Improved Annotation of Sequences of Concern to Better Understand Biorisk in Engineered Microbes

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Problem Statement

As synthetic DNA sequences for microbial engineering become easier to obtain, the risk of an accidental or deliberate generation of a microbial threat increases. Effective screening requires recognition of potentially hazardous sequences.

Working Toward a Solution

- We developed open-source software, SeqScreen, to screen sequences for those with hazardous functions: sequences of concern (SoCs)
- SeqScreen requires that sequences that cause problems be recognized and classified.
- How are hazardous sequences best understood?

Microbial Pathogens for Humans[1-3]

How many microbial pathogens for humans are there? Probably fewer than 1600:

- ~600 fungi,
- ~600 bacteria,
- 250 RNA viruses
- 50 DNA viruses
- 60 protozoa

How Do SoCs Contribute to Disease?

Damaging SoCs

- Cytotoxic
- Degrade Tissue
- Disable Organ
- Induce Inflammation

Other Direct-Acting SoCs

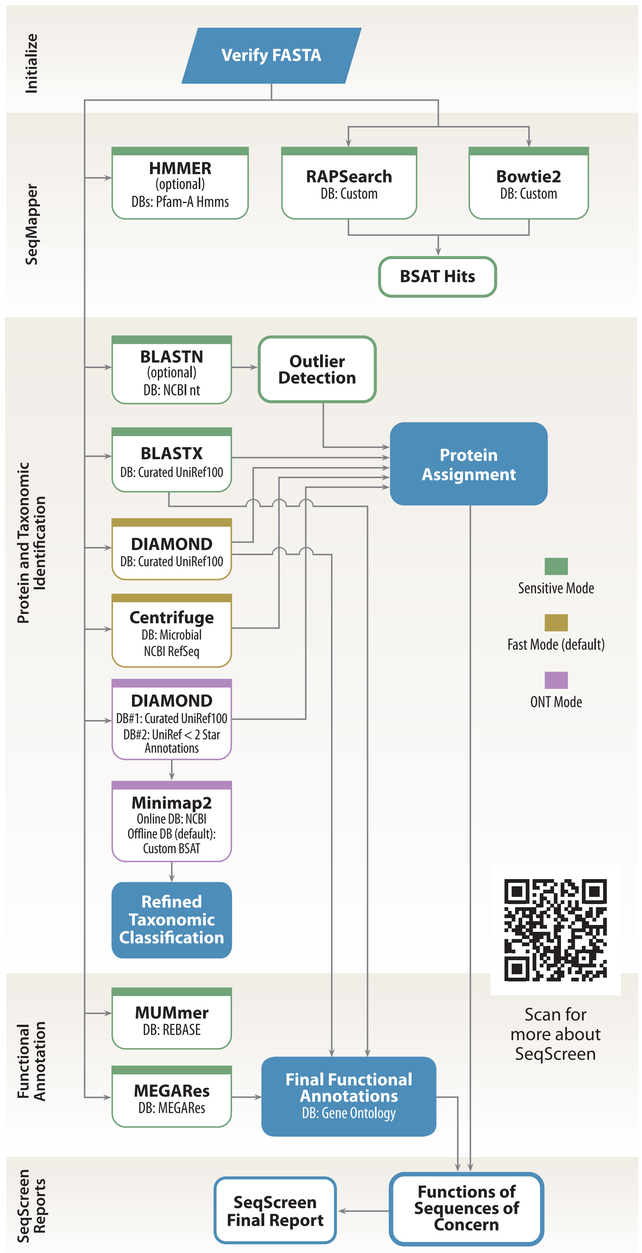
- Adherence to host cell
- Dissemination in host
- Host cell invasion
- Movement in host cell
- Niche-creationin host cell

Immune-Subverting SoCs

- Suppress host immune signaling by disrupting:
  - JAK-STAT
  - MAPK
  - NFκB
  - RIG-I
  - Protein kinase R
  - STING
  - TNF receptor-associated factors
  - Toll-like receptor binding/activation
- Resist host phagocytosis
- Resist host complement-killing (serum resistance)
- Resist host antimicrobial peptide
- Resist host oxidative killing
- Counter host immunoglobulin
- Defeat host chemokine or cytokine
- Inhibit host antigen presentation
- Immunomodulation

We have annotated functions of sequences of concern [FunSoCs] from 105 bacterial, 58 viral, 7 protozoal, and 4 fungal species pathogenic for humans.

SeqScreen Workflows



A Dataset of SoCs Annotated by Function Could Bring Clarity to Dual-Use Research of Concern (DURC) for Researchers, Regulators, and Funding Agencies

Function of Sequence of Concern (FunSoC)	Case 1 – SoC transferred to other pathogen or Case 2 – SoC altered for enhancement of original pathogen	Case 3 – SoC transferred to nonpathogen
Damaging	• Could enhance the harmful consequences of the agent	• Might enable the nonpathogen to have harmful consequences
Immune-Subverting	• Enhances the harmful consequences of the agent • Disrupts immunity or the effectiveness of an immunization against the agent • Alters the host range or tropism of the agent • Enhances the susceptibility of a host population to the agent	• Might enable the nonpathogen to have harmful consequences • Might enable the nonpathogen to infect novel hosts • Might enhance the susceptibility of a host population to the agent
Attachment Protein/ Adhesin	• Alters the host range or tropism of the agent • Enhances the susceptibility of a host population to the agent	• Probably none
Fusion Protein/Invasin	• Alters the host range or tropism of the agent • Enhances the susceptibility of a host population to the agent	• Probably none
Dissemination	• Enhances the harmful consequences of the agent • Increases the transmissibility or the ability to disseminate the agent • Enhances the susceptibility of a host population to the agent	• Probably none

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Work in Progress

We are involved in reforming the Gene Ontology (GO) terms relating to host-symbiont interactions via the Multiorganism Working Group. This will provide a greater comprehension of these processes for both humans and machines.