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High Throughput Hyperpolarization for Drug Screening

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Many limitations of state-of-the-art drug screening by nuclear magnetic resonance (NMR) can be overcome by means of high-throughput hyperpolarization. There is an urgent need for innovative experimental screening techniques to identify new drugs as the resistance of « superbugs » against known drugs, e.g., against mycobacterium tuberculosis and other pathogens. Screening techniques must be capable of ranking promising drug candidates (“ligands”) according to their affinity for a protein, a nucleic acid, or a macromolecular complex (“targets”), in order to inhibit their function. Ligand-based NMR methods can monitor parameters such as chemical shifts, diffusion coefficients, dissociation constants KD, and kinetic kon and koff rates. NMR is particularly powerful to identify weakly binding ligands, which are crucial for fragment-based drug discovery (FBDD). However, even when boosted by current Dynamic Nuclear Polarization (DNP) methods, NMR is exceedingly slow and cumbersome. Our team is working towards the transformation of DNP-enhanced NMR into a competitive method for drug screening by introducing several ground-breaking innovations: multiplexed hyperpolarisation, high-speed transfer of frozen droplets, in situ dissolution, multiplexed detection using a stack of microfluidic detection chambers, and improved contrast due to long-lived states (LLS) of nuclei such as 19F and, more surprisingly, 2H in deuterated heavy drugs.

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