Chemistry of Contrast Media
Small Molecules
Hyperpolarized Probes

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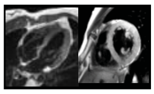
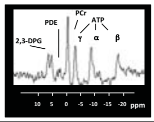
Non-Invasive Assessment Without Ionising Radiation

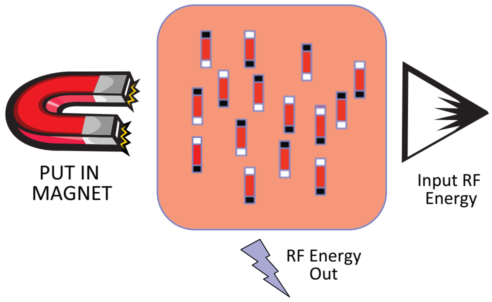
MRI	MRS
Magnetic Resonance Imaging	Magnetic Resonance Spectroscopy
^{1}H (water, fat)	^{1}H, ^{13}C, ^{19}F, ^{23}Na, ^{31}P ...





	MRI	MRS
Info	+++	+++++
Signal	++	+

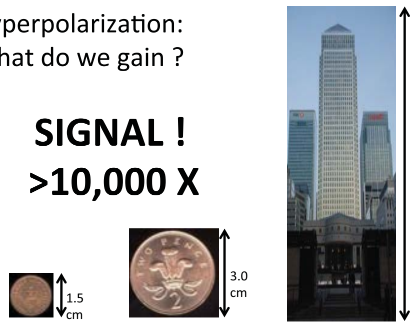
MRI/MRS – How Does it Work ?



Hyperpolarization: What do we gain ?

SIGNAL !

>10,000 X



Hyperpolarization: How can we do it ?

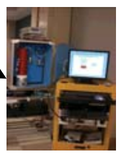
$$P = \tanh\left(\frac{\mu B_0}{k_B T}\right)$$

'Brute-Force' Approach

HYPERPOLARIZATION

Optical Pumping of Noble Gases

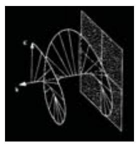
Dynamic Nuclear Polarization (DNP)

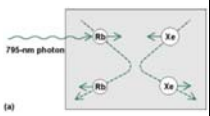


Parahydrogen Induced Polarization (PHIP) or PASADENA

Hyperpolarized Gases

- Laser light with circular polarization can deliver angular momentum to atoms
- Electrons in alkali metal vapor absorb light at 795 nm, acquiring the angular momentum and becoming polarized
- Noble gases (^{3}He / ^{129}Xe) atoms collide with these polarized metal atoms, transferring the polarization to the noble gas nucleus

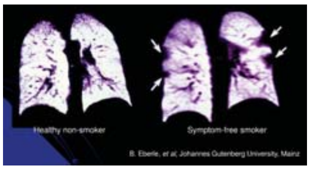


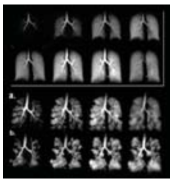


Bill Hersman, http://xenon.unh.edu

Structural Lung Imaging

- Obstructions or restrictions of breathing pathways prevents homogeneous ventilation

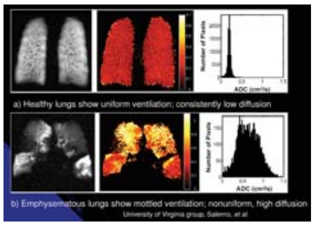




Bill Hersman, http://xenon.unh.edu

Diffusion Weighted Imaging

- Acquisition of ADC maps can reveal structural alterations in patients with emphysema



Bill Hersman, http://xenon.unh.edu

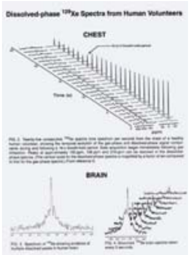
Helium / Xenon Comparison

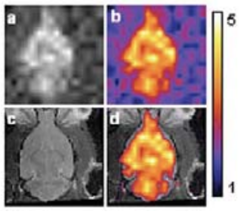
	100% Helium-3	26.4% xenon-129	86% xenon-129
Supply	Artificially produced from decay of tritium	Naturally occurring	Naturally occurring (isotopically enriched)
Present cost	$200/liter	$4/liter	$150-$300/liter
Gyromagnetic ratio (Signal strength)	0.762 of proton	0.278 of proton	0.278 of proton
Gas fraction in a single breath	0.79 (21% oxygen)	0.7 (21% oxygen)	0.7 (21% oxygen)
Solubility in blood / in fat	~0 / ~0	λ = 0.17 / λ = 1.7	λ = 0.17 / λ = 1.7
Lifetime T_1 in lungs / in blood	T_1 ~ 12 sec / n.a.	T_1 ~ 12 sec / T_1 ~ 12 sec	T_1 ~ 12 sec / T_1 ~ 12 sec

Bill Hersman, http://xenon.unh.edu

Xenon – Dissolved-phase Imaging

- Xenon is soluble in blood and tissues

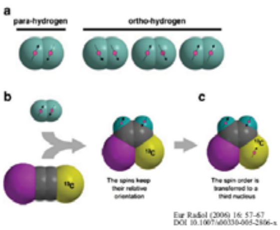




Bill Hersman, http://xenon.unh.edu

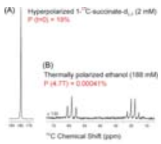
Mazzanti et al, PLOSone 2011

Para-Hydrogen Induced Polarization (PHIP) or Pasadena

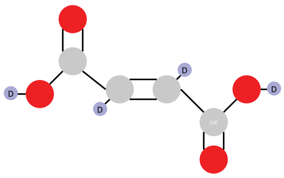


Mark I Malmo Polarizer

Mark II HMRI Prototype



Parahydrogen Induced Polarization (PHIP)



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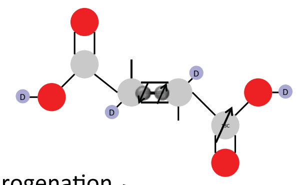
Parahydrogen Induced Polarization (PHIP)

Theoretically it is possible to achieve near 100% polarization with this method



Hydrogenation → Polarization Transfer

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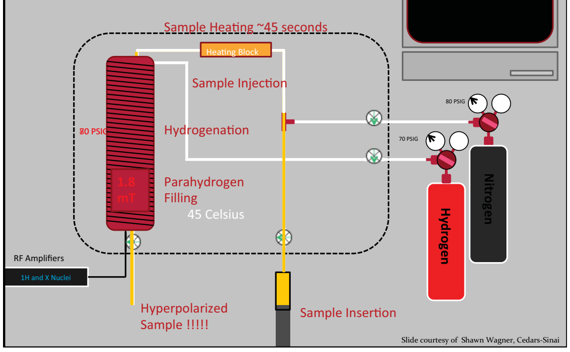
Slide courtesy of Shawn Wagner, Cedars-Sinai

Polarizer Basics

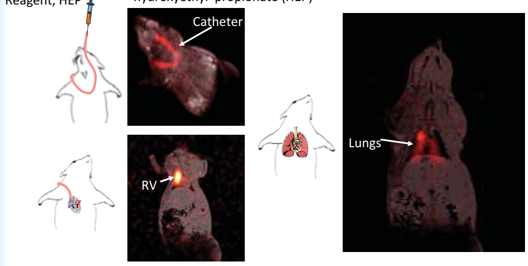


Slide courtesy of Shawn Wagner, Cedars-Sinai

In Vivo PASADENA with HEP

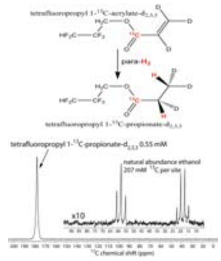
Hyperpolarized Reagent, HEP

Jugular vein injection of 50 mM of 2 mL of contrast agent, hydroxyethyl propionate (HEP)

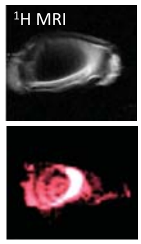


Bhattacharya et al, *MAGMA* 18(5): 2005

Plaque Imaging by PASADENA



Typical ^{13}C hyperpolarized spectrum(P:25%) of 0.55 mM 1-^{13}C-TFPP-d2,3,3 at 4.7T *in vitro*.



^{1}H conventional MRI (top) and ^{13}C PASADENA sub-second image (bottom) acquired utilizing 1-13C-TFPP-d2,3,3 of an isolated pig aorta.

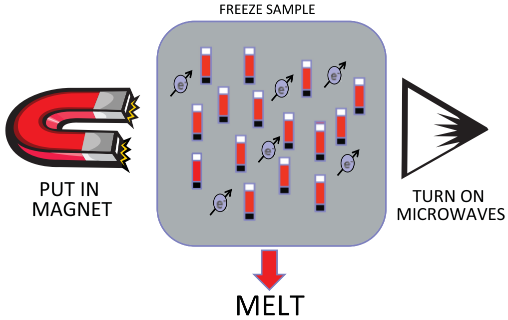
Dynamic Nuclear Polarization (DNP)

- First demonstrated in the 1970s but the solid state criterion limited biological application
- In 2003, Ardenkjaer-Larssen *et al* in Malmo demonstrated that DNP-polarized samples could be dissolved and retain a polarization of >20%

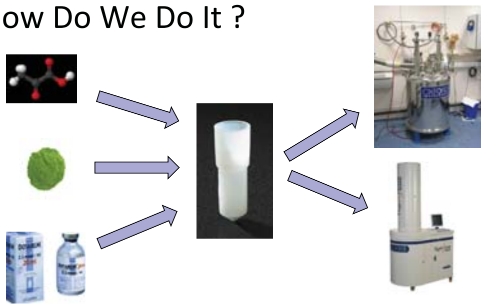
DNP → **Rapid Dissolution** → **Injection**

- Provides the possibility to use DNP-polarized nuclei as an *in vivo* MR contrast media

DNP – How Does it Work ?

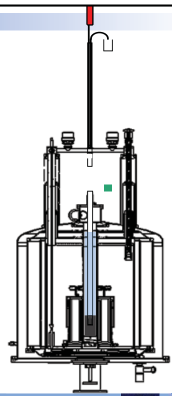


How Do We Do It ?



Dissolution

- The buffer is heated and pressurised
- The sample space is pressurised
- The sample is raised out of the liquid helium
- The dissolution stick is lowered, docking with the sample holder
- The solvent is injected, dissolving the sample, whilst preserving the enhanced polarization

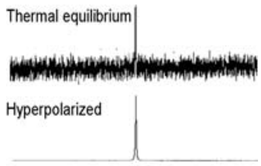


Slide courtesy of Jan Henrik Ardenkjaer-Larsen, GE Healthcare

HyperSense

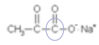
- The HyperSense provides a fully automated system removing the 'variability' of the prototype systems.

DNP: Liquid State Polarization



SNR 1.1 in 3 hours
(SNR 0.025 corrected for 2048 averages)

SNR 480 single acquisition

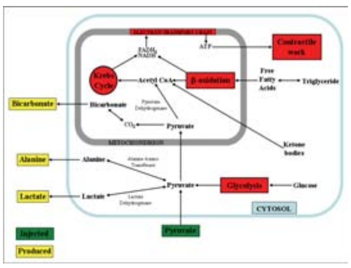


22100 times signal enhancement achieved after dissolution compared to thermal equilibrium polarization
This corresponds to 0.0006% thermal polarization, and 13.3% hyperpolarized polarization

What makes a good DNP probe?

- DNP should work on most small molecules
- But an ideal probe should
  - freeze as a glass
  - achieve a high polarization in a reasonable time
  - have a long relaxation time (T_1)
  - have rapid biological uptake
  - show multistep metabolism

Hyperpolarized [1-^{13}C] Pyruvate



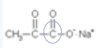
Pyruvic acid freezes as a glass

Pyruvate polarizes to 20-40% in less than an hour

[1-^{13}C]pyruvate has a T_1 of ~60s

Pyruvate is very rapidly taken up through the MCTs

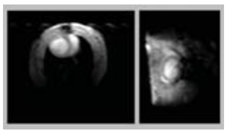
Pyruvate plays a central role in pathways of carbohydrate metabolism



Tyler *et al* – AMR, 2008

Spectroscopic Methods

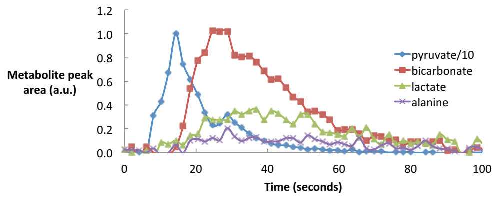
- The tracer is injected via a vein into the anaesthetized animal which is positioned in MR system
- Spectra are localized by the use of a surface coil placed over the ROI (possibly with slice selection)
- Spectra are acquired for 1-2 mins following injection with high temporal resolution and a low flip angle RF pulses



Tyler *et al* – AMR, 2008

Typical [1-^{13}C]Pyruvate Time-course

- Observe pyruvate bolus initially (useful for normalization, etc.)
- Max metabolite/pyruvate ratio reported for spectroscopy
- Potential imaging window @ 18-50 s



Lau A. et al. MRM 2010

Signal Decay

- Following hyperpolarization – T_1 is a decay process !
- This means that RF destroys the signal
- There is no chance to recover the lost magnetization
- Need to use low RF pulses or single shot techniques

Imaging Challenges

- Need to acquire spectroscopic images and therefore shim and spectral resolution are important
- Need to image fast but without too many RF pulses
  - Dynamic images an advantage to observe time-course
- For cardiac imaging, need to cope with motion – ECG & Respiration

Imaging Challenges – ^{13}C Specific

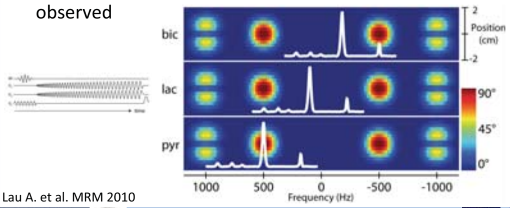
- Chemical Shift is generally broad – a good thing!
- Gamma is low and so gradient demands are high
- Generally need to use surface coils and so homogeneity is an issue

Potential Strategies

- Simple low flip angle CSI
  - Simple / widely available / undemanding
  - Lots of RF pulses / long acquisition / low spatial resolution
  - potential to use parallel / sparse imaging techniques
- Single shot - EPSI / Spiral techniques
  - Fast / Few RF pulses / low RF demands
  - Long acquisition window / B_0 sensitivity / Demanding on gradients
- Single frequency approaches

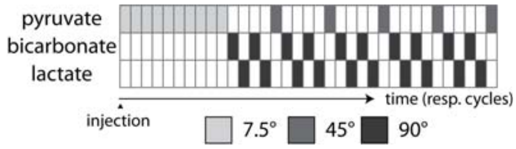
Spectral Spatial RF Pulses

- Allow for simultaneous slice selection and RF selectivity
  - Can select a slice
  - Can selectively excite one particular resonance
- Pulse is designed specifically for the spectral pattern observed



Lau A. et al. MRM 2010

Respiratory-gated ordering scheme

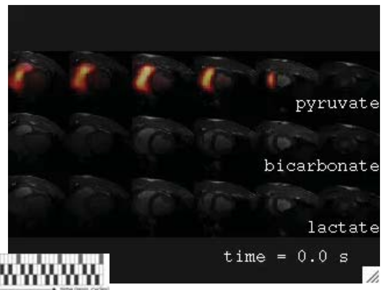


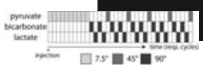
- Respiratory rate is 24 breaths / minute
- Acquire images during diastole + end-expiration
- Total scan time = 35 breaths (1.5 minutes)
- Bicarbonate and lactate: average 3 images together

Lau A. et al. MRM 2010

Time-resolved, multi-slice ^{13}C cardiac dynamic data

Parameters
6 slices
55 ms / slice
12 mm in-plane
10 mm slice thickness
1 mm spacing





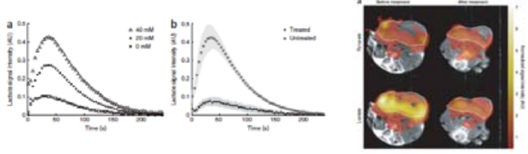
Applications – Tumor Response

TECHNICAL REPORTS

nature medicine

Detecting tumor response to treatment using hyperpolarized ^{13}C magnetic resonance imaging and spectroscopy

Sam E Day, Mikko I Kettunen, Ferdia A Gallagher, De-En Hu, Mathilde Lerche, Jan Wolber, Klaes Golman, Jan Henrik Ardenkjaer-Larsen & Kevin M Brindle

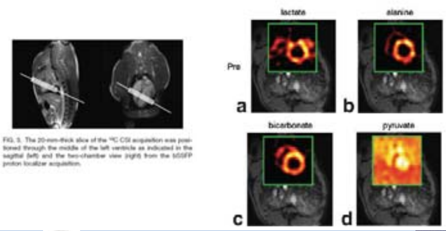


Applications – Cardiac Metabolic Imaging

Cardiac Metabolism Measured Noninvasively by Hyperpolarized ^{13}C MRI

Magnetic Resonance in Medicine 59:1005–1013 (2008)

Klaes Golman, J. Stefan Petersson, Peter Magnusson, Edvin Johansson, Per Åkeson, Chun-Ming Chai, Georg Hansson, and Sven Månsson

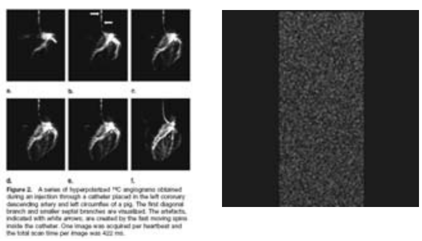


Other Applications – Angiography

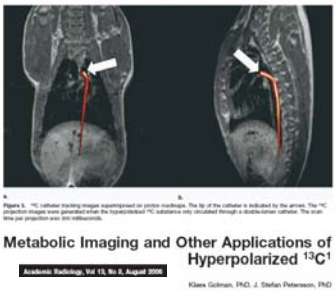
Metabolic Imaging and Other Applications of Hyperpolarized ^{13}C

Academic Radiology, Vol 13, No 8, August 2006

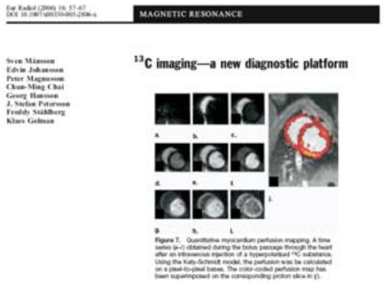
Klaes Golman, PhD, J. Stefan Petersson, PhD



Other Applications – Catheter Tracking



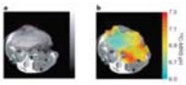
Other Applications – Perfusion Imaging



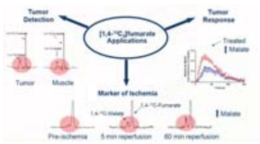
Other Compounds

(1) Gallagher *et al.* Nature. 2008 Jun 12;453(7197):940-3
(2) Zandt et al. ISMRM 2009
(3) Gallagher *et al.* Magn Reson Med. 2008 Aug;60(2):253-7

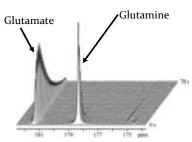
- ^{13}C-Bicarbonate [1]



- ^{13}C-Fumarate [2]



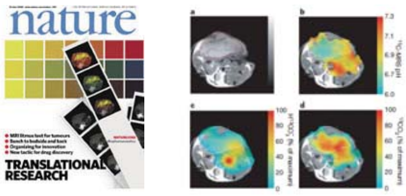
- ^{13}C-Glutamine [3]



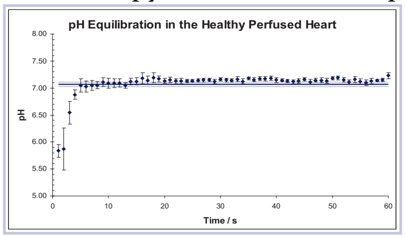
Extracellular pH measurement

Magnetic resonance imaging of pH *in vivo* using hyperpolarized ^{13}C-labelled bicarbonate

Ferdia A. Gallagher, Mikko I. Kettunen, Sam E. Day, De-En Hu, Jan Henrik Ardenkjær-Larsen, René in 't Zandt, Pernille R. Jensen, Magnus Karlsson, Klaes Golman, Mathilde H. Lerche & Kevin M. Brindle



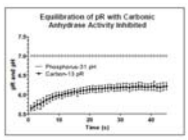
Use of [1-^{13}C]pyruvate to measure pH

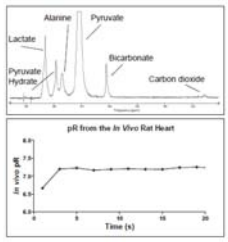


- A brief period of normalization is observed
- After equilibration, pH measured by hyperpolarized ^{13}C matches ^{31}P measurement of intracellular pH (solid blue line)

Schroeder *et al*, Cardiovasc Res 2010

Use of [1-^{13}C]pyruvate to measure pH
Is there a need for caution ?

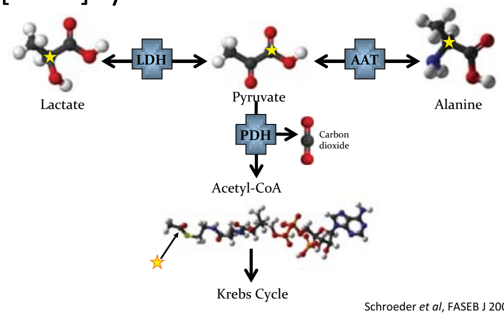




- CA activity must be high enough to yield a true measure of intracellular pH

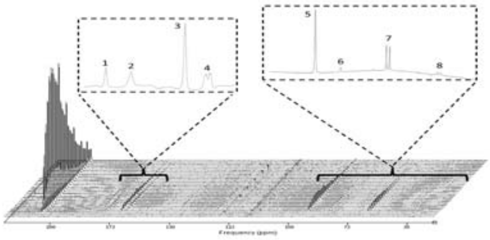
Schroeder *et al*, Cardiovasc Res 2010

[2-^{13}C]Pyruvate



Schroeder *et al*, FASEB J 2009

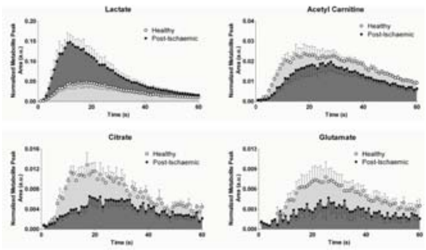
Example: [2-^{13}C]pyruvate



- Assignment of the peaks as (1) glutamate, (2) citrate, (3) acetylcarnitine, (4) C1 pyruvate, (5) C2 pyruvate hydrate, (7) lactate & (8) alanine (8)

Schroeder *et al*, FASEB J 2009

Application: Ischaemic Heart



- Lactate appearance is increased and citrate and glutamate appearance is decreased in the post-ischaemic heart

Schroeder *et al*, FASEB J 2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109,956

STUDY MAY PROCEED

October 8, 2010

University of California, San Francisco
Attention: Andrea Harzstark, M.D.
Helen Diller Family Comprehensive Cancer Center
Urologic Oncology
1600 Divisadero St. 3rd Floor, Box 1711
San Francisco, CA 94115

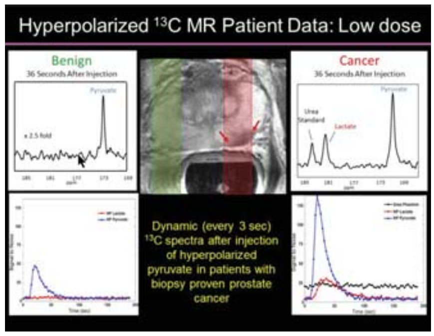
Dear Dr. Harzstark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Hyperpolarized Pyruvate (^{13}C) Injection.

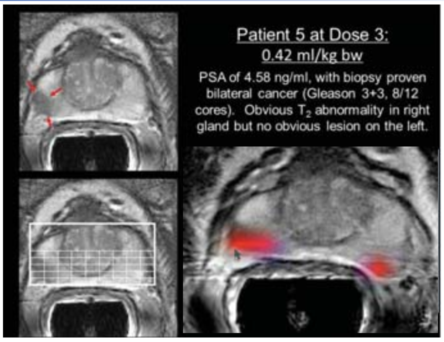
We have completed our 30-day, safety review of your application and have concluded that you may proceed with your proposed clinical study entitled, **"A Phase I ascending-dose study to assess the safety and tolerability and imaging potential of Hyperpolarized Pyruvate (^{13}C) Injection in subjects with prostate cancer."**

Nelson, Vigneron, Kurhanewicz *et al*, UCSF, ISMRM 2011

Nelson, Vigneron, Kurhanewicz *et al*, UCSF, ISMRM 2011



Nelson, Vigneron, Kurhanewicz *et al*, UCSF, ISMRM 2011



Nelson, Vigneron, Kurhanewicz *et al*, UCSF, ISMRM 2011

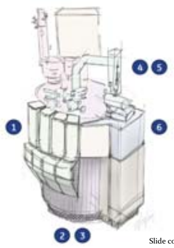
DNP – Moving Towards the Clinic

Key Polarizer Technologies

(1) Simple Operation
Highly automated sample processing and dissolution.

(2) Closed-Cycle Cryogenic
Generates the 1 K environment required for DNP without the consumption cryogens.

(3) Multi-sample Polarization
Simultaneously polarizes four samples for (1) rapid injection protocols and (2) high sample through-put.



(4) Sterile Fluid Path
Seal fluid path contains agent during storage and compounding. Eliminates need for clean room environment.

(5) Large Dose
Fluid path capable of polarizing 2 mL of material. Example: 100 mL of 250 mM pyruvate

(6) Non-Contact QC
Measure six product parameters in less than 10 seconds without compromising sterile barrier.

Slide courtesy of Jan Henrik Ardenkjaer-Larsen, GE Healthcare

Chemistry of Contrast Media – Hyperpolarized Probes

Conclusions

- Hyperpolarized probes can offer increased sensitivity for low SNR MRI/MRS applications
- Several techniques exist – all with their own advantages and disadvantages
- Their use in pre-clinical research is now established and their utility in clinical research is under investigation

Acknowledgements

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Prof Stefan Neubauer
Prof Kieran Clarke

All the members of the CMRG

Slides from Dr. Shawn Wagner, Dr. Pratip Bhattacharya, Dr. Jan Henrik Ardenkjaer-Larsen, Dr Marie Schroeder, and many others

Chemistry of Contrast Media – Hyperpolarized Probes