“Challenges and solutions to conducting clinical research in rare diseases”

Peter A. Merkel, MD, MPH
University of Pennsylvania
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- Genentech/Roche
- PrincipioBio
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- European League Against Rheumatism
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- US Food and Drug Administration
- The Patient-Centered Outcomes Research Institute
- The Vasculitis Foundation

Off-label use of various medications will be discussed in this presentation
Rare Diseases

• What is a rare disease?
  – A disease with a prevalence of <200,000 persons in USA
    • Estimated to be ~7000 rare diseases
    • US estimate: 25-30 million people with a rare disease
      (8-12% of US population)

• Increasing awareness of rare diseases by public via media, internet, advocacy/support groups

• Many major scientific breakthroughs have arisen stemming from investigation of rare diseases that often have impact on common disorders

• Rare disorders have fascinated physicians and non-physicians for centuries
Why do we do rare diseases research?

- When you or a loved one are the patient with a rare disease, the disease is no longer rare
- When you have a patient with a rare disease, your ignorance will not help: become expert or refer
- People are drawn to rare disease research for the same of the same reasons others choose a research focus
  - Fascination with subject
  - Opportunity
  - Inspiration by patient/teacher
Inspiration and motivation comes from many places
Some Joys & Challenges of Rare Disease Care and Research

• Nice to be an expert about things most people don’t know about
• Nobody really knows what on earth you study or see clinically

• There are HUGE unanswered questions for rare diseases
• There are HUGE unanswered questions for rare diseases

• You can carve out your own niche when studying a rare disease
• You must carve out your own niche when studying a rare disease

• Often need to work in collaborative, multi-center research groups
• Markedly increased complexities with multi-center studies

• Face interesting and unique issues in dealing with rare diseases
• Still face the same challenges as studying common disorders
Bench to Bedside is a nice model...
Bedside to Bench is likely more productive and common (esp. for rare disease)
Bedside ↔ Bench is really a bidirectional process, especially for rare diseases
Rare Disease Research: Opportunities

• HUGE unanswered questions for rare diseases

• Potential to make a major impact on a clinically and scientifically underserved population

• The internet is now a key resource for rare disease research
  – Referrals/Recruitment
  – Networking
  – Conduct of research

• Increasing recognition in the scientific community and among funding agencies regarding the importance and benefits of research in rare diseases

• You can carve out your own niche when studying a rare disease
Rare Disease Research: Challenges

• Sample sizes and recruitment:
  – these are rare diseases!

• IRB/HIPPA:
  – must protect privacy

• Funding:
  – these markets are, by definition, small

• Career development
  – mentors/models are harder to find
    – obtain protected time while still a clinical expert

• Still have all the usual challenges of a career in academic medicine...
Solutions: Clinical Piece

• Don’t forget the patient
  – Listen to your patients-they will teach you

• Master the disease
  – Become a student of the disease

• Join/engage with patient advocacy groups
  – Become a citizen of the disease

• Promote your expertise (if it is real)

• Protect your time and focus (well, try)
Solutions: Science Piece

• Do good science
  – There is a limit to compromising due to small sample sizes
  – Be realistic

• Look to “borrow” ideas and approaches from other fields
  – Research approaches for related common diseases may be well-developed and adaptable

• Work collaboratively—Network, including internationally
  – Face the challenges to sharing credit among many people
Solutions: Funding Piece

• Don’t believe the hype
  – There IS funding for research (in US)
  – The NIH budget doubled in the past 25 years
    • Shift to more collaborative and multi-specialty approaches
    • Need to work with the new funding realities
  – Take advantage of opportunities and Grants:
    • Federal: NIH, FDA, PCORI, VA, DOD, Other
    • Non-federal funding: Industry, Patient Groups, Institutional, Others
  – Leverage resources (not just $)
    • Clinical Trials
    • Existing Datasets/Repositories
    • Collaborations
    • Core Resources: Institutional, National/International
  – Expand the focus of your inquiry
    • E.g.: Not just vasculitis but vascular inflammation in general
  – Keep your eyes open
NIH Numerology, Alphabet Soup, and Nomenclature

- K08
- K12
- K23
- K24
- K30
- T32
- NRSA (F32)
- R01
- R13
- R21
- R30
- U01
- U34
- U54
- Grants
- Contracts
- Cooperative agreements
- Networks
- SBIRs
- ISTs
- RFAs
- RFPs

Explore them all!
Solutions: Career Piece

• Find a good mentor or at least a supporter

• Don’t be afraid of learning new research skills

• Create the right environment for research
  – Ask for the resources you need

• Contribute and receive benefit from collaborations
  – Be a team player but don’t just be a follower
Successful Rare Disease Research is *Clearly* Possible!

- The >60 posters at this meeting testify to this fact
- As with any type of research, challenges exist but solutions are available
This is an excellent time to engage in clinical research in rare diseases

Multi-center research collaborations are extremely helpful for conducting high-quality, high-impact clinical research in rare diseases
Research Networks for Rare Diseases

• **Pros:**
  - Reduce start-up time/costs-leverage resources
    - Centers, personnel, systems already in place
    - Forms/data entry/CRFs, training, communications
  - Established cohorts and recruitment streams
  - Share workload & credit → trust
  - Combine expertise
  - Recycle experience
  - Look good to funding agencies/sponsors
Research Networks for Rare Diseases

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**Cons:**
- Must maintain infrastructure
- Need to avoid stagnation → add flexibility
- Require work to maintain cohesiveness
- Takes a long time until productive
- Many, many authors share credit-problem for jr. faculty
The Rare Diseases Clinical Research Network (RDCRN)
Goals of the RDCRN

• Facilitate clinical research by:
  – Creation of Consortia focused on related diseases
  – Cost-sharing research infrastructures
  – Establishing uniform protocols for data collection
  – Making meaningful large-scale studies possible
    • Longitudinal cohorts, pilot projects, and randomized trials

• Directly engage patients and their advocates

• Train new investigators in rare diseases research
History of the RDCRN

- Established by the Office of Rare Diseases Research
- Started in 2003--currently in 3rd 5 year cycle
  - 1st cycle (10 Consortia) supported by ORDR, NCRR, NINDS, NIAMS, NICHD, NHLBI, NIDDK
  - 2nd cycle (19 Consortia) supported by ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIAID, NIDCR, NCI
  - 3rd cycle (22 Consortia) supported by ORDR, NCATS, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIAID, NIDCR, NCI, NIMH, ODS
- Currently involves 267 institutions world-wide
- Collectively studying >200 diseases
- 46,760 patients enrolled in studies (during all 3 grant cycles)
Collaborative Clinical Research
Centralized Data Coordination and Technology Development
Public Resources and Education
Training

DHHS-NIH
ORDR, NINDS, NIAMS, NICHHD, NHLBI, NIDDK, NIDCR, NIAID, NCI, NIMH

Coalition of Patient Advocacy Groups (CPAG)

Dystonia Coalition

Genetic Disorders of Mucociliary Clearance Consortium
Porphyria Rare Disease Clinical Research Consortium
Vasculitis Clinical Research Consortium
Lysosomal Disease Network
Brittle Bone Disease Consortium
Inherited Neuropathies Consortium
Development Synaptopathies Consortium
Urea Cycle Disorders Consortium
Clinical Research in ALS and Related Disorders for Therapeutic Development
Sterol and Isoprenoid Diseases Consortium
Autonomic Rare Diseases Clinical Research Consortium

Consortium of Eosinophilic Gastrointestinal Disease Researchers
North America Mitochondrial Diseases Consortium
Advancing Research & Treatment for Frontotemporal Lobar Degeneration
Primary Immune Deficiency Treatment Consortium
The Data Management and Coordinating Center
Rare Kidney Stone Consortium
Nephrotic Syndrome Rare Disease Clinical Research Network
Chronic Graft Versus Host Disease Consortium
Rare Lung Disease Consortium
Rett Syndrome, MECP2 Duplications, and Rett-related Disorders Consortium
Brain Vascular Malformation Consortium
More centers coming to North America
VCRC Studies now include 8-91 centers worldwide!

Many additional VCRC partner sites in EU, Asia, Australia
Longitudinal Studies
- Longitudinal Study of Giant Cell Arteritis
- Longitudinal Study of Takayasu’s Arteritis
- Longitudinal Study of Polyarteritis Nodosa
- Longitudinal Study of ANCA-Associated Vasculitis
- Longitudinal Study of EGPA (Churg Strauss)

Treatment of Fatigue in Vasculitis

Comparative Efficacy in Cutaneous Vasculitis
- ARAMIS

Gene Expression in Cutaneous Vasculitis
- CUTIS

Pilot Studies

Clinical Trials
- Abatacept for Large Vessel Vasculitis (GCA & TAK)
  - AGATA
- Plasma Exchange for ANCA-Associated Vasculitis
  - PEXIVAS
- Abatacept for Relapsing Granulomatosis with Polyangiitis
  - ABROGATE
- Rituximab vs. Azathioprine for Maintenance of AAV
  - RITAZAREM
- Prednisone Dosing in Remission of AAV
  - TAPIR

Randomized Clinical Trials

Contact Registry
- Vasculitis Pregnancy Registry
  - Online TAPIR Trial
  - Various Online Studies
  - V-PPRN

Clinical Repository

Biomarker Repository

Biomarker Development
- Markers of Inflammation, Injury & Repair
- Cell-Associated Markers
- Autoantibodies
- Microbes
- Candidate Gene Studies & GWAS
- Gene Sequencing
- Epigenetics
- Whole-Exome Sequencing

Tissue Repository

Integrated/Systems Biology & Shared Molecular Targets

Genetics & Genomics

Clinical Data Repository

Clinical Data Outcomes
- Clinical Outcomes & Natural History
- Outcome Measures
- PROMIS
## VCRC Protocols

### Clinical Cohorts Studies & Repositories

<table>
<thead>
<tr>
<th>No.</th>
<th>Study/Repository</th>
</tr>
</thead>
<tbody>
<tr>
<td>02</td>
<td>Longitudinal Protocol for GCA</td>
</tr>
<tr>
<td>03</td>
<td>Longitudinal Protocol for TAK</td>
</tr>
<tr>
<td>04</td>
<td>Longitudinal Protocol for PAN</td>
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<tr>
<td>05</td>
<td>Longitudinal Protocol for GPA/MPA</td>
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<tr>
<td>06</td>
<td>Longitudinal Protocol for CSS</td>
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<tr>
<td>07</td>
<td>Longitudinal Protocol for IA</td>
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<tr>
<td>10</td>
<td>Genetic Repository (One-Time DNA)</td>
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<tr>
<td>11</td>
<td>Tissue Repository</td>
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<td>63</td>
<td>Gene Expression-Vasculitis-Skin (CUTIS)</td>
</tr>
</tbody>
</table>

### Outcome Measures - OMERACT

<table>
<thead>
<tr>
<th>No.</th>
<th>Study/Repository</th>
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<tbody>
<tr>
<td>15</td>
<td>Imaging Protocol for MRI and PET in TAK</td>
</tr>
<tr>
<td></td>
<td>OMERACT Vasculitis Working Group</td>
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<tr>
<td></td>
<td>Validation of PROMIS in Vasculitis</td>
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<tr>
<td></td>
<td>Development of an AAV-Specific PRO</td>
</tr>
<tr>
<td></td>
<td>International Classification of Function</td>
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<td></td>
<td>Outcomes for LVV and Beçhet’s</td>
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</table>

### PCORnet: The Vasculitis Patient-Powered Research Network (V-PPRN)

<table>
<thead>
<tr>
<th>No.</th>
<th>Study/Registry</th>
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<tbody>
<tr>
<td>32</td>
<td>Vasculitis Pregnancy Registry (V-PREG)</td>
</tr>
<tr>
<td>37</td>
<td>Validation of AAV-PRO</td>
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</tbody>
</table>

### Clinical Trials

<table>
<thead>
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<th>No.</th>
<th>Study/Registry</th>
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<tbody>
<tr>
<td>22</td>
<td>Pilot Study: Abatacept in Mild GPA</td>
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<tr>
<td>23</td>
<td>RCT: Abatacept for GCA/TAK (AGATA)</td>
</tr>
<tr>
<td>24</td>
<td>RCT: Plasma Exchange for AAV (PEXIVAS)</td>
</tr>
<tr>
<td>25</td>
<td>RCT: Rituximab vs. Azathioprine for AAV (RITAZAREM)</td>
</tr>
<tr>
<td>26</td>
<td>RCT: Tapering of Prednisone in GPA (TAPIR)</td>
</tr>
<tr>
<td>27</td>
<td>RCT: Abatacept for Mild/Mod GPA (ABROGATE)</td>
</tr>
<tr>
<td>62</td>
<td>RCT: Treatment of Cutaneous Vasculitis (ARAMIS)</td>
</tr>
<tr>
<td></td>
<td>Several others under development</td>
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### Patient Contact Registry Studies

<table>
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<th>No.</th>
<th>Study/Registry</th>
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<tbody>
<tr>
<td>31</td>
<td>Reproductive Health in Vasculitis</td>
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<tr>
<td>33</td>
<td>Vasculitis Illness Perception Study</td>
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<tr>
<td>34</td>
<td>Vasculitis Educational Needs Study</td>
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<tr>
<td>35</td>
<td>Vasculitis Diagnostic Confirmation Study</td>
</tr>
<tr>
<td>36</td>
<td>Work Disability Survey</td>
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</table>
GRANT/FUNDING SUPPORT

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH National Center for Advancing Translational Sciences
pccori
CTSA Clinical & Translational Science Awards
NIH National Heart, Lung, and Blood Institute
RECOVERY.gov
Immune Tolerance Network
NHS National Institute for Health Research
Vasculitis Foundation
ChemoCentryx
Genentech
Bristol-Myers Squibb
Arthritis Research UK
eular European League Against Rheumatism
Penn University of Pennsylvania
This is an excellent time to engage in clinical research in rare diseases

IT CAN BE DONE!