JUNE 29, 2021

Regeneron Genetics Medicines
Building the Pipeline of the Future

Regeneron Pharmaceuticals, Inc.
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Introduction

George D. Yancopoulos, MD, PhD
Co-Founder, President & Chief Scientific Officer
Agenda

1. Regeneron Genetics Medicines: Building the Pipeline of the Future

2. Regeneron Genetics Center (RGC)
   • Novel Target Discovery
   • Genetics Guided Development
     ○ Enhance Probability of Success
     ○ Identify Patients Most Likely to Benefit

3. Future of Medicine: Novel Turnkey Modalities to Drugs
   • siRNA Gene Silencing
   • Genome Editing – Knockout
   • Genome Editing – Insertion
   • Gene Therapy
Supercharging the Future of Genetics and Turnkey Therapeutics Platforms at Regeneron

Learnings from mouse genetics

Unlocking capabilities of mouse and human genetics through

Existing Turnkey Technologies

Biologicals

TRAPs
Antibodies & Bispecifics

siRNA

Genome editing (insertion/knockout)

Gene Therapy
Regeneron Genetics Medicines

Based on Core Regeneron Principles

• Genetics-based target discovery and validation
• Turnkey therapeutics platforms
  o Precision medicines with target specificity
• Speed to the clinic
• Intelligent and innovative clinical design for rapid proof-of-concept

Turning a Distant Dream Into a Near-Term Reality

• 5-10 years of deep investment:
  o Human sequencing and “Big bioData” generation
  o Internal efforts and external collaborations yielding turnkey therapeutics

Genetics Medicines Portfolio

• Three programs in the clinic
• Multiple clinical program initiations planned per year with several potential product approvals by 2025
• Currently 30+ programs in research and candidate selection

Vision for the Future

Continue to build technology and platforms to expand the power and reach of genetics medicines
Regeneron Genetics Center (RGC)

Aris Baras, MD, MBA
Senior Vice President, Regeneron Genetics Center
WHAT IS RGC?

The Regeneron Genetics Center® (RGC) is a uniquely integrated research initiative that seeks to improve patient care by using genomic approaches to speed drug discovery and development.

✓ LARGEST HUMAN SEQUENCE DATABASE
  • ~2 million exomes by the end of 2021
    o Includes entire UK Biobank
  • Almost all linked to detailed electronic health records
  • Most powerful resource linking human genetic variation to disease

✓ INNOVATIVE BIG BIODATA ANALYTICS

✓ LEADER IN ROBOTICS AND SEQUENCING AUTOMATION
  • Amplifies currently available sequencing technology
Regeneron Genetics Medicines

Novel Genetics-based Drug Target Discovery

- RGC discovered >10 novel drug targets e.g.:
  - HSD17B13 for NASH (clinical stage)
  - Novel target for obesity and diabetes
  - Novel target for glaucoma

Genetics-based Drug Development & Precision Medicine

- RGC database links drug targets with disease impact, enhancing probability of clinical trial success
  - e.g., IL-33 & COPD
- RGC database identifies patients most likely to benefit
  - e.g., PCSK9 & high-risk/high-benefit patients

Leveraging New Turnkey Therapeutic Approaches

- siRNA gene silencing
  - Alnylam collaboration leverages RGC discoveries
- Genome editing – Knockout
  - Intellia collaboration
- Genome editing – Insertion
  - Intellia collaboration
- Targeted viral-based gene delivery and expression
  - Decibel collaboration
**Novel Target Discovery: Translating Protective Genetics Into Therapeutics That Mimic Genetic Effects**

**HSD17B13 Target for Liver Disease: Collaboration with Alnylam**

- RGC discovered *HSD17B13* variants that protect against liver disease
  - *Abul-Husn et al. NEJM. 2018*
- *HSD17B13* siRNA, in partnership with Alnylam, reached the clinic in <3 years
  - Phase 1 NASH study underway; healthy volunteer data by YE 2021
- RGC has delivered additional novel protective genetic therapeutic targets for NASH that are part of collaborative efforts with Alnylam

**People With the Protective *HSD17B13* Gene Variant Have ~30-70% Lower Odds of Chronic Liver Disease**

<table>
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<tr>
<th>Description</th>
<th>Genotype</th>
<th>Genotypic Odds Ratio (95% CI)</th>
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<td>TA/TA</td>
<td>0.48 (0.15–1.56)</td>
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</table>

[Diagram showing complete loss of function reduces risk of severe liver disease]

Adapted from Abul-Husn et al. NEJM. 2018
Novel Target Discovery

**Novel Obesity Target**

- Sequenced more than 600,000 participants in UK, US, and Mexico to find rare genetic ‘superpower’ that protects against obesity
- Humans and mice with this rare genetic variant are protected against obesity
- Multiple therapeutic programs under consideration, including VeloclImmune® technology and siRNA
- Publication forthcoming July 2021

Humans With This Rare Genetic Variant Are Protected Against Obesity

Mice Engineered With This Rare Genetic Variant (By VelociGene®) Are Protected Against Obesity
Genetics Guided Development, Enhancing Probability of Success

IL-33 Genetics Guiding Successful Clinical POCs

- IL-33 genetically linked to COPD and asthma via risk increasing variants and protective loss of function variants
- Itepekimab (IL-33 antibody):
  - Two COPD phase 3 studies underway
  - Clinical proof-of-concept in COPD with reductions in exacerbations in former smokers
  - Positive phase 2 results in asthma
- IL-33 genetics are used to identify other indications of interest

Itepekimab is developed in collaboration with Sanofi.
GOF, Gain of Function; LOF, Loss of Function; POC, proof of concept; COPD, Chronic obstructive pulmonary disease
Genetics Guided Precision Medicine: Identify Patients Most Likely to Benefit

**PCSK9 and High-Risk, High-Benefit Populations**

- Praluent® reduced major adverse cardiovascular events by 15% in a large outcomes trial in post acute coronary syndrome patients
- Post-hoc analysis: patients with higher “composite genetic risk scores” (cGRS) and clinical risk factors had higher event rates and greater risk reduction with Praluent
  - Two-thirds had low genetic risk and low lipids and derived little treatment benefit
  - One-third had high genetic risk or high lipids and received greater treatment benefit
- Precision medicine approaches enable larger effect, smaller, and less expensive trials
  - Identify patient populations and indications with greatest patient benefit
  - Inform commercial efforts

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**Post-hoc Analysis Revealed That Patients With Higher cGRS and Clinical Risk Derive Greater Benefit From Praluent**

**Lower Genetic Risk & LDL-C <100 (mg/dL)**

- **HR: 0.78 (95% CI, 0.64-0.94)**
- **p=0.010**
- **22% Risk Reduction**
- **26% of Patients**

**Lower Genetic Risk & LDL-C ≥ 100 (mg/dL)**

- **HR: 0.55 (95% CI, 0.33-0.89)**
- **p=0.015**
- **65% Risk Reduction**
- **3% of Patients**

**High Genetic Risk & LDL-C <100 (mg/dL)**

- **HR: 0.65 (95% CI, 0.43-1.00)**
- **p=0.049**
- **35% Risk Reduction**
- **7% of Patients**

**High Genetic Risk & LDL-C ≥100 (mg/dL)**

- **HR: 0.55 (95% CI, 0.33-0.89)**
- **p=0.015**
- **65% Risk Reduction**
- **3% of Patients**

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Adapted from Damask et al. Circulation. 2019.
Novel Turnkey Therapeutic Approaches

The Future Is Now

INHIBITING GENES
- siRNA Gene Silencing
- Genome Editing: Knockout

RESTORING GENES
- Genome Editing: Insertion
- Gene Therapy: Targeted Viral-based Gene Delivery and Expression
Utilizing the target discovery engine by applying validated siRNA technology

- Rapid path to therapeutics for validated intracellular targets not suitable for antibodies
- Antibody-siRNA combinations for high target load
- Extending dosing intervals

Alnylam collaborates exclusively with Regeneron for CNS and Eye targets, as well as select liver targets

- Initial 5-year discovery period through Apr’24, with an option to extend

**Alnylam Collaboration**

20+ Targets in All Stages of Development and More Coming (CNS, Eye, Liver)

**PHASE 3**
- **C5**: siRNA cemdisiran + pozelimab combination Ph3 for myasthenia gravis to start 2H21
  - Differentiated combination approach for a large market

**PHASE 2**
- **C5**: cemdisiran + pozelimab combination; multiple Ph2s in PNH to start 2H21
  - Phase 3 initiation in 2022

**PHASE 1**
- **HSD17B13**: ongoing for NASH
- **APP**: Planned (early onset Alzheimer’s; cerebral amyloid angiopathy)

**PRE IND**
- 3-5 additional potential targets to advance to IND-enabling studies in next 12 months
Other Novel Turnkey Technologies

Christos Kyratsous, PhD
Vice President of Research, Infectious Diseases and Viral Vector Technologies
Genome Editing – Knockout: TTR Collaboration With Intellia

First Human Proof-of-Concept Achieved for First Systemic CRISPR-based Therapeutic

• First-in-human data validate our CRISPR-based TTR knockout approach
  o Single dose with NTLA-2001 led to dose-dependent reductions in serum TTR
  o Mean serum TTR reduction of 87% at 0.3 mg/kg dose, including one patient with 96% reduction
  o No serious adverse events observed in the first six patients by day 28

Landmark Clinical Data at Peripheral Nerve Society Meeting Showed Deep Reduction in Disease-Causing TTR Protein After Single Infusion of NTLA-2001

Proof-of-Concept With TTR Increases Probability of Success for Both Knockout and Insertion Programs

• REGN has exclusive rights to Intellia’s CRISPR technology for therapies targeting the liver*
  o 20+ preclinical programs under evaluation
• REGN has license to commercialize up to 10 ex vivo CRISPR products in defined cell types

*REGN has rights to develop up to 15 in vivo products; except certain named targets
Genome Editing – Insertion

Factor 9 (F9): Collaboration with Intellia

Technology collaboration with Intellia: co-development of the knock-in technology

• REGN leads F9 and F8 knock-in programs
• Key preclinical data so far:
  o Therapeutic F9 levels are stable through one year
  o F9 levels persist following liver growth and regeneration with REGN/NTLA insertion approach vs. traditional AAV-based gene therapy
• F9 insertion program for Hemophilia B is advancing toward IND-enabling studies
• Additional knock-in programs preclinical work ongoing

Adapted from Annual Meeting of the Oligonucleotide Therapeutics Society (OTS) 2020.
Gene Therapy: Targeted Viral-based Gene Delivery and Expression

Otoferlin (OTOF): Collaboration with Decibel

- Genetic absence of OTOF in the hair cells of the inner ear causes profound hearing loss
  - Est. ~20,000 patients in US and EU5
  - Patient diagnosis expected to increase due to recent adoption of genetic testing at birth
- AAV-based gene therapy for OTOF is appropriate for non-dividing hair cells
- Viral-based gene delivery of OTOF restores hearing in mouse model:
  - >20% of inner hair cells expressing OTOF required to restore hearing
  - Hearing rescue durable out to at least 6 mo
- Non-Human Primates:
  - Full-length OTOF successfully expressed
- Clinical trial initiation in 2022

>20% Expression Required for Hearing Rescue in Mouse Model

Virally-Delivered Human OTOF Detected (red dots) in Nuclei (blue) of Hair Cells of Primate Ear

Adapted from presentation at Association for Research in Otolaryngology (ARO) 2021.
Conclusion

George D. Yancopoulos, MD, PhD
Co-Founder, President & Chief Scientific Officer
Regeneron is investing in and delivering technologies well beyond antibodies

- 3 genetics medicines programs in the clinic
- 3-5 additional potential targets to advance to IND-enabling studies in next 12 months
- 30+ additional programs in research and candidate selection phase
- 10+ novel genetic targets discovered

Several near-term opportunities emerging from Regeneron Genetics Medicines:
- Reported landmark TTR genome editing data in Jun’21
- C5 combo program Ph3 start (Myasthenia Gravis in 2H21, PNH in 2022)
- HSD17B13 siRNA healthy volunteer data readout in 2H21
- APP siRNA Ph1 start for Alzheimer’s
- DB-OTO gene therapy (hearing loss) Ph1/2 start in 2022

Regeneron Genetics Medicines
Building the Pipeline for the Future

Pre-IND
- FACTOR 8 GENE INSERTION
  - CRISPR/Cas9 + AAV Transgene Insertion
  - Hemophilia A
- PNPLA3
  - PNPLA3 siRNA
  - Nonalcoholic Steatohepatitis
- FACTOR 9 GENE INSERTION
  - CRISPR/Cas9 + AAV Transgene Insertion
  - Hemophilia B
- ALN-APP
  - APP siRNA
  - Alzheimer’s Disease

Clinical Development
- POZELIMAB + CEMDISIRAN
  - C5 Antibody + C5 siRNA
  - Myasthenia Gravis
  - Paroxysmal Nocturnal Hemoglobinuria
- ALN-HSD
  - HSD17B13 siRNA
  - Nonalcoholic Steatohepatitis
- NTLA-2001
  - CRISPR/Cas9
  - Hereditary Transthyretin Amyloidosis with Polyneuropathy

ADDITIONAL PROGRAMS
30+ Programs in Research and Candidate Selection

This graphic displays pipeline drug candidates currently undergoing clinical testing in a variety of diseases. The safety and efficacy of these drug candidates have not been fully evaluated by any regulatory authorities for the indications described in this section.