ARM Foundation
*for* Cell & Gene Medicine

# SPEAKING *of* GENES

## THE GENE MEDICINE NOMENCLATURE SUMMIT

FEBRUARY 2020 · SUMMIT REPORT

## Overview

On February 24, 2020 the ARM Foundation for Cell & Gene Medicine convened Speaking of Genes with a group of stakeholders in Washington, DC, hand–selected for their roles and knowledge of genetic nomenclature. The group held a discussion about the terminology and definitions used in messaging about cell & gene medicine for the general public.

Here are the **"FIRST 20"** – a glossary of 20 words and definitions determined by the Speaking of Genes participants.

**AAV** – Adeno–associated viruses (AAV) are small viruses that can be deactivated and used to transmit gene–based treatments to patients.

**Allele** – One of several possible versions of a gene. Each allele contains a distinct variation in its DNA sequence.

In human bodies, genes come in pairs. Each member of the pair is called an allele, and each allele contains a distinct DNA sequence. Some human genes have many allele variants, others have only a few. Located at specific positions on a chromosome, the interactions between alleles lead to distinctive traits. Some alleles contain mutations that could cause diseases. Alleles can be dominant or recessive.

**Allogeneic** – Allogenic refers to the transfer of tissue or cells from one person to another for the treatment of disease, to restore the immune system, or to help repair an injury.

**Autologous** – Autologous refers to therapies that use tissue or cells from a patient to treat the patient's disease or help repair an injury.

**Capsid** – The outside shell that protects a virus and helps it penetrate a cell membrane. A capsid is a protein coat that surrounds a virus. A capsid protects the contents, and helps the virus attach to a targeted cell to penetrate the cell membrane. In gene editing, the special characteristics of a capsid can enable gene delivery to specific cells.

**Cell Therapy** – Cell therapy is the transfer of whole cells into a patient to replace or repair damaged tissue or cells. A bone marrow transplant is the most frequently used cell therapy.

**CRISPR** – CRISPR is a gene–editing technique that allows scientists to alter DNA sequences easily and precisely in order to modify gene function. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats that are a type of DNA sequence in a gene. This type of DNA sequence is understood by scientists who can use molecular tools to modify how the gene functions.

**Chromosome** – A chromosome is a structure, located in the nucleus of a cell, that contains DNA. Genes are located in the chromosomes. A person typically has 46 chromosomes, inheriting half (23) of those chromosomes from each parent. Chromosomes are found in the cell's command center, the nucleus.

**Ex Vivo Gene Therapy** – Gene therapy that is delivered to cells outside a patient's body and then transferred back into the patient. "Ex vivo" means from outside the body. Ex–vivo gene therapy is a therapeutic technique where some of the patient's cells are collected, genetically modified outside the body, and then delivered back into the patient for the treatment of disease.

**Gene Editing** – Gene editing makes targeted changes to existing DNA in genes located on the chromosomes. With gene editing, researchers can enable or disable targeted genes, correct harmful mutations, and change the activity of specific genes. Gene editing is a set of techniques that enable researchers and clinicians to rewrite the instruction encoded in the DNA of genes. These molecular–biology techniques can enable or disable targeted genes, correct harmful mutations, modify expression of genes or change activity of a specific cell, with the goal of restoring normal function. CRISPR is an example of a gene editing technique.

**Gene-Modified Cell Therapy** – A therapeutic approach in which a person's cells are genetically modified in order to help the patient fight a disease. Therapies created this way can also be called Ex Vivo gene therapies.

A therapeutic approach in which a person's cells are modified outside the body, genetically recoded and enhanced. These cells then returned to the patient in order to help the patient fight a disease, for example, in CAR T–cell therapy for cancers.

**Gene Therapy** – Gene therapy is a technique that modifies a person's genes to treat or cure disease. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use. Gene therapies can work by several mechanisms:

- Replacing a disease–causing gene with a healthy copy of the gene
- Inactivating a disease–causing gene that is not functioning properly
- Introducing a new or modified gene into the body to help treat a disease

Gene therapy products are being studied to treat diseases including cancer, genetic diseases, and infectious diseases.

**Genes** – Regions of DNA that direct the production of proteins that are the building blocks of our bodies. Genes are inherited from our biological parents. Defective genes can result in a disease or medical disorder. Genes direct biologically important functions throughout the body. Mutations, or errors, in genes can cause disease by failing to produce sufficient levels of a functional protein.

**In Vivo Gene Therapy** – Gene therapy that modifies cells inside a patient's body.

"In vivo" means within the living body. "In vivo" gene therapies place gene–modifying therapy directly inside the patient's body.

**Lentivirus Vector** – Lentivirus vectors use parts of a lentivirus that are made harmless. The vector can carry genetic information into the nucleus of cells, potentially allowing for stable and durable expression of the genetic information that it integrated into the cells. One of the many vector types used by gene therapy researchers are lentiviral vectors. This vector can integrate its genome into both dividing and non–dividing cells in the body, leading to new gene expression that is designed to be stable and durable.

**Regenerative Medicine** – A field of medicine that aims to improve, replace, or repair cells, tissues, genes or organs. Doctors use cell therapies, gene therapies, and tissue–engineered products to replace or regrow human cells, genes, tissues or organs. This field holds the promise of repairing damaged tissues and organs and restoring function lost due to age, disease, damage, or birth defect.

**Somatic Cells** – Somatic cells are any cells in the body except sperm and egg cells. Changes made to the DNA in a somatic cell will not be inherited by a patient's future children.

**Stem Cells** – Stem cells distinguish themselves from other cell types by two unique characteristics. One, they are unspecialized cells capable of renewing themselves through cell division. When a stem cell divides, each new cell has the potential to remain a stem cell or become another more specialized cell type like a red blood cell or a muscle cell. Two, a stem cell can be induced to become tissue or organ specific stem cells with specific functions. This makes them useful in medical treatments.

The most commonly used stem cell treatment is hematopoietic (blood) stem cell transplantation, for example, bone marrow transplantation, to treat certain blood and immune system disorders or to rebuild the blood system after treatments for some kinds of cancer.

Given their unique regenerative abilities, stem cells offer new potential for treating disease but not all stem cell treatments have been proven to be effective and should be considered experimental.

**Tropism** – The ability of different vectors to target specific cell types or tissues.

A tropism is the natural attraction of a virus or vector to receptors present only on certain cells or tissues. Gene therapy researchers exploit tropisms to help different viruses, lipid particles, or other therapeutic carriers reach their targeted cells.

**Vectors** – Delivery vehicles, or carriers, that encapsulate therapeutic genes for delivery to cells. These include both disabled viruses and nonviral vectors, such as lipid particles.

## Context

Cell and gene medicine uses terms and concepts that are generally unfamilar to the public. To increase the likelihood that these medical treatments become more popular, promising, and acceptable to patients, messaging to the general public needs to be consistent and clear.

The cell and gene medicine community can build a common language and framework for discussions to share information consistently. The common language and framework will assist patients as they seek to make informed decisions.

## Objectives

The meeting goal was to begin a dialogue about effective words to use when talking about cell and gene medicine with the general public. The specific objectives were to:

1. Discuss and decide on the first 20 terms and definitions
2. Gather message direction on six critical topics
3. Provide direction for the post–Summit period

## Participants and Roles

**Host:** ARM Foundation for Cell and Gene Medicine

**Sponsors:**

- Kite, a Gilead Company
- bluebird bio
- Sangamo Therapeutics
- Audentes, an Astellas Company
- Sarepta Therapeutics

**Participants:**

- Foundations and Industry Organizations
- Patient Community & Patient Advocates
- Pharma & Biotech Industry Professionals
- Research Institutions
- Healthcare Systems & Service Providers

**Summit Workshop Facilitation:** Fountainworks, Raleigh, NC

## Welcome and Orientation

The summit planners shared a few words to welcome the 56 participants and orient them to the work of the day.

**Morrie Ruffin, Executive Director of the ARM Foundation for Cell & Gene Medicine**, shared the Foundation's work in cell and gene medicine education. He discussed Healing Genes, an international campaign to provide comprehensive, easy–to–understand, and easy–to–access information on the subject. In building their programs, the ARM Foundation talked with stakeholders about the educational needs of the industry. It became clear that a shared lexicon was a common need. The ARM Foundation's mission is to bring together stakeholders to better educate constituents, especially patients and caregivers. The day's Summit meeting is a starting point in that continuing conversation.

**Kate Lewis, Vice President, beta–thalassemia Program Lead at bluebird bio**, provided the context and the goals for the Summit. She emphasized that current messaging around cell and gene medicine is generally inaccurate and inconsistent. Yet studies show that people are more likely to have positive attitudes about cell and gene medicine when they are informed. Not only does consistent and accurate messaging enable patients to make better informed decisions, it also increases positive public perception regarding cell and gene medicine–related clinical trials.

### *Summit Goals*

- Review the first 20 terms and definitions
- Provide message direction on six critical topics, covering five interest areas
- Consider additional terms for future discussions
- Discuss Working Groups and next steps

### *Long–Term Goals*

- Gain consensus on basic cell and gene medicine terms, definitions and lexicon
- Enable those communicating about cell and gene medicine to be clear and consistent
- Avoid jargon and make accurate information accessible to a general audience

**Sid Reynolds, President of The Signature Agency,** oversaw extensive research prior to the Summit to better understand current messaging and terminology in cell and gene medicine. Partners Versta Research and Glean.info provided additional insight. The research included:

- Online keyword searches (using AI and manual search)
- Examining research publications between 2003–2019
- Reviewing research articles to examine tone and sentiment
- Secondary research on attitudes
- ~45–minute individual interviews with members of the general public and advocates

The research resulted in a glossary of 300+ words, essential to discussion about cell & gene medicine, that would benefit from consensus on definition.

To narrow the terms and propose definitions:

- Five members of the ARM Foundation's Healing Genes Steering Committee and 30 others gave input on which 20 terms of the 300+ listed in the proposed glossary would be discussed at the Summit.
- Multiple definitions for those terms were narrowed down based on scoring factors such as repetition of term's definition in 300+ online dictionaries, glossaries, and articles; number of citations an article with the definition had received; impact factor of the scientific publication in which a definition appeared; and readability indexes such as Gunning Fog Index, Flesch Kinkaid Reading Ease, Flesch Kinkaid Grade Index, SMOG Index, Coleman Liau Index, and Automated Readability Index.
- Prior to the Summit, participants and others responded to surveys to pick the "most accurate, easy–to–understand" definition for each of 20 terms, which were then displayed for Summit participant review during the Speaking of Genes Summit.

The members of the Summit group carried out three exercises in tables of 6.

1. **Terminology and Definitions** – Participants voted on proposed definitions to 20 key terms, discussing and recording their comments.
2. **Message Mapping** – Focusing on six key topics, each group developed a key message.
3. **Next Steps** – Each table reflected on what was missed during the Summit and how to move the work forward. A full–group debrief offered the opportunity to share reflections and suggestions.

## Terminology and Definitions

20 terms and definitions were selected for participants to review and vote on. Following the review of the 20 terms, the group had the opportunity to suggest terms to deprioritize from the list, and to add terms from the larger glossary. The results and examples from this conversation can be seen below.

## Definition Voting and Comments

When reviewing the definitions, participants were asked to consider accuracy and whether the leading definition was understandable to a general audience. Participants discussed what worked and didn't work about each definition.

Following discussion at their tables, each Speaking of Genes participant was asked to evaluate the definition using Poll Everywhere software to select one of three choices.

- **Good to Go** – This definition needs no revisions, and it is good as is.
- **Willing to Go with It** – This definition captures the spirit of the term; it may need a few refinements, but I am willing to move forward with it as is.
- **Needs Work** – I'm not okay with this as it is. It needs revision or to start from scratch.

If more than 1/3 of the votes on a term were "Needs Work," the definition was in need of serious revisions by a Working Group responsible for validation and improvement. Terms sent to the Working Group are marked with a triangle in the example figure.

The terms that received less than 1/3 votes for "Needs Work" were "approved," meaning their definitions required minimal edits and could be passed to the next round of considerations. These are marked with a check mark beside the image.

Data from the Speaking of Genes in person February 24, 2020 meeting was studied by the Working Group to validate, streamline and test drive the definitions.

The Working Group Validation call was held May 13, 2020.

The FIRST 20 definitions are also available in Appendix A.

## Discussion on Glossary

General comments around terminology/definitions. Comments from participants regarding regrouping of definitions, or formatting considerations give good examples of why consensus building is challenging:

- CRISPR could be an example of gene editing
- Gene modified cell therapy might be under cell therapy
- Allogeneic and autologous might be paired with in vivo and ex vivo
- Vector, tropism and capsid might be combined in one definition
- This is a technical/science list – should terms related to the patient experience be prioritized?
- Add phonetic spelling
- Make format of definitions consistent
- Include examples
- Include the reason that the word is important
- Using term or not in definitions
- Interlink terms e.g., hyperlink terms on a website

### *What terms to deprioritize?*

Participants were asked which terms should be deprioritized from the first list of major terms. Their suggestions are listed with more frequent mentions in Bold.

- Chromosomes
- Alleles
- Tropism
- Capsid
- Gene Modified Cell Therapy
- Cell Therapy

### *What terms from glossary should be added to this priority list?*

Participants selected terms to be prioritized; frequently mentioned terms are in bold.

- Antibody
- **Gene expression**
- Deletion
- Genetic marker
- Gene testing

- **Mutation**
- Personalized medicine
- Variance
- Promoter
- Transgene
- What isn't gene therapy – ASOS keeps coming up
- DNA
- RNA – differences between DNA and RNA
- Nucleus
- Cell
- Clinical Trial
- HSC – Hematopoietic stem cell
- Personalized medicine
- Enzyme
- **Antibody**
- Neutralizing antibodies
- Protein
- Off target
- Embryonic stem cells
- **Tissue engineering**
- Cancer stem cells
- Cure
- Genetic counseling
- Principal investigator
- Serious adverse effects
- Newborn screening
- Durability
- Redosing (gene therapy)

In addition to adding the above terms, one group suggested that "Eugenic Genetic Engineering" should be deleted from the glossary.

## Message Mapping

Each table was assigned one of six topics for each of 2 rounds. For each round, every table brainstormed on messages for that topic. The imagined audience for this exercise was the general public. The three prompts were:

- Things we want the audience to know
- Things we think the audience wants to know
- Things the audience is most likely to get wrong

After an initial brainstorm, each group consolidated their ideas into a central message. Each group shared central points aloud, as follows.  Appendix B has the data.

### *Topic: Gene editing | Genome editing | Gene therapy | Gene addition therapy | Gene replacement therapy*

Overview of Topic: Questions to consider – Do we want gene therapy to be the umbrella term? What do we want that to mean? Is it acceptable that gene editing and genome editing are often used as synonyms?

*Group 1*

- Cell and Gene Medicine use various technologies (e.g., gene editing, gene therapy, and cell therapy)
- These transformative therapies hold great promise to significantly impact the trajectory of disease
- We've made tremendous progress. A few things we know:
- Health changes made with gene editing and gene therapy won't be passed on to future generations
- You can't reverse gene editing and gene therapy
- Unanswered questions still remain about the durability of the treatment, the long term safety, and the possibilities for redosing.

*Group 2*

- Gene Therapy encompasses a variety of different techniques that are designed to deliver genetic material with the intent of addressing the fundamental cause of a disease for the long–term
- Understanding of the science around gene therapy has evolved significantly over the past decade
  - Safety is much better understood and defined
- Gene therapy is intended to have a durable, long term, or curative effect
  - There is not enough information available to define gene therapy as a "cure"
  - People have different ways to define "cure"

*Group 3:* Gene therapy is an exciting and rapidly–developing field of medicine. There are many different types of gene therapy. Certain types of gene therapy may work for some diseases and not for others. The risks and benefits

of a gene therapy depend on the disease, the approach, and characteristics of the individual patient. For a given disease, there may be more than one gene therapy possible or in development. Broad access to gene therapy will require innovation across government and healthcare systems as well as innovative science.

### *Topic: Viral Vectors for gene therapy, especially selection rationale*

Overview of Topic: The question to answer is how are gene therapy viral vectors selected and how can the individual patient understand the choice? E.g., lentivirus vs. adeno–associated virus (AAV)

*Group 1*

Vectors are required to deliver gene therapy:

- Vectors enable specific gene targeting
- Each vector has its own risks and durability
- Expectations about the outcome must be managed

*Group 2*

- Viruses are great at delivering materials to cells
- Vectors can be engineered from viruses to deliver therapeutic materials to cells
- Vector choice depends on target cell and disease
- These ideas for products have been in development for decades (25 years)
- Receiving a vector does not mean you can pass it on to others
- Just like with any medicine there could be side effects
- Vector is not equal to virus

*Group 3*

- Safety of today's vectors
- Differences between AAV and Lentiviral vectors.
- Access
- Manufacturing capacity (the selected vector may not be available commercially on demand)
- COGS (and weight–based viability)
- Patient exposure
- $
- Not everyone will qualify (N Antibodies)

### *Topic: Technologies*

Overview of Topic: How do we provide guidance on the rationale of selecting a particular gene therapy technology? 'Technology' in this context means a therapy – a therapeutic modality.

*Group 1:* There are different approaches to gene editing. They are not all the same. Different techniques will have different outcomes because of disease variability.

*Group 2:* Different technologies are selected for different diseases to deliver the most efficacious, durable and safe therapy.

- What is gene therapy?
- What technology options?
- Pros/cons in each disease state

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### *Topic: Mutation and Mutation Types (e.g., Frameshift Mutation | Point Mutation | Missense Mutation | Nonsense Mutation)*

Overview of Topic: Mutations are an area that matters to patients – "Why does that affect my life?" What do we want the patients and public to hear and perceive about mutations?

*Group 1*

- Mutations are personal and require individual interpretation from a professional
- Understanding your mutation may have more significance in one disease area than another
- Not all mutations are disease–causing

*Group 2*

- A mutation is a change in the DNA that is inherited or caused by environment and that may be associated with a medical condition
- Different types of mutations may impact severity or disease and response to gene therapy
- Different types of gene therapies have the ability to treat different mutations in different ways
- In some circumstances, tests are available to determine what mutation you have

*Group 3*

- There are many mutation types

- A disease or disorder could be caused by one specific mutation at a specific location – or it could be caused by many types of mutations in locations within a gene
- Severity of a disease or disorder can be influenced by mutation type
- The mutation type may influence the type of technology or therapeutic approach available to potentially treat the disease or disorder
- You may need a genetic diagnosis or subtyping to be eligible for gene therapy treatment

### *Topic: Cell and Gene Medicine – Can we determine a foundational, evergreen description for our global messages?*

Overview of Topic: Our foundational and global messaging: What is important for the public to hear us say collectively?

*Group 1*

- Cell and gene medicines are an emerging category of therapies that are on the cutting edge of the field of medicine and being developed for severe diseases with significant unmet needs
- The full potential for these therapies and their use is still being developed and understood, as are the ethical issues of misuse
- Cell & Gene medicines may not be applicable to all diseases
- Curative potential may not be possible with all diseases
- These therapies are currently complex to develop and manufacture
- The potential curative and one-time nature of these therapies challenges traditional privacy paradigms

*Group 2*

- Cell and gene medicine aims to address diseases for which there is no current optimal therapy
- We should incorporate things we want the audience to know:
  - We should educate patient about cell and gene medicine
  - There are uncertainties around curative potential or risks
  - People want to know If it's permanent and that there is long–term follow–up

*Group 3*

- Some technology is here now
- Can be life–altering – treats underlying cause of disease (not 100% of the time)

- Blind might see; deaf might hear; lame might walk
- Complex process, not a pill
- Intended to be a one–time treatment
- Research continues to advance
- Improved safety
- More safety
- Carefully monitored
- Might not be a fit for all
  - NAbs
  - Targeted to a specific indication
  - Phenotype
  - Disease progression
  - Age
- Cost/reimbursement (not sure when or where to raise this)

### *Topic: Sensitive Messages*

Overview of Topic: Can we propose foundational messaging around sensitive topics? These include: stem cell clinics, designer babies, enhancing appearance (including athletic performance), patient access.

*Group 1*

- Each stage of development of a gene therapy has a role to show whether it's working
- That's why not everyone qualifies for a trial
- When a trial is completed and therapy is approved, cost needs to be considered for quality of life and reduction of chronic care costs
- Many companies want to assist with patient out–of–pocket cost
- Companies and key stakeholders know big policy changes are required for this to be good for you

*Group 2:* As gene and cell therapy continues to evolve, adherence to regulatory bodies will lead to safer and more efficacious treatment options.

## Reflections and Next Steps

### *Activity: Reflections*

As a final activity, each table was asked to talk as a group about their reflections from the day and how to move this work forward. Below are the notes from the full group debrief to share reflections from their table discussions. (Appendix C contains the full list of notes from all tables.)

Reflections on Today – What did we miss today that Working Groups need to work on?

- Patient and public anxiety and how to get ahead of it
- Patient trust
- An ethics statement
- Recognizing faith based communities may have different needs
- Umbrella term – Aligning on different types of "gene therapy"
- Vector shedding
- May have missed participants – e.g., regulators
- Look at this more globally
- Access for underdeveloped communities
- Manufacturing challenges
- Cautious about focusing on challenges – suggestion to be prepared to respond, but not have it be a piece of the platform
- Manufacturing efficiencies
- Clinical trial differences
- Treatment expectations
- Tissue Engineering
- Ultra–personalized therapy
- Long term follow up, and challenges with payer system
- Connecting gene therapy education to general patient education
- Having a patient advocate perspective would be helpful
- Tested vs. non tested therapies – uniform language

Protocol for Future Terms – What process do we need to use for terms in the future?

- Test terms with civilians
- Need to refresh and review often (annually or every other year)
- Any new term gets cross referenced in the glossary
- Vital to ensure lexicon that is developed is ethically resilient
- Ask patient organizations to submit terms each year
- Important to have consensus as we update (virtual replication of this, or wiki model)
- As a group we all stand by this effort and are working together

Guidance Document – How will we implement as an industry what we've talked about here today?

- Publish as a white paper
- Use Healing Genes platform
- Canvas well–attended conferences (some academics are good at stimulating press)
- Urge everyone here to share internally at your organizations and in professional circles about the work we're doing – help build momentum and keep from duplicating efforts
- Strategy for moving these terms into already existing platforms
- For example: There is a comment period to modernize clinicaltrials.gov
- Targeted messaging for different stakeholders
- We have to think of resources – how do we make this financially viable?

## *What Happens Next?*

Immediately following the Summit, the Steering Committee was chartered to pull together the group's input.

- Help rework the 20 definitions to be shared with a larger audience to get input and buy in
- Provide feedback to the Working Groups as they begin their efforts to develop a lexicon and messaging around key terms and topics.

There was consensus that the activities should continue to keep the conversation going. All found that the in–person format was beneficial; however, there will need to be opportunities to provide input virtually.

Thank you for your participation and interest in Speaking of Genes, The Gene Medicine Nomenclature Summit.

For more information on this report and other activities of the ARM Foundation for Cell & Gene Medicine, please contact:

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The Mission of The ARM Foundation for Cell and Gene Medicine is to serve as the education and information catalyst on issues fundamental to making gene and cell therapies, tissue–engineered products and other regenerative medicine treatments available to patients.

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