ULTRAHIGH FIELD NMR AND MRI: SCIENCE AT A CROSSROADS

WORKSHOP REPORT

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I. EXECUTIVE SUMMARY

The workshop "Ultrahigh Field NMR and MRI: Science at Crossroads", initiated by the scientific community and supported by the National Science Foundation, the Department of Energy, and the National Institutes of Health, took place on November 12-13, 2015, in Bethesda, MD, on the NIH campus. The meeting was held to assess the science drivers, technological challenges, prospects for achieving field strengths for NMR and MRI nearly double their current value, and strategies on how to provide ultrahigh field NMR/MRI capabilities to a national user community. For ultrahigh field NMR spectroscopy the utilization of high temperature superconducting materials (HTS) can lead to a new generation of NMR magnets. Similarly, for human MR it is also possible to consider the design and construction of magnets that would nearly double the field strength available today for imaging and magnetic resonance spectroscopy. The agenda of the workshop focused on the following topics:

- **Scientific Opportunities in NMR and MRI**
- **Future Challenges and Barriers for NMR and MRI Science in the U.S.**
- **Low- & High-Temperature Superconducting Magnet Technologies in MRI and NMR**
- **Shared Ultra-high Field NMR Facilities in Europe**
- **Shared High Field NMR Facilities in the U.S.**

Scientific directions of strategic national importance that must rely on UHF MR to reach their realization were compiled. The new science that will be enabled by the UHF technologies extends throughout wide swaths of physics, chemistry, materials science, biology, engineering, environmental, and biomedical sciences. Transformational science initiatives enabled by higher magnetic field instruments span multiple disciplines, with each identified direction being of strategic interest to at least two of the three Federal funding agencies that attended the Workshop. This conclusion is not surprising given the central role of magnetic resonance in the sciences of molecular systems as well as medical sciences. Magnetic resonance, in its spectroscopic (NMR) and imaging (MRI) modalities is the only method that provides an integrated view of molecular structure, dynamics, and functional mechanisms, in a non-destructive and site-specific fashion, often in a single set of experiments. The knowledge of the molecular structure and dynamics is gained at atomic resolution with NMR. Chemistry, sub-millimeter neuroarchitecture, metabolic function and regulation in living organs are enabled by higher magnetic fields than exist today.by MRI and MRS. MR techniques are therefore capable of probing the broadest range of systems, many of which are not approachable by other structural techniques. The main challenge in the sciences of molecular systems is to connect the *in vitro* information to *in vivo* or *in situ* pictures, and NMR and MRI methods working in synergy are uniquely positioned to provide this link.. For this purpose, the highest resolution and the highest sensitivity are required across the board, necessitating the development of UHF magnet technologies and the establishment of an optimized, ancillary infrastructure.

The US scientific community has an urgent need for UHF MR technologies and infrastructure that are required to address a broad range of societally important problems of strategic national interest. This UHF infrastructure is currently lacking in the US, leading to a progressive loss of the US scientific community leadership position in a number of scientific arenas on the international scene.

Prospects for the development and implementation of ultrahigh fields for NMR are strong. Bruker Biospin has announced that they will start to deliver NMR instruments based on low-temperature/high-temperature superconductor (LTS/HTS) magnets at 28 T in late 2017 or early 2018. JEOL Resonance has published high homogeneity NMR spectra in a 24 T LTS/HTS magnet. The US National High Magnetic Field Lab expects to bring a low homogeneity LTS/HTS magnet to field in 2016 at 32 T. The NHMFL also expressed interest in designing, developing and constructing a high homogeneity 32.8 T NMR magnet and the possibility to make copies for other facilities. MIT is developing a 30.4 T NMR magnet. The principal need for the NMR community in the US is the establishment of facilities that can support the highest field NMR instrumentation with availability to national multidiscipline users. The principal need for the MRI and MRS researchers of the nation is the technological development of MRI instruments capable of safe human subject medical science discoveries.

To address the pressing scientific needs and the emerging technological opportunities in the UHF arena, we recommend a strategic roadmap for developing sustainable UHF MR infrastructure for the nation based on the imminent prospects for high field NMR and MRI magnets. The science needs magnetic fields that far exceed those possible with current technologies. Attaining these fields will require a national effort in engineering and materials science to design and develop high fields, high homogeneity and (for MRI) large bore instruments; and such a project was found to be feasible by the workshop participants. Ultrahigh field NMR and MRI instruments will need to be located in facilities that can maintain the instruments at peak operating performance, ensure that they are maximally utilized by the Nation's large scientific user community, for a broad range of important scientific missions that were identified in this Workshop.

II. INTRODUCTION AND CONTEXT

A. Present state of the art in magnetic resonance

Magnetic resonance plays a central role in academic, industrial and medical research. *Nuclear magnetic resonance (NMR)* is widely used for characterizing the structure, chemistry and dynamic properties of new materials, chemicals and pharmaceuticals, in both the liquid and solid phases. NMR also provides detailed functional information on biological macromolecules and their assemblies, *in vitro*, in membranes and even in whole cells. *In vivo, NMR imaging (MRI) and spectroscopy (MRS)* are used for clinical diagnosis and prognosis of disease, for non-invasive studies of human physiology and metabolism in general, and for evaluating brain function, in particular. MRI/S is also a key technology for imaging small organisms at the cellular level, monitoring catalysis in chemical reactors and other scientific areas where non-destructive characterizations of structure and dynamics in complex systems are needed.

At the heart of all the MR methods are strong, stable and homogeneous magnets built from low-temperature superconductors (LTS), which are essential to these experiments. Further developments in NMR/MRI are hampered because the ultimate limit of the attainable field strengths of persistent LTS magnets has now been reached. Fortunately, recent breakthroughs in new high-temperature superconductors (HTS) and hybrid LTS/HTS magnet technologies promise to greatly increase the achievable field strength of NMR magnets and to decrease the operational complexity of high field human MRI infrastructures, thereby enabling new applications at the forefront of modern multidisciplinary research. What is required, however, is a mechanism for the deployment of "ultrahigh field" magnets (above 23.5 tesla for NMR and above 11.7 tesla for MRI) into shared instrumentation facilities across the nation. The US is presently lacking in such a mechanism, and the resulting lack of infrastructure is hurting further progress in MR-based sciences in the US. These deficiencies have tremendously adverse impacts on our ability to engage in cutting-edge science in several areas of strategic national importance –including several that are main foci of NSF, DOE and NIH interests (*vide infra*). Furthermore, the lack of advanced infrastructure in ultrahigh field NMR/MRI in the nation impacts negatively our ability to train the next generation of scientists who will be the future leaders of the US research enterprise.

The NMR equipment market has grown significantly in the years since Nobel prizes were awarded to NMR scientists Richard Ernst (1991), Kurt Wüthrich (2002), Paul Lauterbur and Peter Mansfield (2003). Further progress in NMR and MRI/MRS, however, is confronting limitations inherent to the technology that has been used since the 1970s to build the ultra-stable, ultra-high-resolution magnets – with respect to both stability and homogeneity parameters at sub-ppm levels.[1] Current magnet technology relies on low-

[1]The recent decision by Agilent to exit the NMR and MRI business was due to their declining market share and profitability in the face of strong investments in R&D by their competition, and reflects the importance of continued technological development to NMR and MRI science.

temperature superconductor (LTS) that, as illustrated in **Figure 1**, have reached an ultimate limit of 23.5 tesla (T) –corresponding to 1 GHz proton Larmor frequency. While very efficient at fields <12T, the cost of LTS-based magnets doubles per 5-10% increment above the 15 T level. Further efforts based on the *preconception* that only persistent LTS-based technologies can deliver the field strengths, stabilities and homogeneities needed to perform MR, will result in enormously large and expensive new magnets, whose siting would be limited to very few facilities. This cost issue has already hurt fundamental developments in magnetic resonance-based science in general, and the US MR-based community in particular. Currently, there are a total of fourteen NMR systems worldwide operating at magnetic field strengths of 22.3 – 23.5 T, of which seven are in Europe, four are in Asia and Australia, and only two are in the US. Two additional 23.5 T systems are undergoing installation in Europe (Bayreuth, Germany) and North America (Toronto, Canada). Seven more 25.8-28.2 T NMR instruments have been ordered by European institutions: one at 25.9 T (Zürich, Switzerland), and six at 28.2 T (Florence, Italy; Göttingen, Germany; Utrecht, The Netherlands; München, Germany; Lille, France; and Jülich, Germany). Additionally, three more orders are planned from institutions in Europe- for two 23.5 GHz and one 28.2 T systems. Constraints have also limited the availability of commercial human MRIs, which can be purchased up to only 7 T for clinical and research applications. Currently, the highest field magnets operating for human MRI studies (9.4 T) are located at the University of Chicago and the University of Minnesota (9.4 T and 10.5 T), with 11.7 T systems planned at NIH and Saclay (France), and a proposed system at 14 T in South Korea. Continued development of ever larger and more expensive high field magnet systems is unsustainable, yet scientific progress critically depends on access to higher fields.

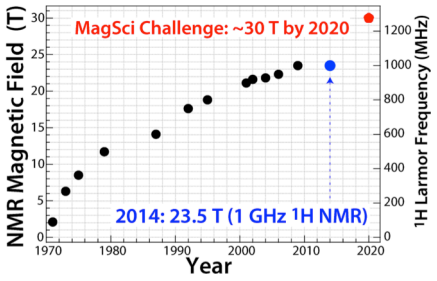

Figure 1: Progress in LTS-based NMR fields, achieved over the last 44 years.

Without exploiting new magnet technologies, the utility of many forms of magnetic resonance – including flagship techniques that have revolutionized chemical, materials, biological and medical sciences - cannot be fully realized. In 2013 two "grand challenges" were issued for which NMR and MRI are of fundamental relevance. One stemmed from the 2013 Report of the National Research Council "Magnetic Field Science in the United States: Current Status and Future Directions". The report compiled by a panel of experts at the request of the National Science Foundation and the Department of Energy [1], called for (1) the US to regain its competitiveness in the field of high resolution NMR by the development and installation of spectrometers based on magnets that approach 30 T by 2020

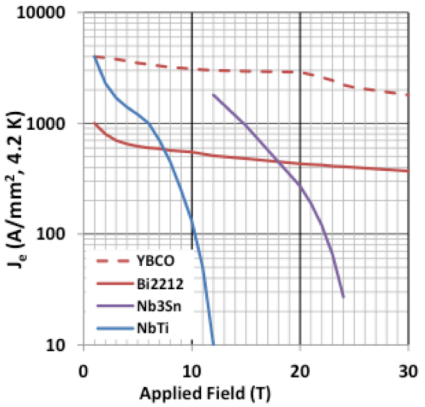

Figure 2: Maximum current density of superconducting wires at 4.2 K as a function of applied magnetic field, contrasting the LTS (blue, purple) vs. the HTS (red) materials.

(**Figure 1**), and (2) development of a human MRI/NMR system for brain research and physiology studies at 20 T. A second grand challenge relates to the BRAIN initiative, which calls for the development of new non-invasive methods for imaging and understanding how the healthy human brain functions and is organized, including the development of advanced MRI systems leading to higher sensitivity and better spatial resolution. *Both of these challenges cannot be adequately addressed if constrained by the "only with persistent LTS-based magnets" preconception*: LTS simply cannot cross the 24 T boundary to deliver the magnetic fields required for further progress in materials and biophysical NMR (**Figure 2**), and 20 T human-capable MRI systems relying on LTS technologies would lead to magnets weighing in excess of ≈400 tons. Moreover, the costs associated with developing these ultrahigh field magnets and the understandable reticence of commercial vendors to assume the associated risks, are prohibiting the development of new technologies that meet these challenges. Fortunately, recent progress in new conductor and magnet technology now presents the opportunity to overcome the limitations of LTS wires (*vide infra*).

B. 2015 Workshop "Ultrahigh Field NMR and MRI: Science at Crossroads"

Objectives. Having recognized an urgent need to move forward at this time to address the pressing needs of the scientific community that require new generation of ultrahigh field MR technologies and infrastructure in the US, a workshop "Ultrahigh Field NMR and MRI: Science at Crossroads" was initiated by the scientific community. The workshop, supported by the National Science Foundation, the Department of Energy, and the National Institutes of Health, took place on November 12-13, 2015, in Bethesda, MD, on the NIH campus.[2]

The specific objectives of the workshop were:

Objective 1. To establish the science drivers for which ultrahigh field magnetic resonance capabilities are essential, and which will lead to transformative applications in strategic areas of national interest.

Objective 2. To discuss the opportunities for the development of novel, cost-effective ultrahigh field NMR and MRI magnets on the basis of HTS and serial LTS/HTS technologies.

Objective 3. To develop a consensus among scientists and agencies regarding the optimal roadmap for the development of ultrahigh magnetic field technologies, and for enabling the acquisition and installation of such instrumentation in national and regional shared user facilities in the United States.

[2] Prior to this workshop a National Research Council report entitled "Current Status and Future Direction of High Magnetic Field Science in the United States" made observations and recommendations consistent with the findings and directions for future strategies concluded by the workshop participants (1),

Format. The meeting brought together scientists from academia, industry, and national laboratories who develop and use ultrahigh field (UHF) technologies and applications, as well as Program Officers from NSF, DoE, and NIH (for the list of participants, see **Appendix B**). Both the science opportunities and the status of high magnetic field technologies were reviewed. The workshop was comprised of plenary and breakout sessions, featuring talks and round table brain-storming sessions, to discuss key technological issues and applications to a broad range of problems, and to establish the basis for developing a roadmap for the development of ultrahigh field technologies that will enable transformative science. The meeting was highly interactive with ample opportunities for everyone to actively participate. In preparation for the meeting, the participants worked in nine task forces, to identify the key issues to be discussed at the workshop. These reports are presented on the Workshop's website (http://sites.udel.edu/uhf-nmr-workshop/). A blueprint for the development of a roadmap that could enable UHF NMR/MRI science in the US is presented in **Appendix A**.

The workshop materials, including the presentation slides and abstracts, can be found on the workshop's website: http://sites.udel.edu/uhf-nmr-workshop/

Outcomes. The workshop's aim was to catalyze the development of a long-term UHF magnetic resonance science program in the United States. Major outcomes of the workshop included a summary of the new scientific frontiers that would be opened by the advent of UHF NMR and MRI, and a summary of the technological breakthroughs that would be needed to enable these. These summaries are presented in Section II. A strategy to make available to the broad scientific community such UHF facilities with the resources to address these crucial high field scientific drivers is underway. To further enable this vision we will seek feedback from the broader scientific community, encompassing both MR experts and non-MR scientists. Key sections of this final roadmap should include i) the transformational science that would arise from ultrahigh magnetic field MR; ii) the development of new technologies, including new HTS materials, that are needed to enable sustainable production and operation of UHF NMR and MRI instruments; iii) specific recommendations for the sustainable models of shared UHF MR centers in the US, including alternative concepts for collaboration between the federal agencies, national laboratories, and industry to enable advancement of technologies and support of proposed facilities. It is our intent to broadly disseminate this final roadmap document throughout the US scientific community and its various funding agencies (including but not limited to DoE, NIH, NSF, DoD), in the expectation of enabling the realization of its recommendations within the coming years.

III. OUTCOME OF THE UHF NMR/MRI WORKSHOP: UHF NMR/MRI IN THE UNITED STATES - ENABLING TRANSFORMATIONAL SCIENCE

A. UHF MR: Transformational science drivers

A major focus of the meeting was, through presentations and roundtable/breakout discussions, to compile scientific directions of strategic national importance, which must rely on UHF MR to reach their realization. The participants concluded that the new science that will be enabled by the UHF technologies extends throughout wide swaths of physics, chemistry, materials science, biology, engineering, biogeochemistry, and biomedical sciences. These transformational science programs span multiple disciplines, with each identified direction being of strategic interest to at least two of the three Federal funding agencies that attended the Workshop. This conclusion is not surprising, given the central role of magnetic resonance in the molecular systems sciences. Magnetic resonance, in its spectroscopic (NMR) and imaging (MRI) modalities, is the only method that provides an integrated view of static structure, dynamics, and molecular mechanisms, in a non-destructive and site-specific fashion, often in a single set of experiments. The knowledge of the molecular structure and dynamics are gained at atomic resolution (NMR) or at micrometer resolution (MRI). MR techniques are capable of probing the broadest range of systems, many of which are intractable by other structural techniques. The main challenge in the molecular systems sciences is to connect the *in vitro* information to *in vivo* or *in situ* pictures, and magnetic resonance methods are uniquely positioned to provide this link. For this purpose, the highest resolution and the highest sensitivity are required across the board, necessitating the development and application of UHF technologies.

Key examples of scientific directions requiring UHF MR technologies and infrastructures are presented below. The workshop participants concluded that gains in sensitivity, resolution, and information content are highly nonlinear with the magnetic field strength, and ultrahigh fields will enable fundamental investigations of emergent phenomena not accessible with the current technologies. Additional directions can be found in the presentation and discussion slides on the workshop's website: http://sites.udel.edu/uhf-nmr-workshop/2015/08/10/program/.

Biomedical sciences

Structural, molecular, cell biology

- *Structural biology of medically and fundamentally important biomacromolecular systems:*
    - *Understanding the structure and dynamics of integral and peripheral membrane proteins (including GPCRs) in native-like environments.* Through the characterization of native structures, the characterization of dynamics and conformational exchange, unique mechanistic insights and understanding of these highly important drug targets will be

obtained. Membrane proteins represent the majority of all drug targets, that are typically undercharacterized and often mischaracterized, such as multidrug transporters targeted by antimicrobials, and receptors targeted by CNS drugs. To understand the chemistry conducted by these important proteins, they need to be studied in the context of native-like and native membranes, and these analyses will be enabled by dramatic increases in resolution and sensitivity obtained at high magnetic fields.

- *Understanding the nature of heterogeneous noncrystalline biological assemblies involved in neurodegeneration and pathogenesis,* such as i) amyloid fibers and oligomeric states that are critical for our understanding of Alzheimer's and related diseases; ii) multicomponent assemblies that constitute viral and bacterial pathogens and that are critical to our understanding of infectious diseases; and iii) molecular machines and motor protein assemblies in the context of intracellular trafficking that are critical for our understanding of numerous neurodegenerative disorders. These systems need the dramatically improved resolution and sensitivity from high field magnets for full characterization.
- *Intrinsically disordered biomacromolecular systems, including low-population transient states involved in catalysis, molecular recognition and metabolic regulatory systems*– a new frontier where only NMR is capable of characterizing nascent structure. Spectral dispersion provided by high magnetic fields is critical for this research.
- *As biologics play an increasingly important role*, there is a pressing need in drug development to better resolve the *complex spectra of intact monoclonal antibodies and other large proteins, RNA, and their complexes*, both as a means for validating manufacturing processes but also for characterizing interaction of these ligands with their large targets, both structurally and dynamically. Spectral dispersion attained at high magnetic fields is critical for the characterization of these systems.
- *Pleiomorphic ensembles (membraneless cellular bodies)* both *in vitro* and in intact cells. These systems are particularly challenging because of disorder (both spatial and temporal) and complexity (multiple components). The phenomenon of liquid-liquid phase separation that drives the formation of these ensembles is opening completely new areas of cell biology and biophysics. Ultrahigh magnetic fields are needed to provide resolution and sensitivity for investigating these systems.
- *Biomolecules that cannot be investigated at high concentrations due to limited solubility, availability or aggregation.* Many proteins and other biomolecules that have "sticky" regions fall into this category. These systems require greatly improved sensitivity and resolution that will be afforded by high field magnets.

- *Metabolomics and in-cell imaging and spectroscopy* are a rapidly expanding frontier in biochemical research*:* the biggest payoffs are expected in this area where sensitivity and resolution directly enhance the ability to quantify metabolic changes and identify intracellular processes. Particular breakthroughs are anticipated in the field of *personalized or precision medicine*, where metabolite detection will be done in the human body, by integrated NMR and MRI, for diagnostics or analysis of drug effects.
- *Bioinorganic chemistry and chemical biology of metallobiomolecules and pharmaceuticals* through measurements of previously inaccessible quadrupolar nuclei. These are critical for studying i) studying physiological processes or for identifying metal binding sites and protonation states in biomolecules; ii) structural analysis of pharmaceutical polymorphs. The use of ultra high magnetic fields enables quadrupolar spectroscopy for many of such systems. Particularly impressive gains are expected for the measurements of rare but biologically essential nuclei, such as ^{43}Ca, ^{67}Zn, ^{25}Mg, ^{17}O, ^{33}S, $^{37/39}$Cl, $^{39/41}$K as well as for other half-integer quadrupolar transition metals.

Physiology, Brain And Developmental Biology

- *Major increases in field strengths will enable unprecedented resolution for human imaging, including*
  - Laminar and columnar resolved fMRI over large regions of cortex and imaging methods for neuronal fiber tracking will enable definition of the range of normal architecture in the human brain as a basis for understanding the architectures associated with: autism, affective disorders, behavioral disorders, dyslexia, epilepsies, learning disorders, and schizophrenia.
  - Increase in resolution and sensitivity will enable functional mapping of the neuronal connectivity of the living human brain during sensory, motor, and cognitive activities.
  - Brain development in primates and anatomical development in embryology can be realized at sub-millimeter resolutions.
  - *In vivo* and sequential brain studies in concussion, Alzheimer's disease, and dementias involving protein aggregates are enabled by susceptibility contrast increases with high field.
  - Imaging of brain stem nuclei; cortical structure in normal brain and disease (MS, epilepsy); structural changes with function and dysfunction.
  - Cardiac and body imaging at unprecedented mesoscopic resolution and speed in large animal models and humans to enable new mechanistic insights into cardiovascular diseases which are the leading cause of death in the nation.
  - New contrasts that will arise at UHF and which will enable the distinction among currently orphaned pathologies and diseases as a key link to personalized medicine.

- *Major increases in sensitivity, spectral dispersion, and relaxation parameter changes with field increases, will allow us to determine*
  - Regional concentrations of the entire major bioenergetic phosphorous molecules, and the relevant biochemical kinetics evaluated using chemical exchange saturation transfer – particularly of amide protons.
  - Small molecules associated with aberrant human behavior, including serine, glycine, gamma-aminobutyric acid, dopamine and possibly folic acid. These will become amenable at less than 0.5 mM concentrations.
  - The action of Na^+, K^+ ATPase [NKA], the brain's most vital enzyme, will become accessible to imaging at less than 1 mm resolution in the human brain. This will be feasible by dynamic contrast enhancement and measurements of mean intracellular water molecule lifetimes, related to the enzyme's activity.
- *Low-gamma and quadrupolar nuclei MRI and MRS will become feasible at high fields*
  - Because of the reduced quadrupolar coupling at high magnetic fields, biological chemistry at oxygen and sodium sites rather than at carbon sites will be enabled using ^{17}O and ^{23}Na.
  - Intracellular vs. extracellular concentrations of sodium and potassium can be evaluated on a regional basis in the living brain and other human anatomy to unravel the mechanisms triggering cardiovascular, metabolic and environmental diseases heavily inflicting our society.
  - Quantitative ^{23}Na MRI has been implemented in a number of laboratories around the world to measure the spatial distribution of tissue sodium concentration (TSC) to derive the regional cell volume fraction (CVF), a measure of cell density, in a number of tissues. Such bioscales (TSC, CVF) are tightly regulated metabolic parameters with small biological variations that are sensitive to pathological processes that compromise brain tissue viability and function. Changes in TSC in the human brain can monitor therapies that attempt to salvage tissue (e.g., stroke) or selectively kill tissue (e.g., brain tumors). The kidney functions to minimize water loss by concentrating urine by osmosis based on sodium concentration gradients in the renal medulla. Loss of these sodium gradients reflects renal dysfunction. The loss of elasticity of cartilage is due to loss of the negative charge from its component proteoglycans. Sodium is the counter charge to the negative charge of these macromolecules and so sodium concentration changes quantify the loss of proteoglycans in the earliest stages of degenerative cartilage disease. The accurate quantification of these bioscales with minimal partial volume errors requires spatial resolutions of better than 2x2x2mm3, a goal that can only be achieved at UHF (>9.4 Tesla) in acceptable imaging times for humans (<10 minutes).
- *B_0 and B_1 field distortions at high MR proton frequencies will enable imaging the electrical properties of the brain, leading to hitherto untapped sources of contrast and information.*

- Status of electrical permittivity and relations to Na and K gradients in normal and abnormal human behavior can be best evaluated at high fields/frequencies.

Chemistry, Catalysis, Materials Sciences

- *Characterization of surfaces as opposed to bulk samples*, enabled by the large gains in inherent sensitivity and resolution through use of ultrahigh fields. This could lead to particular improvements in characterization of catalytic surfaces, with ample implications in the chemical and energy-related industries.
- *Characterization of reactive sites in catalysts, energy-related, and structural materials,* enabled through the enhanced sensitivity and resolution of NMR signals from quadrupolar nuclei with non-integer-spin at high magnetic fields:
  - Solid-acid sites in aluminosilicate zeolites or silica-alumina heterogeneous catalysts to improve their activities or selectivities for processing petroleum, natural gas, or biomass-derived into diverse hydrocarbon products. Enhanced sensitivity and resolution is expected to enable examination of materials (catalysts) with minute concentrations of sites and/or much smaller surface areas than currently possible;
  - Controlled hydration of aluminosilicate cementious materials with improved compositions and structural properties under extreme conditions (deep water oil wells, geothermal wells), with reduced carbon footprints, or in support of modeling analyses to predict cement setting and properties;
  - Metal coordination environments in metal oxides, such as ceramics, semiconductors, ion-conducting solids, and dielectric materials, including in thin films for device applications;
  - Metal chalcogenide (sulfides, selenides) in semiconductors and opto-electronic materials;
  - Complex metal hydrides for energy storage.
- *Characterization of paramagnetically displaced NMR signals in catalysts, energy-related, and structural materials,* enabled by enhanced resolution and sensitivity at high magnetic fields:
  - Rare-earth-doped solid-state phosphor materials for solid-state lighting applications (in conjunction with fast MAS);
  - Energy-storage materials: super-capacitors; batteries;
  - Fe-containing cementious materials;
  - Non-precious-metal catalysts containing Ni, Co, Mn, Fe;
- *Characterization of low-gamma or dilute nuclei sites in biological and inorganic materials,* enabled by enhanced sensitivity and resolution at high magnetic fields:
  - ^{43}Ca NMR of biominerals, bone and teeth, and cementious materials;

- ^{33}S NMR studies of deactivation processes in heterogeneous catalysts, hydrodesulfurization of fossil fuels;
- ^{15}N NMR of nitrides, such as GaN solid-state lighting materials, ceramics, or N-functionalized porous carbons for electrochemical devices;
- ^{17}O NMR of heterogeneous catalysts, solid-oxide fuel cell materials, battery materials, and oxide semiconductors
- ^{13}C and ^{25}Mg NMR of carbon sequestration materials;
- Lanthanide inclusion in glasses and lasing materials;
- Membrane materials for water purification, osmosis, desalination;
- ^{25}Mg NMR of batteries, cements, ceramics, and metal organic frameworks (MOFs);
- ^{239}Pu NMR of oxides and related radioactive materials;
- ^{1}H-detected 2D HETCOR spectroscopy involving low-gamma nuclei: combining increased sensitivity with excellent ^{1}H resolution under ultrafast MAS would lead to tremendous opportunities in catalysis, biorenewables, nanocomposites, etc.

- *In situ UHF NMR measurements at elevated temperatures or pressures will enable to monitor challenging material compositions and structures:*
  - During hydrothermal syntheses of inorganic materials: catalysts, cements, ceramics;
  - Of heterogeneous catalysts under industrially realistic operating conditions: hydrocarbon conversion, automotive emission control, etc;
  - Of energy conversion and storage processes, including batteries, fuel cells, photovoltaic materials complex metal hydrides, batteries.

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry

- *UHF will open new frontiers in bioengineering and biomaterials, including studies of:*
  - Biomineralization processes;
  - Biofilm formation, compositions, and structures;
  - Complex carbohydrates in energy-rich plant cell walls and biotechnology relevant microorganisms;
  - Membrane‐bound protein‐protein complexes by solution and solid‐state NMR for structure-function relations of proteins at membrane interfaces, in synthetic host materials, and metabolism of drugs by enzymes;
  - Structure-function relations of proteins and inorganic species in bone matrices and their roles in bone diseases;
  - Influences of amyloid inhibitors on formation of AD brain plaques.
  - Structural studies that will help the deconstruction of lignocelluloses in plant biomasses.

- *UHF MR will also serve environmental engineering and biogeochemistry:*
    - Soil-mineral matrices;
    - Transport of dilute metal ions or organic pollutants in soils;
    - Automotive emissions catalysts.

The workshop participants stressed the fact that transformational science requires integration of NMR and MRI, to gain unprecedented new insights into systems molecular sciences. Integration with other experimental and computational techniques is also deemed to be a "must" in modern multidisciplinary research. Among the multiple examples of the synergies between NMR and MRI that were presented at the meeting, a case worth highlighting is provided by **studies of neurodegeneration**. Alzheimer's, Parkinson's and Lewy body dementia, traumatic brain injury, and age-related macular degeneration have in common the conversion of proteins from soluble to insoluble states. UHF solution and solid-state NMR and human brain and eye MRI can converge to yield an understanding that leads to possible treatment of these diseases. Indeed, ***NMR-based*** molecular structure studies, in solution and in the solid state, allow for the characterization of important proteins including **Intrinsically Disordered Proteins**, which are considered to be of central importance to neurodegenerative disorders. These biomolecules cannot be studied by most analytic techniques, other than NMR. The utmost sensitivity and resolution afforded by high magnetic fields is required to overcome the narrow chemical shift dispersion and the need for low concentrations to limit aggregation. At the same time, ***MRI*** is uniquely poised to characterize alterations in brain neuronal architecture and inflammation associated with neurodegeneration. **UHF beyond 7 T MRI is expected to detect protein aggregates, including amyloid and tau protein, associated with dementias and brain trauma (e.g. concussion)** because of the magnetic susceptibility contrast associated with aggregates less than 100 micrometers. The same mechanism should prove useful for distinguishing these widespread neurodegenerative disorders from less common ones.

The participants stressed the unprecedented breadth of contemporary scientific directions that require MR-based UHF technologies, and the new synergies that such breakthroughs in UHFs will promote between NMR and MRI. The participants were also gravely concerned that the US was losing its competitiveness in many of the scientific areas described by the NMR science drivers and that urgent action is needed to restore the US leadership in these scientific arenas by investing in high field NMR/MRI instrumentation.

B. UHF MR: New technologies and their development

Scientists from NHMFL (Tallahassee, FL), RIKEN (Yokohama, Japan), Jastec (Kobe, Japan), MIT (Cambridge, MA), and Bruker BioSpin (Karlsruhe, Germany) presented the recent developments of UHF magnets to 30.5 T [2] (1.3 GHz ^{1}H Larmor frequency). These ultrahigh magnetic fields are required to

enable transformational science discussed in the previous section. To attain such fields in the NMR magnets, the participants concluded that high-temperature superconducting (HTS) materials are required. It was discussed that limitations in scientific advances can be overcome by recent developments such as the first test-coils operating in a stable superconducting state at a magnetic field ≥33 T [3,4] and the first demonstrations of high-stability/high-resolution multidimensional protein NMR spectra based on a non-persistent superconducting arrangement [5,6]. At the core of these two achievements is the development of new HTS materials by scientists in the US and elsewhere into practical, high-strength, long-length conductors capable of operating at fields well above 30 T. While HTS materials have been known since 1986, earlier versions had insufficient strength and/or current-density, or required impractical manufacturing processes that precluded their use in ultra-high-field magnets. Three new conductors have emerged in recent years (2007 SuperPower REBCO tape with 600 MPa strength [7], 2012 NHMFL over-pressure-processed isotropic Bi2212 [8], and 2014 Sumitomo Ni-Cr-reinforced Bi2223 [9]). The incorporation of HTS materials together with LTS materials into actively stabilized LTS/HTS duplex designs operating in non-persistent mode promise to lead to a number of important breakthroughs that can affect the long-term future of magnetic resonance. The first of these developments in ultra-high field magnets is best exemplified by a 1.3-GHz NMR magnet composed of an LTS 500-MHz magnet and an 800-MHz REBCO insert currently funded by NIH and a NbTi/$NbSn_3$/YBCO user magnet, funded by NSF (DMR 0923070). This 32-T all-superconducting magnet is being constructed by NHMFL scientists *via* the NHMFL user program. By combining five LTS coils with two HTS coils in a serial, concentric assembly, this magnet will deliver in 2016 a 36% peak field increase over currently existing all-superconducting magnets [10]. The second breakthrough is NMR-quality test-coils using HTS materials. This was first demonstrated by the Japanese ultrahigh field NMR effort in 2009 utilizing LTS and HTS coils at 9.4 and 2.3 T, respectively, running in an ultrastabilized mode that delivered a conventional set of 500 MHz high-resolution biomolecular NMR spectra despite running non-persistently [4,5]. In recent months the Japanese group reached 1020 MHz (23.9 T) with a similar test-coil system [11]. All these features can enable a US-based pre-eminence in HTS-based magnet technologies – a pre-eminence which so far has not translated into state-of-the-art ultrahigh field US facilities in either NMR or MRI.

Developments in HTS materials provide compelling arguments for abandoning conventional magnet preconceptions, and rising to the two grand challenges mentioned earlier by setting a roadmap for the future of ultrahigh field NMR and MRI magnets based on serial LTS/HTS magnet technologies. Given the current state of the art in HTS materials and coils, an appropriate team of experts can develop magnets with sufficient homogeneity and stability for performing NMR as well as microimaging experiments at fields in excess of 30 T and human MRI studies in fields of >14 T. Moreover, by developing the common technologies needed to construct such magnets and placing the resulting systems at the service of the

NMR, microimaging and MRI communities, such a project would cut the Gordian Knot currently holding back those disciplines, which rely on higher fields for continuing progress.

A parallel approach was presented at the workshop by the Bruker Biospin scientists, who are developing ultrastable commercial magnets at 28.1 T using mostly LTS materials, and a small HTS insert. The first of such magnets is projected to be deployed in Europe in late 2017 or early 2018.

Additional discussion points are summarized below.

Magnets (NMR)

- Contemporary high-resolution NMR spectrometers are available up to ^{1}H frequencies of 1 GHz, based on LTS wire technologies delivering fields of up to 23.5T. LTS technologies, however, cannot be used beyond this threshold; from 23.5 T onwards, the inclusion of HTS inside the inner windings of the magnet coil becomes a necessity. This joint LTS/HTS technology is shared by the numerous development projects currently in place towards a 1.3 GHz NMR. Achievement of 30.5 T fields is a technically challenging and costly process, it is a feasible one. The ongoing development of an NIH-funded 1.3-GHz (30.5 T) high-resolution LTS/HTS NMR magnet at MIT as well as an all-superconductor 32T LTS/HTS magnet with sub-ppt homogeneity at the US NHMFL, predicts that the development of a 32.8T, 1.4 GHz NMR-compatible magnet is also within reach.
- While technically feasible, it is likely that the first such UHF NMR magnet made will involve a number of compromises, of the kind that subsequent magnets will strive to minimize. Important aspects to overcome in near future design refinements include magnet size (a parameter where, as mentioned, the LTS/HTS ratio becomes crucial), stray field size, and cryogenic consumption. In the case of a powered LTS/HTS magnet, field stability and homogeneity might need further optimization.
- Given the uncertainties mentioned above, it would certainly be productive to have a multi-group effort working independently on alternative technologies, but sharing know-hows towards the achievement of the same (or similar) UHF NMR goal. In the case of the HTS research this multiplicity of projects might be more costly at the beginning, but would eventually pay off by leading to optimized materials and technologies to be used in repeated platforms. In this respect it would be important to support three or more parallel material technologies –in particular those based on REBCO, Bi2212 and Bi2223 conductors– as well as on magnets of different quenching/insulation designs. This would help cement a solid basis for UHF NMR magnet developments for the next 10+ years, opening up the optimum strategies and timelines –not only for high resolution magnets in the 1.2/1.3 GHz range, but for NMR systems operating at 2 GHz and beyond. As part of this process, choosing the best approach for the LTS/HTS combination is the correct strategy before embarking on one or two NMR construction designs.

Magnets (MRI)

- Moving beyond 11.7 T will require adopting higher field conductors, primarily Nb_3Sn, as well as HTS-based conductors relying on either ReBCO, Bi2212 or Bi2223 superconductors. These may have to be incorporated into cables as well. A staged development program would therefore suit best an UHF MRI magnet development program, with intermediate steps in field and bore size. The challenge in pursuing the incremental steps in field with a bore size to accommodate the human head and body are not linear, given that the stored energy and stresses in magnets scale with square of the magnetic field.

Probes (NMR)

Maximizing the performance of the RF probeheads in solution and solid-state NMR experiments is crucial and highly dependent on the RF frequencies and the specific experiments to be performed. Probes play two critical roles in NMR. They first excite the signal by impressing multiple strong (for solids, ~20 G) and spatially very uniform RF magnetic fields over the sample. These fields are typically applied at three or four frequencies as much as a decade apart. In this process, the probe's electronic components may be required to withstand several thousand volts. A few microseconds after the strong fields are switched off, the probe then detects efficiently small NMR signals, which are then passed to a low-noise preamplifier. For RF decoupling, irradiation continues at one frequency while detection occurs at another. The probe must separate the very strong from the very weak magnetic fields. Mechanical systems in RF probeheads are also critical, in that they control the sample temperature and provide for spinning the sample. Without optimized probes, spectroscopists cannot take full advantage of the magnetic field strength and can neither control the experimental conditions nor accurately detect the signals that arise. Representative examples of probe technologies that are envisioned to be important in the context of ultrahigh magnetic field applications include:

- **^{1}H solution NMR probes, including low-loss cryoprobes** - At the lower end of the anticipated field range to be generated by HTS magnets, the sensitivity is already limited by loss in conductive samples. It is currently not widely appreciated that sensitivity is limited by dielectric loss in commonly used polar organic solvents. As magnets approach 30 T, current probe designs will produce electromagnetic standing waves in standard 5-mm aqueous samples that will compromise RF field uniformity. The answer may lie in adapting the coil technologies developed for high field MRI, such as quadrature birdcage resonators and array coils, to microfabrication techniques.
- **Cryoprobes optimized for heteronuclear detection, and microsample probes for solution NMR** - High field is a great opportunity for heteronucleus detection and microsample detection,

because in these cases the sensitivity is not generally limited by sample loss, and so the scaling with field strength is closer to the theoretical $B_0^{7/4}$ for spin 1/2 isotopes. Direct detection of ^{13}C has advantages in mixture analysis due its large chemical shift dispersion, and is valuable for metabolomics and in particular for tracer studies. At high field, indirect detection probes experience low sensitivity with aqueous samples or even polar organic solvents. The degradation is more significant with cryogenic coils and electronics, since the loss not only reduces Q but also increases the system noise temperature. It has been shown that distorting the cross section of the sample tube from a circle into a slab or oval with its long axis parallel to the B_1 field tends to reduce ^1H loading effects and increase sensitivity. As fields increase and the shaped sample is no longer enough, it may be effective to borrow probe designs from high field MRI and to implement quadrature or even array configurations.

- **Probes optimized for detection of quadrupolar nuclei in solid-state NMR** – Ultrahigh magnetic fields will have major impact on the detection of quadrupolar nuclei, which comprise two thirds of the Periodic Table and are found in a wide variety of natural and man made materials. To realize full benefits of UHF, specialized probes designed for detection of a broad range of quadrupoles under static and moderate-frequency MAS conditions is required.
- **Ultrafast magic-angle-spinning (MAS) NMR probes** optimized for heteronuclear detection- Spinning frequencies >60 kHz is a key new capability with a broad range of applications to materials and biological systems. This requires the development of probes that enable more routine use, including sample packing, stable variable temperature (of significant range, -50 to +50 ºC as a minimum), with full HX and HXY tuning ranges.
- **Probes optimized for ^1H detection in solid-state NMR** - A major opportunity is high-resolution ^1H-detected solid state NMR of large biomolecules. This technique requires ultra-high magnetic fields and ultrafast (>100 kHz) sample rotation. Considerable progress has already been made on micro-MAS spinners, but continued development to enhance stability and improve sample handling is required.
- **Low temperature probes for LN_2 and < 80 K for MAS NMR -** Many MAS spectra of proteins and nucleic acids are missing lines in the spectra due to "dynamic processes" which interfere with the ^1H decoupling. Thus, low temperature spectroscopy provides access to these regions of proteins. At the moment low temperature probes operating to 100 K are commercially available. Operating at lower temperature provides opportunities for higher sensitivity because of larger Boltzmann factors and also DNP. Two groups have recently described closed cycle recirculation systems for these experiments. It is important that they be made commercially available.
- **High-frequency and DNP-compatible oriented-samples probes for membrane research -** A strategy to use routinely DNP with oriented samples and availability of commercial probes would be

a game changer, particularly at UHF, where dramatic sensitivity and resolution gains are anticipated.

- **Microimaging UHF NMR probes for characterizations of energy-storage materials (*in situ* batteries, super-capacitors, water filtration polymers) -** Ultrahigh magnetic fields will enable detection of signals from quadrupolar nuclei and those displaced paramagnetically in energy-storage materials, through dramatically enhanced sensitivity and resolution. To realize full potential for *in situ* characterization of these materials, microimaging probes are required to visualize structural changes in a spatially- and temporally-resolved manner.
- **High-frequency sources for NMR** - As NMR moves into the microwave "L band" it is possible to take advantage of many advances in electronics technology developed for military and communications purposes. In particular, the continued improvement in high frequency RF power transistors utilizing GaAs and more recently GaN technology is improving the performance (the noise figure and linearity) and reducing the cost and size of ^{1}H NMR power amplifiers in the 1 – 2 GHz range.

Microwave sources for DNP NMR at ≥1.2 GHz

Dynamic nuclear polarization (DNP) is an increasingly fundamental component of solid-state NMR research, which has particular promise as the discipline moves into UHF research. In particular, with the recent discovery of Overhauser effects in insulators it appears that DNP will function more efficiently at higher fields. The three possible microwave sources for DNP at **≥**1200 MHz / 789 GHz consists of (1) diodes, (2) extended interaction klystrons (EIKs) operating as oscillators and (3) gyrotrons also operating as oscillators. These platforms should be further investigated; so should be the development of gyro-amplifiers so that pulsed DNP experiments can be performed at these fields.

- At the moment diodes do not have sufficient power above 95 GHz to be useful for DNP except possibly at ~4.2 K and using a high Q resonator.
- Currently EIK's are appearing that operate at 263 GHz / 400 MHz but because of the small size of the slow wave structure they currently do not operate at higher 395 GHz / 600 MHz or higher. However, as technology evolves this situation may change.
- Thus, at the moment the only source that can supply >20 watts at the ~789 GHz needed for 1.2 GHz NMR investigations, is the gyrotron. Presently oscillators are operating in second harmonic mode at 527 GHz. The challenge would be to develop an oscillator operating in 3rd harmonic to reduce the cost of adding DNP to an existing system.
- Pulsed DNP experiments in principle circumvent the ω_0^{-1} or ω_0^{-2} dependence of the cross and solid effects, respectively. Thus, the development of amplifiers operating is an exciting new area for the development of DNP.

Gradients (MRI)

- MRI is currently running at or near the physiological limit imposed by peripheral nerve stimulation threshold limits; a major problem will be to significantly speed up EPI encoding in light of the biological limits. Still, the developments of ultrastrong gradients associated with the Human Connectome project can provide solutions to this limitation.

RF Rx Technology (MRI)

- Parallel receiver (Rx) technology is a relatively well understood problem. Arrays around between 64 and 128 channels are practical and doable without major hurdles.

RF Tx Technology (MRI)

- While initially considered a major hurdle at UHFs, it is now agreed that parallel transmit (Tx) can provide good coverage and uniform excitation –at least in brain and musculoskeletal studies– well beyond 7 T. We need more analysis of high channel Tx arrays for brain MRI at >14T. Parallel transmit will likely be mandatory for good excitation homogeneity. Preliminary studies suggest conventional pTx will work. Body heating temperature constraints will dictate for pulse sequence designs and useful coil congigurations.
- Much useful work can be done with low-SAR sequences.
- On-coil amplification may be important as an enabling technology; safety issues will be one of the major hurdles for some of the applications.

Pulse sequences for the quantitative mapping of small molecules in the human brain

- UHF magnetic resonance spectroscopy *in vivo* has the potentials for detection and mapping of molecules involved in brain energetic as well as essential neuroreceptor pathways and bioamine pathways. This detection of crucial metabolites will be facilitated both when targeting them by direct spectroscopic (MRS) avenues, as well as by indirect CEST/MT-based measurements benefiting from the UHFs.

Motion mitigation/correction (MRI)

- As UHFs will enable functional and anatomic studies approaching 0.1 mm resolutions, patient motion could become a large issue. We need improved real-time feedback or other approaches.

Acquisition strategies which minimize the biological hemodynamic spatial response in fMRI studies

- As fields increase and spatial resolution improves, new functional MRI opportunities will arise that exceed the localization limits of brain activation currently provided by hemodynamic fMRI means (BOLD, CBF, CBV etc.). Questions arose as what will be the new contrast fMRI mechanisms arising at >14T fields, and what will be their resolution limits. Judging from pre-clinical studies, it is likely that new contrast agents going beyond the T_2* window opened by the BOLD effect will open, including diffusion, T_2, T_1 and perfusion mechanisms changing the observable MR signal.
- Equally important will be the search for new functional markers of cognitive activities, emerging as the fields increase substantially past 7T.

Biological effects of UHF MRI

- While detrimental biological effects associated with the exposure of humans to fields beyond 9.4 T have not been observed, studies of animal and human exposure to fields in excess of 12 T will need to be undertaken to insure safety of large animal and human studies, though no harmful effects have been observed in small animal exposures up to 21.1 T. This can be carried out at facilities with available magnets tailored for relatively large animal studies (dogs, pigs); low-homogeneity ≥13 T field facilities also exist, where humans could be accommodated and the effects of static and/or slowly changing magnetic fields be assessed.
- Additional considerations to be assessed in UHF human studies relate to safety and physiological effects associated by pulsing gradients and RF at the high fields and high frequencies to be involved.

Additional information can be found in the presentation and discussion slides on the workshop's website: http://sites.udel.edu/uhf-nmr-workshop/2015/08/10/program/.

C. UHF MR: Instrument deployment and funding mechanisms, shared facilities infrastructure

It was the consensus of the Workshop's participants that a successful implementation of UHF MR technologies for enabling next generation transformational science will require establishing sustainable shared centers that will house UHF instrumentation and which will provide support for users, personnel, instrumentation, and physical infrastructure. At the workshop, the participants discussed extensively the requirements and models for such shared facilities. Two leaders of European ultrahigh field NMR centers, Drs. Lucia Banci and Lyndon Emsley, shared the highly successful models that are implemented by the European Union in such facilities. The directors of shared UHF NMR facilities in the US outlined the current models used in their centers. At the brainstorming discussion sessions current challenges and key

prerequisites for the development of sustainable UHF infrastructure were outlined. These are summarized below.

Models for shared UHF facilities in the US

The establishment is needed for a sufficient number of National High Field NMR & MRI Facilities that develop enabling leading edge technologies in a broad range of science, to take optimal advantage of ultrahigh magnetic fields and make them available to broad scientific communities throughout the US.

- ✓ These facilities will have state of the art commercial instrumentation as well as the ability to develop instrumentation for specific needs at the cutting edge of spectroscopy, imaging and science. There is a great deal of room for these developments especially in an environment in which there is only one major NMR spectrometer manufacturer. In addition to probes, field stabilization technology and novel field shimming capabilities may be required, the development of field gradient technology is also going to be necessary.
- ✓ A single portal for access to the high field NMR/MRI facilities is suggested so that researchers can choose the best facility for their research needs.
- ✓ These facilities will serve the entire high field NMR spectroscopy community in the US, much of it through remote access. While remote access works quite well today (as exemplified especially by PNNL, NHMFL, and NMRFAM facilities) there is a need for enhancing this capability. In order to serve the broad community a well-functioning website must be developed that provides critical information and facilitates access.
- ✓ Each facility does not have to be optimized for all user activities. While many activities will likely be in common, others such as ultra high temperature for materials would be established at only one or two facilities until the demand merits expansion into other facilities. Different focus in each center is expected as well as complementary expertise, with some overlaps in capabilities and scientific themes.
- ✓ Shared protocols, equipment and reagents will lead to improved efficient usage of the instruments. The community has demonstrated their interest and willingness to cooperate in this way.
- ✓ These facilities will establish close working relationships with other facilities (such as APS) to leverage complementary technologies, e.g., SAXS, crystallography, cryo-EM, computation, multimodal imaging. This will be accomplished by identifying infrastructure opportunities for integrating NMR/MRI/MRS science with other complementary methodologies.

While the establishment of National High Field MR Facilities is the vision for housing the next generations of high field magnets, there is an urgent need for current and immediate next generation instruments for the

biological, chemical and biomedical communities in the United States. An interim solution must be found so that American scientists can continue to pursue cutting edge materials, chemical, and biological science. This includes the need for 1 and 1.2 GHz as well as DNP instruments housed in local or regional facilities.

Infrastructure- mechanisms for sustained support

Models need to be established for continued and sustainable funding mechanisms to support:

- ✓ Innovative infrastructure, equipment and highly qualified in-house personnel
- ✓ Equipment acquisition, operation, and maintenance in these facilities.
- ✓ Research and training of in-house and off-campus investigators.
- ✓ Off-campus investigator access (travel and accommodations) and usage of the facilities.

The participants recognized the critical importance of personnel development. To this end, it is essential to:

- ✓ Establish mechanisms for attracting and sustaining young investigators for high field technology and applications. Restore competitiveness of the US UHF MR science on the international arena.
- ✓ Establish mechanisms to recruit and retain trained technical and scientific personnel of the highest caliber in shared resources; this will ensure that users and on-site scientists will mutually push technological advances forward.

It was stressed that likely sustainable support models will include partnerships between Federal, State, industry, and philanthropic organizations.

Additional information can be found in the presentation and discussion slides, on the workshop's website: http://sites.udel.edu/uhf-nmr-workshop/2015/08/10/program/.

The participants concluded that in-depth analysis needs to be conducted by working groups, to identify the viable sustainable model(s) for shared UHF centers. The results of the analysis will be presented in the roadmap document.

IV. NEXT STEPS

The US scientific community has an urgent need of UHF MR technologies and infrastructure that are required to address a broad range of societally important problems of strategic national interest. This UHF infrastructure is currently lacking in the US, leading to a progressive loss of the US's scientific community leadership position in a number of scientific arenas on the international scene. To address the pressing scientific needs and develop sustainable UHF MR infrastructure for the nation, we recommend that the following steps be immediately adopted:

1. A roadmap document be compiled through this post-workshop effort and backed by the scientific community at large. This document will contain detailed analyses of the key scientific, technological, and infrastructure development issues mentioned in Section II of this report, followed by suggestions on how to exploit emerging UHF for the sake of maximizing US scientific and technological leadership. For the general outline of strategies planned to develop the roadmap see **Appendix A**.
2. The final roadmap be discussed and developed with the various agencies that hosted and participated in this workshop. Involvement of other organizations, such as AAAS, national and international professional societies, and private foundations will be encouraged.

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APPENDIX A

UHF MR SCIENCES AND INFRASTRUCTURE IN THE USA: TOWARD A ROADMAP FOR THE COMING DECADE

The proposed strategy for development of a detailed roadmap consists of forming working groups as outlined below. The composition, leadership, format and timeline for these groups will be developed after we receive feedback from the scientific community regarding proposals developed during this workshop, and after discussions with the agencies whose missions are relevant to the workshop goals.

I. SCIENCE NEEDS AND BENEFITS

1. Working group on science drivers for biomedical sciences
    a. NMR
    b. MRI
    c. Integrated MR
2. Working group on science drivers for materials, catalysis, energy sciences
    a. NMR
    b. MRI
    c. Integrated MR

II. TECHNOLOGY DEVELOPMENT

1. Working group on high-temperature superconductor wires and cables
2. Working group on superconducting magnet design and installation
3. Working group on MRI-specific hardware components: fast and high amplitude field gradients, shimming, parallel RF transceiver coils
4. Working group on NMR-specific spectrometer hardware: cryogenic probes for solution and solids, ultrafast magic-angle-spinning, microimaging, terahertz sources for DNP
5. Working group on physiological effects and safety of MRI and MRS for human studies at magnetic fields >9.4 T

III. INSTRUMENT DEPLOYMENT AND FUNDING MECHANISMS: SHARED FACILITIES AND INFRASTRUCTURE

1. Working group on sustainable models for shared UHF MR centers in the US
    a. Models for shared centers
    b. Cost analysis and infrastructure requirements
    c. Funding models
2. Working group on advancing UHF MR-based science in the US
    a. Support of the broader scientific community
    b. Analysis of socioeconomic benefits
    c. Public relations (website, advertising materials, videos etc.)

IV. SUMMARY RECOMMENDATIONS

APPENDIX B

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APPENDIX C

PROGRAM

THURSDAY, NOVEMBER 12, 2015

(attendees arrive at the Visitor entrance at 07:30 for NIH entry)

08:00–08:20	Lister Lobby	**Arrival and Registration**
08:20–08:30	Lister Auditorium	**Introduction and Welcome Remarks** **Tatyana Polenova, Thomas Budinger**
08:30–10:00	Lister Auditorium	**Plenary Session 1A:** ***Low- and High-Temperature Superconducting Magnet Technologies in MRI and NMR*** **Session Chair: Roderic Pettigrew, Director, NIBIB** 8:30–8:50 State of the Art and Challenges in Ultrahigh Field Magnet Technology (David Larbalestier, NHMFL) 8:50–9:10 Toward Super-High Field and Ultra-Compact Size NMR Magnets Operated Beyond 1 GHz (Hideaki Maeda, RIKEN) 9:10–9:30 UHF Magnet Development at MIT (Yukikazu Iwasa, Francis Bitter Magnet Laboratory, MIT) **Plenary Session 1B:** ***Shared Ultrahigh Field NMR Facilities in Europe*** **Session Chair: Robert Tycko, NIDDK** 9:30–9:45 European Large Scale Facilities for NMR Spectroscopy (Lyndon Emsley, École Polytechnique Fédérale de Lausanne) 9:45–10:00 NMR Infrastructures in Europe (Lucia Banci, CERM, University of Florence)
10:00–10:30	Lister Lobby	**Coffee Break**
10:30–12:15	Lister Auditorium	**Parallel Session 2A:** ***Frontiers of NMR*** **Session Chair: Lucio Frydman, National High Magnetic Field Laboratory, The Weizmann Institute of Science** 10:30–10:55 Emerging Trends in Solution NMR (Gerhard Wagner, Harvard University) 10:55–11:05 Discussion 11:05–11:25 Emerging Trends in Biosolids NMR (Ann McDermott, Columbia University) 11:25–11:35 – Discussion 11:35–12:05 Emerging Trends in NMR of Materials (Marek Pruski, Ames Laboratory) 12:05 – 12:15 - Discussion
10:30–12:15	The Claude Denson Pepper Building (31), floor 6, room 5	**Parallel Session 2B:** ***Frontiers of MRI*** **Session Chair: Jeff Duyn, NINDS** 10:30 –10:55 Functional Neuroimaging at Ultrahigh Fields (Bruce Rosen, Harvard Medical School and MIT) 10:55 – 11:05 Discussion 11:05 – 11:25 Non-Proton Metabolic Imaging and Anatomical Proton Imaging (Keith Thulborn, University of Illinois Chicago) 11:25 – 11:35 Discussion 11:35 – 12:05 Emerging Contrasts At Ultrahigh Fields (A. Dean Sherry, University of Texas Dallas, UT Southwestern Medical Center) 12:05 – 12:15 - Discussion
12:15-1:30	NIH cafeteria	**Lunch**

1:30-3:15	Lister Auditorium	**Plenary Session 3:** ***Frontiers in Ultrahigh Field Magnet Technologies*** **Session Chair: Chad Rienstra, University of Illinois at Urbana-Champaign** 1:30–1:55 Development of 1020 MHz NMR Superconducting Magnet Using Bi-2223 Innermost Coil (Mamoru Hamada, Jastec) 1:55–2:20 - UHF Magnets at NHMFL (Mark Bird, NHMFL) 2:20–2:45 – UHF Magnets at Bruker (Gerhard Roth, Bruker) 2:45–3:10 – Designing Ultrahigh Field Magnets for NMR and MRI (Joseph Minervini, MIT)
3:15–3:45	Lister Lobby	**Coffee Break**
3:45-6:00	Lister Auditorium	**Round Table Discussion Session 4:** ***Science Drivers for Ultrahigh Field NMR Science in the US*** **Discussion Leader: Angela M. Gronenborn, University of Pittsburgh** **Scribe: Jean Baum, Rutgers University**
7:00-9:30	Redwood Restaurant and Bar	**Session 5: Dinner Followed by After Dinner Address** ***Frontiers in Magnetic Resonance:- Current Perspective and Looking into the Future*** (Greg Boebinger, Director, NHMFL) **Session Chair: Brad Chmelka, UC Santa Barbara**

PROGRAM

FRIDAY, NOVEMBER 13, 2015

08:30–9:40	Lister Auditorium	**Breakout Discussion Session 6A:** ***Future Challenges and Barriers for NMR Science in the US*** **Discussion Leader: Jeff Hoch, University of Connecticut** **Scribe: Mei Hong, MIT**
08:30–9:40	The Claude Denson Pepper Building (31), floor 6, room 5	**Breakout Discussion Session 6B:** ***Future Challenges and Barriers for MRI Science in the US*** **Discussion Leader: Kamil Ugurbil, University of Minnesota** **Scribe: Eduard Chekmenev, Vanderbilt University**
9:40-10:10	Lister Auditorium	**Breakout Session 7A:** ***Shared Ultrahigh Field NMR Facilities in the US*** **Session Chair: Joanna Long, University of Florida** **Scribe: Christopher Jaroniec, The Ohio State University** 9:40–9:45 National High Magnetic Field Laboratory (Tim Cross, NHMFL) 9:45–9:50 The National Magnetic Resonance Facility at Madison (John Markley, University of Wisconsin) 9:50–9:55 Environmental Molecular Sciences Laboratory (EMSL) (Karl Mueller, Pacific Northwest National Laboratory) 9:55–10:00 MIT-Harvard Center for Magnetic Resonance (Robert Griffin, MIT) 10:00–10:05 Biotechnology Resource Center for NMR Molecular Imaging of Proteins (Stanley Opella, University of California San Diego) 10:05–10:10 New York Structural Biology Center (Arthur G. Palmer III, Columbia University)
9:40-10:10	The Claude Denson Pepper Building (31), floor 6, room 5	**Breakout Session 7B:** ***Ultrahigh Field Magnet Development for MRI*** **Session Chair: Joseph Minervini** 9:40–9:45 UHF Magnet Development at Oxford Instruments (Ziad Melhem) 9:45–9:50 UHF Magnet Development at Tesla (Michael Begg) 9:50–9:55 UHF MRI at Siemens (Michael Schaaf) 9:55–10:00 UHF MRI at GE (Scott Hinks) 10:00–10:10 Discussion
10:10–10:30	Lister Lobby/ The Claude Denson Pepper Building (31), floor 6, room 5	**Coffee Break**

10:30–12:15	Lister Auditorium	**Parallel Session 8A:** ***Emerging NMR Technologies in Liquids and Solids*** **Session Chair: Kurt Zilm, Yale University** 10:30–10:45 Biomolecular Solution NMR at Ultrahigh Fields (Ad Bax, NIH) 10:45–10:50 Discussion 10:50–11:05 Solution NMR Studies of Intrinsically Unstructured Proteins at Ultrahigh Fields (Peter Wright, The Scripps Research Institute) 11:05–11:10 Discussion 11:10–11:30 Challenges of ultrahigh field DNP NMR (Robert Griffin, MIT) 11:30–11:35 Discussion 11:35–11:50 MAS NMR Probes for Ultrafast MAS: challenges for Ultrahigh Fields (John Stringer, PhoenixNMR) 11:50–11:55 Discussion 11:55–12:10 NMR of Half-Integer Quadrupolar Nuclei in Materials: Opportunities at Ultrahigh Fields (Sophia Hayes, Washington University) 12:10–12:15 Discussion
10:30–12:15	The Claude Denson Pepper Building (31), floor 6, room 5	**Parallel Session 8B:** ***Emerging MRI/MRS Technologies*** **Session Chair: Alexej Jerschow, New York University** 10:30–10:45 Ultrahigh Field MRI and Potential Clinical Breakthroughs (Thoralf Niendorf, Max-Delbrueck Center for Molecular Medicine) 10:45–10:50 Discussion 10:50–11:05 High Field Imaging Gradients and Coils (Lawrence Wald, Massachusetts General Hospital-Harvard Medical School) 11:05–11:10 Discussion 11:10–11:30 The Active Transport of Water Molecules in Biological Tissues: Underpinnings of MRI Interpretation (Charles Springer, Oregon Health Sciences University) 11:30–11:35 Discussion 11:35–11:50 *In Vivo* MRI/MRS and Hyperpolarization: Opportunities and Challenges at UHF (Eduard Chekmenev, Vanderbilt University)- CANCELED 11:50–11:55 Discussion 11:55–12:10 Opportunities for MRI/MRS/Pathology Correlations in the Human Brain (Daniel Perl, Uniform Services University) 12:10–12:15 Discussion
12:15-1:30	NIH campus cafeteria	**Lunch**
1:30-3:15	Lister Auditorium	**Round Table Discussion Session 9:** ***Development of LTS and HTS Magnet Technologies in MRI and NMR: Roadmap*** **Discussion Leader: Thomas Budinger, UC Berkeley** **Scribe: Tatyana Polenova, University of Delaware**
3:15–3:45	Lister Lobby	**Coffee Break**
3:45-6:00	Lister Auditorium	**Round Table Discussion Session 10:** ***Development of a roadmap for ultrahigh field NMR/MRI/MRS science in the US*** **Discussion Leader: Tatyana Polenova, University of Delaware** **Scribe: Thomas Budinger, University of California Berkeley**
6:00		**Adjourn**

PRESENTATION TITLES (Abstracts for these presentations are posted on the workshop's website)

SESSION 1A: Low- and High-Temperature Superconducting Magnet Technologies in MRI and NMR
State of the Art and Challenges in Ultrahigh Field Magnet Technology (David Larbalestier, NHMFL)
Toward Super-High Field and Ultra-Compact Size NMR Magnets Operated Beyond 1 GHz (Hideaki Maeda, RIKEN)
UHF Magnet Development at MIT (Yukikazu Iwasa, Francis Bitter Magnet Laboratory, MIT)

SESSION 1B: Shared Ultrahigh Field NMR Facilities in Europe
European Large Scale Facilities for NMR Spectroscopy (Lyndon Emsley, École Polytechnique Fédérale de Lausanne)
NMR Infrastructures in Europe (Lucia Banci, CERM, University of Florence)

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Emerging Trends in Solution NMR (Gerhard Wagner, Harvard University)
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Emerging Trends in NMR of Materials (Marek Pruski, Ames Laboratory)

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Non-Proton Metabolic Imaging and Anatomical Proton Imaging (Keith Thulborn, University of Illinois Chicago)
Emerging Contrasts At Ultrahigh Fields (A. Dean Sherry, University of Texas Dallas, UT Southwestern Medical Center)

SESSION 3: Frontiers in Ultrahigh Field Magnet Technologies
Development of 1020 MHz NMR Superconducting Magnet Using Bi-2223 Innermost Coil (Mamoru Hamada, Jastec)
UHF Magnets at NHMFL (Mark Bird, NHMFL)
UHF Magnets at Bruker (Gerhard Roth, Bruker)
Designing Ultrahigh Field Magnets for NMR and MRI (Joseph Minervini, MIT)

SESSION 5: Dinner Followed by After Dinner Address
Frontiers in Magnetic Resonance:- Current Perspective and Looking into the Future (Greg Boebinger, Director, NHMFL)

SESSION 7A: Shared Ultrahigh Field NMR Facilities in the US
National High Magnetic Field Laboratory (Tim Cross, NHMFL)
The National Magnetic Resonance Facility at Madison (John Markley, University of Wisconsin)
Environmental Molecular Sciences Laboratory (EMSL) (Karl Mueller, Pacific Northwest National Laboratory)
MIT-Harvard Center for Magnetic Resonance (Robert Griffin, MIT)
Biotechnology Resource Center for NMR Molecular Imaging of Proteins (Stanley Opella, University of California San Diego)
New York Structural Biology Center (Arthur G. Palmer III, Columbia University)

SESSION 7B: Ultrahigh Field Magnet Development for MRI
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UHF Magnet Development at Tesla (Michael Begg)
UHF MRI at Siemens (Michael Schaaf)
UHF MRI at GE (Scott Hinks)

SESSION 8A: Emerging NMR Technologies in Liquids and Solids
Biomolecular Solution NMR at Ultrahigh Fields (Ad Bax, NIH)
Solution NMR Studies of Intrinsically Unstructured Proteins at Ultrahigh Fields (Peter Wright, The Scripps Research Institute)
Challenges of ultrahigh field DNP NMR (Robert Griffin, MIT)
MAS NMR Probes for Ultrafast MAS: challenges for Ultrahigh Fields (John Stringer, PhoenixNMR)
NMR of Half-Integer Quadrupolar Nuclei in Materials: Opportunities at Ultrahigh Fields (Sophia Hayes, Washington University)

SESSION 8B: Emerging MRI/MRS Technologies
Ultrahigh Field MRI and Potential Clinical Breakthroughs (Thoralf Niendorf, Max-Delbrueck Center for Molecular Medicine)
High Field Imaging Gradients and Coils (Lawrence Wald, Massachusetts General Hospital-Harvard Medical School)
The Active Transport of Water Molecules in Biological Tissues: Underpinnings of MRI Interpretation (Charles Springer, Oregon Health Sciences University)
Opportunities for MRI/MRS/Pathology Correlations in the Human Brain (Daniel Perl, Uniform Services University)