HESI PROPOSAL FORM

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Is this proposal submitted on behalf of more than one person / institution? If yes, identify co-submitters below.

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Proposal title: Application of Genomics to the Human Safety Assessment of Microbes

Key words: bacterial genomics, microbes, safety framework

Describe the problem to be addressed. Why is the issue important? To whom is this issue important?

Microbial product development is an important and rapidly evolving component of all three major HESI areas of interest- food, pharmaceuticals, and agriculture (1). Genomic assessment of microbes, particularly prokaryotes, can help identify a variety of theoretical environmental and health concerns. However, consensus paradigms appropriate for risk characterization, risk assessment, and regulatory management of these concerns do not presently exist. This proposal will ultimately focus on the development of a conceptual framework for human safety assessment of microbial agents, used along or in the manufacture of other products. Due to the complexity of the issue, we have recommended beginning with a selected area (antibiotic resistance). A parallel framework for environmental risk assessment may be equally necessary but will not be immediately addressed.

The increasing interest in the human microbiome, the use of microbes in pharmaceuticals (probiotics), the use of microbes in agriculture, and the growing understanding of the role of the environment as a reservoir/source of microbial resistance is driving a need for microbial safety assessment. In the past, microbial classification employed classical culture techniques and physical properties (e.g., shape, Gram stain). The rapid development of -omics techniques during the past decade has revolutionized our conception of the microbial world, allowing insight into underlying genomic content, rapidly expanding the number of microbial “species,” reclassifying many organisms, and raising new possibilities for genomic-based safety assessment. Metagenomic techniques now allow us to “see” a wide array of unculturable or previously unrecognized microbes and thereby develop a more comprehensive characterization of the background into which products and their associated genomes and risks will be inserted.

A recent publication by the National Academies (2) focuses on antimicrobial use as a driver for resistance, but the “one health” approach employed in the document identifies a number of foundational issues relevant to genomics and safety assessment and suggests some approaches to addressing current data gaps.

Issues raised by genomic safety assessment include (but are by no means limited to):

- Which antibiotic production or antibiotic resistance genes should or should not be introduced into the environment?
- What genes represent “pathogenicity factors,” in what microbes, and when are such genes appropriate for introduction in the environment?
- What assessment is appropriate for microbial toxins and what criteria will determine acceptability in the environment.
- What, if any, assessment is needed for allergenicity (for bacterial and especially fungal organisms)?
- What is the importance of bacterial endotoxin in Gram-negative organisms in regards to environmental and human or animal health impacts?
- What does the background of antibiotic production/resistance and pathogenicity genes in the environment look like, and when might an introduced organism represent a meaningful change in this background?
- To what extent do these various genes or phenotypes mobilize among environmental and human-associated microbes?
- What characteristics of the proposed organisms increase or decrease risks of gene transfer (e.g., mobile elements, conjugation competence), and how might this be altered if desired?
- How does gene location (chromosomal vs plasmid, incorporation into resistance cassettes) impact risk?
- How do we think about deletion or other mutants which may recombine in the environment or which may facilitate acquisition of genes of concern via homologous recombination or other means?
- How do we assess genes which may undergo spontaneous mutation to produce genes of greater concern?

The availability of ready answers to these and other questions will vary. For example, metagenomics will allow us to characterize the presence of various genes of potential concern in the environment, although the available data may not have been analyzed in this regard. In contrast, comprehensive models of gene mobility among organisms in the environment do not yet exist.

The output of this exercise is intended to be two-fold. The first would be a conceptual framework for microbial risk assessment, analogous to other risk assessment framework efforts of HESI in the past (e.g., Childhood exposure to carcinogens). The second output would be a “needs list”- identifying data and/or analyses or other resources needed to carry out the framework as described. This would serve to drive further research necessary to improve or implement the risk assessment framework within HESI and by our multisector stakeholders.

Due to the diversity of the overall issue, we propose that the project initiate with a relevant sub-topic which will help focus discussion and which can inform planning of the broader framework development effort. We suggest that the assessment of antibiotic resistance markers (known and putative) and phenotypic resistance (which is not always synonymous with the presence of an ARM) would serve as an appropriate model given that: 1) there is currently concern around antimicrobial resistance in general; 2) we have available databases (not necessarily complete) surrounding ARMs and at least some data characterizing mobility in the environment.

Describe the basic project steps or stages to the best of your ability, including an expected timeline, milestones, and deliverables for the first two years.

July-September 2018: Voting by HESI membership

November 2018: Launch of new EI (if adopted)

Jan-June 2018: Form working groups, conduct literature review and engage in expert consultation.

November 2019: Publish Gap Analysis

Early 2020: Workshop on Findings:

- Consensus report on Evaluation Criteria and Acceptance Criteria for ARMs
- Proposal for next steps in developing a framework for additional gene classes and genome-related issues.

What is the potential or anticipated impact of successfully achieving the milestones described above? *(Describe scientific, regulatory, policy, public health, and/or other impacts.)*

This effort is expected to identify existing data and analyses and drive further research necessary to refine and implement the Framework. On the regulatory side, existence of the Framework will assist relevant agencies (FDA, USDA, EPA) in developing internal regulatory approaches as well as policy development relevant to genomic-bases risk assessment. The ultimate impact is intended to both protect and improve public health, as the data and analyses needed to understand a range of pathogenicity factors and to understand genotypic and phenotypic mobility in the environment will have deep implications relevant to pathogenic organisms as an offshoot of understanding safety assessment for products to be commercialized. The Framework will facilitate and accelerate the introduction of a variety of pharmaceutical, food, and agricultural products which will likely produce significant benefits to health via therapeutic agents, probiotics, improved food productivity, and enhanced nutritional value. Agricultural microbes are expected to enhance productivity, minimize applied nutrient excess and/or improve nutrient availability, minimize use of traditional/synthetic chemical pest control agents (insecticides, fungicides), and minimize the agricultural environmental footprint, impacting both human health and the environment.

Describe the interdisciplinary, collaborative nature of the proposed project, and identify potential partners: *(identify institutions, organizations, companies, and or consortia)*

This proposal is expected to have significant interest across multiple sectors, as impacted industries will require a Framework and, ultimately, policy and practices surrounding the registration and use of microbial products. This will necessarily help to drive internal framework, policy, and procedural activity in relevant agencies, which would include US FDA, USDA, and EPA and counterpart agencies around the globe. Academic research will clearly play an integral role in both conceptualizing the Framework and in generating the research, data, and models needed to achieve effective implementation.

How did you hear about HESI's proposal solicitation? (e.g., HESI email or website, society announcement):

Existing HESI EIC member (DAG) and participant in Microbiome Committee (KK).

Other Comments

The proposers recognize the existence of the Microbiome Committee, and understand that this proposal is broader than, but has substantial scientific and conceptual overlap with the microbiome effort. We defer to HESI on the structural considerations, but would point out the workload and the breadth of the issues to be addressed would appear to justify a separate effort for Framework Development even if there is some degree of overlap.

REFERENCES:

1) Waltz, E. A new crop of microbe startups raises big bucks, takes on the establishment. Nature Biotechnology 35, 1120–1122 (2017) doi:10.1038/nbt1217-1120. December 6, 2017, online at: https://www.nature.com/articles/nbt1217-1120
2) U.S. National Academies. Combating Antimicrobial Resistance: A One Health Approach to a Global Threat: Proceedings of a Workshop. ISBN: 978-0-309-46652-3. DOI: https://doi.org/10.17226/24914 Available online at: https://www.nap.edu/catalog/24914/combating-antimicrobial-resistance-a-one-health-approach-to-a-global