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IDSA
Infectious Diseases Society of America

June 8, 2011

Anthony S. Fauci, MD, FIDSA
Director
National Institute of Allergy and Infectious Diseases
Building 31, National Institutes of Health
31 Center Drive, Room 7A03
Bethesda, MD 20892-2520

Dear Dr. Fauci:

We write on behalf of the Infectious Diseases Society of America (IDSA) to comment on the National Institute of Allergy and Infectious Diseases' (NIAID) plan to expand its clinical trials infrastructure to focus on infectious diseases (ID) other than HIV/AIDS; to propose a meeting to discuss the creation of a self-sustaining ID specimen repository; and to invite NIAID to participate in a webinar about the new clinical trials network for potential leadership group applicants.

IDSA members appreciate NIAID leaders' recognition of the need to expand its clinical trials infrastructure to ID priorities other than HIV/AIDS and that the Institute has selected antibiotic-resistant bacterial infections as the initial priority for the expansion. Antibiotic resistance is a present and growing public health crisis with implications for national security and requires urgent action. We are aware that there have been significant and extensive discussions among NIAID leadership and the broader infectious diseases community about the goals and needs of an expanded network. IDSA applauds NIAID for being responsive to the community and for the commitment to research that will address critical clinical questions about antibacterial resistance.

As we commemorate the 30th anniversary of the start of the HIV/AIDS epidemic, we are acutely aware of the power of concerted clinical research efforts to solve difficult disease questions. We believe it is important to incorporate lessons learned from the investigators and administrators who built the HIV/AIDS clinical trials networks. As has been the case with the HIV/AIDS networks, an established network of clinical trial sites focused on drug-resistant bacterial infections will improve the quality of study data and enable timely enrollment of patients. Also, an NIAID-funded clinical trials network will be able to undertake investigations that industry and others are unwilling to work on, which will move the field forward scientifically.

We support several general principles which we believe will help to ensure the success of the ID clinical trials network. While there is a need for an administrative structure, it should be flexible and agile because an overly bureaucratic structure would stifle innovation. Pediatric populations should be

included whenever possible, and to facilitate this, network leadership can seek out opportunities to collaborate with other institutes such as the National Institute of Child Health and Human Development (NICHD). Because of the nature of the onset and disease course of resistant bacterial infections, clinical trial sites must include primarily in-patient populations (including critical care units and transplant patients) in addition to outpatient populations.

In addition to conducting trials that industry is unable or unwilling to work on, IDSA believes it is important that the network be able to collaborate with industry in registrational clinical trials of experimental preventive and therapeutic agents that address drug-resistant bacterial infections. Such trials could be financially supported by industry through a Cooperative Research and Development Agreement (CRADA) or other similar mechanism, in order to augment the limited resources currently available for the ID clinical trials network.

Antibacterial resistance research priorities for the ID clinical trials network

As you are aware, IDSA recently published a policy paper, "Combating Antimicrobial Resistance: Policy Recommendations to Save Lives", which enumerates research, public health, and legislative recommendations for responding to the converging crises of the rise in antibiotic resistance and dearth of new antibiotics in the drug development pipeline. The paper's research-focused recommendations stem in part from the July 2010 joint Food and Drug Administration (FDA), NIAID, and IDSA workshop on antibacterial resistance and related drug and diagnostics research. The new ID clinical trials network can develop and implement a research agenda which will begin to address some of the critical unanswered questions raised at this and other similar workshops. IDSA believes that the clinical trials network should focus on the resistant pathogens with the greatest unmet clinical need, i.e. the multidrug resistant aerobic gram-negative bacilli like *Escherichia coli*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species. Other pathogens of public health importance include *Enterococcus faecium, Staphylococcus aureus, Clostridium difficile,* and *Neisseria gonorrhoeae.*

One of the highest research priorities should be establishing a multi-center, prospective observational cohort study. There is a need for a stronger evidence base of observational data for patients with drug-resistant bacterial infections and those who are at risk for developing disease from serious resistant infections. Conducting a well-defined prospective cohort study will provide a wealth of information that will help to determine patient risk factors associated with becoming infected, developing disease from infection, course of disease and particular outcomes. The data gathered through this study will help to inform the design and conduct of future clinical trials, including those for evaluating new agents, evaluating diagnostics, and examining optimal duration of therapy. Additionally, it will enable the development of more tools for predicting and treating serious infections in clinical practice. Risk factors utilized in practice are limited to demographic characteristics such as age because of a lack of evidence on other variables, such as host inflammatory markers and microbiological information, which may be more predictive and help identify patients with the worst outcomes. The identification of patient factors that contribute to disease progression and outcome will also aid in the identification of potential treatment endpoints and validation of patient biomarkers. An example of how a cohort study advanced HIV/AIDS research is the Multicenter AIDS Cohort Study (MACS), which led to the identification of viral load as a predictor of disease progression and use as a surrogate endpoint.

Another promising area for study is the development of clinical trials that examine pharmacokinetic and pharmacodynamic (PK-PD) parameters for antibiotic therapy. One interesting question would be to examine whether PK-PD optimized regimens fare better than standard of care therapies in terms of efficacy and preventing the emergence of antibiotic resistance. It also would be beneficial for the design of future clinical trials to investigate the independence of commonly used PK-PD parameters such as the drug exposure parameter 24-hour area under the curve (AUC) and the antibiotic activity parameter minimal inhibitory concentration (MIC).

Finally, it is important to continue and extend ongoing NIAID-funded post-licensure studies of shorter antibiotic treatment duration and early cessation of therapy. Validation of biomarkers could help to guide shorter courses of therapy, similar to how procalcitonin levels are currently used by some to guide initiation and termination of antibiotic therapy. Additional trials of interest include the possibility of addressing treatment safety and efficacy by organism rather than by clinical syndrome; superiority clinical trial design; and the efficacy of drug combinations against multidrug resistant bacteria. Given enough resources, the ID clinical trials network should also include flexibility to address other issues such as infection control interventions and novel surveillance strategies.

Establishment of a self-sustaining repository of clinical ID specimens

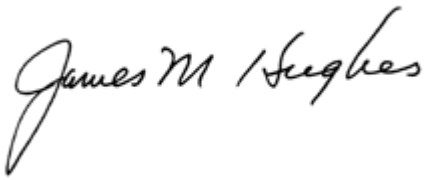
IDSA supports using the new clinical trials network and other clinical trial sites to help populate a proposed new clinical ID specimen repository. Such a repository would contribute to the conduct of other clinical trials and to the development of diagnostics, as highlighted in an FDA diagnostics presentation during the 2010 joint workshop. Prospectively archived ID specimens would be highly valuable for the development of rapid point-of-care molecular diagnostic devices capable of detecting pathogenic organisms from patient samples. Rapid diagnostic tests improve physicians' ability to prescribe antibiotics in a manner consistent with antibiotic stewardship. Better diagnostics reduce the costs of new antibiotic development by increasing the number of microbiologically evaluable patients in the clinical trial population. We envision a program where companies will pay user fees in order to access the specimens, thereby making the repository self-sustaining over time.

IDSA recently raised the idea of the self-sustaining ID specimen repository with congressional staff involved in the reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA) and the Generating Antibiotic Incentives Now Act. Some of those staff immediately recognized the value of advancing the development of new diagnostics to address drug-resistant and other high priority infections. In response to their requests, IDSA produced a draft legislative proposal which we enclose. Our hope is that this proposal will serve as a basis for discussions among key stakeholders including NIAID, FDA, the Centers for Disease Control and Prevention (CDC) and members of Congress and their staff. We understand that agency officials will not be able to take a position on the draft legislation itself. <u>However, we would highly value the opportunity to meet with you and/or other NIAID leaders in the next month to hear your technical comments about the proposal and/or other alternative ideas you might have.</u>

Proposed joint webinar to educate potential leaders of the ID clinical trials network
IDSA also would like to invite NIAID representatives to participate with us in a webinar intended to educate IDSA members and possibly other members of the ID research community about the new antibiotic resistance focused clinical trials network. The webinar could be held just before or immediately following NIAID's issuance of its request for applications for the leadership group so that interested individuals could hear the latest information about the planned expansion and ask questions that hopefully will lead to high quality submissions.

To schedule a follow-up meeting to discuss IDSA's proposal for a repository and the potential joint webinar, please have your staff contact Audrey Jackson, PhD, IDSA Program Officer for Science and Research, at (703) 299-1216 or ajackson@idsociety.org.

Sincerely,



James M. Hughes, MD, FIDSA
President

Louis B. Rice, MD
Chair, IDSA Research Committee

Enclosure: IDSA draft legislative proposal for clinical ID specimen repository

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SELF-SUSTAINING BIOREPOSITORY.

(a) AMENDMENT.—Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended by adding at the end the following:

"SEC. 409K. SELF-SUSTAINING BIOREPOSITORY

"(a) IN GENERAL.—The Secretary, acting through the Director, in consultation with the Director of the Centers for Disease Control and Prevention and the Commissioner of the Food and Drug Administration, shall establish and maintain, directly or by contract, a self-sustaining biorepository of prospectively collected specimens to assist with the research and development of diagnostic tests or other activities intended to advance the treatment, detection, identification, prevention or control antimicrobial-resistant infections.

"(b) ACTIVITIES.—In carrying out subsection (a), the Director shall—

"(1) establish a single point of authority to manage operations of the biorepository;

"(2) establish and disseminate quality standards and guidelines for the collection, processing, archiving, storage, and dissemination of human biological specimens and biorepository data for research and clinical purposes;

"(3) develop and promulgate guidelines regarding procedures, protocols, and policies for the safeguarding of the privacy of human biological specimens and biorepository data, in accordance with applicable Federal and State regulations, guidelines, and policies, as appropriate;

"(4) review and make recommendations to address ownership, patient access issues, and analyses with respect to human biological specimens and biorepository data;

"(5) develop and promulgate guidelines regarding procedures, protocols, and policies for access to human biological specimens and biorepository data by nongovernmental entities for research purposes;

"(6) develop and disseminate guidelines for structuring informed consent forms that address—

"(A) privacy and confidentiality of human biological specimens and biorepository data;

"(B) understanding of research procedures, benefits, risks, rights, and responsibilities;

"(C) voluntary participation; and

"(D) the development of informed consent agreements that allow for future research in advance of clear research objectives.

"(7) incorporate human biological specimens and biorepository data from federally conducted or supported initiatives, as feasible;

"(8) encourage submission of human biological specimens and biorepository data obtained or analyzed with private or non-Federal funds which may include establishing contracts or providing a nominal reimbursement to such entities to offset the costs of associated with contributing specimens to the biorepository;

"(9) facilitate submission of biorepository data, including secure and efficient electronic submission;

"(10) allow public use of human biological specimens and biorepository data only—

"(A) with appropriate privacy safeguards in place; and

"(B) for research purposes;

"(11) determine appropriate procedures for access by nongovernmental entities to human biological specimens and biorepository

data for research and development of new or improved tests, and submission of data generated from research and development to the Food and Drug Administration or appropriate agencies as part of the approval process.

"(c) CONSULTATION.—Before carrying out activities outlined under this section, the Director shall hold a public meeting and provide other opportunities for public input from relevant stakeholders, including other relevant federal agencies, diagnostic and drug companies, professional medical societies, and patients, about the scope and size of the repository needed, the types of samples needed to support research and development, how and from where such samples should be secured, and other key aspects of this program.

"(e) SELF-SUSTAINABILITY THROUGH USER FEES.

"(1) IN GENERAL.—In developing the guidelines required under subparagraph (5) (related to access to human biological specimens and biorepository data by nongovernmental entities for research purposes), the Director shall establish a user fee program under which a non-governmental entity shall pay to the Director a fee for each human biological specimen, as determined under paragraph (2).

"(2) FEE AMOUNT.—The amount of the user fee shall be determined each fiscal year by the Director based on the average cost incurred by the biorepository in order to sustain the overall operation and maintenance of the biorepository.

"(3) OFFSETTING COLLECTIONS.—Fees collected pursuant to this subsection for any fiscal year—

(A) shall be deposited and credited as offsetting collections to the account providing appropriations to the National Institutes of Health; and

(B) shall not be collected for any fiscal year except to the extent provided in advance in appropriation Acts.

"(f) REPORT.

"(1) IN GENERAL.—Not later than one year after the date of the enactment of this section, and annually thereafter, the Secretary, shall submit to the appropriate committees of Congress a report regarding the self-sustaining biorepository.

"(2) CONTENTS—The report submitted under subparagraph (A) shall—

"(A) discuss the status of the establishment of the biorepository;

"(B) identify additional specimen collections that would prove useful in carrying out the functions of the biorepository;

"(C) examine any access or participation issues affecting the establishment and operation of the biorepository, including—

"(i) intellectual property concerns;

"(ii) access to collected specimens;

"(iii) costs associated with accessing, procuring, and securely transporting specimens to the biorepository, including a discussion related to the user fee;

"(iv) costs incurred by public and private entities to access specimens in the biorepository;

"(v) costs incurred by public and private entities to contribute specimens to the biorepository; and

"(D) other issues determined appropriate.

"(g) DEFINITIONS.—In this section:

"(1) BIOREPOSITORY.—The term 'biorepository' means a shared respository of human biological specimens collected for medical or research purposes that includes biorepository data.

"(2) BIOREPOSITORY DATA—The term `biorepository data'—

"(A) means data associated with a human biological specimen stored in a biorepository collected for medical or research purposes; and

"(B) includes health information and demographic data associated with a specimen.

"(3) DIAGNOSTIC TEST.—The term 'diagnostic test' is a device as defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321).

"(4) HUMAN BIOLOGICAL SPECIMEN.—The term 'human biological specimen' means any human body fluid, tissue, blood, or cell; any material derived from any human body fluid, tissue, blood, or cell; and any data associated with such specimens including associated health information and demographic data.