

**Biomedical Investigations with Laser-Polarized
Noble Gas Magnetic Resonance**

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Technical Progress Report

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PRINCIPAL INVESTIGATOR

Dr. Ronald L. Walsworth

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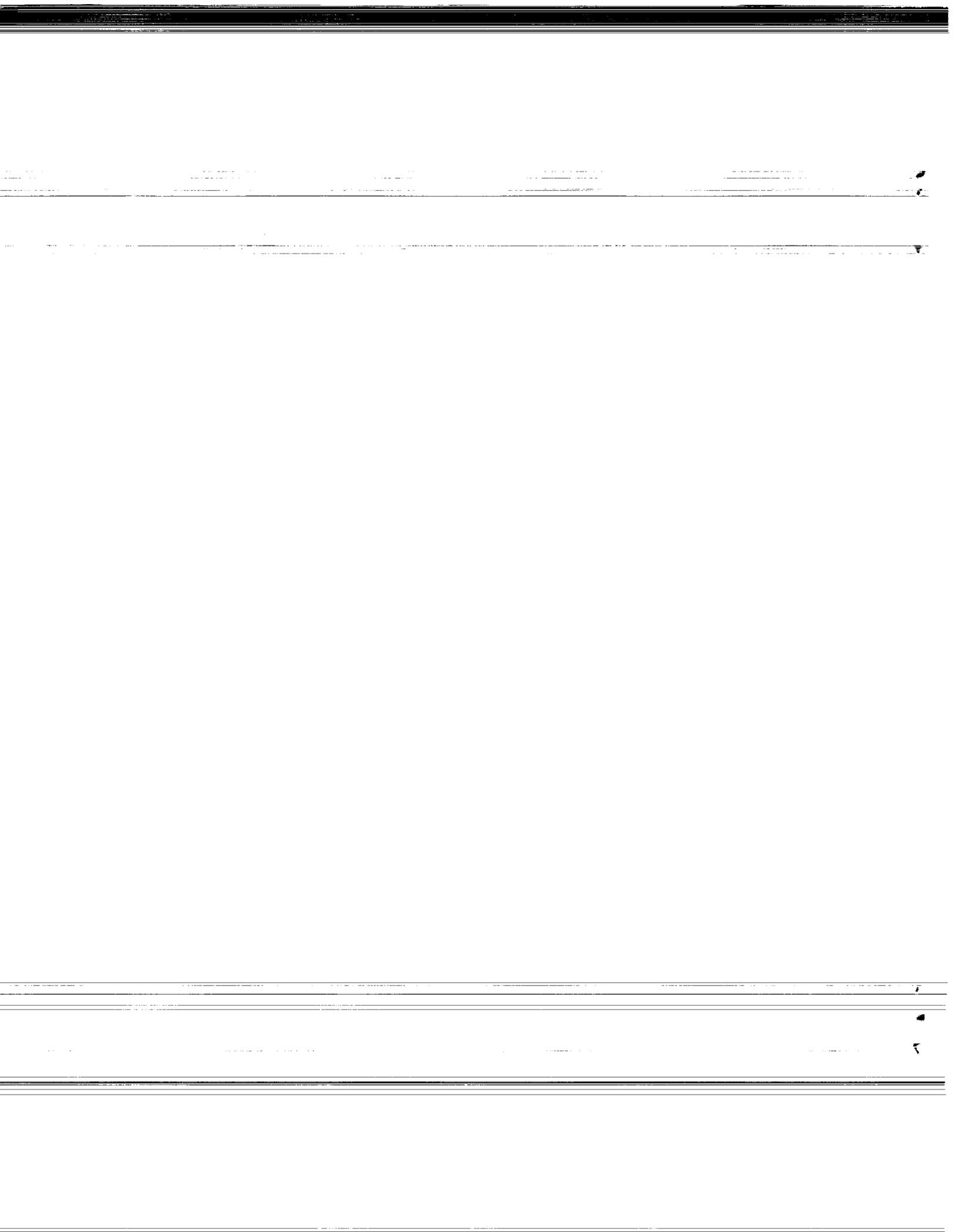
by

Smithsonian Institution

Astrophysical Observatory

Cambridge, Massachusetts 02138

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Background and specific aims

We are developing laser-polarized noble gas nuclear magnetic resonance (NMR) as a novel biomedical imaging tool for ground-based and eventually space-based application. This emerging multidisciplinary technology enables high-resolution gas-space magnetic resonance imaging (MRI)—e.g., of lung ventilation—as well as studies of tissue perfusion. In addition, laser-polarized noble gases (^3He and ^{129}Xe) do not require a large magnetic field for sensitive detection, opening the door to practical MRI at very low magnetic fields with an open, lightweight, and low-power device. We are pursuing two specific aims in this research. The first aim is to develop a low-field (< 0.01 T) instrument for noble gas MRI of humans, and the second aim is to develop functional MRI of the lung using laser-polarized ^{129}Xe and related techniques.

Accomplishments during current grant year

Development of an open human-scale low-field MRI system

Initial demonstration images of water (^1H) and laser-polarized ^3He gas were obtained from a very-low magnetic field MRI system. The system is designed to provide open-access human-scale imaging at or below 50 gauss, permitting free variation of subject orientation within the applied field. The magnetic field is created by an optimized 4-coil system, and features three-dimensional planar gradients, which do not inhibit subject access. Attention to noise reduction has permitted ^1H images from water phantoms to be obtained. ^3He images with high sensitivity indicate the potential for high-quality imaging of inhaled laser-polarized gases in human subjects.

Operation at low field strengths allows the use of magnet designs radically different from traditional solenoids used in high-field superconducting magnets. The use of Helmholtz pairs to generate the B_0 field, along with planar gradient sets, permits a wide area of access, and orientation of the subject at any angle in a two-dimensional plane. This will permit us to image lung ventilation as a function of human orientation, and allow the exploration of gravitational effects on inhalation, a subject of much

debate in the lung physiology community [e.g., J. West, H. Guy, D. Michels, *Physiologist*. 25, S21 (1982)].

The open-access human MRI system, shown in Figure 1, can operate at fields ranging from 0 - 70 Gauss. The B_0 field is created by two pairs of coils approximately 2 and 0.8 meter in diameter. The custom-designed three-dimensional planar gradients provide complete orientation of subjects in a two-dimensional plane approximately 75 cm wide, and are driven by conventional Techron gradient amplifiers. Audio-frequency control is provided by a SMIS console, modified to mix down its 10 MHz reference signal to kHz frequencies, and interfaced to an Outlaw home-theater amplifier that provides up to 250 W of B_1 power.

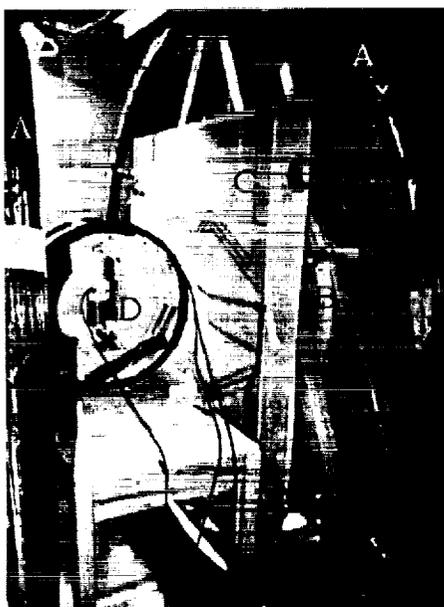


Figure 1. Human-scale, open, low-field MRI system operating at ~ 50 G. The B_0 applied field is provided by a primary coil pair 2 m in diameter, ~ 75 cm apart (A), combined with a secondary coil pair 80 cm in diameter (B). The system has planar gradient sets (C) that deliver 0.15 G/cm at 110 A (x and y) or 0.38 G/cm at 80 A (z) over a 60 cm spherical volume. The system is pictured with a small solenoid B_1 coil used for phantom testing (D).

Initial images of water (^1H) and laser-polarized ^3He phantoms demonstrate the successful operation of the instrument using small B_1 coils. Simple spin-warp images have been acquired with gradient and spin echo pulse sequences. Figure 2(a) shows a 1-D projection of a water sample, acquired with 64 signal averaging scans. Figure 2(b) shows a 2-D image of two laser-polarized ^3He phantoms and exhibits SNR comparable to that obtained at high-field with commercial instruments.

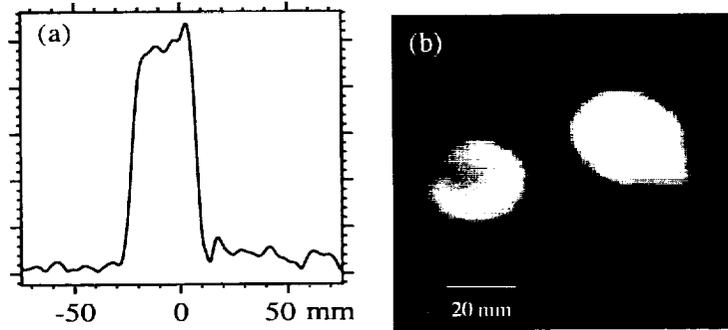


Figure 2. (a) One-dimensional projection of a ~ 4 cm water sample, acquired at 46 G applied field (195 kHz), using a gradient echo sequence with TE = 11 ms, TR = 1 s, NEX = 64. (b) Image of two ~ 3.8 cm spherical cells containing laser-polarized ^3He with different levels of spin polarization, acquired at 41 G (135 kHz). A gradient echo sequence was used with TE = 15 ms and TR = 200 ms. Four signal averaging scans (NEX), with $\sim 2^\circ$ flip-angles, were acquired solely for phase-cycling purposes.

Studies of gas diffusion NMR as a probe of porous media

We performed a systematic study of xenon gas diffusion in random packs of mono-sized glass beads, focusing on: (i) diffusion of spins on the order of the pore dimensions during the diffusion encoding gradient pulses, and (ii) the ability to derive long-length scale structural information. We find that the observed normalized time-dependent diffusion coefficient, $D(t)/D_0$, of the xenon gas at short diffusion times can be significantly influenced by the gas pressure and the presence of background gradients.

NMR is a commonly used, non-invasive probe of *liquid-saturated* porous materials. The restricted diffusion of water molecules can provide a wealth of information including the pore surface-area-to-volume ratio (S/V_p) and the average pore size in model systems. We have recently shown that *gas* diffusion NMR can be a powerful probe of porous media. The spin 1/2 noble gases (^3He and ^{129}Xe) are particularly well suited for such studies, given their rapid diffusion, inert nature, low surface interactions which reduce surface T_1 effects, and the ability to tailor the diffusion coefficient by altering the gas pressure in the sample. The enhanced signal due to the laser-polarization process has enabled measurements of noble gas diffusion in the lung, however attempts to link reduced observed diffusion coefficients to structural

detail in the lung have often overlooked effects that are known from porous media study to influence such results. Hence we systematically studied the effects of diffusion by spins over distances on the order of the pore dimensions during the diffusion encoding gradient pulses on measured short-time diffusion coefficients, and the ability to determine the tortuosity, a parameter that describes pore connectivity.

NMR spectroscopic measurements of the diffusion coefficient of ^{129}Xe gas and water in random packs of spherical glass beads were made as a function of the diffusion time in the Stejskal-Tanner PGSE sequence. A highly modified pulsed-gradient stimulated echo technique incorporating alternating bi-polar gradient pulses was used to alleviate the effects of very short T_2 and the presence of large susceptibility-induced background field gradients. The experiments were performed on either a GE Omega/CSI NMR system or a Bruker AMX2, both at 4.7 T, (55.3 MHz for ^{129}Xe , 200 MHz for ^1H). 6.5 or 3 bar pressure of isotopically enriched ^{129}Xe gas and 1.5 bar of O_2 were frozen into glass cells containing the packed beads, which were then sealed before the cells warmed to room temperature. Water diffusion was measured in samples of beads that were saturated with water under vacuum.

Figure 3 shows the measured time-dependent diffusion coefficients $D(t)$, of thermally-polarized xenon gas, and water, in a pack of 0.5 mm glass beads, normalized to the free diffusion coefficient, D_0 . Indicated on the figure are the theoretical relationships for the sample's S/V_p (valid at short diffusion times) and tortuosity (the asymptote at long times). It can be seen that at short times, the xenon $D(t)/D_0$ data deviates from the expected relationships, however this effect is reduced as the pressure of the gas is increased. Water $D(t)/D_0$ unambiguously lies on the short time limit.

The power of gas diffusion NMR is the ability to derive long-length scale structural information from the asymptotic limit. The concept of tortuosity to describe pore connectivity in rocks could also be a useful parameter to describe the alveolar spaces in lung tissue. However, measurements of $D(t)/D_0$ in small pore volumes at low gas pressures can often be misleading. At these pressures (a few bar) the gases can easily diffuse across the pore or alveolar dimensions during the application of the gradient pulses, violating the Narrow Pulse Approximation of the PGSE method. Such significant diffusion distances will also tend to reduce the effectiveness

of background gradient correction in sequences where this is attempted. The data clearly shows the effect on $D(t)/D_0$ as a result of changing D_0 , by first increasing the gas pressure, and then by changing the observation spin to water. Such effects in the lung will seriously influence $D(t)/D_0$ measurements, resulting in misleading structural information if airspace dimensions are simply concluded from the observed $D(t)/D_0$ data.

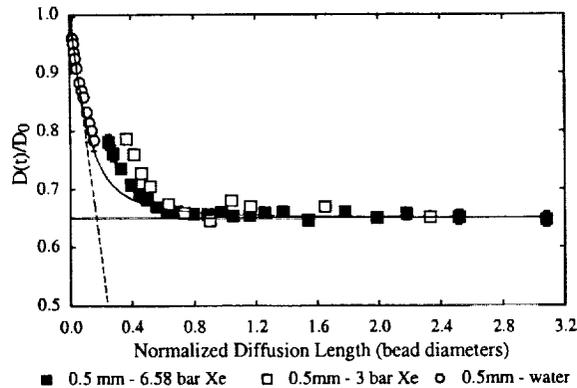


Figure 3. $D(t)/D_0$ in a sample of 0.5 mm diameter glass beads. ^{129}Xe $D(t)$ was measured at ~ 6 bar (black squares) and 3 bar gas pressure (white squares). Water $D(t)$ data is shown in white circles. $D(t)/D_0$ is plotted against the normalized diffusion length, $b^{-1}\sqrt{D_0 t}$, where b is the bead diameter. The short- t (S/V_p) and long- t (tortuosity) limits for $D(t)/D_0$ are shown by the dashed and solid lines respectively. The curved line extrapolates the long and short- t limits to give an indication of medium- t behavior.

Relevant journal papers during grant period

Measurement of persistence in 1-D diffusion.

G.P. Wong, R.W. Mair, R.L. Walsworth, and D.G. Physical Review Letters **86**, 4156 (2001).

Tortuosity measurement and the effects of finite pulse widths on xenon gas diffusion NMR studies of porous media.

R.W. Mair, M.D. Hürlimann, P.N. Sen, L.M. Schwartz, S. Patz, and R. L. Walsworth, Magnetic Resonance Imaging **19**, 345 (2001).

Novel MRI applications of laser-polarized noble gases.

R.W. Mair and R.L. Walsworth, to appear in Applied Magnetic Resonance (2001).

The narrow pulse approximation and long length scale determination in xenon gas diffusion NMR studies of model porous media.

R.W. Mair, P.N. Sen, M.D. Hürlimann, S. Patz, D.G. Cory, and R.L. Walsworth, submitted to Journal of Magnetic Resonance (2001).

Measuring surface-area-to-volume ratios in soft porous materials using laser-polarized xenon interphase exchange NMR.

J.P. Butler, R.W. Mair, S. Patz, D. Hoffmann, M.I. Hrovat, R.A. Rogers, G.P. Topulos, and R.L. Walsworth, submitted to Physical Review E (2001), preprint cond-mat/0108344.

Relevant conference abstracts during grant period

Novel MRI applications of laser-polarized noble gases.

R.W. Mair and R.L. Walsworth, Proceedings of the Sixth Conference on Magnetic Resonance Microscopy, Nottingham, UK, 2001, p. L-8.

Basic and material science applications of hyperpolarized gases.

R.L. Walsworth, ISMRM Workshop on Limits of Detection in Nuclear Magnetic Resonance, Berkeley, CA, June, 2001.

Multidisciplinary applications of laser-polarized noble gas magnetic resonance.

R.L. Walsworth, 2001 Winter Meeting on the Physics of Quantum Electronics, Snowbird, Utah, January, 2001.

Design and operation of an open human-scale low-field MRI system.

R.L. Walsworth, R.W. Mair, S. Patz, M.I. Hrovat, M. Briggs, F.W. Hersman, and M.B. Leuschner presented at the DAMOP Meeting of the American Physical Society, London, Ontario, 2001.

Design and operation of an open human-scale low field imaging system.

S. Patz, M.I. Hrovat, M. Briggs, M.B. Leuschner, F.W. Hersman, R.W. Mair, and R.L. Walsworth, presented at the 42nd Experimental NMR Conference (ENC), Orlando, FL, 2001.

New applications of xenon diffusion in porous and granular media.

R.W. Mair, M.D. Hurlimann, P.N. Sen, S. Patz, D. Candela, D.G. Cory, and R.L. Walsworth, presented at the 42nd Experimental NMR Conference (ENC), Orlando, FL, 2001.

Research plans for the upcoming year

- Complete testing and optimization of open human-scale low-field MRI system.
- Design and build signal detection coils for human-scale low-field MRI of laser polarized noble gas.
- Obtain low-field NMR images of laser polarized noble gas in phantoms of comparable volume to human lung (~ 30 cm diameter).
- Apply gas diffusion NMR to animal models: both the *ex vivo* and *in vivo* lung of rabbits and/or rats
- Continue detailed studies of gas diffusion NMR in model porous systems.
- Apply xenon interphase exchange NMR to an animal model: the *in vivo* rat lung.

