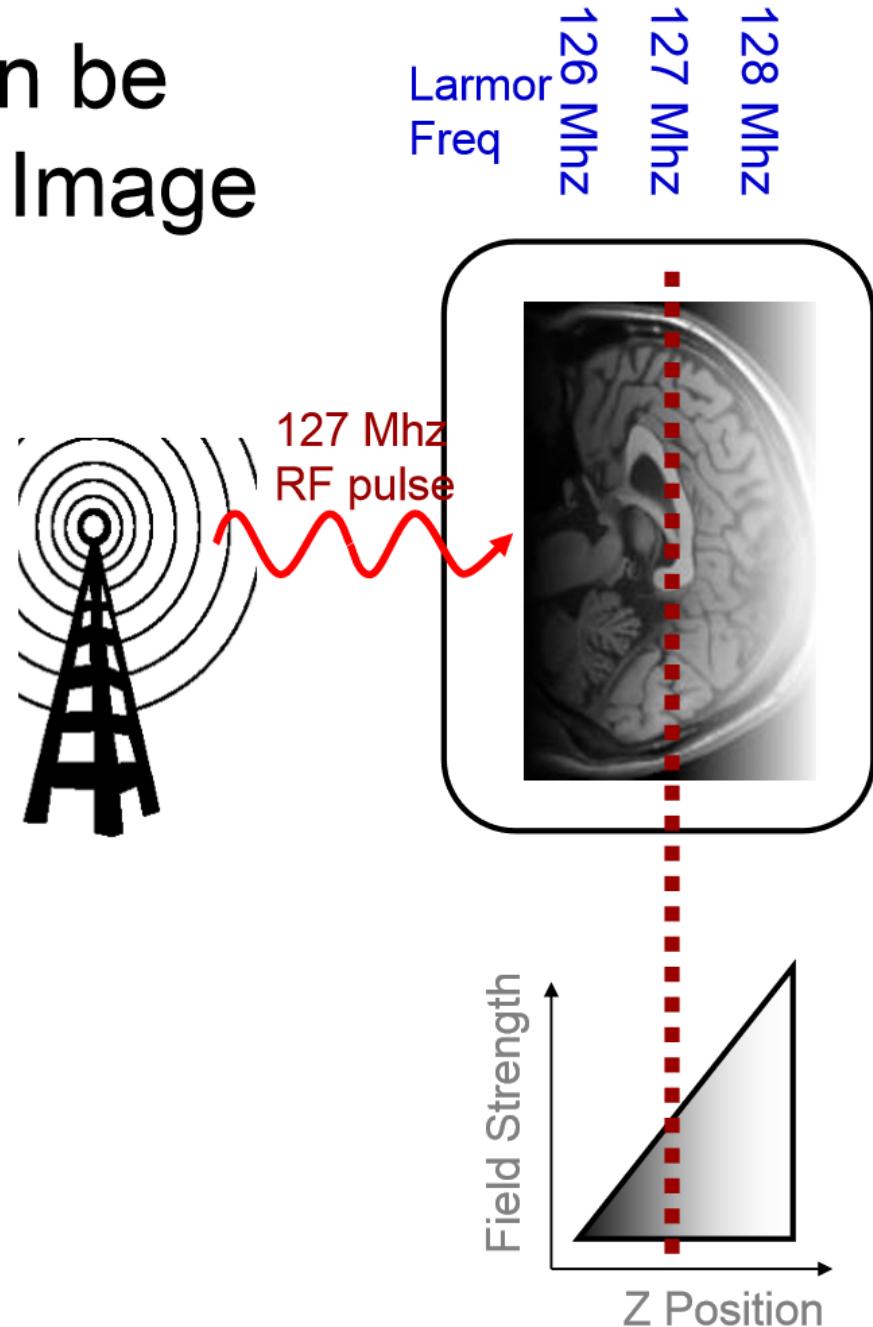
Echo Planar Imaging – Speeding up Acquisitions



- t_2 will have spatial image (needs to be reversed in even dw)
- t_1 can sample a number of different properties
- t_1 could have a gradient in another dimension – 2D map
- t_1 could sample chemical shift dispersion - MRSI

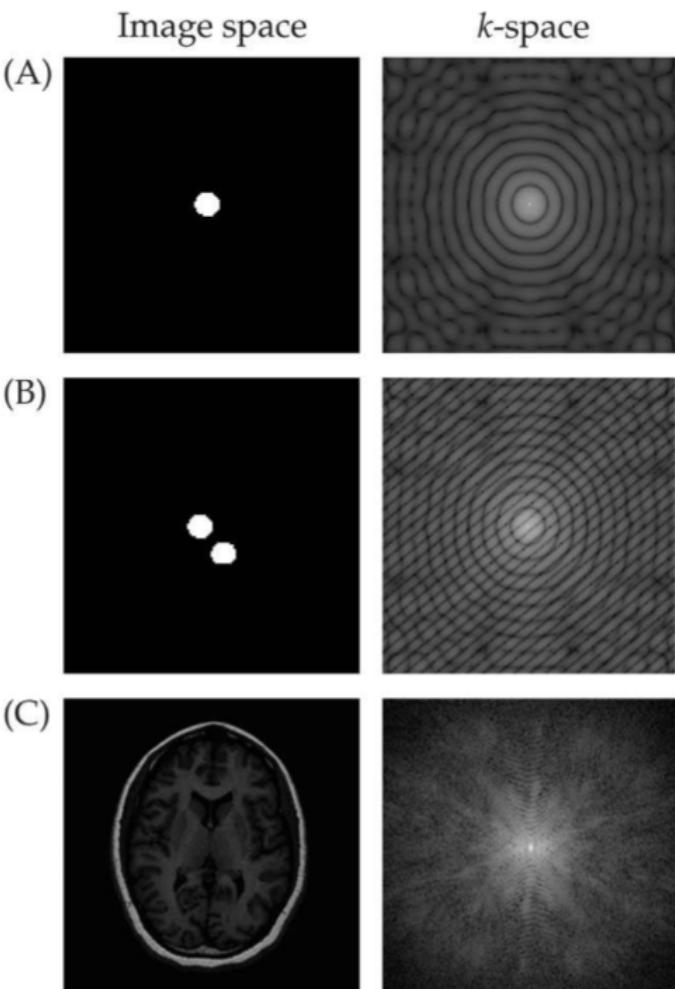
Slice Selection can be combined with a 2D Image

- Strong gradients make Larmor frequencies different at different positions.
- A long (often shaped) RF pulse only energizes slice where field strength matches Larmor frequency.



Data Processing

Fourier Transform in k Space



$$k(t) = \int^t \gamma (dB/dx) dt'$$

for a time independent gradient

$$k(t) = \text{const} \cdot t$$

k can replace t in normal in t/ω FT

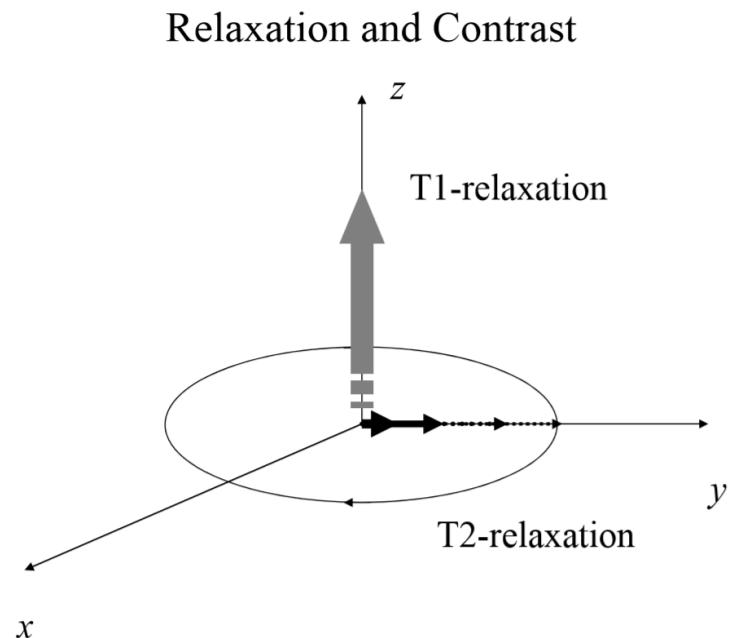
to generate a space/reciprocal space FT

$$\rho(x) = \int_{-\infty}^{\infty} S(k) e^{-i2\pi \cdot kx} dk$$

1. A simple circle at the center of the image space and the representation of the circle in k-space. Note that the k-space has the greatest intensity at the center.
2. Additional of a second circle to the image space introduces a grating pattern to the k-space.
3. An image of the brain contains much more spatial information, with much more complex k-space representation

CONTRAST MECHANISMS in MRI

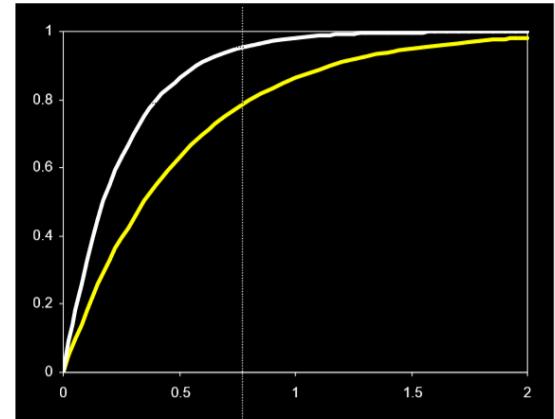
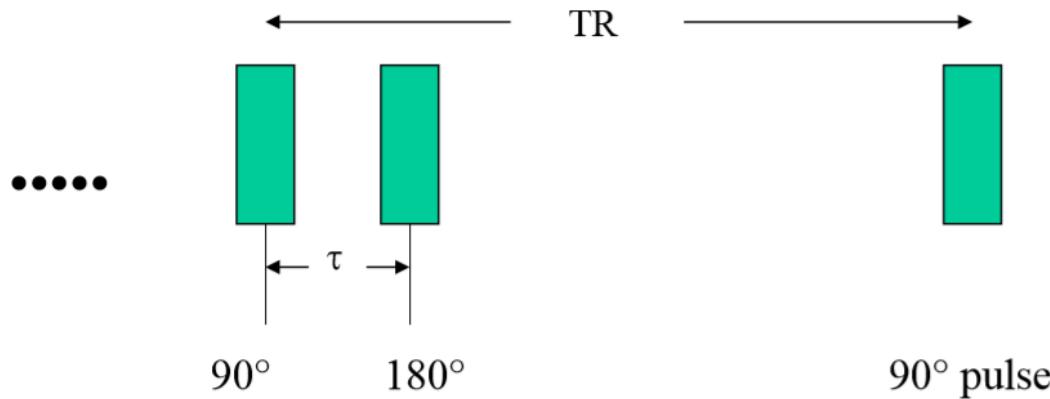
- T1(Spin-lattice Relaxation time) relaxation along B_0
 - T2(Spin-spin relaxation time) relaxation perpendicular to B_0
- T2*(Signal decay perpendicular to B_0) due to dephasing plus T2



Relaxation in Tissue

- Image intensity in MRI depends on a number of factors, including proton density, relaxation, blood flow, diffusion, and magnetic field strength. But the most important factors are the relaxation processes.
- Relaxation in Tissue
- Thermal motion depends on molecular size and structure and environment
- Relaxation times of protons are thus highly dependent on its environment
- Diffusion of protons near efficient relaxation sites enhances the relaxation of the entire population
- This also suggests the possibility of introducing efficient relaxation promoters as contrast agents
- In general, relaxation times in biological systems are shortened compared to those in pure water.
- In addition, T2 is often several times smaller than T1.
- In disease states, the microscopic environment is likely altered, changing the relaxation times

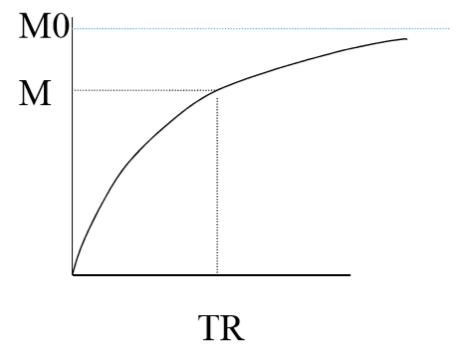
T1-Relaxation



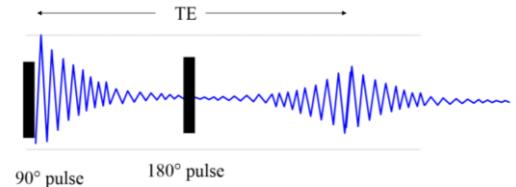
T1-relaxation: Growth of magnetization for next nutation

$$M = M_0 \left(1 - 2e^{-(TR-\tau)/T_1} + e^{-TR/T_1} \right)$$

$$\tau \ll TR \Rightarrow M = M_0 \left(1 - e^{-TR/T_1} \right)$$



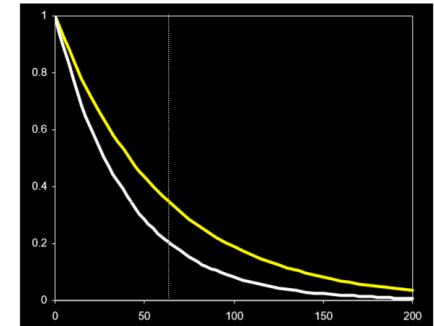
T2-Relaxation



$$s(TE) = s(0)e^{-TE/T_2}$$

Signal decay due to transverse relaxation

- Irreversible processes (T_2)
- Dephasing due to different frequency of precession in the presence of magnetic field inhomogeneities (reversible) (T_2').



$$1/T_2^* = 1/T_2 + 1/T_2'$$

Characterizes decay due to both processes.

Spin-echo Signals vs Weighting Schemes

Signal for a spin-echo sequence

$$\begin{aligned}s_{se} &= s(0)e^{-TE / T_2} \\&= M_0(1 - e^{-TR / T_1})e^{-TE / T_2} \\&\propto \rho(1 - e^{-TR / T_1})e^{-TE / T_2}\end{aligned}$$

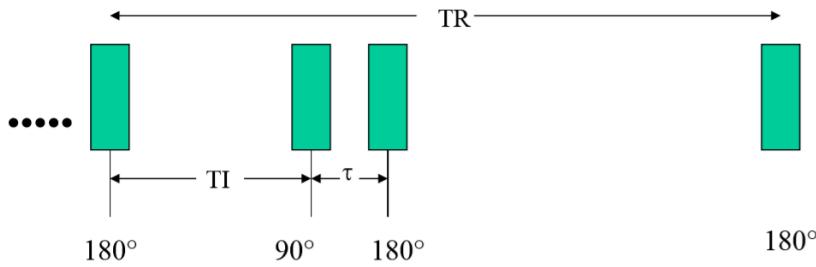
Weighting Schemes

weighting	Proton-density	T1	T2
TR	Long	Short	Long
TE	Short	Short	Long

- Contrast in a spin-echo sequence
 - Dependence on tissue and sequence parameters
 - Various types of weighting

Inversion Recovery IR

Inversion recovery sequence

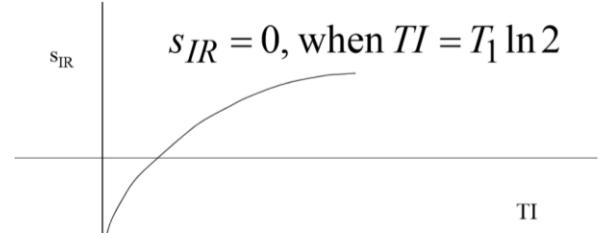


$$\dots \dots s_{IR} = M_0(1 - 2e^{-TI/T_1} + e^{-TR/T_1})e^{-TE/T_2}$$
$$\propto \rho(1 - 2e^{-TI/T_1} + e^{-TR/T_1})e^{-TE/T_2}$$
$$\text{if } TR \gg T_1, s_{IR} = \rho(1 - 2e^{-TI/T_1})e^{-TE/T_2}$$

$$M(TI) = M_0(1 - 2e^{-TI/T_1} + e^{-TR/T_1})$$

assuming $\tau \ll (TR - TI)$

$$\text{If } TR \gg T_1, M = M_0(1 - 2e^{-TI/T_1})$$



- Signal can be negative –An artificial line may be seen if magnitude is displayed – Accurate phase information needed for signed display •Bigger dynamic range and more contrast •IR nulling point can be used to determine T_1 •Usually more time consuming •

Applications: STIR, FLAIR

Bruker TD-NMR Minispec Relaxometry

the minispec Range of MRI Contrast Agent Analyzer

Analyzer	Frequency	Magnetic Field	Relax. time	Remark
mq60	60 MHz	1.41 T	T1, T2, T1rho, T2e etc.	unique benchtop TD-NMR system at clinical MRI field
mq40	40 MHz	0.94 T	T1, T2, T1rho, T2e etc.	unique benchtop TD-NMR system. Relaxation time information at ca. 1 T
mq20	20 MHz	0.47 T	T1, T2, T1rho, T2e etc.	Relaxation time information at common TD-NMR field
mq10	10 MHz	0.23 T	T1, T2, T1rho, T2e etc.	Relaxation time information at common TD-NMR field
mq7.5	7.5 MHz	0.17 T	T1, T2, T1rho, T2e etc.	Relaxation time information at low field



Key minispec TD-NMR Applications:

- Solid Fat Content Analysis (SFC) in Fat Compositions (ISO, AOCS, IUPAC International Standard Methods)
- Solid Fat Content Analysis (SFC) in Chocolate Products
- Total Fat Content in Chocolate
- Total Fat Content in Cacao Powder
- Total Fat Content in Chocolate Liquor
- Total Fat Content in Cacao Beans

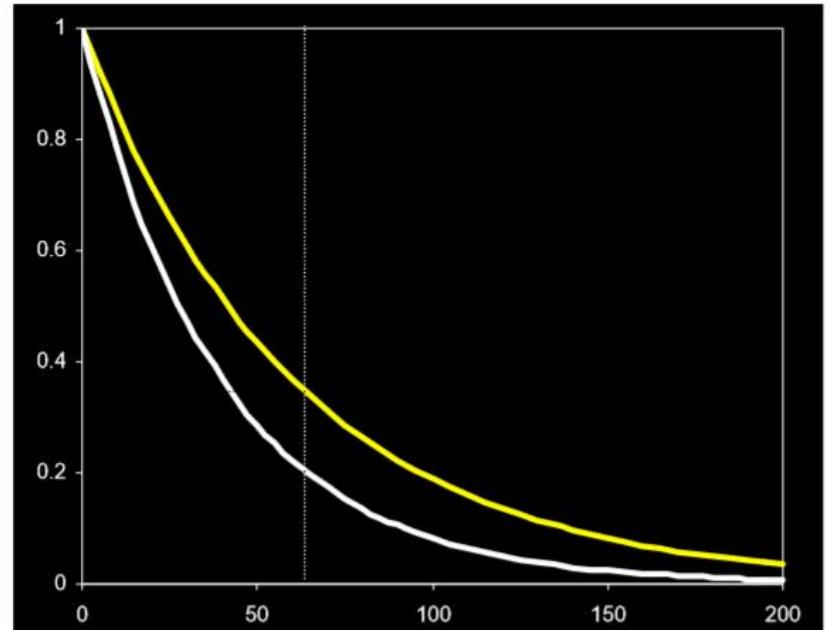
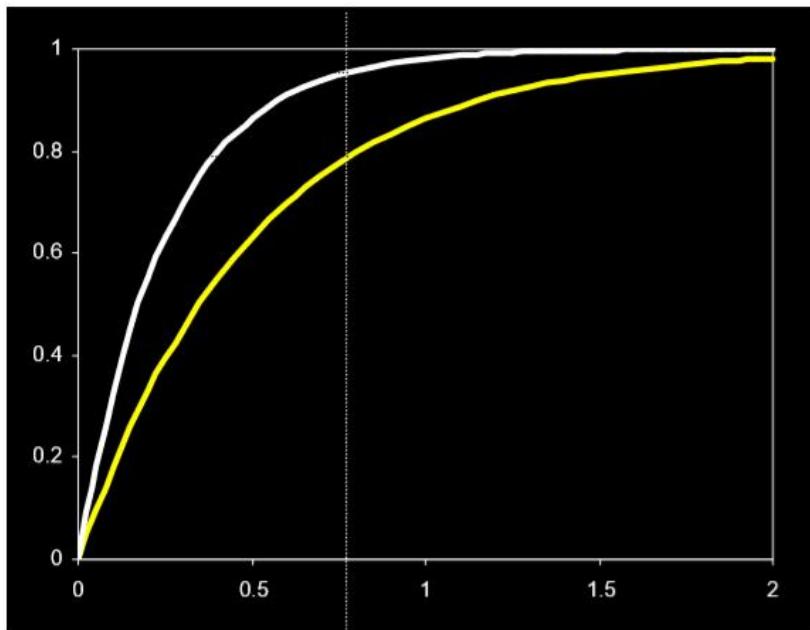
R&D Applications:

- Droplet Size Analysis in Emulsions
- 1d Profiling of Chocolate Samples, like for investigation of fat migration and bloom
- Investigation of Fat Crystal Structures

MR Contrast Agents

- In MRI, contrast agents are usually used to improve the visibility of diseased tissues.
 - T1 contrast: increase R1 relaxation rate, e.g. Gadolinium (Gd), Mn²⁺
 - T2 contrast: increase R2 rate, e.g. iron oxide nanoparticles
 - Chemical exchange saturation transfer (CEST): nucleus exchanges between two or more chemical environments
 - Heteronuclear contrast: non-proton based, e.g. ¹⁹F, ¹²⁹Xe, or ¹³C

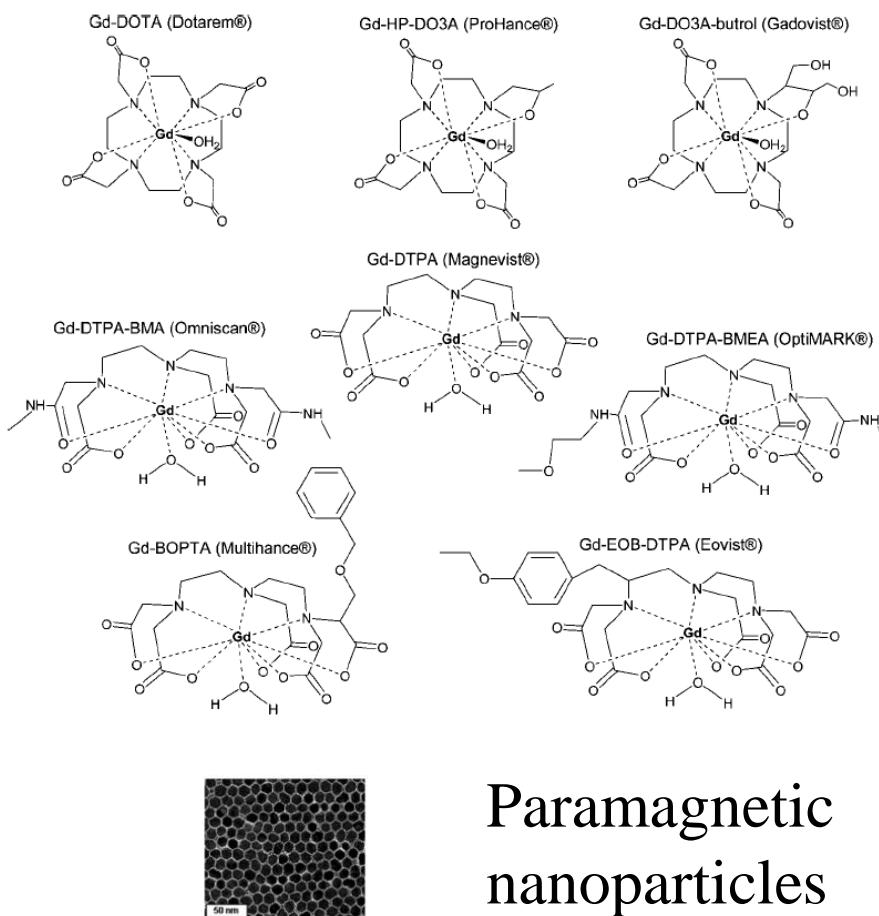
Relaxation and Contrast



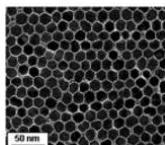
T1-relaxation: Growth of magnetization for next nutation

T2-relaxation: decay of magnetization being detected

Limitations of Clinically approved Contrast agents

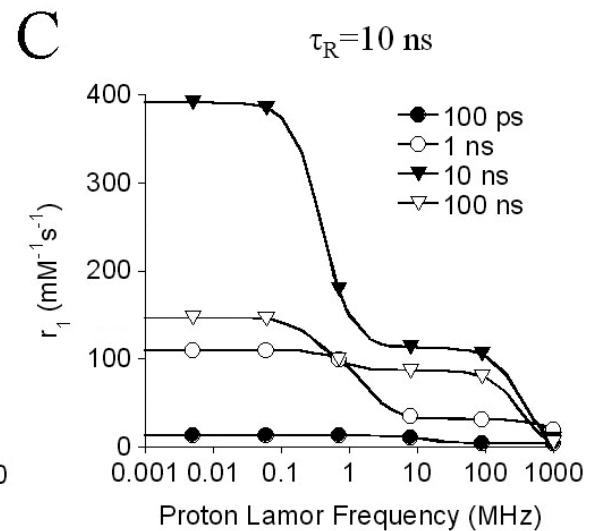
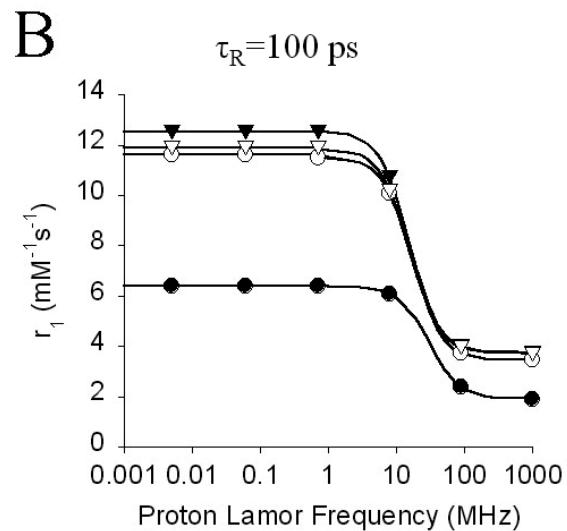
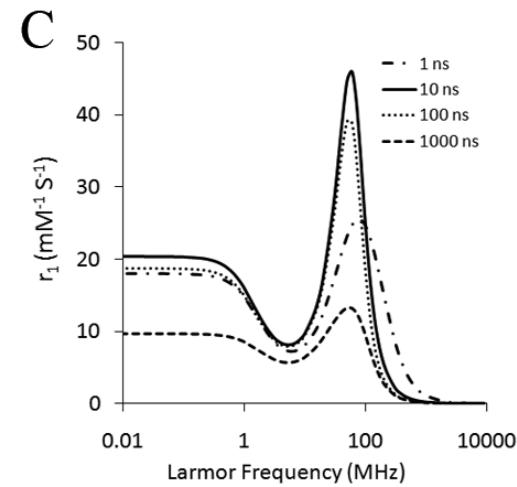
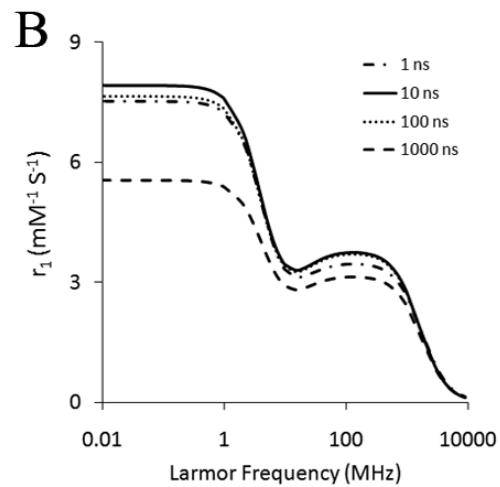
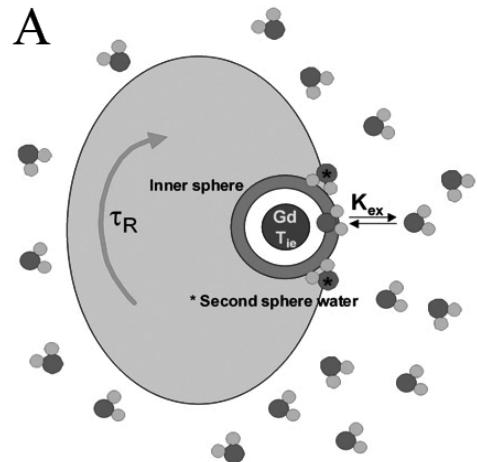


- Low relaxivity and requires high dose injection (0.3-0.5 M)
- **Low sensitivity**, and low accuracy/specificity
Low S/N, Conc > 0.10 mM
No capability for biomarkers at $\mu\text{M} \sim \text{nM}$ for molecular imaging
- **Low resolution**
 - Detection size > **1-2 cm**
 - Non-ideal PK/PD with limited MRI window required for high quality imaging
- Gd Toxicity/Blackbox warning

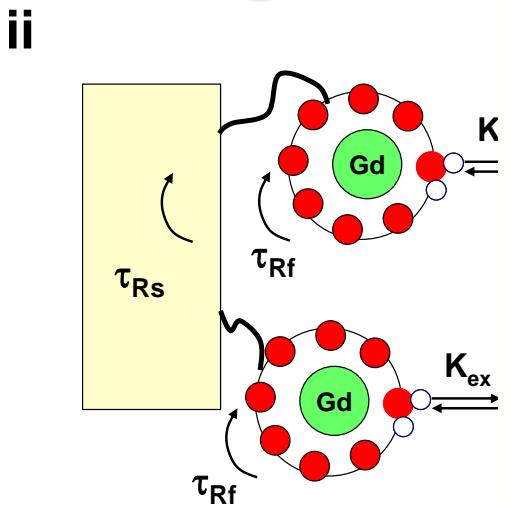
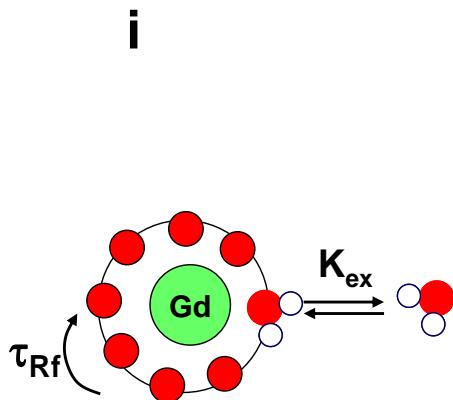


Paramagnetic nanoparticles

There is a strong need to develop MRI contrast agents with high relaxivity, optimized *in vivo* retention time, organ preference, and targeting capability.

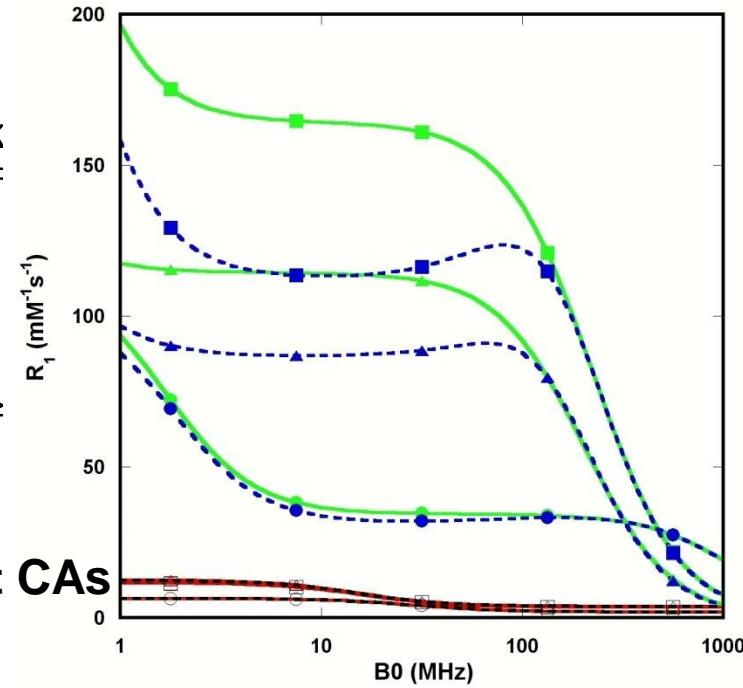


Contrast Agents vs. relaxation



$$\frac{1}{T_1} = \frac{cq}{T_{1M} + \tau_M}$$

$$\frac{1}{\tau_c} = \frac{1}{T_{1e}} + \frac{1}{\tau_m} + \frac{1}{\tau_R}$$



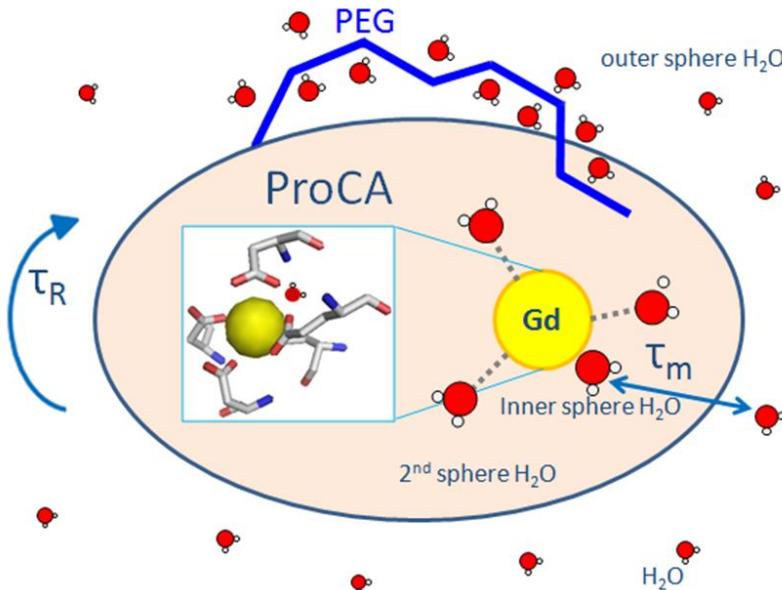
Current CAs

A major barrier to the application of MRI technique is its low sensitivity and contrast limited by the fast rotational correlation time of the molecule (ps).

Macromolecule generated by either covalent binding or the non-covalent nature of the binding between the monomeric agent and the macromolecules has the improvement in proton relaxivity is much less than the expected increase based on the molecular-weight increase due to high internal mobility of the paramagnetic moiety and limited water exchange rate.

ProCAs developed by protein design with increased relaxivity by controlling relaxation and the capability of targeting specific molecular entities such as cancer biomarkers.

Increase Both R1 and R2 by Protein Design

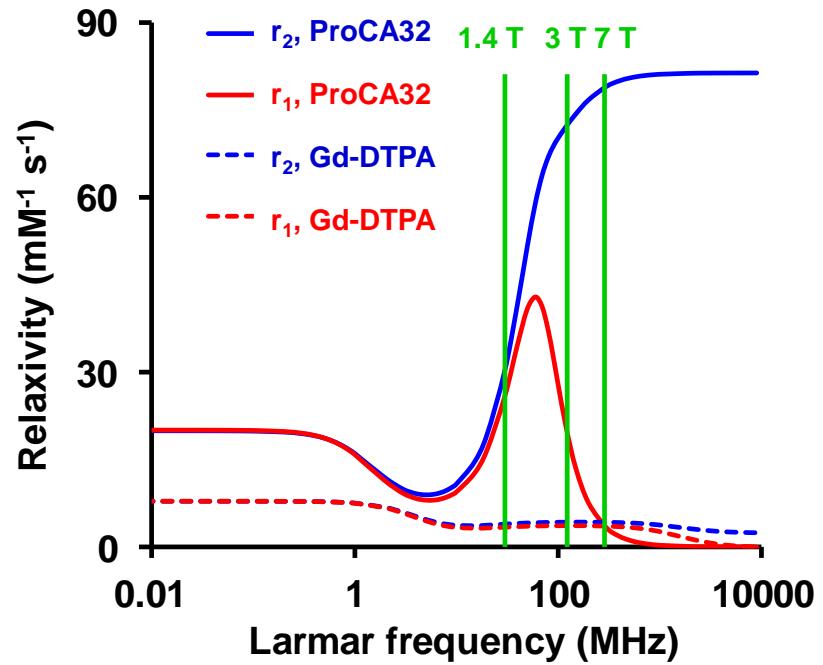


$$\frac{1}{T_1} = \frac{cq}{T_{1M} + \tau_M} \quad \frac{1}{\tau_c} = \frac{1}{T_{1e}} + \frac{1}{\tau_m} + \frac{1}{\tau_R}$$

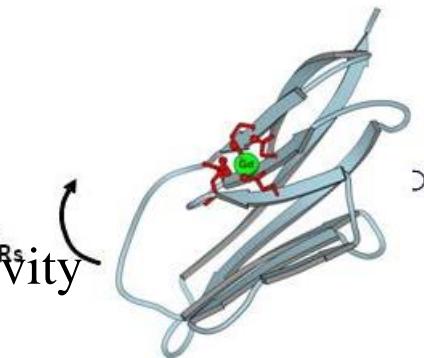
$$\frac{1}{T_1^{2nd}} = \frac{cq^{2nd}}{T_{1m}^{2nd} + \tau_m^{2nd}}$$

$$\frac{1}{T_{1m}^{2nd}} = \frac{2}{15} \frac{\gamma_I^2 g^2 \mu_B^2}{(r_{GdH}^{2nd})^6} S(S+1) \left(\frac{\mu_0}{4\pi}\right)^2 \left[\frac{7\tau_{c2}^{2nd}}{(1+\omega_s \tau_{c2}^{2nd})^2} + \frac{3\tau_{c1}^{2nd}}{(1+\omega_I \tau_{c1}^{2nd})^2} \right]$$

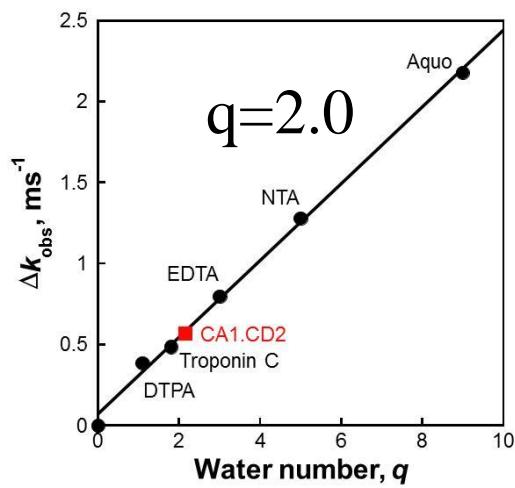
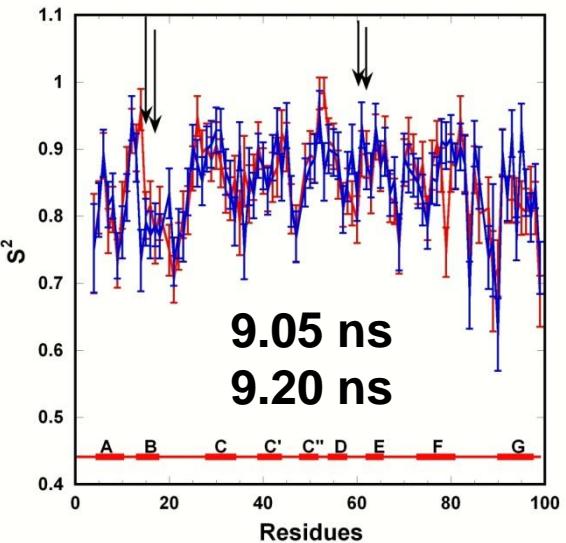
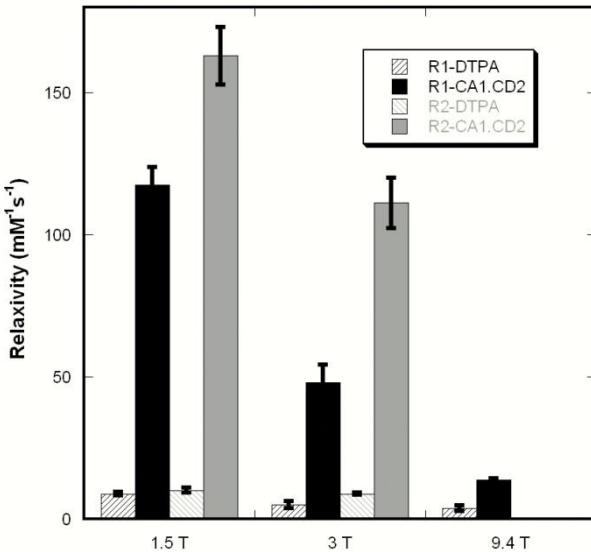
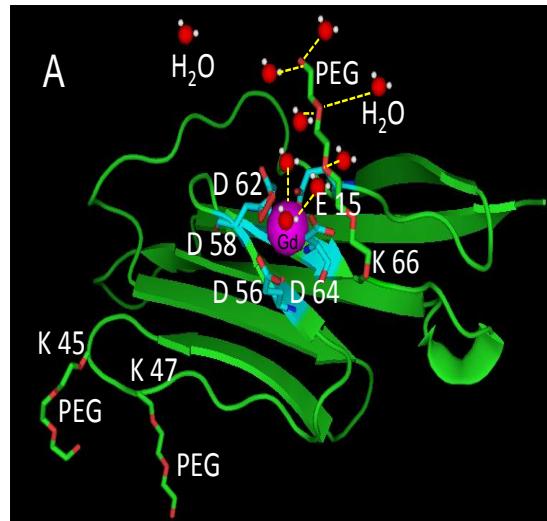
At 20 MHz with rGdH2nd=5 Å and q=6, the second sphere relaxivity could potentially increase to 5.2 mM⁻¹ s⁻¹.



Protein-based Contrast Agents (ProCAs)

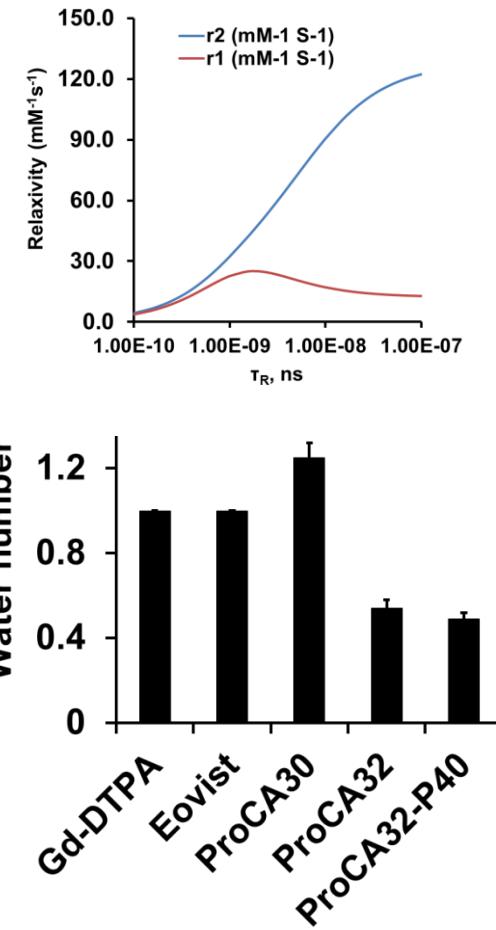
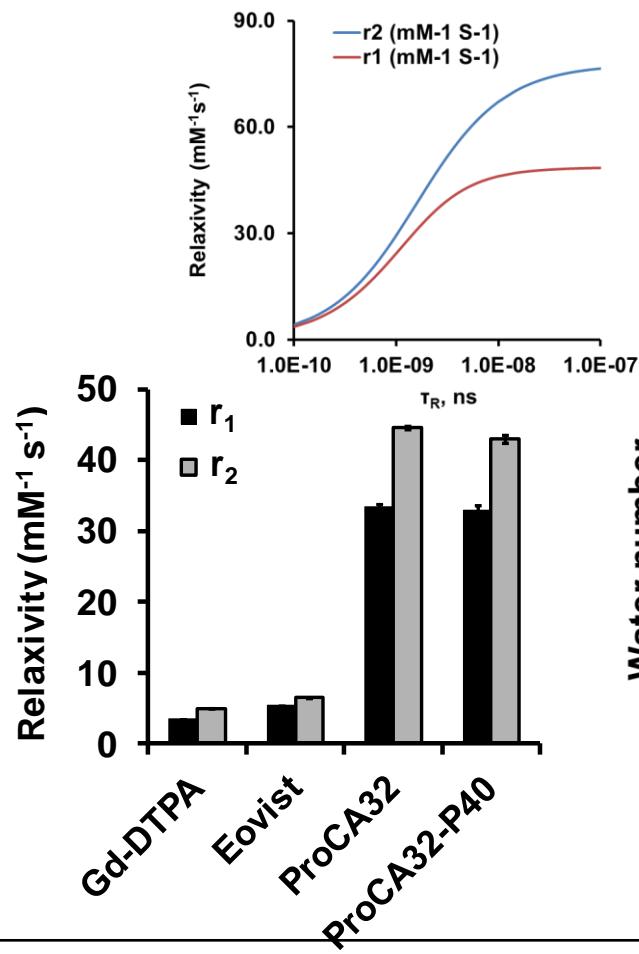
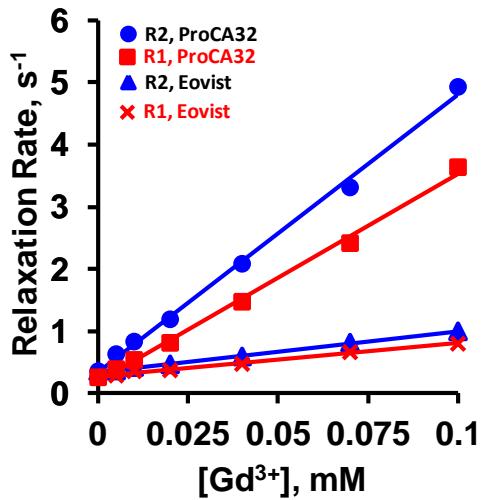
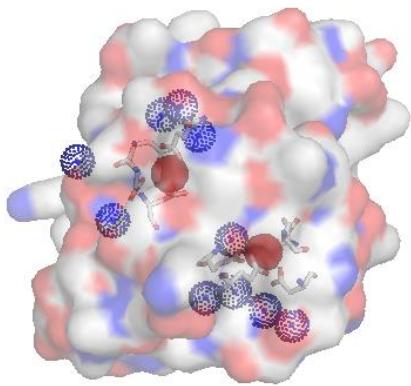


ProCA1 as a MRI contrast agent



Sample	Gd ³⁺	Zn ²⁺	Ca ²⁺	Mg ²⁺	Log (K _{Gd} /K _{Zn})	Log (K _{Gd} /K _{Ca})	Log (K _{Gd} /K _{Mg})
DTPA ²⁸	22.45	18.29	10.75	18.20	4.17	11.70	4.25
DTPA-BMA ⁴¹	16.85	12.04	7.17	na*	4.81	9.68	na*
CA1.CD2	12.06	6.72	<2.22	<2.0	5.34	>9.84	>10.06

ProCA32 with multiple Gd^{3+} binding sites

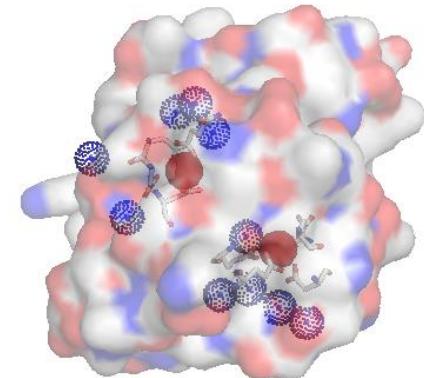
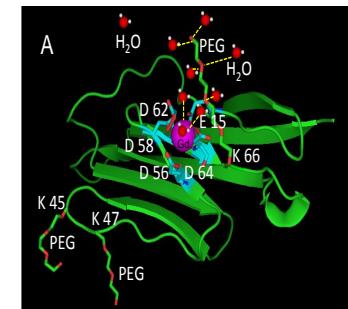
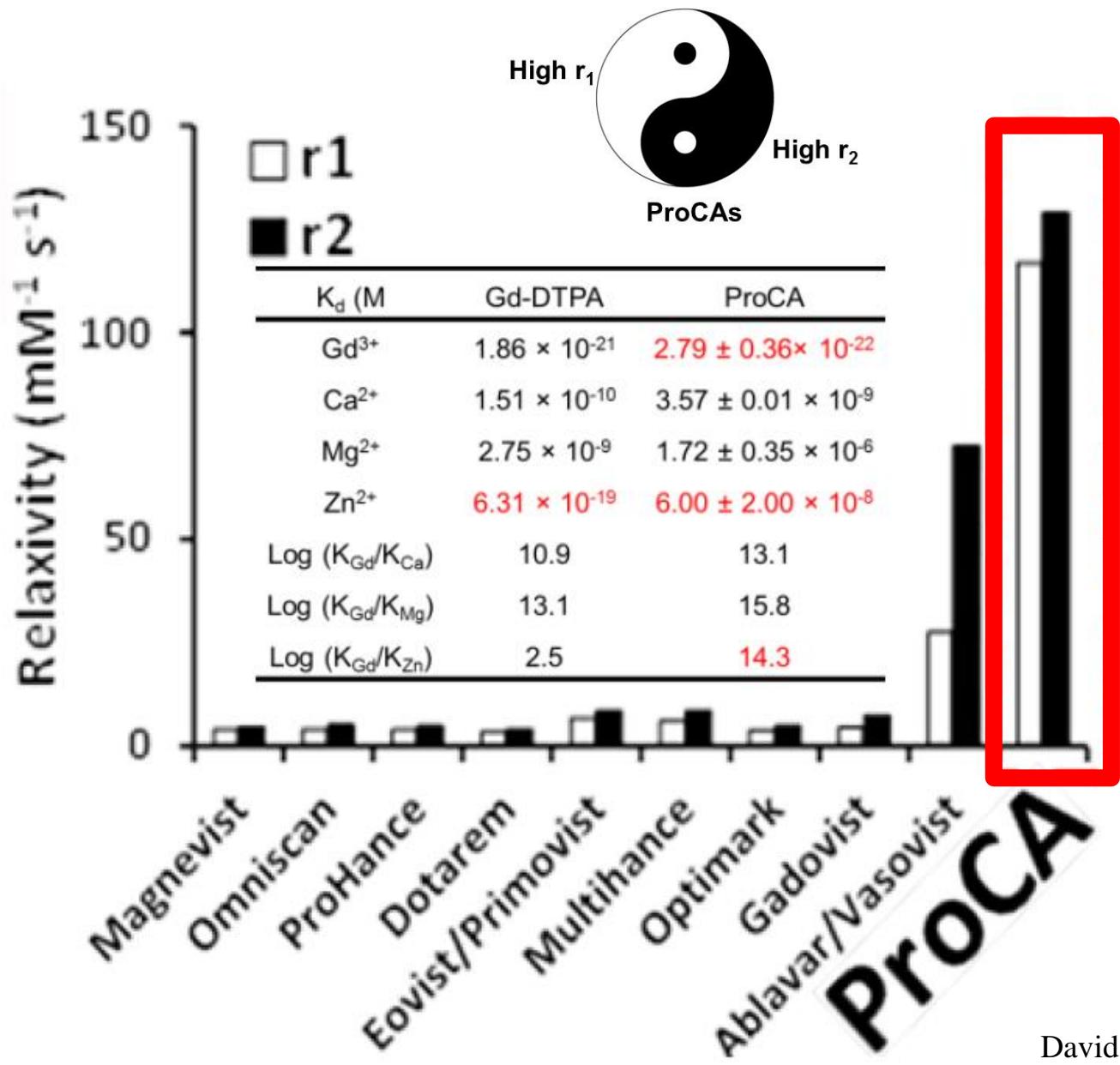


per Gd relaxivities

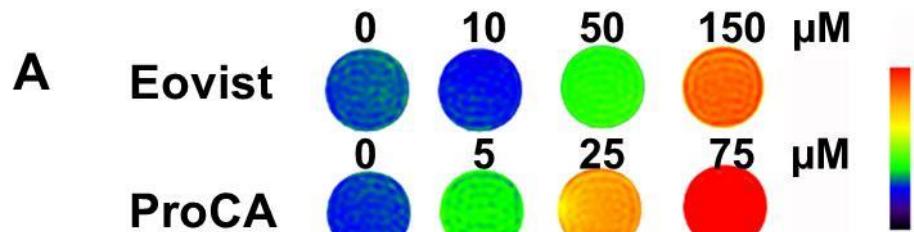
per molecular relaxivities

	r_1 ($\text{mM}^{-1}\text{s}^{-1}$)	r_2 ($\text{mM}^{-1}\text{s}^{-1}$)	r_1 ($\text{mM}^{-1}\text{s}^{-1}$)	r_2 ($\text{mM}^{-1}\text{s}^{-1}$)	r_2/r_1
Eovist (1.4 T)	5.38 ± 0.02	6.54 ± 0.06	5.38 ± 0.02	6.54 ± 0.06	1.2
ProCA32 (1.4 T)	33.41 ± 0.32	44.61 ± 0.12	66.80 ± 0.32	89.22 ± 0.24	1.3
Gd-DTPA (7 T)	5.1	9.4 ± 1.3	5.1	9.4 ± 1.3	1.8
ProCA32 (7 T)	18.9	48.6 ± 0.1	37.8	97.2 ± 0.2	2.6

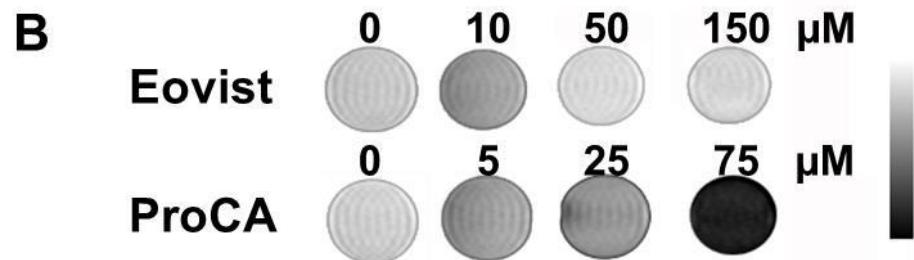
ProCAs: Protein MRI Contrast Agents



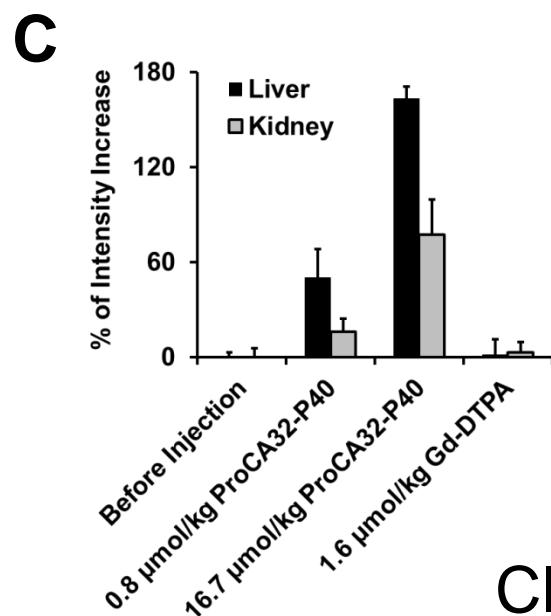
ProCA32 has low detection limit and reduces injection dose



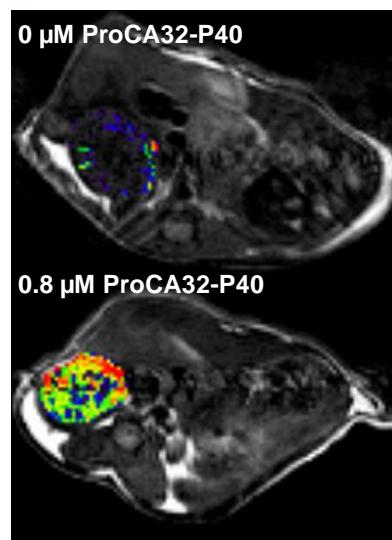
T1-weighted



T2-weighted

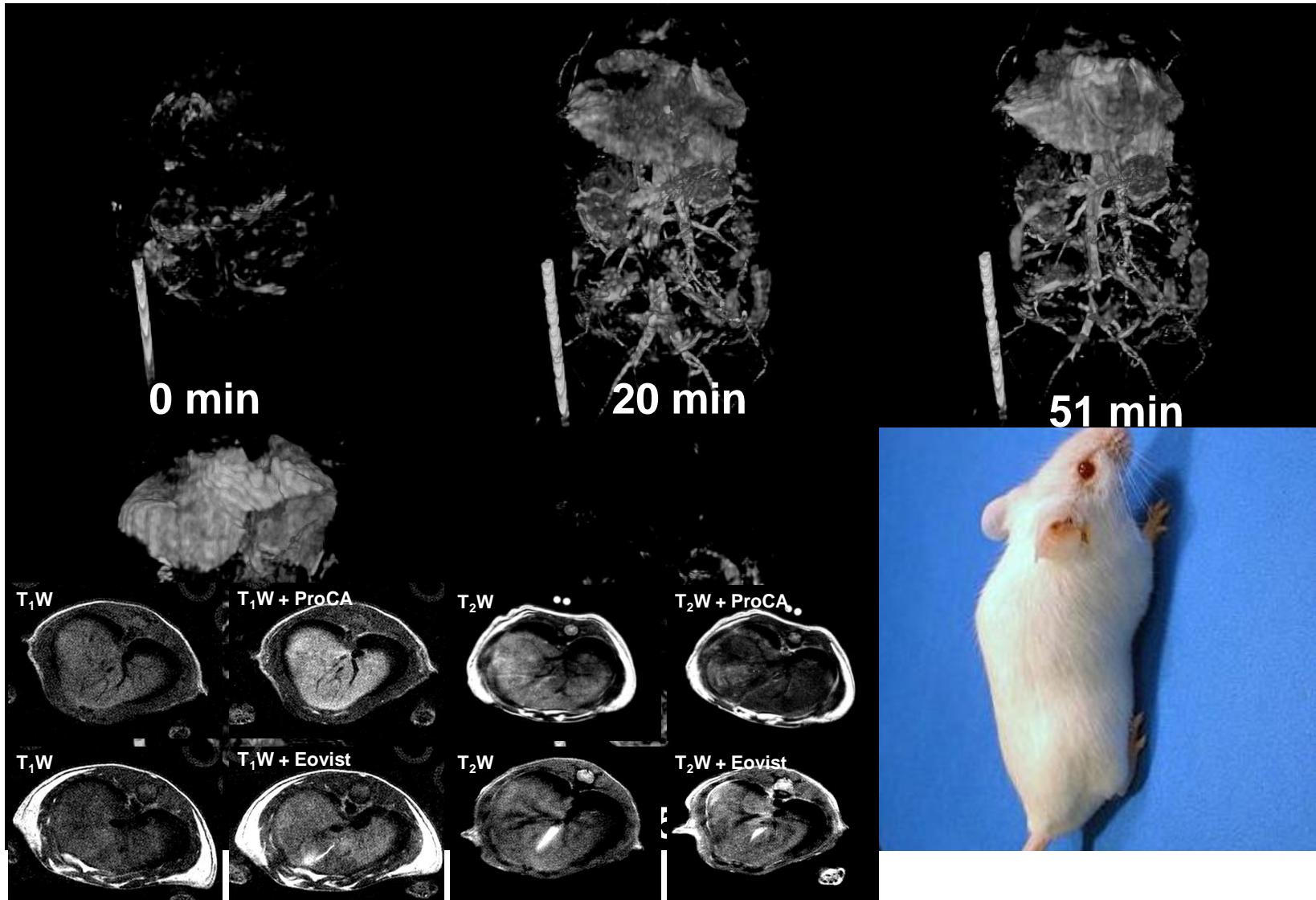


D

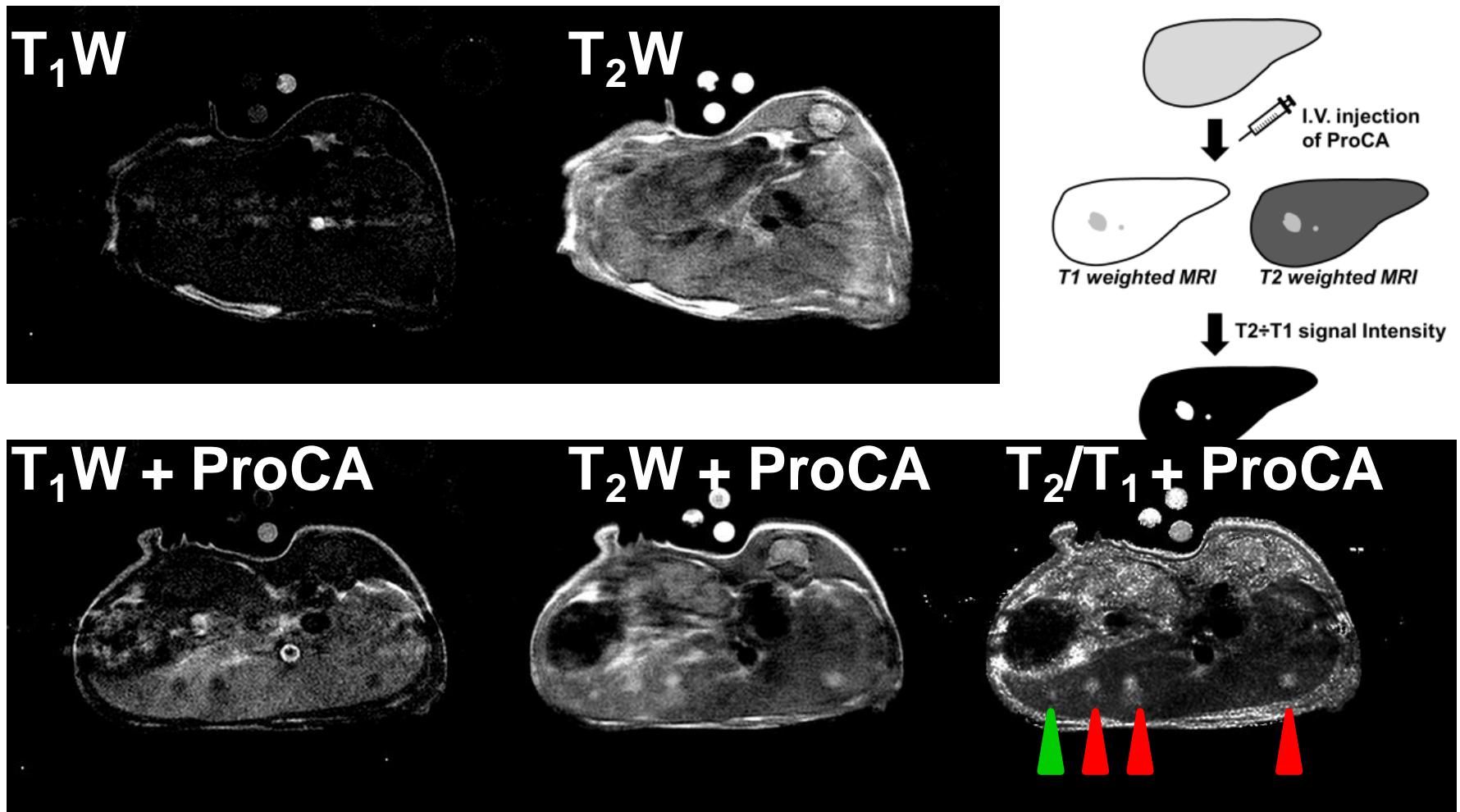


Clinical injection dosage for Gd-DTPA:
100 – 200 $\mu\text{mol/kg}$

Three dimensional MRI with IV injection ProCA32-P40



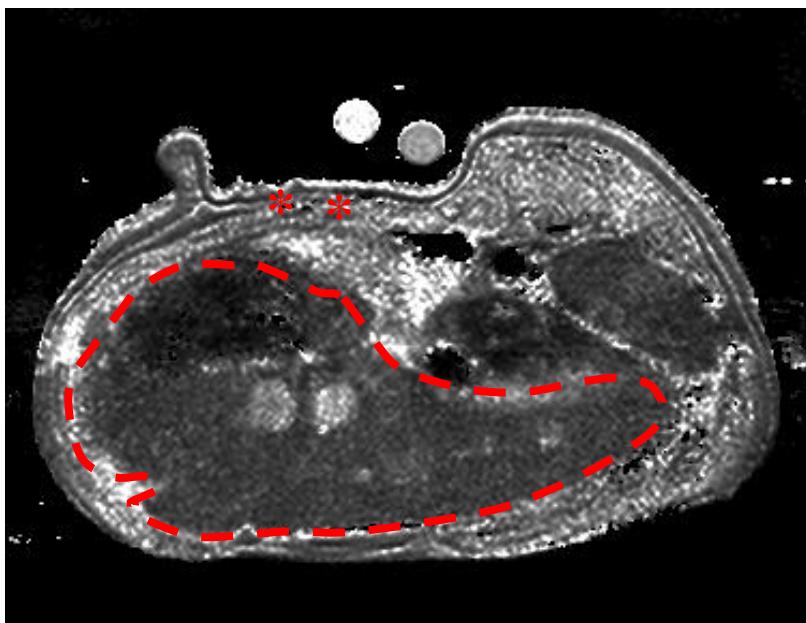
MRI Dual Imaging Uveal Melanoma Liver Metastases



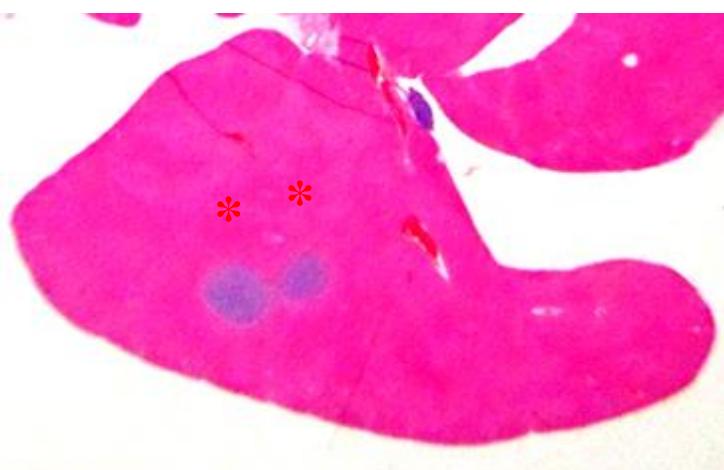
0.24 mm 0.85 mm 0.94 mm 0.77
mm

ProCA Enables Detection of Liver Micrometastasis with tumor size from ~ 20 to < 0.2mm with high Confidence

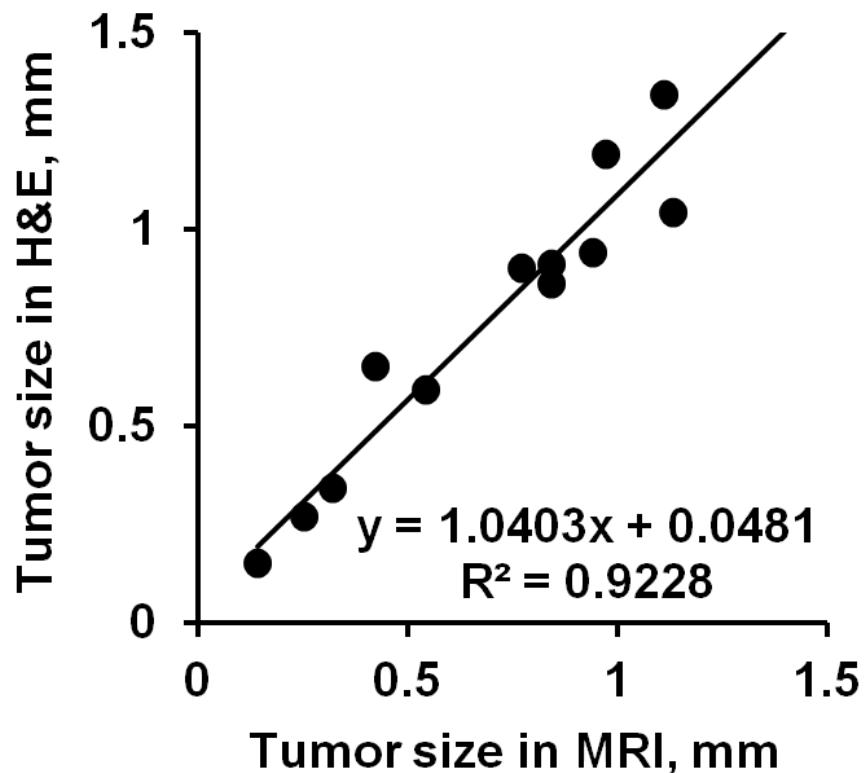
A



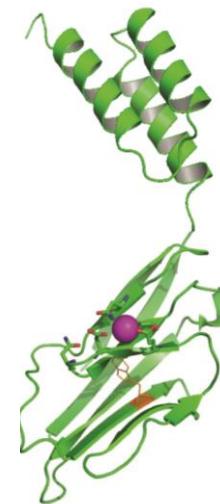
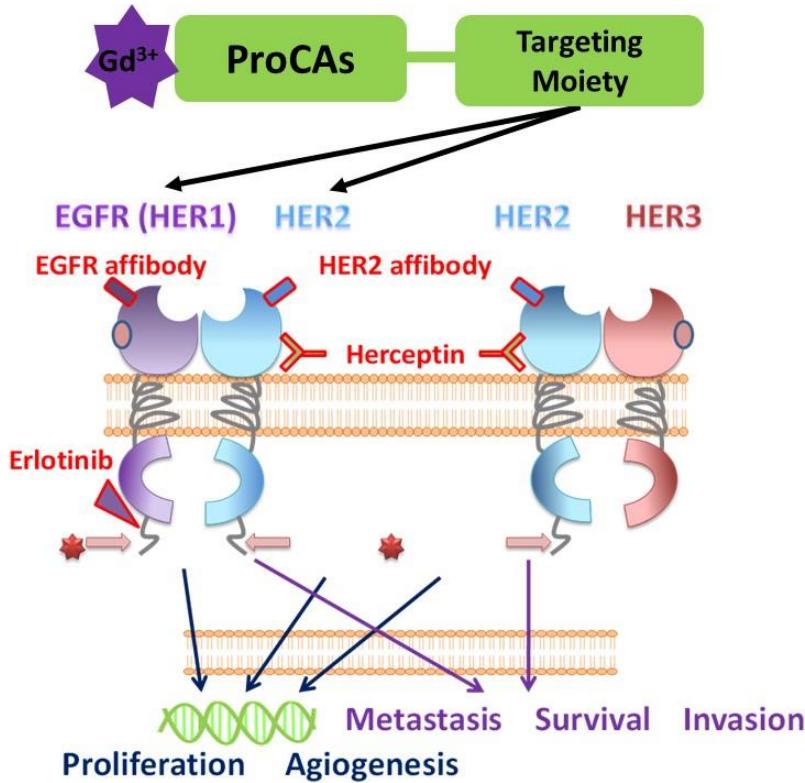
B



C

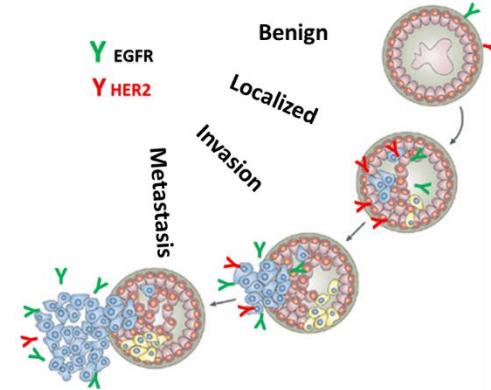


Designing of Dual Imaging Moeities for Multiple Biomarkers



Affibody

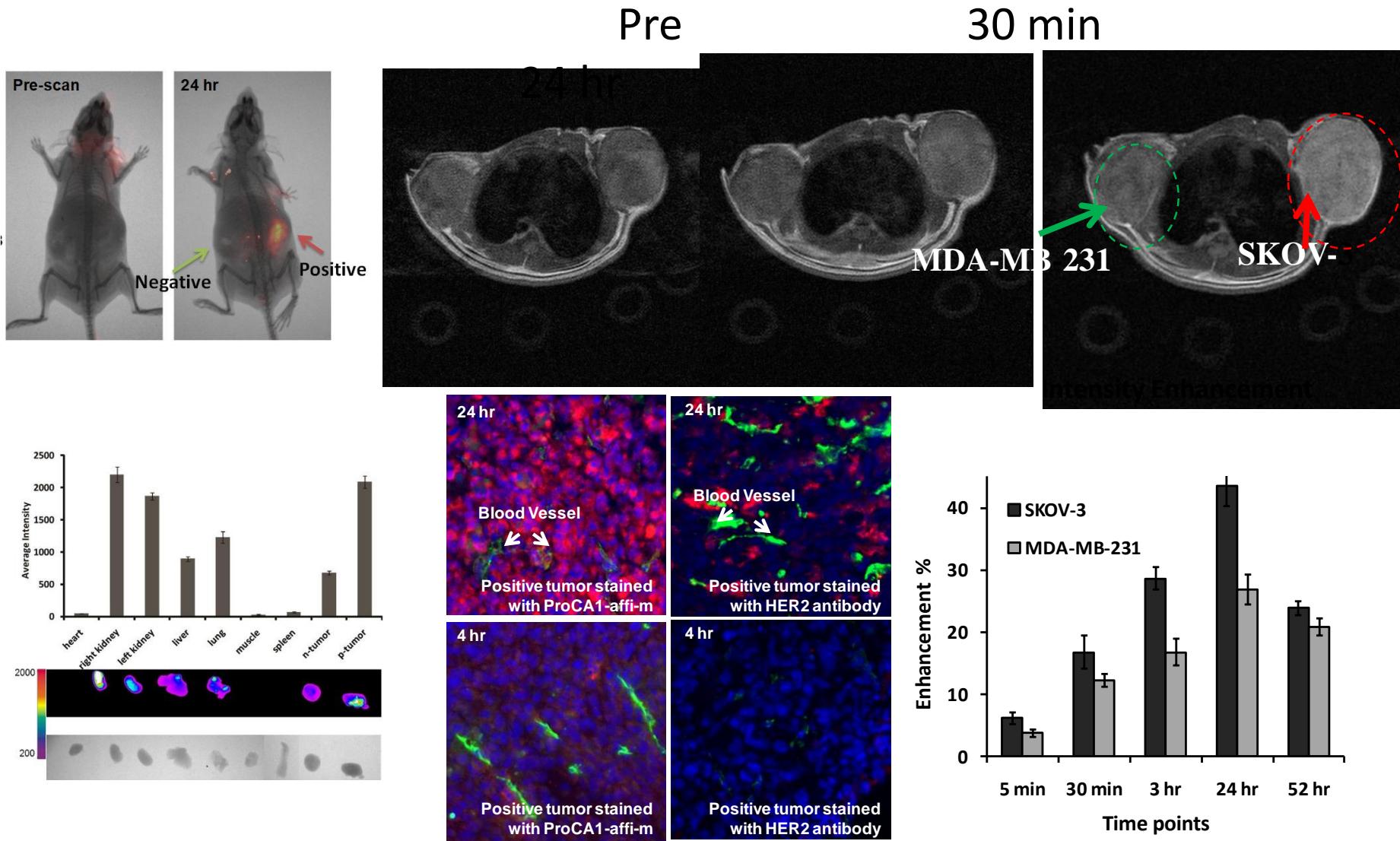
ProCA1



Detect receptor specifically?
Quantification?
Progression?
Monitoring treatment?
Non-invasive biopsy?

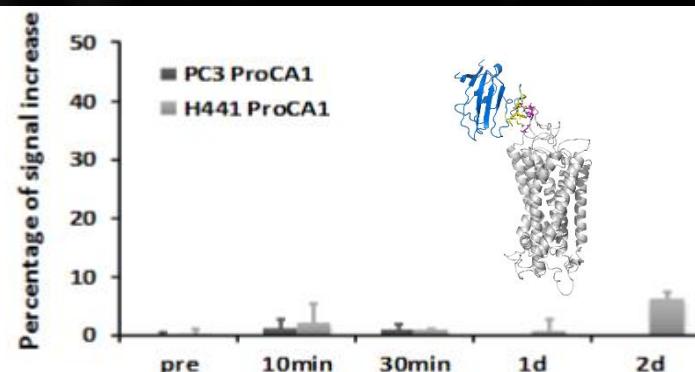
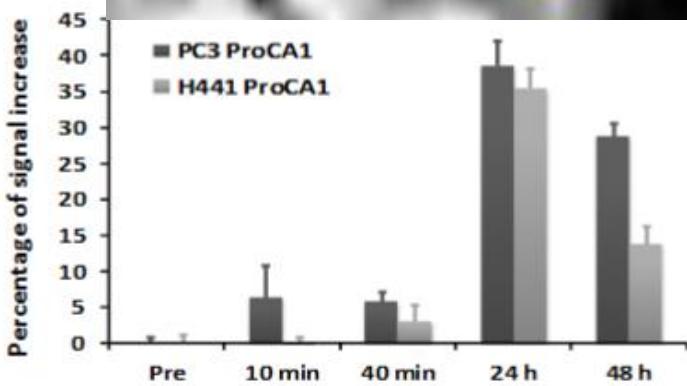
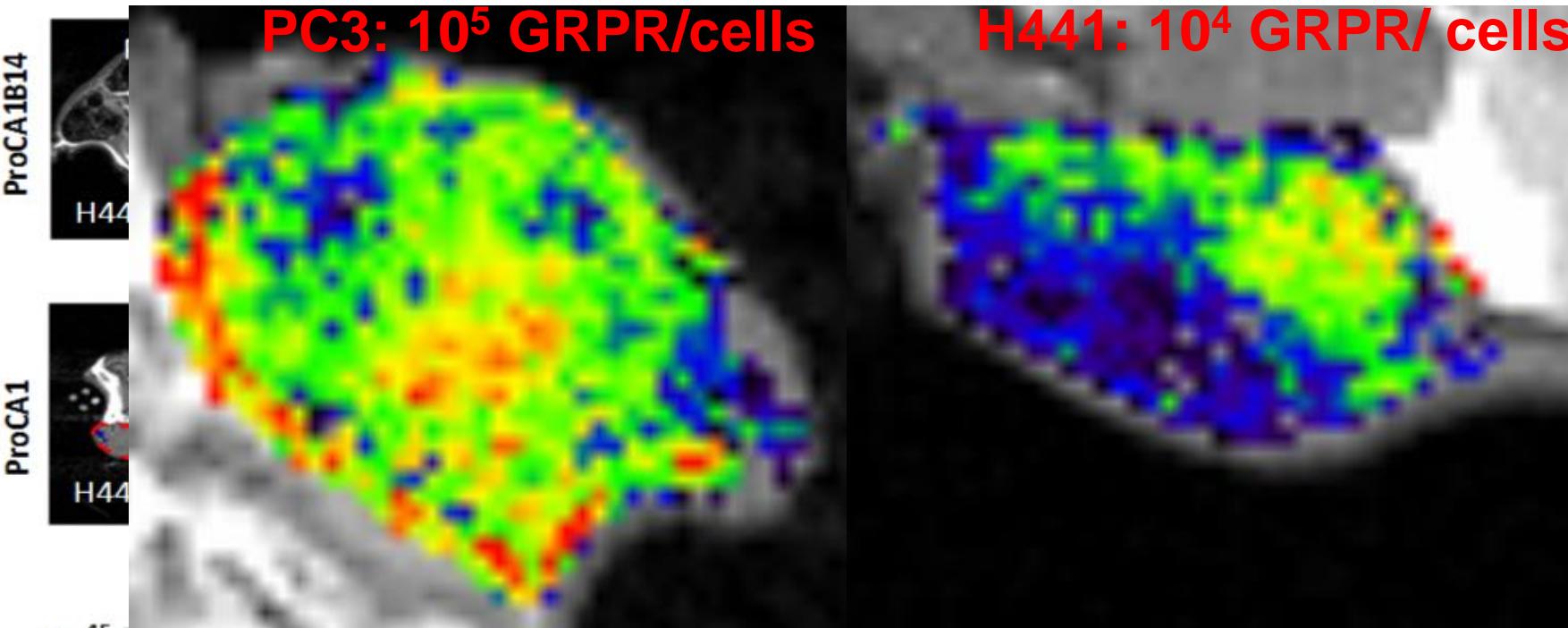
HER2 targeted ProCA1-HER2 Affibody $Z_{\text{HER2}:342}$
EGFR targeted ProCA1-EGFR Affibody $Z_{\text{EGFR}:1907}$

HER2targeted ProCA Detects Breast and Ovarian Cancers depending on HER2 Expression Levels

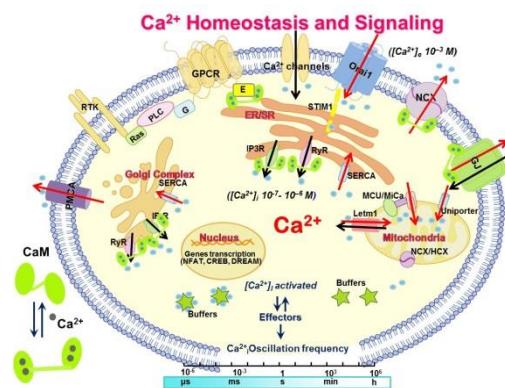
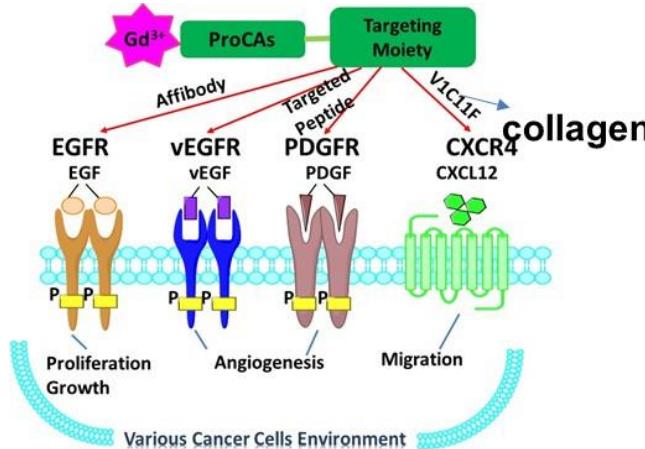
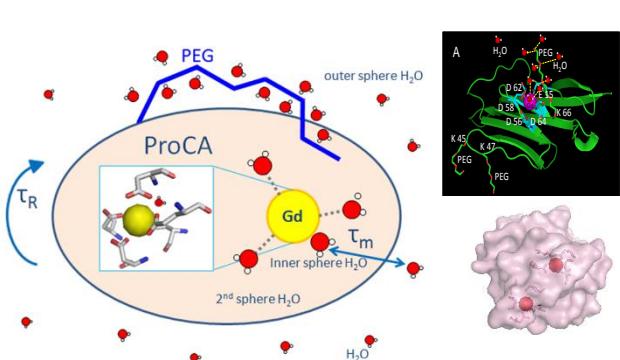


Excellent Tumor Penetration And Distribution, Superior Than Antibody

Temporal and Spatial Detection of GRPR expressions in Prostate and Lung Cancer using ProCA1.GRPR

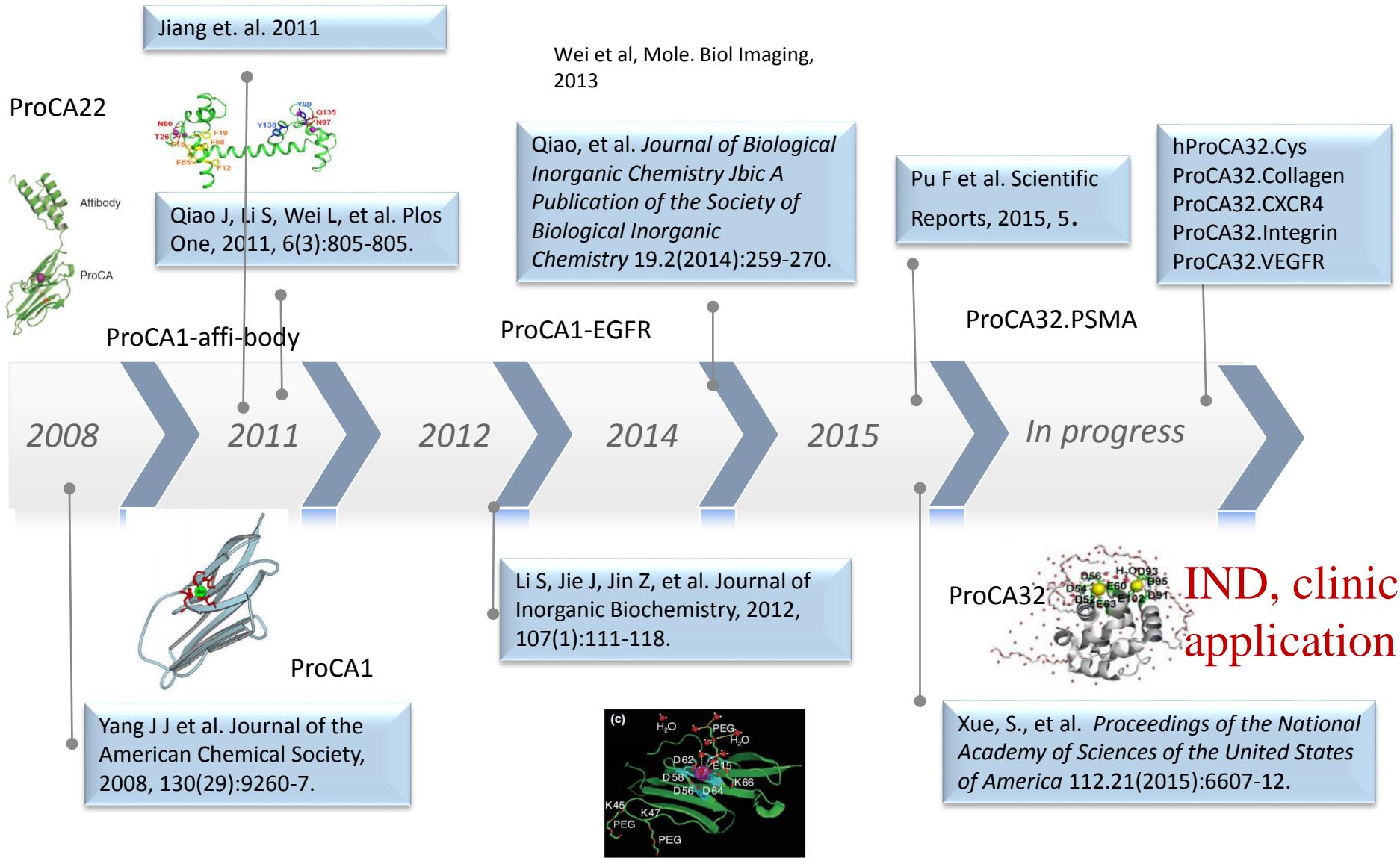


Protein-based Contrast Agents (ProCAs)

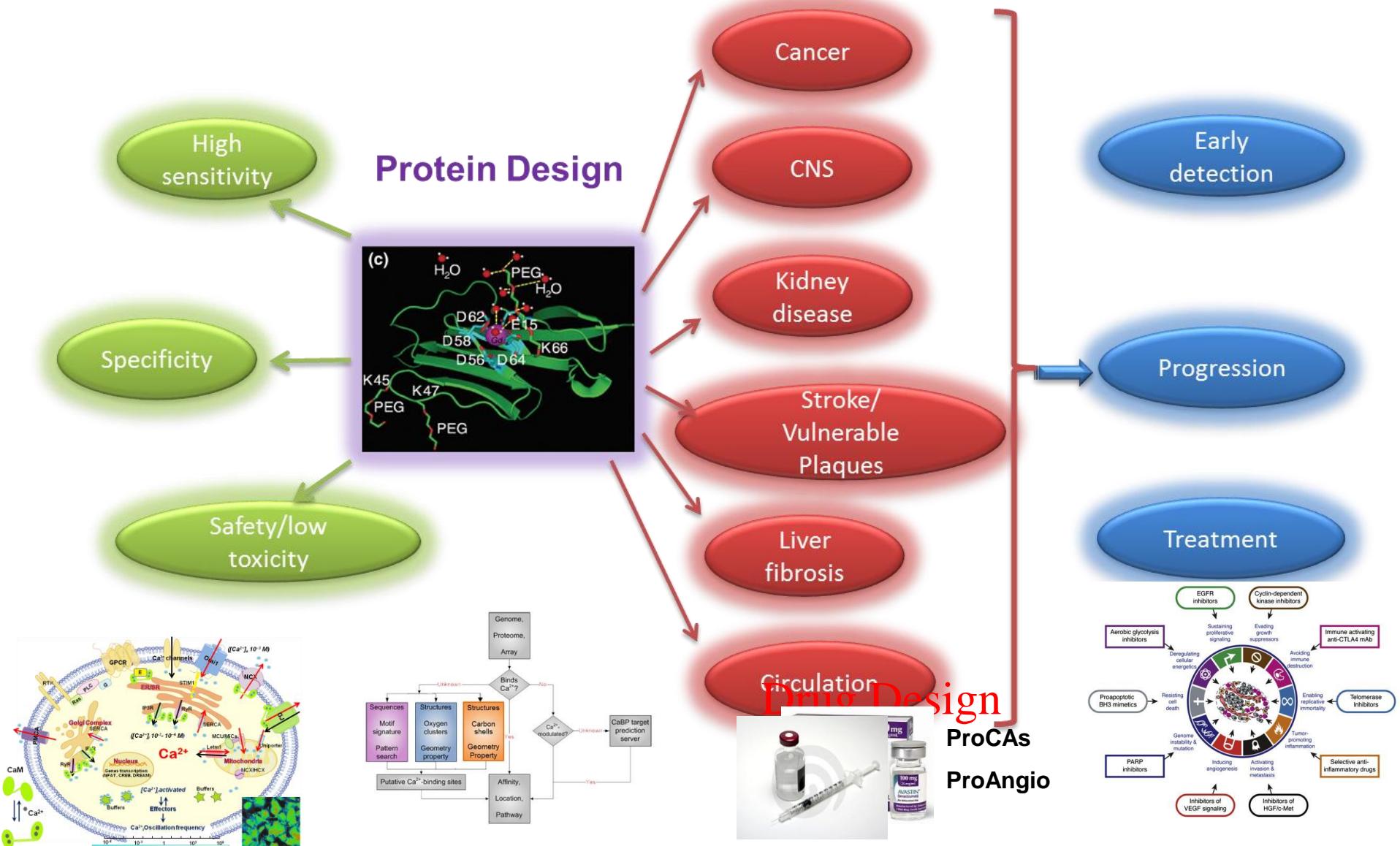


- First computational design of Gd^{3+} -binding site in proteins as novel protein MRI reagents with strong metal stability and selectivity
- 10-20 fold in vitro increases in R_1 and R_2 , high R_1 at 7T
- 100 fold increase in in vivo detection **resolution**. Extend to earlier and **accurate** detection of liver lesion size from $> 2 \text{ cm}$ to $< 0.25 \text{ mm}$ micrometastasis by dual imaging
- ProCAs increase **specificity** by enabling molecular imaging of biomarkers Her2/EGFR and GRPR, collagen, CXCR4, VEGFR, PSMA, and integrin for breast, lung, ovarian, prostate cancer and liver metastases from uveal melanoma, breast and ovarian cancer
- 20-100 fold low dose injection, biocompatible, no acute toxicity

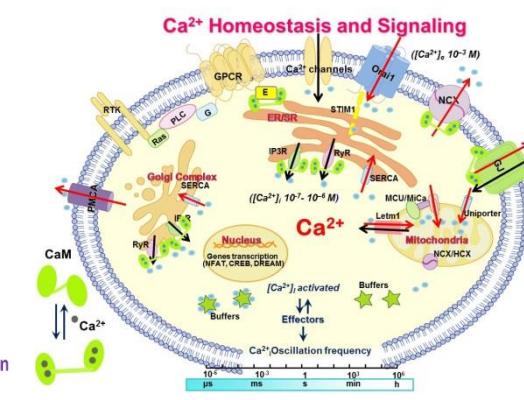
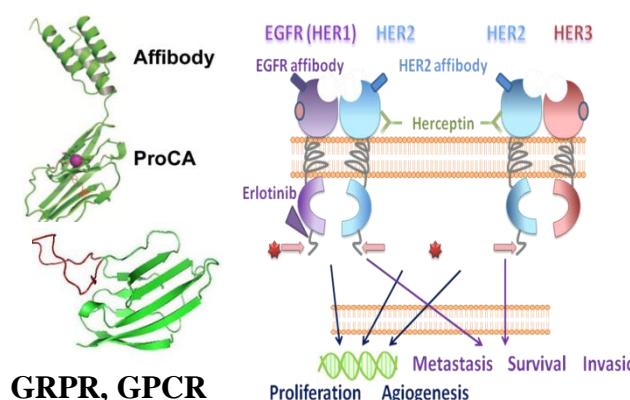
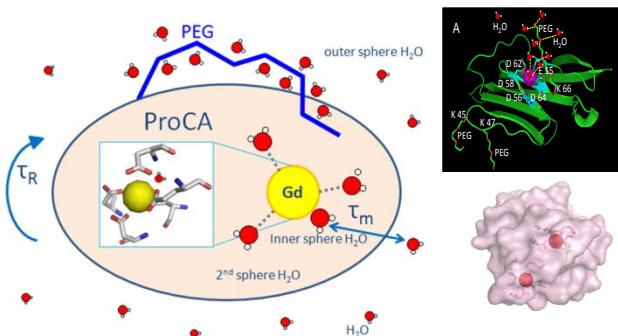
Progress of ProCAs



Precision Molecular Imaging



Protein-based Contrast Agents (ProCAs)



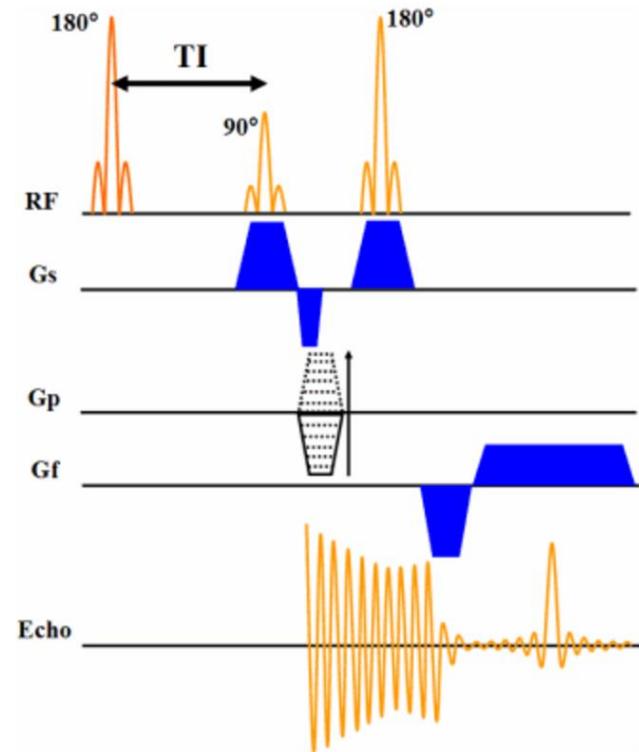
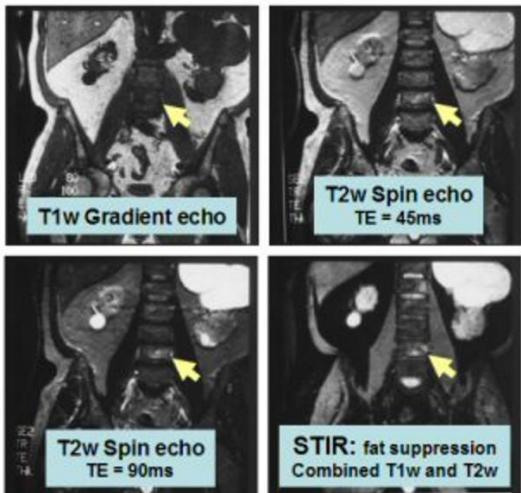
- First computational design of Gd³⁺ -binding site in proteins as novel protein MRI reagents with strong metal stability and selectivity
- 10-20 fold in vitro increases in R1 and R2, high R1 at 7T
- 100 fold increase in in vivo detection resolution. Extend to earlier and accurate detection of liver lesion size from > 2 cm to <0.25 mm micrometastasis by dual ratiometric imaging
- ProCAs increase specificity by enabling molecular imaging of breast and prostate cancer biomarkers Her2/EGFR and GRPR with enhanced sensitivity, optimized retention time, and proper tissue/tumor penetration
- 20-100 fold low dose injection, biocompatible, no acute toxicity

STIR: Clinical Applications

- STIR has the advantage in the diagnosis of bone marrow diseases.
- It can evaluate multiple sclerosis of the cervical spinal cord and is useful in the rib chondrosarcoma with intramedullary progression completely resected.
- In bone marrow abnormalities of foot and ankle, STIR images and T1-weighted contrast-enhanced fat-suppressed MR images demonstrate almost identical imaging patterns, and diagnoses determined with these findings show little difference.
- Because of low cost and no intravenous injection required, use of the STIR sequence is preferred.
- STIR, widely used in spine MRI, has a lot of advantages in displaying spinal cord injury, in interpreting whether acute vertebral compression fracture or chronic, and in detecting the occult fractures. This pulse sequence has been reported as an ideal tool to determine the integrity of the posterior ligamentous complex (PL-C) which has been proposed to be an integral aspect in the treatment algorithm for spinal trauma.
- It also has a high value in the diagnosis of osteoporotic vertebral fractures.

STIR (Short TI Inversion Recovery)

- STIR (Short TI Inversion Recovery) is an inversion recovery pulse sequence with specific timing so as to suppress the signal from fat.
- An inversion recovery pulse sequence is a spin echo pulse sequence preceded by a 180° RF pulse



A STIR image, revealing cancer lesions within spinal vertebrae at 1.0 T.