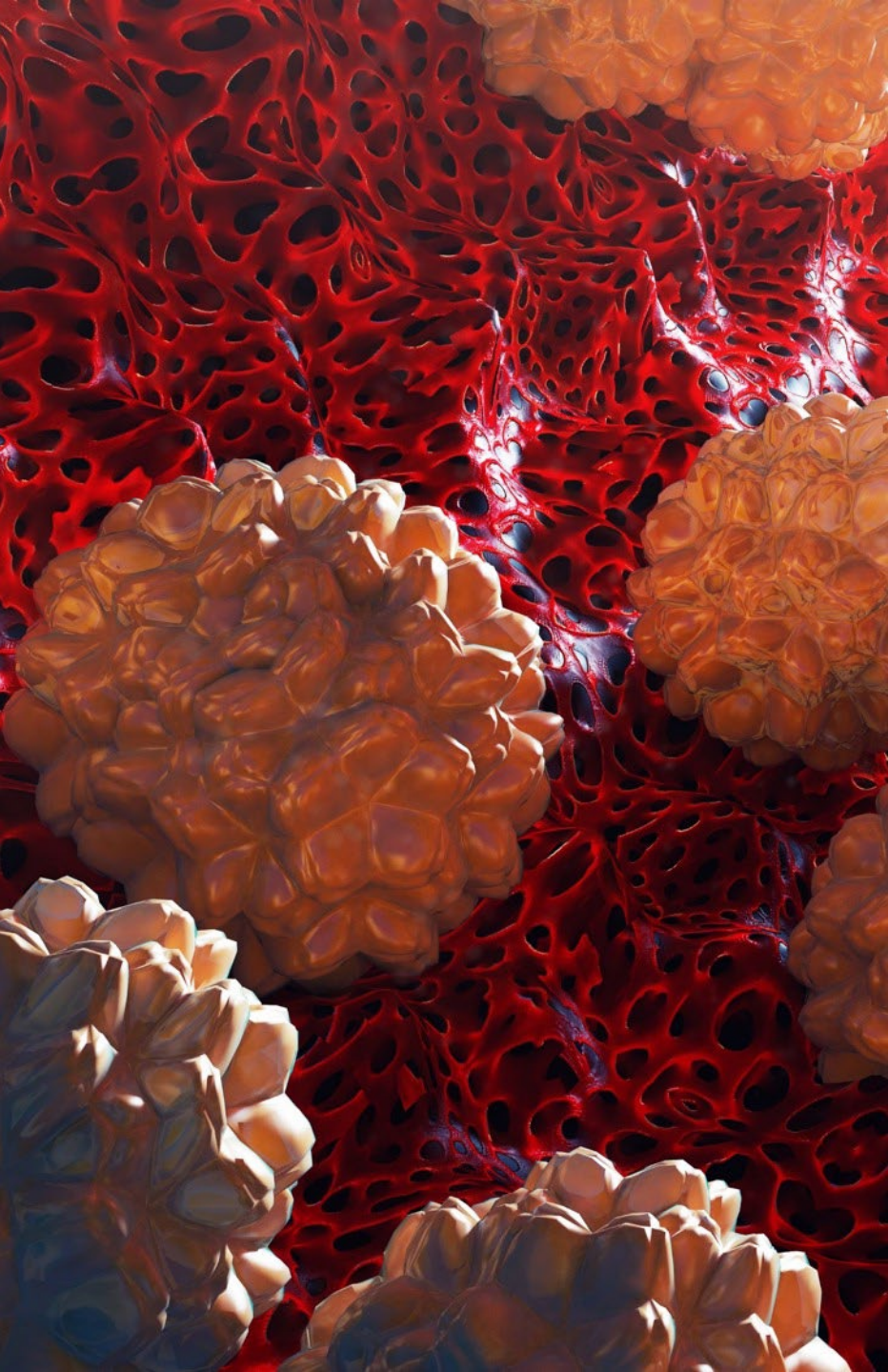


signature
science[®] LLC

© 2024 Signature Science, LLC



Sequences of Concern. Individually and in Pathogens. Some Thoughts.

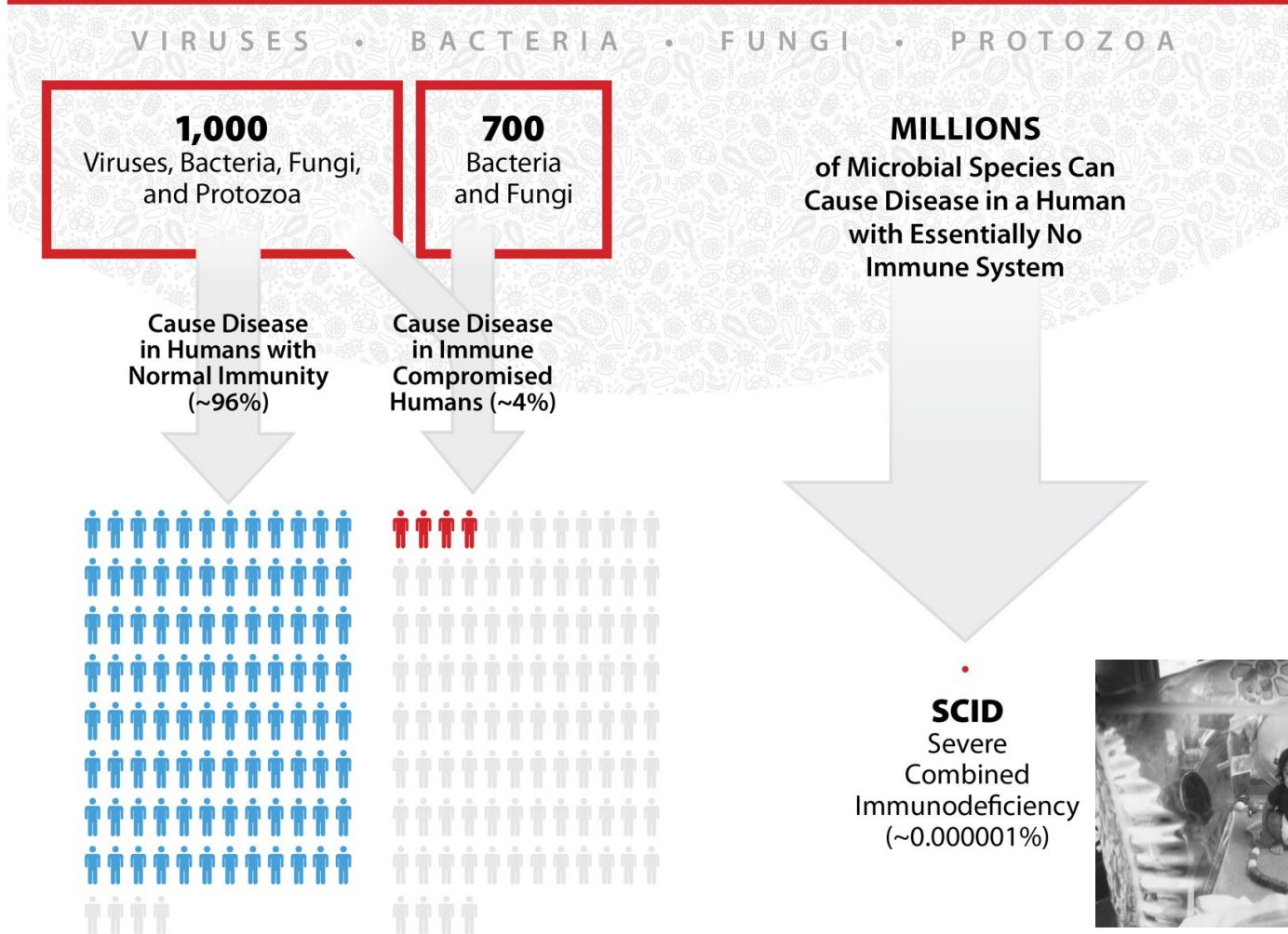
Raytheon (RTX) Sequence
Screening Workshop #2
10 October 2024

Gene D. Godbold

signature[®]
science LLC

How Many Human Microbial Pathogens?

There are Approximately **1 TRILLION** Microbial Species on Earth



Why Can't Most Microbes Harm Us?

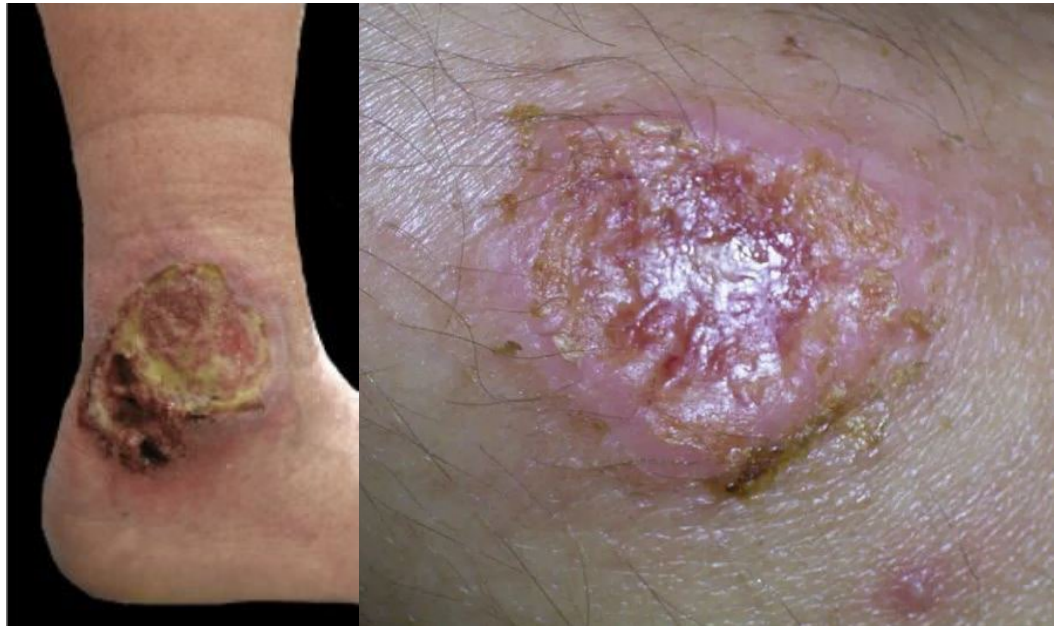


Is it them?

Is it us?

The Outcome of Host-Parasite Encounters is Chiefly Governed by Host Immune Defense and Parasite Virulence Factors = Sequences of Concern

Hypothesis: Sequences that subvert and evade immunity make hosts susceptible.



... based on annotated SoCs from 140+ bacterial,
85 viral, and 25 eukaryotic pathogens

Functions of Sequences of Concern

Direct-Acting Sequences of Concern

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-creation in host cell

Immune-Subverting SoCs

- Suppress host immune signaling
- 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



Microbial Parasites Subvert 9 Host Cell Processes

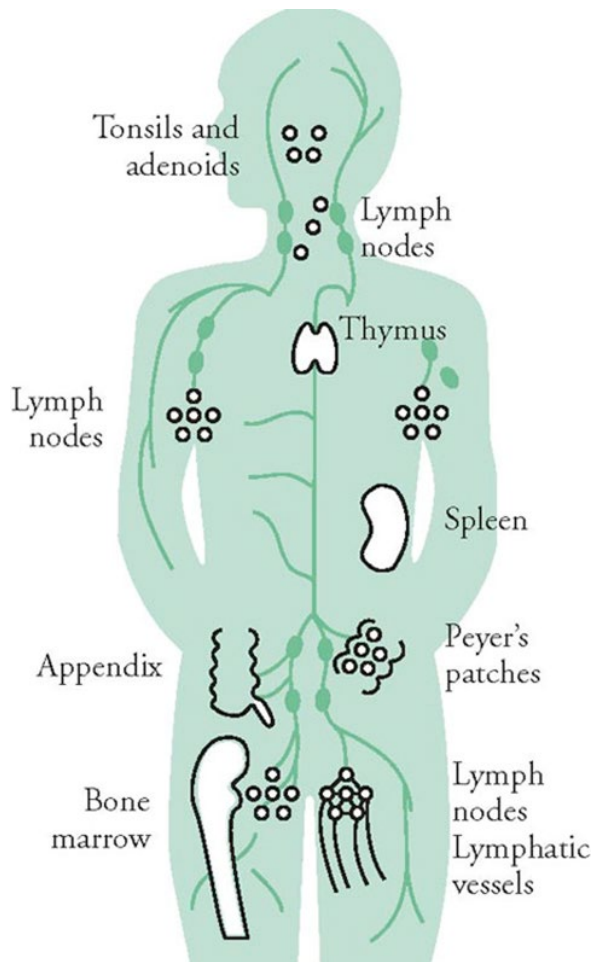
- Cell cycle
- Cytoskeleton
- Endomembrane dynamics
- Programmed cell death
- Small GTPase biology
- Transcription
- Translation
- Ubiquitination
- Xenophagy

New Gene Ontology (GO) Terms for Microbial Pathogenesis

- **Pascale Gaudet** of the GO Consortium
- Renovated host-symbiont branch of GO: “Symbiont-mediated (perturbation/suppression/activation) of host [biological process]”
- Only 30 FunSoCs—need more granularity
- 60 new GO terms, ~90 renovated/renamed terms
- More granular annotation allows us to understand what sequences do to the host



Scoring FunSoCs and GO Terms

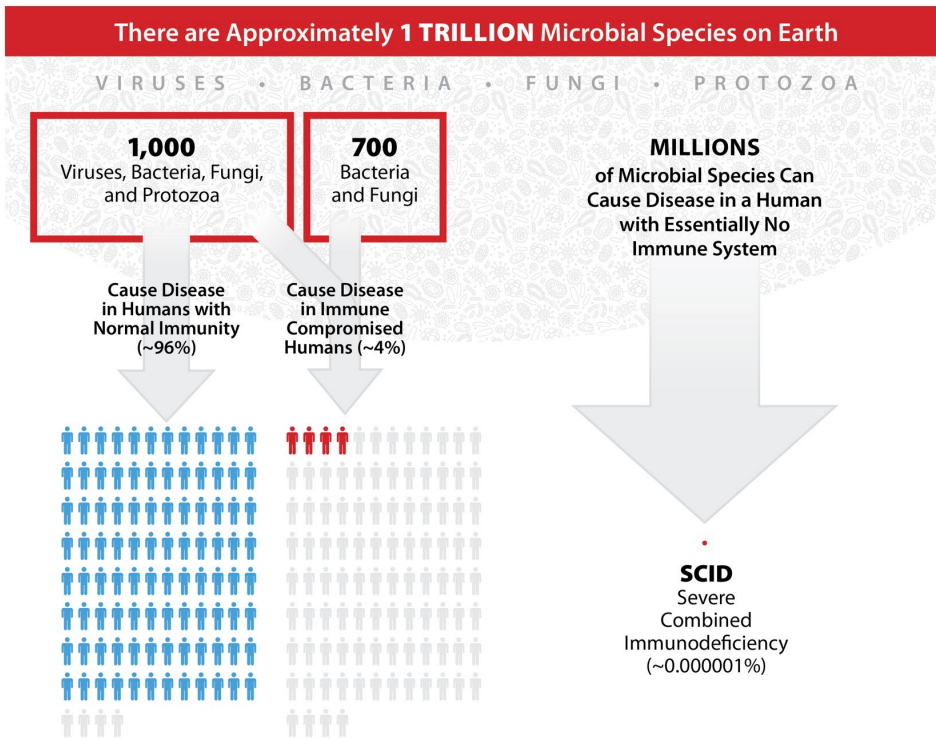


- Damaging: 3-9 pts
- Immune-subverting
 - Upstream immune signaling: 4-5 pts
 - Downstream immune signaling: 3 pts
 - Defeat immune effectors: 2-3 pts
- Immune-evading: 1 pt
- Adhesion/Invasion: 2 pts
- Disseminating: 3 pts
- Manipulating host cell biology: 1-3 pts

Tiers of Concern for *Sequences*

Score	SoC type	Our Dataset (FunSoCs only)
< 1	Not of concern	
1-2	Minimal SoC	651 bacterial; 71 viral; 57 eukaryotic
3-8	SoC	629 bacterial; 312 viral; 186 eukaryotic
9+	Maximal SoC (very concerning)	176 bacterial; 53 viral; 5 eukaryotic

Nonviral Pathogen Species Took Independent Routes to Pathogenicity



- SoCs exploit host innate immunity similarly, but evolved convergently
- Not every component of host innate immunity are subverted by pathogens. (Excess immune capacity present?)
 - To replicate/transmit effectively, pathogens only need “enough” immune subversion for “long enough”.
- **Conclusions:**
 - Many ways to pathogenicity.
 - Not all have been realized vis-à-vis human biology.
 - In silico *could* produce novel pathogenic possibilities...even against previously untested innate immune components.

signature
science[®] LLC

© 2024 Signature Science, LLC