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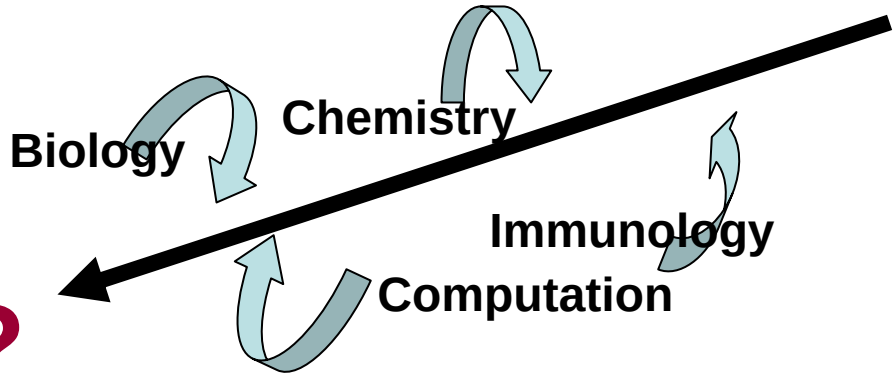
**Big Problem in Biomedicine**

**Disruptive Innovation or Invention**




**Solution?**

# Center for Innovations in Medicine

# APPROACH to SCIENCE

# Current CIM Programs

- **Cancer Eradication***: Universal prophylactic vaccine for preventing cancer*
- **Genomes > Vaccines**: *Discover Algorithm to predict vaccine subunits and convert to chemical vaccines*
- **DocInaBox**: *Create in the house diagnostic unit for PreSymptomatic BioSignatures*

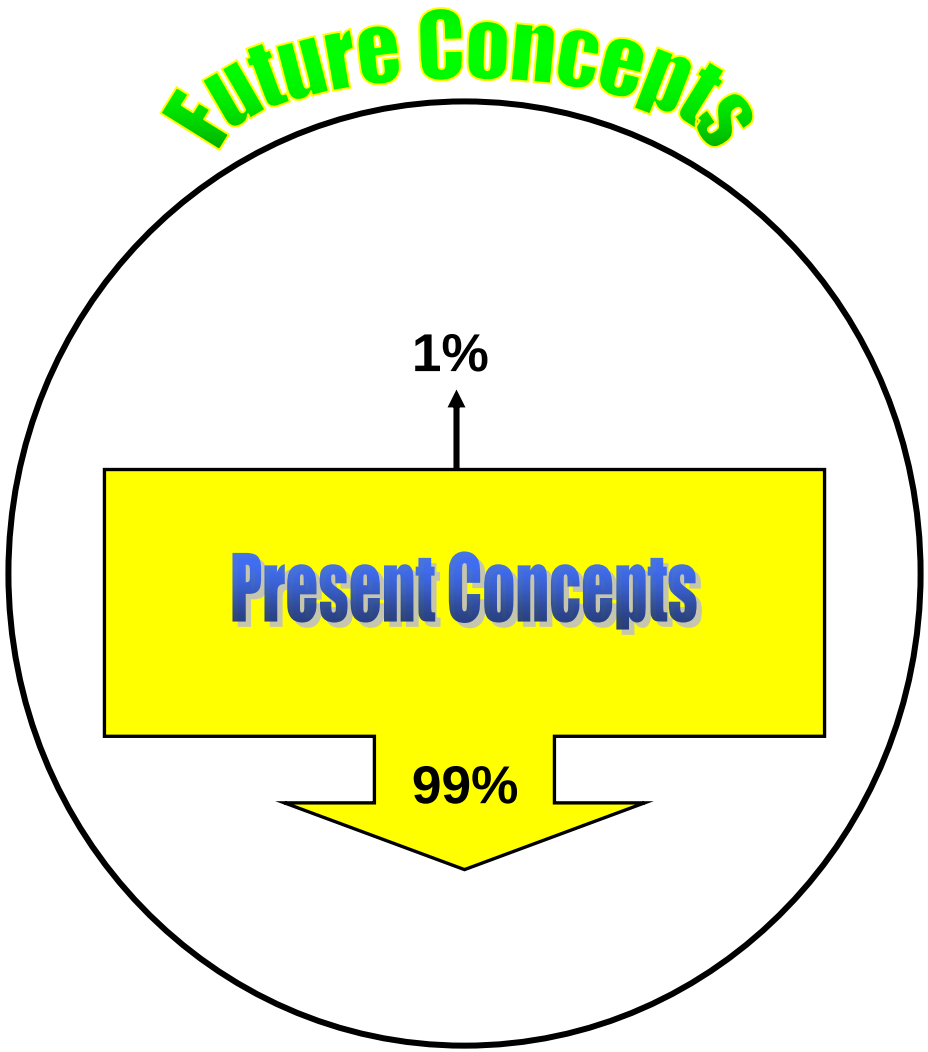
# Infinity Research

$$YourContribution = \frac{WhatYouDid}{WhatOthersDid}$$

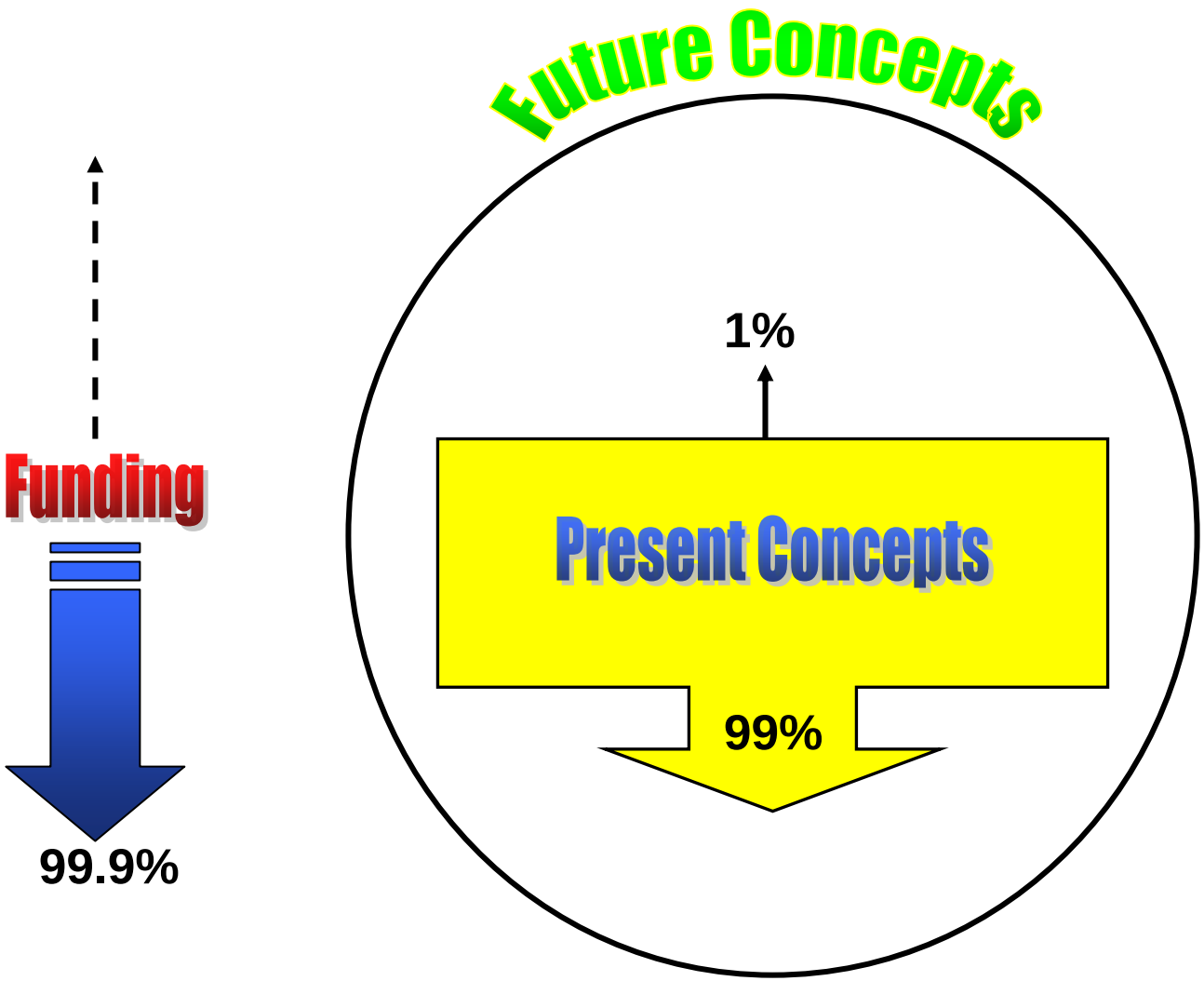
# Infinity Research

$$YourContribution = \frac{AnythingYouDo}{0} = \infty$$

# Value of the Contrary



# Value of the Contrary – Funding



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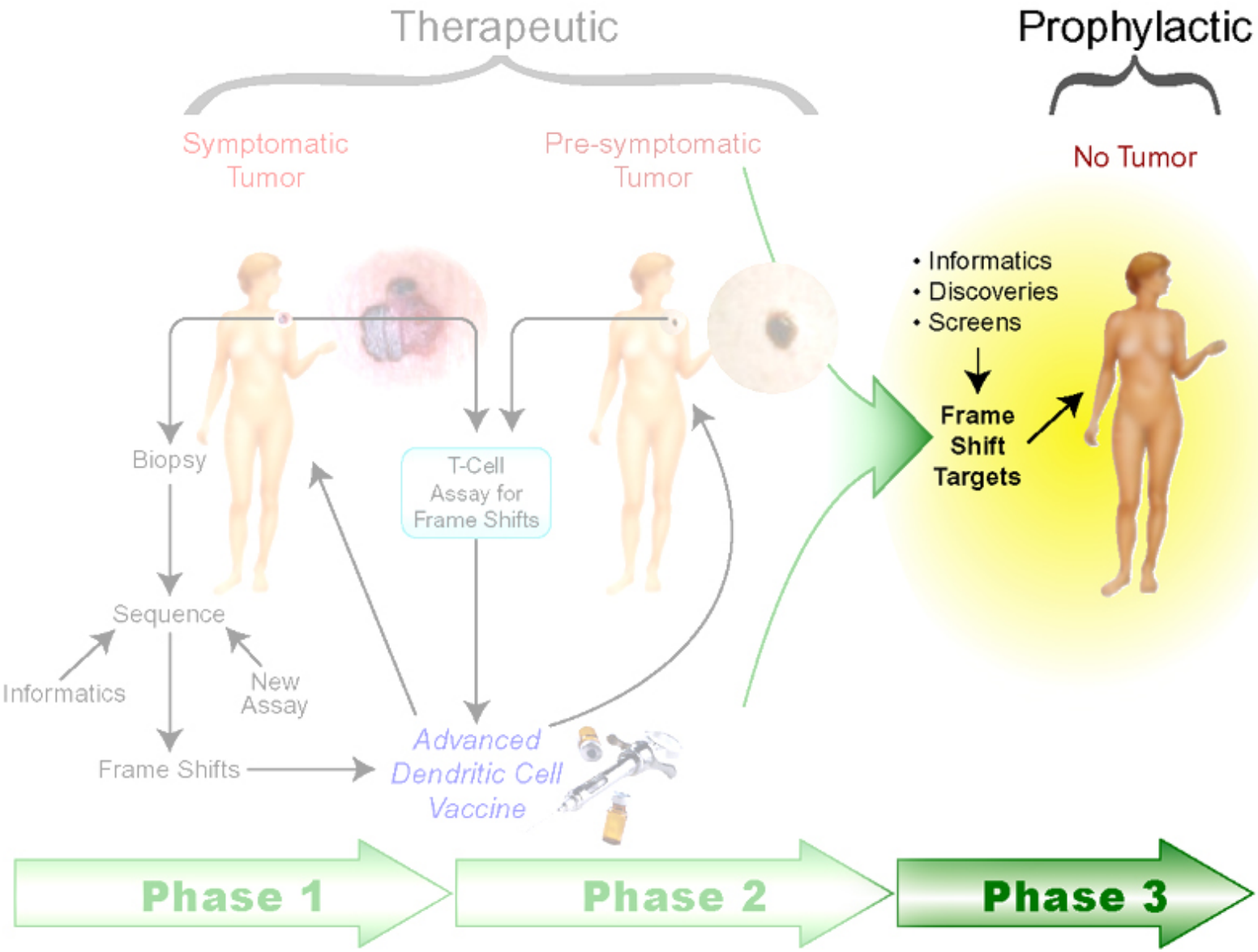
# Cancer Eradication Project:

## Dr. Doug Lake



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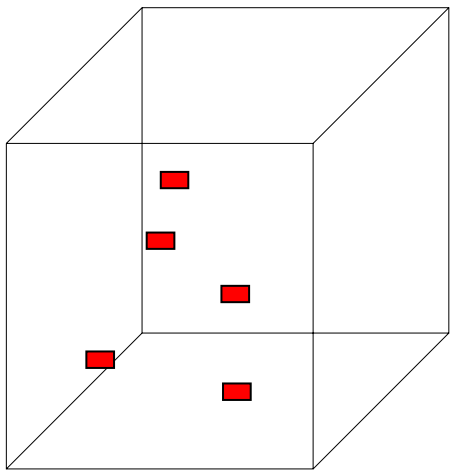
# Genomes → Vaccines:

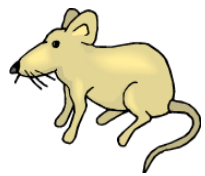
**Dr. Kathryn Sykes**

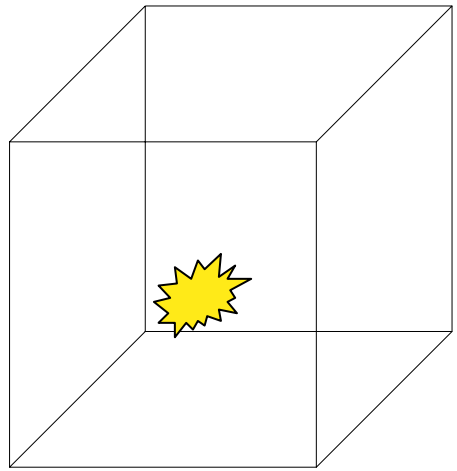
**Design genes from GenBank files**

**Construct library**

**1,000s**







**3D Array All Genes of the Pathogen**

**Conduct One Animal-Protection Experiment**

**Pinpoint Candidates**

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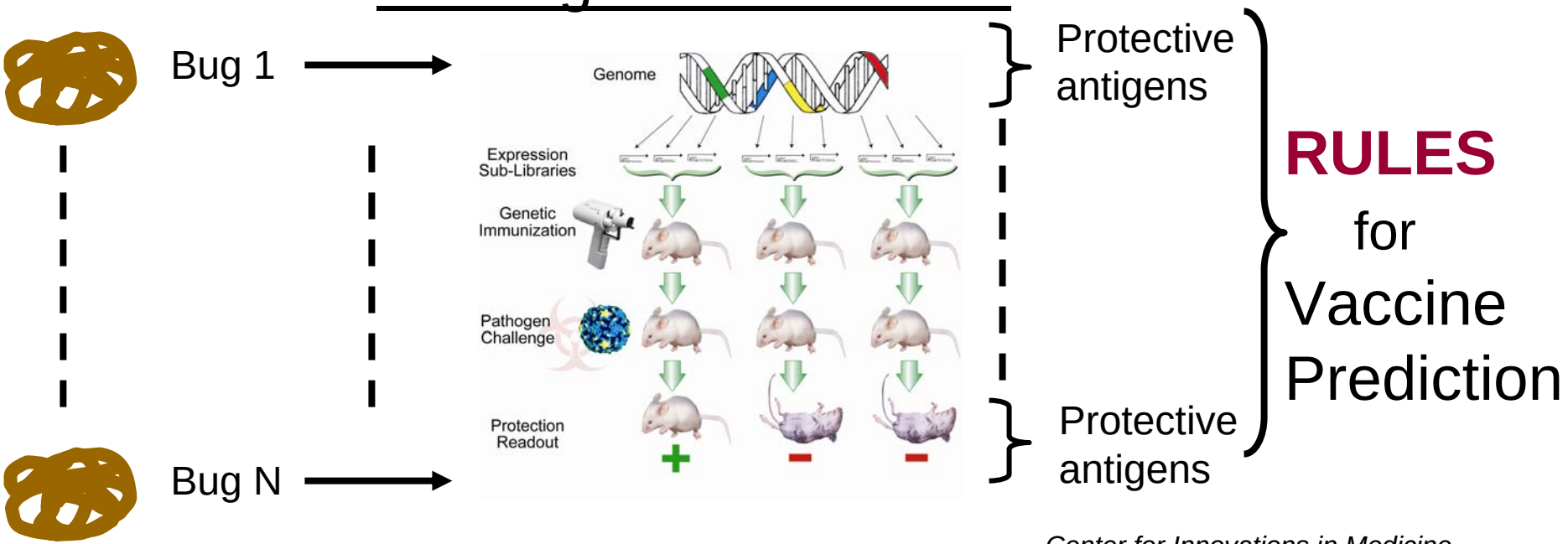
# The Algorithm Problem

**NO Existing Algorithm for Predicting Vaccine Works**
**NO Combinations Work**

**Conclusion: The Rules Need to be DISCOVERED**

## The Algorithm Solution



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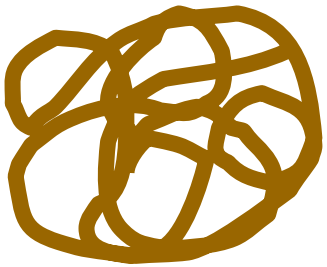
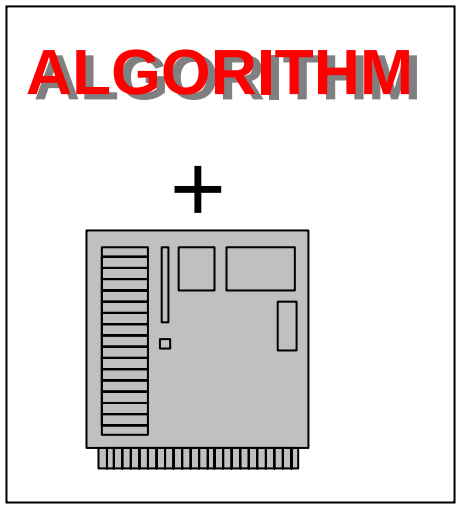
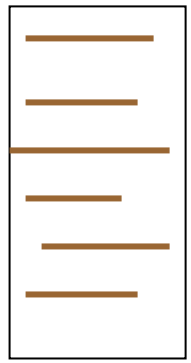
# IDEAL VACCINE WORLD



Pathogen's
Genome Sequenced
< 3 days

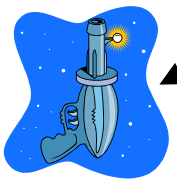


10 or less genes
for the vaccine

Chemical Synthesis
Of GENE VACCINES

CHEMICAL
VACCINES



Protective Vaccine
In Days to Weeks

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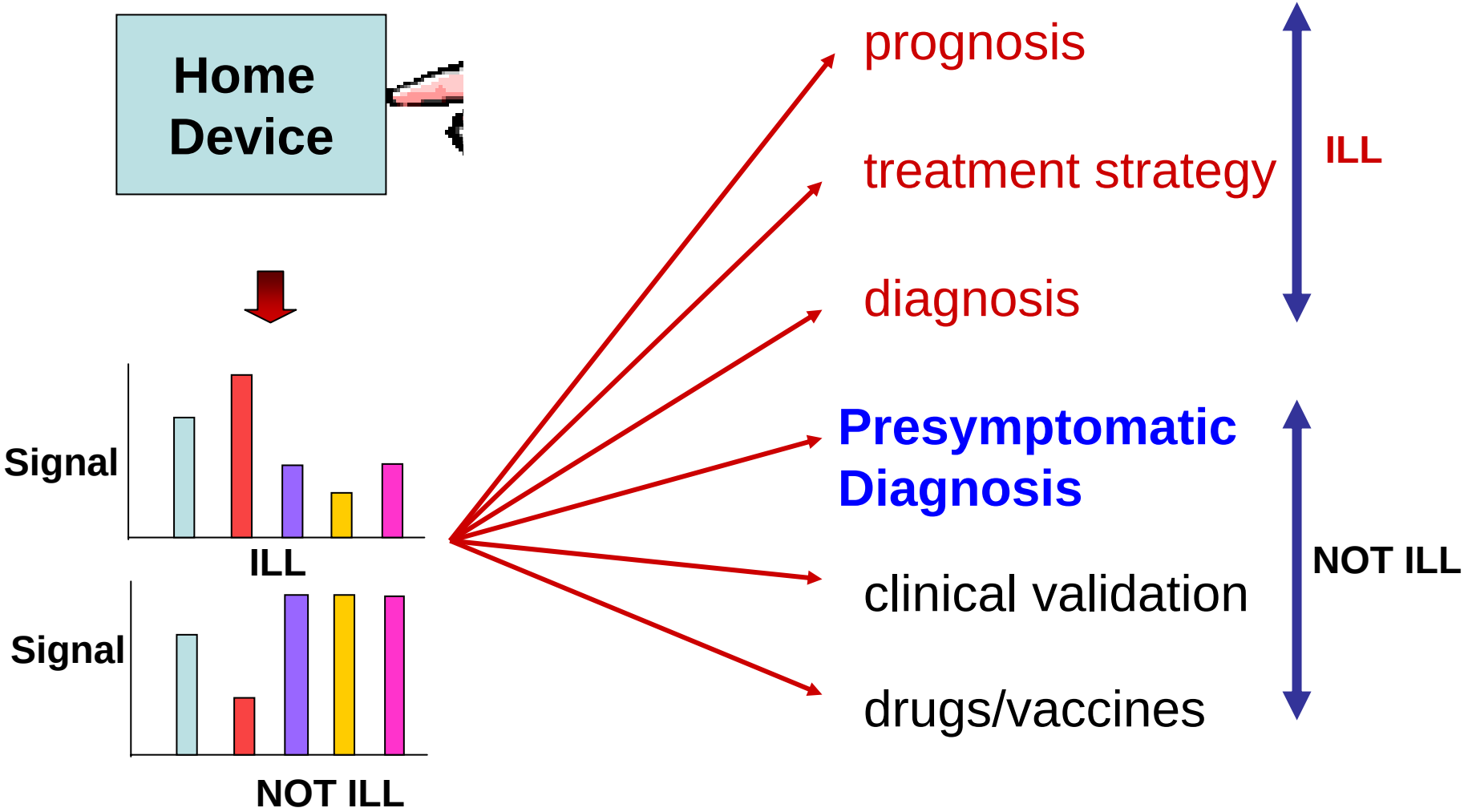
# Doc InA Box:

## SAJ/Dr. Neal Woodbury



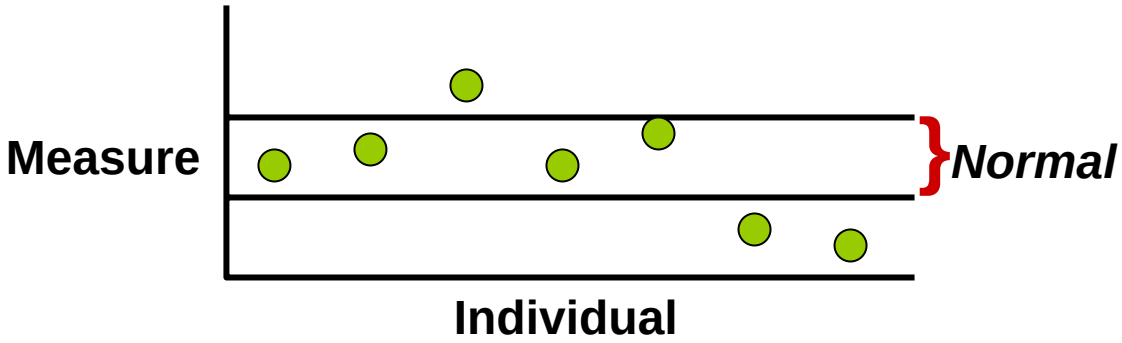
# Biomarkers versus BioSignatures

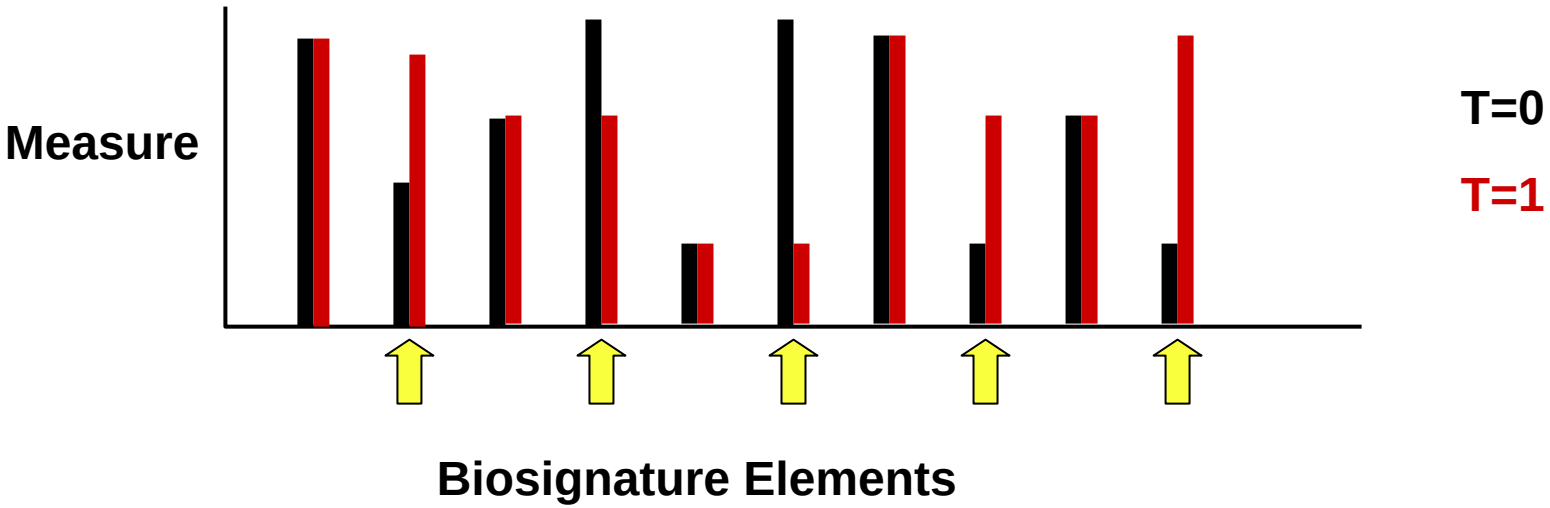
**Biomarkers:** ~70 clinically approved

**Biosignatures:** ***1000-1,000,000*** elements
(proteins,peptides, metabolites, nucleic acids, cells)

# Biosignatures vs Biomarkers

*Individual vs. Population Normalization*

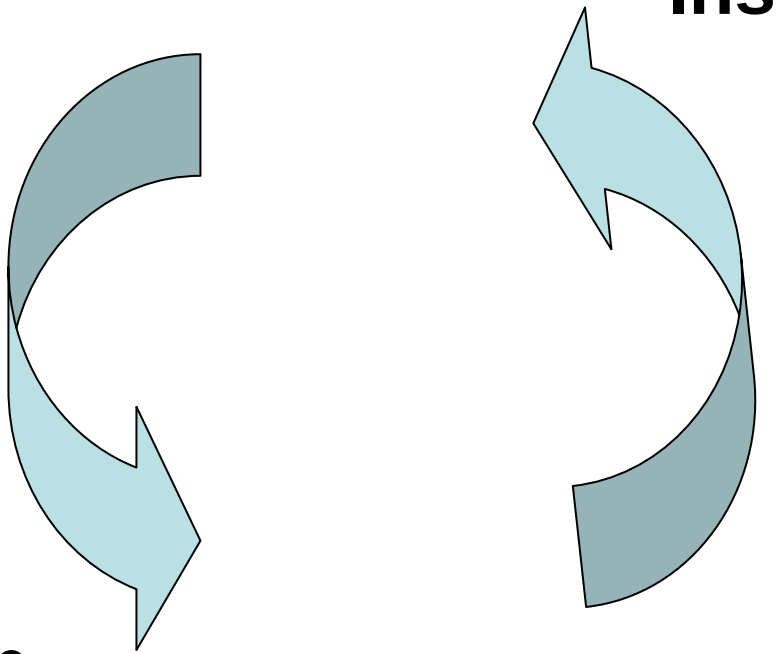


# Components to Make BioSignatures Reality

**Animal Models Human Trials**

**Instrumentation**



**Ligands**

↓

***The Problem!***

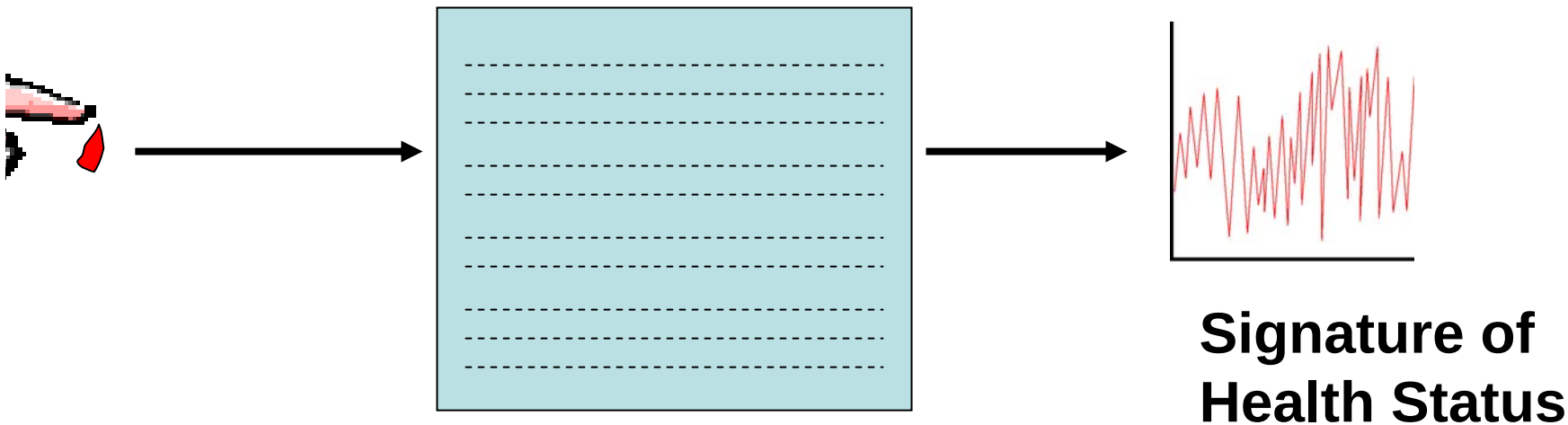
**Target Identification**

**Computation**

# LIGANDS are the LYNCHPIN

***We need a system to make 10,000s of antibody-like molecules to read-out all the informative Components of blood, saliva etc.***

**GOAL:** ***SuperArray***



**Signature of Health Status**

**$10^4$ to $10^6$ binding agents for proteome**

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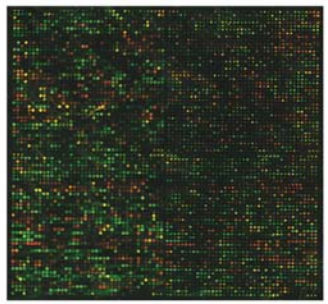
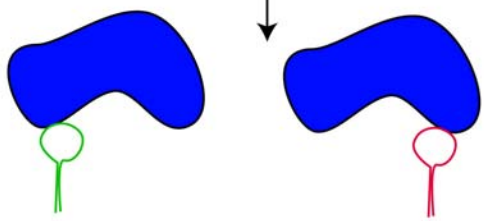
# Our Solution:
## HTP Artificial Antibody Production

$10^{11}$ - $10^{13}$ member peptide or nucleic acid libraries contain ligands with $K_d < 10^{-7}$ for essentially all proteins

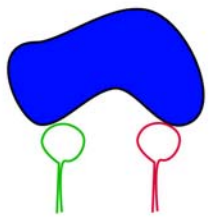
Computational modeling and library reduction

Create computationally reduced master library of $10^4$ - $10^6$ members using optically or electrochemically directed array synthesis and probe with labeled protein targets. This should result in multiple hits with $K_d<10^{-5}$





Identify multiple weak ligands to the target protein. Individually, the ligands have $K_d<10^{-5}$



Combine weak binding ligands to form one strong binding ligand. The combined binding strength of ligands approach the product of their individual $K_d$'s: $10^{-8}$ - $10^{-10}$

Neal Woodbury

# RESOURCES

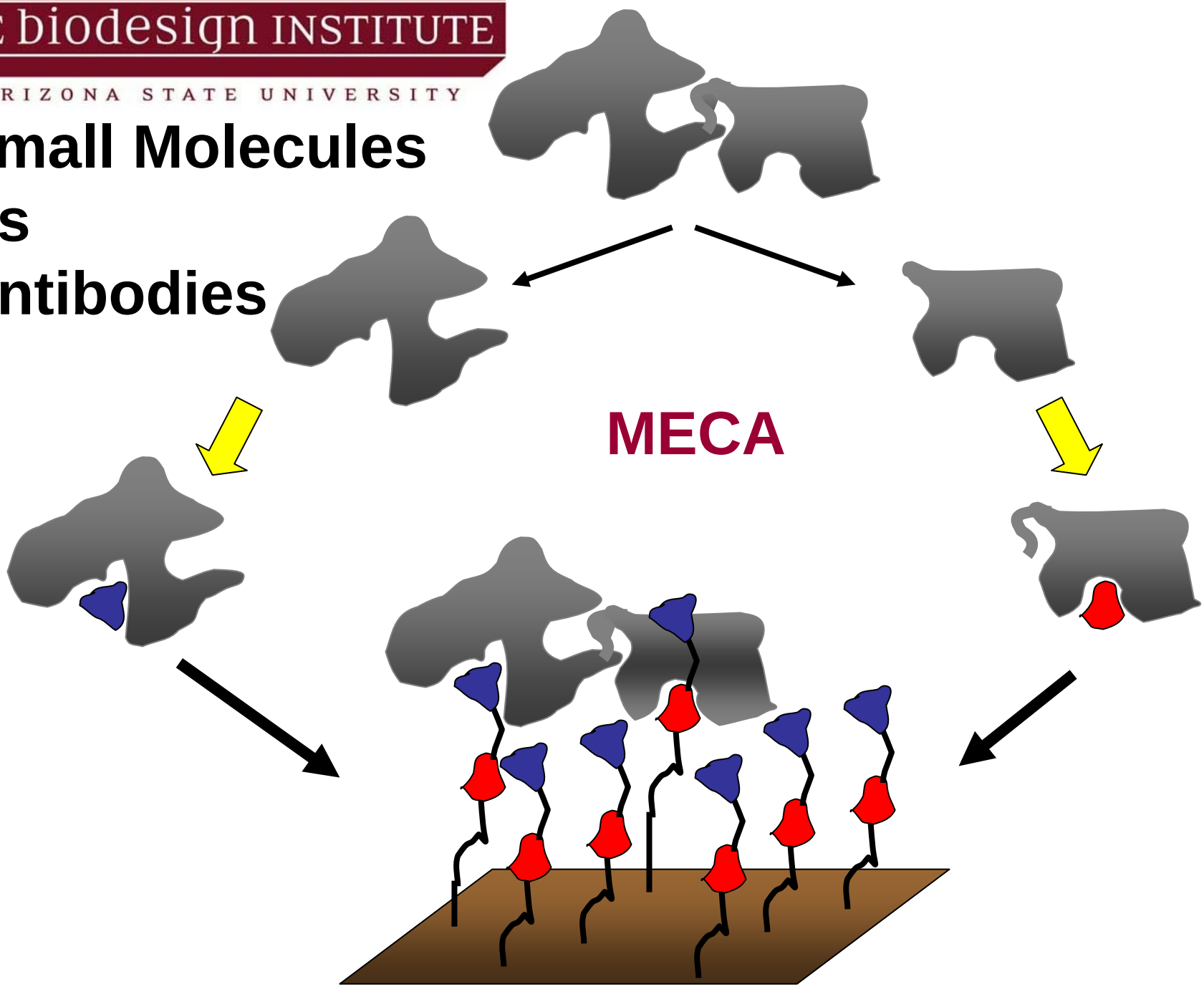
- **Invention**
- **Robotics**
- **HTP systems**
- **Gene building**
- **Proteomics**
- **Antibody Production**
- **Immunology**
- **Infection models**

**Arrays**

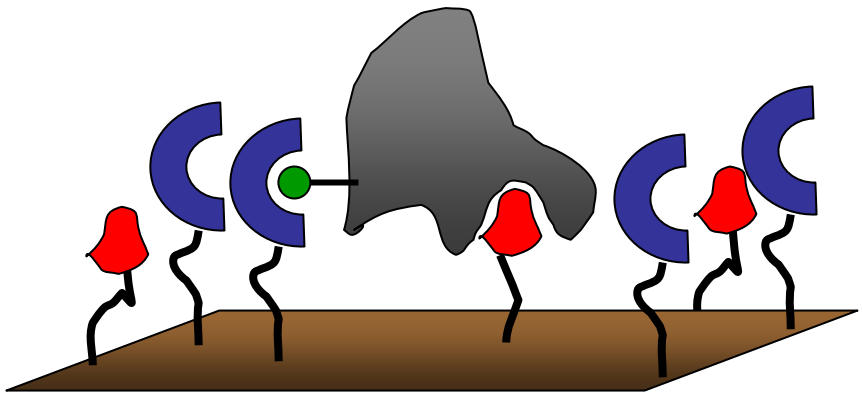
**Vaccinology**

**InVitro Translation**

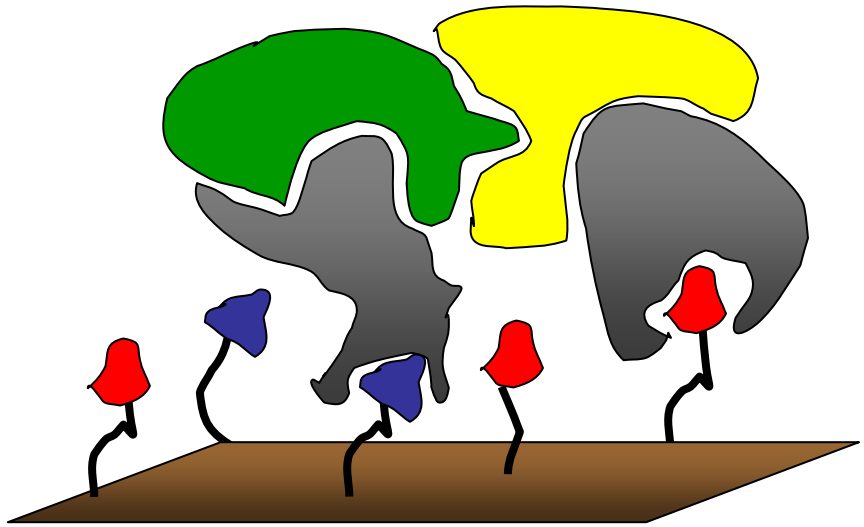
# Small Molecules As Antibodies



# PINCER: SmMol "Antibodies" binding Protein Modifications/Complexes



High affinity binding of a particular post-translationally modified protein through a two-point contact.



Bivalent binding of a multi-protein complex

# BioSignatures of Infection

***Presymptomatic/Prognostic***

**NOW** → **5 years**

**+/- Infection**
**Animal Models**

**DOC-IN-BOX**

# Nested Product Opportunities

## NOW

## 5 Years

**Diagnosis** → **Point of Care** → **Shopping Centers** → **Home Devices**

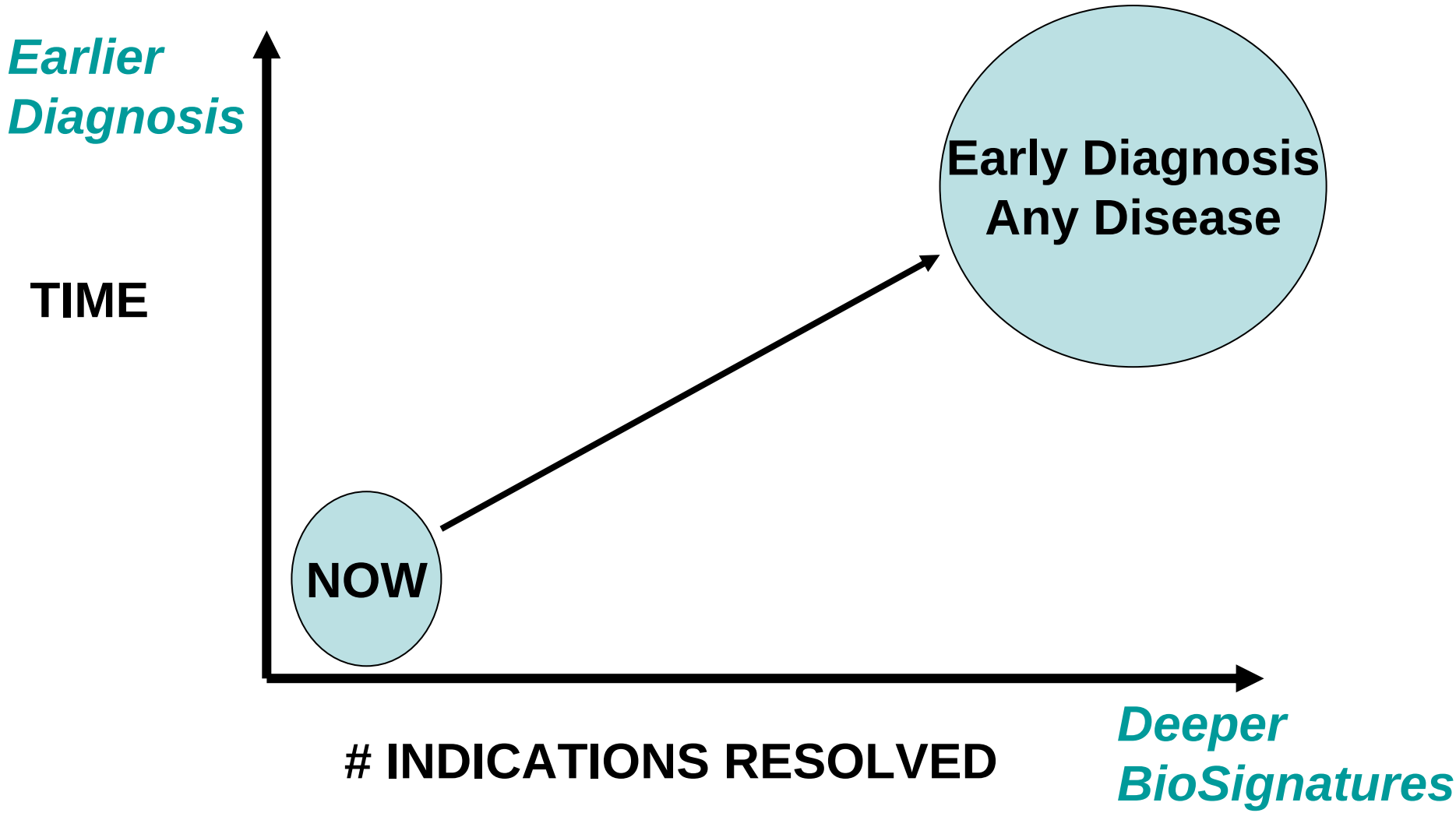
**Biothreats**
**Clinical Trials**

**Single, Few Features**

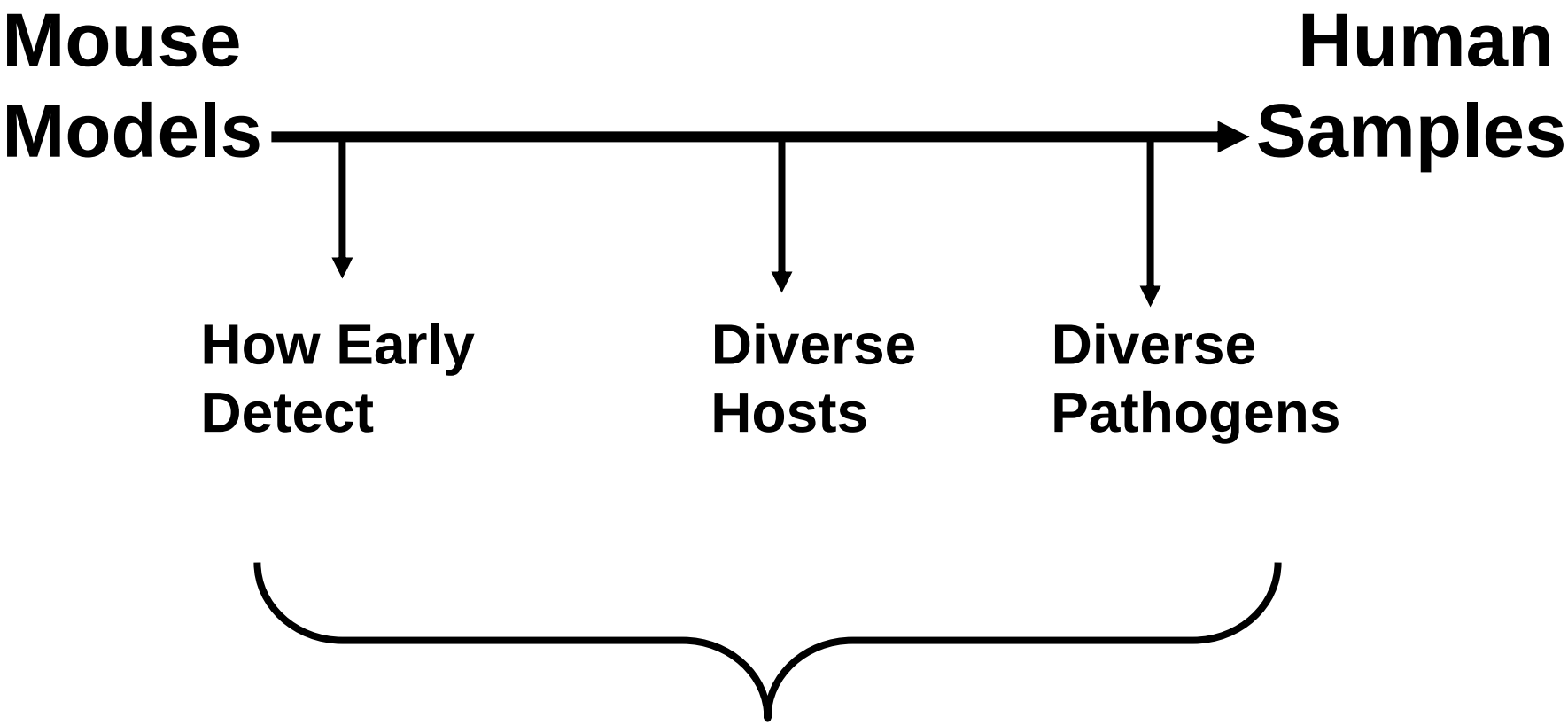
**Multiple Indications**

**Complete Health Profile**

# Evolving BioSignature Capabilities

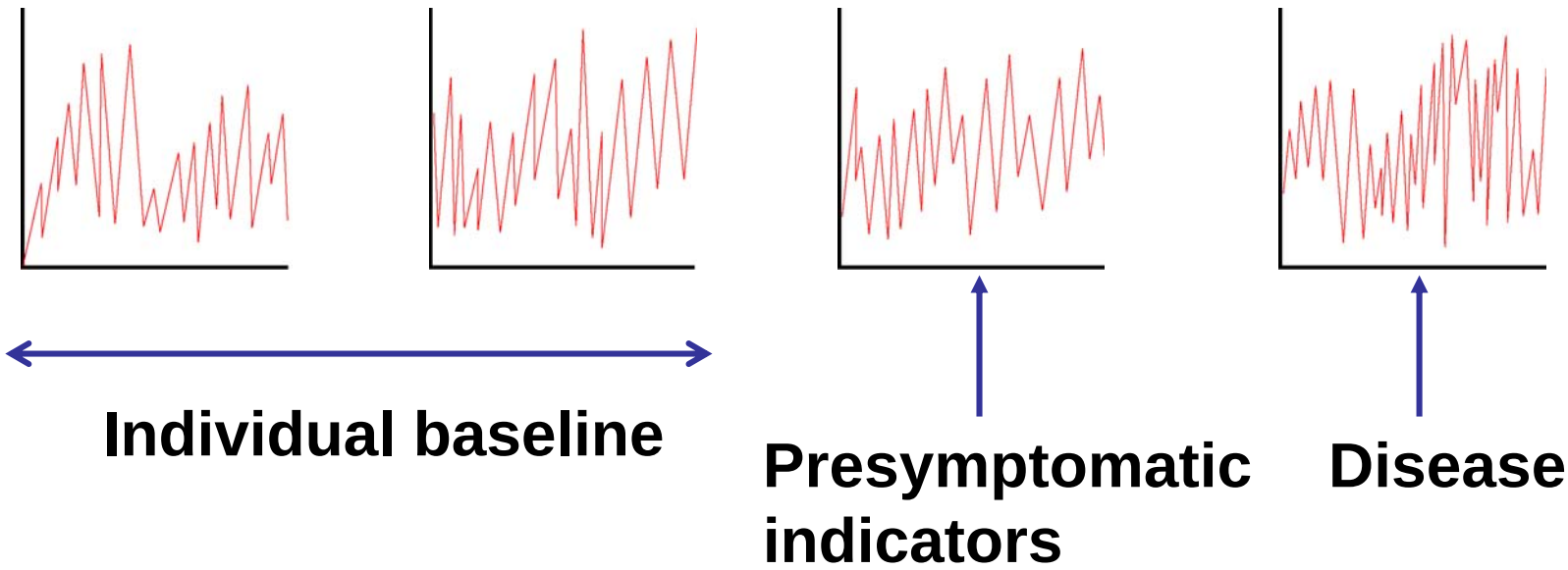


# Strategic Plan




**Sampling the SAME Invidual Over Time**

# Biosignatures / Biomarkers Over Time



# Biosignatures / Biomarkers

| |
|---|
| 33 Cancer Biomarkers |
| 1 Infection Biomarker |
| 0 Heart Biomarkers |
| 0 Biosignatures |

# Challenges

## *…for Biosignatures*

- **Diagnosis/Prognosis against population diversity genotype integration**
- **Resolution of diseases and status**

## *…for Presymptomatic Biosignature Diagnostics*

- **Cost → inexpensive so used widely & often**
- **Robust**
- **Real time**
- **Computation → immense data and opportunities**

# Comprehensive Approach to Biosignatures

## *Basic Components*

- Animal Models
- Highly selected human samples
- Technologies for signature generation → Target identification
- Computation / Bioinformatics
  - ♦ Target identification
  - ♦ Signature analysis
- Ligands for targets
- *Instrumentation*

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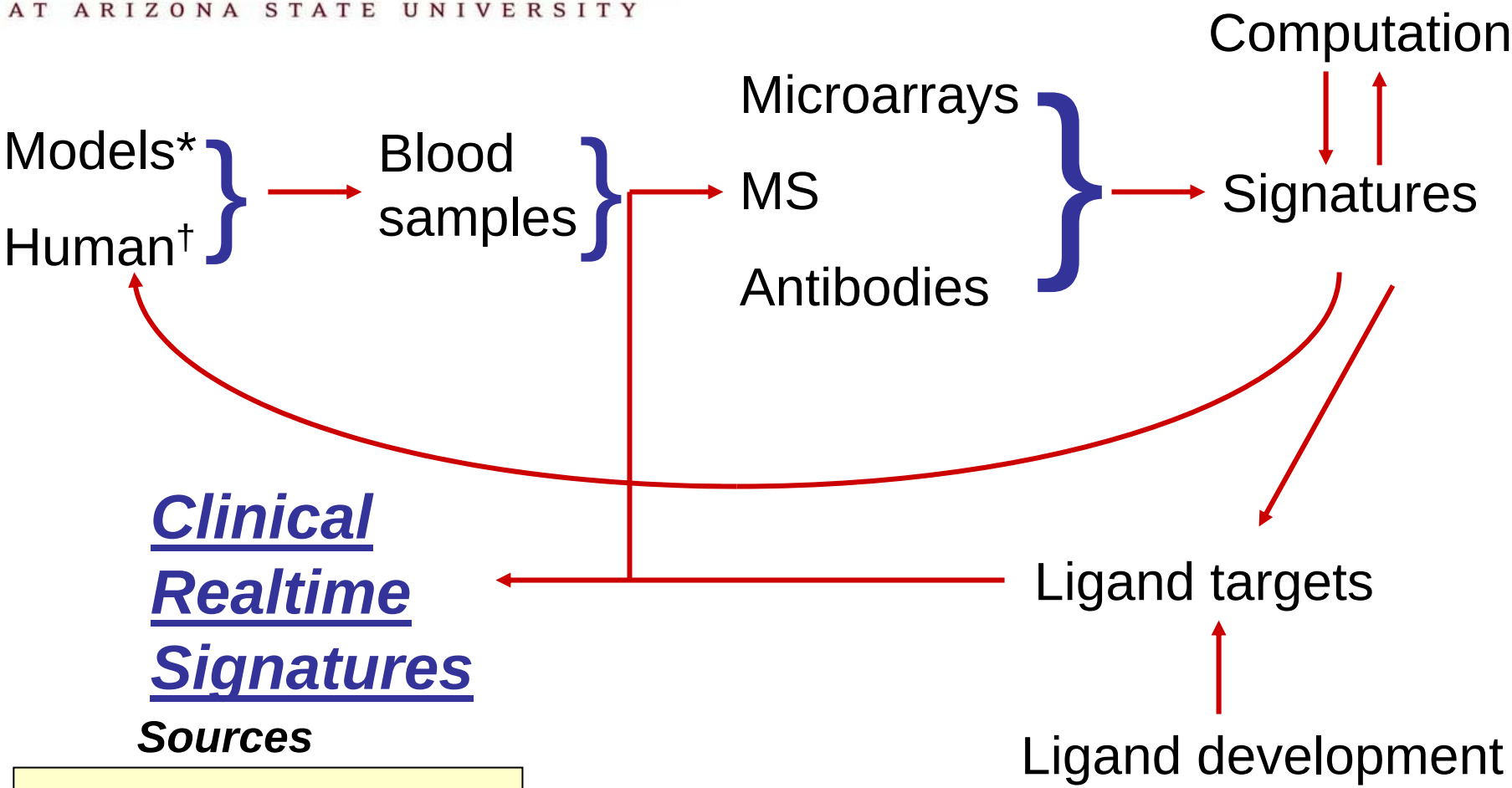
# Our Approach




***Sources***

| | |
|---|---|
| ****Animal:*** | Mouse |
| | Rat (Rhys Gen) |
| †***Human:*** | Cath Lab |
| | ER |

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# Signature Teams

## *Signature generation*

**Microarrays on:** Affected tissues (animals); WBCs (animals, humans)

**Mass spectrometry:** SELDI; MS/MS

**Advanced AB systems:** Luminex; Multiplex; SPR

## *Computation*

**Data analysis / statistical**

**Bioinformatics for targets**

**Computational approaches to biosignatures**

## *Ligands*

**AB-based detection systems:**

→commercial sources; ~1000 generated by PGA; new HTP synthesis

→system for AB → purification → screen on samples

**New ligands:** peptoid-based system

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# PPG Biosignatures of Ischemia Team

**Mouse/Rat Models: Ralph Shohet UTSW**

**Human Samples: James DeLemos UTSW**

**Mass Spec Signatures: Kevin Rosenblatt UTSW**

**Computation: Andrew Quong Georgetown Univ.**

**Ligands/Assays: Stephen Albert Johnston UTSW**
**Thomas Kodadek**