

EMERGENCY CARE RESEARCH OPPORTUNITIES: THE NIH ROADMAP & CTSA

Glen N. Gaulton Ph.D.
Executive Vice Dean/Chief Scientific Officer
University of Pennsylvania
May 28th 2008

Why a Roadmap?

- Accelerated pace of discoveries in the life sciences through the 80s-90s
- Limited specific NIH focus on translation into medical practice
- Opportunities to build more integrated systems and develop novel approaches
- Politics - an impression that the NIH investments have not paid off in terms of better health care!

Roadmap Chronology

August 2002	Consultation with over 100 thought leaders
September 2002	IC Directors' Leadership Forum
March 2003	Formation of 15 Working Groups - 300 outside experts
April 2003	Presentation to Council of Public Representatives
May 2003	Working Groups propose initiatives
June 2003	IC Directors commit to initiatives
June 2003	Presentation to the Advisory Committee to the Director
September 2003	Presentation to advocacy groups, press
FY 2004-2013	Staged implementation

Initial Questions Asked?

- What are today's key scientific challenges?
- What are the roadblocks to progress?
- What do we need to do to overcome roadblocks?
- What can't be accomplished by any single Institute
 - but is the responsibility of NIH as a whole?

Criteria for Roadmap Initiatives

- Is it 'transforming' -- will it change how or what biomedical research is conducted in the next decades?
- Would its outcome enhance the ability of all ICs to achieve their own missions?
- Can the NIH afford to NOT attempt it?
- Will it be compelling to our stakeholders, especially the public?
- Is it something that no other entity can or will do?

- Note what is not said: downside if over orchestrated - attempted with a flat/lower budget - competing mandates at NIH - is this compatible with the US scientific system

Roadmap Implementation

- All Institutes and Centers committed to invest jointly in a pool of resources to support Roadmap initiatives
- \$128 M in year 1 - FY 2004
- \$2.1 B total investment by FY 2009

“Many of the initiatives are difficult
– some may fail!”

Three Core Themes

- New Pathways to Discovery
- Research Teams of the Future
- Re-engineering Clinical Research



New Pathways to Discovery

Bench ↔ **Bedside** ↔ **Practice**



**Building Blocks
and Pathways**
Molecular Libraries
Bioinformatics
**Computational
Biology**
Nanomedicine

New Pathways

Biological Function-Based Drug Discovery

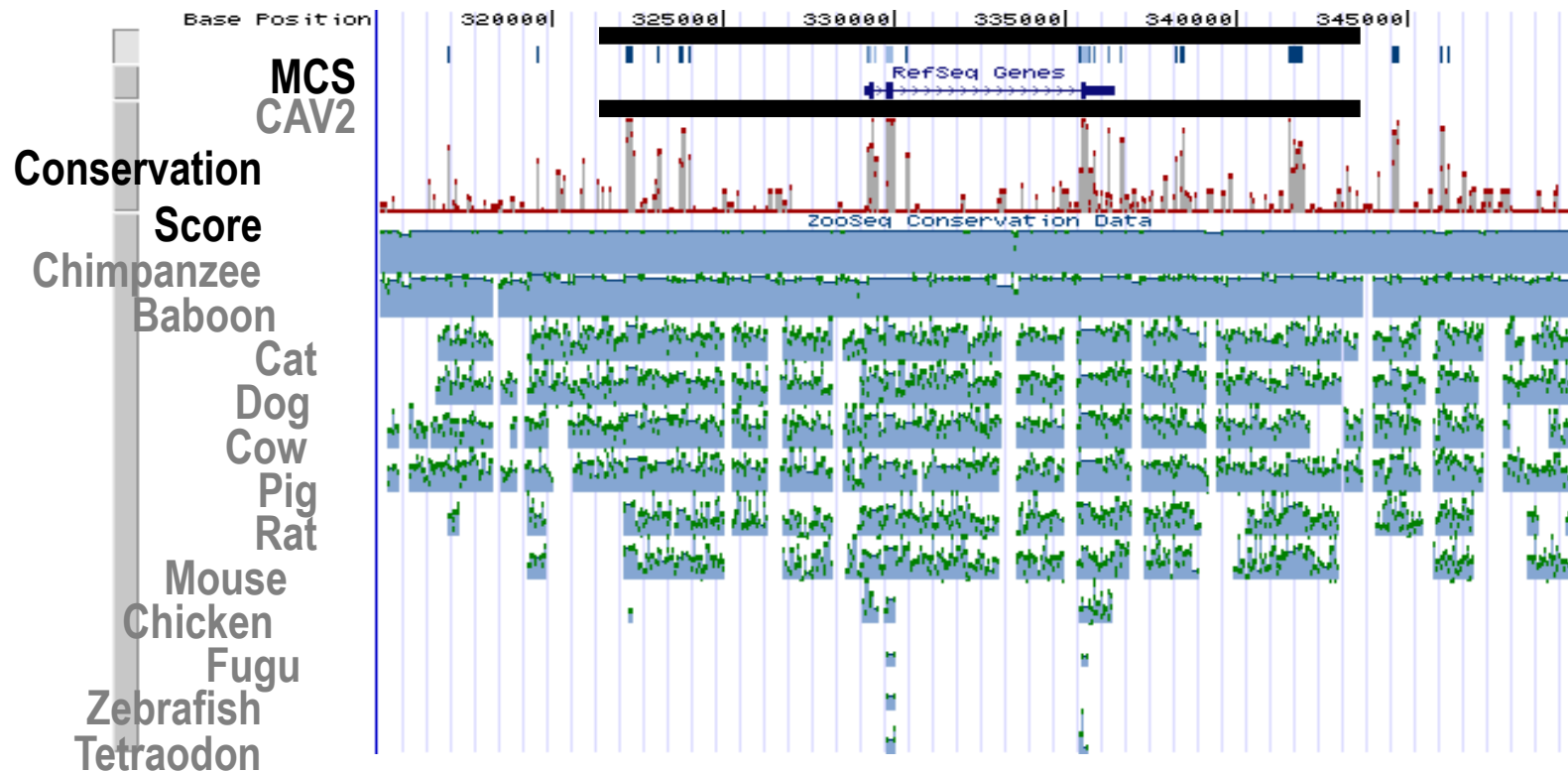


Genomic-Based Drug Discovery



Computational Biology: Modeling the Cell's Information Superhighway

National Centers for Biomedical Computing



Structural Biology: Life in Three Dimensions

- >**500** 7 trans-membrane receptors
- ~**2%** of human genome
- Targets of **33%** of all therapeutic drugs with sales >\$500 M/yr
- **BUT** only a small minority of these receptors are currently targeted
- The structure of integral membrane proteins – the next frontier!



Molecular Libraries: Putting Chemistry To Work for Medicine

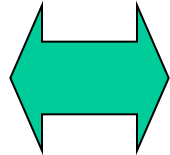
- Library representing essentially all of 'chemical space'
- Six national centers for screening activities of small molecules
- Technological advances in combinatorial chemistry, robotics, 'virtual screening'
- Public database

Research Teams of the Future

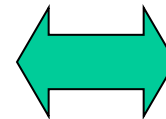
Interdisciplinary
Research Teams;
Innovator Award

Public-Private
Partnerships

Bench



Bedside



Practice

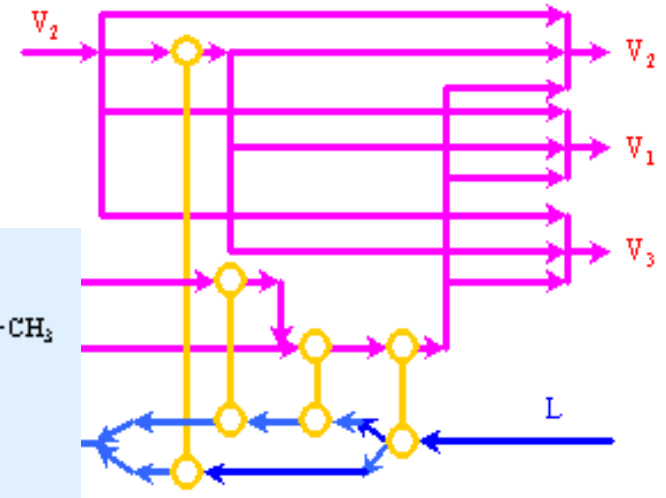
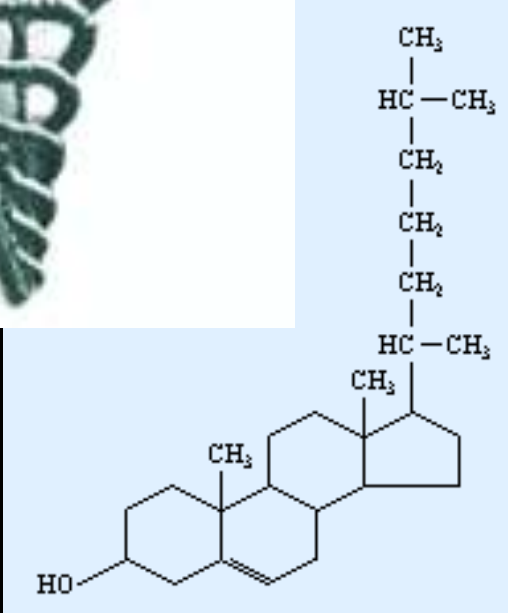
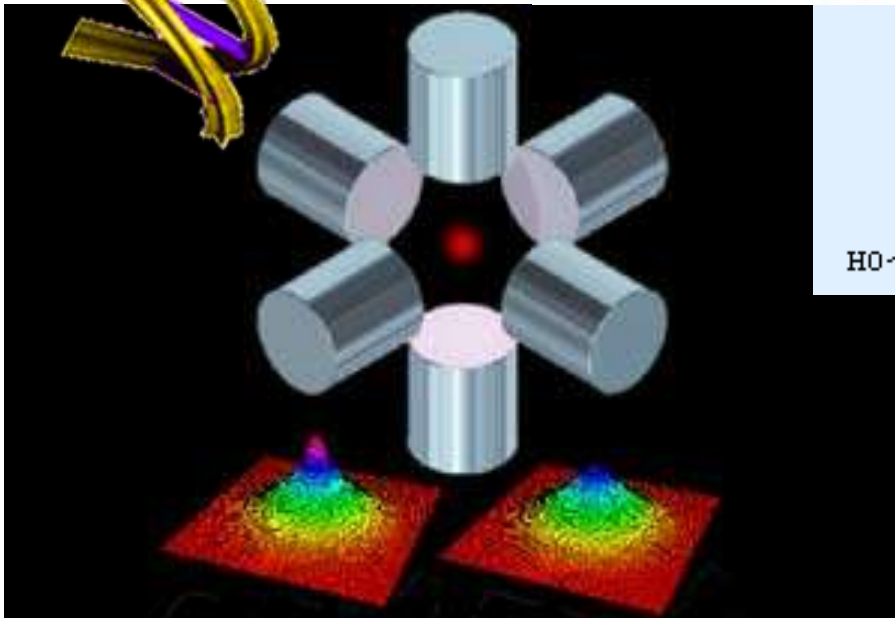
Building Blocks
and Pathways
Molecular Libraries
Bioinformatics
Computational
Biology
Nanomedicine

Research Teams of the Future

Scale and complexity of current science require novel team approaches

- Interdisciplinary Research Teams
- Public-Private Partnerships
- New types of awards & support

Interdisciplinary Research Centers



Lowers barriers that slow interdisciplinary studies

Allows the interdisciplinary team to evolve

New Types of Awards & Support

- NIH Director Pioneer Awards:
 - Supports individuals with untested ideas that are potentially groundbreaking
 - Provides \$500 K/year for 5 years
 - Self-nominated & highly competitive
- Expand junior investigator awards (K99 & R00)
- K12 awards - additional clinical research training with 75% effort support
- Allow multiple-PI on grants

Re-engineering Clinical Research

Interdisciplinary
Research

Innovator Award

Public-Private Partnerships

Bench

Bedside

Practice

Building Blocks
and Pathways
Molecular Libraries
Bioinformatics
Computational
Biology
Nanomedicine

**Translational
Research
Initiatives**

**Integrated Research Networks
Clinical Research Informatics
NIH Clinical Research Associates
Clinical/Translational Science
Awards (CTSA)**

Cross cutting: Harmonization, Training

A Broken Model of Drug Development

- Despite increasing investment and a plethora of new drug targets, NDAs have been falling: ~20 new drugs per year since 1998
- High cost of goods in the US has insulated drug development from reform
- A short term strategy of merger has further undermined a highly inefficient and costly process
- Downward pressures on the cost of goods
- Pervasive concern about drug safety
- Increasing volatility in big pharma

Predictability Problem

- Product development success rate has declined:
 - New compounds entering Phase I development today have 8% chance of reaching market vs. 14% chance 15 years ago
 - Phase III failure rate now reported to be 50%, vs. 20% in Phase III 10 years ago.

Altered Perceptions of Drug Safety

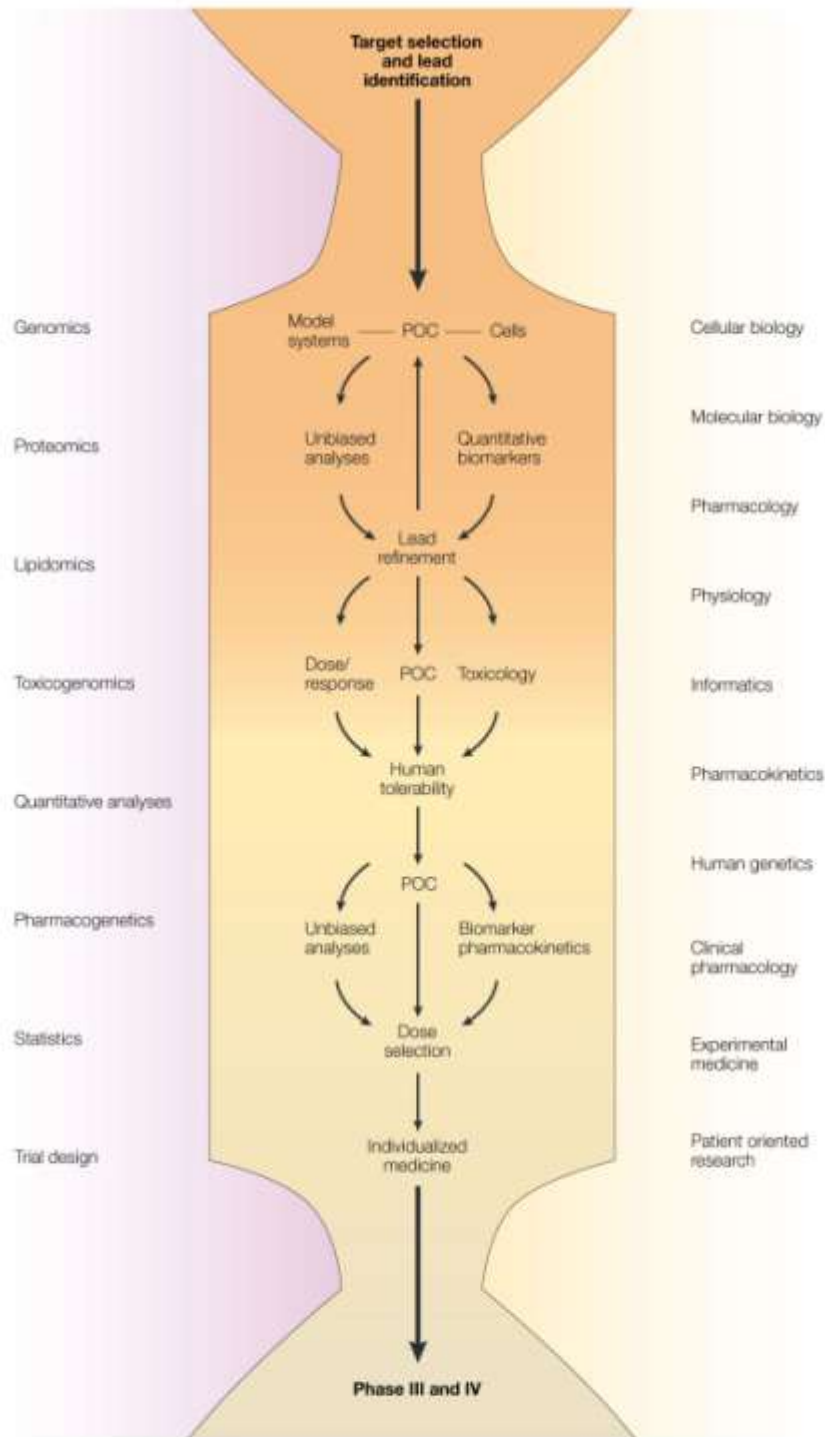
- Roughly half of approved drugs have safety related label changes after marketing
- ~4% of approved drugs are withdrawn
- ~ 20% of approved drugs get “black box” warnings after approval
- Reaction to Direct to Consumer advertising

Structural Reform in Academic Medical Centers

- Talented physician scientists in one focal location
- BUT often poorly educated in basics of drug development, design...
- Access to patients
- BUT silos between and within institutions
- GCRC model of central support
- BUT too isolated - resource limited - no incentives for herding the cats
- Poor infrastructure for scale, unfocussed mission and consequent delay in process

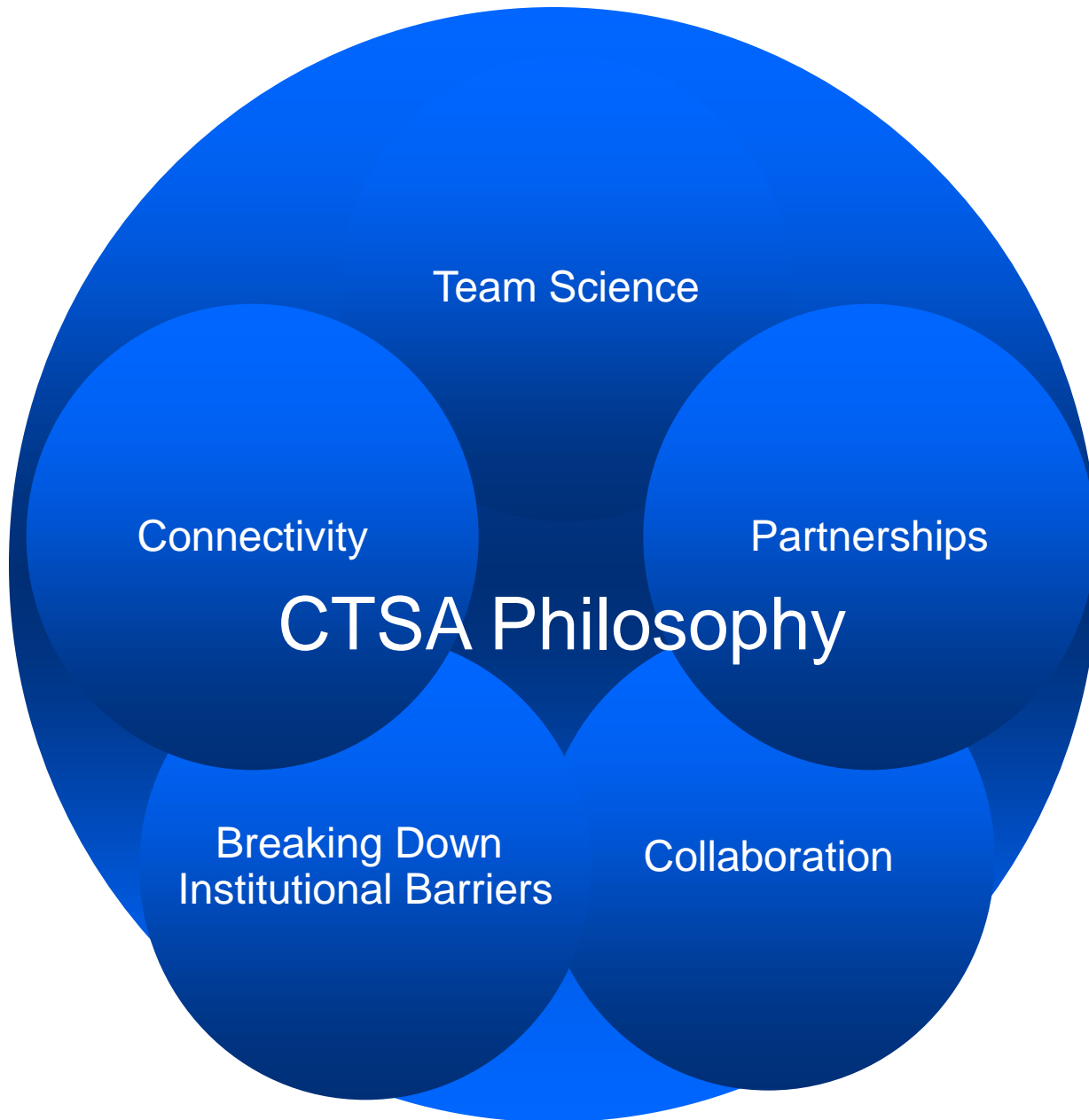
Launching a New Discipline?

- Develop and project mechanism based quantitative biomarkers from model systems into humans.
- Evoking phenotypic responses in humans to guide individualization of rational dose selection
- Harness the unbiased technologies to select amongst molecules directed against a single target



NIH Action: Clinical & Translational Research Centers

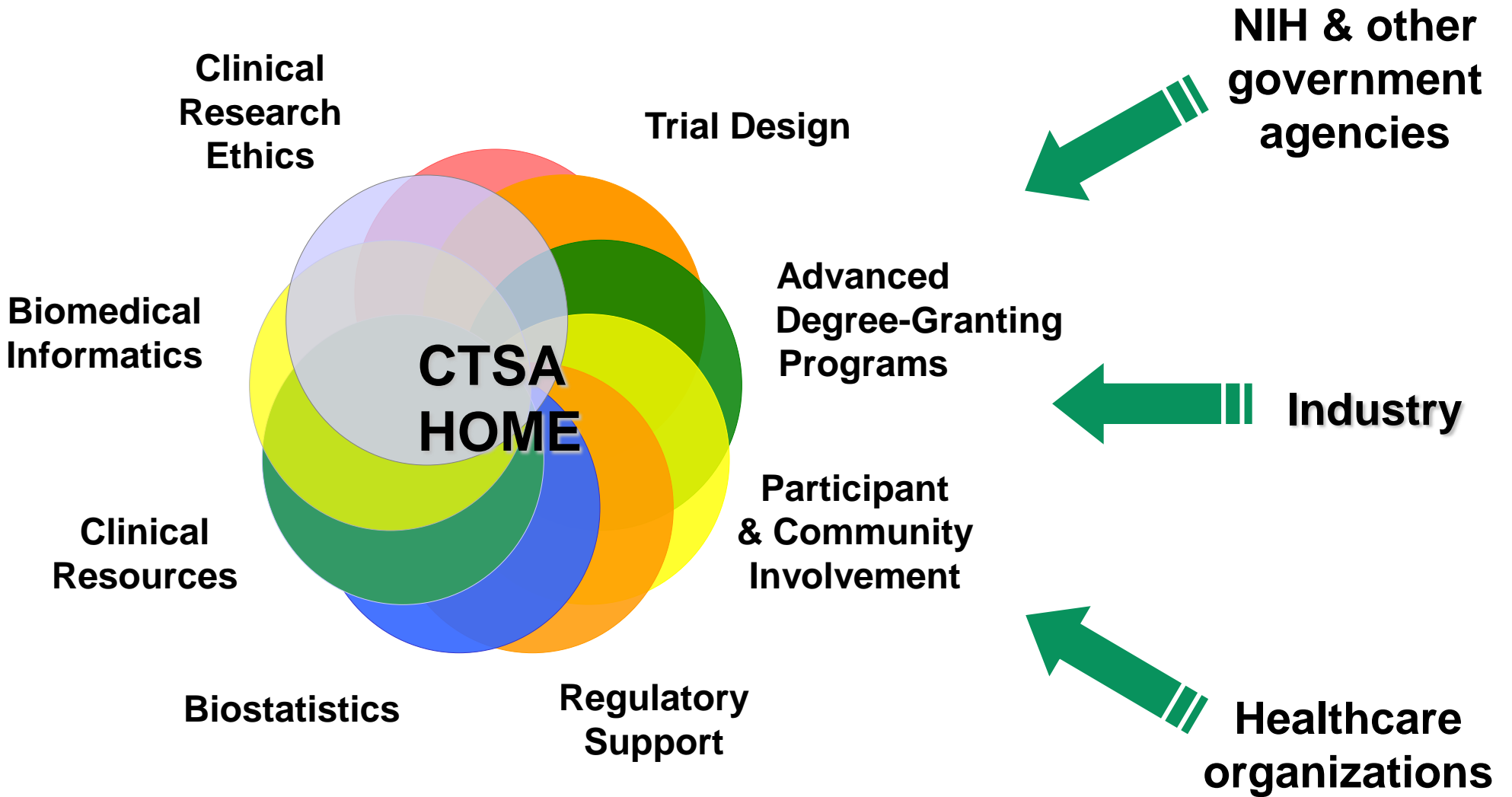
- Establish Regional Translational Research Centers
 - Core resource program
 - Regional centers program
 - Regulatory advice, preclinical drug synthesis, toxicity testing, pharmacology,
 - Translational research fellows
 - Pilot project support
- Enabling technologies for improved assessment of clinical outcomes



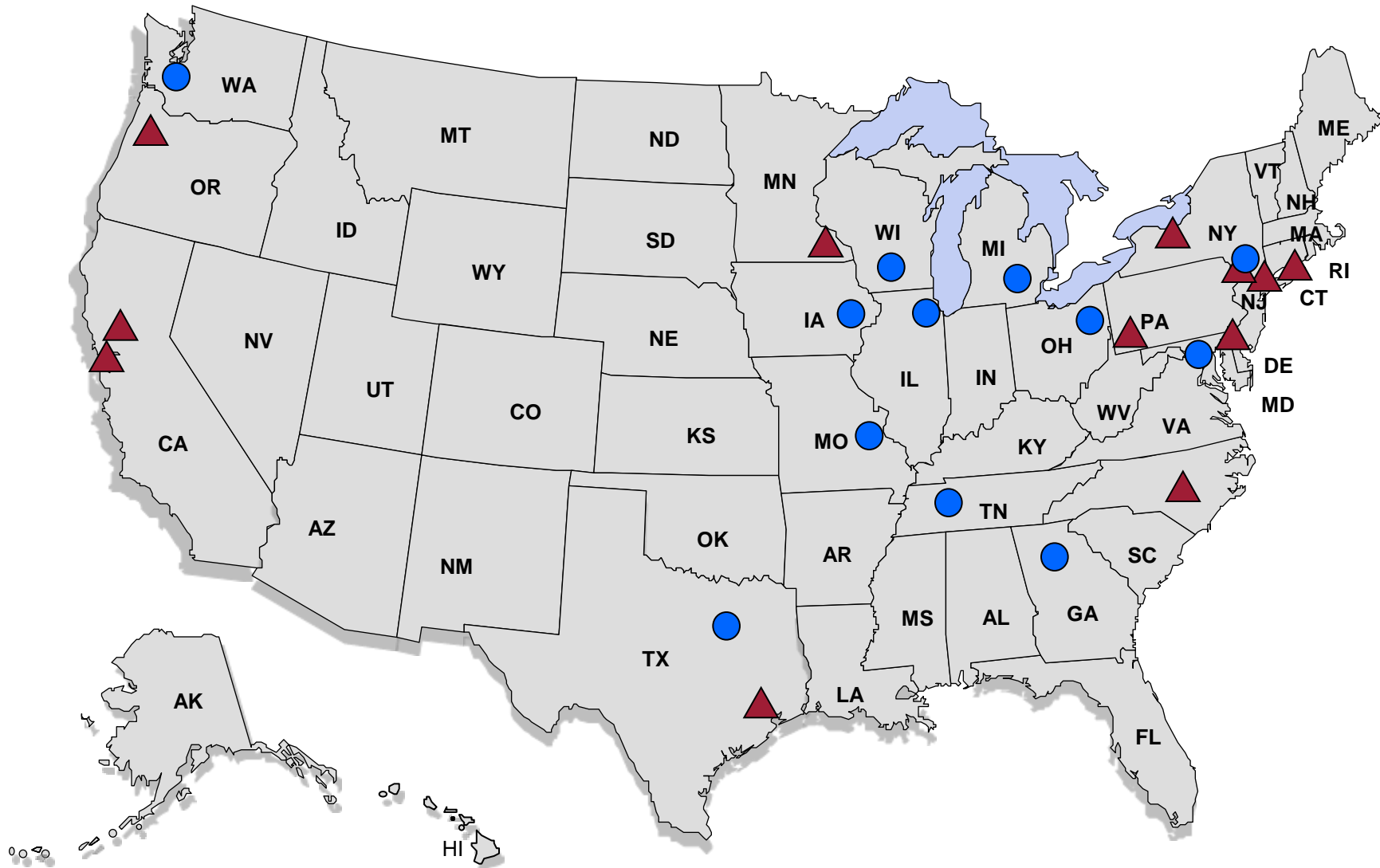
The CTSA: A Threat and a Promise

- Bid for up to \$6M/yr incremental total costs – fund 6-9/year from ~36
- Grant submissions ~ \$50-90M/5 years
- Increment comes from closing GCRCs
- Consolidates GCRC/T32/K30 mechanisms
- Heavily reliant on institutional cohesion and investment
- Favors multi-school and cross institutional programs

CTSA Idealized Components



CTSA Awards



Participating Institutions

▲ Since 2006

● Since 2007

CTSA Award List

FY06 Grantees

Center for Clinical and Translational Science

The Rockefeller University

Center for Clinical and Translational Sciences

University of Texas Health Sciences Center at Houston

Clinical and Translational Science Center

University of California, Davis

Clinical and Translational Science Institute

University of Pittsburgh

Clinical and Translational Science Institute

University of California, San Francisco

Clinical and Translational Sciences Institute

University of Rochester School of Medicine and Dentistry

Duke Clinical and Translational Science Institute

Duke University

Institute for Translational Medicine and Therapeutics

University of Pennsylvania

Irving Institute for Clinical and Translational Research

Columbia University

Mayo Center for Translational Science Activities

Mayo Clinic

Oregon Clinical and Translational Research Institute

Oregon Health and Science University (partnering with Kaiser Permanente)

Yale Center for Clinical Investigation

Yale University

FY07 Grantees

Atlanta Clinical and Translational Science Institute

Emory University (partnering with Morehouse College)

CTSA at Case Western University

Case Western University

CTSA at Washington University

Washington University

CTSA at Weill Cornell Medical College

Weill Cornell Medical College (partnering with Hunter College)

Institute for Clinical and Translational Research

University Of Wisconsin Madison

Institute for Clinical and Translational Research

Johns Hopkins

Institute of Translational Health Sciences

University Of Washington

Michigan Institute of Clinical and Health Research

University Of Michigan At Ann Arbor

North & Central Texas Clinical and Translational Science Initiative

University of Texas Southwestern Medical Center - Dallas

University Of Chicago CTSA

University Of Chicago

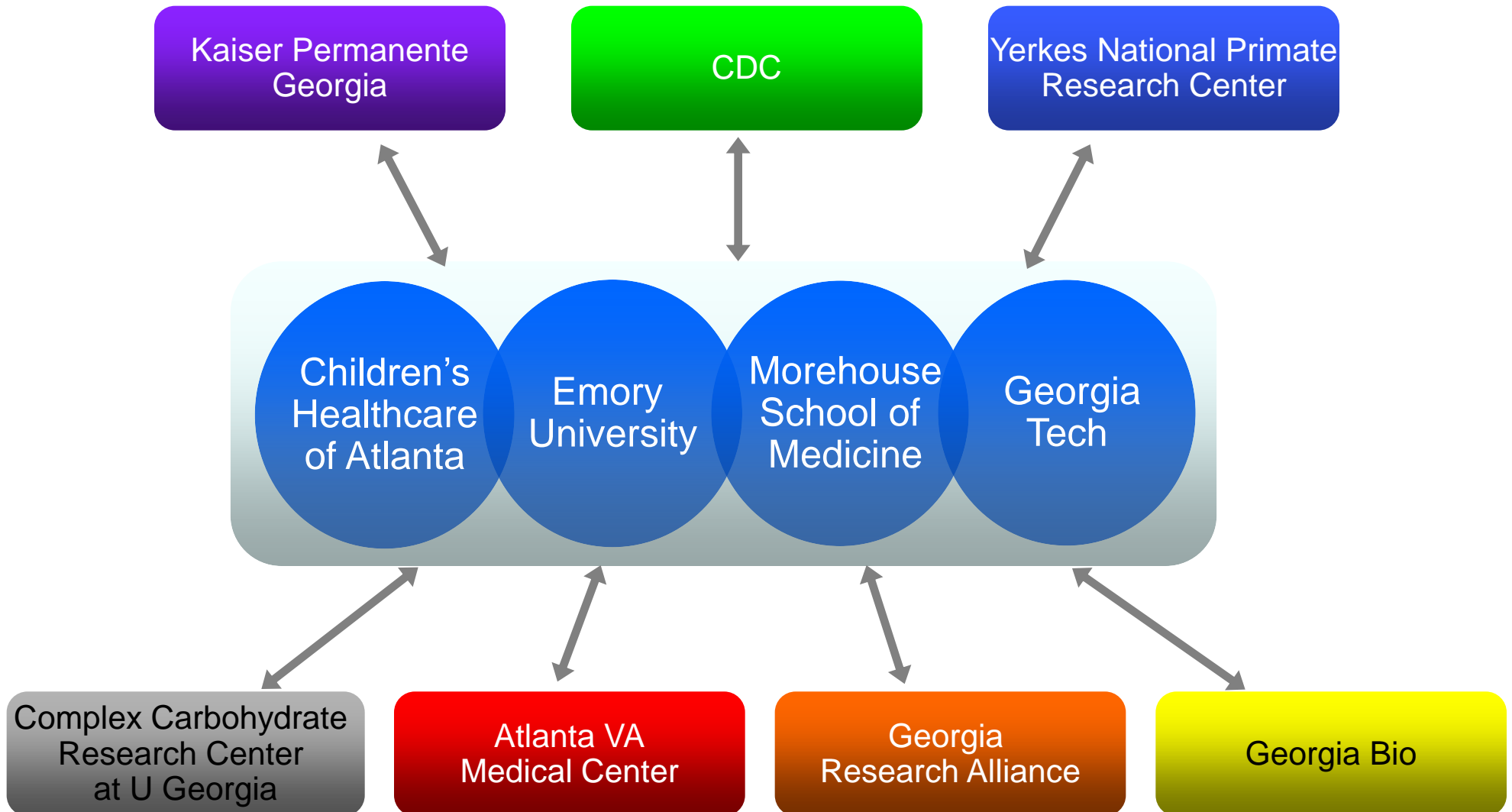
Univ of Iowa's Inst for Clinical and Translational Science

University Of Iowa

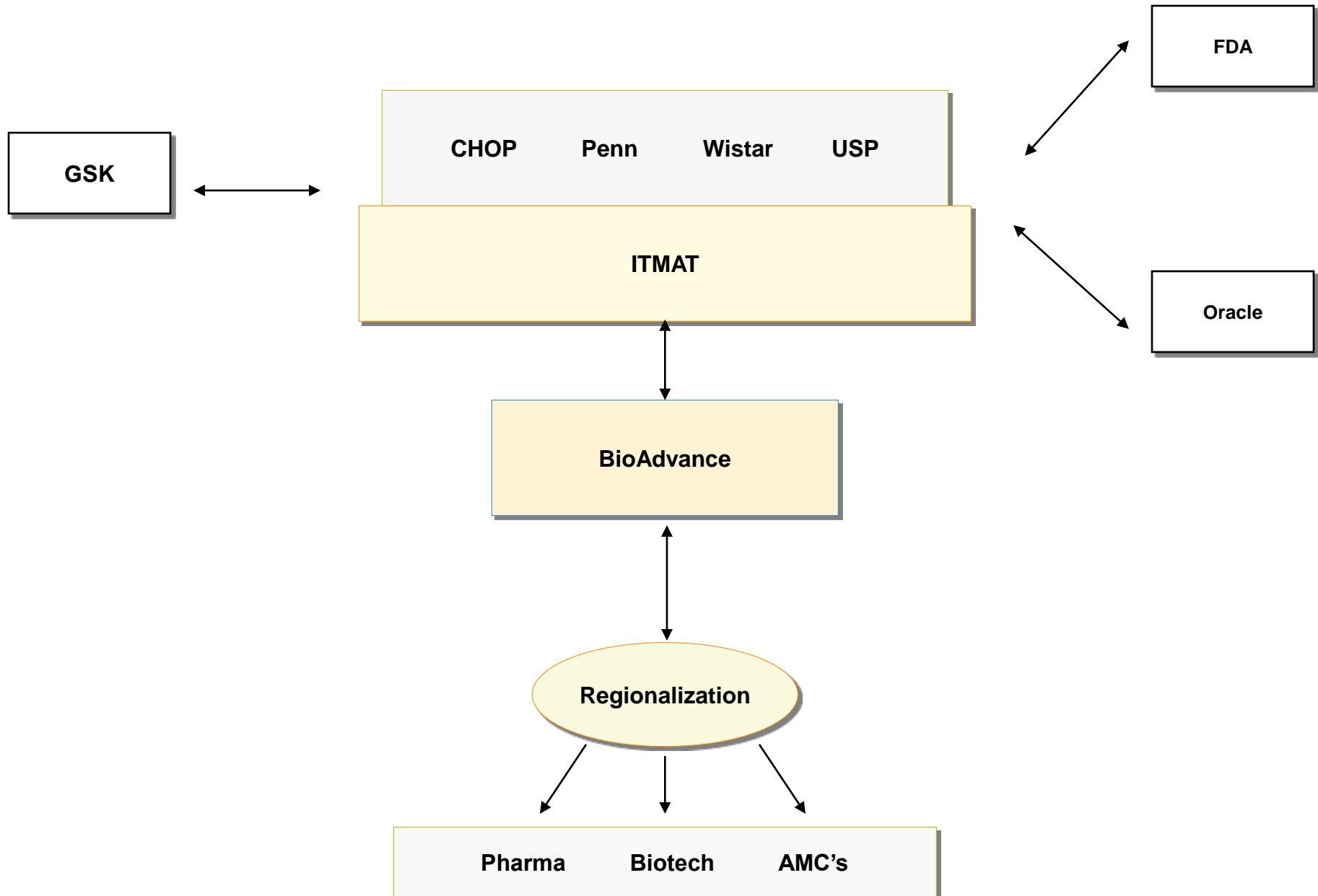
Vanderbilt Institute for Clinical and Translational Research

Vanderbilt University (partnering with Meharry Medical College)

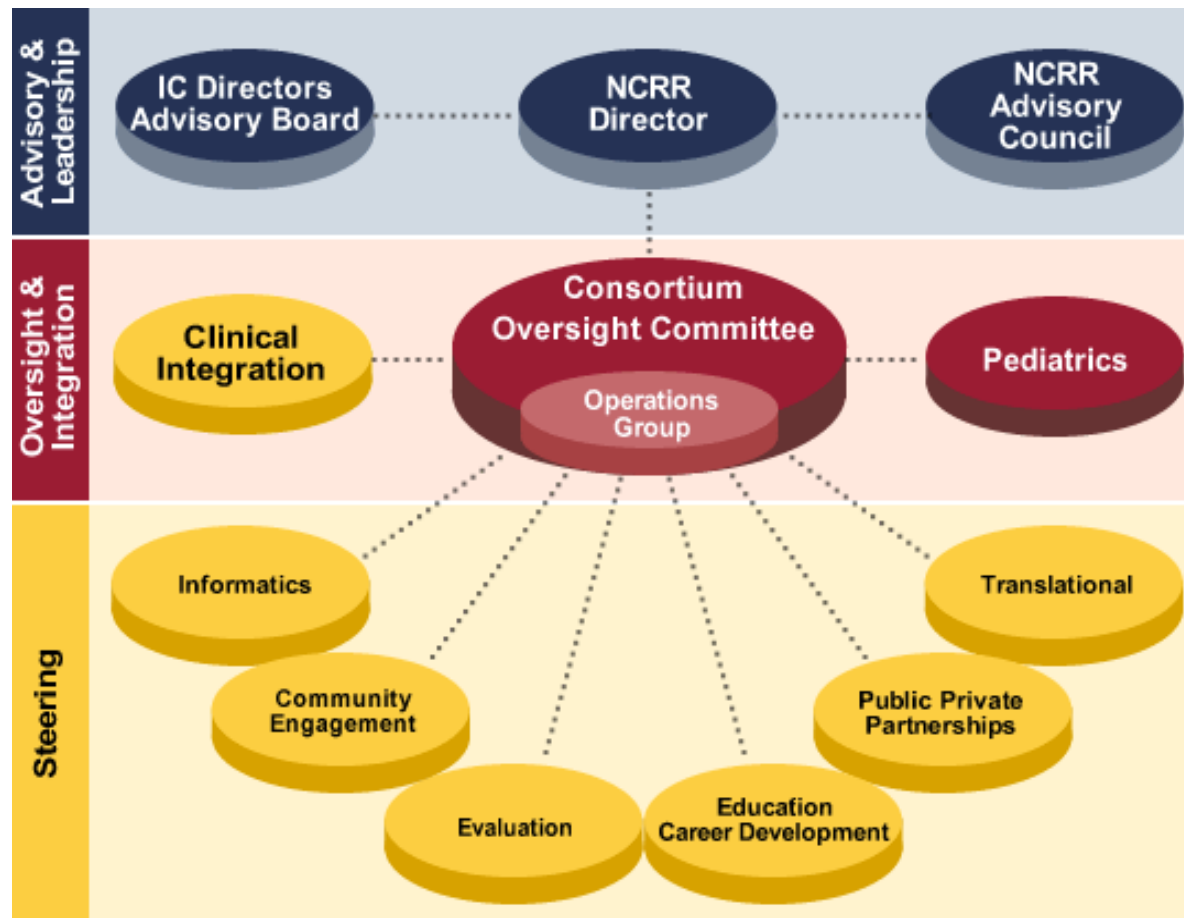
Atlanta Clinical and Translational Science Institute (Atlanta-CTSI)



Penn's Response: ITMAT



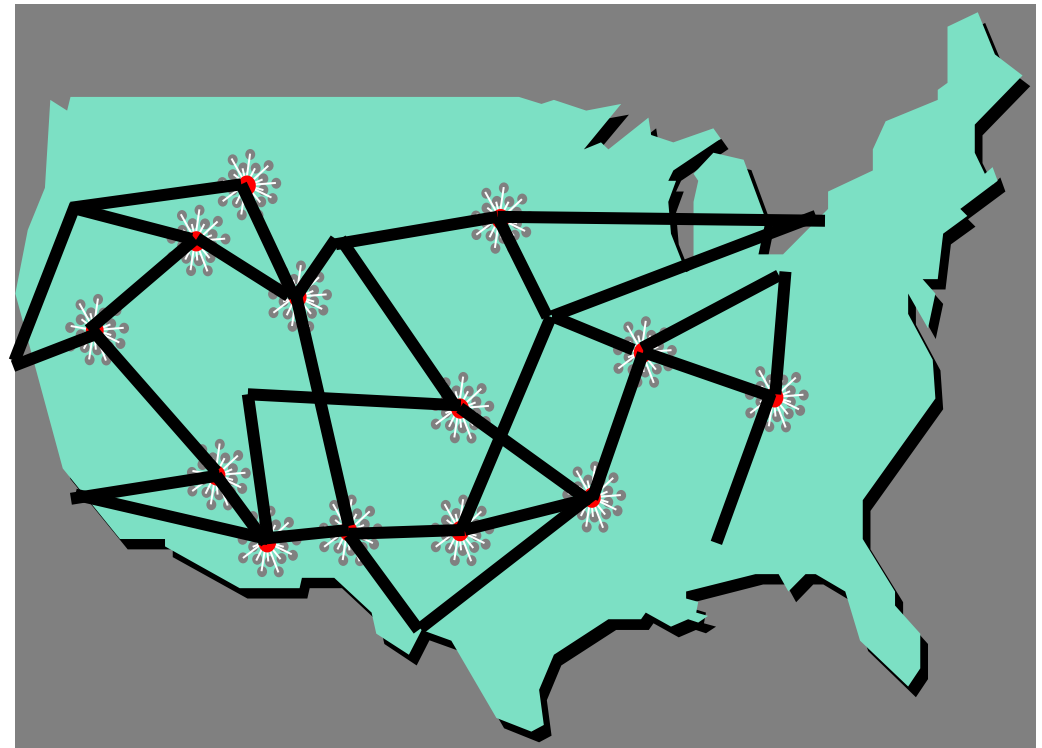
CTSA Oversight



- **Advisory:** providing guidance and input to the NCRR Director on the CTSA Consortium
- **Oversight:** identifying and selecting collaborative opportunities to facilitate research throughout the CTSA program, coordinating Consortium-wide approaches to research and overseeing topic-specific efforts across the Consortium
- **Steering:** coordinating institutional topic-specific efforts with the national CTSA Consortium; each Steering Committee has an Operations subgroup that takes timely action on emergent topic issues

The Second Wave - Integration of Clinical Research Networks

- Link existing networks so clinical studies and trials can be conducted more effectively
- Ensure that patients, physicians, and scientists form true “Communities of Research”



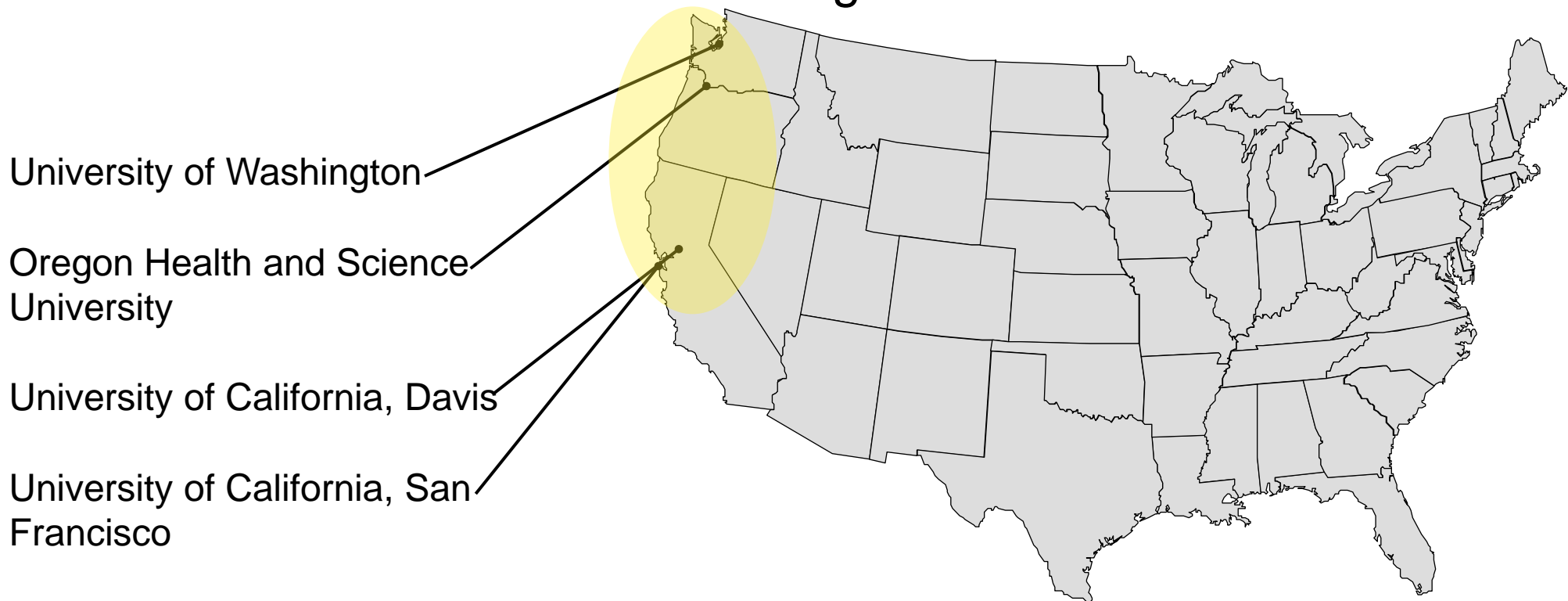
Integration of Clinical Research Networks

- Create interoperable 'Network of Networks'
 - National Electronic Clinical Trials/Research Network (NECTAR)
 - Common data standards, informatics
 - Software application tools for protocol preparation, IRB management, adverse event reports
- Use existing networks to more rapidly address questions beyond their traditional scope

Regional Alliances - A Big Plus

Four CTSA Institutions have come together to form a West Coast Alliance:

- ❑ Opportunities to collaborate and share strengths
- ❑ Focus on building investigator and scientific collaborations—opportunities across centers
- ❑ Possible model for additional regional alliances



Where are the Opportunities in Emergency Care Research?

- If you have one - get integrated into your CTSA ASAP !
 - Advisory boards, trainees, pilot projects...
 - Give them a reason to say yes
- If not - get involved in your planning process ASAP !
 - Most institutions are running scared
 - Every CTSA needs an identity -why not (in part) you?
 - Internal politics/turf create an opportunity for the little guy to emerge (you don't threaten anyone)

Position Emergency Care Research: a Prototype for Next Phase CTSA

- If no CTSA is planned at your institution bridge to others
- Biomarkers - Biomarkers - Biomarkers
- Post market outcomes - pharmacoepidemiology
- Community outreach
- Integrated networks
 - Research projects
 - Clinical trials
 - Trainees across institutions

VIEWS OF THE FUTURE FROM THE LESSONS OF THE PAST

Shifting coalitions of the willing to address
discrete therapeutic opportunities

"I would not say that the future is necessarily less
predictable than the past. I think the past was not
predictable when it started."

D. Rumsfeld