Novel hyperpolarized probes for the development of metabolic imaging

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Hyperpolarisation (HP) is a means to overcome the lack of sensitivity of magnetic resonance (MR) and has enabled real-time metabolic imaging (i.e. monitoring metabolic processes *in vivo*, in real time). From the clinical perspective, it can provide valuable diagnostic and prognostic tools. Diagnostics is based on that altered metabolism is usually related to pathological conditions (i.e. the Warburg effect in tumours). Concerning prognosis, the response to the administration of therapies can be detected early, on the basis of the observation of metabolic adjustments.

ParaHydrogen Induced Polarization is an affordable, easy to implement method that may allow wider application of MR hyperpolarized agents than the expensive and technically demanding gold-standard hyperpolarization tool named dissolution-Dynamic Nuclear Polarization (d-DNP). The introduction of PHIP-SAH (PHIP by means of Side Arm Hydrogenation) allowed to considerably extend the applicability of parahydrogen to hyperpolarization of metabolites (pyruvate and lactate) that seemed unobtainable, before, using this hyperpolarization source.

This process relies on the following steps: 1) functionalization of the acid with an unsaturated alcohol (side-arm), 2) addition of parahydrogen to the side arm, 3) polarization transfer from parahydrogen to the target ^{13}C carboxylate signal, 4) side arm removal (hydrolysis of the ester). In this context, ^{13}C-HP pyruvate is the most studied metabolite (e.g. pyruvate conversion in lactate can be monitored).

My PhD work shows the applications of these substrates for metabolic studies *in vitro* (on breast cancer cells) and *in vivo* (healthy mice, cardiac dysfunction model and breast cancer model). The team I belongs carried out leading-edge experiments during the last years in the field of PHIP-SAH for the hyperpolarization of pyruvate and lactate. We obtained hyperpolarized injectable solutions of pyruvate and lactate with polarization in the range of 4-7% that have been used for metabolic studies both *in vitro* and *in vivo*. The production method is fast, starts from stocked reagents and has been optimized to be as simple as possible with the potential to be translated to an automatic production process.

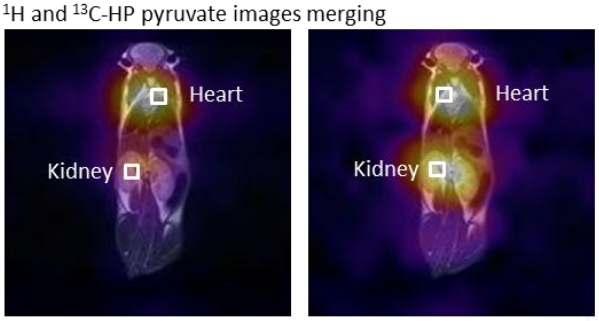
During these three years, it has been demonstrated that the biocompatible aqueous solution of HP-pyruvate and HP-lactate obtained by the PHIP-SAH method provide information about the rate of metabolic conversion that are consistent with results obtained with other conventional methods.

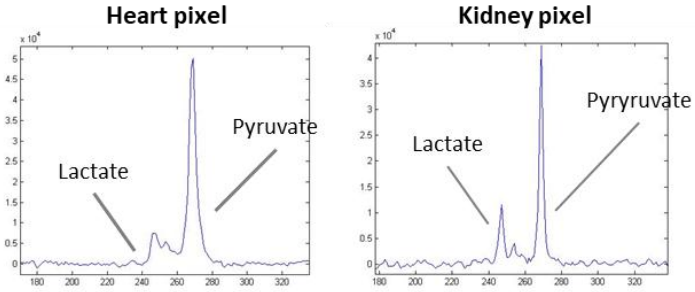
My PhD work was the first metabolic imaging study of cancer carried out using ^{13}C hyperpolarized pyruvate obtained through the cost effective and easy to handle PHIP-SAH method.

Today, preclinical development of PHIP-SAH is ongoing, but, despite solid preclinical results are still needed to guide and stimulate its clinical translation, a translation of PHIP-SAH into a standard preclinical research tool and even to clinical trials can be easily foreseen.

In conclusion, the introduction of PHIP-SAH methods in the clinical use will provide clinicians with better diagnosis and prognosis leading to more personalized and effective patient treatments.

^{1}H and ^{13}C-HP pyruvate images merging





^{1}H and ^{13}C-HP lactate images merging