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Preliminary investigations on the synthesis, physicochemical and biological characterization of a new stilbene derivative grafted to USPIO dedicated to MRI diagnosis of Alzheimer disease

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1. Purpose

Alzheimer disease (AD):

- neurodegenerative pathology and the principal cause of dementia in the elderly in the developed countries.

Pathological hallmarks of AD ([ESMRMB_STB_Fig1.JPG] Figure 1):

- substantial neuronal loss in the late clinical phases
- deposition of senile plaques (SPs) and neurofibrillary tangles (NFTs)

MRI:

- high spatial resolution
- better suited to assess SPs in AD, which could require a spatial resolution of less then 200 micrometers ([ESMRMB_STB_Fig2.jpg] Figure 2) [1]
- However, the image acquisition requires high magnetic fields (often higher than 7T) and long acquisition times (1 – 2 hours)

Stilbene derivatives:

- extensively explored for the detection of SPs by PET and SPECT, as well as by histochemistry

Purpose: This study reports preliminary investigations on the synthesis, physicochemical and biological characterization of a new stilbene derivative [4-amino-4(N,N-dimethylamino)stilbene] grafted to USPIO (USPIO-g-STB) dedicated to MRI-based diagnosis of AD. The stilbene vectorization of USPIO particles may help to the detection of SPs by MRI, which has the advantage of a better spatial and anatomical resolution as compared to the imaging techniques of nuclear medicine.

2. Methods and Materials

Synthesis and physico-chemical characterization of USPIO-g-STB

- Synthesis: 4-amino-4(N,N-dimethylamino)stilbene grafted on magnetic nanoparticles by reaction with the dextran coating of USPIO previously treated with epichlorhydrin ([ESMRMB_STB_Fig3.jpg] Figure 3).
- Iron concentration: determined by relaxometry at 20 MHz (Bruker Minispec, Bruker, Karlsruhe, Germany) and 37°C after mineralization in acidic conditions (0.6 ml HNO_3 and 0.3 ml H_2O_2) by microwaves (Milestone MSL-1200, Sorisole, Italy).
- The hydrodynamic size: measured by PCS and evaluated to 33 nm.

- Relaxometric characterization:
  - the proton NMRD profile was recorded between 0.01 MHz and 10 MHz
  - additional measurements at 20 and 60 MHz were respectively obtained on Minispec PC-20 and Mq 60 Series systems (Bruker, Karlsruhe, Germany)

In vivo MRI evaluation

Animal model of Alzheimer disease: eighteen months old double transgenic mice APP[V717I] x PS1-A246E [2]. The histology and MRI investigations previously performed [2, 3] demonstrated the presence of amyloid plaques (SPs) both in the cortex and in the thalamic areas (

[ESMRMB_STB_Fig2.jpg] Figure 2).

Contrast agent administration:

- i.v. injection of 80 micromol Fe/kg of USPIO-g-STB; USPIO was used as control.
- to open the blood-brain barrier, the mice were first injected with a solution of 25% mannitol i.v. The wild type (WT) control mice received the same treatment.

MRI protocol:

- 4.7 T Bruker AVANCE-200 system, vertical bore, mini-imaging device
- SE T_2-weighted, TR/TE = 2000/15-60 ms, NA = 3, NE = 4, matrix 256x256, slice thickness = 2 mm, FOV = 4 cm, spatial resolution = 1.56 mm

3. Results

Relaxometric characterization: The NMRD data demonstrate that grafting did not significantly alter the particle size and relaxometric properties ( ).In vivo MRI evaluation: The molecule used to target the SPs in this experiment is a stilbene derivative, which is specific for the protein beta-sheets. As a consequence, this molecule can target not only the SPs, but also the NFTs [4]. Nevertheless, solely the SPs are accessible for targeting since they are located extracellularly.Mannitol was used to open the blood-brain barrier (BBB), although its integrity might already be compromised and the permeability probably enhanced in AD [5, 6] due to the lesions produced by SPs on different types of cerebral blood vessels ([ESMRMB_STB_Fig5.jpg] Figure 5) [7].Two hours post-contrast, USPIO-g-STB produced a significant decrease of the signal intensity in the cortex and the thalamic areas in the brain of the transgenic mouse ([ESMRMB_STB_Fig6.jpg] Figure 6) [3], which is probably associated to the SPs localization.The negative contrast is more important in the brain of the AD mouse as compared to the WT control mouse ( ). It is also remarkable that the negative contrast in cortex is solely present in the brain of the AD mouse but not in the WT control. The effect produced by USPIO-g-STB is not explained by a simple diffusion of the contrast agent in the brain of the transgenic mouse, since amyloid deposits are known to restrict the diffusion within the interstitial space [8].The spatial resolution is low (1.56 mm), which means that the precise epitope of the contrast agent interaction cannot be certainly identified. The micro-imaging seems to be indispensable for the SPs detection. On the other hand, the blow-up effect of USPIO-g-STB allows to diagnose the disease. Of course, it remains to be proven if this brain distribution is specific, and not common to other neurodegenerative pathologies. The patchy distribution of USPIO-g-STB in the brain of AD mouse argues for a rather specific accumulation at the level of SPs compared with USPIO, which seems to diffuse homogeneously in the nervous tissue ([ESMRMB_STB_Fig8.jpg] Figure 8).

4. Conclusion

The preliminary characterization of the new USPIO-grafted stilbene derivative emphasizes its potential as a tool for the non-invasive diagnosis of AD, which may help in the treatment and monitoring of this pathology.

5. References

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6. Personal Information

Acknowledgements

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7. Mediafiles

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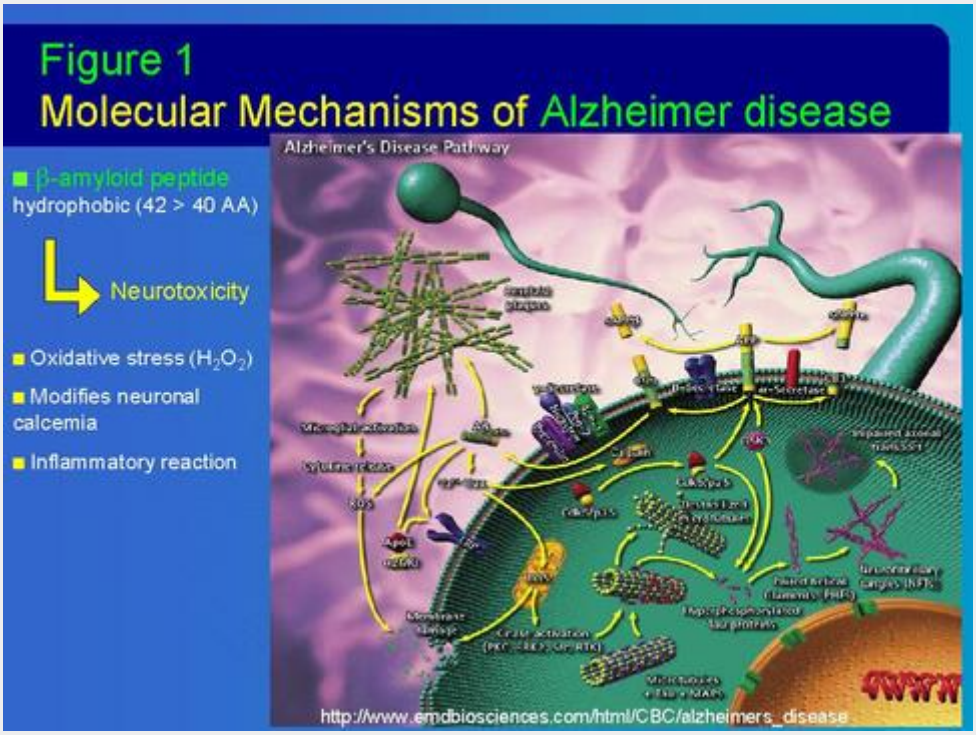

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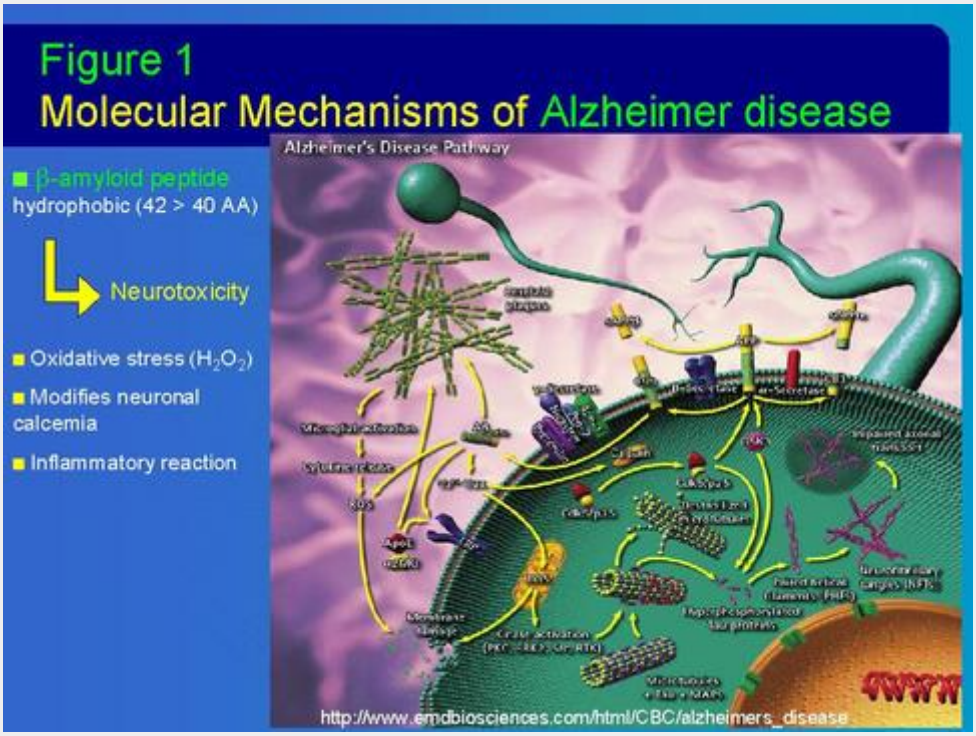

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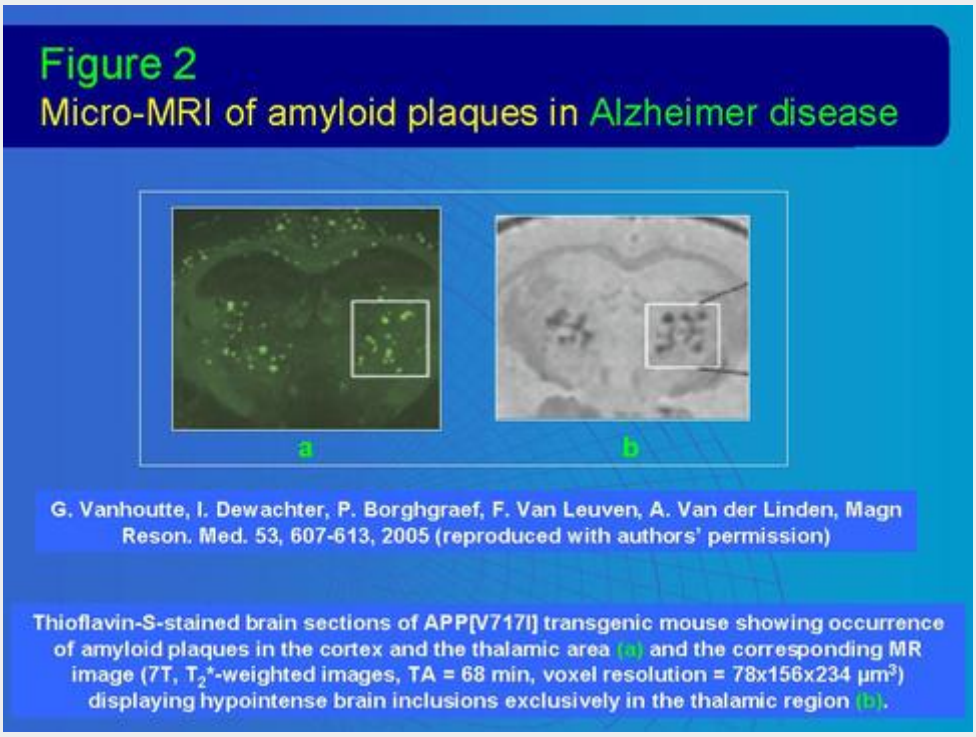

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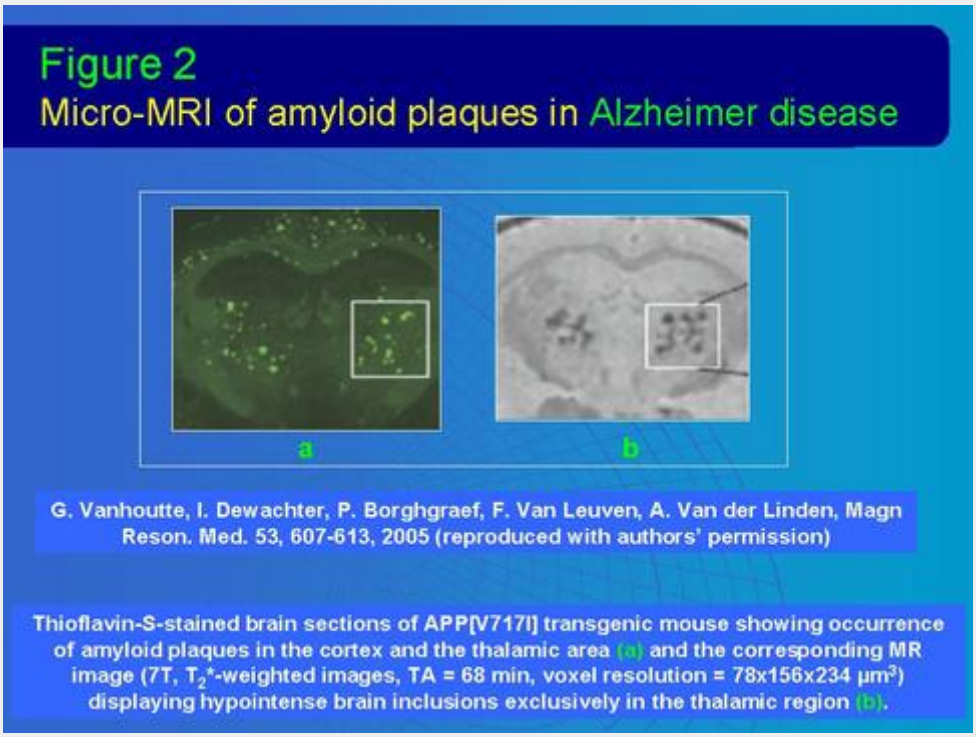

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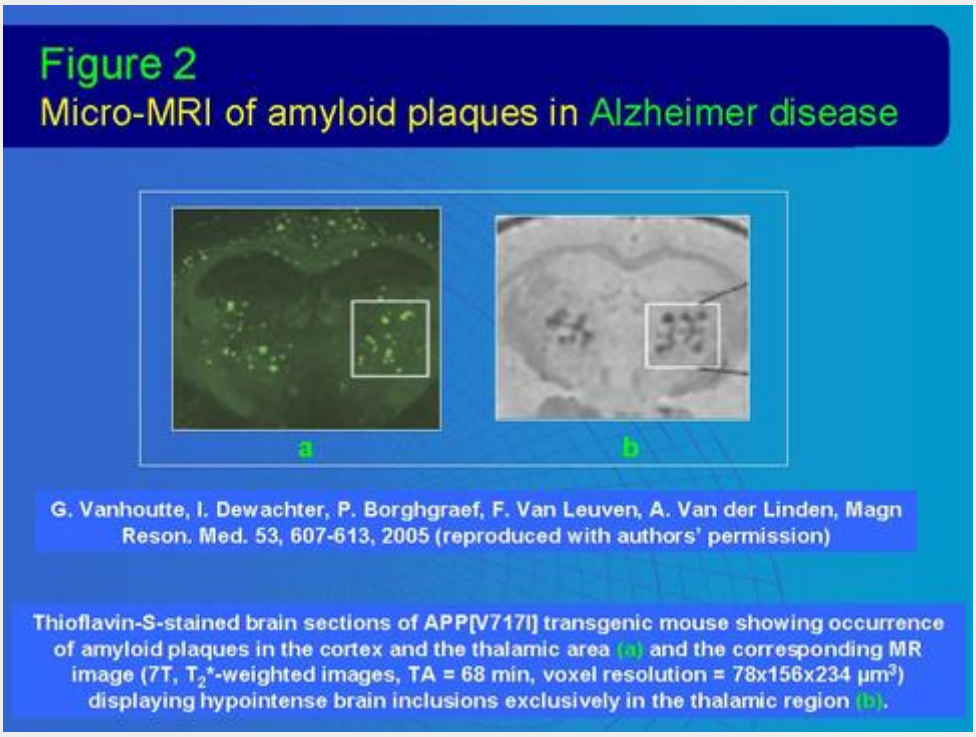

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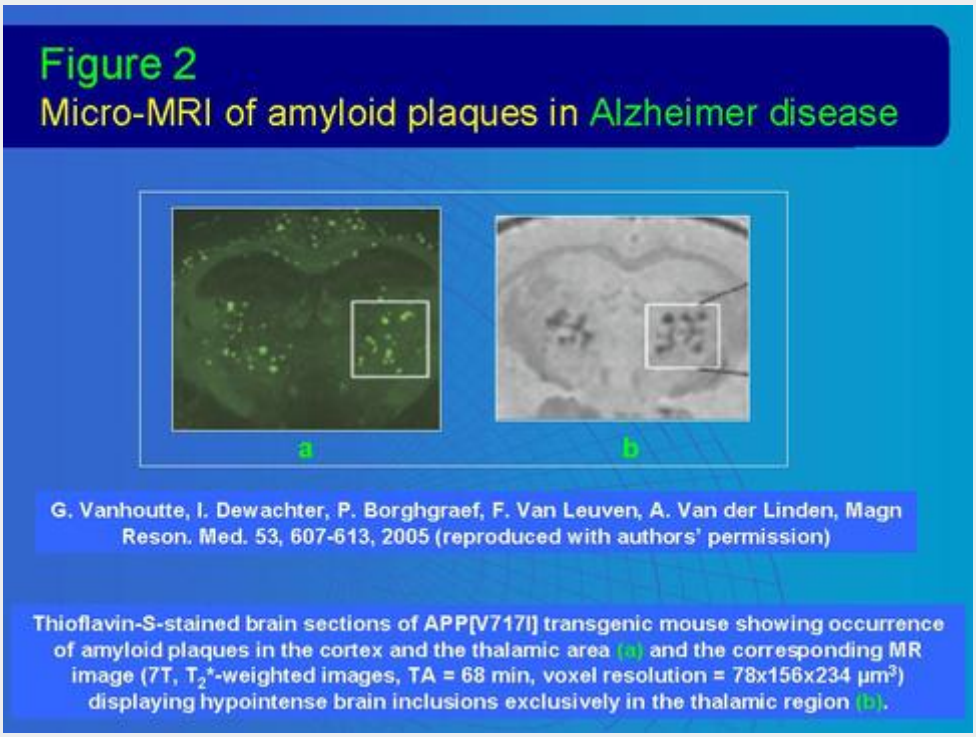

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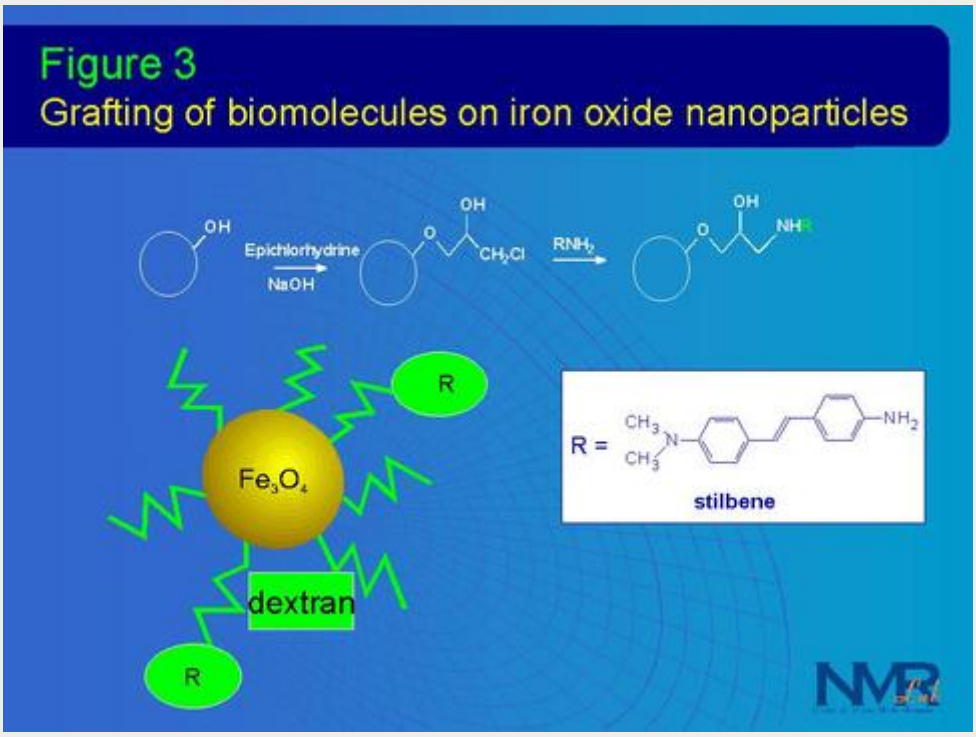

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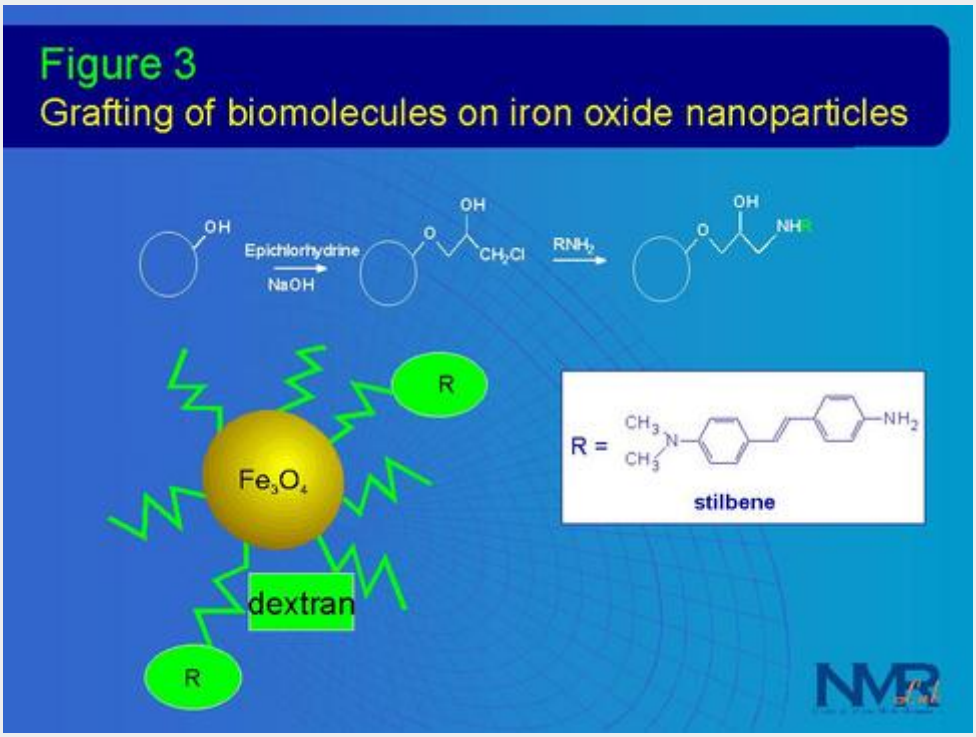

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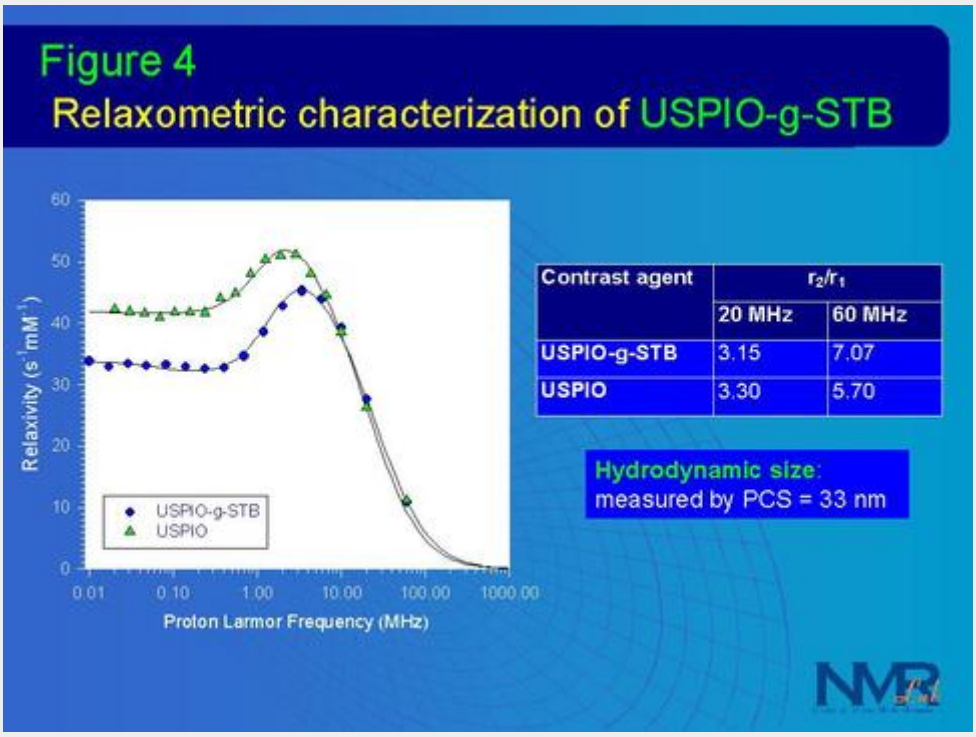

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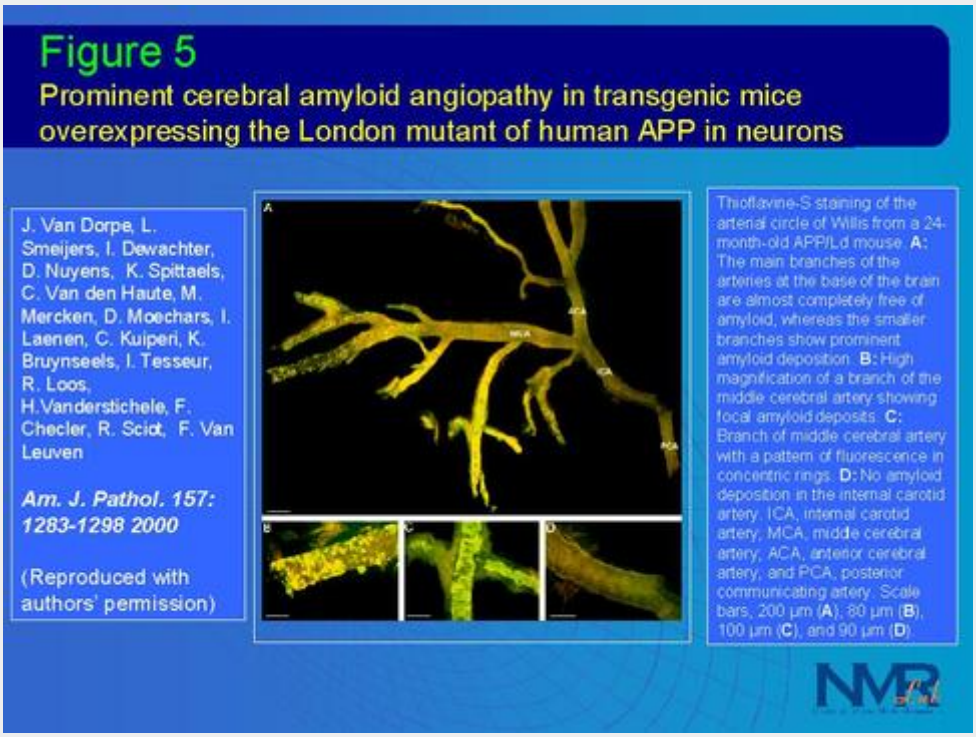

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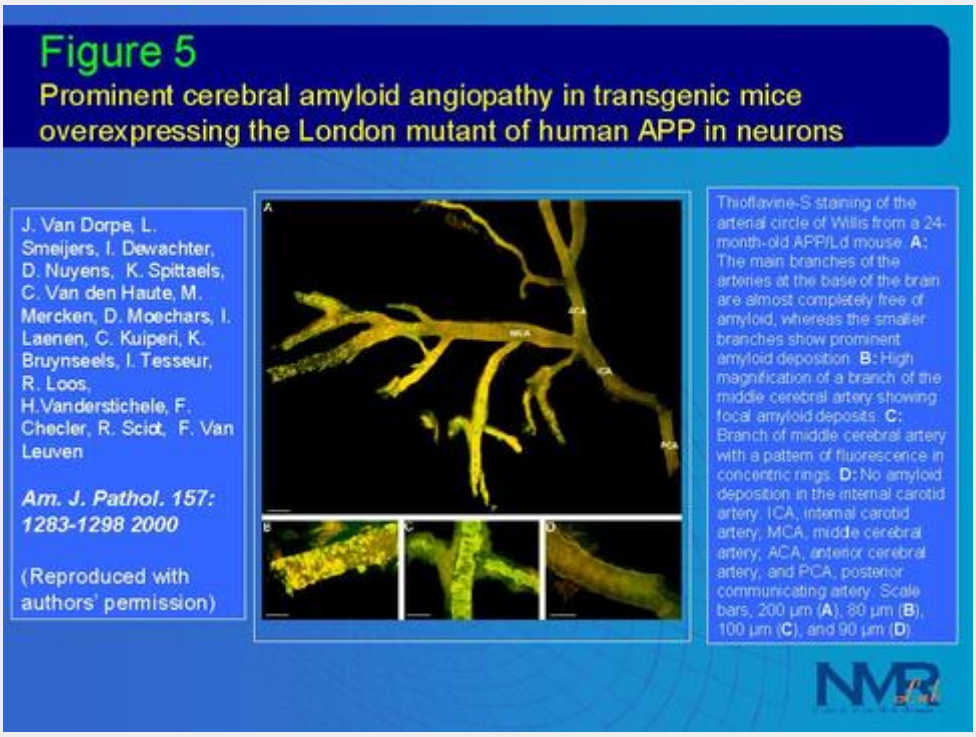

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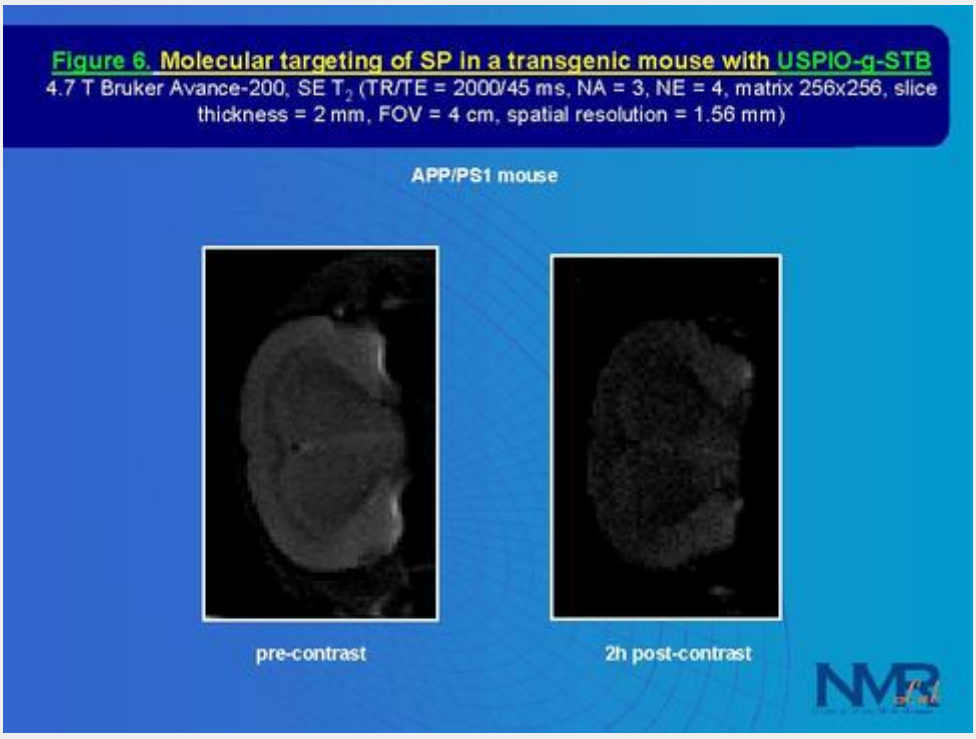

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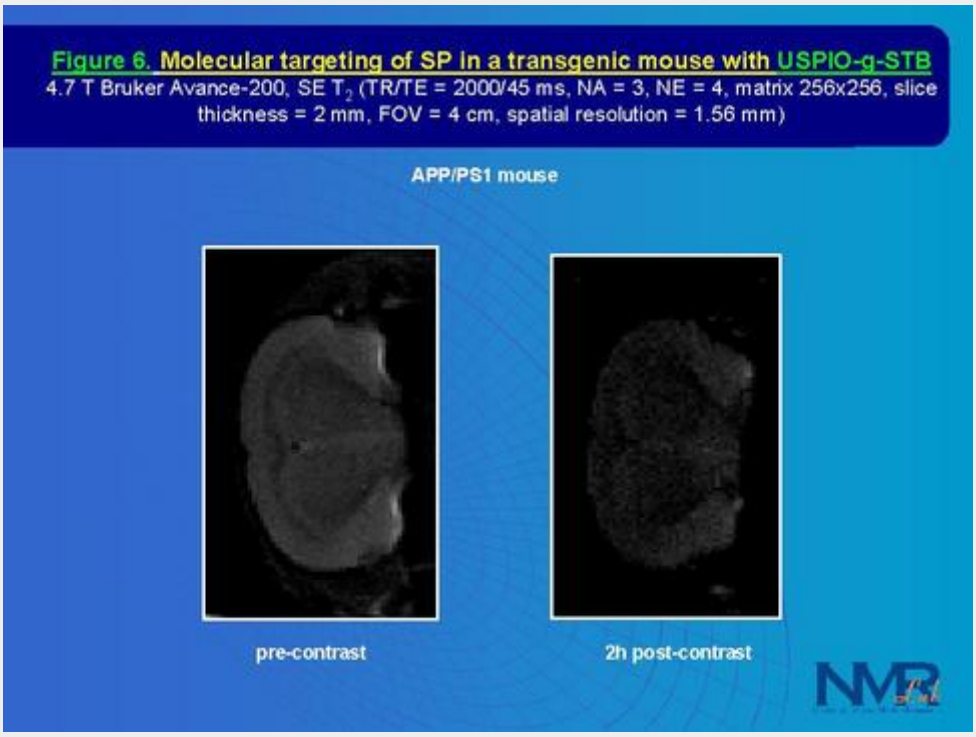

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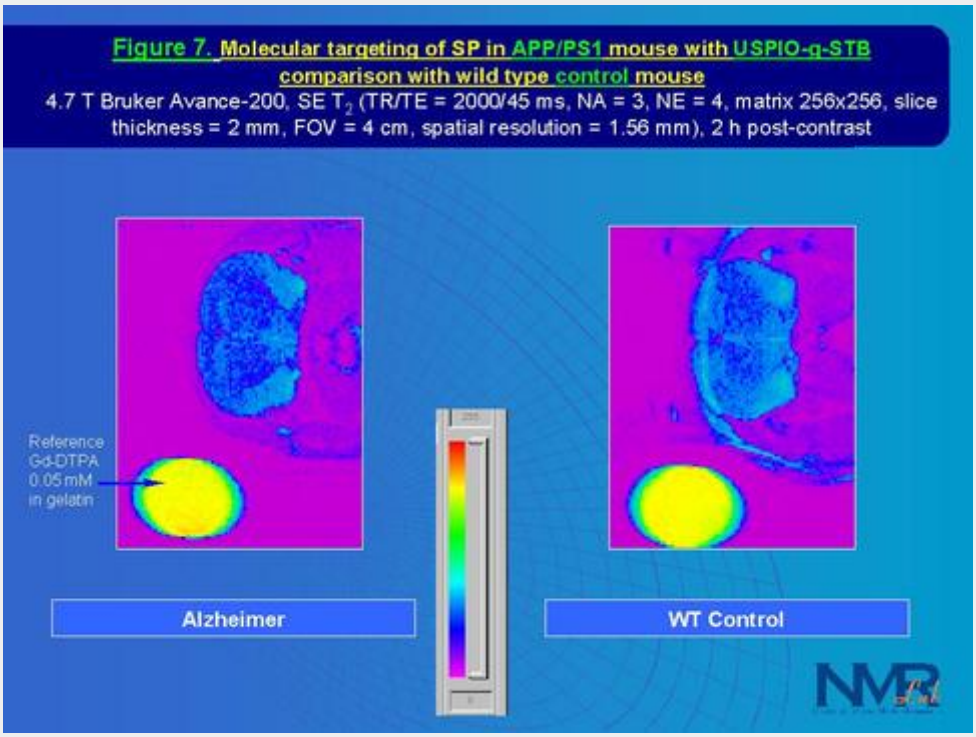

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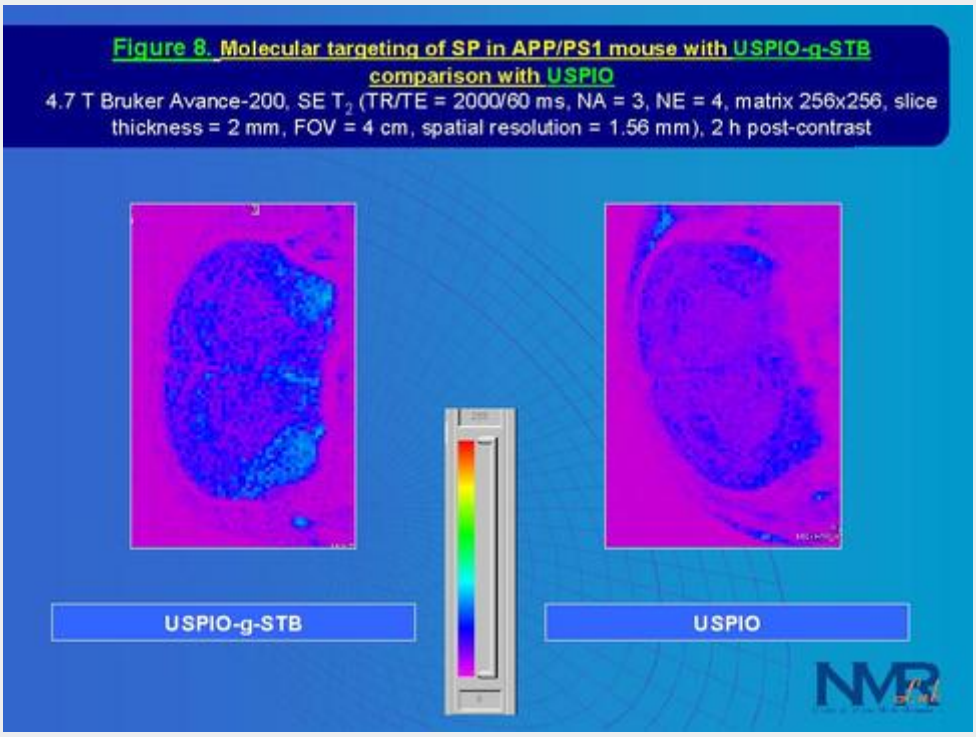

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