An H/F/X/Y Fast-MAS NMR Probe Particularly for Alzheimer’s and Cancer Research

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An H/F/X/Y Fast-MAS NMR Probe Particularly for Alzheimer’s and Cancer Research

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Research Abstract
? DESCRIPTION (provided by applicant): More than 20% of current drugs (and a much greater fraction of those in development) are fluorinated (including such block-busters as Prozac, Lipitor, and Ciprobay). Steady progress over the past decade has shown magic angle spinning (MAS) solid-state NMR (ssNMR) to be arguably the most powerful analytical tool for studying macro-molecular structures and their dynamics. Yet, MAS probes suitable for the needed multi-

channel studies of fluorinated drugs and their interactions are not available for high-field NMR instruments. While a few 1H/19F/X (3-channel) MAS probes (with inadequate spinning speeds and spectral resolution) have been demonstrated for fields up to 500 MHz, the technical challenges have been seen as too daunting at higher fields because of the difficulties of known single-coil rf circuits in handling close resonances at high frequencies. Quad-tuned H/F/X/Y MAS probes have apparently never been made, even for low fields. For solution NMR on the other hand, four-channel multinuclear 1H/19F/X/2H probes have recently become more readily available, and such have proven to be extremely valuable for identification and characterization (using 1H/15N, 19F/13C, and 19F/2H/15N methods) of active fragments, their binding to soluble proteins, and their effects on such protein-protein interactions. The problem is that such methods don’t work with insoluble proteins – such as the aggregates and fibrils that are central to Alzheimer’s disease (AD), Parkinson’s disease (PD), and probably even prion-mediated diseases. The amyloid beta (A?) cascade hypothesis is beginning to bring unity to the field of neurodegenerative diseases, but a key tool for understanding aggregate progression and treatment beyond the stages of the initial seeds is not available. This Phase-I proposal seeks funding to develop, build, and test a prototype H/F/X/Y fast-MAS probe based on a novel “”single-coil”” rf circuit optimized for 19F detection with simultaneous irradiation or detection on ny or all of the other channels, and suitable for MAS at fields from 7-22 T, with rotor diameters from 0.7-3 mm. Analysis suggests that a substantial portion of the spectral line broadening seen in many MAS experiments is from J-couplings (which is not averaged by MAS) to heteronuclei, and spinner-dependent effects – thermal gradients, axial vibration, and magnetism. The ability to simultaneously decouple 1H, 2H, and 13C or 15N during 19F detection with fast-MAS in a spinner optimized for high resolution with a circuit compatible with B0 up to at least 900 MHz will permit a dramatic increase in spectral resolution and sensitivity on, for example, 19F-labeled ligands in amyloid assemblies and their precursor aggregates, or in 19F labeled DNA-carcinogen adducts. The novel probe would allow the powerful suite of NMR acquisition and automated structure determination protocols developed for solution NMR, which rely mostly on indirect-detected triple- and quad- resonance schemes, to be successfully applied to rigid fluorinated samples smaller than a milligram. The Phase-II probe will be compatible with automated sample exchange and sample temperatures from 90 K to 420 K. Moreover, it will be essentially devoid of problematic background signals for all the primary nuclides (1H, 19F, 31P, 13C, 2H, 15N, and 17O), and it will be tunable to virtually all combinations of interest, thereby making it also invaluable in such areas as metabolism, materials science, catalysis, and sustainable energy.

Further information available at:

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