



Origins of the PPRU – Therapeutic Orphans

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**“By an odd twist of fate,
infants and children are
becoming therapeutic or
pharmaceutical orphans.”**

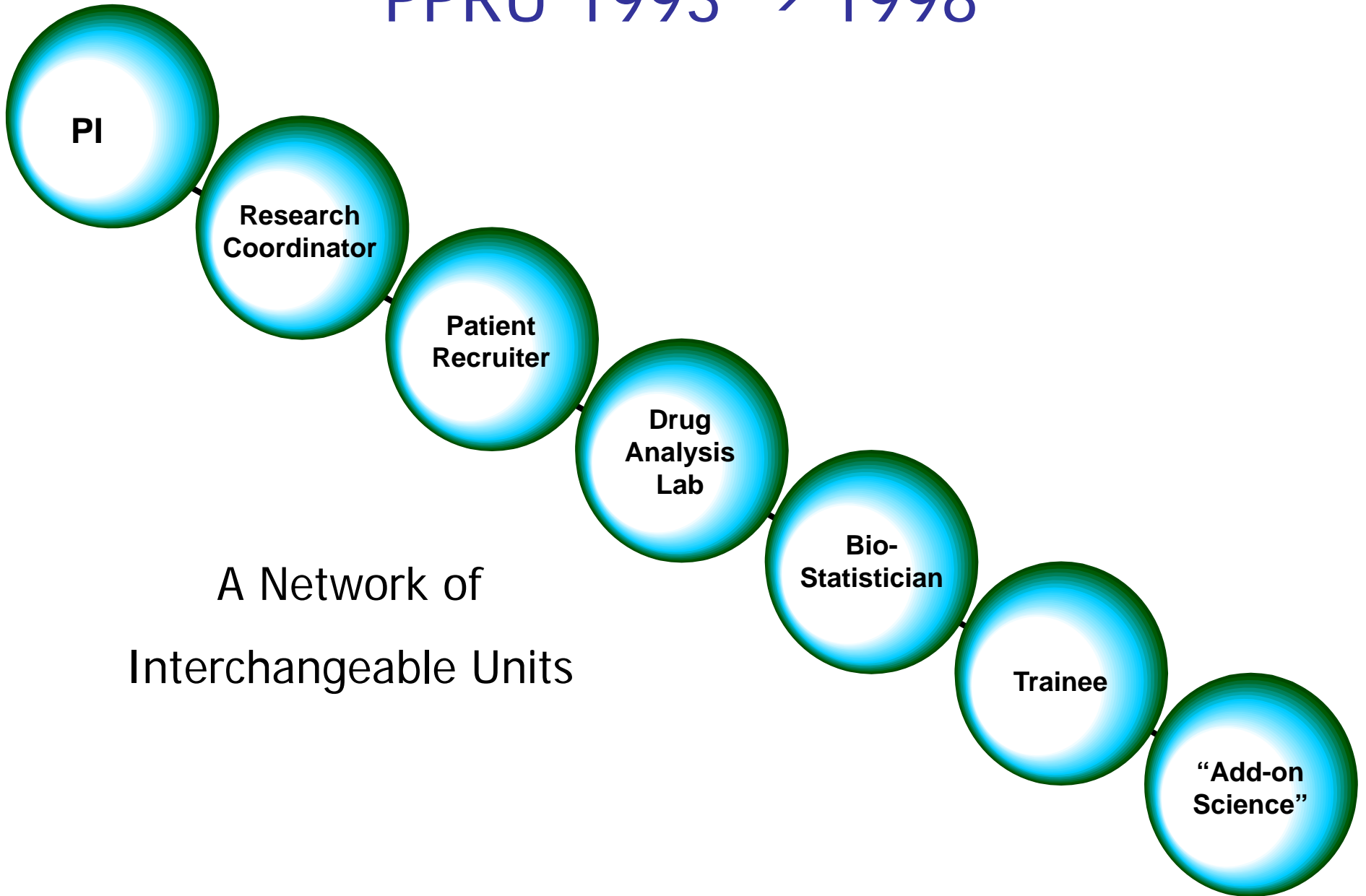
Harry C. Shirkey, M.D., 1963.
Conference of Professional and
Scientific Societies. Commission on
Drug Safety



The PPRU Network

- First awards in 1993 to 5 centers
- Network increased to 7 centers in 1994
- Recompetition in 1998 resulted in the addition of 6 new sites
- Recompetition in 2003 resulted in replacement of 6 sites with new ones maintaining 13 sites total

PPRU 1993 → 1998



A Network of
Interchangeable Units



Our Specific Aims

- I. To provide a locus for conduct of studies in bioavailability, drug metabolism, PK, PD, safety and effectiveness of new drugs and drugs already on the market**
- II. To gather or promote the accrual of the necessary data for pediatric age-specific labeling of drugs**
- III. To carry out research on novel approaches and innovation in pediatric pharmacology**

- IV. To implement studies on the developmental characteristics and genetic polymorphisms of drug metabolizing enzymes, transporters and receptors. Phenotypic-genotypic correlations**
- V. To apply pharmacogenomic and proteomic tools in clinical studies**
- VI. To provide training in clinical and developmental pharmacology**

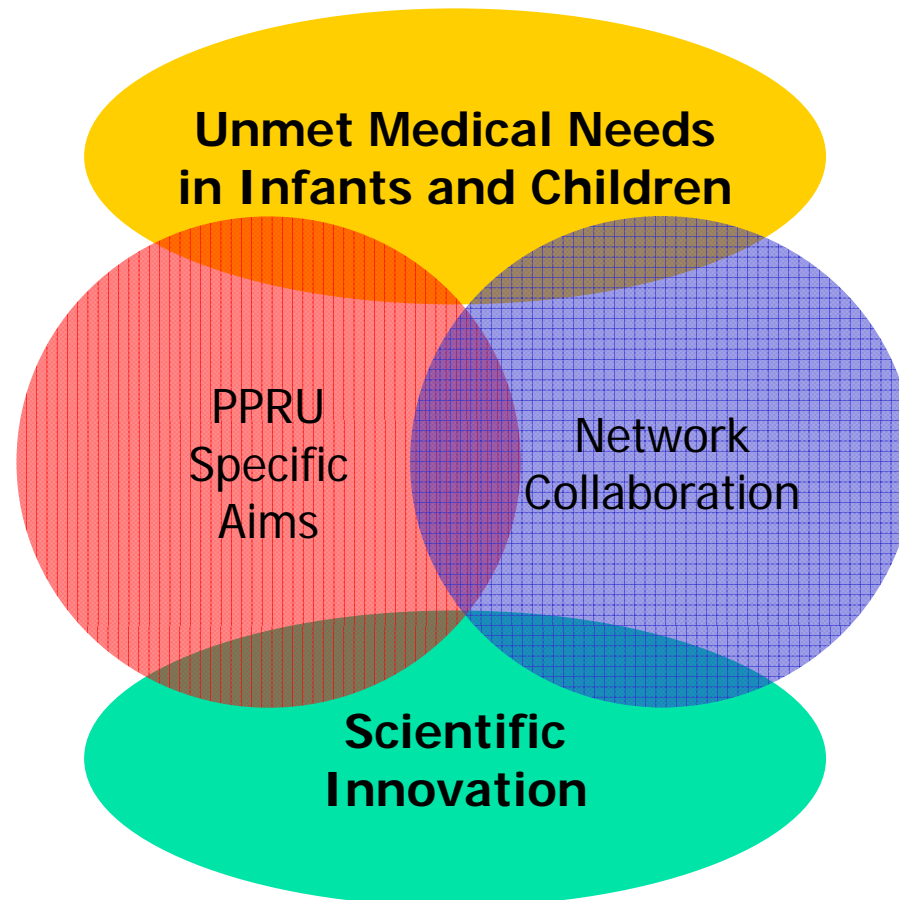


PPRU Network: Impetus for Evolution

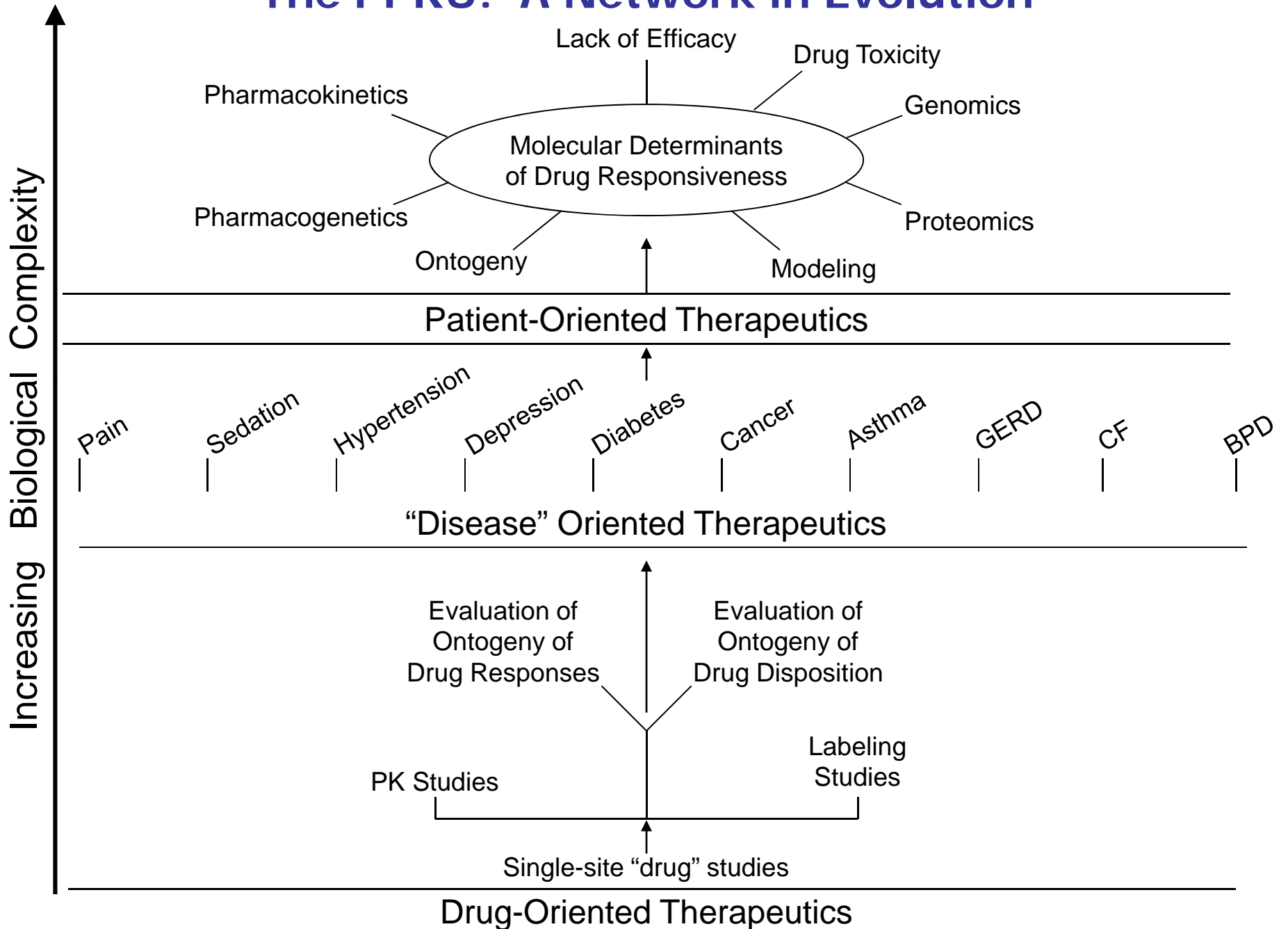
- The Network is the first collaborative group of investigators dedicated to the translation of scientific discoveries into safe, effective therapeutic products for pediatric patients
- The Network and its accomplishments harness the spirit and implementation of the NIH Roadmap and FDA Critical Path to address the unmet needs in pediatric therapeutics



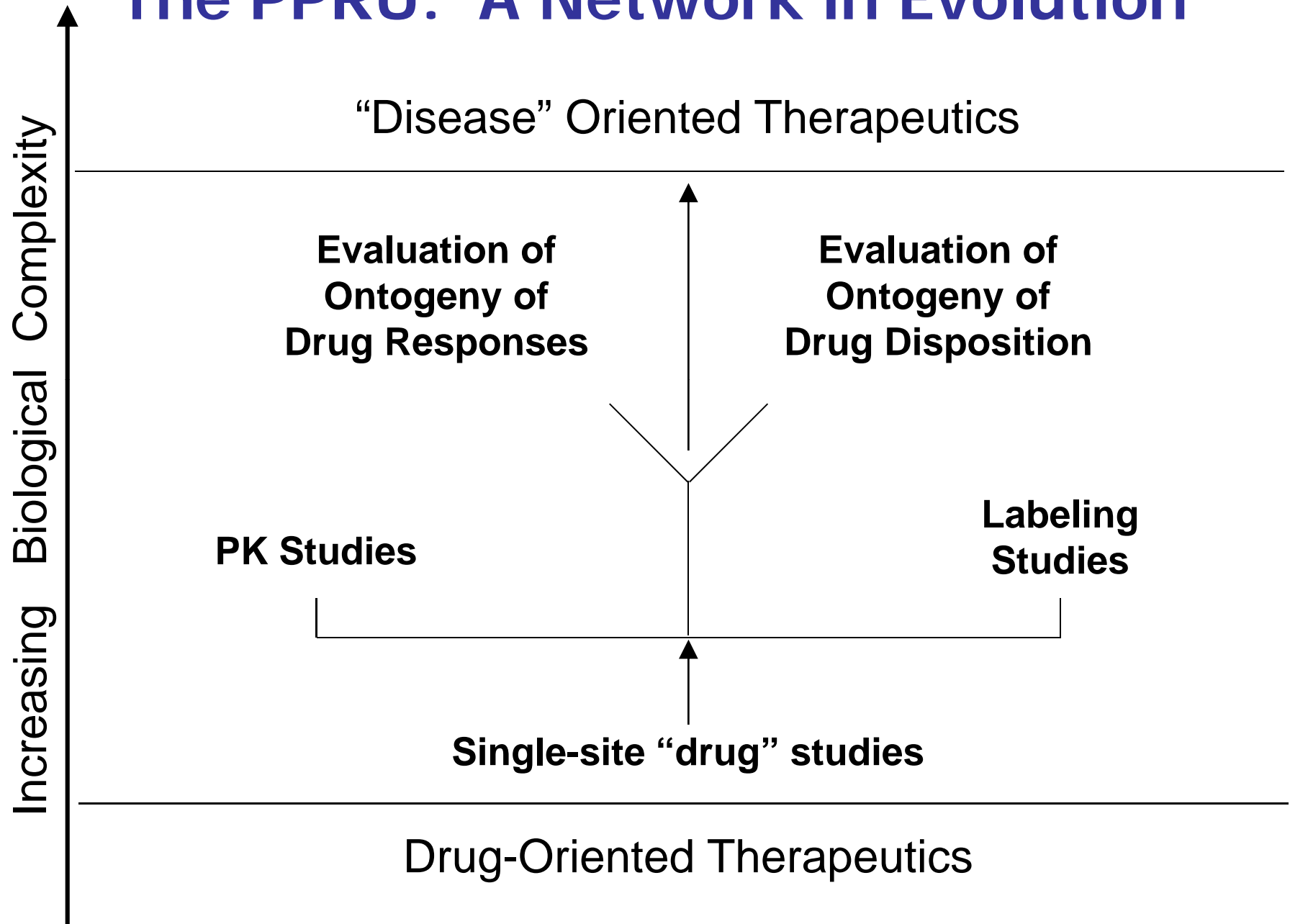
A Nexus of Mandates



The PPRU: A Network in Evolution



The PPRU: A Network in Evolution





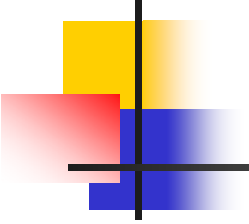
Traditional Approaches in Pediatric Pharmacology

- Generally “drug-oriented”
 - FDA approved
 - Not previously studied in children
 - Clinical indication in children similar or identical to that for adults
 - Generally limited to agents with large therapeutic index
 - Acceptable formulation available (+/-)



Traditional Approaches in Pediatric Pharmacology

- Limited research questions addressed
 - What drug?
 - What dose?
 - What route of administration?
 - How long?
- Studies focused on what was needed for treatment without asking more probing questions about mechanisms of action or developmental changes in responses; which patients won't respond



Traditional Approaches in Pediatric Pharmacology

- Approach to evaluation

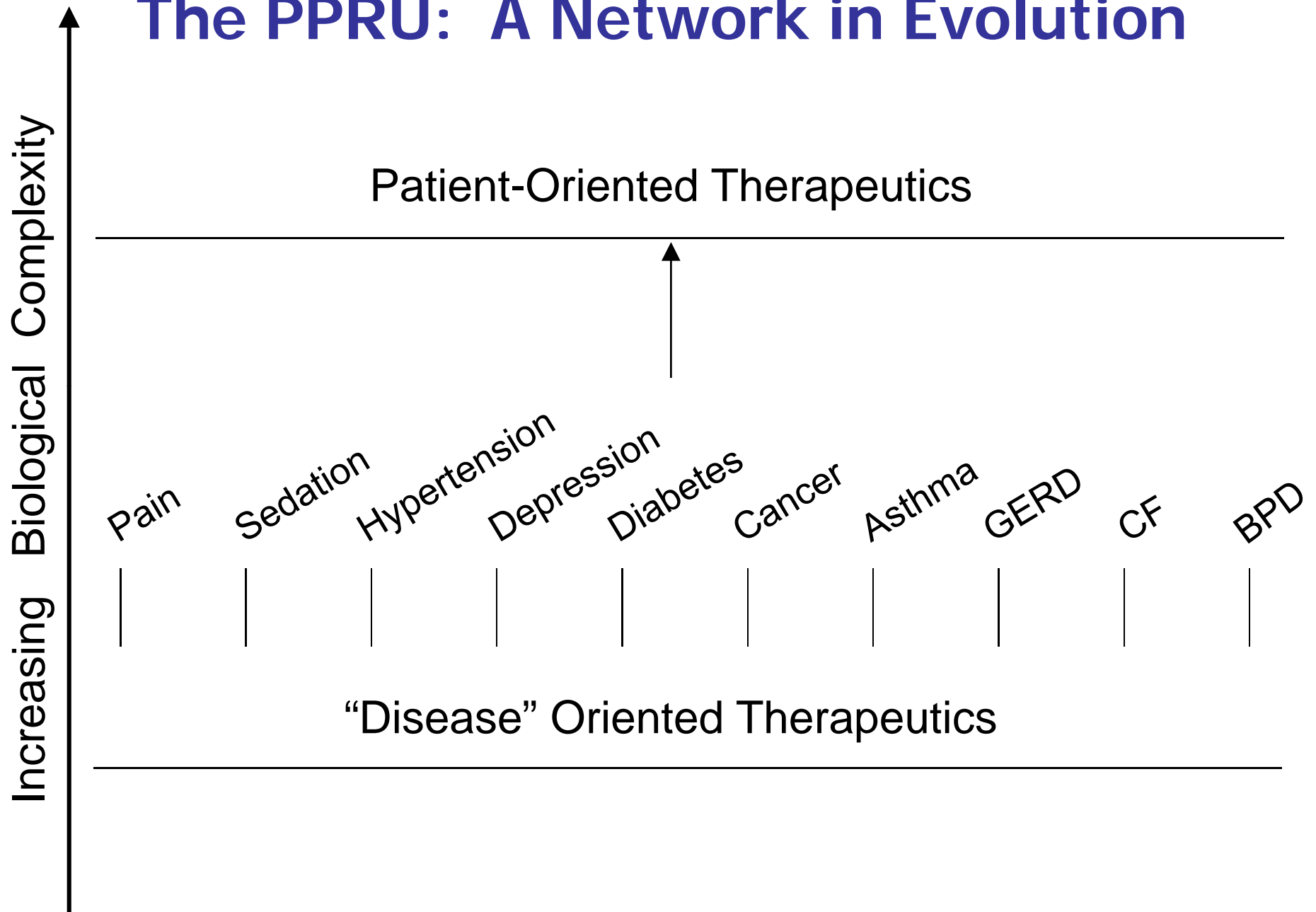
- Usually one dose level studied; which then becomes "THE DOSE"
- Dose selection derived from transformation of adult doses on a mg/kg basis vs comparable AUC
- Studies performed by a single group of organ system-based "ologists" ie

antihypertensive \longleftrightarrow nephrologist

H₂ receptor antagonist \longleftrightarrow gastroenterologist

- Most studies underpowered and open label

The PPRU: A Network in Evolution



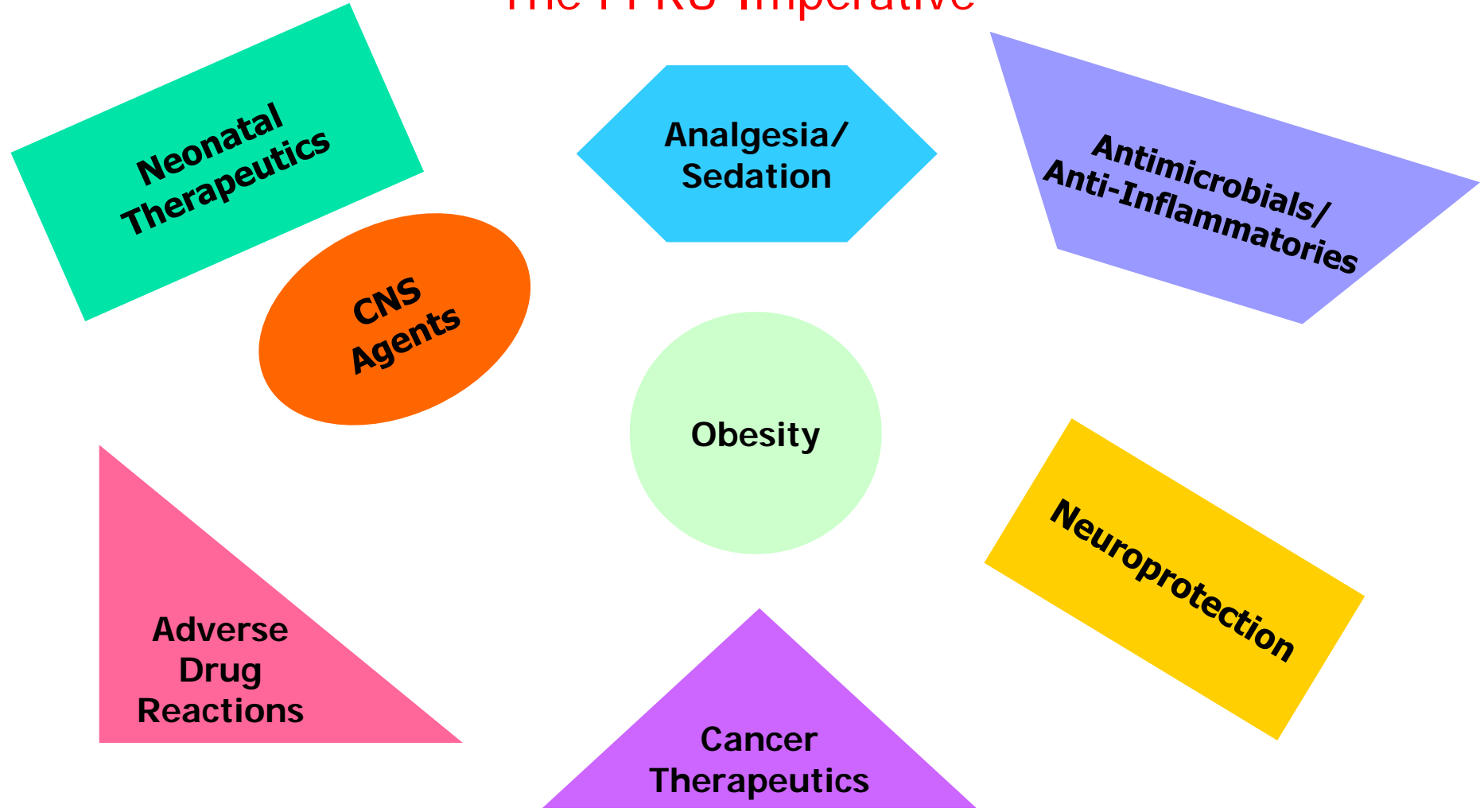


Innovation in Pediatric Pharmacology

- Transition from “drug-oriented” to “patient-oriented” research
- Reintroduce basic science principles into pediatric clinical trials
 - Dose-response relationships
 - Ontogeny of ADME processes
 - Unleash the power of modeling
 - Recognize molecular determinants of drug response and then developmental differences in pediatric populations
 - Efficacy
 - Toxicity
- Develop supportive analytical techniques
- Transition from single subspecialty-based investigators to multidisciplinary teams
- Create the PPRU

Unmet Medical Needs – A Therapeutic Imperative

-- The PPRU Imperative --



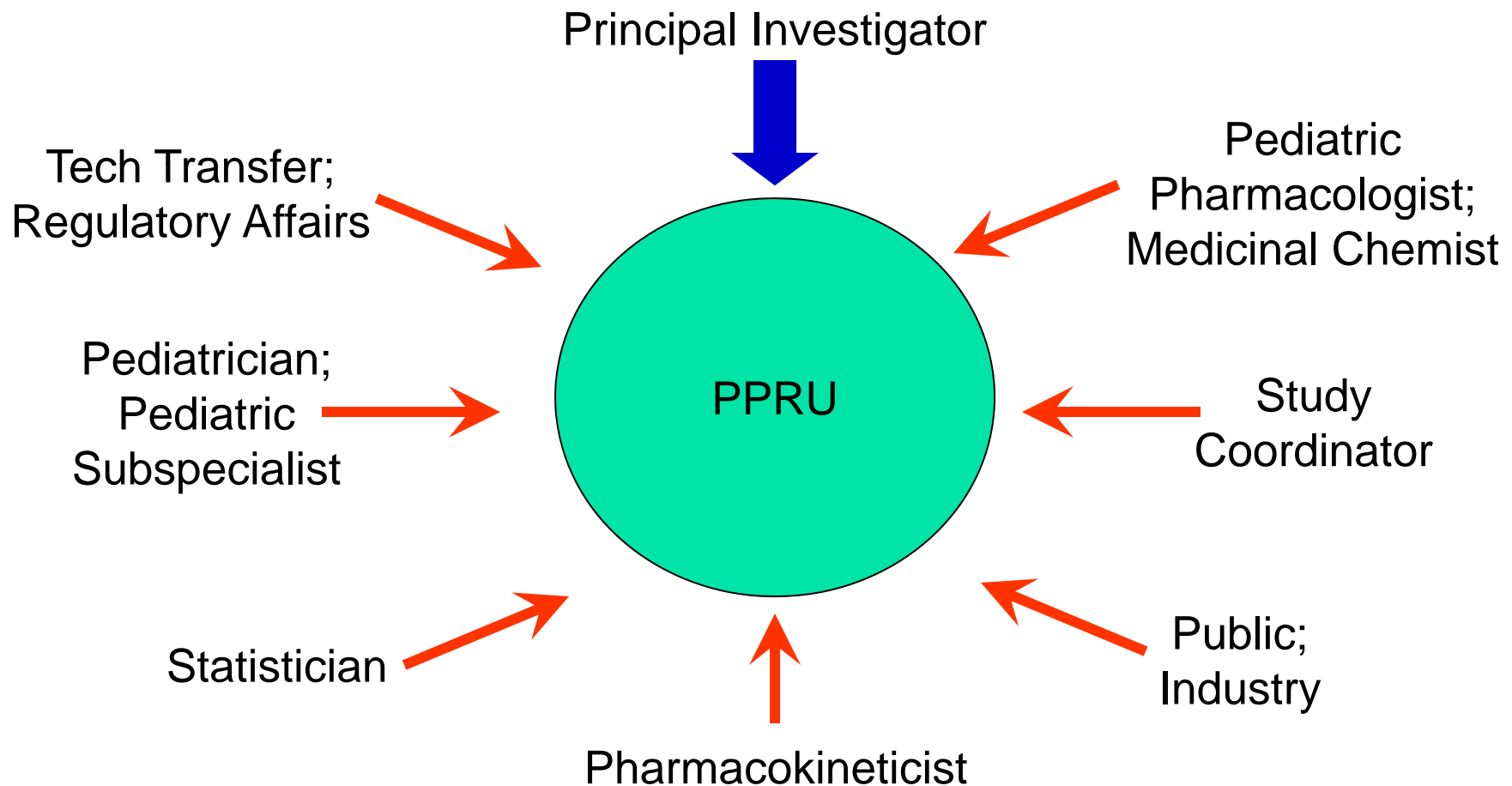


The PPRU Network and Pediatric Pharmacology

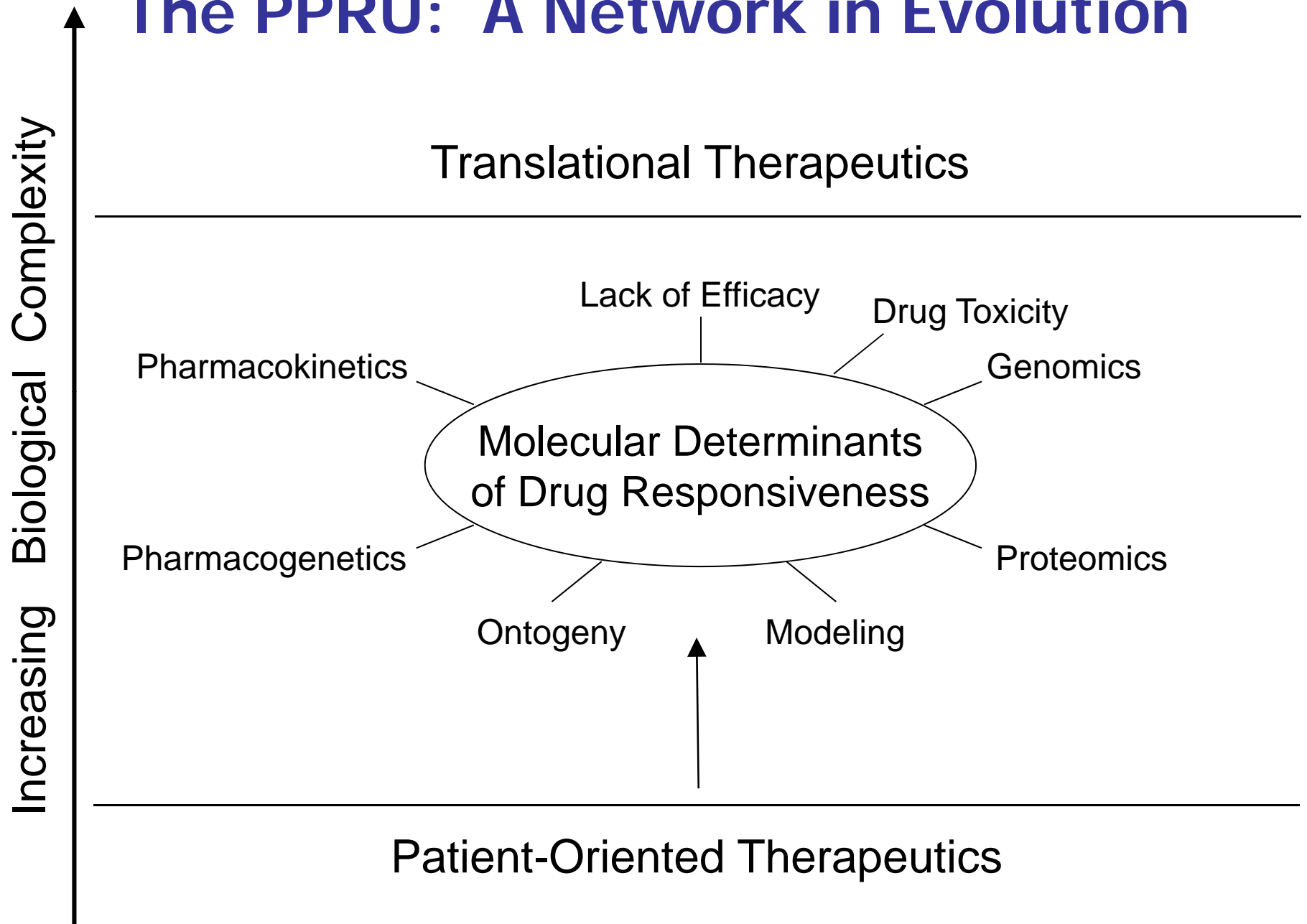
- Formation of an innovative network of investigators characterized by:
 - In depth understanding of the unique language base of pharmacology and therapeutics
 - Clinicians with pediatric therapeutics trial experience
 - Strong tradition of academic center – industry collaboration
 - Multidisciplinary collaboration including subspecialists, general practitioners, and basic scientists (pharmacologists have no patients)
 - The creation of a “toolbox” for the conduct of pediatric therapeutic research
 - An emphasis on training of the next generation of Pediatric Pharmacologists -- MSCIDA

A Pediatric Pharmacology Multidisciplinary Clinical Research Team

Members have unique skills and career paths



The PPRU: A Network in Evolution





The PPRU “Toolbox”

- **Pharmacometric Expertise**
- **Analytic Pharmacology**
- **Innovative Study Design**
- **Multidisciplinary Teams**
- **Pharmacogenetics**



The PPRU “Toolbox”: Pharmacometric Expertise

- Pharmacokinetics
 - Traditional PK
 - Sparse sampling PK
 - Population PK
 - PK modeling
- Physiologic modeling of drug disposition
- Study simulation and predictive modeling
- Data warehousing, data mining, data sharing



The PPRU “Toolbox”: Analytic Pharmacology

- Microsample capabilities LC/MS/MS technology
- GLP assays available for a large number of drugs and drug metabolites
- Direct integration with pharmacometric and pharmacogenetic cores
- Ability to support multisite trials due to sophisticated sample handling approaches



The PPRU “Toolbox”: Innovative Study Design

- Introduction of hypothesis driven clinical investigation
- Demonstration of the feasibility of dose finding studies in pediatrics
- Study design informed by simulations
- Introduction of sample size justification into pediatric therapeutic studies
- Application of extreme phenotype and adaptive randomization strategies



The PPRU “Toolbox”: Multidisciplinary Teams

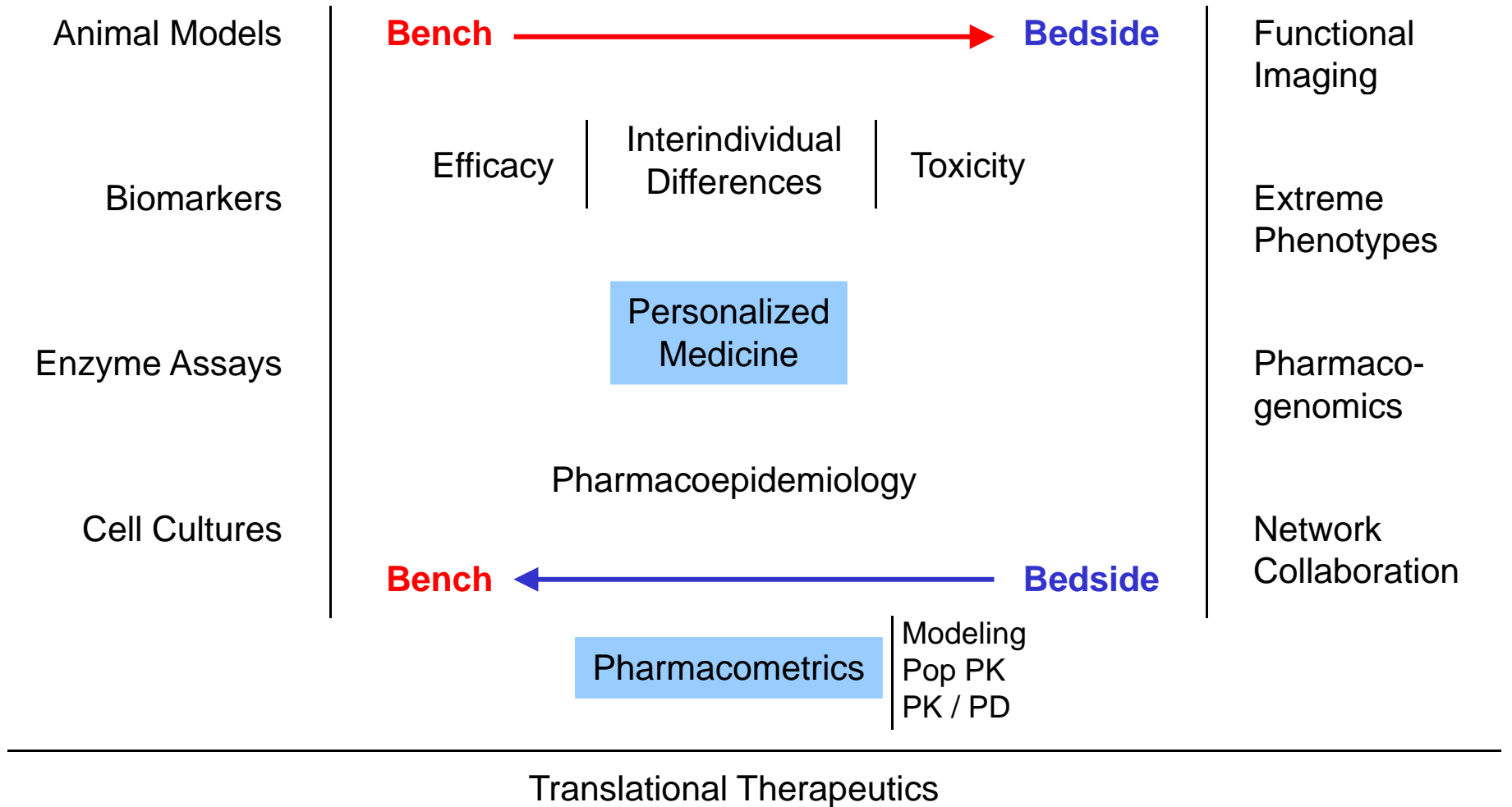
- Network investigators represent a broad range of pediatric specialists
- Network investigators routinely catalyze interaction among subspecialists to achieve research goals
- PPRU structure facilitates effective integration of basic science with clinical medicine



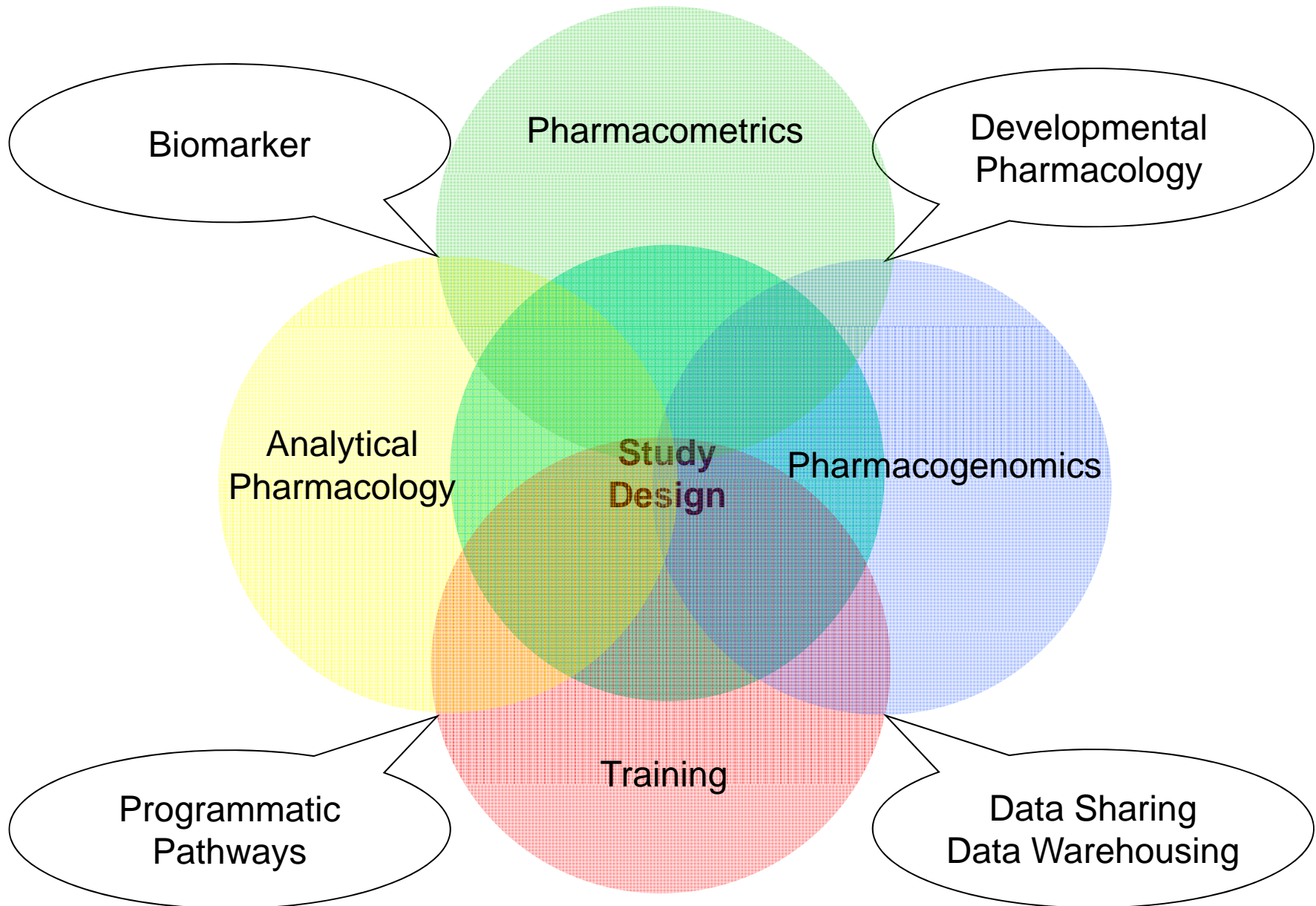
The PPRU “Toolbox”: Pharmacogenetics

- The search for mechanistic determinants of interindividual differences in drug responsiveness as integral part of all PPRU protocols
- Assessment of drug metabolizing enzyme genotypes and receptors

Analytical Pharmacology



The PPRU Network -- Now



The PPRU: Continuing Evolution

