Opportunities for International Collaboration
With the ASU Biodesign Institute and CIM

Stephen Albert Johnston
Center for Innovations in Medicine*
The Biodesign Institute at Arizona State University
Stephen.johnston@asu.edu
*CIM is co-directed by Dr. Neal Woodbury
Interdisciplinary Research
Translational
Big Impact
Use-Inspired Basic Research
CENTERS

Center for Bioelectronics & Biosensors *Nongjian Tao*
Center for BioEnergetics *Sidney Hecht*
Center for Biosignature Discovery Automation *Deirdre Meldrum*
Center for Evolutionary Medicine & Informatics *Sudhir Kumar*
Center for Infectious Diseases and Vaccinology *Roy Curtiss*
Center for Innovations in Medicine *Stephen Albert Johnston, Neal Woodbury*
Center for Single Molecule Biophysics *Stuart Lindsay*
Swette Center for Environmental Biotechnology *Bruce Rittmann*
Center for Sustainable Health *Michael Birt, Leland Hartwell*
Virginia G. Piper Center for Personalized Diagnostics *Joshua LaBaer*
By the Numbers

10 research centers

$45M annual research expenditures

50 annual invention disclosures and patents

200 active research projects

$187M FY12 proposals submitted

500 employees

100 volunteers

1 Arizona’s first Nobel laureate in Physiology or Medicine

4 National Academy scientists

350,000 sq. ft. of LEED certified laboratories
What are the Costs of Medicine?

$2.4T/Year*

Drugs  
Diagnostics  
Care

*expenditures for 2008

The Cost of Post-symptomatic Medicine

Patient Care 88%
Drugs 10%
Diagnostics 2%

~$2 Trillion in Direct Medical Costs per Year
And It Is About to Get Worse
How Might We Move the Healthcare Needle?

The Biodesign “SPUTNIK” Projects:

• Vaccines (prevention)
• Diagnostics (early detection)
• Personalized therapeutics (early/targeted mitigation)
A Prophylactic Vaccine to Prevent All Types of Cancer
The Challenge: Find Enough Tumor Specific Antigens in Common

Any Tumor Arising Would Have 100% Chance of Presenting One or More Antigens
Tumor multiplicity curve of FS antigen based prophylactic cancer vaccine in BALB-NeuT mouse breast tumor model

Note: the pool Antigens groups are using different immunization regime. Pool 2 has 4 FS antigens and pool 1 has 3 FS antigens of pool 2.
A System to Comprehensively, Continuously, Cheaply Monitor Everyone’s Health Status
Immunosignaturing

- Facile sampling of easily obtained blood/saliva
- No sample prep other than dilution
- Potential for broad, specific pathogen detection
- Samples stable dry on filter paper for weeks
Dry Blood Works as Well as Fresh Blood
Dried vs. Undried Whole Blood Immunosignature Correlations

0 Week Dried vs. Undried Whole Blood

1 Week Dried vs. Undried Whole Blood

3 Week Dried vs. Undried Whole Blood

Storage conditions: 25°C

R² = 0.919

R² = 0.916

R² = 0.843
Early Detection: Immunosignaturing

- Your immune system already monitors essentially everything that is happening in your body
- About a billion sensors roam your blood looking for pathogens, cells gone wrong, or other changes
- Resulting signals are amplified tremendously
- Can we read the immune system in a drop of blood?
- Can we do this simply and inexpensively?
Fungal Spores
Distributed by Dust

Massive Dust Storm Hits Phoenix, Az
July 5th, 2011

http://www.youtube.com/watch?v=8W4Cx44XKZ4
Diagnosing Valley Fever: A Sonoran Desert Pathogen

- 90 blinded samples from patients presenting at the clinic
- Zero false positives (100% specificity)
- Zero false negatives (100% sensitivity)
- 100% accuracy on patients mis-diagnosed by standard methods

Collaborator: John Galgiani
Univ. of Arizona
Breast Cancer

In Collaboration with:

Hoda Anton-Culver
University of California Irvine

Sam Hanash
Fred Hutchinson Cancer Center

Adi Gazdar
University of Texas Southwestern
Smaller, Faster, Cheaper...

Lessons Learned from the electronics industry

Using Electronic Fabrication Equipment to Make Millions of Molecular Sensors
HealthTell

• Producing arrays as vendor
• Working closely with ASU to optimize arrays
• New CEO, Bill Coston (formerly CEO of QuantaLife and before that staff at LLNL)
• Production and assay facilities in ASU research park and Chandler innovation center
## Major Causes of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>Russia</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CardioVascular</td>
<td>52%</td>
<td>23%</td>
</tr>
<tr>
<td>Cancer</td>
<td>14%</td>
<td>22%</td>
</tr>
</tbody>
</table>
A Success Story: Heart Disease:

This was made possible in large part due to the combination of a few simple, inexpensive tests coupled to viable intervention strategies.
NextGen Therapeutics and Anti-Infectives

Therapeutic Pipeline Dying

More Bug Resistance Than New Antibiotics

Early Disease Diagnosis Will Require New Classes of Therapeutics
Synbody vs Antibody

- Low MW (~5 - 10 kDa)
  - Target Unique Sites
  - \textit{In vitro} selection
  - Chemically Synthesized
  - Stable

- High MW (~150 kDa)
  - Target “knobs” on proteins
  - Limited Control
  - Biological Production
  - Can be Unstable
**Synbody Development**

Target protein

Bind to 10,000 peptide library

Low affinity peptides

Affinity improved peptide*

High affinity Synbody

Bacterial Binding Peptides

SYTO9-ECo0111:B4+/Intensity (raw) vs. ECo0111:B4+/Intensity (raw)

E. coli 0111 binding peptides competed with LPS

E. coli 0111 binding to single peptide spot

E. coli 0111 growth inhibition

Used peptide arrays to identify peptides that specifically bound E. coli 0111
Circle of Health

Targets for Early Treatment

Invention: Decipher

Prevention
Invention: Prophylactic Cancer Vaccine

Pre-Symptomatic Diagnosis
Invention: Immunosignatures

NextGen Therapeutics
Invention: Synbodies

Early Treatment
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  - Hoda Anton-Culver, Ph.D., UC Irvine
  - Sam Hanash, Ph.D., Fred Hutchinson Cancer Center
  - Adi Gazdar, Ph.D., UT Southwestern
  - Adrienne Scheck, Ph.D., Mayo Clinic
  - Dawn E. Jaroszewki, Ph.D. Mayo Clinic

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HealthTell, Inc.
The Defense Threat Reduction Agency
The National Science Foundation
Population-Based Comprehensive Health Monitoring

Central Analysis

Biothreat Detection
Detection = $\left(\text{Pop}_M\right)\left(\text{Freq}\right)\left(\text{Sensitivity}\right)$
Three Options to Solve HC Crisis

• Greatly Increase GNP

• REDUCE CARE PROVIDED

or

• TRANSITION TO PRE-SYMPTOMATIC DIAGNOSIS AND PREVENTATIVE MEDICINE
Health Futures

Implementation Will Require:
- Scientists - all types
- Clinical Science
- Epidemiology
- Data Management
- Pattern Math
- Law / Ethics
- Behavior
- Education
- Political
- Economists

* Early Detection of Biothreat, Outbreaks

VISION
The Problem

Projected Medicare Spending Increases Over Time

Source: Congressional Budget Office
Synbody Ligands

• Search Small Libraries

• Use Long Peptides

• Simple Optimization

• Chemical Synthesis of Products

Synbody Development - Backwards

AKT1 synbody
$K_d = 1.5 \text{ nM}$

2,500 fold excess protein

AKT1 selective
Purification of Norovirus VLP

1 – Screened in cell lysate
2 – Identified >90 peptides
3 – Synthesized 6 peptides
4 – 2 showed high specificity (>95%)
5 – Gentle elution conditions
6 – DBC = 2 mg/mL
Immunosignaturening Process

Add diluted blood
Immunosignaturing Process
Immunosignaturing Process

Read
Diagnosing Brain Tumors
Collaborator: Adrienne C. Scheck, BNI

100% accurate detection training and testing on samples taken years apart

Not only can immunosignaturing detect the brain tumor, it can distinguish accurately between the common types of brain tumors
Diagnosing Esophageal Cancer vs. Barrett’s Esophagus

In every case immunosignaturing was able to distinguish Barrett’s Esophagus from Adenocarcinoma.
Alzheimer’s Disease
Collaborator: Alex Roher, Banner Health

Human
Distinguishing Normal from Disease

This picture is from Institute Douglas at flickr.com
Synthetic Antibodies
Stephen Johnston, PI

- Rapidly produced
- Small (usually <6000 MW)
- High affinity and specific (nM)
- Chemically pure
- Not restricted to aqueous solutions or physiological conditions
Synbody Concept

- Scaffolded or branched peptide
- nM binding
- High specificity
- Chemically robust and pure
Current Synbody Development

Target protein → Bind to 10,000 peptide library → Low affinity peptides → Affinity improved peptide → High affinity Synbody
Proposed Synbody Discovery

Target protein or mixture → Array of 1-10 million fully-formed synbodies → High affinity Synbody
Example: AKT1 Synbody

\[ K_D = 1.5 \text{ nM} \]

**AKT1 is Specific and Selective**

- Synbody specifically captures AKT1 from cell lysate.

- Synbody is selective for AKT1 vs AKT2 vs AKT3.

- Sequence identity with AKT1:
  - AKT2 (92% identity)
  - AKT3 (87% identity)

Several Additional Examples

<table>
<thead>
<tr>
<th>Target</th>
<th>Affinity</th>
</tr>
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<tbody>
<tr>
<td>AKT-1</td>
<td>1.5 nM</td>
</tr>
<tr>
<td>Gal-80</td>
<td>8 nM</td>
</tr>
<tr>
<td>TNF-α</td>
<td>9 nM</td>
</tr>
<tr>
<td>Influenza</td>
<td>&lt;10 nM</td>
</tr>
<tr>
<td><em>Staph. aureus</em></td>
<td>&lt;1 nM</td>
</tr>
</tbody>
</table>
Antimicrobial Development

Bacteria → Bind to 10,000 peptide library → Select Binding or Lytic Peptides → High affinity Synbody

Domenyuk, V., et. al, manuscript in preparation.
Growth Inhibition in Solution

Domenyuk, V., et. al., manuscript in preparation.
Nanostructured Enzyme Systems
Hao Yan and Neal Woodbury, PIs

• Peptide “minidomains” that stabilize or enhance enzyme function
• Self assembled multi-enzyme systems
• Coupling enzymes via proximity
• Coupling enzymes via constrained carriers
Selecting Enzyme Modulators
pH and Thermal Stability Enhancement

$\beta$-galactosidase
Coupling Enzymes on Nanostructures
Bridging Between Enzymes
Coupling Enzymes with a Flexible Arm

Self-assembled Dehydrogenase Complexes
Coupling Enzymes with a Flexible Arm

**Graphs:**
- **Fluorescence Intensity vs. Time (second):** Shows a comparison between Flexible Arm Assembly and Free enzyme control.
- **Normalized Specific Activity:** Displays a significant increase in activity for Flexible Arm Assembly compared to Free enzyme.
Political Solutions: Pay More or Get Less?
The Inventors of Immunosignaturing
Drs. Stephen Johnston and Phillip Stafford

Dr. Stephen Johnston

Dr. Phillip Stafford