MATRICS Mandate: Treatment Development for Cognition in Schizophrenia

Wayne S. Fenton, M.D.

Director, Division of Adult Translational Research

Associate Director for Clinical Affairs, NIMH, NIH, DHHS

NIMH
National Institute of Mental Health

NIMH: Mission

- To reduce the burden of mental illness through research on mind, brain, and behavior.
- Priorities:
  - Scientific Opportunity
  - Public Health Importance
- **Schizophrenia:** Public Health Imperative.

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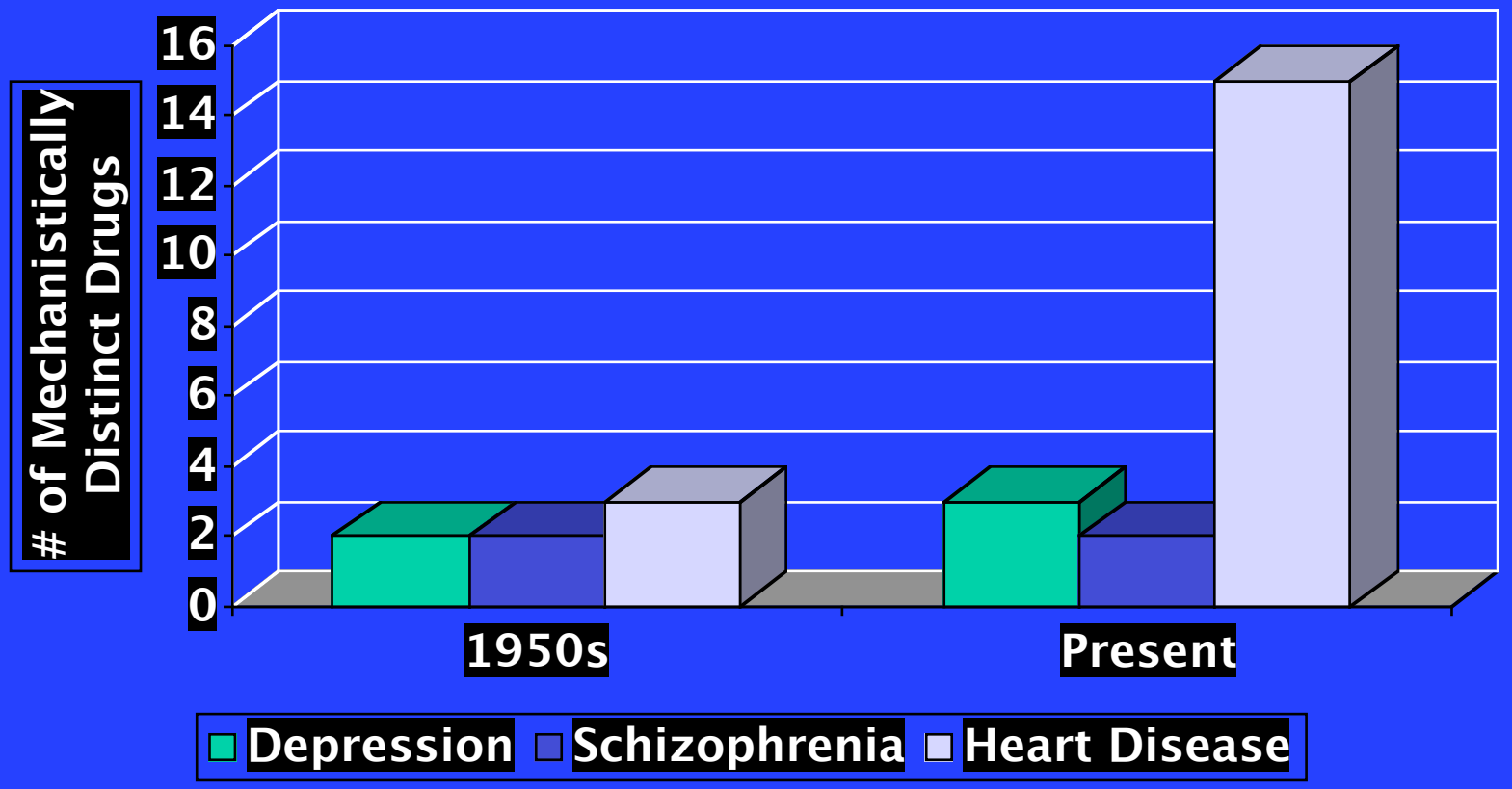
Schizophrenia Therapeutics: Why Are We Stuck?

- Static Molecular Targets: monoamine receptors.
- Static Clinical targets: Positive Symptoms.

Mechanistically Distinct Drugs



Schizophrenia: Cognition, not Positive Symptoms Predicts Long-term Disability

Clinical Dimension	Correlation with Functional Outcome
Delusions	- 0.08
Hallucinations	- 0.09
Thought Disorder	- 0.22 *
Cognitive Impairment *(Immediate verbal memory)*	- 0.40 **

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Cognition in Schizophrenia: Scientific Opportunity

- Glutamatergic modulators (d-serine, cycloserine, glycine)
- Dopamine D1 receptor agonists
- Serotonin 5-HT_{2A} Receptor Antagonists
  - alpha-2 Noradrenergic agonists
  - Cholinesterase inhibitors
  - Muscarinic agonists
  - Nicotinic agonists

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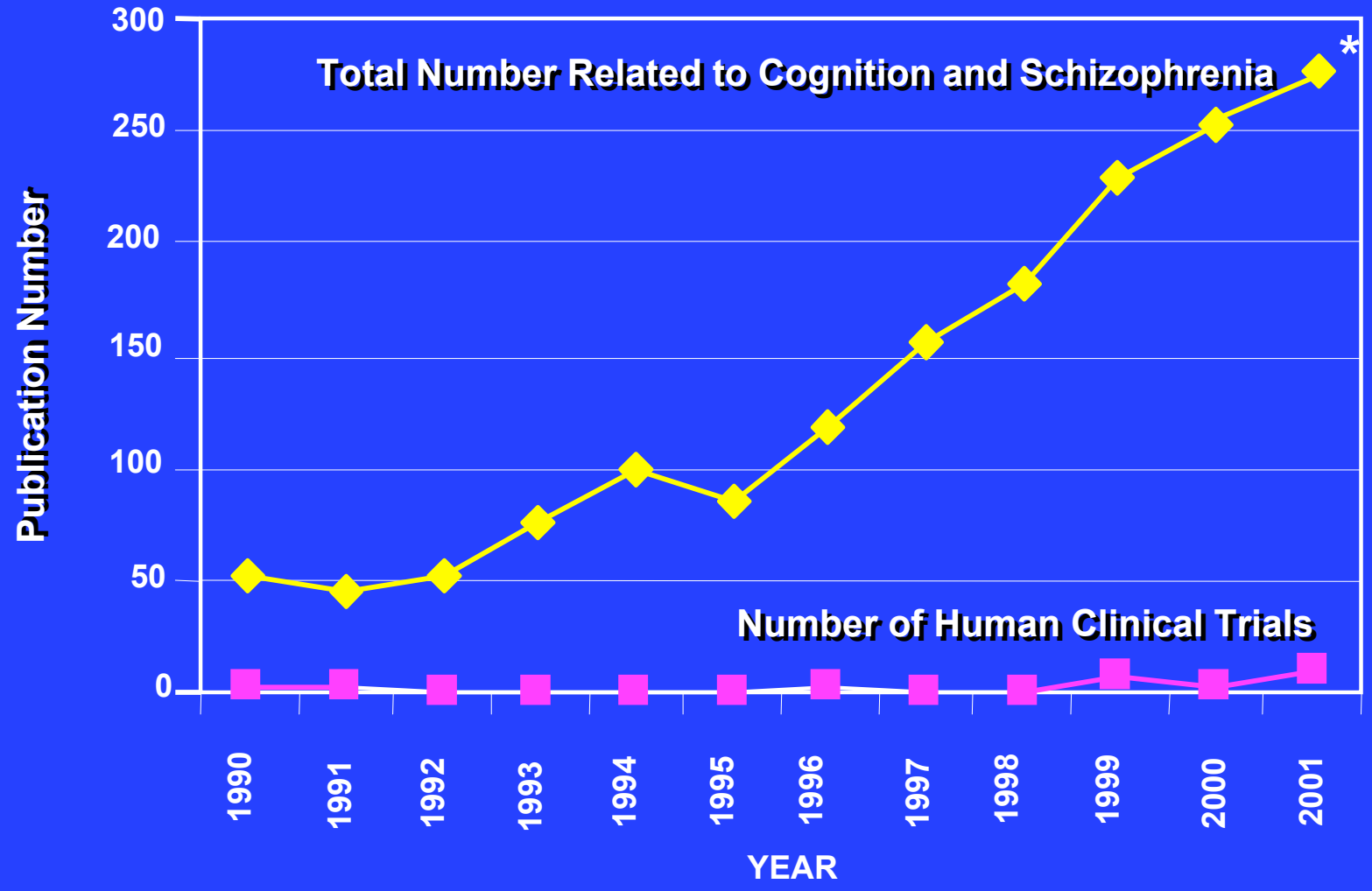

Total Publication Number in 2001 Based upon 9 Months of Data

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Targeting Cognition in Schizophrenia: Why the Bottleneck?

- Lack of consensus regarding cognitive targets.
- No widely accepted endpoint.
- Ambiguity regarding optimal clinical trial design.
- Unclear path to FDA approval and labeling.
- Barriers to compound acquisition for testing.

Clinical Psychopathology:
FDA Processes Focus Industry Efforts

- FDA registration often targets DSM disorders
- "No fundamental objection to syndrome-based clinical targets (fever, pain, agitation)"
- "We will not accept a new clinical endpoint for the convenience of any drug company"
- NIMH can use its convening authority as independent scientific entity to define new and valid clinical endpoints.

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Cognition in Schizophrenia: NIMH Initiatives

- **MATRICS**: Measurement and Treatment Research to Improve Cognition in Schizophrenia
- **PASS**: Psychometric and Standardization Study
- **TURNS**: Treatment Units for Research on Neurocognition and Schizophrenia

MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

Steve Marder, M.D., Co-P.I.

Michael Green, Ph.D., Co-P.I.

www.matrics.ucla.edu

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MATRICS RFP-0006: Deliverables

- Consensus- Oriented Conferences & Papers to address obstacles to discovery.
- Validate & Publish “Standard” Cognition Battery.
- Database of potential lead compounds.
- Guidelines for clinical trial design.

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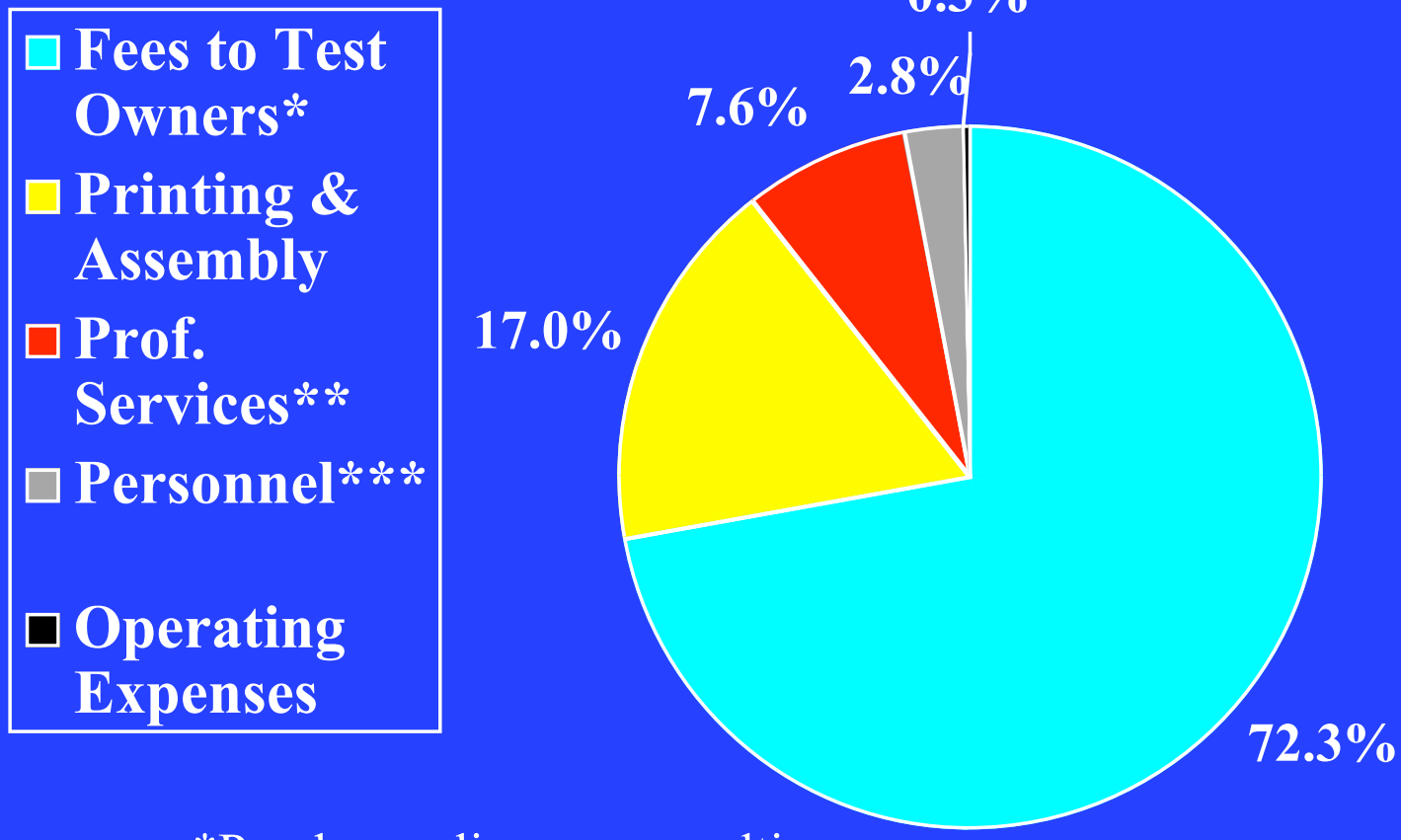
MATRICS Consensus Cognitive Battery (MCCB)

- **Ten Tests – Seven Cognitive Domains.**
- **Evidence-based Consensus Approach.**
- **Evaluated in PASS Study.**
- **Reviewed and Approved By National Mental Health Advisory Council (NMHAC) May, 2005.**
- **Executive Summary Including Guidance for Trial Design Submitted by NIMH Director to FDA June, 2005.**

MATRICS Consensus Cognitive Battery (MCCB)

- Five tests owned by large publishing companies.
  - The Psychological Corporation
  - Multi-Health systems
  - Psychological Assessment Resources, Inc.
- Creation of non-profit required.
- MATRICS, INC

Distribution of Costs for Battery for MATRICS Assessment, Inc.



*Purchases, licenses, royalties

**Business insurance, accountant, auditor

***Office manager, financial officer

FY:2004:
Trials Network for Cognition
RFP No. NIMH-03-DM-0003

Treatment Units for Research on Neurocognition and Schizophrenia (TURNS)

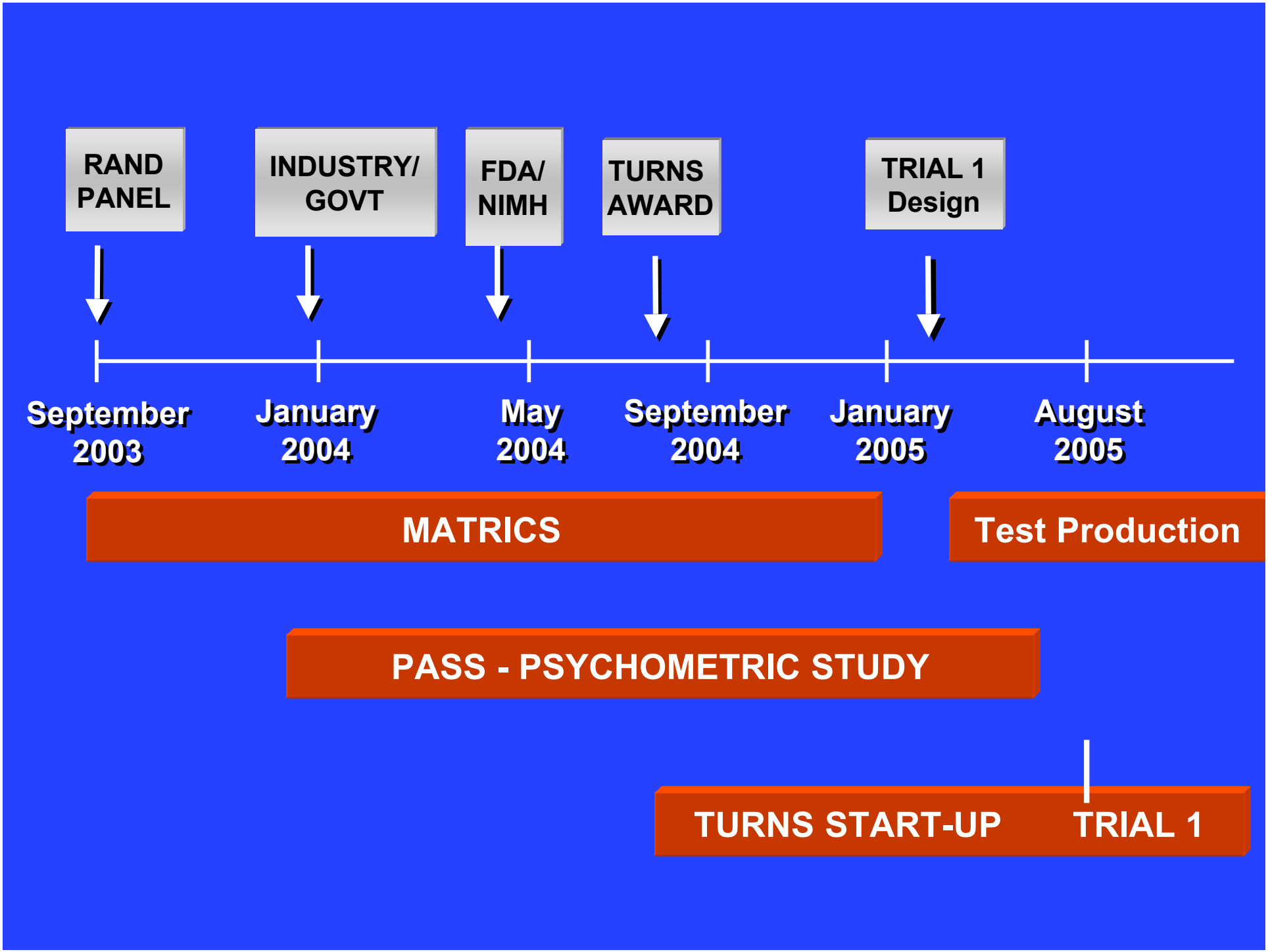
http://www.nimh.nih.gov

Treatment Units for Research on Neurocognition and Schizophrenia (TURNS)

- UCLA
- Columbia
- Washington University/St. Louis
- Nathan Klein Institute
- Mass General/Harvard
- Maryland Psychiatric Research Center
- Duke University

Treatment Units for Research on Neurocognition and Schizophrenia (TURNS)

- Academic Performance Sites
- Chief Psychophamacologist
- Chief Neurospsychologist
- Capacity for Proof of Concept & pK/pD
- Capacity for Biomarkers
  - Psychophysiology - PET
  - fMRI - MRS


RAND PANEL
INDUSTRY/ GOVT
FDA/ NIMH
TURNS AWARD
TRIAL 1 Design
September 2003
January 2004
May 2004
September 2004
January 2005
August 2005
MATRICS
Test Production
PASS - PSYCHOMETRIC STUDY
TURNS START-UP
TRIAL 1

MATRICS: Evolving Issues

- Translation of Battery
- Computerization
  - Scientific Standards
  - Proprietary Considerations
- Cognitive Neuroscience-based Measures
- Negative Symptoms
- Continued Federal Role

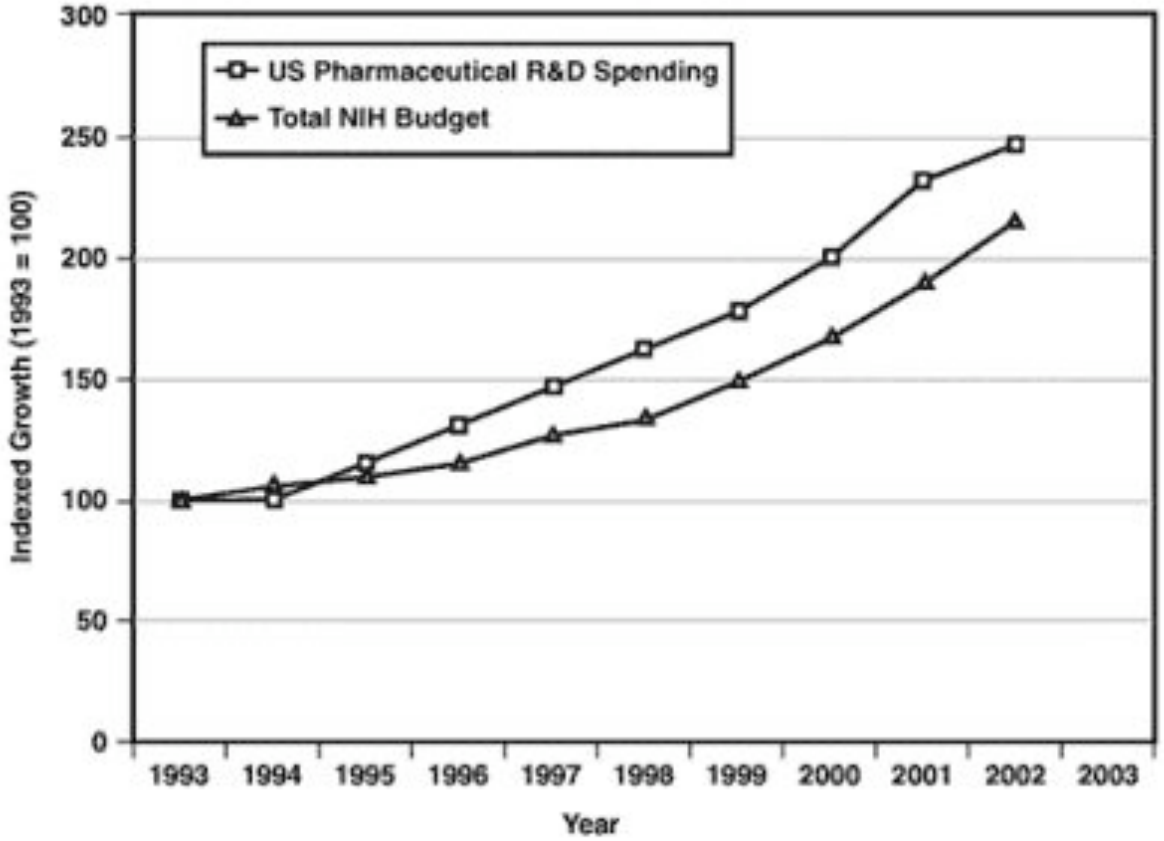
Evolving Issues

- MATRICS Development
- FDA Critical Path Initiative
- Models for Government-Industry Collaboration

Challenge and Opportunity on the Critical Path to New Medical Products

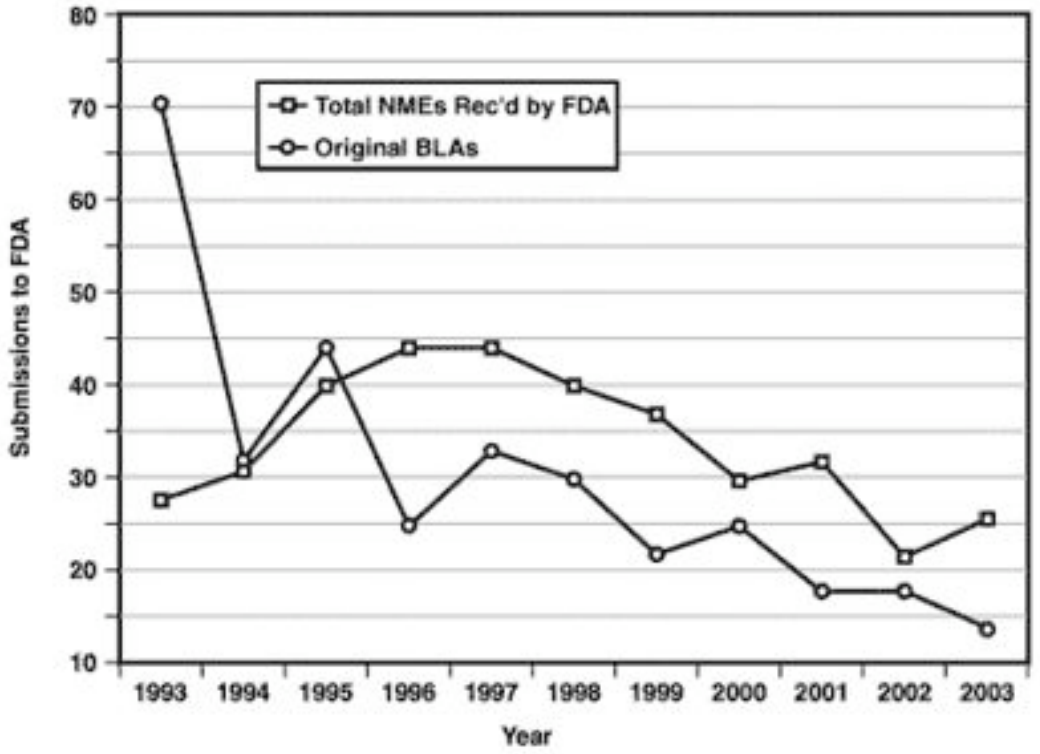
U.S. Department of Health and Human Services
Food and Drug Administration
March 2004

Figure 1: 10-Year Trends in Biomedical Research Spending



The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies' research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statiststical Sourcebook 2002/2003).

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA



The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.

Pipeline Stagnation: FDA View

- **In FDA's view, the applied sciences needed for medical product development have not kept pace with the tremendous advances in basic sciences. The new science is not being used to guide the technology *development* process in the same way that it is accelerating the technology *discovery* process.**

- **In many cases developers have no choice but to use the tools and concepts of the last century to assess this century's candidates.**

Critical Path or Development Science

- Better animal models and predictive pre-clinical screening methods.
- Biomarkers or surrogate endpoints for effectiveness: (H. pylori, CD4).
- Better paradigms for proof of concept trials in humans.
- Increase efficiency of clinical trials such as selection of patients based on genotype and Bayesian approaches to randomization.
- Methods for early prediction and detection of safety problems.
- Consensus regarding new meaningful clinical endpoints.
- Guidance for development pathway.

Government-Industry Collaborative Models

- NIA: Osteoarthritis Initiative
- NIH Molecular Libraries Project
- NIMH Collaborative Drug Development Groups (CDDG)
- NIMH Centers for Intervention Development and Applied Research (CIDAR)

NIA- Osteoarthritis Initiative (OAI)

- Today, 35 million people — 13 percent of the U.S. population-are 65 and older, and more than half of them have evidence of osteoarthritis in at least one joint.
- Drug development hindered by lack of standard measurement of disease progression.
- Goal:Define Biomarker for Progression of OA.
- Data and specimen repository will establish standards of disease progression against which potential biochemical and imaging markers can be evaluated

NIA- Osteoarthritis Initiative (OAI)

- Public/Private Partnership
  - NIH, FDA, GSK, Merck, Novartis, Pfizer
  - 8 million per year x 6 years
- Prospective radiological (X-ray, MRI) and biological assessment (blood, urine, DNA) of 5000 patients at risk for osteoarthritis progression.
- Finances managed by NIH Foundation.
- Enrollment March 2004.

NIH Roadmap: Molecular Libraries/Imaging

- ***Goal: offer public sector biomedical researchers access to small organic molecules that can be used as chemical probes to study the functions of genes, cells, and biochemical pathways.***

- ***Molecular Libraries Screening Center Network* (MLSCN).**
  - Accept Assays adapted to high throughput screening.
  - Establish library of 500,000 chemically diverse small molecules
  - Perform optimization chemistry to produce useful invitro chemical probes to study disease.

NIH Roadmap: Molecular Libraries/Imaging

- ***Cheminformatics***. A new and comprehensive database of chemical structures and their biological activities: PubChem
- ***Technology Development***.
  - **Chemical Diversity:** new synthetic methods
  - **Assay diversity**. novel assays for types of proteins and biological phenomena.
  - **Instrumentation:** new methods for high-throughput measurement of novel biological assays.
  - **Predictive ADME/Toxicology:** data sets and analysis methods to allow better prediction of ADME (absorption, distribution, metabolism, and excretion) and toxic properties of novel molecules.

Collaborative Models

- NIMH Collaborative Drug Development Groups (CDDG)
- NIMH Centers for Intervention Development and Applied Research (CIDAR)

www.nimh.nih.gov

Government-Industry Collaboration: January 22, 2004

Goal: Define non-redundant role for NIMH in hastening availability of new medicines for mental illness.

Process: Overview of Intramural and Extramural treatment development efforts.

Expert Panel: Including Research/CNS Directors from 14 leading pharmaceutical and biotech companies.

Government-Industry Collaboration: January 22, 2004

1. What useful and non-redundant role might NIMH play in hastening the availability of new treatments for mental illness ?

2. Can large clinical trial networks be of utilized within a public-private partnership?

3. What are major barriers to government-academic-industry collaboration and how might they be overcome?

Government-Industry Collaboration: January 22, 2004

1. NIMH should maintain a strong basic research portfolio focused on elucidating pathophysiology of mental illness.
2. Concerns were expressed regarding a molecular libraries project focused directly on human therapeutics. The molecular libraries project should focus on developing new ligands, radiotracers, and small molecule tools for pre-clinical research.
3. NIMH research should focus on clarifying disease phenotypes both for genetic studies and to define new clinical targets for treatment development.

Government-Industry Collaboration: January 22, 2004

4. The MATRICS process might be used as a paradigm for defining non-DSM clinical endpoints and refining measurement of psychopathology as dependent variables for treatment trials.
5. The large clinical trial networks focus on important public health questions. Grafting longitudinal studies, studies of biomarkers, and pharmacogenetic studies onto large pragmatic trials may be a useful strategy for government-industry partnership.
6. Some regular forum for communication between NIMH and industry might facilitate future collaboration.

- FDA Perspective on MATRICS.ppt