**Scalable Hyperpolarized MRI Enabled by SLIC-SABRE of [1-13C]Pyruvate in Acetone-Water**

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**Abstract:** Hyperpolarized (HP) MRI using [1-13C]pyruvate is emerging as a promising molecular imaging approach. Among hyperpolarization methods, Signal Amplification By Reversible Exchange (SABRE) is attractive because SABRE polarizes the substrates directly in room-temperature solutions avoiding complex hardware. Most SABRE experiments have historically been performed in methanol, a relatively toxic and difficult to remove solvent. Here we first demonstrate the use of a acetone-water-solvent system (ace/water = 80/20) to provide hyperpolarized [1-13C]pyruvate with up to 40% polarization, then implemented a solvent processing protocol to achieve injectable solutions, and lastly demonstrate HP *in vivo* spectroscopy and imaging using the acetone/water platform (Ace-SABRE) showcasing metabolic tracking in a hepatocellular carcinoma (HCC) tumor as well as HP-MRI, both in direct comparison to dissolution dynamic nuclear polarization (d-DNP) experiments. The Ace-SABRE promises faster adoption of SABRE hyperpolarization in biological experiments, overall lowering the barriers to entry for HP-NMR and HP-MRI.

**Introduction**

Hyperpolarized magnetic resonance imaging (MRI) has emerged as an important technology that facilitates non-invasive metabolic imaging by enabling the real-time study of cellular and molecular processes through its remarkable sensitivity[1]. It is the process of hyperpolarization that overcomes the intrinsic limitations in sensitivity of conventional MRI, by enhancing nuclear spin polarization levels by several orders of magnitude, which enables the detection of low-concentration metabolites and the monitoring of their biochemical transformations. One biomarker in particular, [1-13C]pyruvate has proven particularly valuable in this regard due to its central role in metabolism, giving critical *in vivo* insights into glycolytic and oxidative metabolic pathways in real time.[2–6] These capabilities make hyperpolarized pyruvate a powerful diagnostic tool for probing ailments such as cancer,[7,8] cardiovascular disease,[9,10] and neurodegenerative disorders.[11,12] HP-MRI realizes this advantage for diagnostic and therapeutic MRI applications because the detected response responds immediately to chemical transformations, thereby enabling the simultaneous tracking of multiple metabolic processes in one measurement. This benefit contrasts with the powerful conventional metabolic imaging techniques, PET and SPECT, whose gamma-ray signal does not immediately respond to changes in chemical structure. Since HP-MRI does not expose patients to ionizing radiation, longitudinal studies with frequent assessments become feasible, which allows for the real-time observation of disease progression or indeed response to treatment. For example, HP pyruvate can distinguish between normal and diseased tissues by encoding changes in metabolic flux, thereby offering critical insights into tumor biology,[7,8] neurodegenerative pathways,[11,12] or ischemic injuries.[13–16] Unlocking these benefits in a cost effective way is critical to not only improving our understanding of disease mechanisms, but also enhancing patient outcomes through efficient treatment.

Currently, dissolution dynamic nuclear polarization (d-DNP)[17] is the leading technique for the production of HP metabolic contrast agents such as [1-13C]pyruvate. In fact, studies using d-DNP have demonstrated the utility of HP-MRI in both preclinical and clinical settings by providing high agent polarization levels with minimal excipients in the injectable solutions.[1,18,19] These efforts have led to Phase I and Phase II trials focusing on applications in cancer diagnostics and treatment.[1] However, successful d-DNP faces potential challenges such as a high cost, operational complexity, and lengthy hyperpolarization build-up time, that researchers are targeting to improve its accessibility and scalability, in order to enable high-throughput commercial clinical MRI assessments. These limitations certainly pose challenges for applications that utilize more frequent repeated measurements to monitor treatment progression, or disease dynamics, during a time-critical treatment regime.

To address the current limitations of d-DNP, and access new applications whilst providing the scalability HP-MRI needs, an alternative pathway to the hyperpolarization of pyruvate and other molecules has been examined. This involves the readily formed feedstock parahydrogen, and in its broadest sense has been term parahydrogen induced polarization (PHIP). The resulting side-arm hydrogenation (PHIP-SAH) method is already showing significant promise in preclinical studies by achieving sufficient polarization levels for *in vivo* metabolic imaging with low excipient levels in the injectables.[20–29] This work has demonstrated the value of PHIP-based methods in characterizing metabolism for high-throughput applications. A potential difficulty associated with chemically changing PHIP-SAH though is the need for molecular precursors to pyruvate that are challenging to synthesize and store.[24] The PHIP-SAH approach involves both chemical and physical transformations stemming from the hydrogenation of these precursors, followed by hydrolysis of the product and further purification.[20–29] The benefits of this method though are clear as HP-pyruvate can be created in minutes meaning there are significant opportunities for future broad dissemination in the healthcare community.

Chemically benign Signal Amplification by Reversible Exchange (SABRE) is emerging as a simpler, more accessible parahydrogen-based hyperpolarization technique that is being widely explored.[30] This is reflective of the fact that in contrast to PHIP-SAH, SABRE transfers hyperpolarization directly from parahydrogen into the target molecule via the assembly of a metal complex whose role is simply to bring the two species into contact. It therefore eliminates the need for any complex precursor synthesis and acts quickly because there is no need for a chemical transformation.[30–37] Ultimately, these advantages are likely to translate into lower costs and greater ease of adoption. However, the early implementations of SABRE faced challenges, including lower hyperpolarization levels and the use of toxic solvents such as methanol. Recent work has been shown to circumvent some of these challenges by unlocking the first preclinical demonstrations of SABRE based HP-MRI.[38–41] One of the key steps was the implementation of rapid methanol gas-stripping, however, small amounts of methanol in the injected solutions remained unavoidable in these solutions. Accordingly, there remain challenges relative to PHIP-SAH, which uses less toxic solvent and delivers hyperpolarization levels commensurate with early by d-DNP.

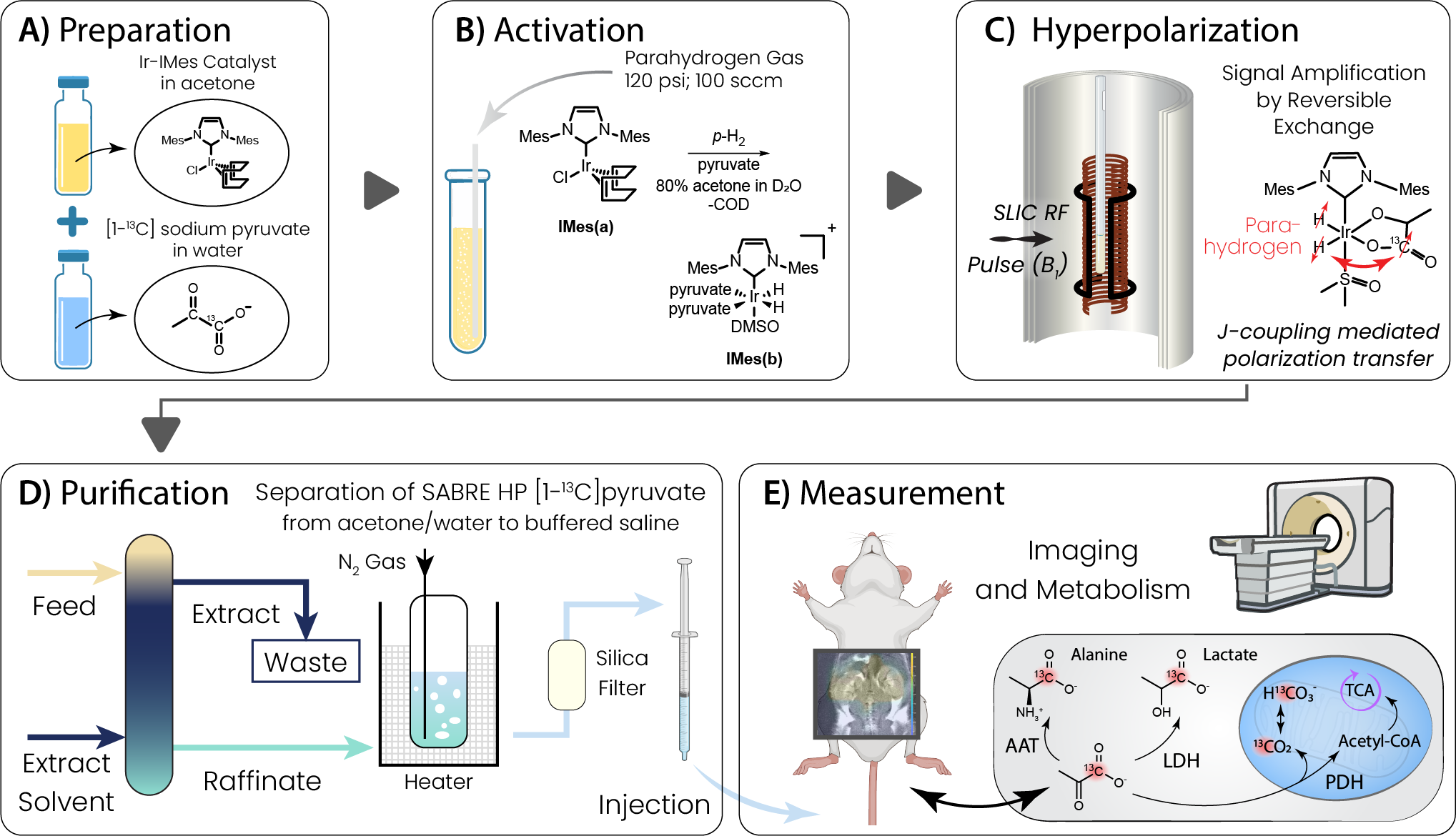
The work presented here showcases on-going advancements in SABRE hyperpolarization that seek to address these challenges, and thereby illustrate a route on the pathway to clinical viability for SABRE. The current work replaces methanol with acetone, delivers up to 40% polarization, demonstrates the generation of a truly biocompatible solution, provides preclinical *in vivo* data at multiple sites, and for bench-marking purposes details a side-by-side comparison to d-DNP. The use of the acetone-water (A/W) mixture in the hyperpolarization process involves a more biologically tolerable and easier to remove solvent than methanol, and thereby mitigates some of the safety concerns that arise when producing injectable solutions for *in vivo* imaging and future clinical translation. In the following article we call this approach Ace-SABRE.

The A/W mixtures used in this work were purified using common purification methods, liquid-liquid extraction (LLE) and gas stripping[42–44]. Furthermore, the organometallic SABRE catalyst (Ir-IMes, where IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) is most readily soluble in non-polar solvents, and alcohols like methanol. Conversely, pyruvate is soluble in polar solvents, like H2O and methanol. Traditionally, this has led to the use of methanol as the solvent of choice for SABRE hyperpolarization chemistry, simplifying the formulation of the hyperpolarization mix and subsequent reaction network. However, methanol is not only a difficult solvent to remove, requiring significant heat and gas flow to remove even small quantities,[45–47] but is also a Class 2 solvent (FDA/ICH Q3C),[48] restricted to minimal permissible daily exposure due to its toxicity. Although previous work has demonstrated the use of ethanol to generate SABRE-polarized pyruvate, the separation of ethanol from water is difficult to complete under the time-constrained conditions of hyperpolarized sample processing (requiring removal of impurities and optimization of relaxation effects requiring magnetic field, temperature, and material controls).[49,50] Thus, the choice of a solvent with similarly low toxicity to ethanol such as acetone introduces a simple alternative that can be more easily removed due to its lower polarity and hence higher affinity for extracting solvents, lower boiling point, and high vapor pressure.[42,43] We note that very recently the use of acetone/water mixtures for SABRE was also demonstrated by Bondar et al. to polarize [2-13C]pyruvate, but polarization levels, however, remained well under 1%. [51]

In summary, the optimization of Ace-SABRE enables polarization levels exceeding 40%, demonstrating the effectiveness of mixed solvent systems surpassing critical thresholds required for effective metabolic imaging. The results are achieved with non-deuterated [1-13C]-pyruvate, further reducing costs by circumventing the need for deuterated derivatives. These innovations are combined to demonstrate preclinical imaging, where hyperpolarized pyruvate was used to track both spatial distribution and metabolic activity characterizing diseased tissue *in vivo*.

**Results and Discussion**

In the following results we show that high polarization (>40%) is achievable on [1-13C] pyruvate hyperpolarized with Ace-SABRE using optimized chemistry in A/W solvent mixtures combined with optimized pulsed SABRE techniques (specifically using spin-lock induced crossing, SLIC, excitation[52,53]). **Figure 1** shows how the A/W dual solvent system is coupled with SABRE hyperpolarization to generate aqueous solutions of HP pyruvate that can be injected, imaged, and measured by MRI. First, the sample is prepared (Fig. 1A) by mixing the SABRE pre-catalyst [IrCl(COD)(IMes)], [1-13C]pyruvate and DMSO in a 80:20 acetone water mixture. Next, the sample is activated (Fig. 1B) by bubbling parahydrogen gas through the solution at 120 psi (8.3 bar). Subsequently the [1-13C]pyruvate is hyperpolarized by SLIC-SABRE (Fig. 1C) and HP-pyruvate 13C polarizations of up to 40% are quantified (Fig. 2D).



**FIGURE 1.** Sample preparation, hyperpolarization, and purification scheme using the present SABRE-based method. [A] Here, an acetone and water (in these experiments, D2O) mixture solubilizes the organometallic catalyst and aqueous pyruvate in a homogeneous mixture. [B] Introduction of parahydrogen gas hydrogenates the SABRE catalyst precursor to generate a catalytically active system, where [C] a pulsed magnetic field controls transfer of the spin order via *J*-couplings from parahydrogen-derived hydrides on the SABRE catalyst to target molecules like pyruvate in free, reversible exchange on the catalytic center. [D] The HP pyruvate product is purified by first extracting the bulk acetone solvent and organic catalyst excipients by liquid-liquid extraction and subsequent gas stripping of the remainder of the solvent to render an aqueous solution of HP pyruvate that can be injected into a target subject for imaging.

After the hyperpolarization step, the solution is purified using the standard chemical purification and processing techniques of Liquid-Liquid Extraction (LLE) and gas stripping and filtration (Fig. 1D). Finally, the in-vivo measurements are performed (Fig. 1E). The details of these purification, processing, and exemplary in vivo imaging measurements are further detailed below.

Optimization of SABRE in acetone/water

In a 35 mM [1-13C]-pyruvate SABRE solution, using acetone/water as a solvent, polarization of over 35% is reproducibly achieved before extraction and processing, with 40 ± 1% polarization observed in a singular case (Fig. 2D, E). For hyperpolarization of these solutions, a mixture of 80% acetone and 20% D2O is used to dissolve a ratio of ~6:1 pyruvate to Ir-IMes SABRE catalyst (i.e. 35 mM [1-13C]-pyruvate, 6 mM catalyst). Additionally, DMSO is added as previously described to modulate the exchange rate of the pyruvate.[54–57] In these experiments, a 2:1 ratio of DMSO to catalyst is used (i.e. 12 mM DMSO, 6 mM catalyst). The SABRE precatalyst [IrCl(COD)(IMes)] was prepared as previously described.[54,55] The resulting solution is polarized as shown in **Figure 2A**, where a shimmed B0 field controls the magnetic field of the sample (~50 μT), a B1 saddle coil provides a transverse CW excitation field for spin transfer, and a constantly pumped cooling system provides stable temperature control for the hyperpolarization process.

A diagram of graphing and graphs

Description automatically generated with medium confidence

**FIGURE 2.** SLIC-SABRE setup, optimization, and quantification of hyperpolarization. A) SLIC setup operating with a *B*0 of 53.8 μT, which is shimmed with the depicted shim solenoid. Water cooling provides sample-temperature control. B) Hyperpolarized signal as a function of the *B*1 frequency. C) Hyperpolarized signal as a function of *B*1 amplitude D) Hyperpolarized signal as a function of catalyst concentration at constant DMSO concentration of 12 mM. All samples were prepared from the same catalyst batch with identical conditions and run in sequence on the same day. E) Achieved Hyperpolarization and Reproducibility noted in polarization in % and molar polarization (= polarization × concentration). The temperature of the samples was 6.5 °C for all experiments.

One of the most important aspects needed to achieve high polarization reproducibly is a strict optimization of the catalyst:DMSO ratio, coupled with optimization of the SLIC pulse parameters (*B*1, *B*0 and their homogeneity). This is due to the synchronization of both chemical exchange and polarization transfer dynamics in the SABRE hyperpolarization scheme as described previously.[58–61] Because the *J*-coupling interaction between hydrides and the 13C target is relatively weak (~0.55 Hz),[62,63] the exchange rate must be very finely tuned to allow for sufficient polarization flow from hydrides to 13C, while retaining sufficient catalyst turnover to enable continuous pumping.[59–61] Similarly, B0 and B1 homogeneity are critical within the setup to ensure that all SABRE complexes experience the same conditions and contribute to polarization build-up irrespective of location in the solution being mixed by the bubbling parahydrogen gas. **Figure** **2A** shows a schematic of our coil configuration, where homogeneity is ensured using magnetic shielding and a shimming solenoid. **Figure 2B-D** depict separate elements of the multi-dimensional optimization space, where optimization of the SLIC *B*1 frequency, *B*1 amplitude, and catalyst concentration at a temperature of 6.5 °C are shown to yield maximization of hyperpolarization on the 1-13C site in pyruvate. Close to on-resonance, SLIC generates the hyperpolarization aligned with the spin-locking field in the transverse plane,[64] and an adiabatic switch-off pulse is used at the end of the SLIC period to align x-y magnetization to z-magnetization as implemented previously. [65] In **Figure 2B**, the *B*1 frequency is optimized including the application of this adiabatic switch-off pulse.,[65] This implementation results in a sharp inversion of the peak signal at the resonance frequency of the system at ω0=γ13CB0 in the *B*1 frequency dependance. This is due to production of -z vs. +z magnetization above or below resonance. In Figure 2C, the B1 power is optimized, also including the application of the adiabatic switch-off pulse. The optimal B1 power corresponds to a value close to the strength of the *J*HH coupling.[64–66] Deviations from the exact match can be induced by the exchange dynamics.

We also observe a minimal threshold to the chemical exchange of the system, where below a specific exchange rate driven by the DMSO to catalyst ratio there is no longer efficient spin transfer due to suppression of exchange and dominating effects of relaxation in the catalytic intermediate (**Figure 2D**). These results build on past work demonstrating the importance of chemical exchange in modulating the pyruvate and broader alpha-keto acid SABRE systems,[59–61] further experimental and theoretical investigation of the broad multi-parameter space will be the subject of future studies.

Interestingly, we find no difference in achievable hyperpolarization between the [1-13C]-pyruvate and [1-13C, 3,3,3-d3]-pyruvate isotopomers, which we hypothesize to be due to effects on the *J*-couplings and active chemical species in the reaction network due to use of acetone and water as a solvent instead of methanol. Further investigation of the theoretical composition of this reaction network will build on prior work as shown by Lin et al.,[67] seeking to deconvolute the differences between these reaction networks.

Pyruvate processing and purification

To obtain more overall signal (i.e. higher molar polarization), we have achieved reproducibly achieved *p* ~18.5% (**Fig. 2E**, n=4) on 70 mM pyruvate. On 70 mM [1-13C]-pyruvate, polarization (*p*) > 25% was achieved in a single experiment. Ratios of DMSO and catalyst for the 70 mM formulation were maintained as above. The variability in these results is due to the stringent chemical and environmental conditions required for hyperpolarization under the reported method, and a fully detailed multi-parameter optimization of the 70 mM formulation remains an important future task. These values correspond to 18 mM molar polarization (concentration × polarization) for the single (p=25%) experiment and 14 mM molar polarization for the average, which is well above the molar polarization achieved with the 35 mM formulation. Accordingly, we used 70 mM samples for *in vivo* experiments.

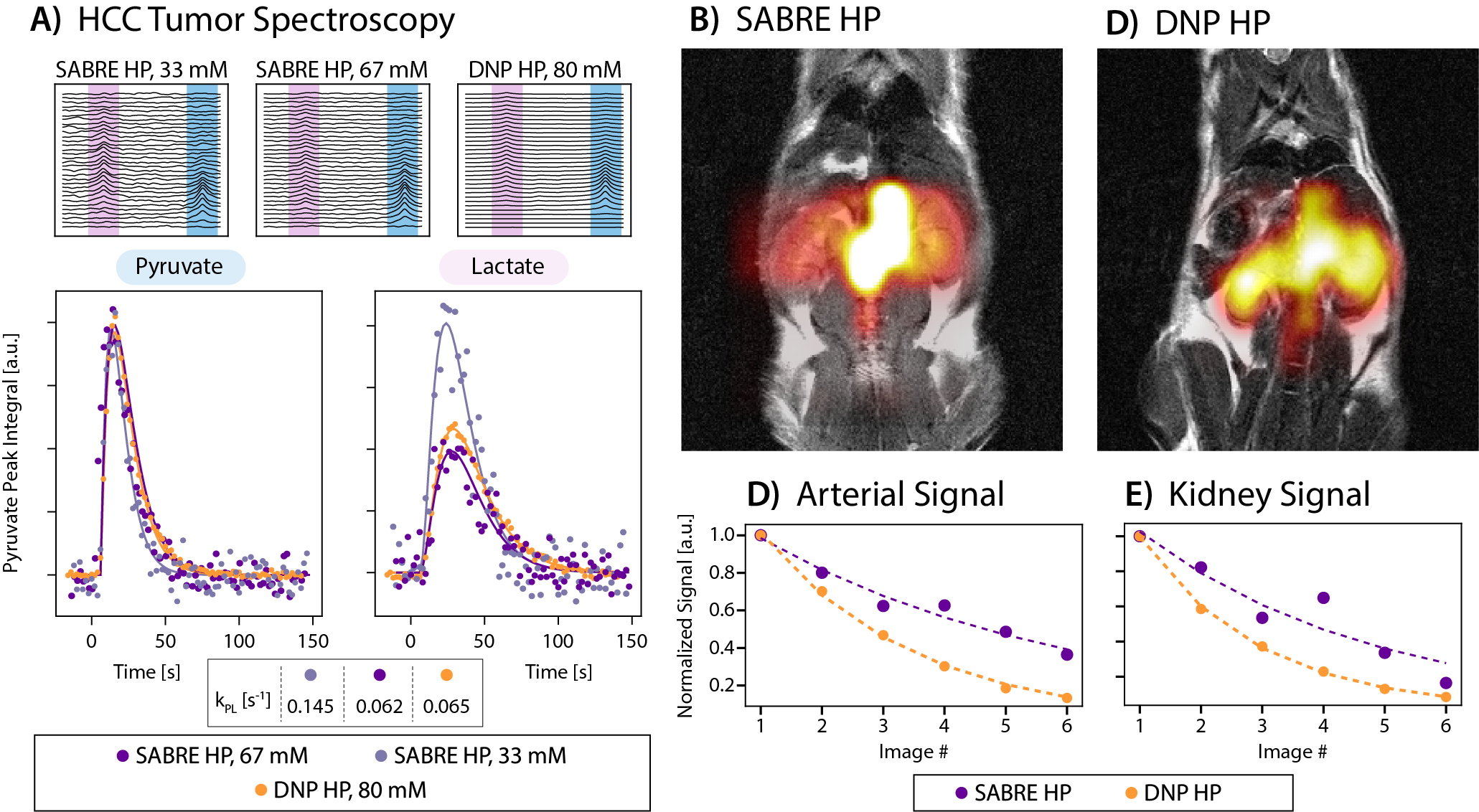
**TABLE 1**. Resulting concentrations remaining after for the purification of SABRE HP, 70 mM [1-13C]-pyruvate using the method described (n=3). The iridium, acetone, and butyl acetate concentrations are below those of the no observed adverse effect level (NOAEL) for rats using respective FDA/ICH Q3D and Q3C guidelines. Excipient concentrations and pyruvate concentration quantification methods are detailed in the supplementary information.

|  |  |
| --- | --- |
| Solution Output Metrics | Concentration or Polarization |
| Iridium | 2.7 ± 0.8 µg mL-1 (14 ± 4 µM) |
| Acetone | 120 ± 25 mM |
| Butyl Acetate | 0.7 ± 0.1 mM |
| [1-13C] Sodium Pyruvate | 67 ± 2 mM |
| Polarization (after extraction) | 14.2 ± 0.5 |

The first purification step (Fig. 1D) follows a traditional LLE scheme,[68–71] where the HP solution of acetone, water, catalyst, and HP [1-13C]pyruvate is fed into the extracting solvent butyl acetate. Butyl acetate is chosen due to the low toxicity,[48] low water solubility,[72] and high affinity of esters for acetone extraction.[42,44] The raffinate then consists of the recovered aqueous fraction, containing HP [1-13C]pyruvate and residual amounts of acetone, butyl acetate, and iridium catalyst. The goal of the extraction is to maximize the concentration and the polarization of [1-13C]-pyruvate in the aqueous layer, while minimizing the concentrations of acetone and catalyst. In addition to LLE, the raffinate is further purified using gas stripping (nitrogen) at elevated temperature to further reduce the residual acetone. The last purification step is filtration with a C18 silica cartridge filter to further reduce the residual iridium catalyst level. The results of processing a 70 mM SABRE HP [1-13C]-pyruvate solution to produce a purified solution using these combined purification methods are shown in **Table 1**. Importantly, the average polarization observed after the processing steps is *p* =14.2 ± 0.5 % (**Table 1**). This corresponds to a retention of 76 ± 4% of the original polarization (*p* =18.5 ± 0.7%) during processing.

*In vivo* demonstrations

Using these methods, *in vivo* 13C imaging and spectroscopy demonstrates the utility of the technique and enables the results to be compared with established d-DNP methods. d-DNP pyruvate doses were prepared with an Oxford Instruments Hypersense polarizer as previously described.[73,74] Polarization of [1-13C]pyruvate in the d-DNP produced solutions was ~20%. All *in vivo* data was acquired using an MR Solutions 7T cryogen-free MRI. In **Figure 3**, we present characterization of tumor biology using ace/water HP pyruvate (**A**) and spectroscopic imaging in a healthy animal (**B-E**).



**FIGURE 3.** Comparison of results from SABRE and d-DNP injections of hyperpolarized [1-13C]pyruvate in both a tumor mouse model (patient-derived xenograft hepatocellular carcinoma flank tumor) (A) and healthy mouse model (BALB/C) (B-E). A) One mouse underwent three subsequent injections with 67 mM SABRE HP [1-13C]pyruvate, 80 mM d-DNP HP [1-13C]pyruvate, and 33 mM SABRE HP [1-13C]pyruvate. Acquired surface coil spectroscopy is shown on top, with pyruvate peaks highlighted in blue and lactate peaks highlighted in pink. Integration of these signals is shown in the plots below, with fitting of both the pyruvate and lactate signal evolution to derive the pyruvate to lactate conversion kinetics (kPL), shown in the table below the plots. B) EPSI summed image of the pyruvate distribution in a healthy mouse from an injection of 67 mM SABRE HP [1-13C]pyruvate. C) EPSI summed image of the pyruvate distribution in a healthy mouse from an injection of 80 mM DNP HP [1-13C]pyruvate. D,E) Sum of the arterial voxels (D) and kidney voxels (E) evolving over 6 acquired EPSI images for SABRE HP and DNP HP [1-13C]pyruvate. Differences in signal decay are possibly due to varied respiration of the animal and gating of the acquisitions in the respective experiments.

Pyruvate to lactate metabolic conversion was evaluated in a tumor-bearing mouse (patient-derived xenograft hepatocellular carcinoma flank tumor[75]) receiving three intravenous HP [1-13C]-pyruvate injections via the tail vein. Injections were spaced every 30 minutes, as previously shown to have little impact on the animal metabolism.[25] Following d-DNP or Ace-SABRE, samples were injected (6.7mL/kg) via central line catheter over a 10-second period. Using a 15 mm surface coil placed over the tumor, 13C spectra were acquired every 2 s, for 80 transients using a 15-degree flip angle. All injections were made in TE (Tris-EDTA) buffered saline. In **Figure 3A,** the acquired data is plotted for all three injections with 15 Hz exponential line broadening and analyzed by a custom Python code to calculate the pyruvate to lactate conversion kinetics (*k*PL, pyruvate to lactate conversion rate). The observed SNR is lower from the Ace-SABRE injections due to lower injected polarization level, as well as the lower injected concentrations of pyruvate. However, we show that even with these lower SABRE molar polarizations (concentration × polarization), the same *k*PL values are obtained for experiments with a similar injection concentration. These results show pyruvate transport, LDH activity, or depletion of the NADH pool when varying pyruvate concentrations are injected, mirroring previously published literature results. Additionally, we demonstrate that at a lower concentration of pyruvate, we observe an increased *k*PL due to the lower relative saturation of the pyruvate transporters, mirroring previously published literature results[76–78].

Additionally, we demonstrate imaging of HP pyruvate in a healthy mouse model (BALB/C nude mouse) using both Ace-SABRE and DNP. Two separate mice were injected with HP pyruvate produced by either Ace-SABRE or d-DNP (**Figure 3B, C**). Following dissolution (d-DNP, 80 mM HP pyruvate) or our Ace-SABRE purification (SABRE, 67 mM HP pyruvate), samples were injected (6.7mL/kg) via tail vein catheter over a 10-second period, and respiratory gated coronal echo-planar spectroscopic imaging (EPSI) was acquired every 3.5 seconds, starting 15-seconds after injection start. Mice imaging was conducted using a volume coil and EPSI with the following parameters: matrix size/resolution/TR/flip angle/slice thickness of 12x12/2x2mm/60ms/5-degrees/6.5-7mm. The data was analyzed using custom MATLAB code. Anatomic distribution of the pyruvate signal across the arterial and kidney voxels is similar in both the d-DNP and SABRE injections, but higher relative pyruvate signal in the kidneys is observed with the d-DNP injection. In separate experiments, we saw similar effects on the biodistribution of the pyruvate in healthy mouse models, implying that the decreased pyruvate signal in the kidneys is due to either lower overall molar polarization of the current SABRE injection or difference in the excipients between the two injections. Additionally, integration of the arterial and kidney voxels in both the SABRE and d-DNP injections shows similar evolution of both signals during the series of images acquired (**Figure 3D, E**), with differences in the signal decay possible due to differences in the respiration and gating of the EPSI acquisitions in the respective experiments.

**Conclusion**

This study demonstrates the viability of Ace-SABRE for preclinical HP-NMR and HP-MRI experiments. We belive that Ace-SABRE will enable the cost-effective, safe, and scalable production of a hyperpolarized agent, whilst avoiding the use of problematic solvents like methanol or perfluoro alky substances (PFAS). Ace-SABRE therefore may open up new opportunities for longitudinal studies of metabolic dysregulation and treatment efficacy without the need for a d-DNP polarizer. At this stage in the development process, the optimized, 35 mM pyruvate solutions delivered up to p = 40% polarization, corresponding to a molar polarization level of 14 mM. In contrast, the 70 mM pyruvate solutions yielded p = 25% polarization levels reflective of a molar polarization of 18 mM. These polarization levels were reached by careful parameter optimization of SLIC B1 frequency, B1 amplitude, and catalyst concentration. It is noteworthy that catalyst optimization studies have delivered over 60% 1H and 80% 15N polarizations[79,80], so we are confident that future developments will see this work produce outputs comparable to d-DNP.

Subsequently a processing protocol involving liquid-liquid extraction, gas-stripping and filtration was implemented to yield well tolerated injectables. Finally, HP spectroscopic tracking in an xenografted HCC tumor and HP MRI in healthy mice were demonstrated and compared to studies using d-DNP as the polarization source. Clearly, Ace-SABRE delivers sufficient polarization to facilitate rigorous analysis. However, whilst at this stage in the development process the images produced by d-DNP provided better signal strength, we are confident that this difference will be overcome in the future. In summary, these advancements pave the way for the broader adoption of hyperpolarized imaging tools in preclinical research, with potential translation to clinical applications, representing a critical step towards fulfilling the promise of hyperpolarized MRI as a cornerstone technology in diagnostics and therapeutic monitoring.

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P.T. and C.D. are founders, employees, and equity holders of Vizma Life Sciences (hereafter, Vizma). M.S.R., T.T. are also founders and equity holders of Vizma and serve on Vizma’s scientific advisory board. E.Y.C. is an equity holder of Vizma and serves on Vizma’s scientific advisory board. M.S.R. is a founder and equity holder of Hyperfine Inc. M.S.R. is an equity holder of DeepSpin GmbH. M.S.R. also serves on the scientific advisory boards of ABQMR, Synex Medical, Nanalysis,and O2M Technologies. E.Y.C. and B.M.G. and co-founders and equity holders of XeUS Technologies LTD.

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