

emergence, resurgence, resistance

new approaches to combat antibiotic resistance

The Shared Global Threat from Infectious and Parasitic Diseases

Emergence



Resurgence



Resistance



Zoonoses



Ecoshifts



Over-Use of Antibiotics



Urbanization of LDCs

Political Instabilities

Market Incentives

NO ESKAPE!: Resistant Bugs and Few New Drugs



- increasing resistance in G⁺ and G⁻ pathogens in hospital and community settings

- the **ESKAPE** pathogens

Enterococcus faecium

Staphylococcus aureus

Klebsiella pneumoniae

Acinetobacter baumannii

Pseudomonas aeruginosa

Enterobacter species

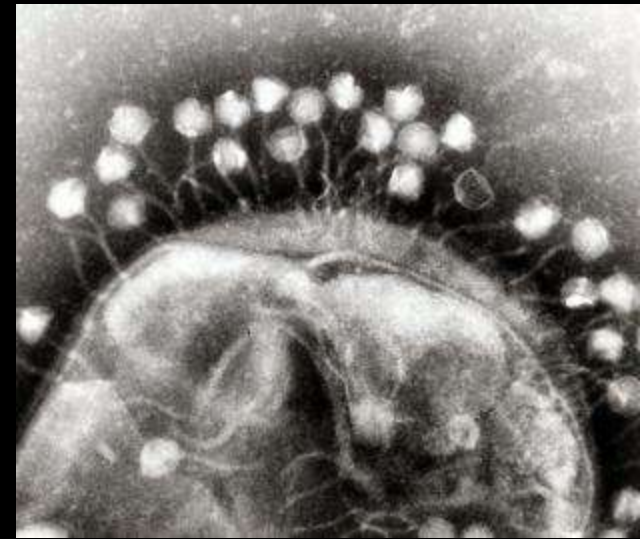


Bacteriophages as Anti-Microbials

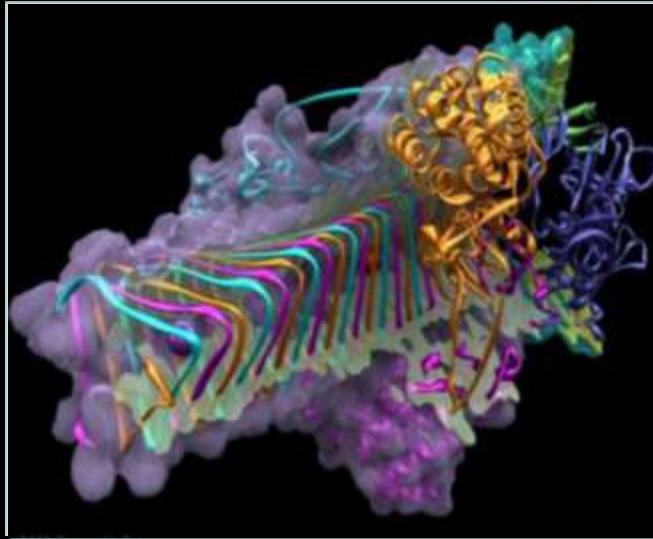
Felix d'Hérelle



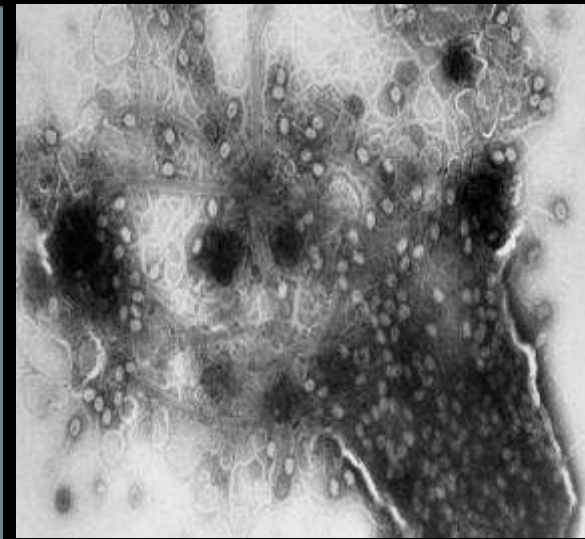
Frederick Twort



Phage Receptor Targets



Genome Injection Complex



Replication and Lysis

Synthetic Biology and the Design of Synthetic Bacteriophages

- **advances in genome assembly (size, cost)**
- **in silico design of phages with no evolutionary counterpart**
- **challenges**
 - **engineer activity against broad spectrum of bacteria versus single species**
 - **thwarting evolution of bacterial resistance**
 - **selective engineering of bacterial lysis versus bacterial growth inhibition for different clinical settings**

Synthetic Bacteriophages

- **massively parallel synthesis of designer phage genomes**
- **rapid design flexibility based on genome sequence(s) of new target organisms (patient-specific/outbreak-specific)**
- **digital DNA design for e-transfer to any location for production**

“The Matternet”

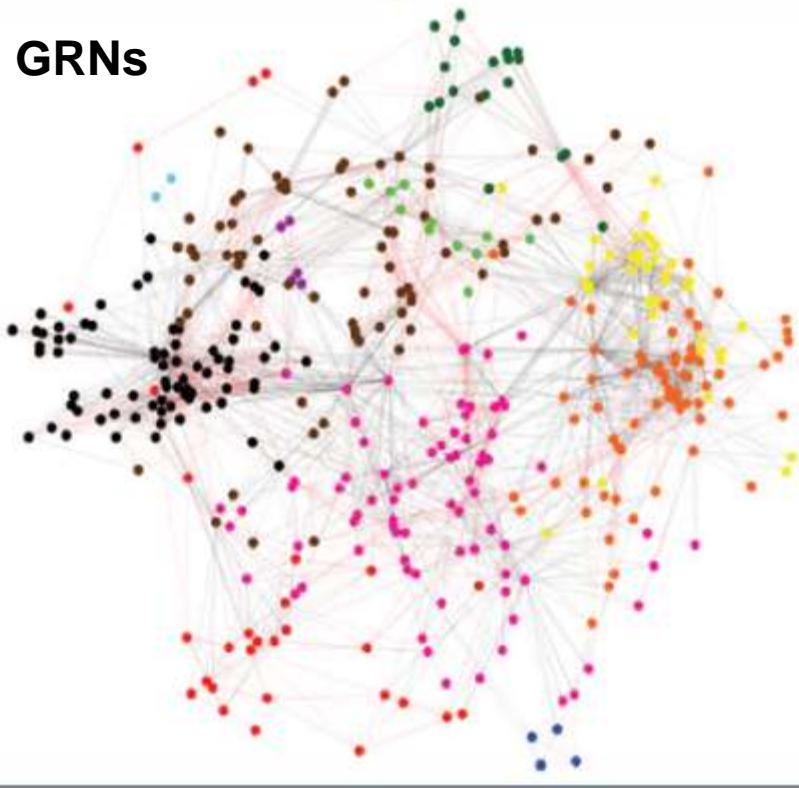
- **internet for objects**
- **digital coding of fabrication specifications to point-of-need (PON) synthesis units**
 - **digital “omics” and synthetic biology**
 - **broader concept of digital 3D printing/manufacturing of diverse materials**
- **proposals to complement PON synthesis with local drone/UAV delivery of packages (DroneEx)**
 - **startup companies: Matternet, Aria**

**Evolutionary and Developmental Influences
on Physiological Regulatory Networks and Disease Patterns**

A Neglected Dimension in Biomedical Research and Public Health

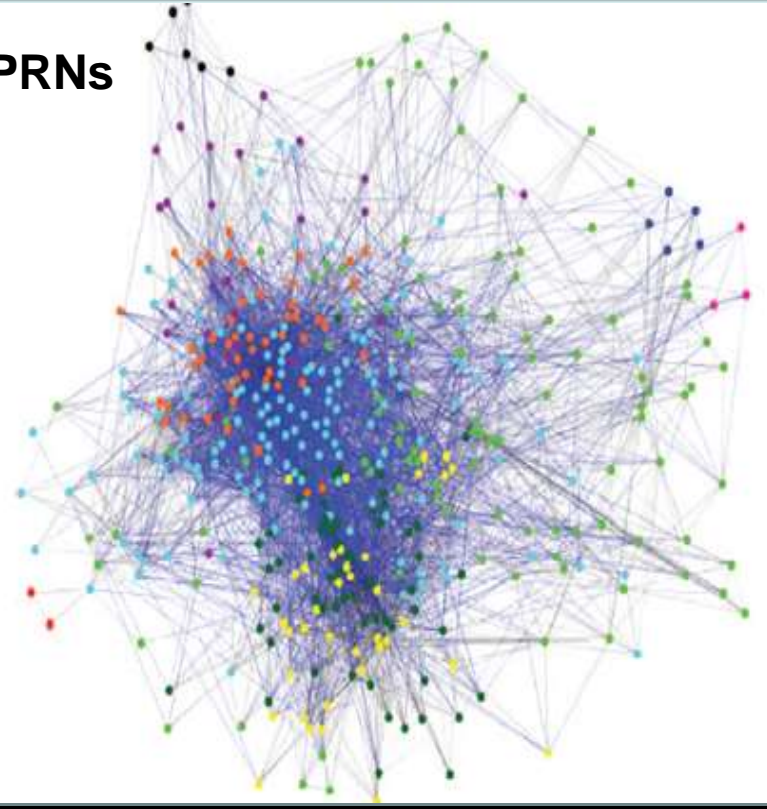
Gene Regulatory Networks (GRNs) and Phenotypic (clinical) Networks (PRNs) in Human Disease

GRNs



- nodes are diseases
- edges are shared genes

PRNs



- nodes are diseases
- edges are comorbidities

Adapted from: D. A. Davis and N. V. Chawla (2011) PLoS One 6, e.22670

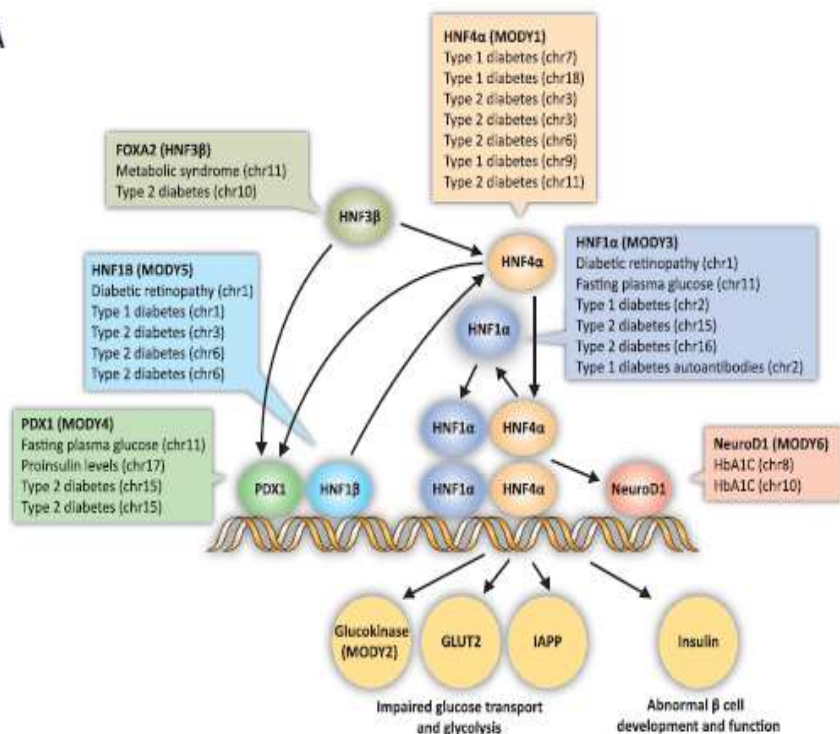
CAS and Clinical Medicine

- **new taxonomies for disease predisposition risk and pathogenesis of disease progression**
 - **disruption of homeostatic (physiological) regulatory networks (PRNs) and their underlying genetic regulatory networks (GRNs)**
- **extensive coupling and co-evolution of PRNs (symmorphosis)**
 - **intracellular, across different cell lineages**
- **pathological perturbation in a PRN network will trigger ripple effects' (cascades) of graded perturbations in coupled PRNs (disease co-morbidities)**

Variants for Common Disease in Related Disease Categories Cluster in Shared Regulatory Networks

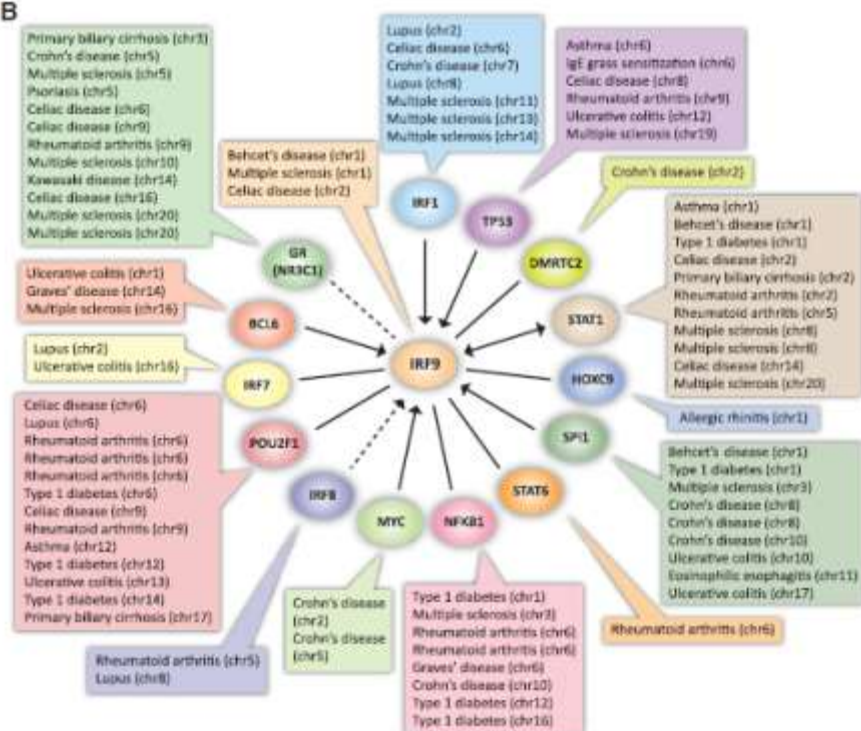
Diabetes

A



Autoimmune Disorders

B



From: M. T. Maurano et al. (2012) Science 337, 1190

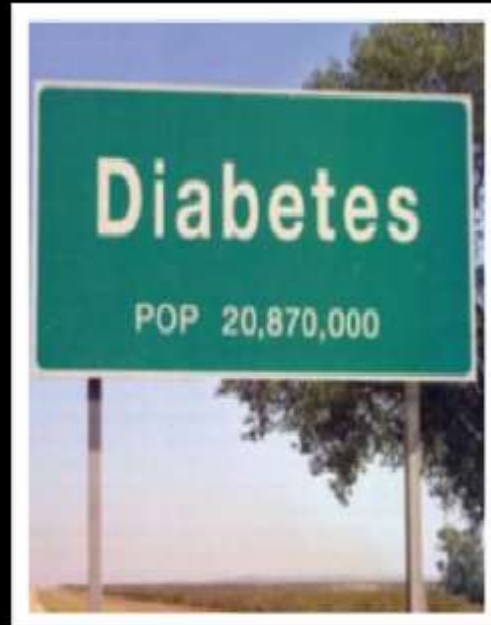
Evolutionary Medicine: Anthropology, Behavioral and Social Dynamics and Contemporary Disease Risk and Patterns

- **evolutionary history of genetic- and physiological-regulatory network structures define the cell/organ plasticity/adaption repertoire to changing ecological/environmental conditions**
- **asynchrony between rapid change in human lifestyle and pace of evolutionary change in GRNs/PRNs**
 - **increased lifespan and chronic disease**
 - **lifestyle diseases**
 - **global mobility and evolutionary fitness to “evo-econiche” risks (immune response to pathogens)**

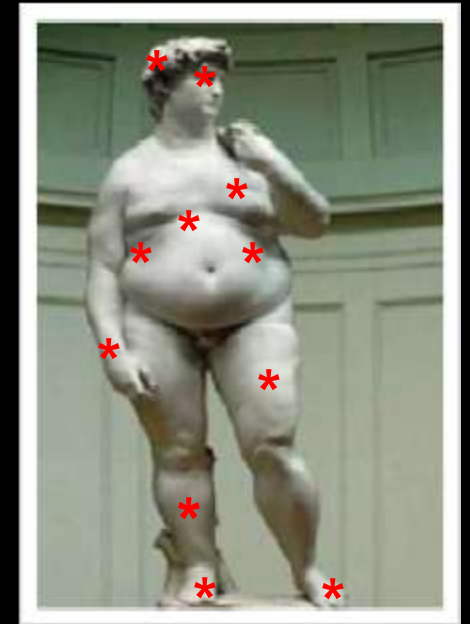
Combating Diabetes



**After a Short Stay
in America,
Michelangelo's David
Returned to Europe**



**The Number One
Healthcare Cost in 2020**

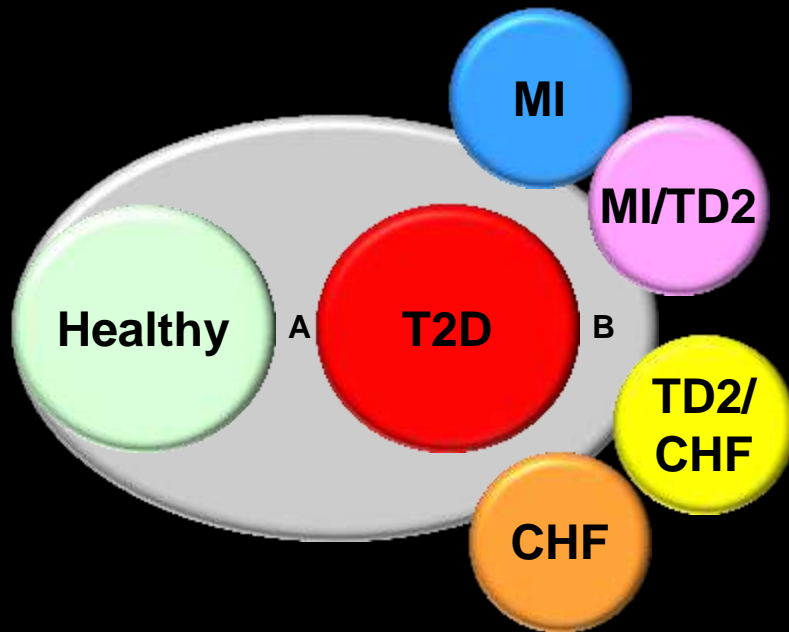


**A Multi-Organ
Disease**

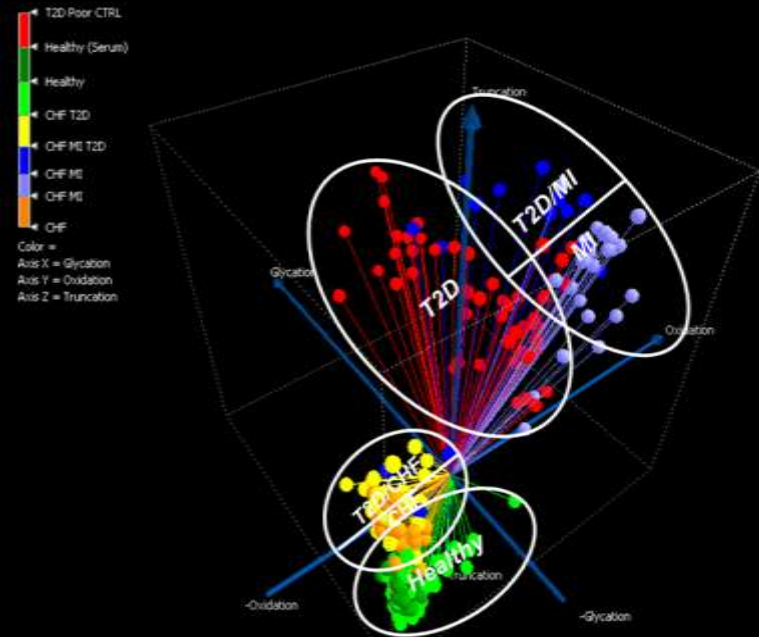
Human Anthropology and Contemporary Disease

- **metabolic disease and obesity**
- **shift from hunter-gatherer 'thrifty genotype' to calorific overloads**
- **progressive dysregulation of multiple metabolic modules**
- **shifts in intestinal microbiota and T2D microbiome**

Network Perturbations in Coupled Physiological Regulatory Networks (PRNs) and Co-Morbidities (data courtesy of Dr. R. Nelson, ASU Biodesign Institute)



**Co-morbidities:
Coupled PRNs and
“Adjacencies in
Network Disruption”**



**Biosignatures and
Segregation of Comorbidity
Cohorts in T2D**

**Friendly Fire:
The Adverse Effects of Persistent, Low Grade (sub-clinical)
Inflammatory Processes In Promoting Chronic Diseases**

Friendly Fire: The Adverse Effects of Persistent, Low Grade (sub-clinical) Inflammatory Processes and Chronic Diseases

- **recognition of complex recruitment and retention networks for leukocyte/macrophage populations in body organs**
- **pro-inflammatory activated macrophages (M1 phenotype) release inflammatory mediators that increase insulin resistance**
 - **adipocytes (white fat), liver, muscle and brain raising blood glucose levels to sustain effective acute immune responses**
- **restoration of nutrient intake to homeostatic levels and/or increased metabolic burn reestablishes equilibrium tissue-set point and M2 phenotype macrophage population**
- **prolonged mismatch in nutrient intake and expenditure results in new tissue-set point and M1 macrophage domination and systemic-insulin resistance**
- **emerging relationships between insulin resistance, metabolic syndrome and neuropsychiatric disorders**

Genomic and Physiological Regulatory Networks (GRNs/PRNs), Evolution and Disease Patterns

- **additional potential influence of epigenetic events in modulation of GRN/PRN structure**
 - fetal origins of disease hypothesis
 - anthropogenic eco-environmental shifts
- **evolutionary medicine**
 - neglected component in both research and clinical medicine
 - major opportunity for ASU leadership (teaching and research)