DNP lab

Hyperpolarizing ^{13}C spins by DNP for MRI applications

Arnaud Comment

GE Healthcare

CANCER RESEARCH UK | CAMBRIDGE INSTITUTE

Magnetic resonance imaging (MRI)

- Image $^{1}H_2O$ in the body

  High concentration (40M)

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- Image $^{1}H_2O$ in the body
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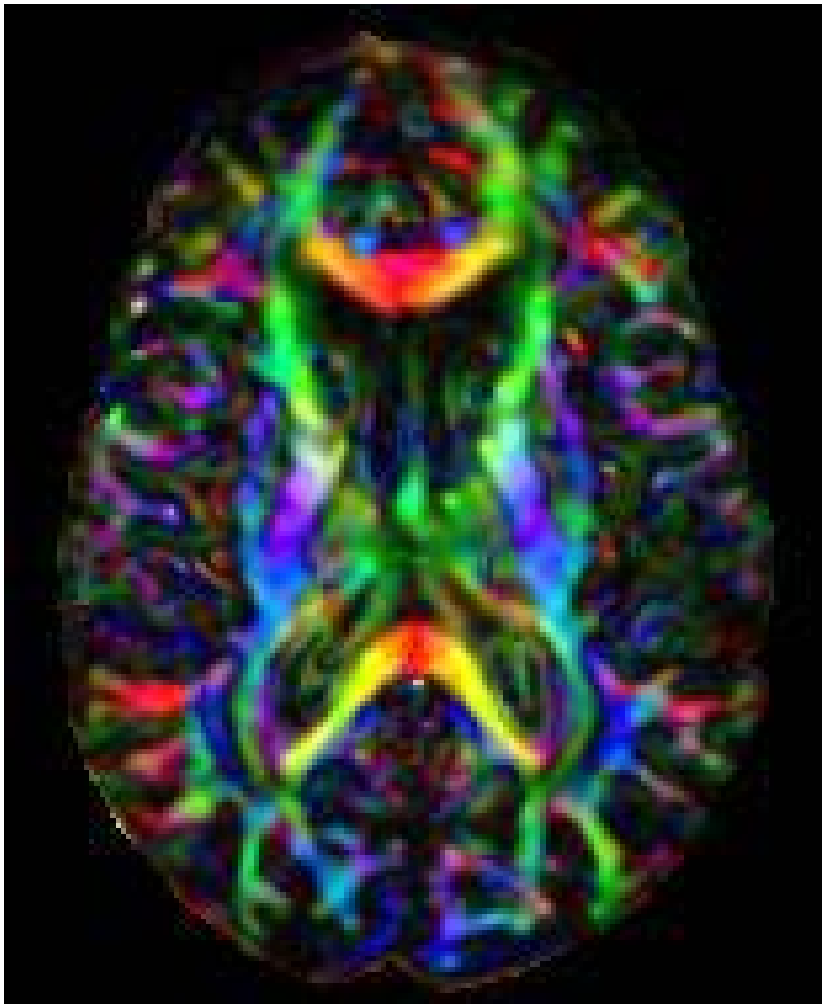
- Anatomical images with various contrast
- Dynamic blood flow

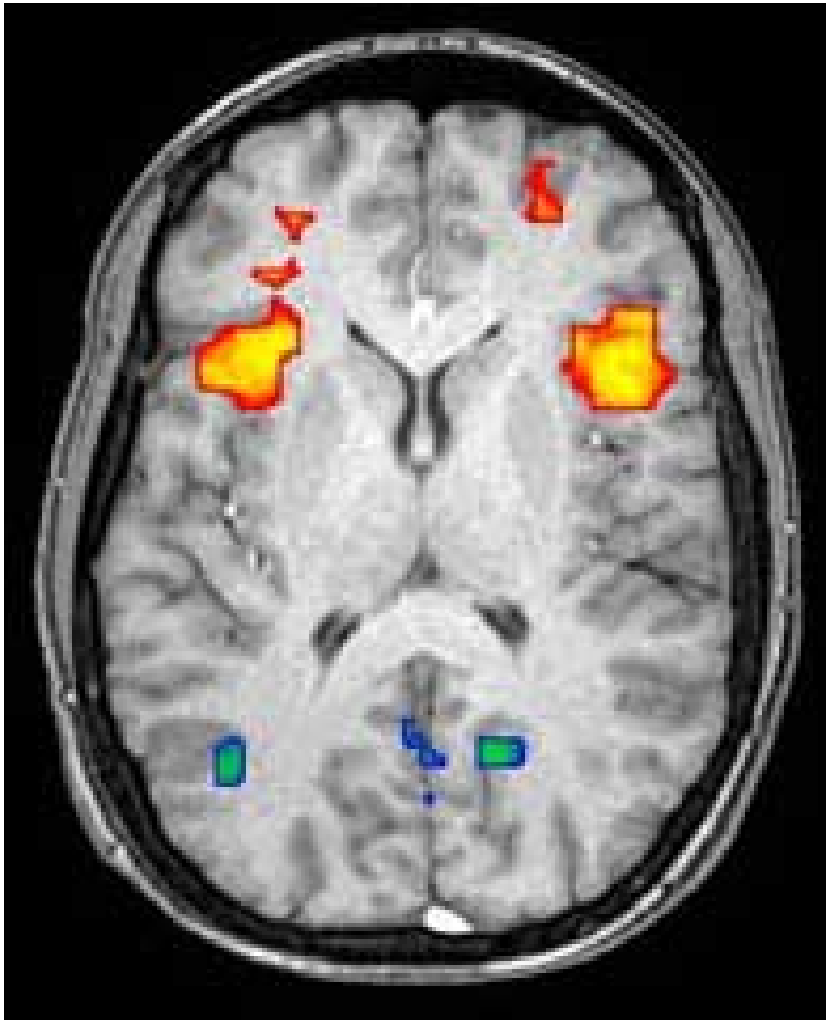
Magnetic resonance imaging (MRI)

- Image $^{1}H_2O$ in the body
  High concentration (40M)
- Anatomical images with various contrast
- Dynamic blood flow
- Diffusion imaging



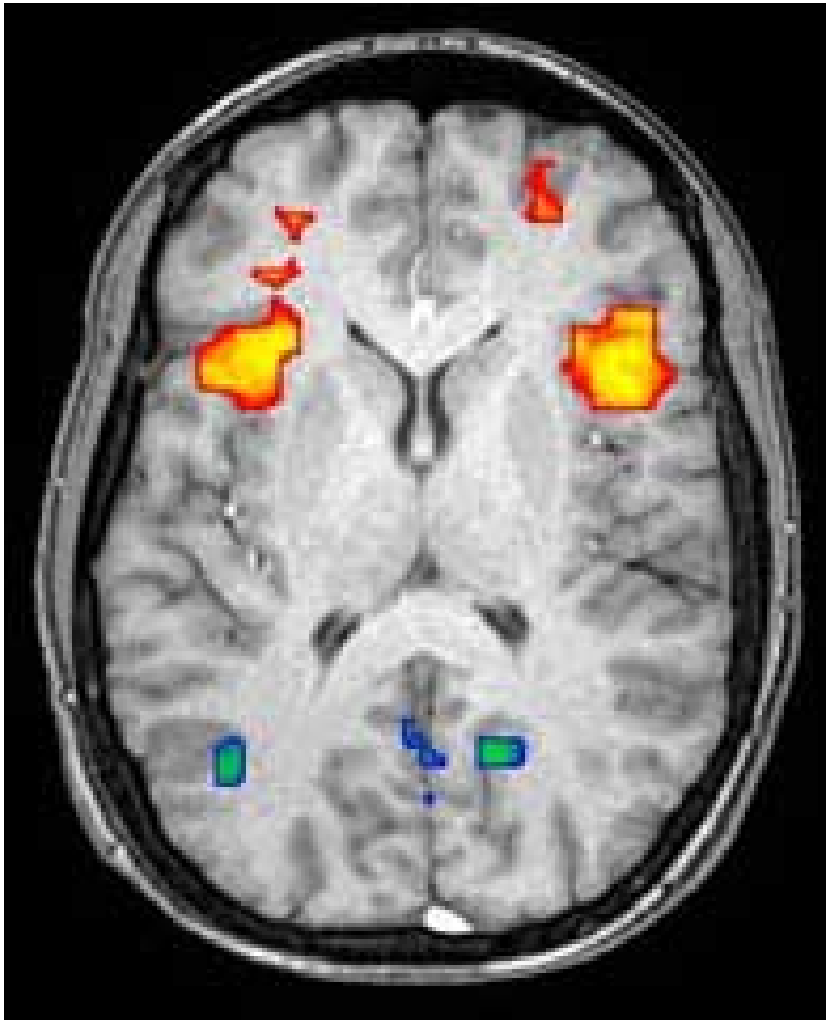
Magnetic resonance imaging (MRI)

- Image $^{1}H_2O$ in the body
  High concentration (40M)
- Anatomical images with various contrast
- Dynamic blood flow
- Diffusion imaging
- Functional MRI



Magnetic resonance imaging (MRI)

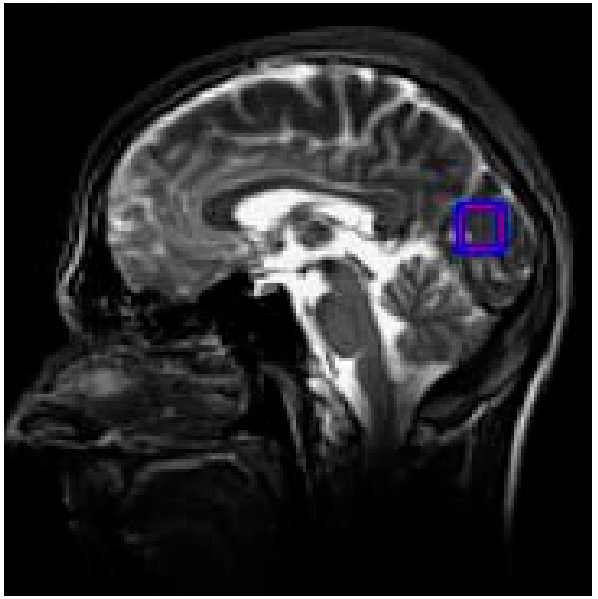
- Image $^{1}H_2O$ in the body
  High concentration (40M)
- Anatomical images with various contrast
- Dynamic blood flow
- Diffusion imaging
- Functional MRI
- **Beyond water**
  What about chemical information, i.e., biochemistry and metabolism?

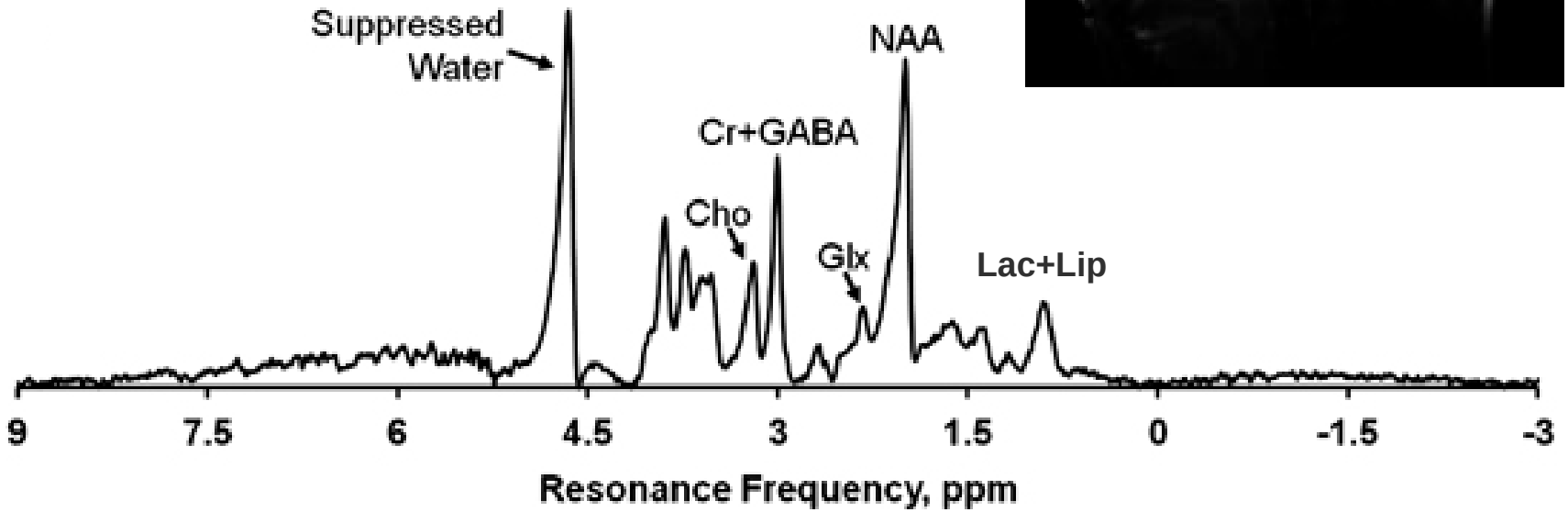


^{1}H Magnetic resonance spectroscopy (MRS)

- Low concentration (< mM)

  $\Rightarrow$ Only highly concentrated metabolites observable
- Inherent low ^{1}H MRS spectral resolution
- No dynamic information

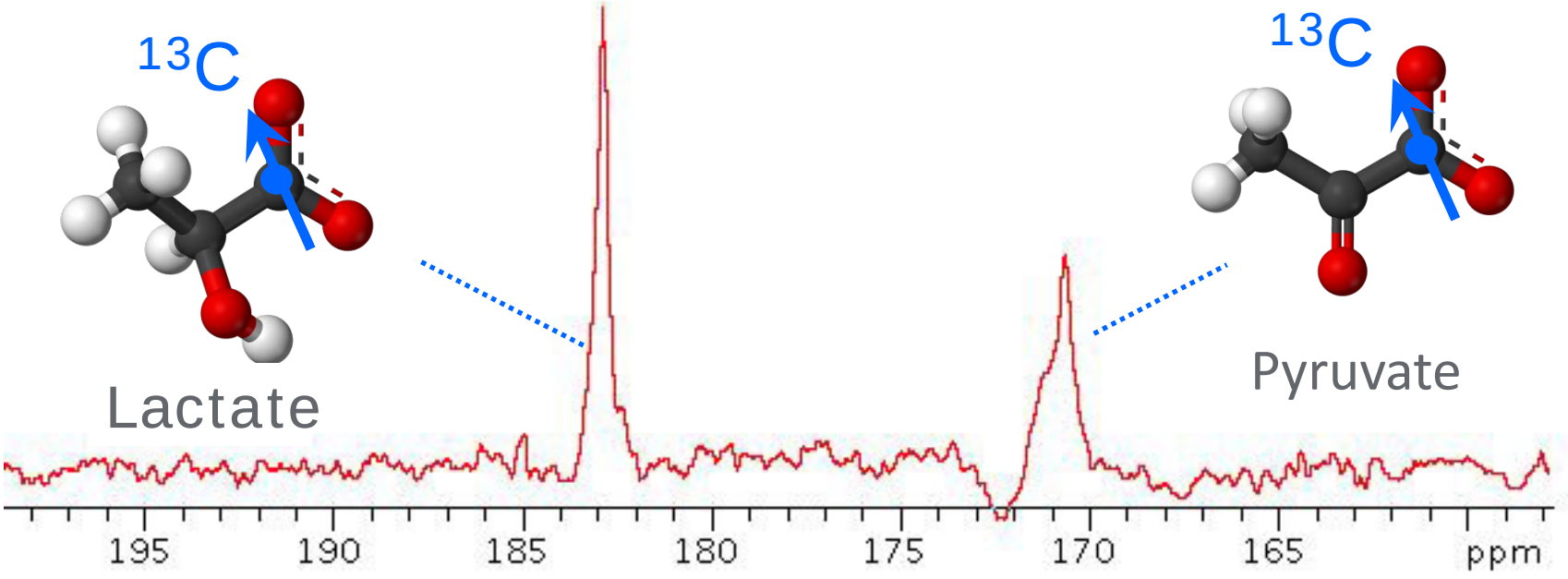




K. Cai *et al.*, Neuropsychopharmacol 2012

^{13}C MR for probing metabolism

- Natural abundance ^{12}C : 99% ; no spin and therefore MR inactive
- **^{13}C** has a spin 1/2; isotopically labeled substrates
- Much higher spectral resolution than ^{1}H



^{13}C frequency shift

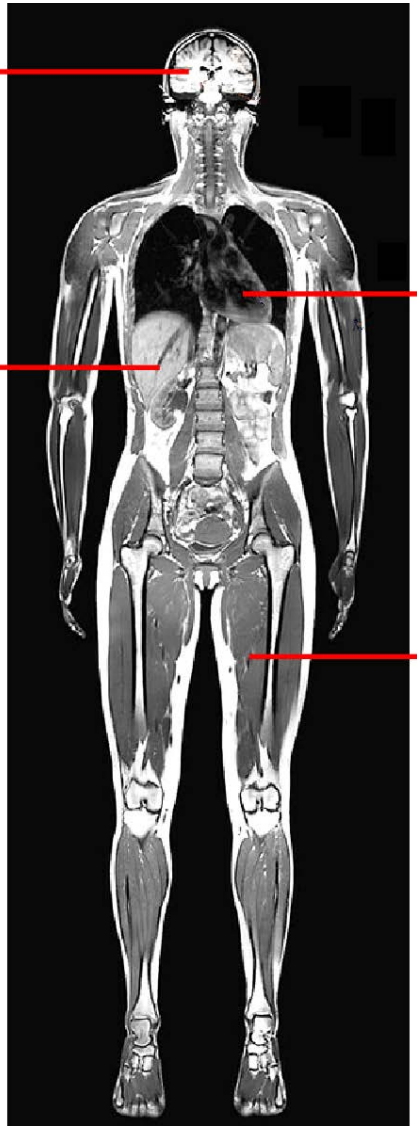
Mammalian metabolism

Brain

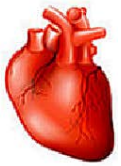
Uses ~50% of total blood glucose

Liver

Stores and releases carbohydrates, ketone bodies and fats; regulate blood glucose level



Heart



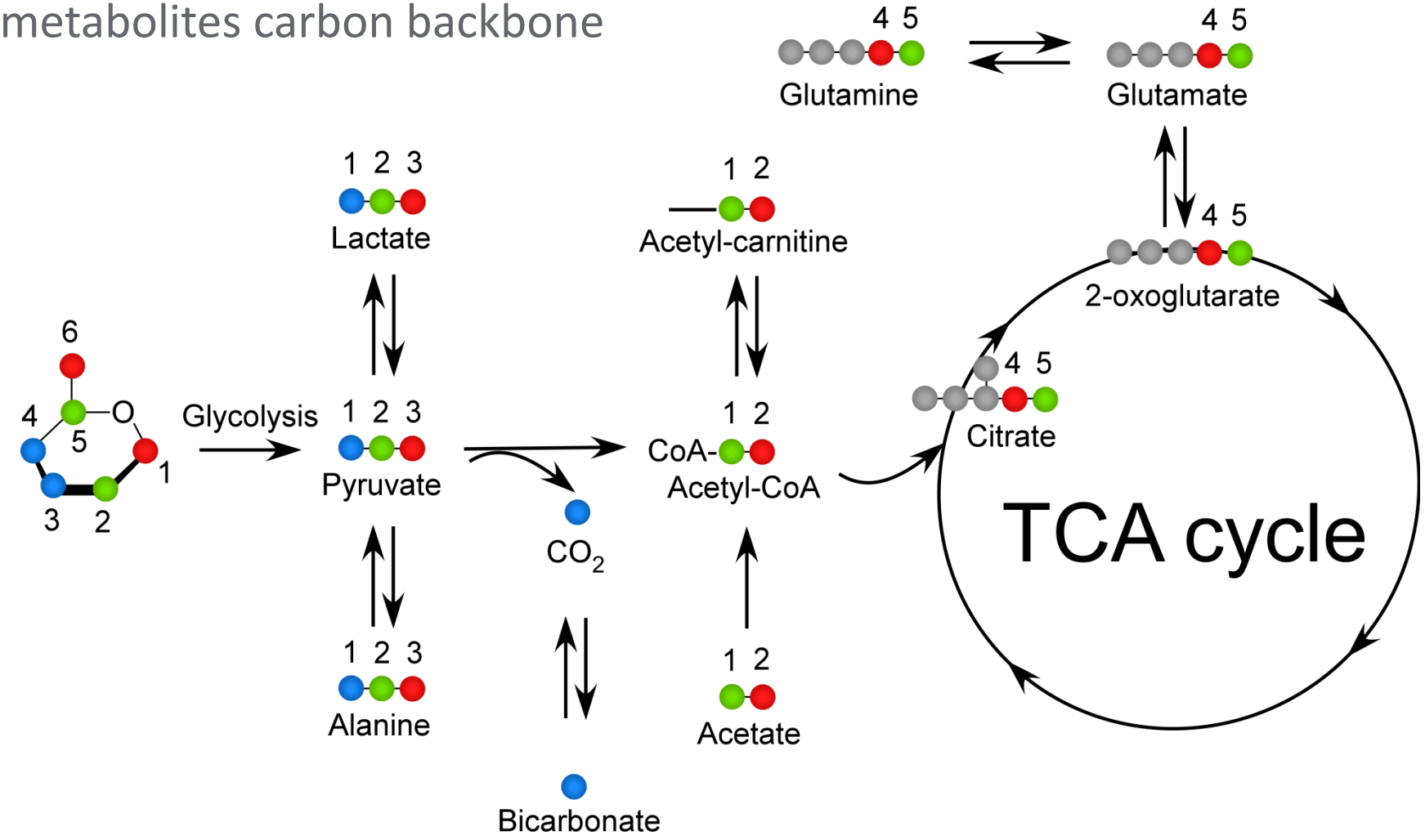
Uses fatty acids, ketone bodies and carbohydrates to produce mechanical work

Skeletal muscles

Diseases are generally characterized by abnormal metabolism

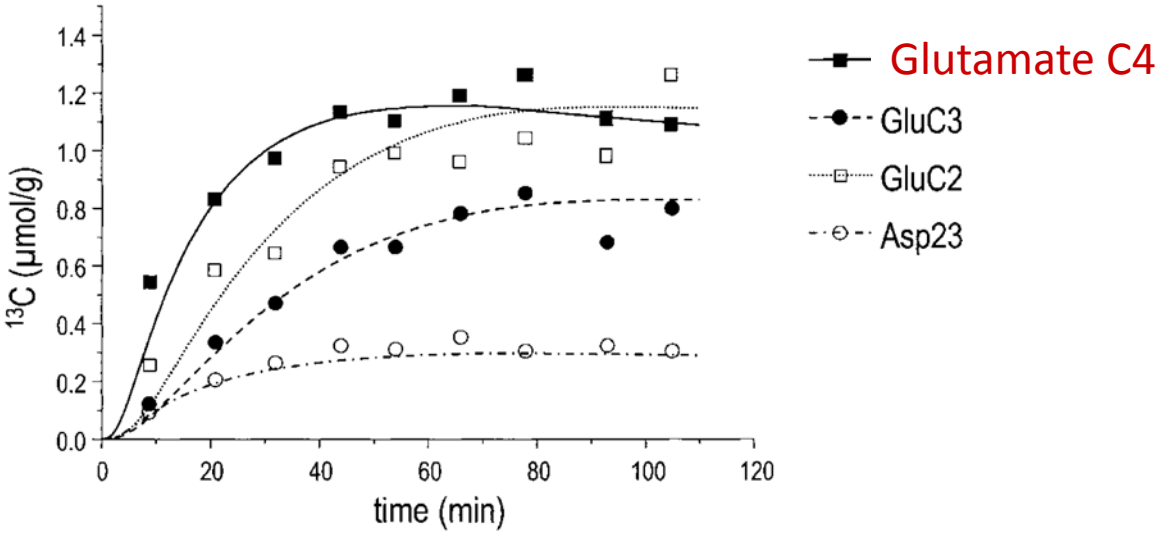
^{13}C metabolic studies

Stable isotopes enable unambiguous tracking of individual atoms in metabolites carbon backbone

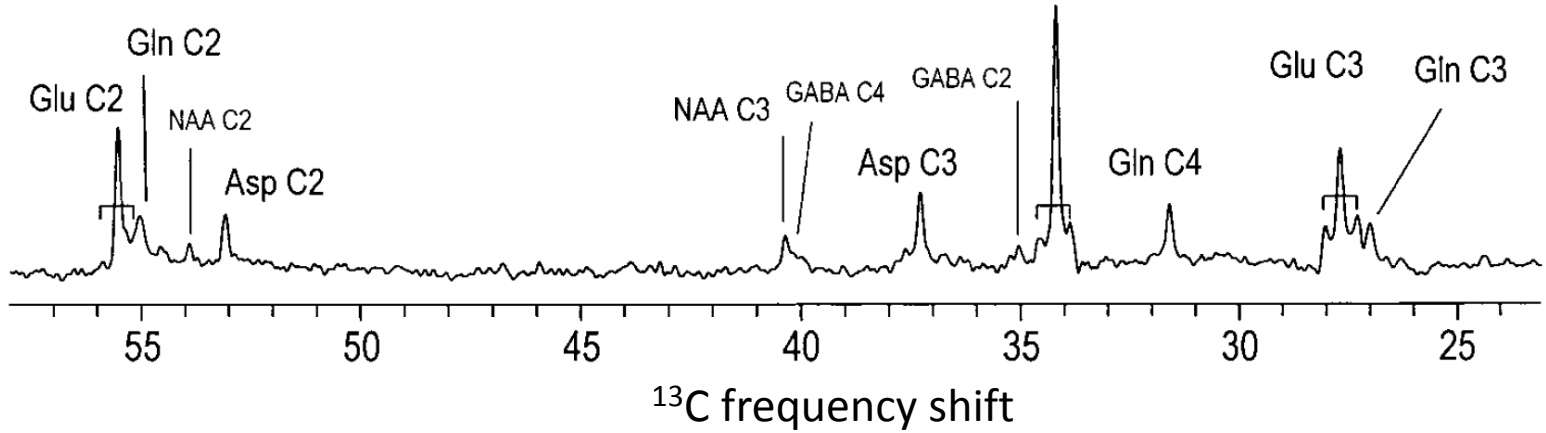


Conventional ^{13}C NMR for metabolism

- Injection of ^{13}C-glucose into animals or humans
- Only the **most concentrated metabolites** can be detected *in vivo*

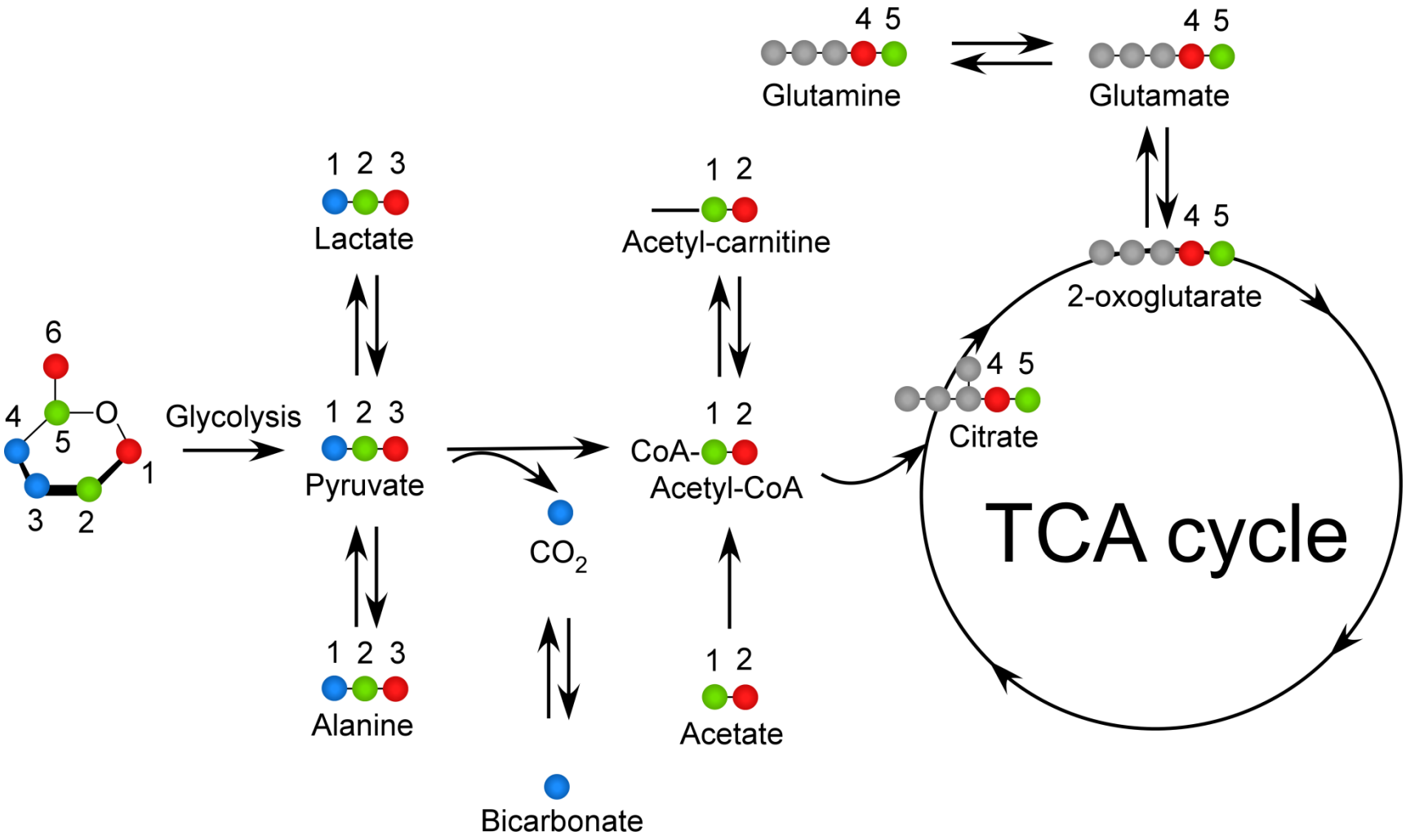


Glutamate C4

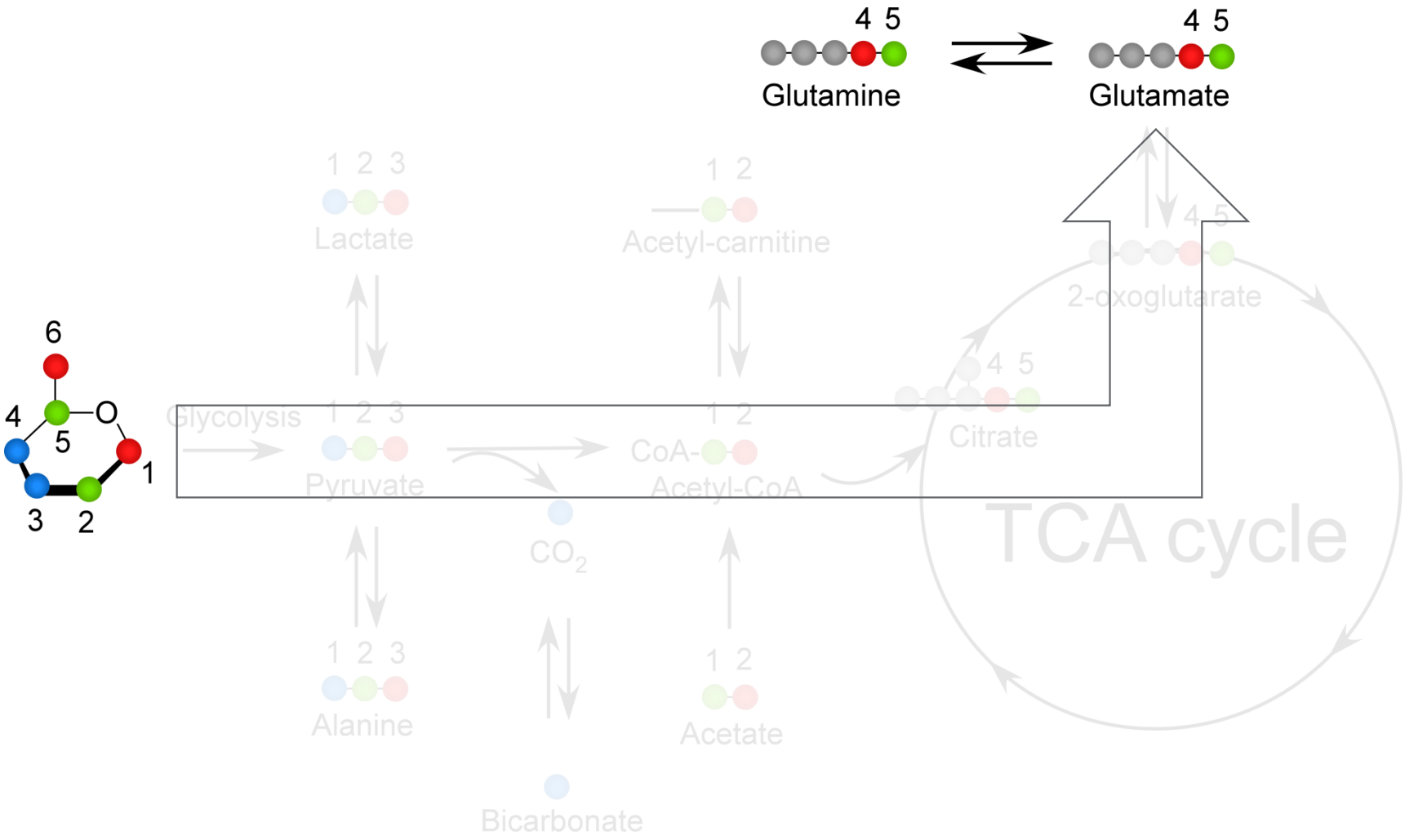


R. Gruetter *et al.*, Am. J. Physiol. Endocrinol. Metab. (2001)

Conventional ^{13}C NMR for metabolism



Conventional ^{13}C NMR for metabolism



New frontier in ^{13}C MR

Hyperpolarized ^{13}C MR

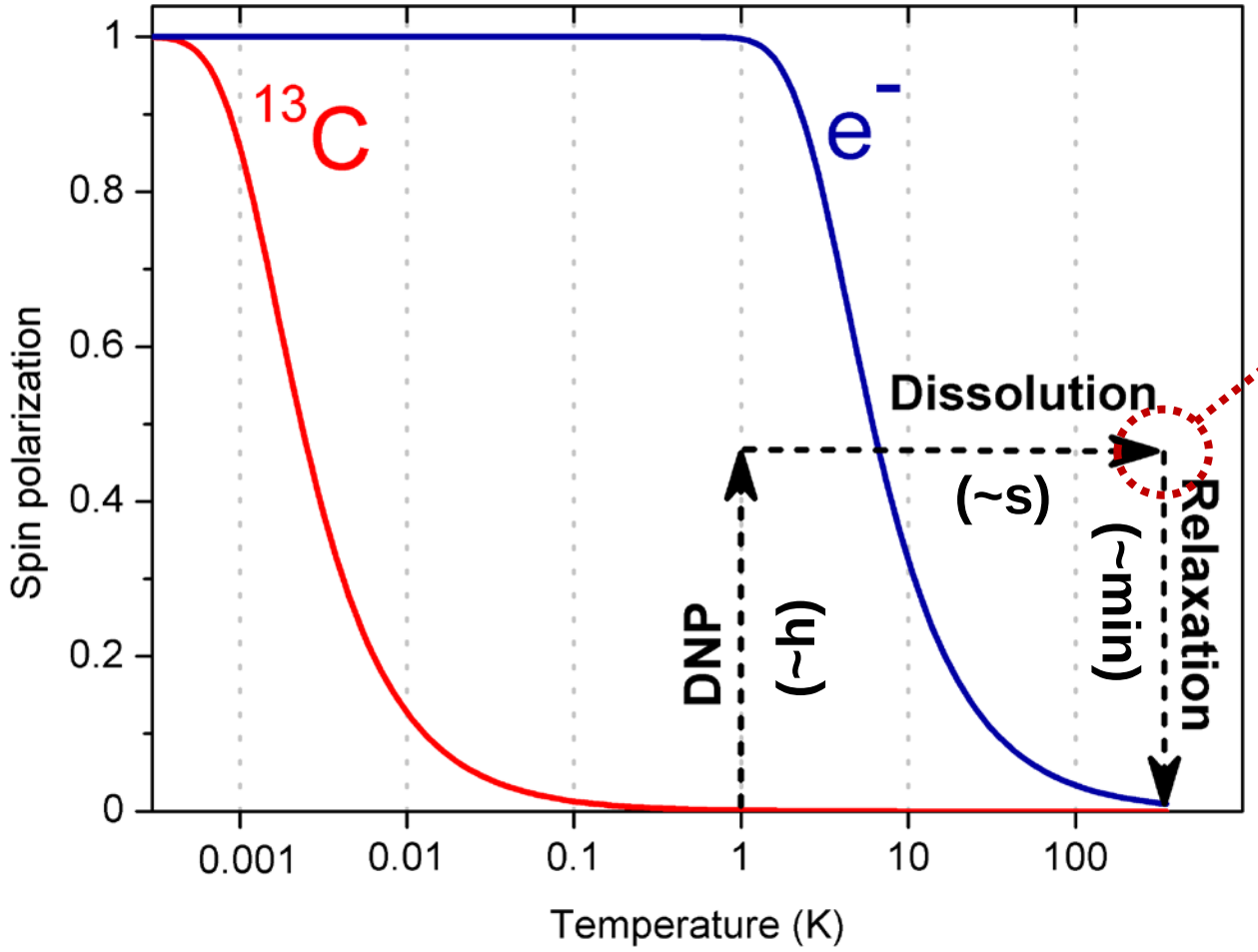
- **Why?**
  Need for higher spatial and temporal resolution

- **How?**
  Larger ^{13}C MR signal

Dynamic nuclear polarization (DNP)

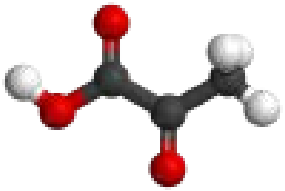
Dissolution dynamic nuclear polarization

NMR signal is proportional to the nuclear spin polarization

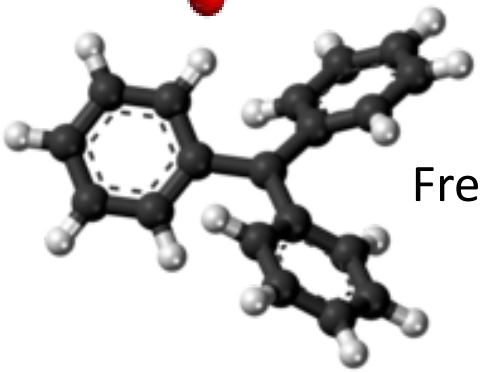


Injection and measurements

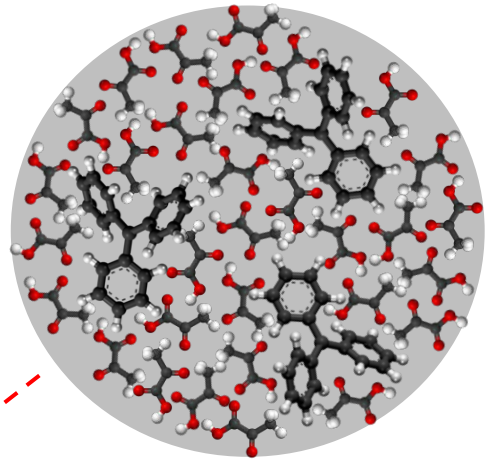
Preclinical *in vivo* studies

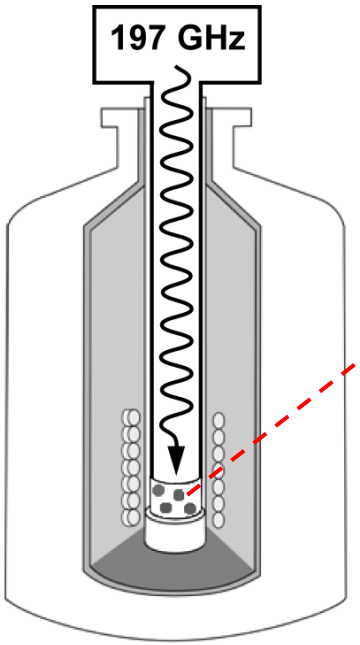


^{13}C-substrate



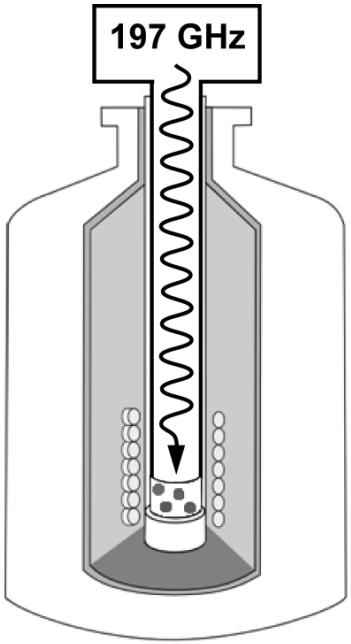
Free radical





7 T / 1 K hyperpolarizer

Preclinical *in vivo* studies



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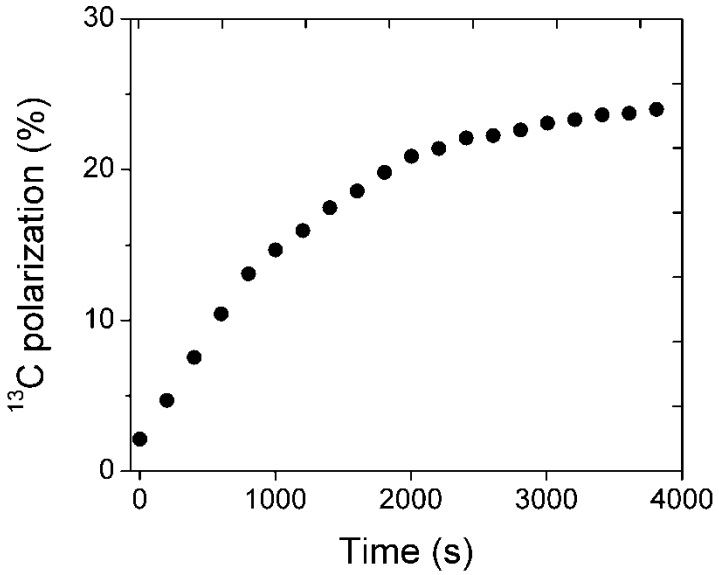
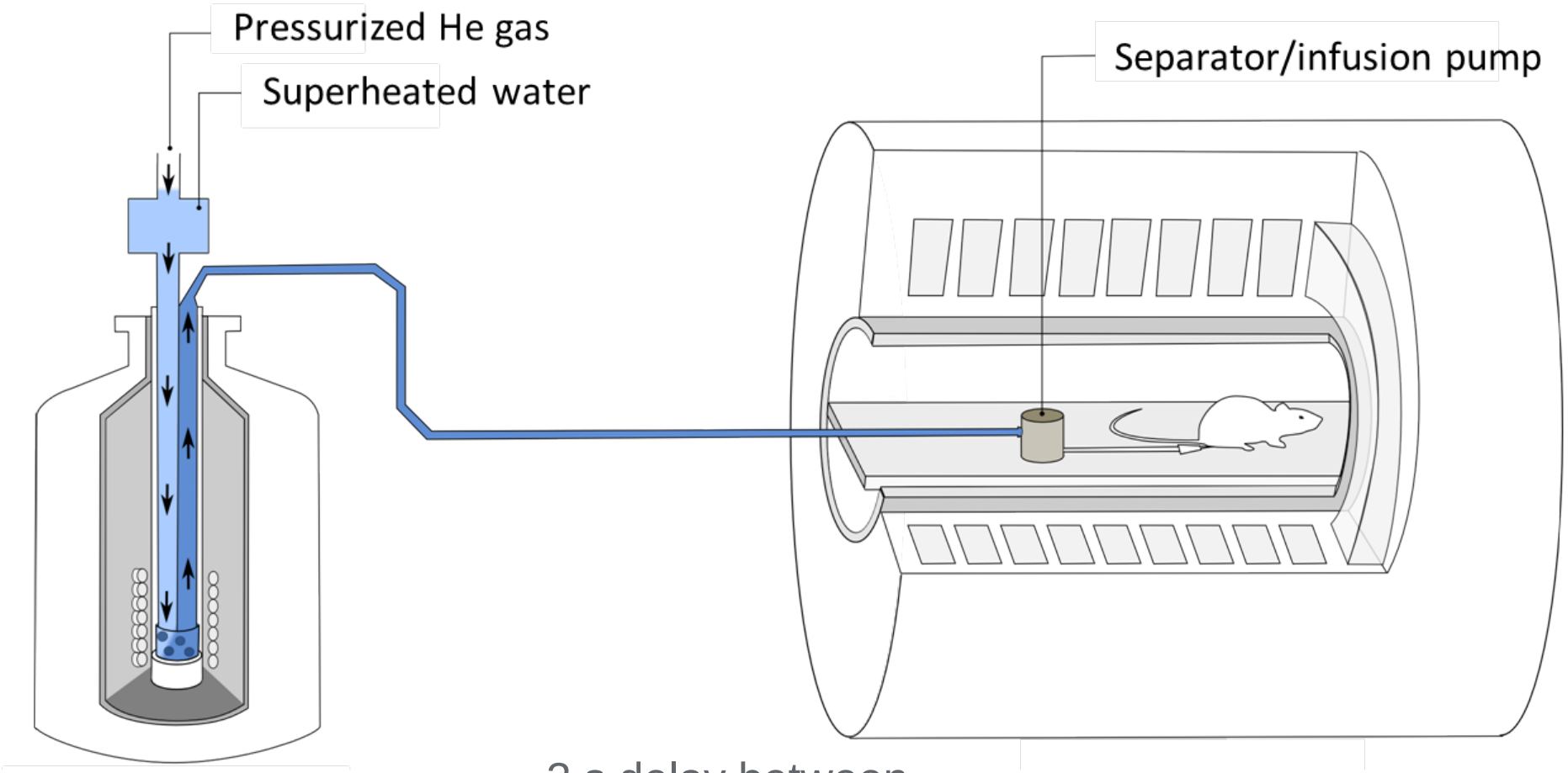


Preclinical *in vivo* studies

Ardenkjær-Larsen *et al.*, PNAS 2003

Comment *et al.* Concepts Magn. Reson. 2007

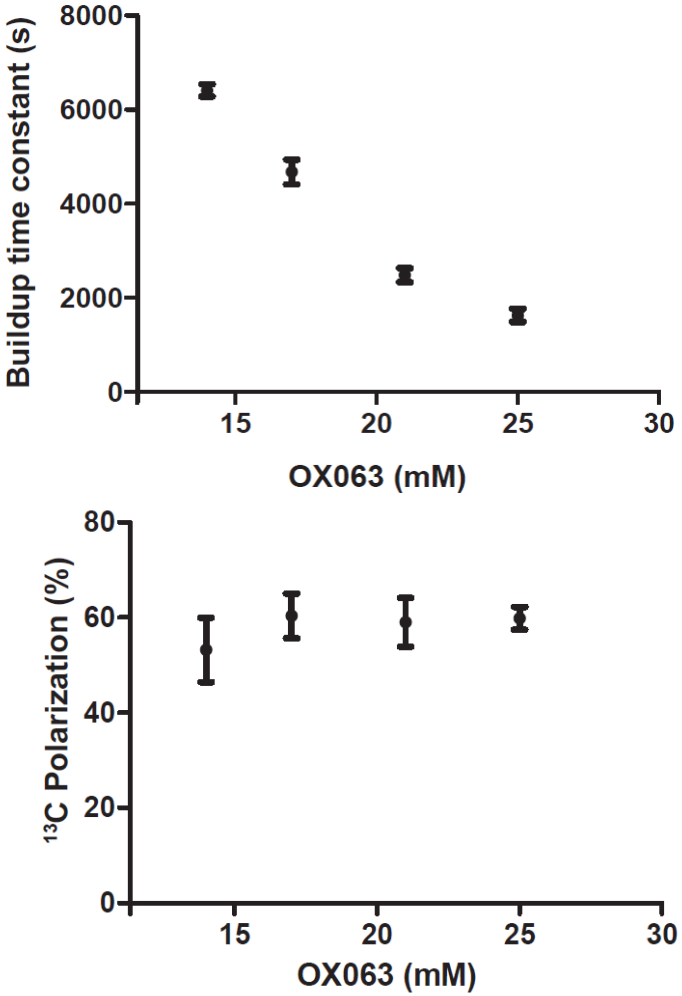


7 T / 1 K hyperpolarizer

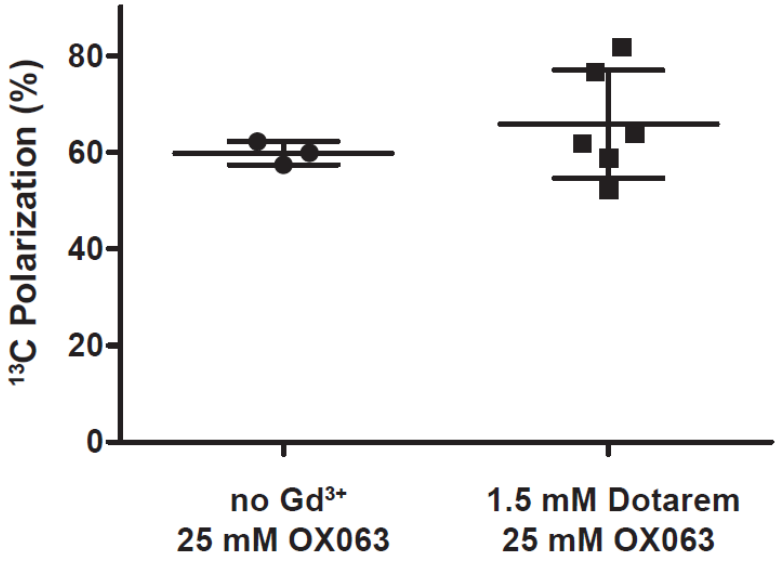
3 s delay between dissolution and injection

MR scanner

[1-^{13}C]PA polarization at time of injection



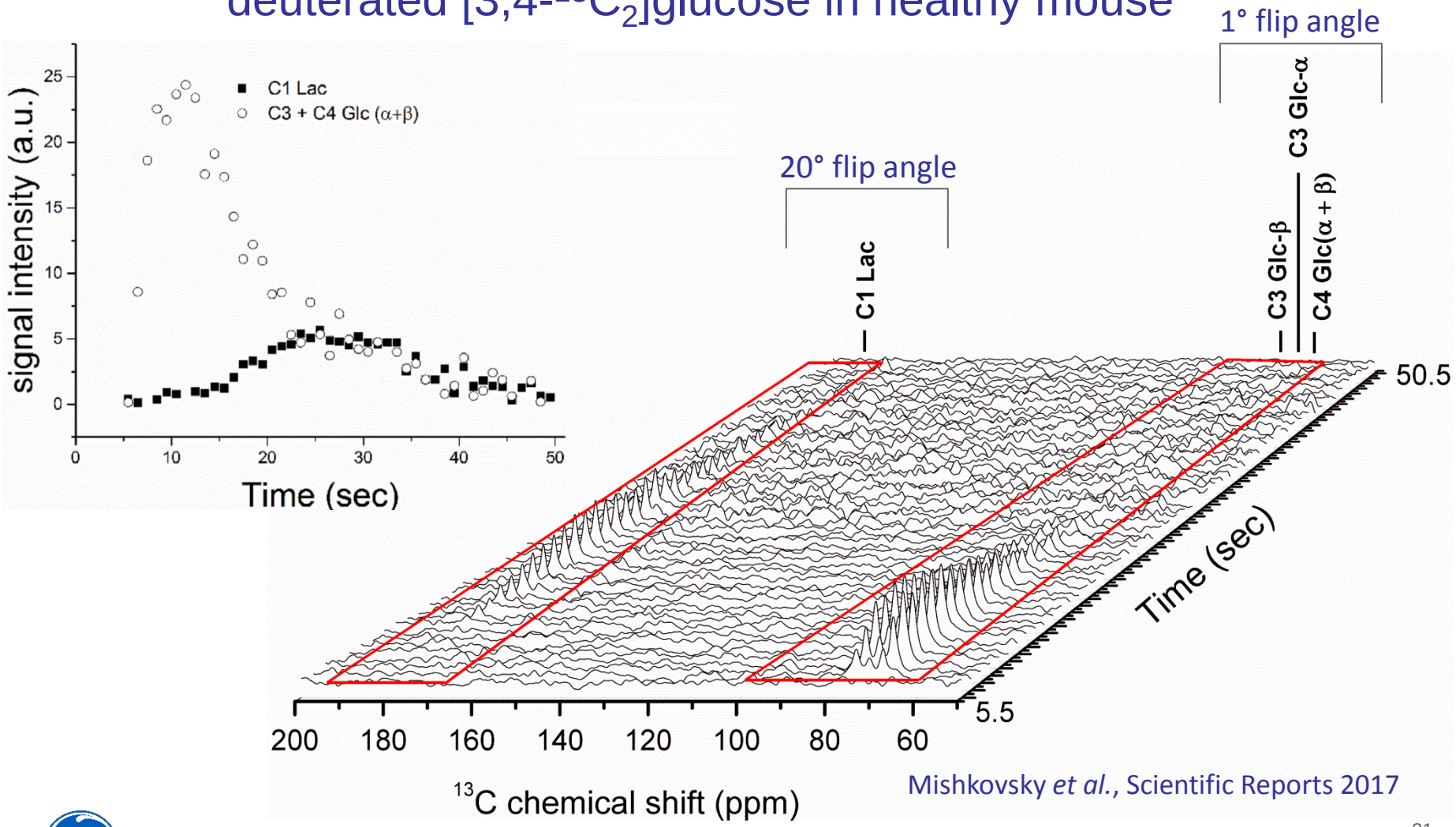
DNP at 7 T / 1 K can lead to up to 80% ^{13}C polarization



H.A.I. Yoshihara *et al.*, Phys Chem Chem Phys 2017

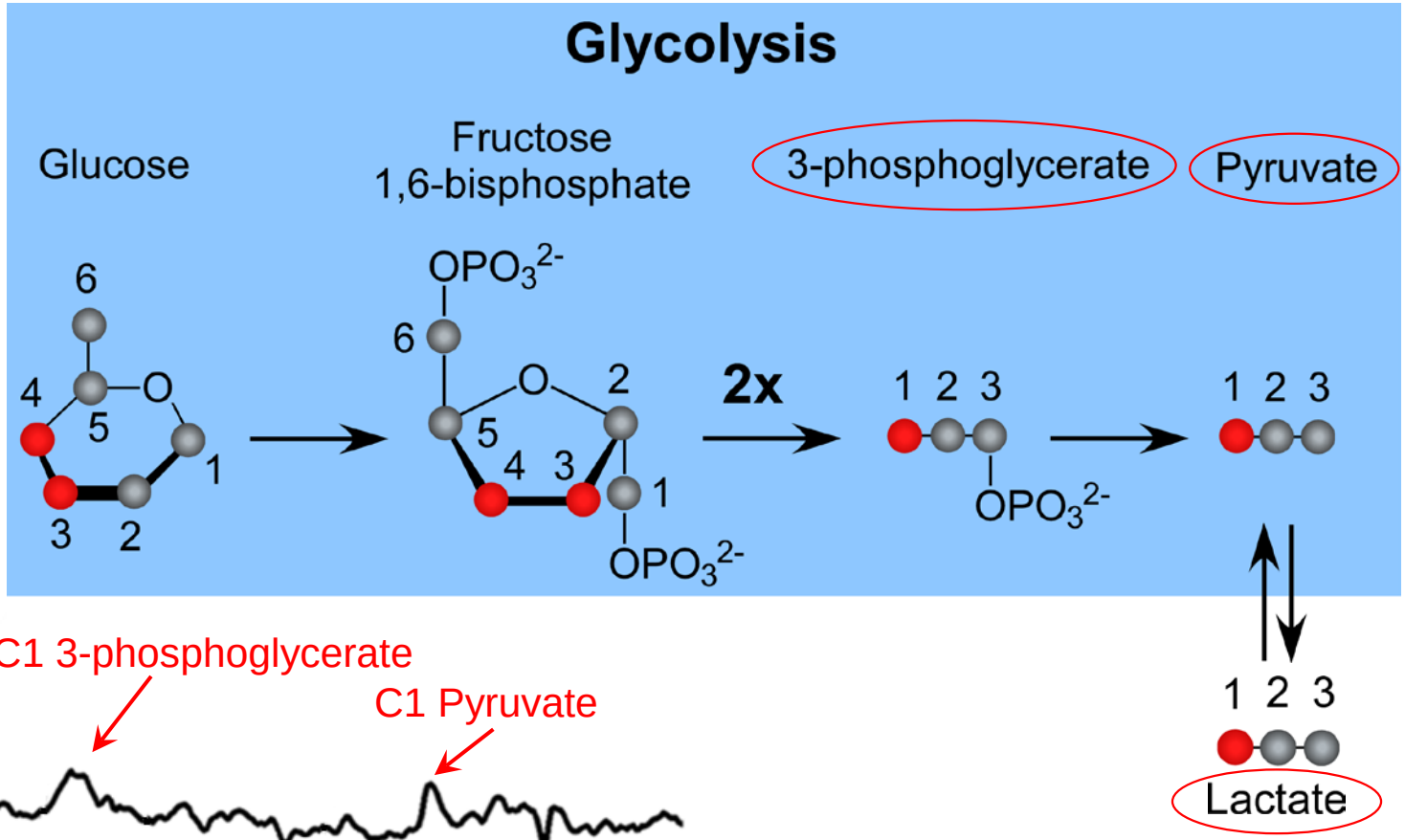
Real-time cerebral glucose metabolism

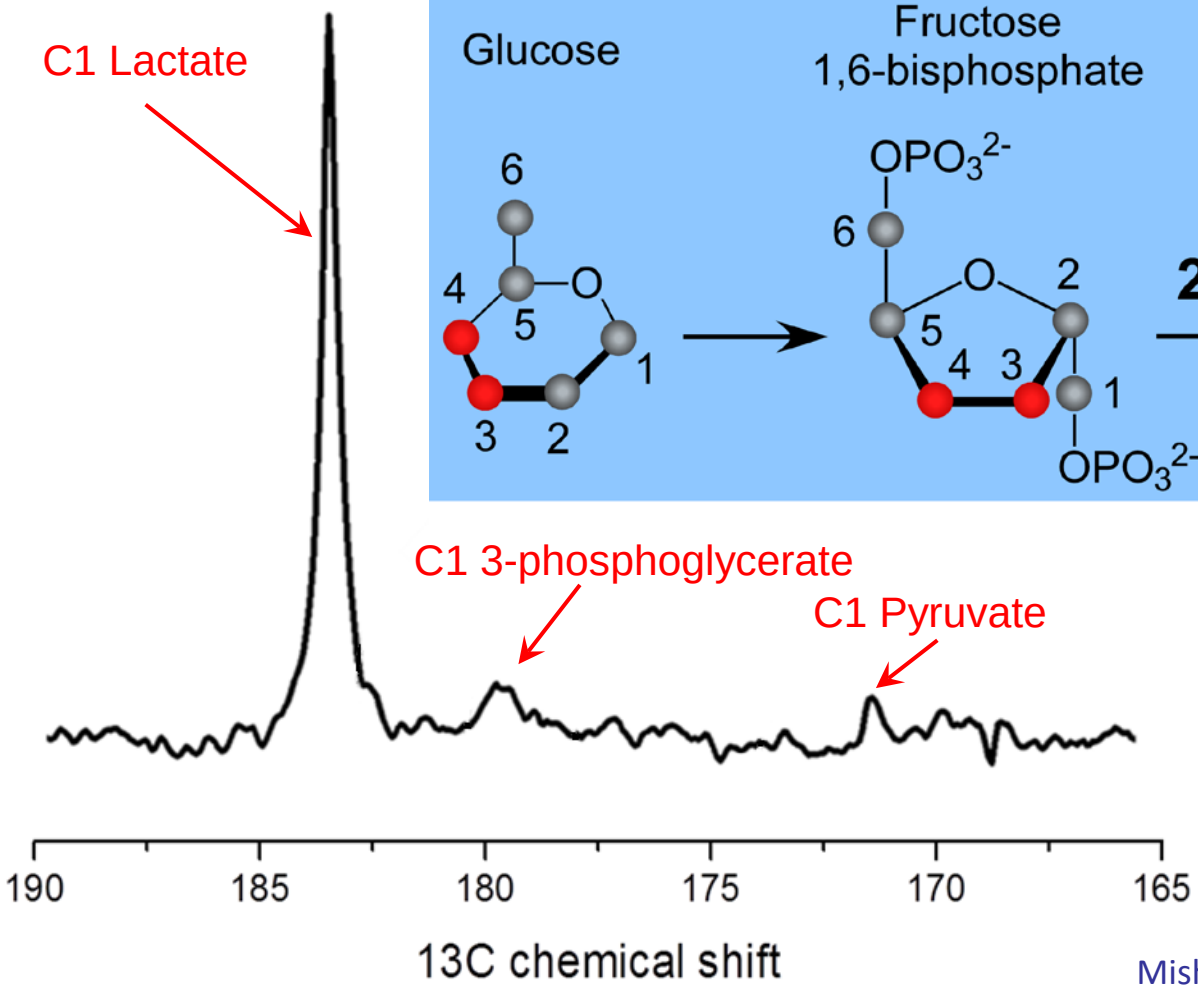
^{13}C polarization >20% at time of injection of hyperpolarized deuterated [3,4-$^{13}C_2$]glucose in healthy mouse



Mishkovsky *et al.*, Scientific Reports 2017

Glycolytic intermediates





Lactate-to-pyruvate ratio
17.6 ± 2 (n = 5)

Mishkovsky *et al.*, Scientific Reports 2017

Clinical hyperpolarizer: SpinLab™

About 50% ^{13}C polarization in 40 mL [1-^{13}C]pyruvate solution

Around 60 s delay between dissolution and injection into human (equivalent to ^{13}C T_1 of [1- ^{13}C]pyruvate)

SpinLab™ : key features

- Operates at 5T
- Very low working temperature (<1K)
- No cryogenic fluid required
- Low overall heat leak allowing a >12h working window
- Efficient sample cooling procedure, i.e., low helium evaporation during sample loading
- Automated dissolution and QC analysis
- Cryogenic and DNP compatible fluidpath for pharmacy usage
- Relatively small tower size/foot print

Global SPINlab™ sites

- 24 installed worldwide
- 8 ongoing clinical studies

US / Canada

- ✓ UCSF 3T
- ✓ **UCSF 5T**
- ✓ **Sunnybrook**
- ✓ MSKCC 3T
- ✓ **MSKCC 5T**
- ✓ NIH
- ✓ U Maryland
- ✓ Stanford
- ✓ U Penn
- ✓ **UT Southwestern**
- ✓ MD Anderson
- ✓ GRC

Europe

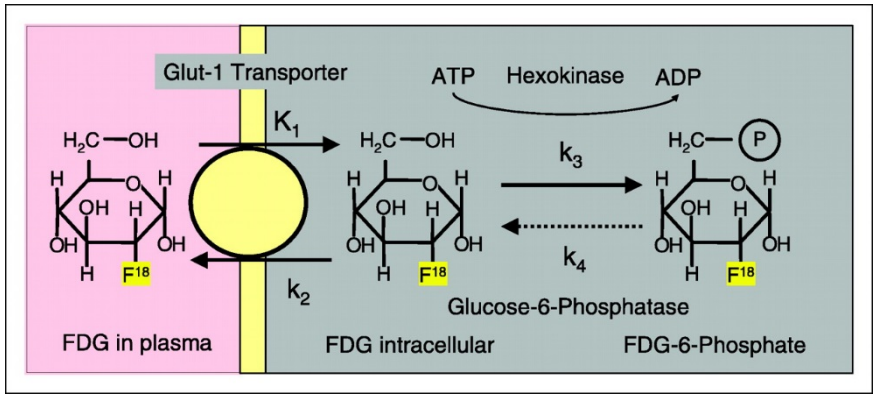
- ✓ **Oxford University**
- ✓ **University of Cambridge MRIS**
- ✓ University of Cambridge WBIC
- ✓ Rigs Hospital Copenhagen
- ✓ **Aarhus University**
- ✓ ETH Zürich
- ✓ Lublin
- ✓ University of Nottingham
- ✓ **UCL London**
- ✓ Warsaw
- ✓ University Hospital Tübingen

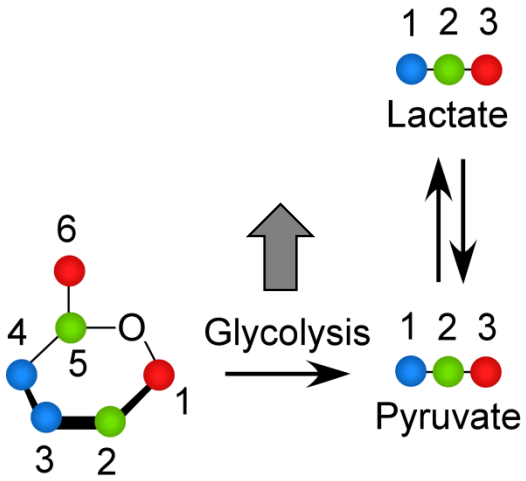
Asia

- ✓ **A*Star**

Applications in oncology

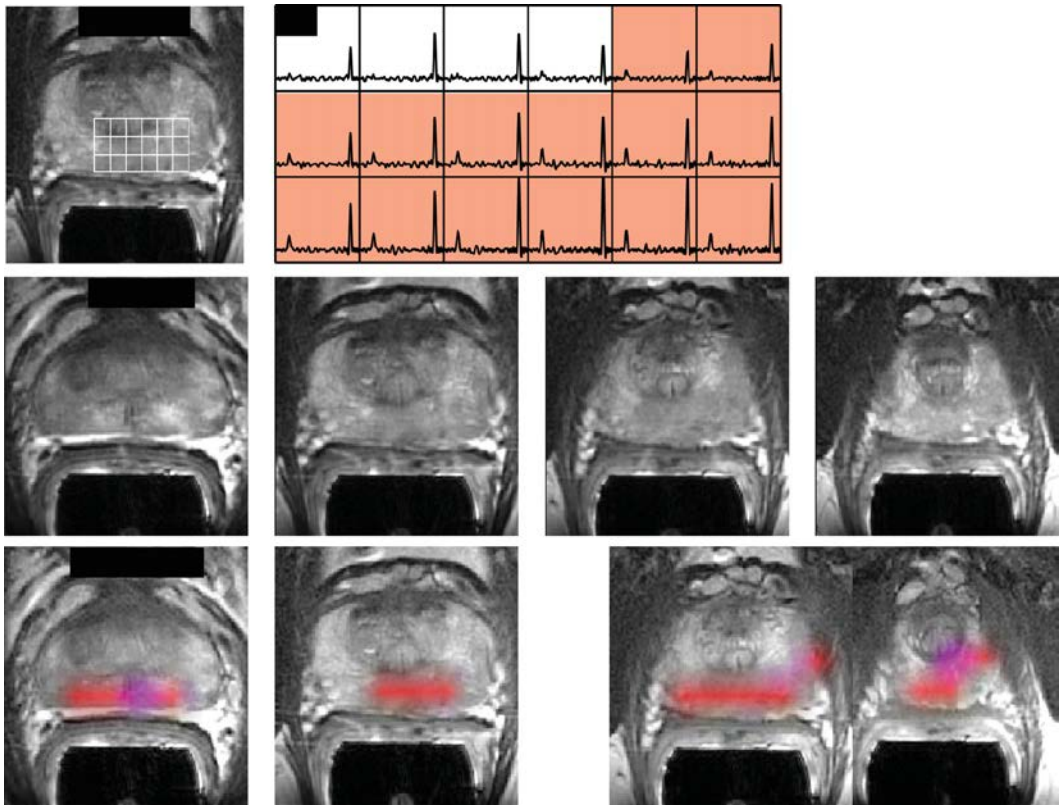
- Glycolytic pathway is perturbed in most cancer cells (Warburg effect) ⇒ Lactate production is increased



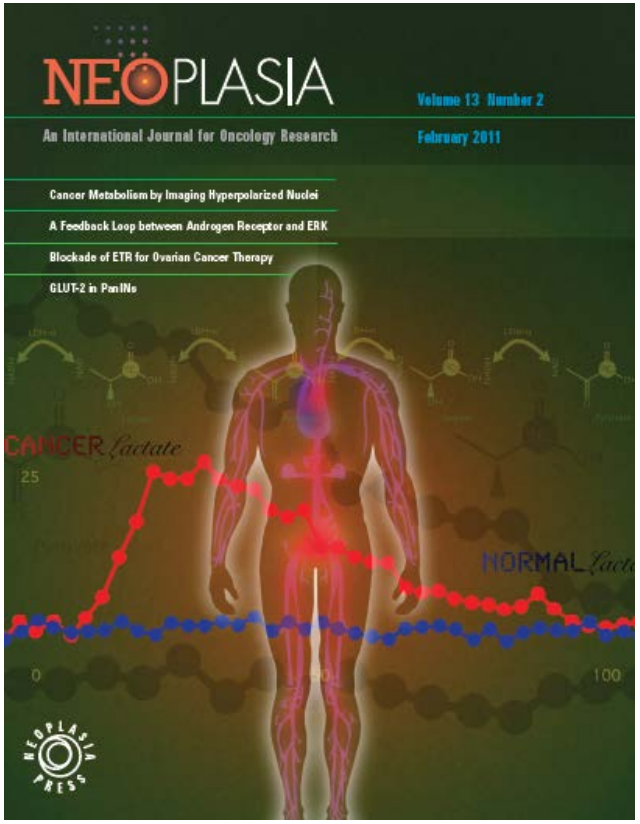


Applications in oncology

First in-human trial at UCSF: prostate cancer patients

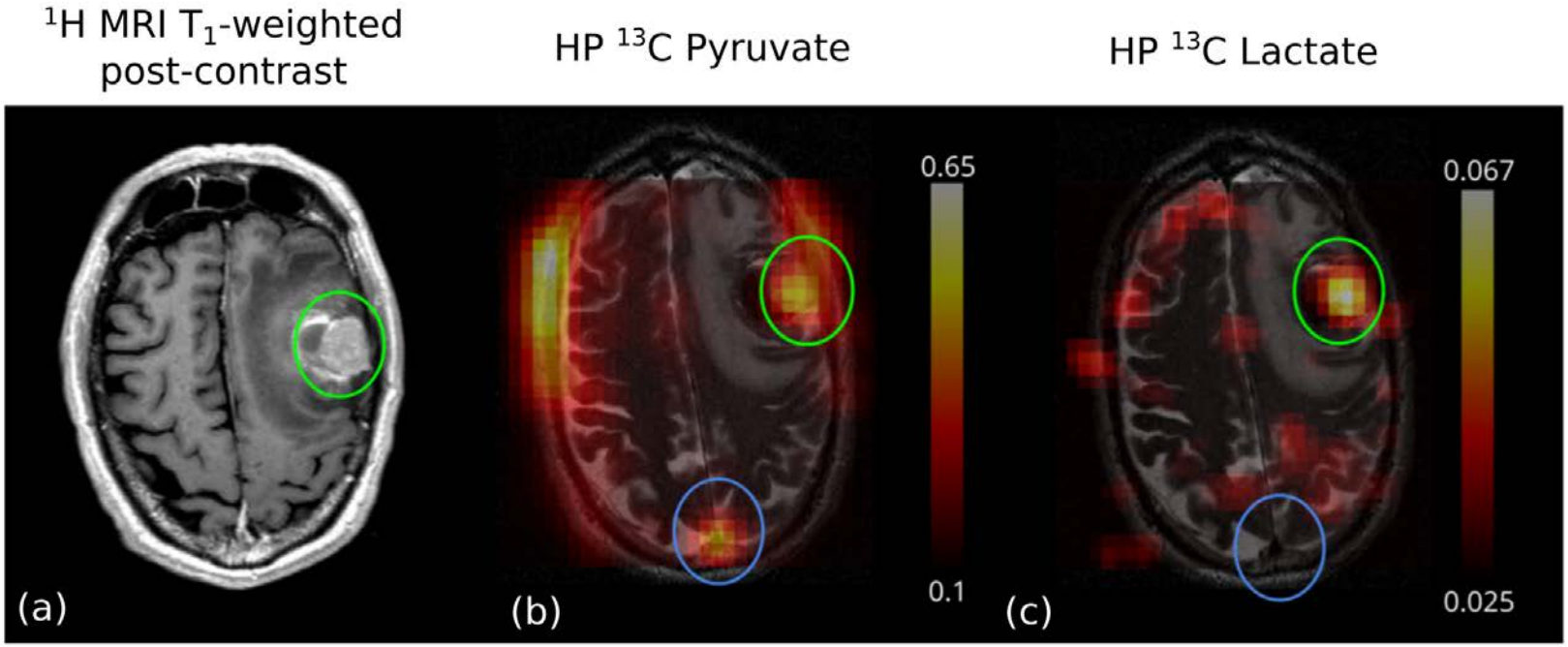


S.J. Nelson *et al.*, Science Translational Medicine **5**, 198ra108 (2013)



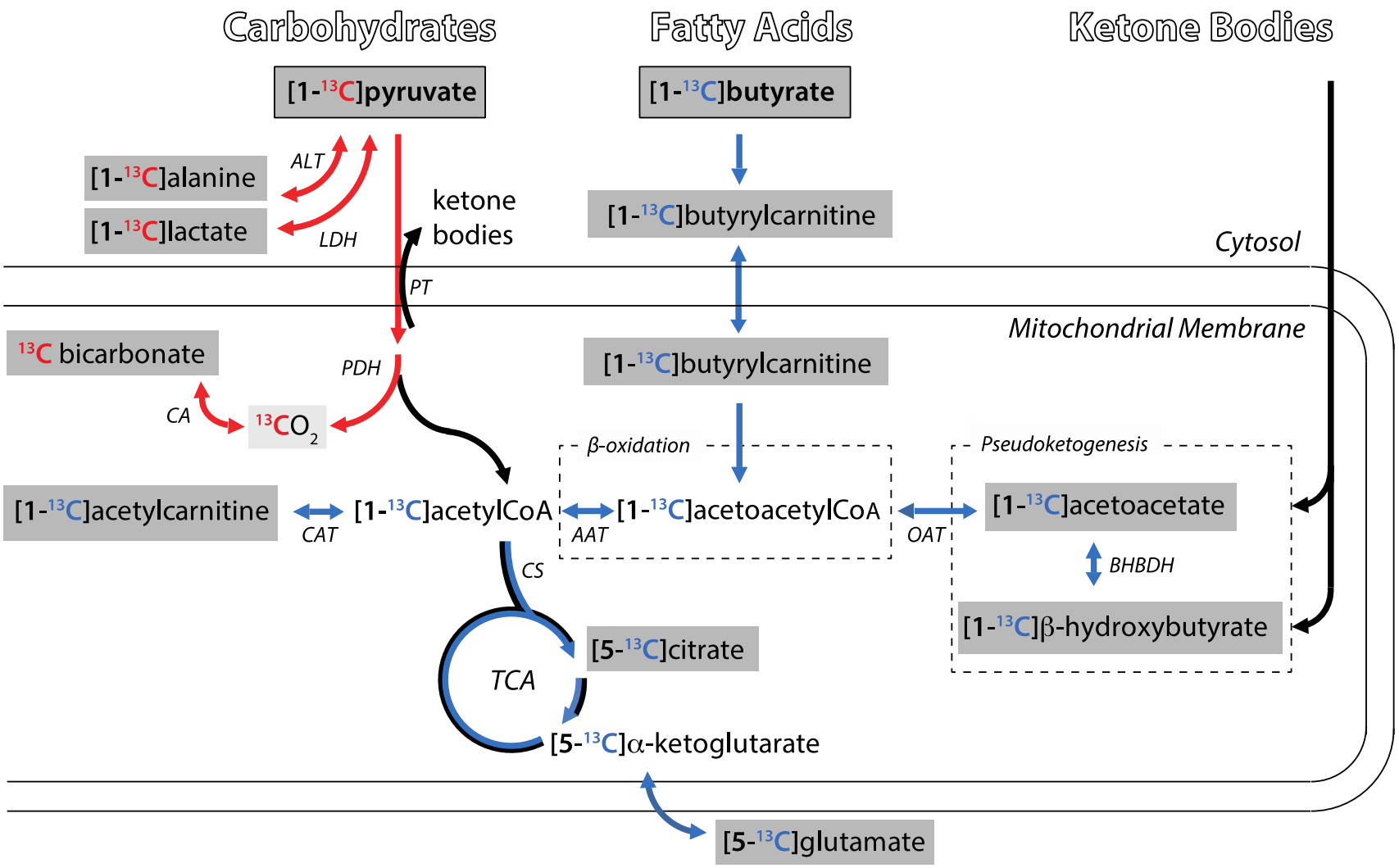
J. Kurhanewicz *et al.*, Neoplasia **13**, 81 (2011)

^{13}C Lactate Production in Brain Tumor



V. Z. Miloushev *et al*., Cancer Res. **78**, 3755 (2018)

Applications in cardiology

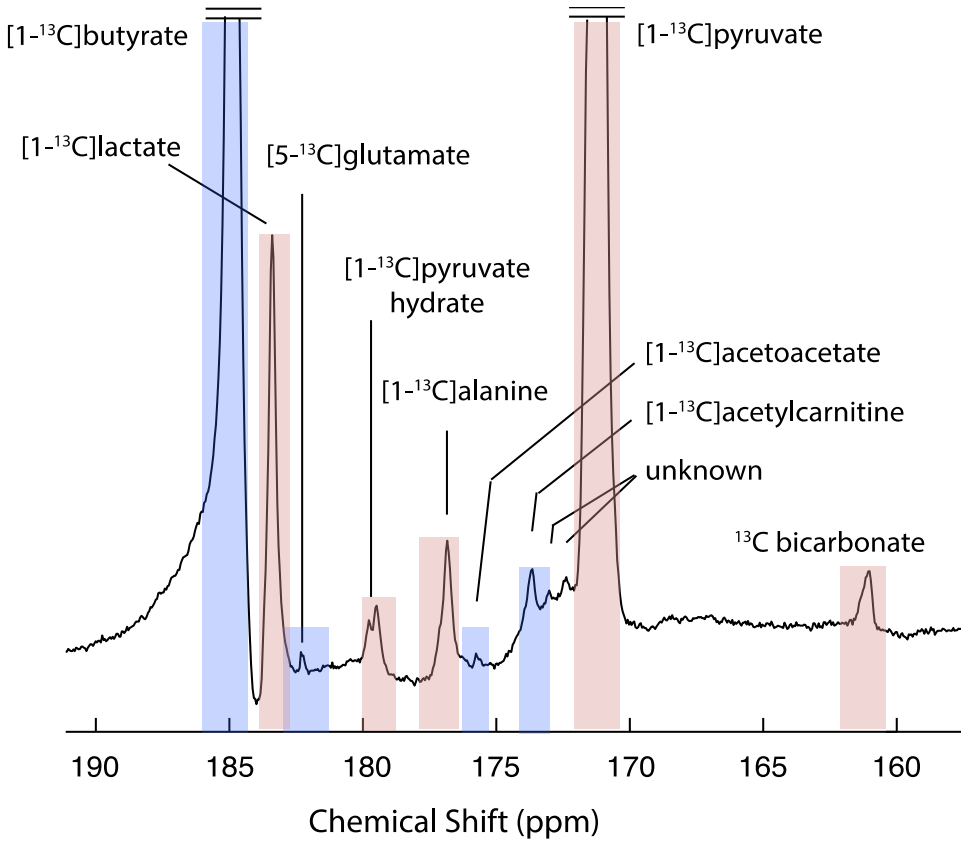


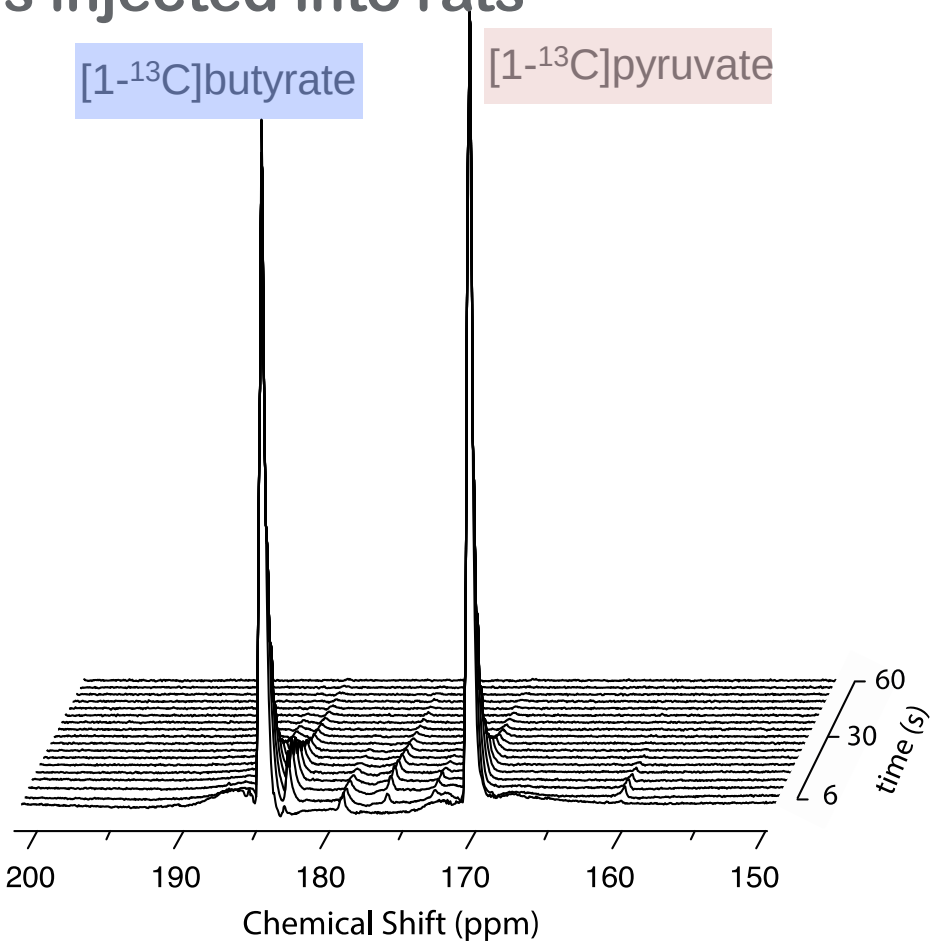
J. A. M. Bastiaansen *et al.* Scientific Reports 2016

Carbohydrates vs. fatty acids

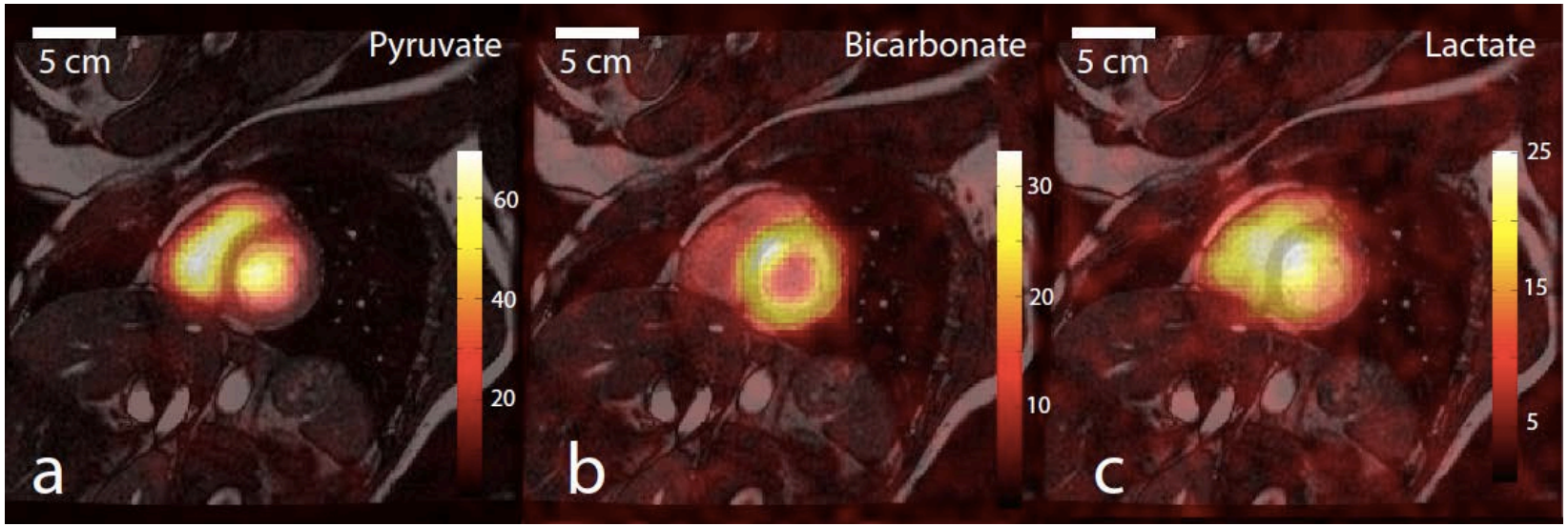
J. A. M. Bastiaansen *et al.* Scientific Reports 2016

- Potential Co-injection of pyruvate and butyrate
- Equal amount of both substrates injected into rats



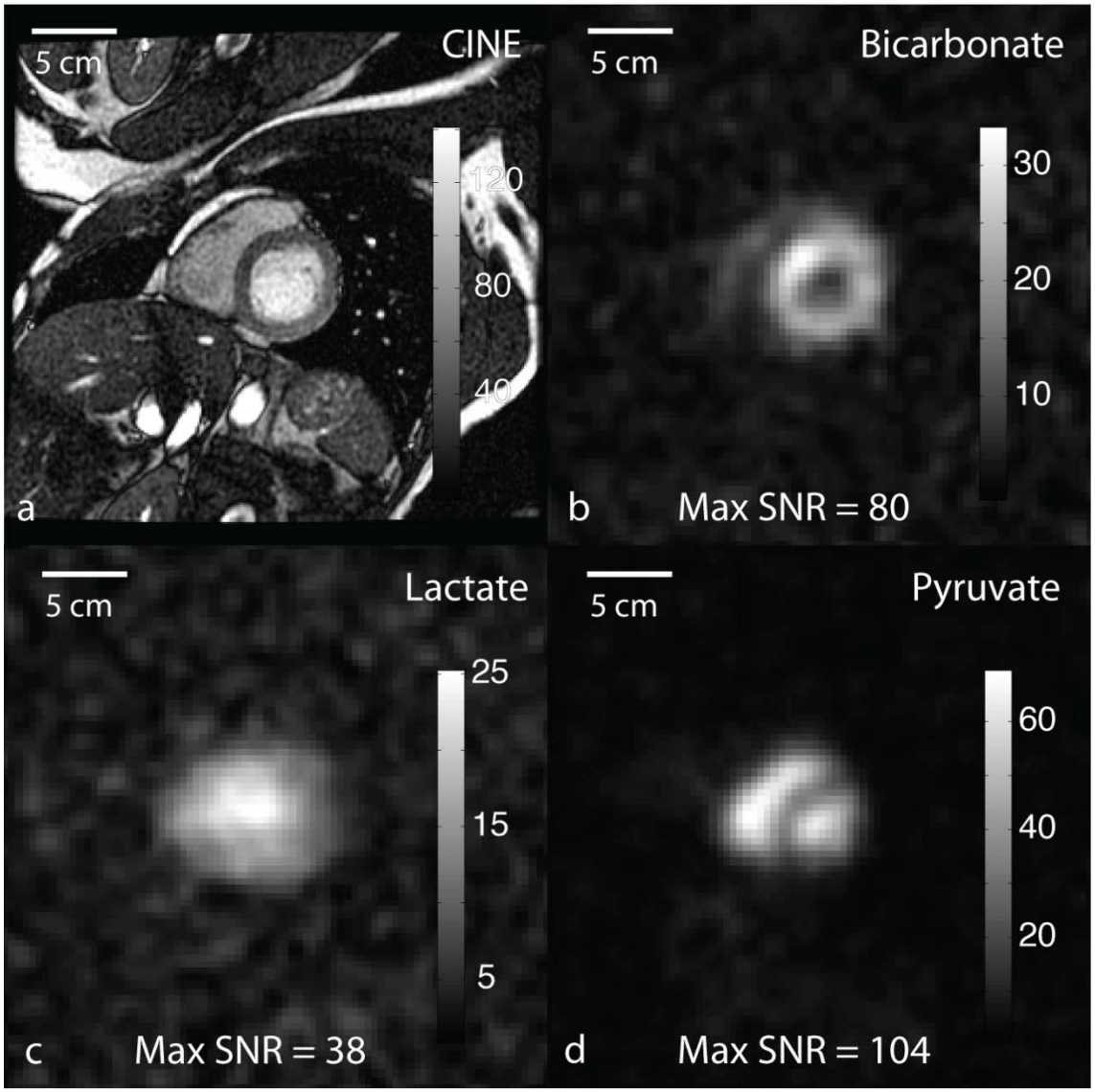


HP-^{13}C Metabolic Imaging of the Human Heart



C. H. Cunningham *et al.*
Circulation Research 2016

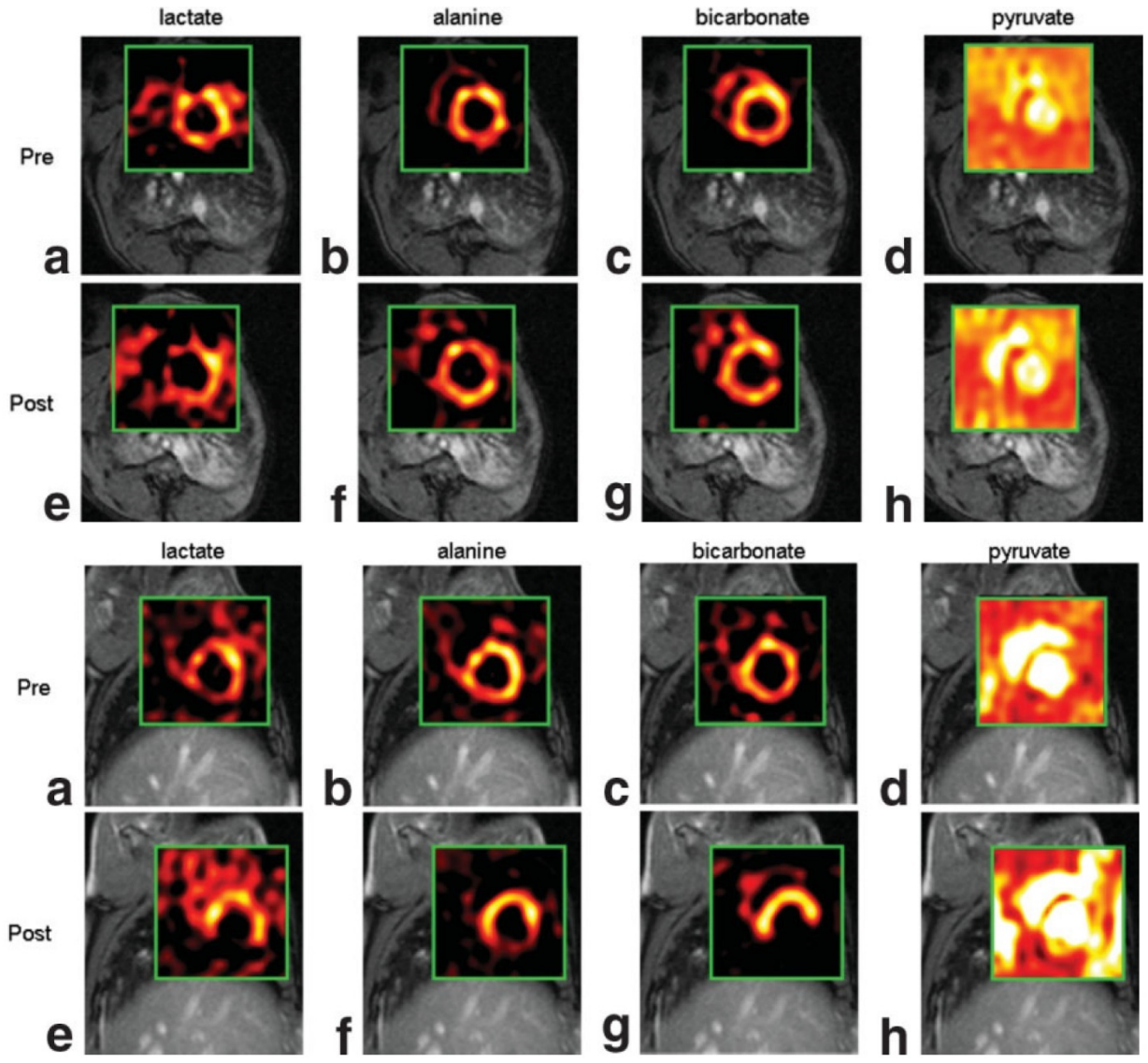
HP-^{13}C Metabolic Imaging of the Human Heart



Tissue compartments visible in ^{13}C images

C. H. Cunningham *et al.*
Circulation Research 2016

Diagnosing ischemic heart



Pig heart pre- and post-15-min occlusion

Pig heart pre- and post-45-min occlusion

K. Golman *et al.*, MRM 2008

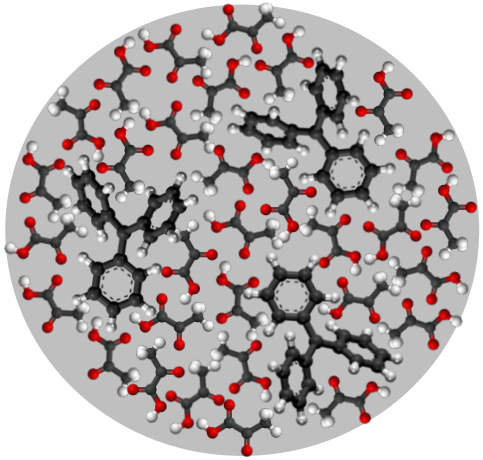
Current developments

- Simplify delivery and quality control of hyperpolarized ^{13}C-substrates
- Reduce delay between production and injection
- Improve hardware and methods to increase robustness
- Increase the number of substrates available for clinical applications

Demonstrate clinical benefit of this technology

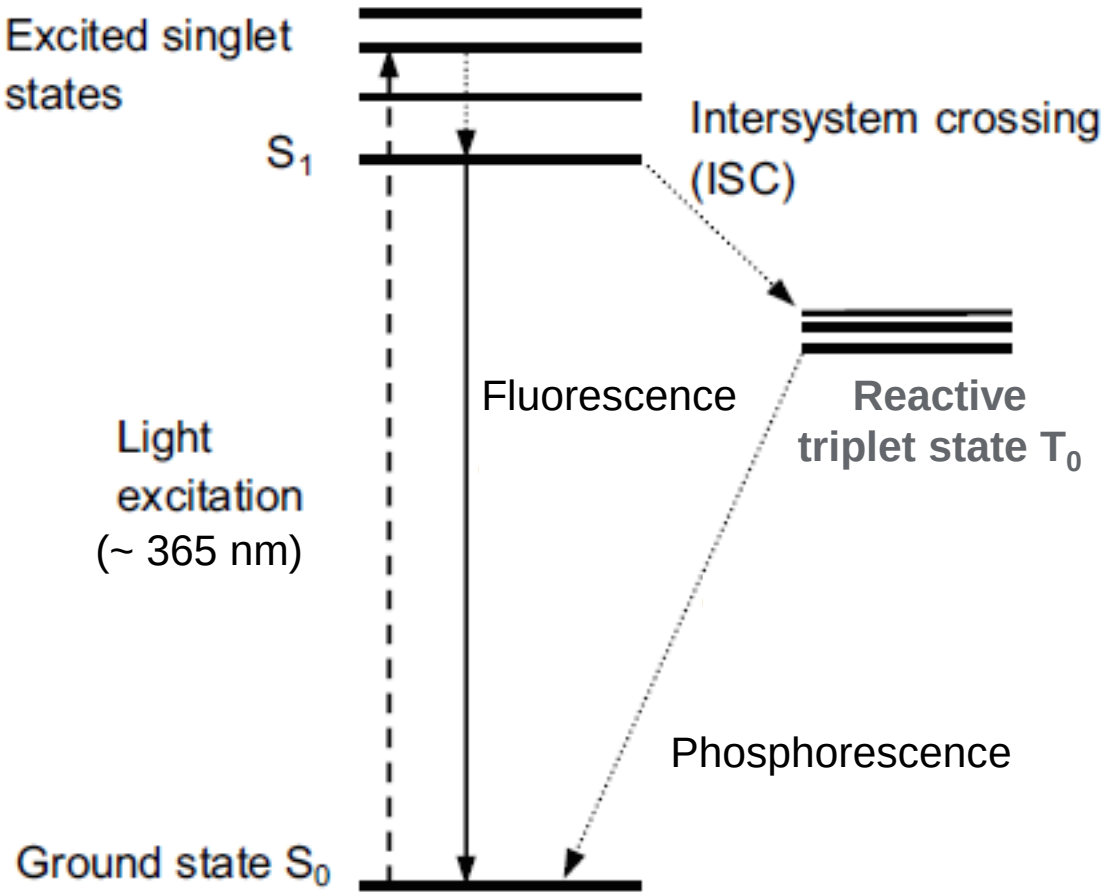
Future developments

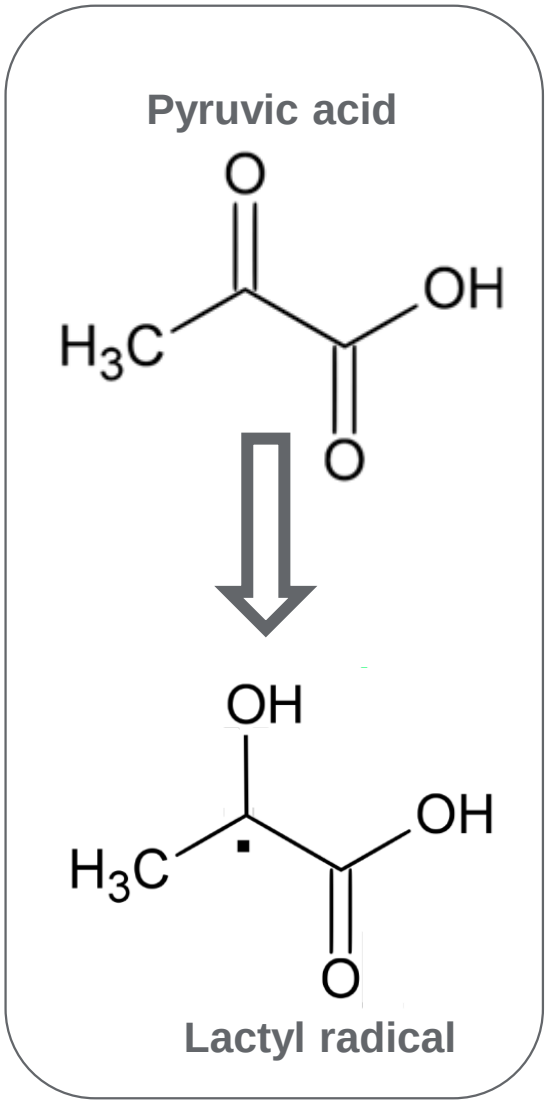
- Can we store hyperpolarized substrates?
- Can we transport them?
- Can we inject them in a continuous manner?



Use non-persistent polarizing agents

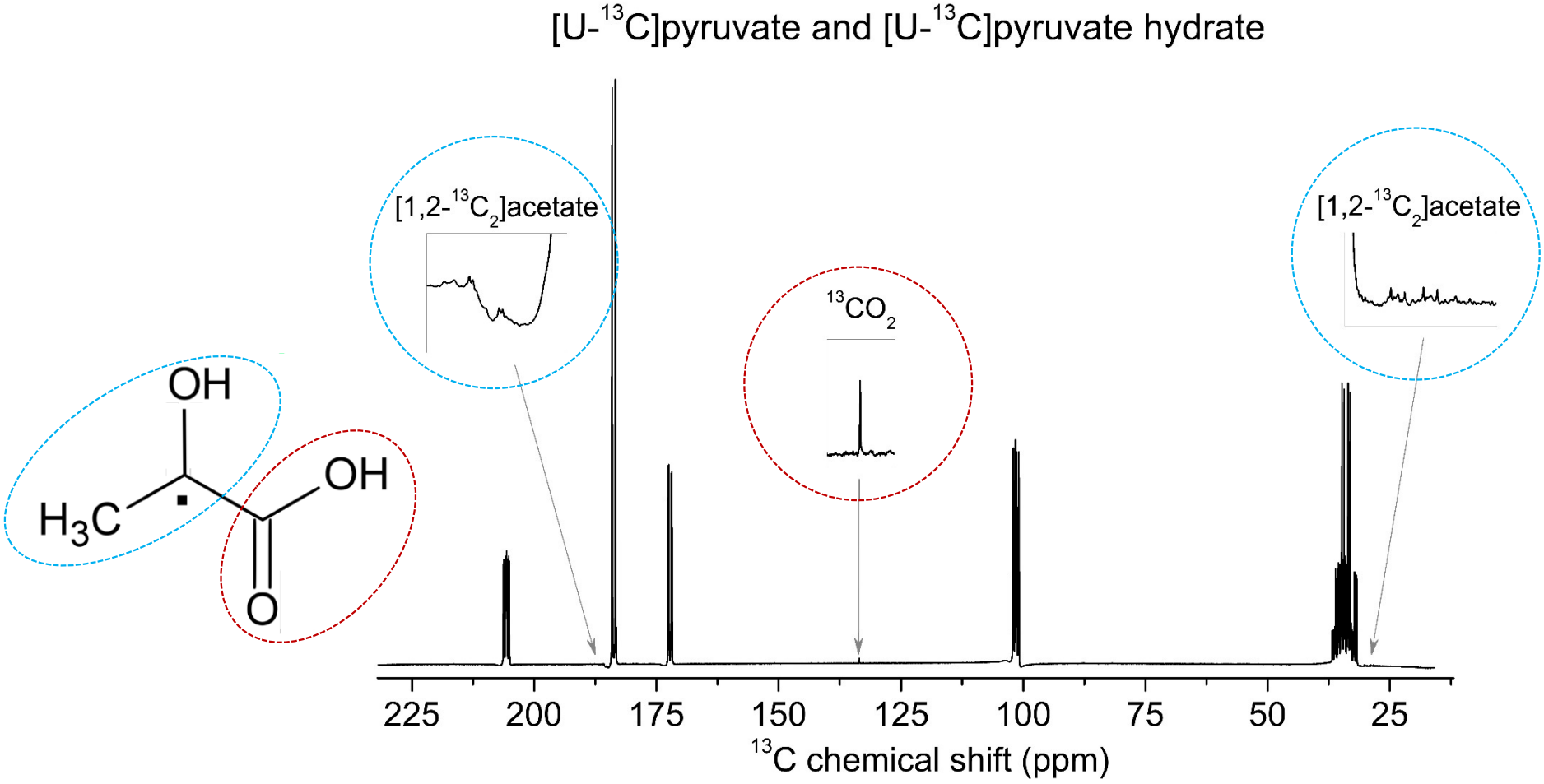
Photo-excited reactive triplet state





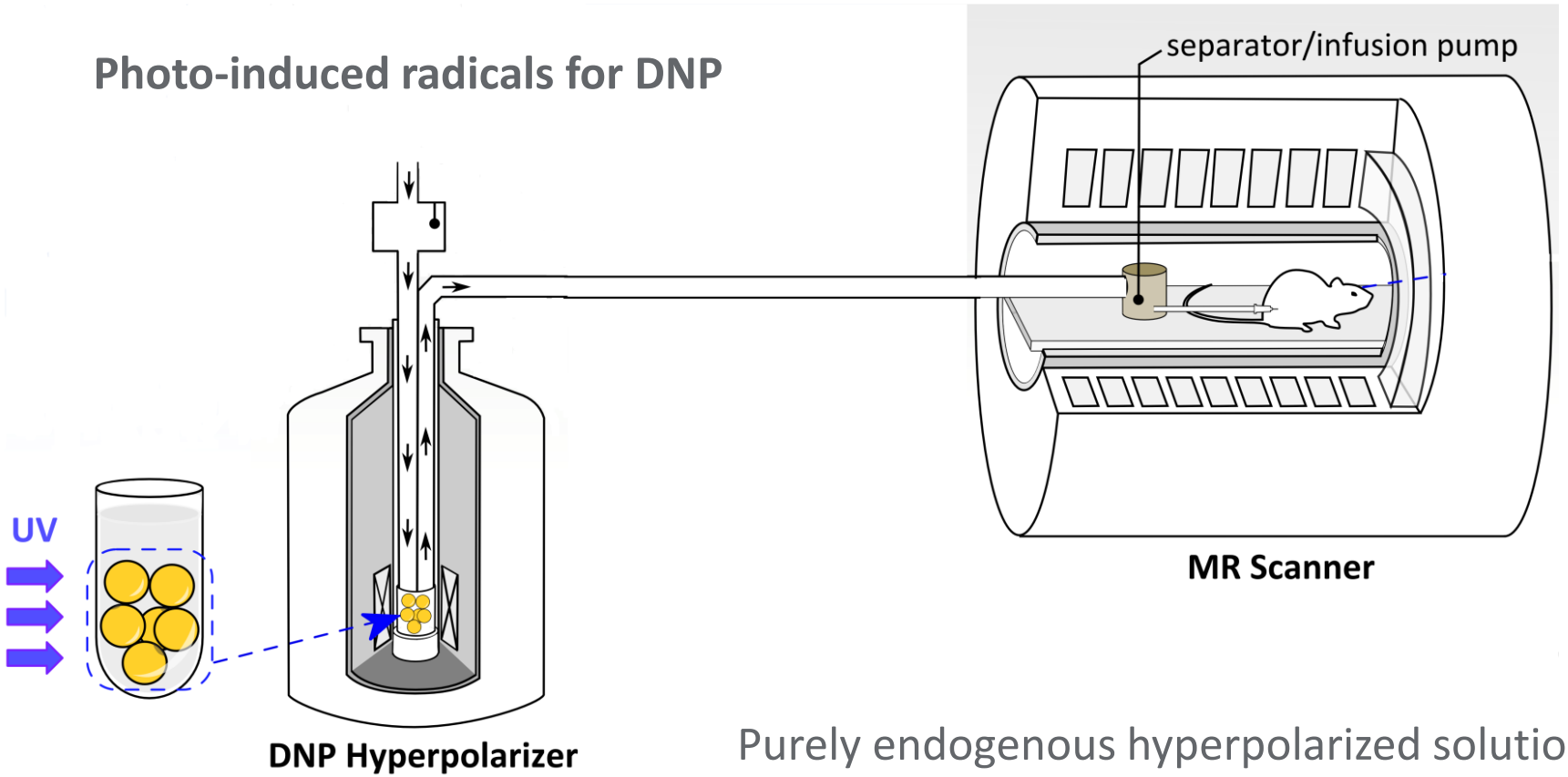
T. R. Eichhorn, *et al.*, PNAS 2013

Spontaneous radical quenching upon dissolution



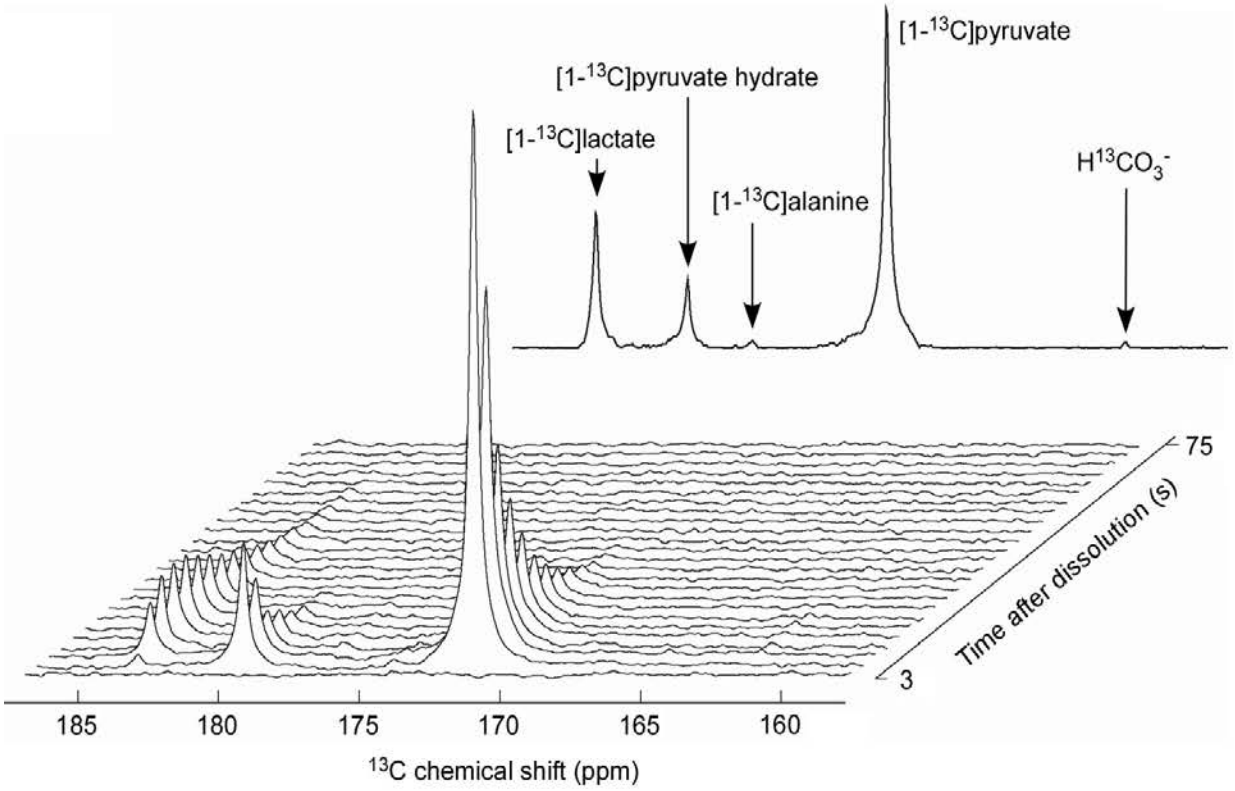
T. R. Eichhorn, *et al.*, PNAS 2013

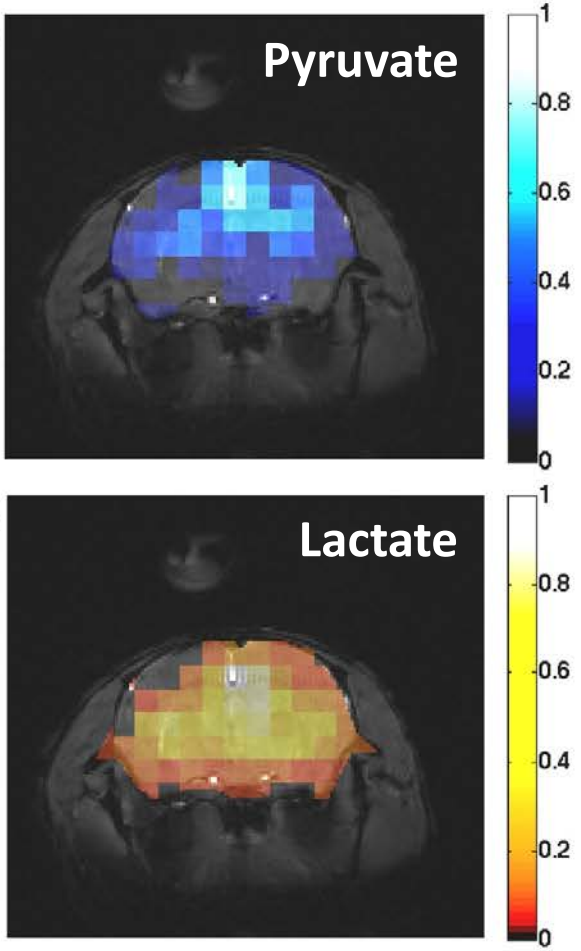
Preclinical in vivo studies



Purely endogenous hyperpolarized solutions without filtration and without additional delay (3s between preparation and injection)

Real-time in vivo metabolism in mouse brain

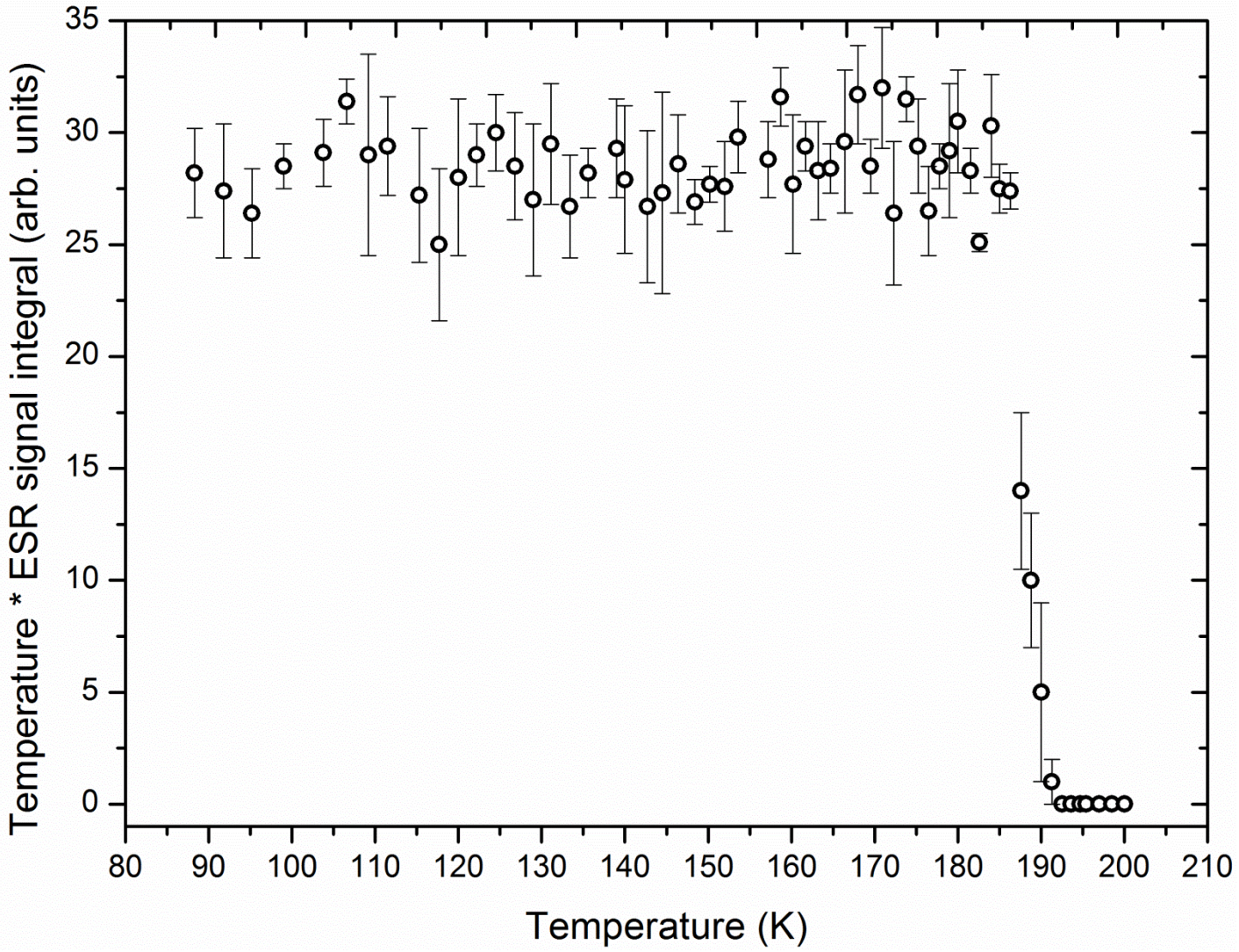




Injection of hyperpolarized [1- ^{13}C]pyruvate

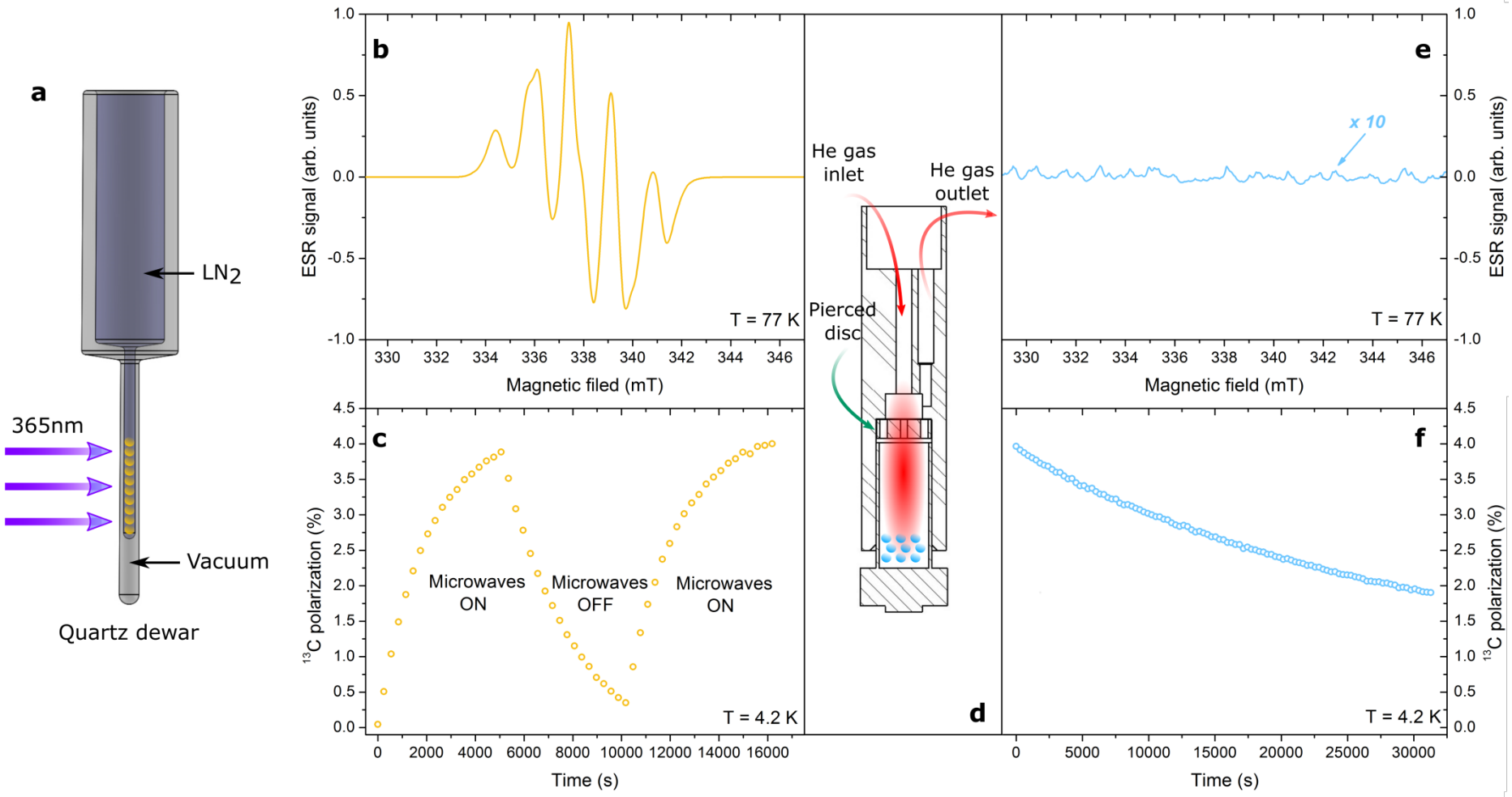
T. R. Eichhorn, *et al.*, PNAS 2013

Annihilation temperature of photo-induced radicals



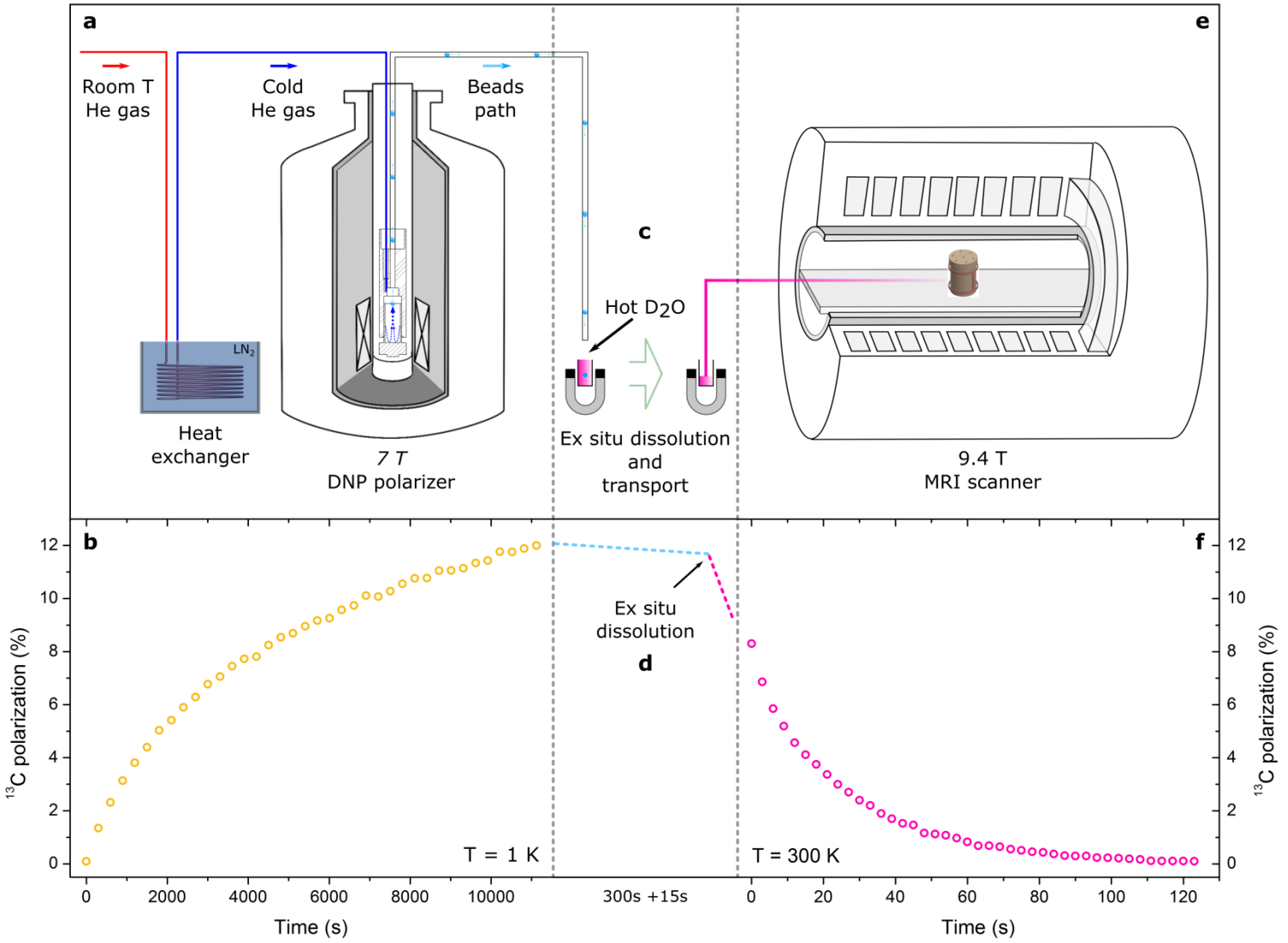
A. Capozzi *et al.*, Nat. Commun. 2017

Rapid thermalization method



A. Capozzi *et al.*, Nat. Commun. 2017

Ex situ dissolution



A. Capozzi *et al.*, Nat. Commun. 2017

Conclusions

- Recent results show that valuable clinical information can be highlighted using this technology
- We are aiming at scanning the first few hundreds patients with current implementation
- Improved hardware and methods under developments
- Future implementations might allow to produce hyperpolarized substrates at remote sites

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