Advancing Rare Disease Discoveries Through Collaborations

@Third International Conference on Rare & Undiagnosed Diseases

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REGENERON

Program Management

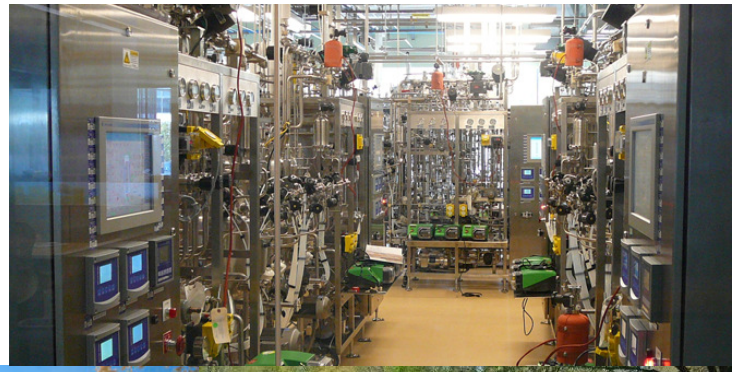
Integrating our Science and Business

Outline

- Introduction to Regeneron Pharmaceuticals Inc.
- Introduction to the Regeneron Genetics Center (RGC)
- Why is Regeneron & RGC interested in Rare and Undiagnosed diseases?
- Our success stories in rare and ultra-rare diseases
- Lessons learned through our recent collaborations
- How to collaborate with Regeneron

Regeneron Pharmaceuticals Inc., *Science to medicine®*

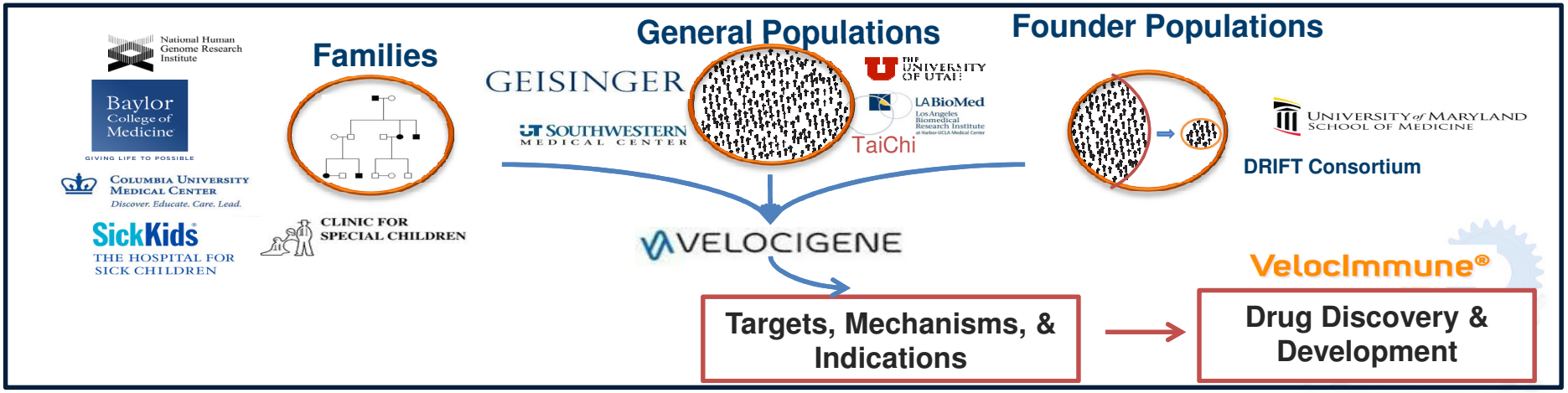
- Regeneron is a fully-integrated biopharmaceutical company headquartered in Tarrytown, New York.
- Founded in 1988
- 4 approved products
  - PRALUENT® (alirocumab) injection
  - EYLEA® (aflibercept) injection
  - ZALTRAP® (Aflibercept) injection
  - ARCALYST® (rilonacept) injection
- Driven by the science, and a passion to treat patients
  - "Doing well by doing good"



Regeneron Genetics Center™: Breadth of Human Genetics Resources and Fully Integrated Capabilities

- **Founded in January 2014**
- **Fully integrated** from gene discovery to functional studies to therapeutics development
  - Large-scale sequencing and analysis fueling novel gene discovery
  - Functional studies leveraging genetically humanized animal models
  - Natural history studies and "call-back" phenotyping by genotypes of interest
- **Synergistic approaches:** large populations, families, and founder populations

REGENERON™ GENETICS CENTER



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Why is Regeneron & RGC Interested in Rare And Undiagnosed Diseases?

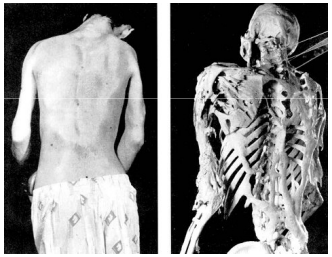
- Science drives our business, we are agnostic to specific therapeutic areas
  - Driven to advance science to medicine by improving the lives of patients
- Rare phenotypes provide insights into complex pathways/biology
  - Discover novel targets for common diseases
  - Develop new technologies
  - Share findings by publishing in high impact journals

- "For over 25 years, Regeneron's vision has been to build an **innovative company** that consistently **brings new medicines to patients** with serious diseases."

Our Success Stories in Rare and Ultra-Rare Diseases

- ARCALYST® (rilonacept) approved in 2008 to treat Cryopyrin-Associated Periodic Syndromes (CAPS), a group of rare inherited auto-inflammatory diseases.
  - Successful treatment for all 3 sub-types of CAPS: FCAS, Muckle Wells, and NOMID
  - Utilizing the same "Trap technology" that eventually led to our block-buster EYLEA®(aflibercept)
  - Actively investigating additional indications

- PRALUENT® (alirocumab) approved in 2015 to treat heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL- C.
  - REGN validated the target and developed blocker antibodies
  - Together with Sanofi, developed, manufactured and commercialized anti-PCKS9 Abs
  - Opportunity to expand approval to other, more common hypercholesterolemias



- Currently in pre-IND stage~~s~~ to test a monoclonal antibody to treat **Fibrodysplasia Ossificans Progressiva (FOP)**, an ultra-rare and extremely debilitating disease
  - REGN Skeletal diseases team elucidated the molecular mechanism of pathogenesis in FOP:
    - "ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A" (Hatsell et al. 2015 *Sci Transl Med*)

- Recent RGC-academic collaborations studying rare disease cohorts (2014-Present)
  - Early discovery efforts in analyzing families with rare Mendelian syndromes with several academic collaborations
  - Actively pursuing functional modeling projects with 2 academic collaborators
  - Sharing results through presentations and publications

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Lessons learned through our recent collaborations

- Science can be serendipitous
  - One hypothesis can lead to a new hypothesis
- Need to be selective in the projects we undertake (i.e well thought-out research proposals)
- Constant and open communication between collaborators is key
  - Leverage each others strengths
- Timing is key
- Together we can achieve more!

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How to collaborate with Regeneron

- Regeneron Genetics Center Collaborations
  - Next-gen sequencing of DNA from well-phenotyped patient populations and/or families by RGC
  - Collaborative analysis & interpretation of the genomic data
  - Functional modeling work and/or reagents generated by Regeneron's VelociMouse® Suite technology
  - Opportunities for generating joint publications
  - Leverage Regeneron's pipeline/tech capabilities/experience to bring new treatments to market!

- Pre-clinical collaborations between Regeneron's Therapeutic Focus Areas or Technology Development Centers
  - Support academic research through access to Regenerons therapeutic candidates, animal models, cell lines and other technologies
  - https://regeneron.envisionpharma.com/vt_regeneron/

- Investigator Initiated Studies (IIS) interested in studying Regeneron products and drug candidates in disease states of interest.
  - Support external investigators interested in studying Regeneron products and drug candidates in disease states of interest as well as epidemiological and other non-interventional studies focused on Regeneron's areas of interest.
  - http://iisgrants.regeneron.com/account/logon?ReturnUrl=%2f

- Science-driven discussions/brainstorming/ideas

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  - Frederick Dewey
  - Aris Economides
  - RGC Leadership Team
  - RGC's Mendelian Team

Collaborators (Mendelian Genetics)

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  - William Gahl & David Adams
- Clinic for Special Children
  - Kevin Strauss & Erik Puffenberger
- Baylor College of Medicine
  - James Lupski & Richard Gibbs
- Columbia University Medical Center
  - Wendy Chung
- Toronto Hospital for Sick Children
  - Alexio Muise

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GENETICS CENTER

Call for Research Collaboration to Understand the Genetic Architecture of Founder Populations Throughout the World to Impact Health and Disease

Announcing the DRIFT Consortium:
Discovery Research Investigating Founder Population Traits

The Regeneron Genetics Center (RGC), located in Tarrytown, New York, is a large-scale, fully integrated genomics program that builds on Regeneron Pharmaceuticals, Inc. well-established expertise in genetics and related technologies. The objective of the RGC is to use DNA sequencing to gain new insights into disease mechanisms, identify novel therapeutic targets and ultimately speed drug discovery and development to help patients in need. We work collaboratively with academic colleagues worldwide and use a number of study designs and experimental approaches. One approach is to identify and study individuals with rare loss of function mutations and their associated phenotypes. Founder populations offer a unique opportunity to identify these informative alleles since they may be enriched in the population through drift and also may be more often found in their homozygous state through endogamy.

We have founded the DRIFT Consortium with the goals of (i) cataloging population-specific allelic architecture; (ii) understanding the biological and functional consequences of specific mutations identified; and (iii) sharing and establishing best practice approaches to relieve disease burden in these populations.

DRIFT is planning two tiers of collaboration models (see details below). For both models, we intend to broadly share data and results with the research community. If exciting new results are generated from a Tier 1 or Tier 2 collaboration, there will be potential for the design and funding of follow-up "genotype-first call-back" studies for additional collaborative research to delve more deeply into biological mechanisms and pathways.

Model for DRIFT Collaboration

Tier 1

GOAL: To canvas the allelic architecture of the population by exome sequencing and GWAS chips from relatively unrelated individuals

- Collaborator provides the RGC de-identified DNA samples (300-400)
- RGC provides high-depth exome sequence and GWAS chip data back to collaborator free of charge
- No exchange of phenotype information is necessary for Tier 1
- If the joint sequence data is used for any genotype-phenotype analyses, we ask that results be shared with Regeneron; collaborator is free to publish results
- A short form material transfer agreement governs the collaboration

Tier 2

GOAL: To establish a partnership/ collaborative effort focused on novel gene discovery for phenotypes of mutual interest

- An academic collaboration model where Collaborator and the RGC jointly develop the research plan
- A larger number of DNA samples (100s – 10,000s) are provided by Collaborator; the exact number will be determined jointly
- RGC provides all exome sequence and GWAS chip data to Collaborator free of charge
- As part of the collaboration, deidentified phenotype data is shared
- Data analyses of the combined sequence and phenotype data set is performed collaboratively and each party is free to use the data set for its internal research
- Collaborators are encouraged to publish results and each party is free to use published results for any and all purposes

- 6 Active collaborations (Amish, Mennonite, French Canadian, Mormon, Finns/Swedes)
- >30 in planning stages (Ashkenazi (US and Israel); Native American, Oceana, Greek, Croatia, Orkney, South America, Arab, and African populations)

RGC Program Management Drives Discovery and Development Programs through Genomic Research

- **Key liaison for establishing research collaborations**
  - Communicates and manages the workflows regarding new genetic projects with REGN scientists, academic institutions and health-related organizations
- **PM Leads for genetic projects**
  - Ensures alignment of project goals between the RGC, internal (REGN scientists) and external (collaborator) partners
- **Manage and track portfolio of collaborator activities and active projects**
  - Oversee the initiation, planning, execution of Population-based, Family-based (Mendelian) and Founder population genetic projects, and the functional modeling of new variants
- **Provide timely vertical and horizontal communication of RGC activities and results**
  - Organize and manage meetings with Senior Management and REGN scientists to discuss novel findings and opportunities