Presentation to the Committee on Accelerating Rare Disease Research and Orphan Product Development

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Executive Director, PXE International
President, Genetic Alliance Registry and BioBank
Transforming Health Through Genetics

• Create and maintain novel partnerships.

• Integrate individual, family, and community perspectives to improve health systems.

• Revolutionize access to information to enable translation of research into services and individualized decision making.
Elizabeth and Ian diagnosed with a genetic condition

1994

2008
You can’t just take a deli number
Herding Cats
Therapeutic Pipeline

Industrialized Process

Technology
Platforms

Sequencing
Automation

Proteomics
Combi-Chem

Pharmacology

Gene Identification

Target Validation

Assay Experiments

Pre-Clinical

Lead Identification

Animal Testing

Clinical Trials

Diagnostics

Therapeutic Intervention

Biology
Computation

Chemistry
Informatics

Pathology
Imaging

SNPs/Chips
Medicine

Computing Modeling

Comparative

MicroChips

Clinical Trials

Patient Mngmnt.
LOGIC: Data Collection + Data Integration + Time/Serendipity + Knowledge

Diagram: Flowchart showing relationships between various scientific and medical fields from 1997 to 2008, including:
- Proteins, Gene Structure, Function
- Genomics, SNP/RSNPs
- Proteomics, Regulomics
- Cellular Modeling
- Delivery Vectors
- Epidemiological Research
- Genotype / Phenotype Associations
- In Vivo Studies
- Sequencing Analysis
- Code Sequence
- Associated Expression
- Protein Expression
- Cellular Model Organisms
- Rational Intervention Design
- Therapeutic Treatment
- Experimental Assays
- Accurate Correlative Linkage
- Phenotype Prediction

Key:
- Orange: Protein Expression
- Yellow: Genomics, SNP/RSNPs
- Blue: Proteomics, Regulomics
- Green: Cellular Modeling
- Red: Delivery Vectors
- Black: Epidemiological Research
- Grey: Accurate Correlative Linkage
- Blue: Phenotype Prediction
- Blue: Rational Intervention Design
- Blue: Therapeutic Treatment
- Red: Code Sequence
- Orange: Associated Expression
- Green: Genotype / Phenotype Associations
- Yellow: Experimental Assays
- Red: Experimental Assays
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- Orange: Rational Intervention Design
- Orange: Therapeutic Treatment
Business models must be based on new economic constructs

<table>
<thead>
<tr>
<th>Industrial Age (old)</th>
<th>Information Age (new)</th>
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<tbody>
<tr>
<td>Control means of production</td>
<td>Open means of production</td>
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<tr>
<td>Based on scarcity</td>
<td>Based on abundance</td>
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<tr>
<td>Hierarchical / Command &amp; Control</td>
<td>Network / Collaboration</td>
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<tr>
<td>Linear / Sequential</td>
<td>Organic</td>
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<tr>
<td>Win / Lose</td>
<td>Win / Win</td>
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<td>Material</td>
<td>Information</td>
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Results
Demise of advocacy organizations as we know them, new pathways and multiple lead focus of industry: Opportunity abounds as interests coalesce
20 months of preparation

Bimonthly meetings of senior people
Consultations with 50+ companies, BIO, PhRMA
Discussions, surveys, interviews with hundreds of disease groups
Registry and biorepository landscape analysis
Stakeholder meetings 12/08, 1/09, 7/09

30 Companies  25 Advocacy Orgs  225 Mixed
GRANDRx Initiative
Gateway to Rare and Neglected Diseases
Therapeutics
Public-Private Partnership
Develop test system ("assay") to identify compounds that affect target

Implement high throughput screening assay and identify proof-of-principle chemical probe

Perform iterative chemical modification and testing to identify compounds safe and effective in test animals

Perform increasingly demanding clinical testing to identify compounds that are safe and effective in humans

Obtain FDA approval for use in humans

Phases:  I  II  III

Recruit patients for clinical trials, determine clinical endpoints.

Hope for the best...

Patients

Science

Current Drug Development Process
GRANDRx

Paradigm development to shorten timelines, decrease costs, increase success rates

GRAND Assay Development
NIH Chemical Genomics Center and Molecular Libraries Initiative

GRAND Preclinical Development
Pharma/Biotech NIH Clinical Center
Phases: I II III
Obtain FDA approval for general use in humans

Clinical Endpoints
GRAND Clinical
Regulatory Sufficiency

Organized, Trained, & Funded Trust Networks
GRANDRx
*Gateway to Rare and Neglected Disease Therapeutics*

**Steering Committee:** In process

**Membership:** Rare and Neglected Disease Stakeholders From Academia, Advocacy, Industry, Federal Health Agencies, and Others

**Workgroups:** Assay, Preclinical, Clinical, Regulatory and Policy

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**Federal Agencies**

- National Institutes of Health (LOS)
  - National Human Genome Research Institute
  - Office of Rare Disease Research
  - NIH Chemical Genomics Center and Therapeutics for Rare and Neglected Disorders
- Food and Drug Administration (LOS)
- Centers for Disease Control and Prevention – OPHG, NCBD

**Academia, Advocacy, Industry, Others**

- Genetic Alliance
- Grand Therapeutics
- Faster Cures
- NORD
- Dozens of disease specific advocacy orgs
- Dozens of companies: biotech, pharma, CROs
- A dozen university programs

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**Partnerships**

**Initiatives**

**Systems Change**

**Programs**

**Projects**

**Change**
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<th>Natural History</th>
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<td>Existing Free Resources</td>
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**GRANDRx Clinical**

- Access to Credible Genetics Resources Network
- Genetic and Rare Disease Information Center/ORDR

**Disease InfoSearch**

**Resource Repository**

**WikiGENETICS**

**WikiADVOCACY**
GRANDRx Clinical

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Joint Collaborative Effort

• Collaborate on Drug Development Barrier Issues
  – Tools, Resources, Trainings, Bootcamps, Summer School, Other Educational & Engagement Opportunities
  – Registry and biorepository Infrastructure
  – Bioinformatics, Analytic Tools, and Evaluation Infrastructure
  – Appropriations for TRND/FDA/GRANDRx Initiatives
  – Policy and regulatory related activities on GRANDRx Initiatives
    • i.e., Genetic testing registry, reimbursement...
GRAND Therapeutics Foundation

Early Potential Projects:

- R13 GRANDRx Pathway Template
- Assay Design Fellowships
- GRANDRx Applied Science Grants
- Rx Clinical Registries Bootcamp
- Clinical Endpoint Think Tank
- Industry & VC Rx Development Salons
- Selection Criteria Design Worksheet: Mechanism of Action, Assay, Molecule
- Matching Database: Disease, Assay, Drug, Development Opportunities
- Catalog & tracking sheet of approved drugs: Class, family, action, incidental findings, off target effects, clinical reported antidotes.
GRANDRx Industry Commitments (~40 M)

Evaluate the Landscape of Opportunities for Compounds, Shelved, Abandoned, Others

De-risked Compound Development (Via TRND, CTSAs, Alternative Funding Models, New Commercial & IP Strategies)

Industrialized Approach to Repurposing Existing Internationally Approved Therapeutics for Rare Disease [Provisional Approval and Registry Studies]

Flexible Clinical Trial Designs, Conduct, & Advanced Statistical Methods

Unique Clinical & Observational Study Protocols (Precedent Setting. Applied to PM trials in the future?)
Systems Approach to Rare Disease Research

Engage Affected Community
- Shared Goals
- Authentic Partnership
- Establish Community ofTrust

MOUs / MTA / Formal Agreements/Contracts & Licensing

Engage Research Community
- Literature Review
- Identified Experts
- Meetings/Exchanges

Provided Resources
Seed Funding, Services, Biologics

Social Network

Ongoing Process

Utility of the Network
- Support
- Education
- Empowered Exchange
- Advocacy

Research Enterprise
- Informed Decision Making
- IRBs / Expert Reviews
- Patient Registry

MOUs / MTA / Formal Agreements/Contracts & Licensing

Consortium & Joint Projects & Shared Execution

Biorepositories
Clinical Data

Small World Network

Establish Community of Trust

Engage Affected Community

AUTHENTIC PARTNERSHIP

Informed Decision Making

IRBs / Expert Reviews

Patient Registry

Biorepositories

Clinical Data

Consortium & Joint Projects & Shared Execution

Support

Education

Empowered Exchange

Advocacy

Literature Review

Identified Experts

Meetings/Exchanges

Provided Resources Seed Funding, Services, Biologics

Research Enterprise

MOUs / MTA / Formal Agreements/Contracts & Licensing

Consortium & Joint Projects & Shared Execution

Biorepositories
Clinical Data
Figure 1 | The PXE International strategy. PXE International uses a variety of approaches to bring the PXE community together with research scientists to accelerate translational research. IRB, institutional review board.

Terry SF, Terry PF, Rauen K, Uitto J, Bercovitch L. Advocacy Organizations as Research Organizations: the PXE International example. Nature Reviews Genetics. 2007 Feb; Vol. 8, No. 2
There is no rare, there is no ‘other’

- Age of individualized/personalized medicine
- All disease is personal
- Need to focus on phenotypes/pathways
- Break down silos
- Allow scale and proportion in FDA regulatory processes
- Create an even playing field through transparency

We are all responsible: no us vs. them, no bad guys
Priority Recommendations

More than just increasing the flow into the funnel, change the funnel!

- Create alternative pathways to approval similar to those allowed for cancer drugs
- Increase industry’s interest through incentives: risk ready, regulatory flexibility, allow amended claims to expand to common conditions
- Flexible trial designs optimization
- Modern mathematical & statistical analysis
- Registration and transparency protected by expansion of the Orphan Drug Act or equivalent - reduce liability in cases of high risk due to rare disease limitations, limit liability to Phase III
- Community participation from trial design to recruitment through analysis, to advisory committees
Priority Recommendations, cont’d

• Capitalize network models such as Rare Disease Clinical Research Network, ICORD, and CETT to reduce competition and redundancy
• Support information exchange between advocates, academics and industry to increase targets (6000 rare conditions, reduce competition)
• Coordinate all Federal & international agencies – cross talk and interoperability, tie NIH funding to evidence development, cognizant of FDA requirements, require rare disease surveillance by CDC
• Public/private partnerships
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