Novel peptides for anti-amyloid therapy and MRI diagnosis in Alzheimer's Disease

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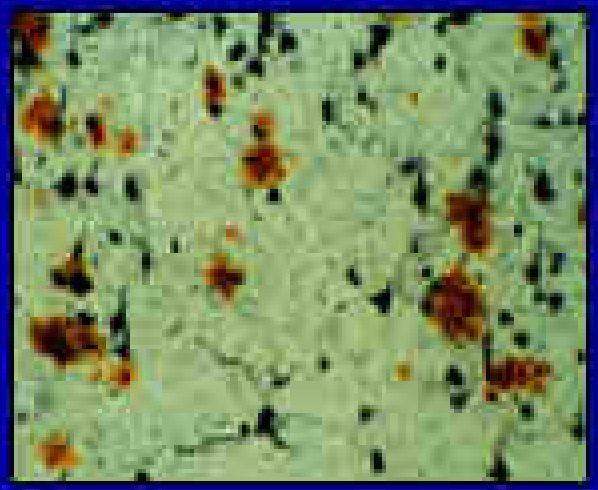
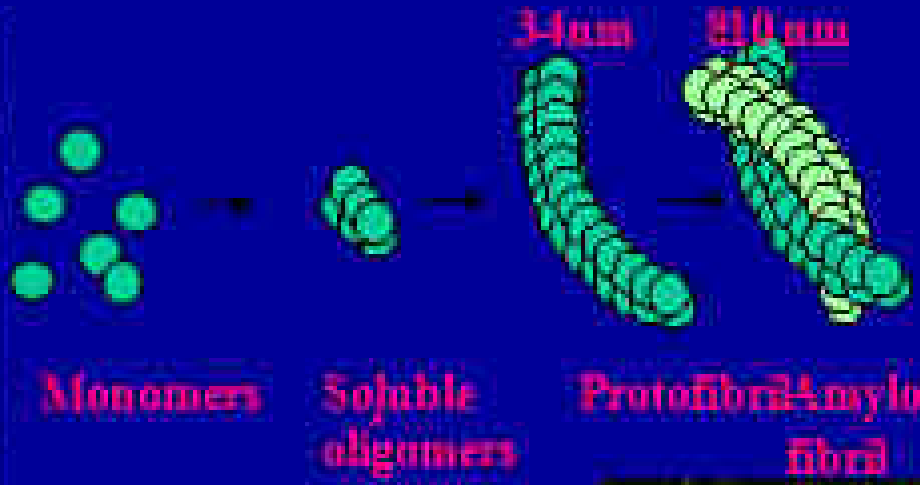
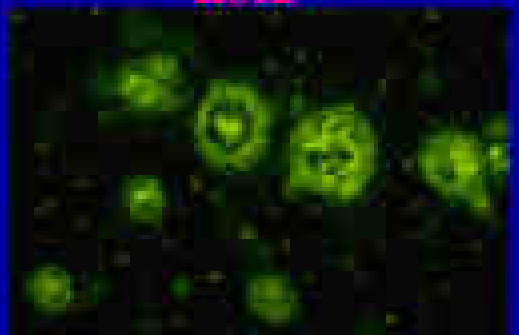
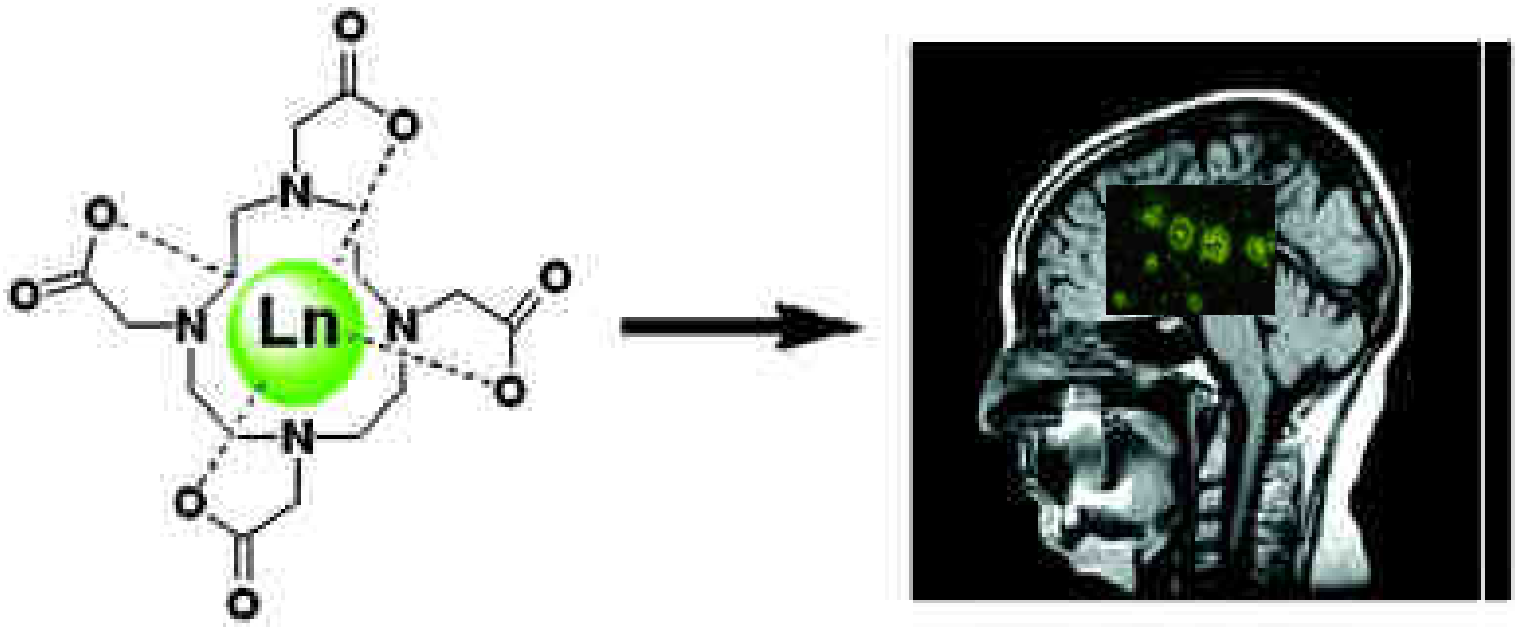
Alzheimer's disease

"Amyloid hypothesis" explains the pathogenesis of the disease.

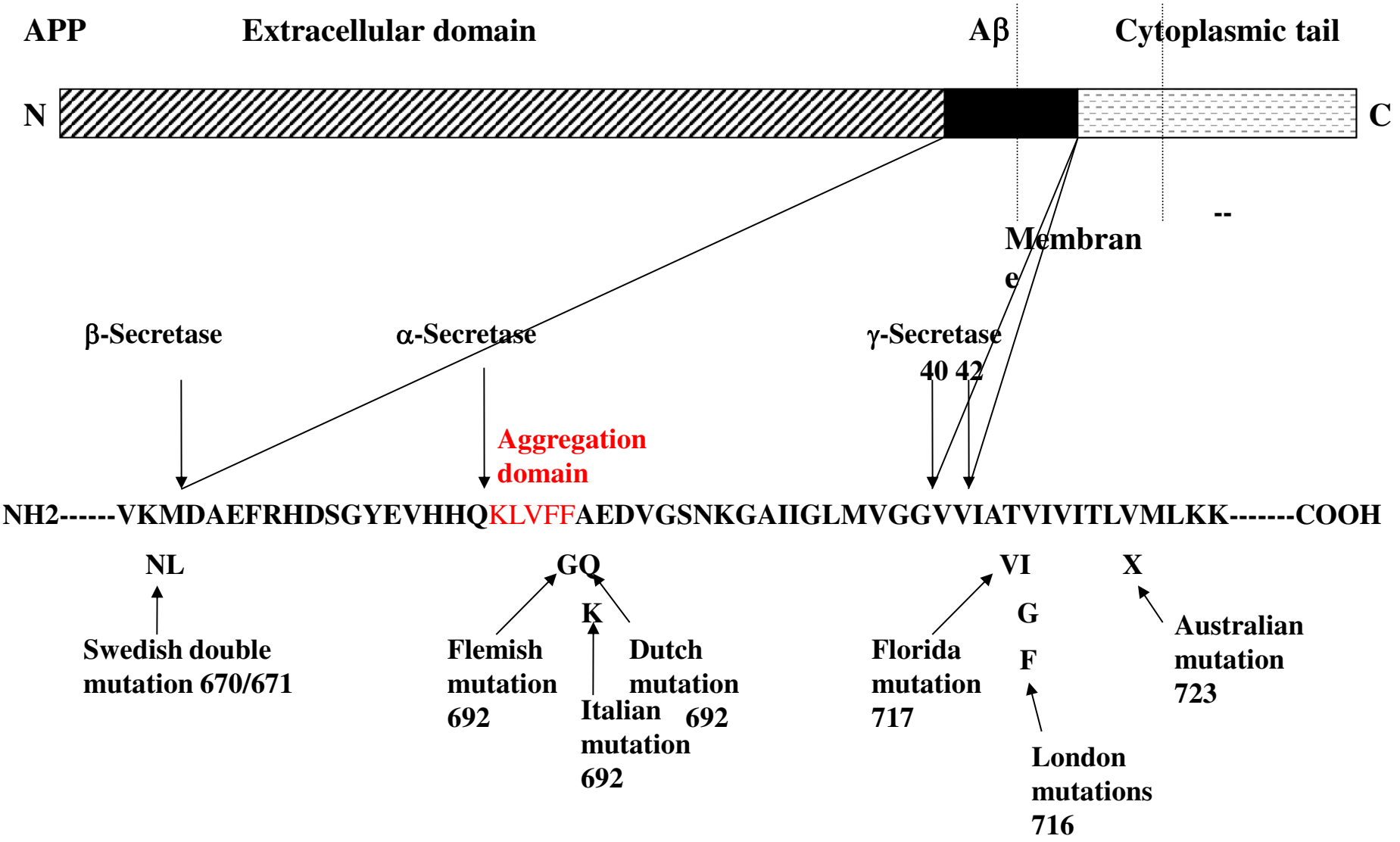








Many (35%) MRI scans on patients are performed with the use of contrast agents which enhance selective tissues by increasing relaxation of adjacent water protons. Gd is the most common contrast agent, chosen as it contains 7 unpaired electrons which increase T1 longitudinal relaxation (protons realigning with the external field) and reduce T2 transverse relaxation (time for protons to exchange energy with other nuclei). Free Gd is toxic unless complexed with a stable ligand.



Retroinversion ffvlk (D-amino acid residues)

Anti-toxicity properties published in Peptides (2010) 31;1866-1872

Synthesised MRI contrast agents for neurodegenerative disease

R1

DOTA- Gly-DArg-DPhe-DPhe-DVal-DLeu-DLys-Gly-DArg-Gly-Pentadiamine
Gd

R2

DOTA –Gly-DArg-DPhe-DPhe-DVal-DLeu-DLys-Gly-hexaDArg
Gd

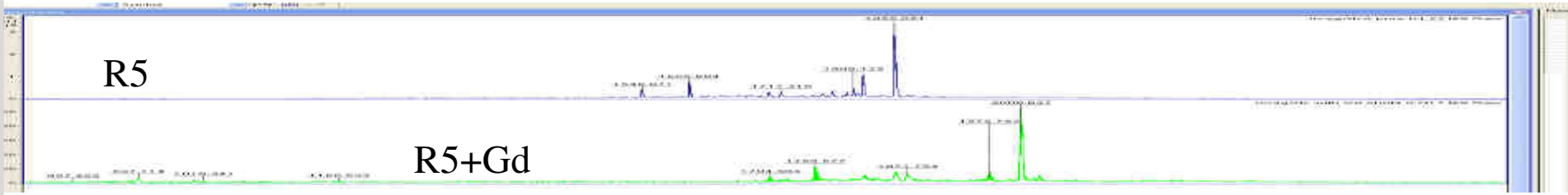
R3

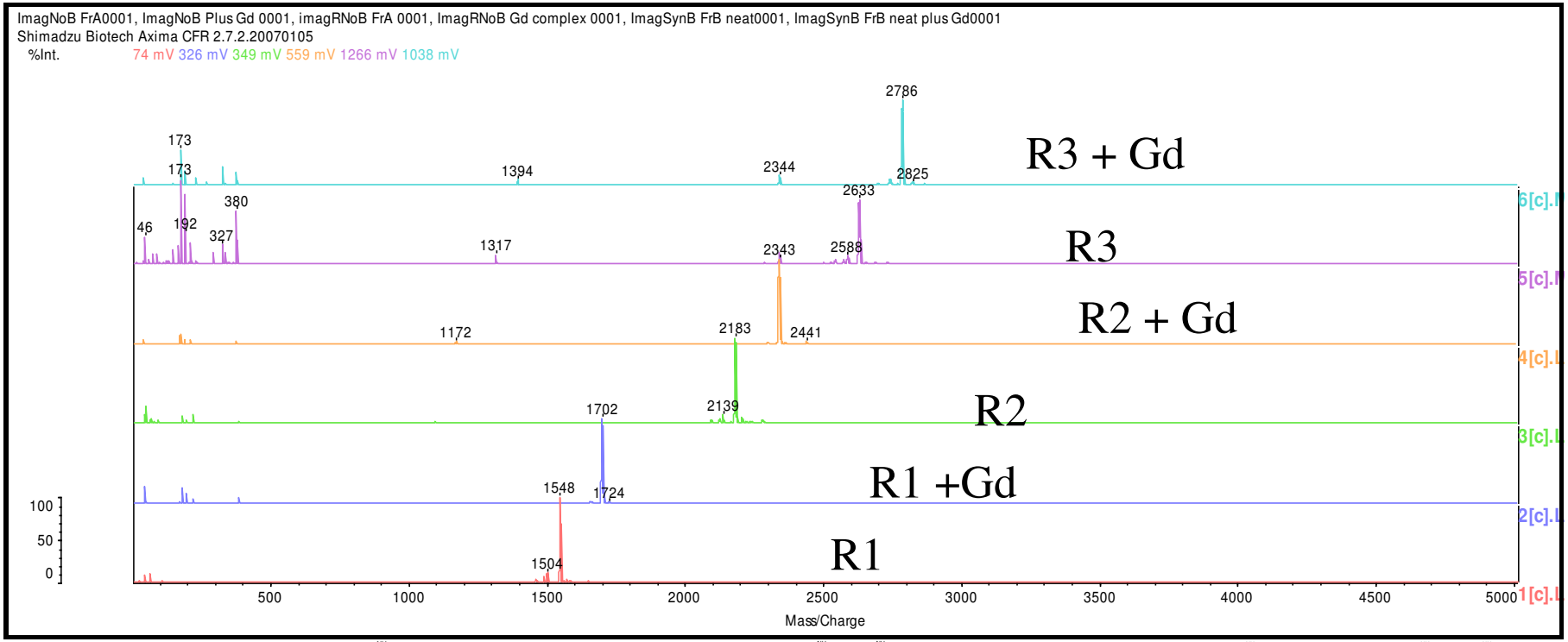
DOTA –Gly-DArg-DPhe-DPhe-DVal-DLeu-DLys-DArg-rlsysrrrf-NH2
Gd

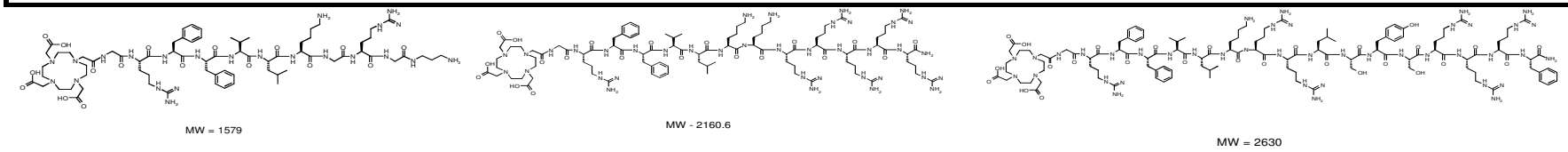
R4 DOTA-Gly-Darg-Lys-DGly-DThr-DThr-DVal-DAla-DThr-Arg-NH2

R5

DOTA-Gly DArg-DPhe-DPhe-DVal-DLeu-Lys(Biot)-r-Ser(Glc)-Gly-NH2

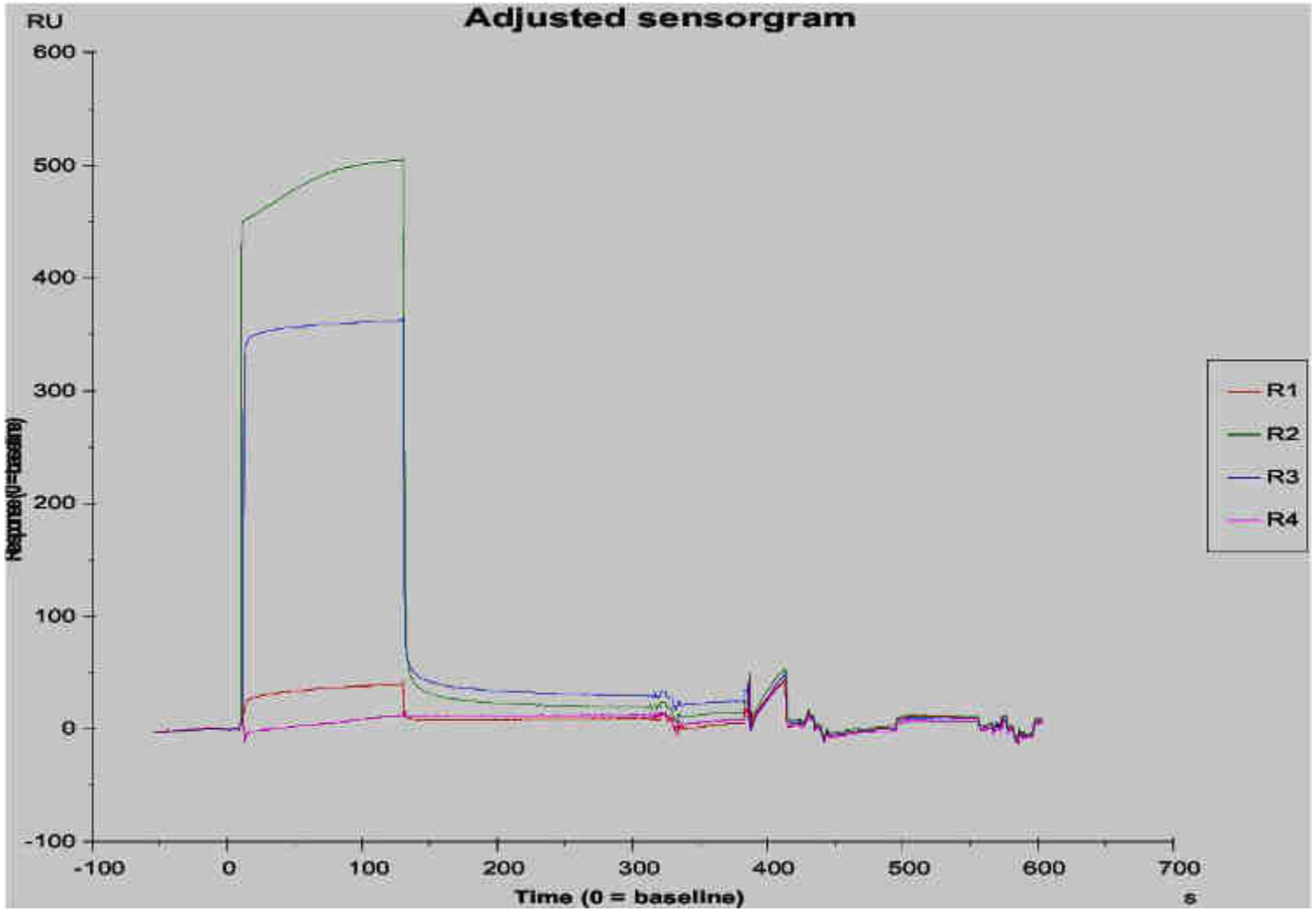

R5
R5+Gd


ImagNoB FrA0001, ImagNoB Plus Gd 0001, imagRNoB FrA 0001, ImagRNoB Gd complex 0001, ImagSynB FrB neat0001, ImagSynB FrB neat plus Gd0001
Shimadzu Biotech Axima CFR 2.7.2.20070105
%Int.
74 mV 326 mV 349 mV 559 mV 1266 mV 1038 mV
R3 + Gd
R3
R2 + Gd
R2
R1 +Gd
R1
Mass/Charge


MW = 1579
MW - 2160.6
MW = 2630

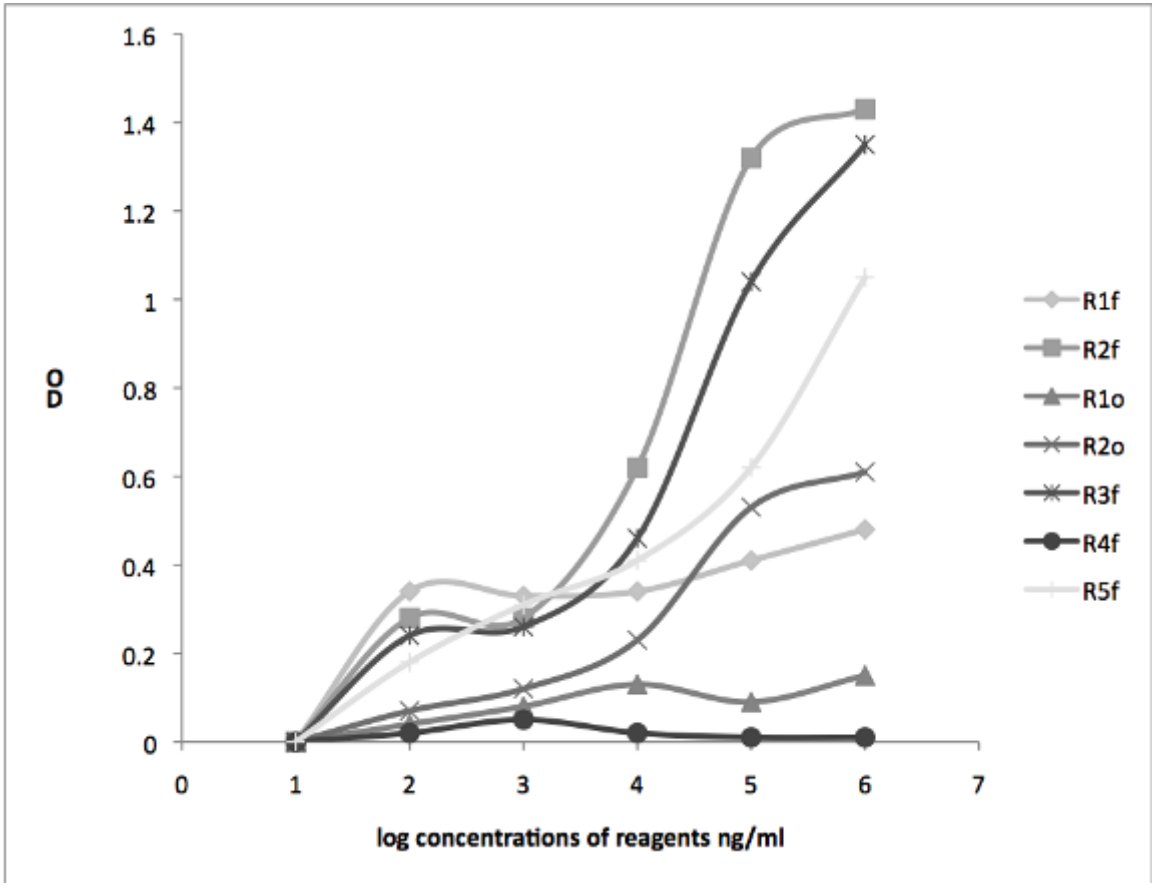
R1 R2 R3

FC2-1 100uM R1-R4 binding to amyloid 1-40 fibrils



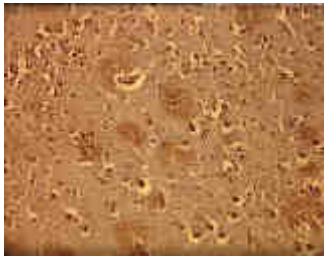
Interaction analysis on Biacore

Binding of biotinylated reagents to Abeta40 oligomers (o) and fibrils(f).



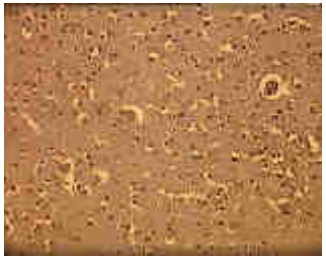
Preliminary data has validated the function of these agents, but further work is needed to optimise their effectiveness at highlighting β-amyloid and to validate the correlation of MRI to histopathology

(A) AD section plus R2

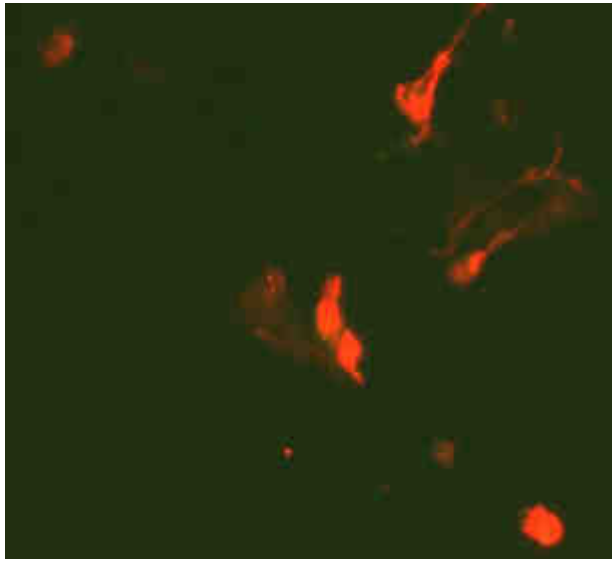


(B) AD section plus R2

(C) Young control plus R2



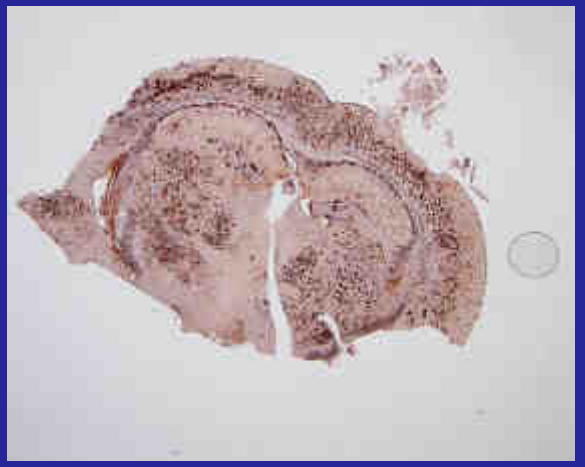
(D) AD section plus antibody



In AD post-mortem sections, R2 stained plaques (A) and vascular amyloid (B), in a similar fashion to Aβ antibodies (D). Sections froma control young patient did not bind R2 (C). SW-APP 293 cells transfected with the amyloid precursor protein, treated with proteasome inhibitor, lactalysin, to accumulate Aβ, took up and retained R2. Visualised via incorporated biotin in R2.

Amyloid deposition with age 5X FAD mice

4 months

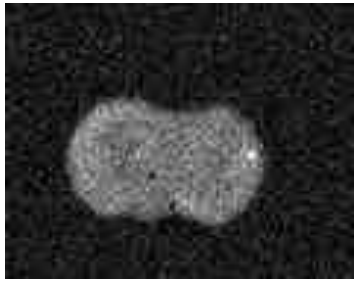


6 months

Ex-vivo MRI

Reagent

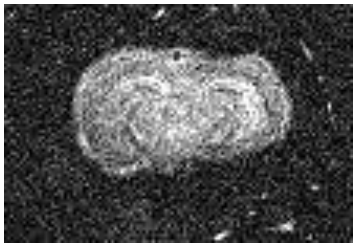
R1



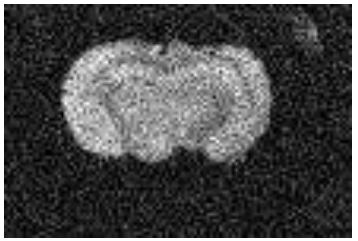
TG

R2

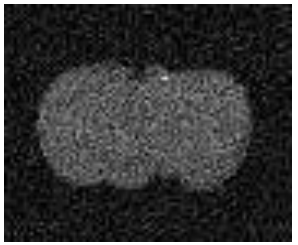
Non-TG



TG



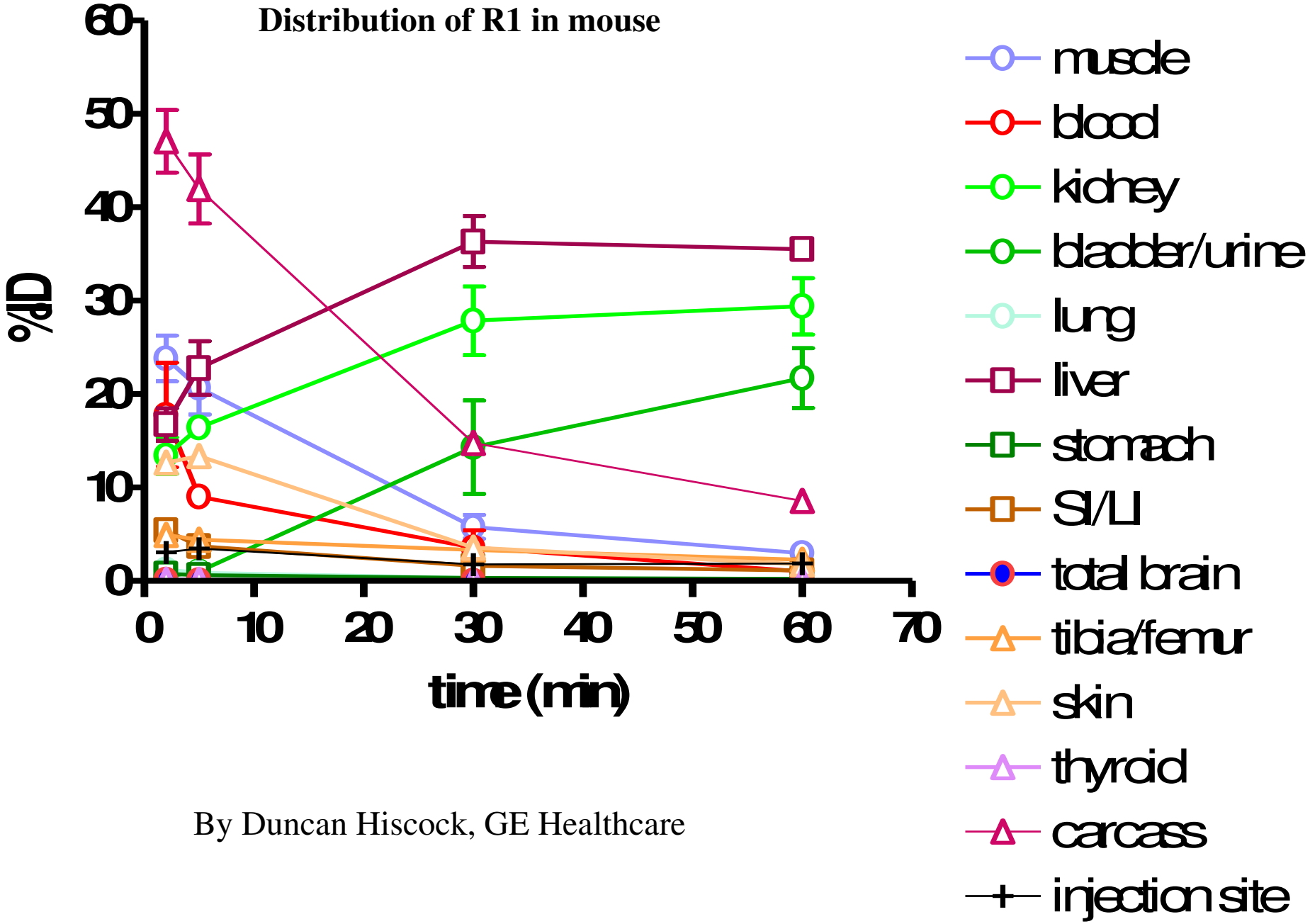
TG



Pre-incubation

R3

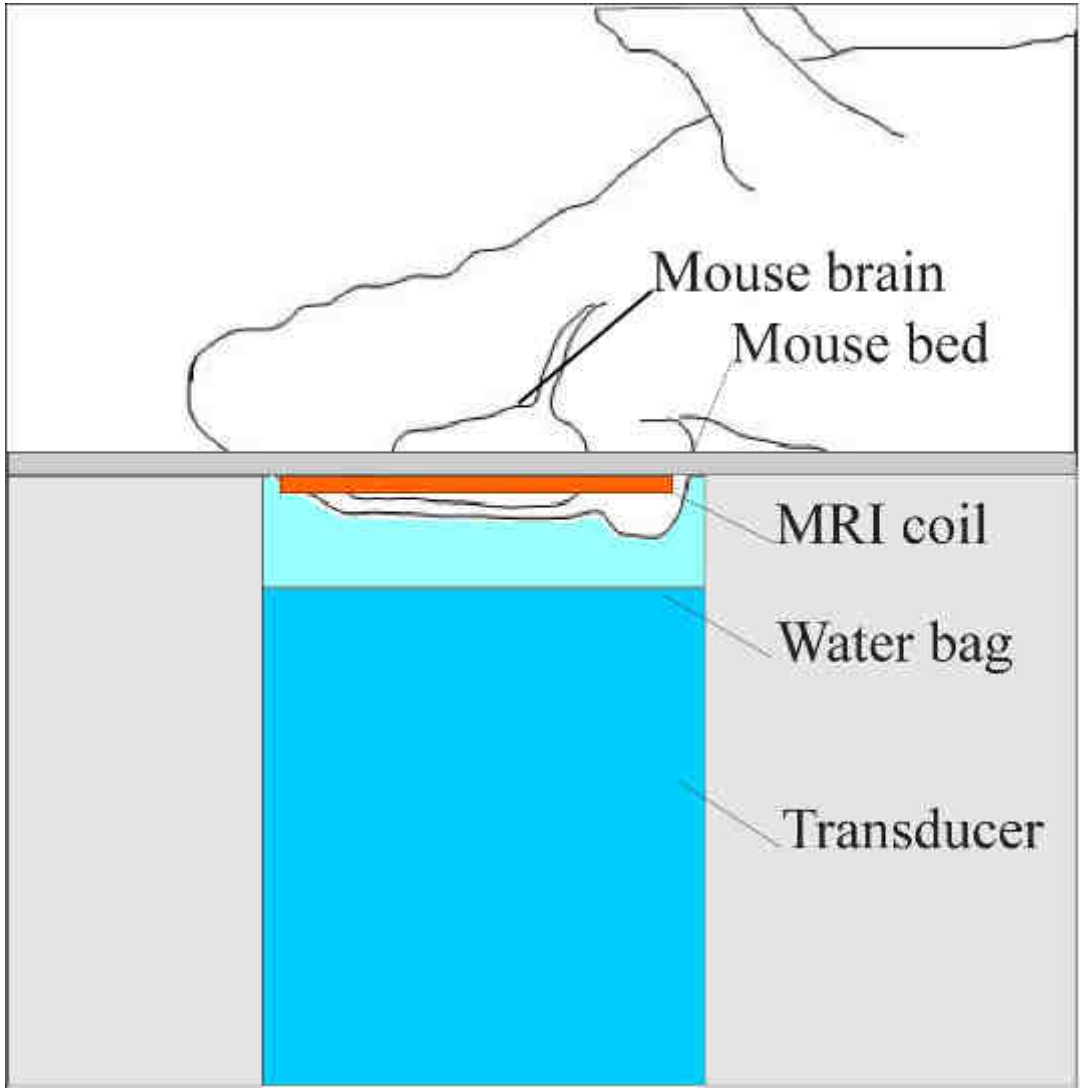
TG



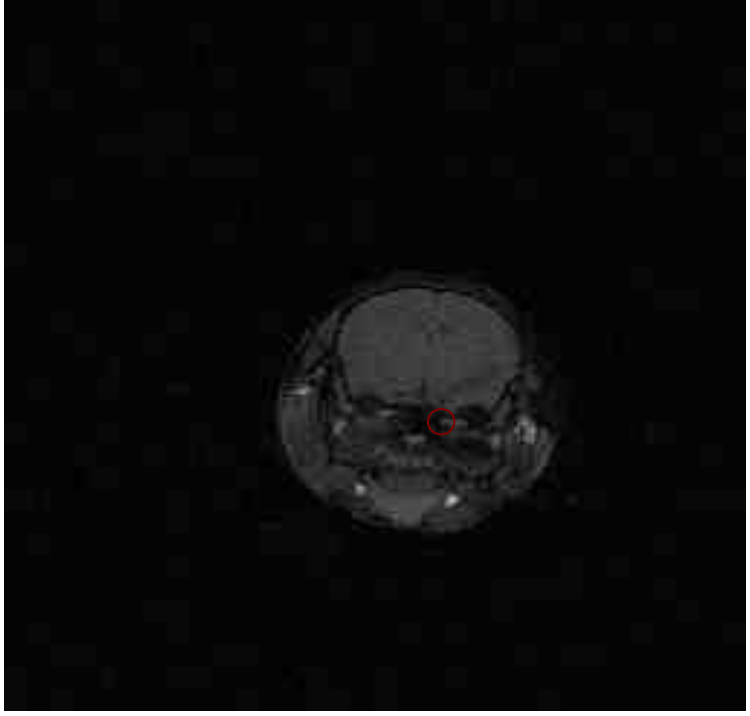
By Duncan Hiscock, GE Healthcare

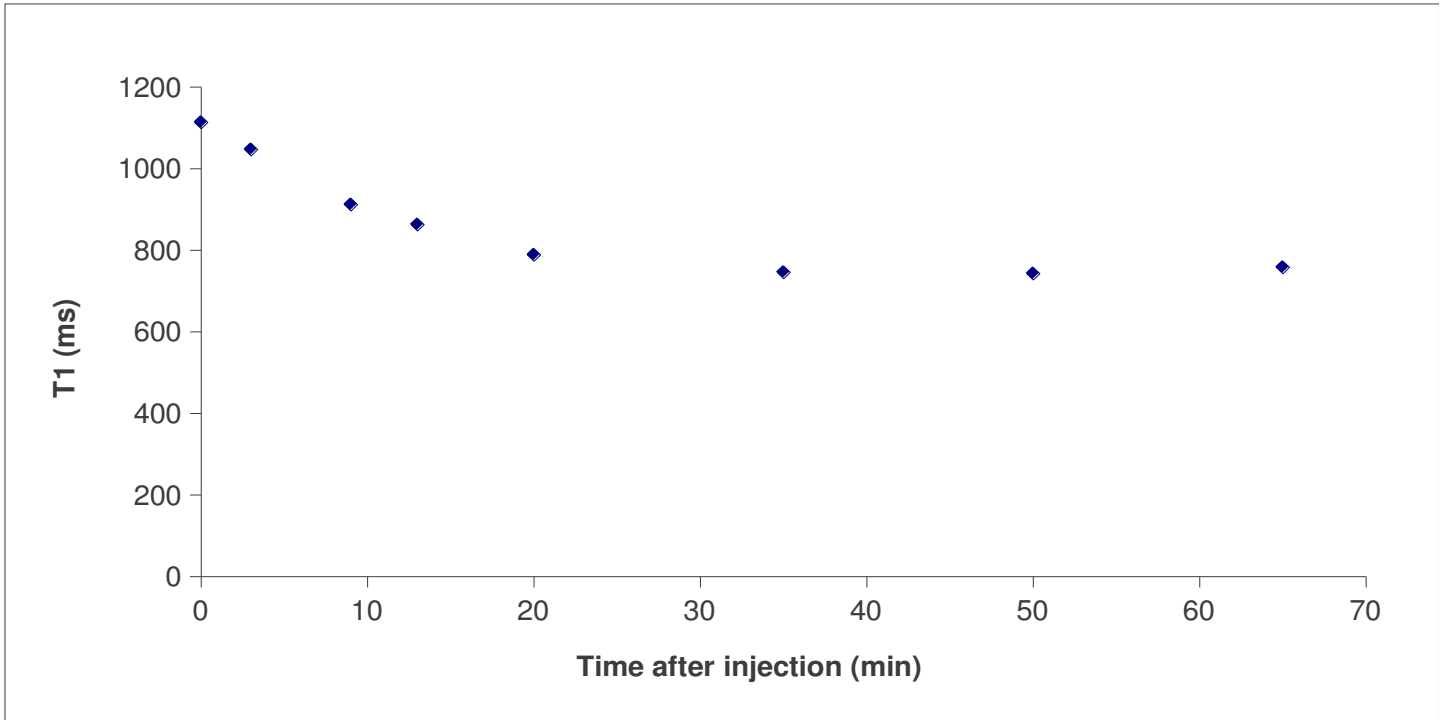
Compound	2 minute brain uptake (%ID-kg/g)	Brain Clearance (2:30 minute ratio)
^{153}Gd-(DOTA)-rGffvlkGrG-pentadiamine	0.0046	**3.3**
^{153}Gd-(DOTA)-rGffvlkKrrrrrrr-NH2	0.0058	**7.9**
^{153}Gd-(DOTA)-Grffvlkrrlsysrrrf-NH2	0.0052	**2.1**
PET gold standard	0.22	**9.0**
SPECT gold standard	**0.09**	**12.2**

US/MR SYSTEM



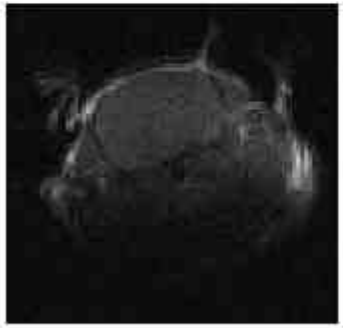
T1 change after injection

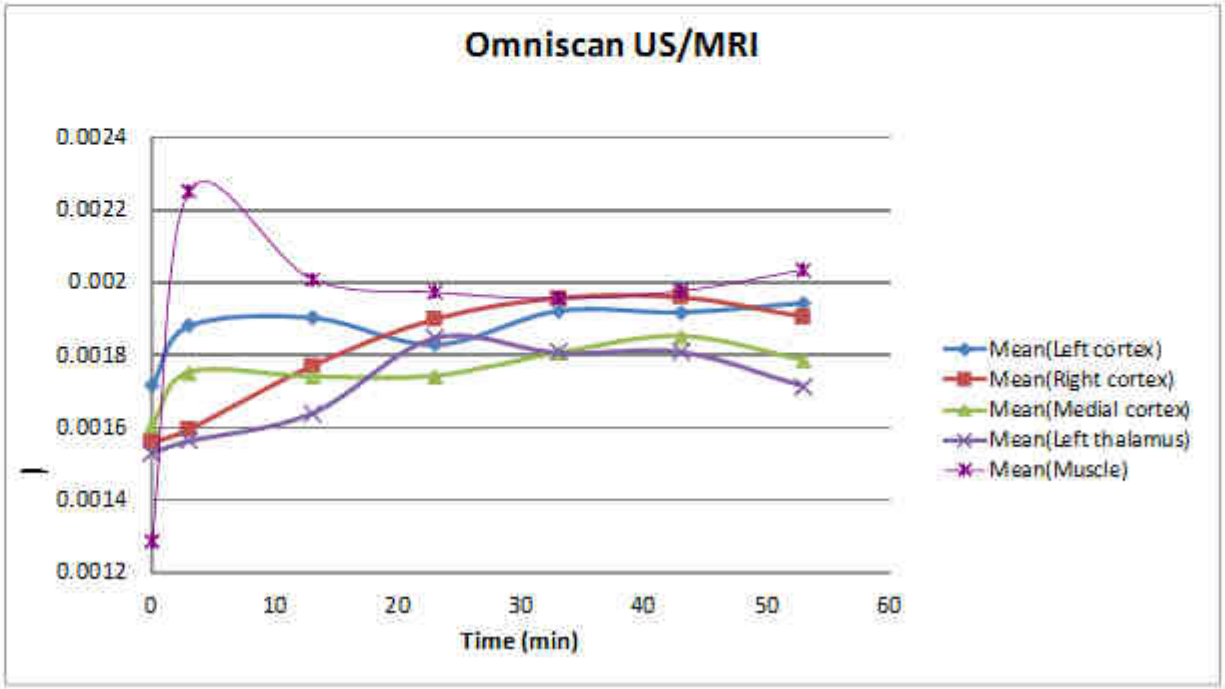




20 ul Omniscan, Optison & US

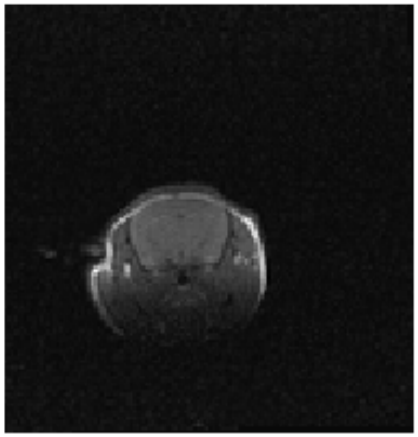
11-05-12



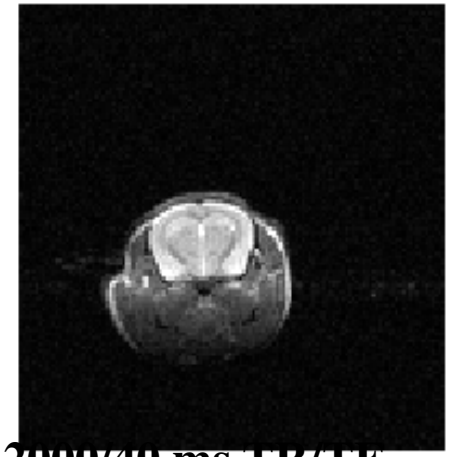


20 ul Rnob, Optison & US

- 15-05-2012



500/14 ms TR/TE



2000/40 ms TR/TE