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The United States Department of Energy and National Institutes of Health Collaboration: Medical Care Advances via Discovery in Physical Sciences

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CONFLICT OF INTEREST

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Abstract

Over several months, representatives from the U.S. Department of Energy (DOE) Office of Science and National Institutes of Health (NIH) had a number of meetings that lead to the conclusion that innovations in the Nation's health care could be realized by more directed interactions between NIH and DOE. It became clear that the expertise amassed and instrumentation advances developed at the DOE physical science laboratories to enable cutting edge research in particle physics could also feed innovation in medical healthcare. To meet their scientific mission, the DOE laboratories created advances in such technologies as particle beam generation, radioisotope production, high-energy particle detection and imaging, superconducting particle accelerators, superconducting magnets, cryogenics, high speed electronics, artificial intelligence and big data. To move forward, NIH and DOE initiated the process of convening a joint workshop which occurred on July 12th and 13th, 2021. This Special Report presents a summary the findings of the collaborative workshop and introduces the goals of the next one.

1. Introduction

The joint NIH-DOE workshop was held in the summer of 2021 from July 12th to 13th. This workshop came out of a desire of NIH and DOE to leverage technology expertise and advances coming out of the basic science-driven missions of DOE Nuclear Physics and High Energy Physics laboratories to facilitate NIH goals. The DOE Nuclear Physics and High

Energy Physics laboratories host physicists both domestically and internationally to pursue experimental physics. Moreover, DOE has an international agreement and investment in physics research and instrumentation development undertaken by the European Organization for Nuclear Research also known as CERN. This global cooperation to advance the physical sciences provides countless opportunities for innovations and new tools to tackle medical research challenges. NIH also has a global reach through funding research internationally.

The inaugural meeting was held in the form of a workshop entitled *Advancing Medical Care through Discovery in the Physical Sciences*, aimed at developing critical collaborations for synergistic advancement between the Department of Energy Office of Science (SC) and the NIH's National Institute of Biomedical Imaging and Bioengineering (NIBIB) and National Cancer Institute (NCI), with the intention to enhance the mission, expand the scope, and optimize the resources of all. The workshop was formulated to be a forum for discussion of capabilities, challenges, and emerging technologies of interest to both the medical and physical international scientific communities. Additionally, the workshop was aimed at enhancing an ongoing dialogue of shared information for synergistic advancements and exploring a path forward to form partnerships. Originally, the plan was to have NIH-funded researchers meet with DOE scientists and engineers through an in-person gathering to explore the unique technologies developed for physics research that could fill technology gaps on the clinical research side. Because of the COVID-19 pandemic, this meeting was held virtually; however, this format allowed non-presenting participants to attend. As a result, there were nearly 150 registered attendees.

Working groups within the workshop were dedicated to identifying crosscutting challenges and opportunities in the overlap of both agencies' objectives, with two-hour sessions covering the state-of-the-art in detectors, magnetics, isotopes, electronics, data processing, radiotherapy devices, and data science, as summarized in the following sections. These scientific foci of mutual interest served as junctions to identify significant opportunities for cooperative efforts. The DOE-NIH relationship was noted to be broad, long-standing, and successful both for critical science/technology development as well as the training of the current and future scientific workforce.[1, 2] The meeting facilitated a condensation of topics expected to offer the optimal utilization of resources and to drive high-value breakthroughs for the country. Subsequent meetings will be designed to focus on one specific topic with the second, upcoming workshop to focus on detector science.

2. Summary of the Initial Workshop of 2021

We summarize here the latest NIH-DOE workshop collaboration series in two parts: (1) the proceedings and findings of a multi-disciplinary group assembled in an initial meeting to explore capabilities, challenges, and emerging technologies of high importance to both the medical and physical science communities and (2) a brief outline of the upcoming, focused meeting which will explore the science of detectors and will serve as an example of the format of subsequent, focused meetings.

2.A. Inaugural Workshop Introduction

Links that currently exist between NIH and DOE have proven to be impactful – and additional links can and should be developed. This was the universal theme presented by leadership from DOE, NIBIB, and NCI. Infrastructure across the country was summarized, as was the grant portfolio that supported taking DOE science to patient care. Areas where relationships were already strong were highlighted: nuclear medicine detectors, beamlines, radiopharmaceuticals, and data science/computing. Improving the coordination of grant opportunities via closer communication and development of new ways to co-optimize synergy and resource utilization were areas identified for attention. By working together, it was hoped the scope and scale of proposed research could be expanded within the same funding limit. This “scope scale up” was noted as a focus area. Translational opportunities were felt to be many, and all speakers concluded it was the proper time and of mutual benefit to move the agencies’ scientific collaboration closer. One challenge identified for productive collaborations between national DOE laboratories and NIH investigators is how to match long-term priorities with the timeline of funding opportunities, the latter being typically two to five years. This is particularly true in the computation and the electronics/ instrumentation fields where the national laboratories have cutting-edge instrumentation. However, the technical developments are on a timeline that is typically longer than the NIH funding timescale. Special emphasis was placed on the development of the next generation of scientists. Mentorship was noted to be a universally valued area on which to focus.[3, 4]

2.B. Crystals, Cameras and Detectors

The range of energy and types of radiation exploited by the DOE community are broad compared to the interest of the NIH community. For example, NIH focuses on x-ray and gamma-ray photons in the energy ranges of ~10^4 to 10^6 electron volts (eV) and it is here that collaboration can be utilized for improved photon detection. Medical imaging systems provide powerful clinical tools for disease diagnostics and treatment. Positron emission tomography (PET) and single photon imaging with a gamma camera, including the tomographic implementation in single photon emission computed tomography (SPECT), are widely available clinically. Often PET and SPECT systems are combined in hybrid systems for anatomical correlation and attenuation/scatter corrections with x-ray computed tomography (x-ray CT) scanners and occasionally magnetic resonance imaging (MRI). Technology overlap opportunities include the use of scintillating crystals, gas-based detectors, photodetectors, solid-state detectors, digital silicon photomultipliers and high-speed electronics for PET, whole-body PET, SPECT, x-ray CT and also proton/hadron therapy where particle beams are deployed.[5] Nuclear medicine camera developments rely on continuous innovation in radiation detectors, photodetectors and electronics, which are of great interest for both the DOE and NIH communities. High-speed photodetectors developed for particle physics such as large area picosecond photodetectors (LAPPD) and low gain avalanche detectors (LGADs) could advance nuclear medicine imaging.[6] Pushing time resolution down to 10 picoseconds (ps) is of common interest in both communities for applications in time-of-flight (TOF) PET[7] for medical and fast ring-imaging Cherenkov (RICH) detectors for particle physics could lead to locating annihilation photons by timing alone to ~1.5 mm resolution.

Nuclear physics instrumentation for interrogating the interactions of hadron beams (protons, carbon ions, etc.) with matter for range detection and other treatment planning verification is another area of research. Imaging approaches here target positron-emitting radionuclides produced by hadron irradiation or using gamma cameras or Compton cameras designed to detect beam-induced prompt gamma rays. Micropattern gas detectors (MPGDs) are charged particle-tracking detectors for particle physics research which provide ~50 μm resolution while tolerating very intense beams such as in cancer therapy applications.[8] This technology is being explored for beam diagnostics as well as proton computed tomography. Finally, artificial intelligence (AI) techniques under exploration for particle physics detector design and optimization clearly can be leveraged for improving patient care via medical imaging and adaptive planning development.

2.C. Advanced Magnetics

There are three major entities interested in the development and applications of superconducting magnets: DOE, NIH, and industry. The key medical industry applications of superconducting magnets include MRI, compact cyclotrons, and hadron therapy. Proven and promising methods include the following: magnetocardiography, magnetoencephalography, magnetic imaging technology, magnetic particle imaging (MPI), MRI (low- and high-field), magneto-stimulation, optically pumped magnetometry, radiofrequency hyperthermia, and transcranial magnetic stimulation, along with new technologies that are constantly being considered. The biological interface is often the limiting factor, where modeling and optimization can present significant challenges.

The MRI industry is advancing on development of a 16 tesla (T) magnet, with a manufacturable design using superconducting wire derived from DOE-funded research and development. Functional MRI (fMRI) is currently widely used in research settings for measuring neural activity across the entire human brain and is entering clinical use, e.g., pre-surgical evaluation.[9] New superconducting magnet technology enabled variable-energy, iron-free cyclotron designs which remove the energy degrader, enable ultra-high dose (FLASH) radiation therapy, and expand affordable patient access to critical proton and ion therapies.[10] MPI is an emerging new technology with tremendous potential, and crucial to the advancement of this technology is the development of appropriate ferrous, safe nanoparticles to serve as MPI tracers.

A robust, sustainable superconducting magnet research and development ecosystem will benefit a broad range of applications. It is imperative for the major entities to work together and coordinate such efforts for the biggest investment return and advancement of the field.

2.D. Radiopharmaceuticals for Diagnosis and Therapy

Theranostics is a term derived from the combination of ‘therapeutics’ and ‘diagnostics’. In this emerging field of medicine, drugs and/or techniques are uniquely combined to simultaneously or sequentially diagnose and treat medical conditions. For example, the pharmacokinetics of diagnostic radiopharmaceuticals should correspond to the disease process of interest so that imaging readout is linked to the therapeutic outcome. Development of diagnostic radiopharmaceuticals involves: (i) identifying targets;

(ii) designing of target-specific delivery agents; (iii) radiolabeling with appropriate radionuclides; (iv) preclinical studies; and (v) clinical translation. Currently, there is an urgent need for identifying new targets and developing new radiopharmaceuticals.

Radiopharmaceutical therapy, on the other hand, uses tumor-targeting molecules to transport therapeutic radionuclides to cancer cells or to their microenvironment. They contain radioisotopes with known physical characteristics, including their half-life and the range and linear energy transfer of the emitted radiation. The radionuclide physical half-life must match the biological half-life of the tumor-targeting agent to maximize the radionuclide decay at the target. There are unique advantages of using combined diagnostic/therapeutic radioisotope pairs of the same element for theranostics. For the translation of these agents to clinic, one of the most important factors is understanding and mitigating their side effects. This requires the development and use of personalized radiation dosimetry and reflects a move toward personalized, precision radiation therapy.[11, 12]

The DOE isotope program provides diagnostic and therapeutic radioisotopes nationwide. Over the past decade, nuclear reactors and particle accelerators at both national laboratories and academic partners have been progressively used for this purpose. Of particular interest are alpha-emitters, such as Ra-223, At-221, and particularly Ac-225, which is broadly used in both preclinical and clinical studies. A method to produce Ac-225 using accelerators rather than nuclear reactors has been recently developed. The Facility for Rare Isotope Beams is a new physics laboratory that came online in May of 2022 with an isotope harvesting program recently funded by DOE for the extraction and evaluation of thousands of new isotopes for various purposes, including medical applications.

To support research that accelerates the translation of preclinical radiopharmaceuticals, there is a need for trans-agency cooperation between NIH and DOE. Support for trainees is important to ensure a supply of experts in the relevant disciplines. Isotope production capabilities must meet anticipated demand and there is a need to enhance the visibility of centers developing new radiopharmaceuticals to promote cross-institutional partnerships.[13]

2.E. Electronics, Data Processing, and Image Reconstruction

National laboratories are leaders in computing infrastructure. These resources can be harnessed and shared for AI and Monte Carlo computing in medical applications. Several avenues were discussed including providing access to the impressive supercomputers of the national laboratories as well as allocating NIH grant funds to support the use of these computing facilities.[14]

Significant progress is being made in brain PET along multiple axes: ultra-high spatial resolution approaching 1mm^3 to visualize key brain structures involved in neurodegenerative diseases, as well as ultra-high sensitivity to capture input function and improve statistics in dynamic imaging. Another direction of technical progress is along coincidence timing resolution. There was agreement during discussion that all these directions are valuable and will likely yield improved technology and new knowledge on brain function. An interesting result provides some insight into the respective role of spatial and timing resolution in PET image quality: the improvement in spatial resolution from 2 to 1 mm far outweighed the gain in timing sensitivity from no TOF to 100ps.

In SPECT and PET, there is a resurgence of interest in using imaging to guide radionuclide therapy. Moreover, the role of quantitative imaging is increasing as it is being used to maximize the risk/benefit and optimize treatment based on radiation dosimetry instead of minimizing toxicity (which is often low), hence the value of diagnostic/therapeutic pairs. This has become manifest in recent high-impact papers demonstrating improvement in patient outcome when the maximum tolerable dose was delivered following personalized treatment planning.

2.F. Radiotherapy Instrumentation

Significant progress understanding the biology of cancer, together with tremendous advances in technologies for non-invasive imaging and external beam radiotherapy, have provided life-saving treatment to millions of patients worldwide. Research continues to advance our understanding of the biological mechanisms of cancer and how ionizing radiation in various forms kills cancer cells or makes cancer cells more susceptible to other treatment modalities. Innovations in medical imaging techniques and ionizing radiation sources continue to improve the precision and efficacy of treatment.

Today, lifesaving x-ray treatments are accessible to a fraction of the world’s population, with a significant portion of the developing world having limited or no access. An estimated 10,000 x-ray treatment machines are needed to fully meet the needs of the population of India alone, with similar numbers for Africa and other regions. Developing radiotherapy machines and techniques that are as cost-effective and reliable as they are curative is crucial for making the treatment more accessible.

There is an interesting confluence of technology advances now occurring. These include the significant increase in data science research including machine learning (ML) made possible by advances in computing power, the significant gains in self-diagnostic capability and process automation, the decreasing size and increasing performance of accelerator technology, and the increased capabilities of detector and imaging systems. Taken together these advances will lead to smaller, automated, self-diagnosing radiotherapy systems that can work in a wider variety of environments and deliver high-quality, safe treatment with reduced reliance on human technical expertise.[15–17]

Advances in treatment methods - such as FLASH radiotherapy, advanced high-speed scanning and depth modulation techniques for particle beam therapy, and very-high energy electron (VHEE) therapies - offer new tools for treating cancer that may provide significant advantages. Collaborative research and development on the radiobiology, clinical application, and underlying treatment technology is needed to move these new modalities into widespread practice. Significant collaboration is greatly hampered by the cost of the types of systems that need to be developed and by the lack of available funding to develop them.[18] Complicating the picture is that the research for the development of these systems does not fall within the mission space of the federal agencies charged with either medical research or physical science research.

A new paradigm must be established that facilitates the interaction of the medical and physical science communities and has a level of funding sufficient to achieve critical mass to result in advanced technology demonstrations. Catalyzing robust partnerships between federally funded researchers and the private/commercial sector is critical to deploying new, life-saving technologies worldwide.

2.G. Data Science

Data science is a central resource to both agencies today and will impact any DOE/NIH interrelationship. While data science has many definitions, the role of ML/AI is a significant part and will continue to profoundly impact research as was shown by several powerful examples. The synergy between those that understand AI and those that understand the domain of the source training data is paramount and needs further development through appropriate mechanisms of collaborative research communication and training. By its nature data science is multi-scale and so it is poised to address the needs of the current biological challenges of NIH and the physical discovery science of DOE, separately and together.

The DOE exascale capabilities can facilitate AI applications as part of a data and computing focus as opposed to more of a computing-only focus. The interrelationship between high-performance computing in its various forms (national labs, grid, cloud, institutional resources, etc.) remains unclear when considered in the context of data science applications. Developing the means to share and ramp up big jobs from local computers to exascale national resources was an identified gap.

DOE representatives noted that they had developed a human health records storage capability that met all national legal requirements for security and privacy. In addition, DOE has currently placed NCI into the groups of primary “pillars” for the largest computers in operation with multiple years of collaborative science led by the Joint Design of Advanced Solutions for Cancer (JDACS4C) initiative.[14, 19] The goal of allowing researchers funded by NCI to use DOE hardware facilitates the goal of helping to bring predictive modeling to cancer. Health applications to date using AI have tended to focus on image analysis where great success has been achieved. Predictive modeling in other areas is still in its infancy.

3. The Second Workshop: Focus on Detector Science

The planning and speaker invitation process for a second workshop to hopefully be held on the campus of the DOE’s Jefferson Lab in Newport News, Virginia is well underway. Presently the following sessions, bracketed by an introduction by leadership and concluding with an integration and next steps session, are planned:

Cameras, Detectors for External Imaging – X-rays, Protons, and Beyond;

Cameras, Detectors for Internal Diagnostic Imaging – SPECT, PET, and Beyond;

Cameras, Detectors for Radiotherapeutics;

Electronics and Data Acquisition;

Image Reconstruction, Pre- and Post- Processing;

Applications of Artificial Intelligence.

More information about the second workshop will be posted online and a summary report will be produced shortly after the workshop concludes. The hope is to conduct an in-person meeting over one and a half days. Following the previous format, each sessions will have two overview talks, one each from NIH and DOE, and then focused talks on cutting-edge topics that present opportunities for cross-cutting collaboration and present areas of need that may not be appreciated by the sister agency.

4. CONCLUSIONS

After a year of reflection and communication with attendees and leadership, the consensus remains that DOE and NIH share overlapping mission objectives, currently work together in some areas, and have common areas of aligned interest. However, these agencies will continue to benefit from linking together to generate additional “force-multiplied” science via frequent dialogue - such as this workshop series - to help teams develop collaborations and new areas of research. In addition to the science itself, it is felt that each agency can achieve better training and workforce endpoints by having coordinated programs that crosscut technologies and create more “outside of the box” thinking in both early career and senior scientists. In all, there is profuse and strong enthusiasm for establishing paradigms and mechanisms that facilitate increased interaction of the medical and physical science communities. Synergistic collaboration can leverage state-of-the-art technology for medical applications, spur development of new technology of interest to both the medical and physical sciences, and foster academic-industry partnerships (AIPs). Substantial prospects exist for new discoveries within both communities working in collaboration. Many areas exist in both agencies’ spaces where collaboration would achieve tangible mission benefits; a small subset of examples is summarized in the following table (Table I). The organization committee of this workshop series plans to continue to hold subsequent annual workshops, moving the area of focus from year to year to create programs of mutual focus and benefit.

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DATA ACCESSIBILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed.

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Table I.

Some *examples* of workshop-identified areas of collaboration expected to facilitate new technology breakthroughs and/or major improvements

	1–2 years	**2–5 years**	**5–10 years**
Magnetic Particle Imaging (MPI) - could challenge nuclear medicine and MRI in cost, ease of imaging and reduced normal tissue toxicity	Screening of existing particles to see if they are amenable to further development	Development of MPI tracer particles with necessary characteristics	Less expensive and more broadly available particles
Prompt Gamma Imaging (PGI) - for particle therapy range determination and other applications	Enhancement of speed and image resolution of Compton cameras	Advanced onboard electronics and enhanced processors (e.g. faster ASICs)	AIP product development and deployment to particle therapy facilities
Photon Counting Detectors (PCDs) - under development, not yet available in commercial dual-energy/spectral CT	Demonstrate counting speeds (with energy measurements) comparable to currently used flux levels	Demonstrate tissue composition for human tissues	Investigate tissue composition for diagnosis and diseases
Detectors capable of measuring position and incident angle of single photon (gamma rays), collimator-less SPECT (higher E range)	Propose new detectors/ cameras/ isotopes	First prototypes	Imaging in humans
Low Gain Avalanche Detectors (LGADs) - possible candidate for FLASH real-time dosimetry	Application to beam pulse structure and cross-calibration with national dosimetry standards	AIPs to commercialize detector products	Clinical deployment of LGAD detectors for multiple radiotherapy applications
New high critical temperature (Tc) superconductors – high magnet field, small size accelerator magnets	Deployable in small numbers of specialized systems up to 15T for gantry development and linear accelerator beamlines	More complex shaping of the magnets to allow for fewer units and possibly more efficient beam focusing to promote FLASH beam delivery with heavy particles	Helium-free and less expensive
Pixelated detectors for TOF PET utilizing scintillator depth of interaction at high sensitivity	Prototyping underway with novel materials, explore AI utilization	Engineering for mass production in an affordable state.	Clinical trials to test and optimize timing aspects of PET/CT to expand the spatial resolution, improvements would allow exploration of biological insights
Use of Cherenkov radiation and other non- scintillator-based techniques for PET TOF resulting in reconstruction-less imaging and leveraging AI	**1** Develop prototype PET camera using Cherenkov radiation for timing **2** Explore novel high energy particle interaction in detector medium	**1** First commercial prototype **2** Prototype development	Several cameras installed in hospitals for patient studies
Micropattern Gaseous Detectors (MPGDs) for tracking, dosimetry, large area, and improved spatial resolution	**1** Develop high-rate capability for medical dosimetry and imaging applications in both x-ray and proton/hadron radiotherapy **2** Evaluate whether MPGDs can	Deploy in clinical scenarios, develop applications, investigate proton computed tomography (pCT)	Leverage for imaging using tracking, revolution in improved spatial resolution

	1–2 years	2–5 years	5–10 years
	measure x, y, energy, and incident angle for diagnostic gamma imaging		
Streaming readout electronics techniques for fast data acquisition, fully digital front ends and image display	Development of new FPGA-based processes to leave machines in a constant collection state as opposed to on/off control process usage	Incorporate these processes and data collection methods into the clinical workflow in a way to avoid data overload	Development and optimization of the software tools and hardware devices to lower costs and introduce this to the broad market – and to develop methods to use this to achieve “big data” input capacity for patient care in a continuous fashion to better understand biological dose
VHEE radiation therapy	New waveguide design, > 150 MeV/m	AIP for prototype manufacture for VHEE and other radiation therapy applications	Product commercialization
Laser plasma acceleration (LPA)	Accelerator “on a chip” for electron brachytherapy	LPA for VHEE and/or ion beam sources	AIPs for new laser target and compact/high intensity laser beam source
Tera-Hertz (THz) imaging	Develop reliable THz radiation sources with industry engagement	Optimization of THz radiation imaging detectors and application identification	Clinical trials
AI/ML	**1** Remote online beam monitoring and diagnostics for medical accelerator operations **2** Special image reconstruction tasks	Predictive medicine utilizing multiscale data, digital twins, and AI/ML	Development of methods to confirm and test AI with other AI tools to focus on bias removal and false conclusion discovery methods that AI can hide from humans (an ongoing issue)- and the optimization of computing infrastructure to allow broad, ethical, equitable AI/ML use
Development of new targets for new radiopharmaceuticals and their dosimetry	Ongoing biologic research by NIH to find targets and chemistry development to create agents	**1** Development of new and better theranostic-capable compounds and methods to allow for dosimetry and treatment optimization on clinical trials in a cost-effective and safe manner. **2** Development of faster, cheaper and more accessible methods for radiopharmaceutical synthesis and purification	**1** Development of new combination treatment trials to combine agents and other therapies to optimize patient outcomes **2** Development of platform technologies for synthesis of binding partners for targets
Imaging and dosimetry of alpha particle emitting radiopharmaceuticals	Design and prototypes of designated scanners	Development of treatment planning systems	Clinical validation and implementation
Single scan-based radiopharmaceutical therapy (RPT) dosimetry - including enabling AI/ML applications	Application of AI/ML to treatment planning	Validation	Clinical implementation
MRI	Biological image processing and modeling	Functional MRI (fMRI) included	Helium-free devices
Magnet development, both superconducting and conventional	Leverage cryocooler technology and novel superconducting materials	Implement high field MRI & iron free medical cyclotrons	Clinical validation and implementation