

# Translational Research in the PPRU Network

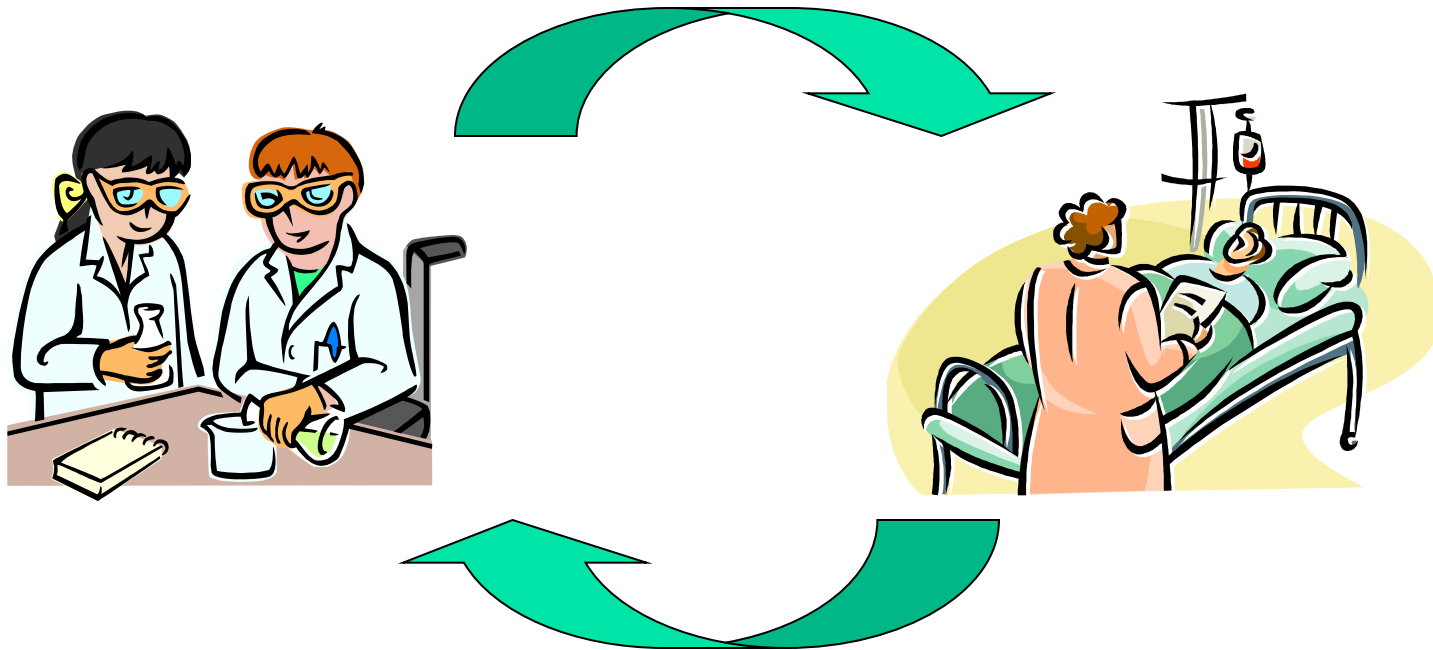


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# Translational Research....What others say it is



**“a move to a more open, patient driven research process, and the embrace of a more research-driven clinical practice of medicine”**

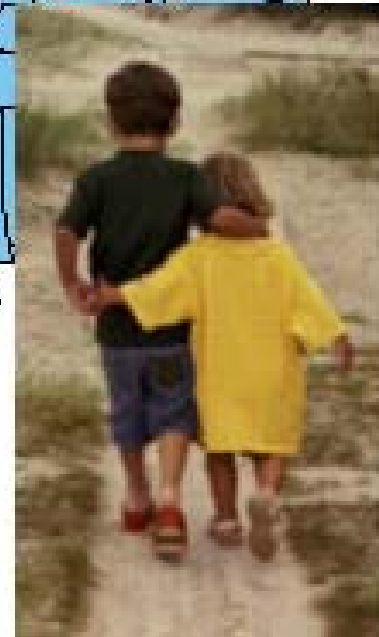
**[http://en.wikipedia.org/wiki/Translational\\_research](http://en.wikipedia.org/wiki/Translational_research)**



# Realizing the Goal of Translational Medicine Is Attainable but Requires a Multidisciplinary, Coordinated Team....

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- **Laboratory-based investigators**
  - Pre-clinical target validation
  - Assessment of biologic markers *in situ*
  - Measurement of surrogate endpoints
- **Clinical investigators**
  - Clinical trialists
  - Clinician scientists (eg., clinical pharmacologists, relevant “..omics” experts)
  - Medical sub-specialists
- **Statisticians (including pharmacometricians, genetic epidemiologists)**
- **Research nurse coordinators**
- **Data managers**





# Translational Research in the PPRU Network...a Mission-Centric Evolution

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- RFA HD-98-002 (1<sup>st</sup> competitive renewal)
  - *“To conduct studies on the developmental characteristics and genetic polymorphism of drug metabolizing enzymes, pharmacokinetic modeling and simulation technology”*
- RFA HD-03-001 (2<sup>nd</sup> competitive renewal)
  - *“To implement studies on the developmental characteristics and genetic polymorphisms of drug metabolizing enzymes, transporters and receptors”*
  - *“Conduct studies examining phenotypic-genotypic correlations”*
  - *“To apply pharmacogenomics and proteomic tools in clinical studies”*



**Adoption of an Amalgamated Model to Embrace  
Translational Medicine in the PPRU Network.....A  
Deliberate and Necessary Convergent Evolution**



# Embracing Translational Research in the PPRU: Evolving Technology and Capacity

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## ■ Pharmacometrics

- Bioanalytical Techniques → Traditional PK → Population PK → Integrated PK/PD/PG Analyses → *In silico* Trial Simulation → Disease Progression Modeling → Molecular Modeling → Data Warehouse (cross study modeling/simulation)

## ■ Clinical Trial Design

- Pharmaceutical “single goal” classical designs → Investigator initiated multi-faceted, multi-variate (eg., PK/PD/PG) designs → Ontogeny-driven target exposure/response designs



# Embracing Translational Research in the PPRU: Evolving Technology and Capacity

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## ■ Pharmacodynamics

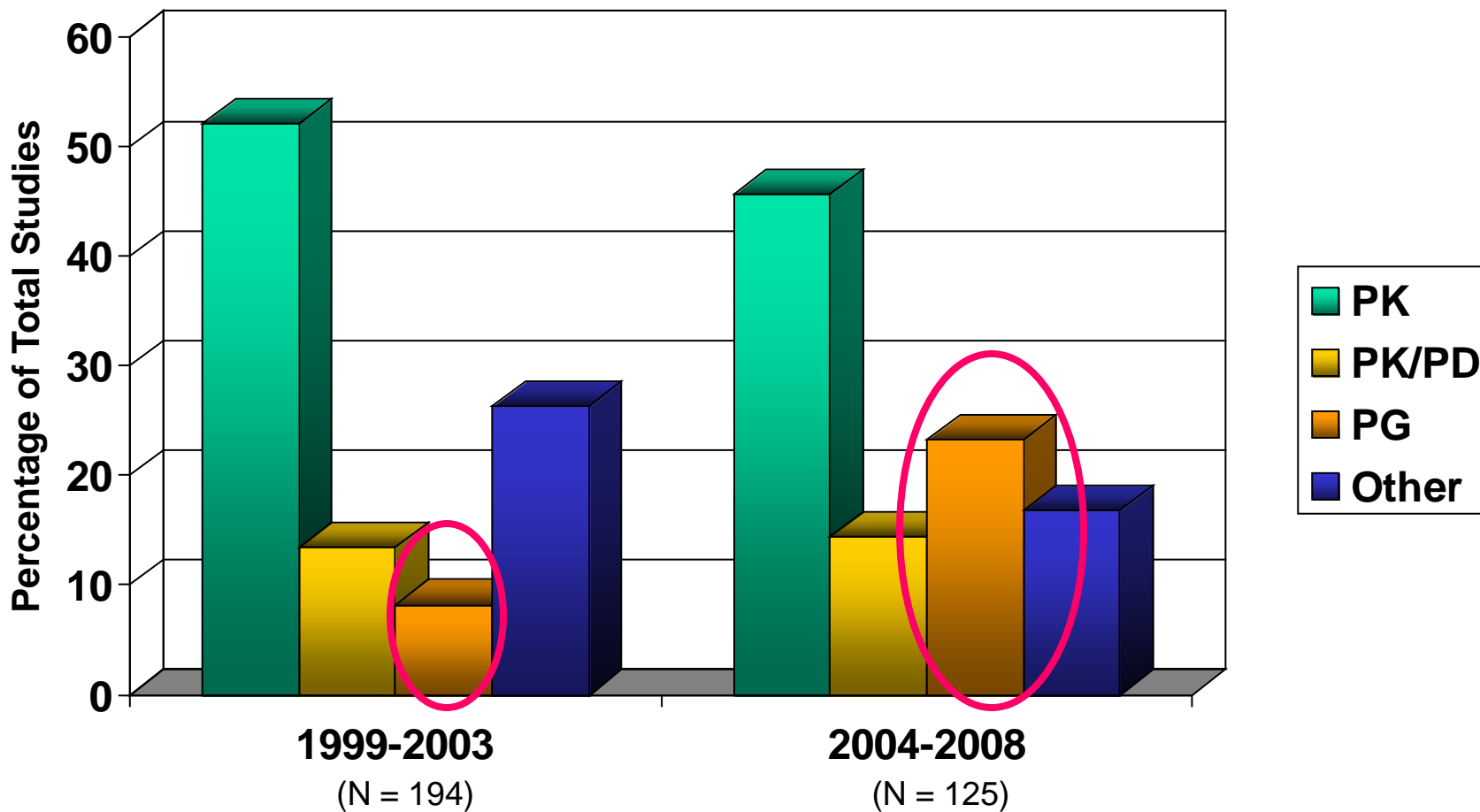
- Clinical, biochemical and physiologic endpoints → *In vitro* biomarkers → *In vivo* biomarkers → Surrogate PD endpoints (eg., pupilometry, neurometry, microvascular flowimetry)

## ■ Pharmacogenomics (and beyond)

- Pharmacogenetics → Pharmacogenomics → Gene sequencing → Reaction phenotyping → Developmental Bio-repository → Genotype/phenotype association → Gene expression profiling → Proteomics → Genome-wide association studies



# Evolution of Translational Science in the PPRU Network: Comparison of 2<sup>nd</sup> and 3<sup>rd</sup> Funding Cycle





# Translational Research in the PPRU Network: Scholarly Accomplishment in the Arena of Pharmacogenomics

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- 98 total peer-reviewed publications over past 12 years
  - Studies exploring developmental PG (ontogeny): n=9
  - Integration of PG into a clinical drug trial designed to assess PK and/or PD: n=20
  - Studies characterizing gene frequency and/or genotype/phenotype associations: n=18



# Translational Research in the PPRU Network: Current Areas of Endeavor

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- Clinical trials exploring effect of age, disease and/or concomitant treatment as modulated by gene expression
- Predictive association between genotype and exposure-response
- Use of pharmacogenomics and proteomics to investigate adverse drug effects
- Development of *in vivo* biomarkers as surrogate pharmacodynamic endpoints
- Use of gene expression profiling to develop therapeutic endpoints for drug treatment