2nd Workshop on Isotope Federal Supply and Demand

New Opportunities and Clinical Trials of Medical Isotopes

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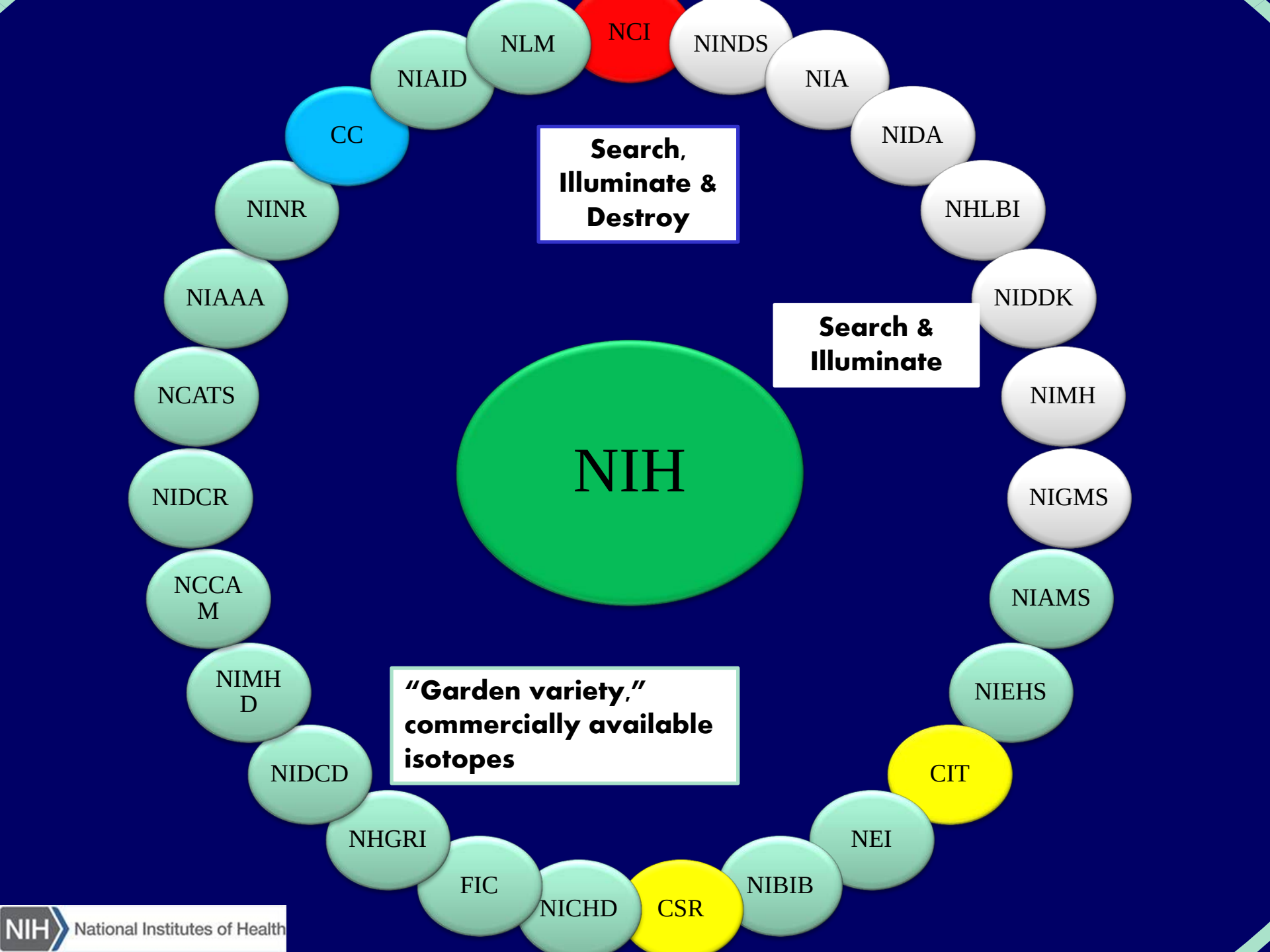
NIH National Institutes of Health

NIH and NIH <-> DOE Interactions

- NIH is made of 27 Institutes and Centers (ICs), each with its own mission; 24 of the ICs have external funding authority
- The NIH Director designates a rotating POC for NIH<-> DOE interactions, the POC is always an IC Director
  - Past POCs have included the NIDA and NIGMS Directors
- The current POC is the NIBIB Director, Roderic Pettigrew, Ph.D., M.D.

IC Areas of Isotope Interest

- Each IC's research mandate dictates the type of isotope-based work their researchers and grantees engage in.
- Some ICs' needs are fully satisfied by conventional, commercially-available isotopes.
- Some ICs are leaders in biomedical imaging, structural and functional, at the highest attainable resolutions – this includes all modalities of nuclear-based imaging.
- Some ICs, in addition to imaging, engage in isotope-based theranostic / therapeutic procedures.
- These differences influence ICs' isotope needs.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NLM
Search, Illuminate & Destroy
Search & Illuminate
"Garden variety," commercially available isotopes

Isotope Drivers in Biomedical Research and Treatment - 1

- For detection / imaging, availability of new probes with the requisite biological specificity.
- “Optimal” isotope selection depends on:
  - isotope availability
  - desired half-life
  - match of available radiochemical synthetic platforms to the:
    - structure
    - molecular weight
    - physical characteristics of the probe (biological half-life)
  - dosimetric considerations

Isotope Drivers in Biomedical Research and Treatment - 2

- For neurotransmitter receptor / transporter brain imaging, highest spatial resolution is paramount coupled to lowest absorbed dose.
- PET isotopes (co-registered with another modality for structural information as in PET/CT or PET/MRI) are the first choice, even with less-than-optimal half-lives.
- With new developments in SPECT detectors and cameras, these isotopes and their more versatile chemistry are becoming more popular.

Isotope Drivers in Biomedical Research and Treatment - 3

- New technologies can drive interest in different isotopes.
- PET intrinsic spatial resolution and contrast recovery for PET/MRI dual modality systems improve with increasing B_0 from positron diffusion range compression due to the Lorentz force (Peng and Levin, 2012). The effect is most marked for ^{82}Rb, intermediate for ^{68}Ga and trivial for ^{18}F.
- Although not examined in this study, it is anticipated that ^{64}Cu, ^{76}Br, ^{89}Zr and ^{124}I to show effects similar to those for ^{68}Ga and ^{82}Rb.

Positron Diffusion Range Compression Due to the Lorentz Force (^{82}Rb, B_0 = 10T)

Figure courtesy Dr. Craig Levin (Stanford)

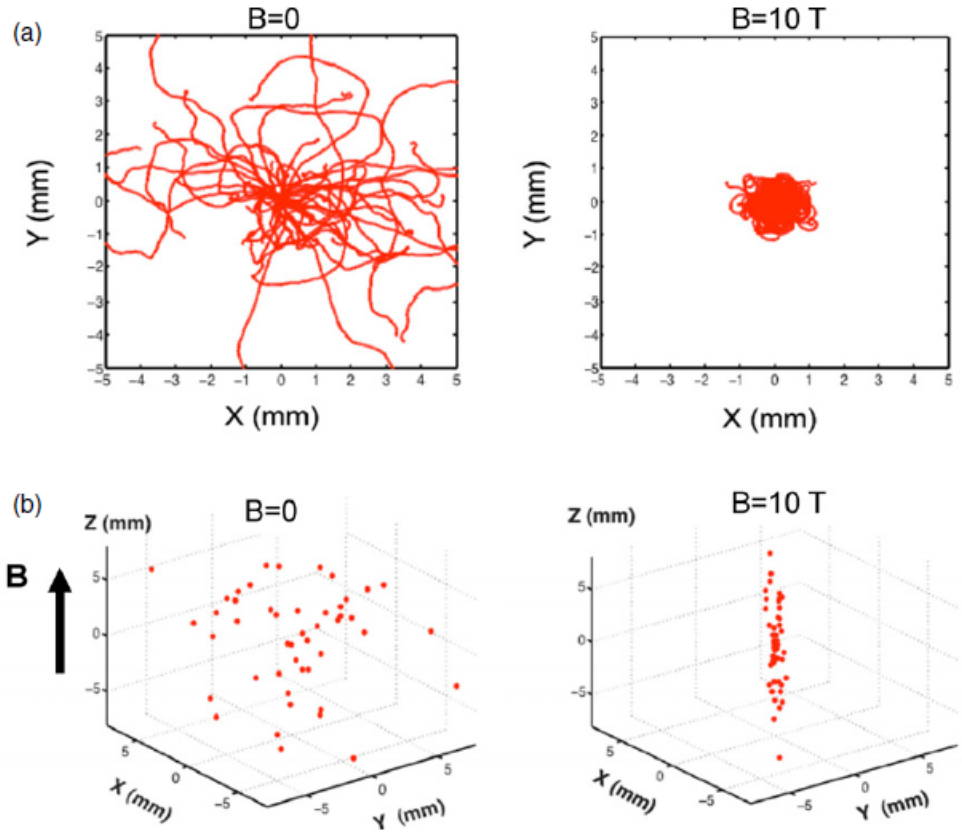
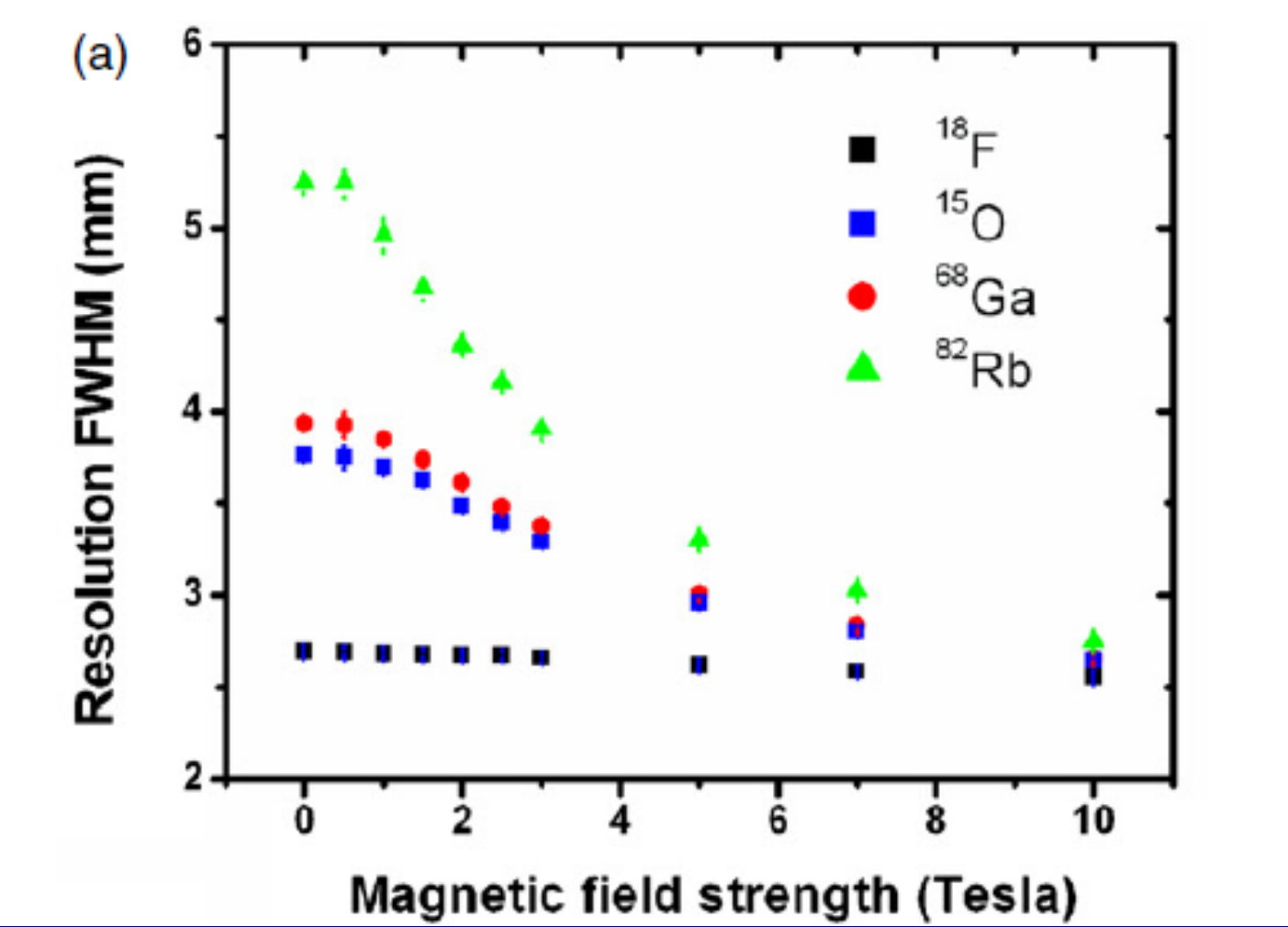


Figure 3. (a) Illustration of the lateral (orthogonal to *Z*) positron diffusion range compression inside strong magnetic fields. Radionuclide: ^{82}Rb. $N = 50$. (b) The distribution of end points in three dimensions. Positron diffusion reduction occurs only in the *X* and *Y* dimensions. The field in the simulation was applied along the *Z* direction.

Whole-Body PET/MRI overall system spatial resolution as a function of B_0 field strength

Figure courtesy Dr. Craig Levin (Stanford)



Isotope Drivers in Biomedical Research and Treatment - 4

- Selective probes can drive interest in different isotopes.
- Alpha emitters (e.g., ^{225}Ac, ^{211}At) are particularly attractive, due to their short tissue penetration, for cancer therapy.
- Interest in these isotopes has been heightened by successful coupling to antibodies for radioimmunotherapy (^{225}Ac-Lintuzumab; ^{211}At-Chimeric monoclonal antibody 81C6) and promising results in clinical Phase I and Phase II trials.
- ^{223}Ra dichloride has received FDA approval for treatment of metastatic prostate cancer. Clinical trials are underway for other malignancies. A limitation is the lack of suitable chelation / conjugation chemistry for Ra(II).

Isotope Drivers in Biomedical Research and Treatment - 5

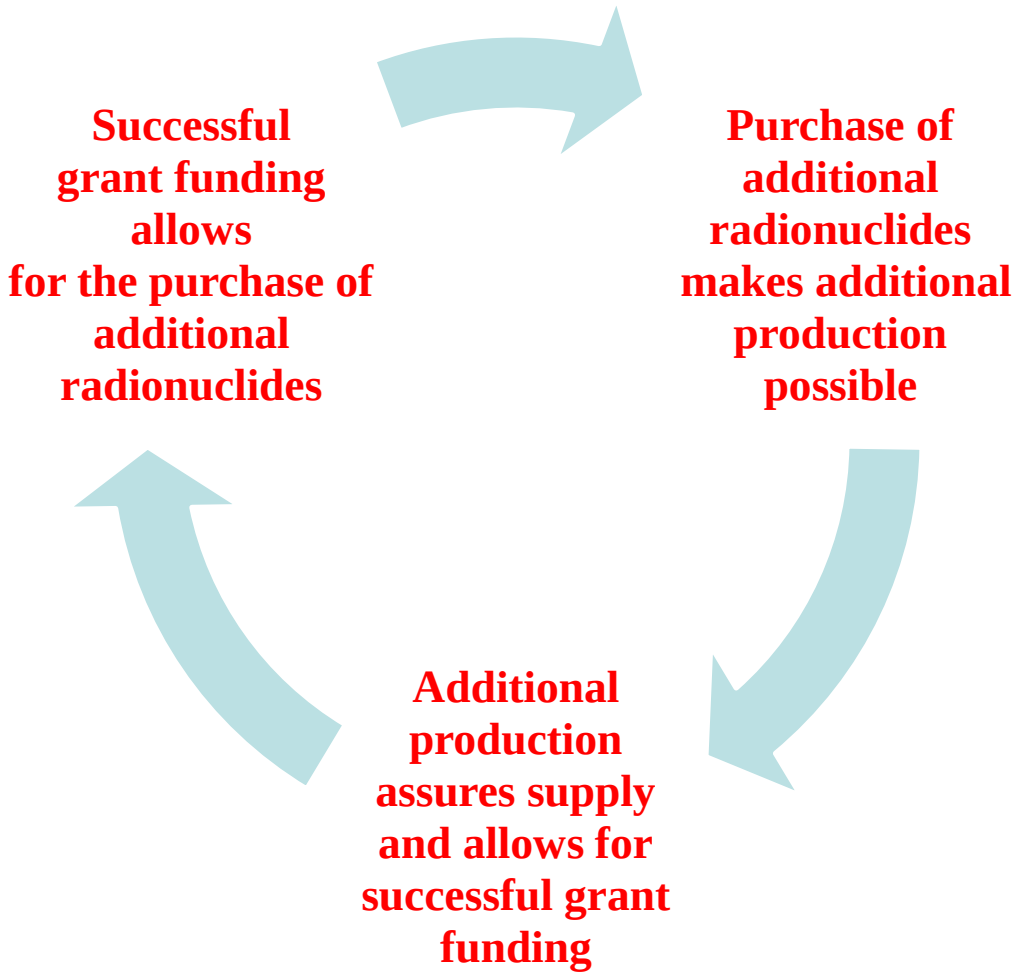
- Lack of isotope availability can delay promising research and clinical avenues. Exemplar: ^{67}Cu
- Smith et al (Argonne NL, 2012) note:

"Widespread use of this isotope for clinical studies and preliminary treatments has been limited by unreliable supplies, cost, and difficulty in obtaining therapeutic quantities."

- Systemic immunotherapy half-lives are often 2 - 4 d; the 2.6 d ^{67}Cu half-life, and robust ^{64}Cu peptide/protein radiolabeling chemistries developed in the past decade are ready for pre-/clinical development.
- Reports from Europe indicate potential superiority of ^{67}Cu labeled antibodies and fragments over ^{177}Lu labeling.

National Cancer Institute

The Challenge of Predicting Radioisotope Needs: The Radionuclide/Grant Merry-Go-Round



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Questions and Issues for Discussion

- The radionuclides suitable for PET imaging currently are supplied, in general, from cyclotron facilities and meet needs local to those sites. Some have capabilities to support additional research and clinical sites.
- Assembly of a functional, *coordinated* supply network between cyclotron sites would be seen as a positive response to future supply requirements as demand increases for various radionuclides, e.g., ^{89}Zr.
- Limited high chemical and radiochemical purity production of therapeutic radionuclides, e.g. ^{225}Ac, ^{211}At, ^{224}Ra/^{212}Pb remains a concern.

Questions?

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