Synergistic Targeting-Imaging Approaches for Sensitive Virus and Tumor Detections

Yung-Ya Lin[1], Chaohsiung Hsu[1], Zhao Li[1], and Lian-Ping Hwang[2]
[1]*Chemistry and Biochemistry, UCLA, Los Angeles, CA, United States,*
[2]*Chemistry, National Taiwan University, Taipei, Taiwan*

I. Introduction. Sensitive *in vivo* MR imaging of virus (especially the ability to quantify virus concentrations and type/subtype) and tumors (especially at early stages) are important and challenging for medical development and clinical applications. For this purpose, effective synergistic targeting-imaging approaches for sensitive virus and tumor detections were developed and demonstrated.

II. A Targeting-Imaging Approach for Sensitive Virus Detection
Theory & Methods. Our analytical formulation and molecular dynamics simulations suggested [1]: (i) Spin-locking efficiency is sensitive to the field fluctuations induced by magnetic nanoparticles (SPIOs). (ii) Different virus concentrations result in virus-SPIO aggregates with different sizes but similar inter-particle distance. (iii) Spin-locking fields cannot suppress the dephasing of H1 spins embedded in rapidly fluctuating magnetic fields induced by small-sized virus-SPIO aggregates, but they are able to lock the dephasing induced by large-sized virus-SPIO aggregates.
Results. As *in vitro* demonstrations to the above targeting-imaging principles, we conjugated SPIO with HA-specific antibodies and then mixed them with influenza virus (subtype H5N2) solutions of different concentrations (Fig.1A). Under spin-locking fields, the three solutions exhibit different relaxivities (Fig.1C), due to distinct SPIO-virus aggregates produced in different solutions (Fig.1B). In addition, we carried out simulations with estimated experimental parameters and reproduced consistent results (Fig.1D).

III. Targeting-Imaging Approach for Sensitive Tumor Detection
Theory & Methods. "Active Feedback MR" is based on the feedback-induced nonlinear spin dynamics that we discovered, for examples [2-4]. Here, its specific applications to sensitively image SPIO/aggregates was developed [5]. In the presence of the Zeeman field, a dipolar field is induced by SPIO/aggregates. Such dipolar field creates a spatial and temporal (water diffusion) variations to the precession frequency of the near-by water 1H magnetization. Sensitive imaging of SPIO/aggregates can be achieved by manipulating the spin dynamics by "selective self-excitation" and "fixed-point dynamics" under active feedback fields.
Results. First, an active-feedback electronic device was home-built to generate feedback fields from the received FID current. The device is to filter, phase shift, and amplify the signal from the receiver coils and then retransmit the modified signal into the RF transmission coil, with adjustable and programmable feedback phases and gains, allowing us to utilize the active feedback fields in novel ways. Next, an active-feedback pulse sequence was developed for early tumor detection and was statistically tested on *in vivo* tumor models of colon cancers (COLO 205 human colon adenocarcinoma cell line) from nude mouse xenografts (Fig. 2). The tumor was labeled by COLO 205 antibody-conjugated SPIO through tail vein i.v. injection. Due to resonance mismatch, the SPIO-labeled tumor can resist "selective self-excitation" from the active feedback fields generated by the bulk water and the active feedback device. Therefore, the dynamics of its longitudinal magnetization is mainly T1 relaxation with a longer T1 time and higher T1 fitting-correlation-coefficient. On the other hand, for muscles and unlabeled tumors, "selective self-excitation" rapidly rotates the bulk water magnetization back to the stable +z fixed-point (as if T1 is short), creating dynamics very different from simple T1 inversion recovery (lower T1 fitting correlation coefficient).

IV. Conclusions. (i) Computer simulations and *in vitro* H5N2 images (Fig. 1) suggest 4-10 times of improvements in imaging sensitivity to virus concentrations can be achieved by this this targeting-imaging approach over conventional methods. (ii) *In vivo* mouse images of colon cancers targeted by SPIO (Fig. 2) suggest this targeting-imaging approach can provide enhanced, robust, and positive contrast for sensitive tumor detection.

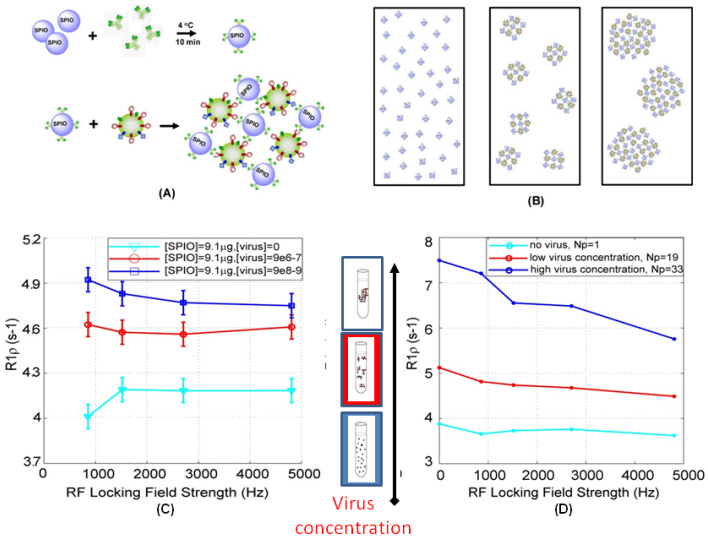

Fig. 1: A synergistic targeting-imaging approach for sensitive virus detection. (A) Targeting: we conjugated magnetic nanoparticles (SPIO) with HA-specific antibodies and then mixed them with H5N2 influenza virus solutions to form virus-induced aggregates. (B) Its degree of aggregate depends on virus concentrations. (C) Imaging: a rotating frame spin-locking method was invoked to enhance the variations in magnetic nanoparticles' relaxivities in these three different solutions, (D) as also confirmed by molecular dynamics simulations.

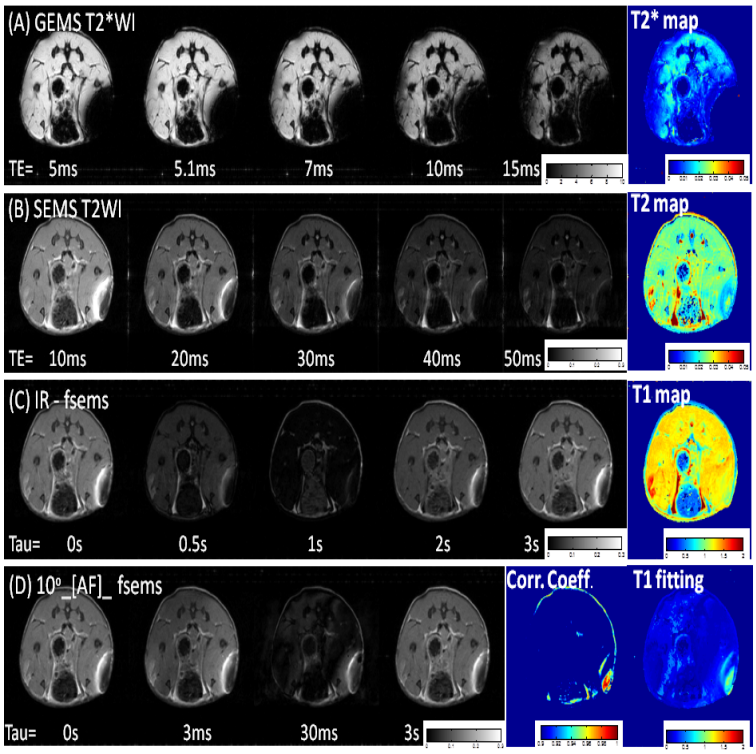

Fig. 2: A synergistic targeting-imaging approach for sensitive tumor detection. In vivo images and parameter mapping of human colon cancers (at right flank) from nude mouse xenograft. Targeting: SPIO were conjugated with COLO 205 antibody and then delivered through i.v. injection from the tail vein. Imaging: an innovative "Active Feedback MR" method was devised to enhance the perturbation to the H1 spin dynamics from the SPIO-induced dipolar fields. (A) T_2*-weighted image and T2* parameter mapping. (B) T_2-weighted image and T2 parameter mapping. (C) Inversion recovery T_1-weighted image and T1 parameter mapping. (D) Active feedback image, T1 parameter mapping, and fitting-correlation-coefficient mapping (colorbar 0.9-1) that clearly highlight the colon cancer. Please see text for explanation.

Reference: [1] JACS Nano (submitted) [2] Science 290, 118 (2001) [3] MRM 56, 776 (2006) [4] MRM 61, 925 (2009) [5] MRM (2011)