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June/July 2020 Report

Regeneron - https://www.regeneron.com

- Regeneron is a leading biotechnology company that was founded over 30 years ago
  - Company is led by physician-scientists
  - Developed 7 FDA-approved treatments
  - Have 20+ product candidates in clinical development across multiple therapeutic areas
  - Published over 200 peer-reviewed publications in 2019
  - 8100+ employees worldwide
- Their medicine and pipeline are designed to help patients with eye disease, allergic and inflammatory disease, cancer, cardiovascular and metabolic diseases, infectious diseases, pain and rare diseases
- All drug candidates are invented and developed in-house
- Regeneron focuses on therapeutic antibodies
  - They engineer therapeutic antibodies that specifically recognize drug targets
- The company does not limit its innovations to any one therapeutic area
  - They are open to collaboration opportunities with the potential to offer important benefits to patients
- Leadership
  - The company has multiple Nobel Naureates and 5 members of the National Academy of Science among its leadership
  - Was one of the first companies to form a Science and Technology Committee as part of its Board
    - This has now become industry standard
- Current collaborators:
  - Bayer
  - Sanofi
  - Icahn School of Medicine at Mount Sinai
  - Colunbia University
  - Teva Pharmaceuticals
  - Intellia Therapeutics
  - Adicet Bio
  - Alnylam Pharmaceuticals
- 2019 Financial report: https://investor.regeneron.com/static-files/cbebda5b-c02d-466b-8be9-e0d8a4052cf8
- Pipeline drug candidates currently undergoing clinical testing:
- https://investor.regeneron.com/static-files/cbebda5b-c02d-466b-8be9-e0d8a4052cf8
- Proprietary technologies include: VelociSuite®

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- **VelociGene®** enables rapid, automated and high-scale manipulation of mouse DNA with almost no limitations on the size and sophistication of modifications
  - Enables unprecedented speed and capacity for the validation of therapeutic targets and the creation of animal models of human disease
  - Target validation
  - Traditional technologies for producing genetically modified mice were slow and labor-intensive
  - This led to the development of VelociGene
  - A core element of VelociGene technology are Bacterial Artificial Chromosomes (BAC) which are used to manipulate the mouse DNA
  - The unique properties of BACS allow the deletion or insertion of very large pieces of DNA → resulting in BACVec: these permit the complete humanization of the variable regions of antibody genes that empower the use of the drug discovery platform VelocImmune
  - The engineered BACVec is delivered into mouse embryonic stem cells which are progenitor cells that ultimately produce every other cell in the mouse
  - Once introduced into the ES cells, the BACVec replaces the target gene with unmatched precision through a process called Homologous Recombination
  - A key component of VelociGene is the Loss of Allele Assay which used thoroughly automated and scalable processes to rapidly identify embryonic stem cells with the desired genetic modification among the vast majority of non-targeted cells
  - VelociGene offers the fastest path to modifying very large portions of the mouse genome with unmatched precision
  - VelociGene is a critical step in the drug discovery process at Regeneron such as the creation of VelocImmune mice which are used to produce fully human antibodies
- **VelociMouse®** - enables the immediate generation of genetically altered mice directly from modified embryonic stem cells
  - The modified stem cells are injected in to the mouse embryo at a very early stage to ensure that the resulting mice are completely derived of the modified embryonic stem cells
  - After the genetic modified embryo is implanted into a surrogate mother, the first generation of mice born now directly contain the desired genetic modifications
    - Avoid the need to breed multiple generations
  - This dramatically shortens the time needed to engineer genetically modified mice while reducing costs and improving precision

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        - Together, VelociGene and VelociMouse offer the fastest path to validate the function of possible targets for drug discovery
        - Using these technologies to produce preclinical disease models in order to study a disease in more detail or to determine the efficacy of a new drug allows for Regeneron to have higher confidence in a potential therapeutic solution for humans at an earlier stage in the process
    - **VelocImmune®** - Regeneron's unique technology for producing fully human monoclonal antibodies
        - Creates a multitude of optimized antibody drug candidates efficiently and directly from immunized mice
        - By injecting the previously identified drug protein into the mice, an infection is simulated and the immune system is triggered to produce a multitude of target specific antibodies
        - Conventional methods require the subsequent humanization of these antibodies to reduce rejection by the patients' immune system
        - VelocImmune overcomes the limitations of traditional platforms by rapidly creating fully human antibodies that tightly bind to therapeutic targets and avoid potential immune responses that may occur in patients receiving antibodies that contain nonhuman components
        - In VelocImmune mice, the gene's coding for the variable regions of antibodies are precisely replaced by their human counterparts using VelociGene and VelociMouse technologies
        - By keeping the constant region of the antibody gene of mouse origin to avoid compromising the immune system, VelocImmune triggers a strong immune response and takes advantage of the natural process that produces a broad diversity of high quality antibodies
        - VelocImmune mouse if one of the largest genetic engineering projects every undertaken in mammals
        - these
    - **VeloviMab®** - a group of technologies that allow Regeneron to move with unprecedented speed from identification of a therapeutic antibody into clinical studies
        - VelociMab technologies used Flow cytometry of FACS
        - Enables the high-throughput screening of potential therapeutic antibodies and the rapid generation of cell lines for recombinant human antibodies
            - With the high through-put automated method, cells are labelled with a fluorescent dye and sorted at up to 70 thousand cells per second according to specific characteristics

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- From these, VelociMab is able to quickly identify and isolated the thousands of cells producing the antibody with the therapeutically desirable properties
- The genetic blueprint for each of these antibodies are then transferred from mice into cells using ESSYR technology developed at Regeneron
- Antibody producing cells are identified by FASTR and NICE technologies
- In this step, the mouse constant region is replaced by human constant region
- The cells can then produce antibodies in sufficient quantities to allow pre-clinical testing for the antibody with the best safety and efficacy characteristics

    - Once the most promising target-specific antibody producing cell is selected, a seamless jump to clinical testing is possible because the cell liens used for testing are already capable of producing thousands of litres of antibodies in specialized bioreactors
    - With the combination of VelocImmune and VelociMab, Regeneron has shortened he timeline and increased the efficiency of fully human antibody development for clinical use
    - Allows researchers to go from mouse immunization to production cell line bioreactor harvest within 8 months

- **VelociT™ -** their unique mouse technology for producing fully human therapeutic T-cell receptors (TCR) against tumor and viral antigens
    - Used as part pf Regeneron's efforts to discover and develop novel immune-oncology therapeutic candidates and assist collaborators in producing fully human therapeutics TCRs
- **VelociHum™** - Regeneron's immunodeficient mouse platform that can be used to accurately test human therapeutics against human immune cells and study human tumour models
    - VelociHum mice have been optimized to allow for better development of human immune cells in vivo through genetic humanizations
    - This also allows for engraftment of primary patient-derived tumours that do not take in other commercially available mice
- **Veloci-Bi®** - allows for the generation of full-length bispecific antibodies similar to native antibodies that are amenable to production by standard antibody manufacturing techniques, and likely to have favorable antibody-like pharmaco kinetic properties
- **Regeneron Trap technology -** creates circulating "decoy receptors" capable of reducing or eliminating the harmful effects of a signaling protein
- **EESYR** – provides site-specific integration into a transcriptional hot spot in the eukaryotic cell genome

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        - Results in rapid isolation of cells capable of high-level expression of recombinant therapeutic proteins
    - **FASTR** – a quantitative cell surface display technology that enables the use of flow cytometry to select eukaryotic cells that secrete the highest levels of recombinant therapeutic proteins
    - **NICE** – enables the control of the expression of secreted, recombinant therapeutic proteins in eukaryotic cells

Regeneron Genetics Center®

- Regeneron Genetics Center® is a uniquely integrated research initiative that seeks to improve patient care by using genomic approaches to speed drug discovery and development
    - One of the words largest human genomic research efforts
    - They collaborate with a large network of collaborator institutions to gather and analyze data, exchange expert perspectives, and search for discoveries
    - Some collaborators:
        - Geisinger Health System
        - UK Biobank
        - Accelerated Cures Project
        - Columbia University Medical Center
        - The Florey Institute of Neuroscience and Mental Health on Behalf of the Australia and New Zealand MS Genetic Consortium
- Scientists from the Regeneron Genetic Center were the first to identify a variant in the HSD17B13 gene that is associated with reduced risk of, or protection from, various chronic liver diseases for which there are currently no approached therapeutics
- They are now collaborating with Alnylam to discover potential RNAi therapies for this target
- Regeneron Genetics Center® is collaborating with the Hospital for Sick Children (SickKids) to study the genetic determinants of infantile and pediatric onset cases of IBD through exome sequencing and analysis of families
- On February 28, 2020, the Regeneron Genetics Center® celebrated the sequencing of its 1,000,000th exome

FDA-approved Medicines

- **Arcalyst (rilonacept) injection for Subcutaneous Use** – used to treat Cryopyrin-Associated Syndromes including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)
- **Dupixent (dupilumab) injection** – used to treat atopic dermatitis and an add-on maintenance treatment for moderate-to-severe asthma and chronic rhinosinusitis with nasal polyposis

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- **Eylea (aflibercept) Injection** – used to treat Neovascular Age-related Macular Degeneration, Macular Edema following Retinal Vein Occlusion (RVO_, Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR)
- **Kevzara (sarilumbab) injection** – used to treat moderately to severely active rheumatoid arthritis
- **Libtayo (cemiplimab-rwlc) injection** – used to treat patients with metastatic cutaneous squamous cell carcinoma or locally advanced CSCC who are not candidates for curative surgery or curative radiation
- **Praluent (alirocumab)** injection - to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease
    - As an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).

News

BARDA Procures Regeneron's REGN-EB3 Investigational Ebola Treatment for National Reparedness

- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) announced on July 19th that the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response within the U.S. Department of Health and Human Services (HHS), has entered into an agreement to procure REGN-EB3 as part of the HHS' goal of building national preparedness for public health emergencies.
- REGN-EB3 is Regeneron's investigational triple antibody cocktail treatment for Ebola virus infection and is currently under Priority Review by the U.S. Food and Drug Administration (FDA), with a target action date of October 25, 2020.
- Contingent on FDA approval, Regeneron expects to deliver an established number of treatment doses over the course of six years and receive compensation of approximately $10 million in 2021 and an average of $67 million per year for each of the next five years (2022-2026).

Regeneron Announces Manufacturing And Supply Agreement For Barda And U.S. Department Of Defense For Regn-Cov2 Anti-Viral Antibody Cocktail

- Regeneron Pharmaceuticals, Inc. announced on July 7th that the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services, and the Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense have awarded Regeneron a $450 million contract to manufacture and supply REGN-COV2.

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- REGN-COV2 is Regeneron's investigational double antibody cocktail that is currently in two Phase 2/3 clinical trials for the treatment of COVID-19 and in a Phase 3 trial for the prevention of COVID-19 infection.

Regeneron And Sanofi Provide Update On Kevzara® (Sarilumab) Phase 3 U.S. Trial In Covid-19 Patients

- Regeneron Pharmaceuticals, Inc. and Sanofi announced on July 2, 2020 that the U.S. Phase 3 trial of - - Kevzara® (sarilumab) 400 mg in COVID-19 patients requiring mechanical ventilation did not meet its primary and key secondary endpoints when Kevzara was added to best supportive care compared to best supportive care alone (placebo).
- Minor positive trends were observed in the primary pre-specified analysis group (critical patients on Kevzara 400 mg who were mechanically ventilated at baseline) that did not reach statistical significance, and these were countered by negative trends in a subgroup of critical patients who were not mechanically ventilated at baseline.
- Serious adverse events that occurred in at least 3% of patients and more frequently among Kevzara patients were multi-organ dysfunction syndrome (6% Kevzara, 5% placebo) and hypotension (4% Kevzara, 3% placebo).
- Based on the results, the U.S.-based trial has been stopped, including in a second cohort of patients who received a higher dose of Kevzara (800 mg).
- A separate Sanofi-led trial outside of the U.S. in hospitalized patients with severe and critical COVID-19 using a different dosing regimen is ongoing.

Fda Approves New Dupixent® (Dupilumab) Pre-Filled Pen Designed To Support More Convenient Self-Administration

- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) and Sanofi today announced that the U.S. Food and Drug Administration (FDA) has approved a 300 mg single-dose pre-filled pen for Dupixent® (dupilumab).
- The pre-filled pen is approved for all Dupixent indications in patients aged 12 years and older, which includes use in certain patients with atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP), for at-home administration.
- This new pre-filled pen will provide patients with a more convenient option for administering Dupixent.
- The 300 mg pre-filled pen is expected to be available in the U.S. in the third quarter of 2020.
- The pre-filled pen features a hidden needle and single-press auto-injection, along with visual and audio feedback to help with administration.
- Regeneron and Sanofi are working with the FDA to provide additional data they require to complete their review of the 200 mg pre-filled pen

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- Dupixent is a fully-human monoclonal antibody that inhibits the signaling of the interleukin-4 (IL-4) and interleukin-13 (IL-13) proteins, and is not an immunosuppressant.
- Data from Dupixent clinical trials have shown that IL-4 and IL-13 are key drivers of the type 2 inflammation that plays a major role in atopic dermatitis, asthma and CRSwNP.