MTS Health Partners

Strategic Advisory Analytics

Gene Therapy - Near-term Revolution or Continued Evolution?

Part 2: The Gene Therapy Ecosystem

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MTS' Report on Gene Therapy

Part 2: The Gene Therapy Ecosystem

This is an abbreviated version of MTS' Report:
Gene Therapy – Near-term Revolution of Continued Evolution – Part 2

Please contact Ravi Mehrotra for the full report
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MTS' Report on Gene Therapy

Full Report Divided into Three Parts

Part 1: Published Aug'17

Global Proprietary Data

Key valuation and performance data from MTS' proprietary database of 145 global public and private Gene Therapy companies. We look at the late-stage pipeline of the Gene Therapy subsector and put this in context of the totality of the Biopharma pipeline.

Part 2: Published today

Gene Therapy Ecosystem

Description of the Gene Therapy space, the various technologies, and current business models. We analyze the clinical, regulatory and manufacturing hurdles that could set apart the winners from the not-so-much winners in the space.

Part 3: To be published Q4'17

Conclusions for the Future of the Gene Therapy Space

We will provide key insights and potential actionables with goal of outlining a detailed roadmap to successfully navigating the coming era of Gene Therapy.

Previously Published Strategic Advisory Analytics Reports

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Reports and Notes on Drug Pricing

Principled Drug Pricing Centered on Innovation and Choice: Part 1
Strategic Advisory Analytics Report #1

Will Drug Pricing Still be as Big of an Issue Going Forward with the New US Administration?
Strategic Advisory Analytics Feedback #1

Unprincipled Price Rises: Where is the Value in the Unbearable Symptom?
Strategic Advisory Analytics Feedback #2

The Frictional Cost Break-up in Drug Pricing: It's not Me, It's You
Strategic Advisory Analytics Feedback #3

Orphan Drug Pricing – Unlikely to be Left Alone in the Current Pricing Debate
Strategic Advisory Analytics Feedback #4:

#complex drug pricing in 140 characters or less
Strategic Advisory Analytics Feedback #5

Reports on Gene Therapy

Gene Therapy: Near-term Revolution or Continued Evolution?

Part 1 – Global Proprietary Data

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Part 2 – The Gene Therapy Ecosystem

Our Gene Therapy report is comprised of 3 parts:

- **Part 1 - "Global Proprietary Data"** was published in August 2017 and looked at key valuation and performance data from MTS' proprietary database of Gene Therapy companies. We also looked at the late-stage pipeline of the Gene Therapy subsector and put this into context of the totality of the Biopharma pipeline.
- **Part 2 - "The Gene Therapy Ecosystem"** describes the Gene Therapy space in detail, highlighting the various technologies and current business models, and dives deep into the unique sensitivities each approach faces in the near-term.
- **Part 3 - "Conclusions for the Future of the Gene Therapy Space"** (to be published December 2017), will provide key insights and potential actionables with goal of outlining a detailed roadmap for successfully navigating the coming era of Gene Therapy.

In the same approach we took to our drug pricing work (link), the main goal of this Gene Therapy report is to act as a forum for continued debate on the subsector, meaning feedback from corporates and investors is welcome!!!

Please email mehrotra@mtspartners.com

Executive Summary

Part 2 – The Gene Therapy Ecosystem

The Gene Therapy subsector has evolved into a diverse group of companies with complex and technologies, each confronting significantly different clinical, regulatory, and manufacturing hurdles, as well as business models

- Major scientific breakthroughs during the last several decades have driven the development of a complex and heterogeneous set of technologies that can be broadly classified as Gene Therapy. Many of these could easily be described as standalone technologies (or at least discreet subsets of Gene Therapy), such as RNAi, CAR-T, TCR, CRISPR, etc.
- Concomitantly, the term "Gene Therapy" captures an incredibly wide set of approaches in current day biopharma. Adding to this complexity, the underlying business models of pure-play Gene Therapy companies also show a disparate range, from platform technology developers to single asset plays, to companies attempting a fast route to a "FIPCO-like" model.

MTS' method to demystifying the opportunities and treats in the Gene Therapy space…

- The commonality of all companies within the Gene Therapy subsector is the use of genetic material (DNA and RNA) to treat disease, from monogenic disorders to multi-factorial diseases such as cancer.
- Our central approach to demystifing the totality of the Gene Therapy space has been to assign each company to one of four groups, which we call "approaches" - (1) Gene transfer, (2) Gene disruption, (3) Gene-modified cell therapy and (4) Gene editing.

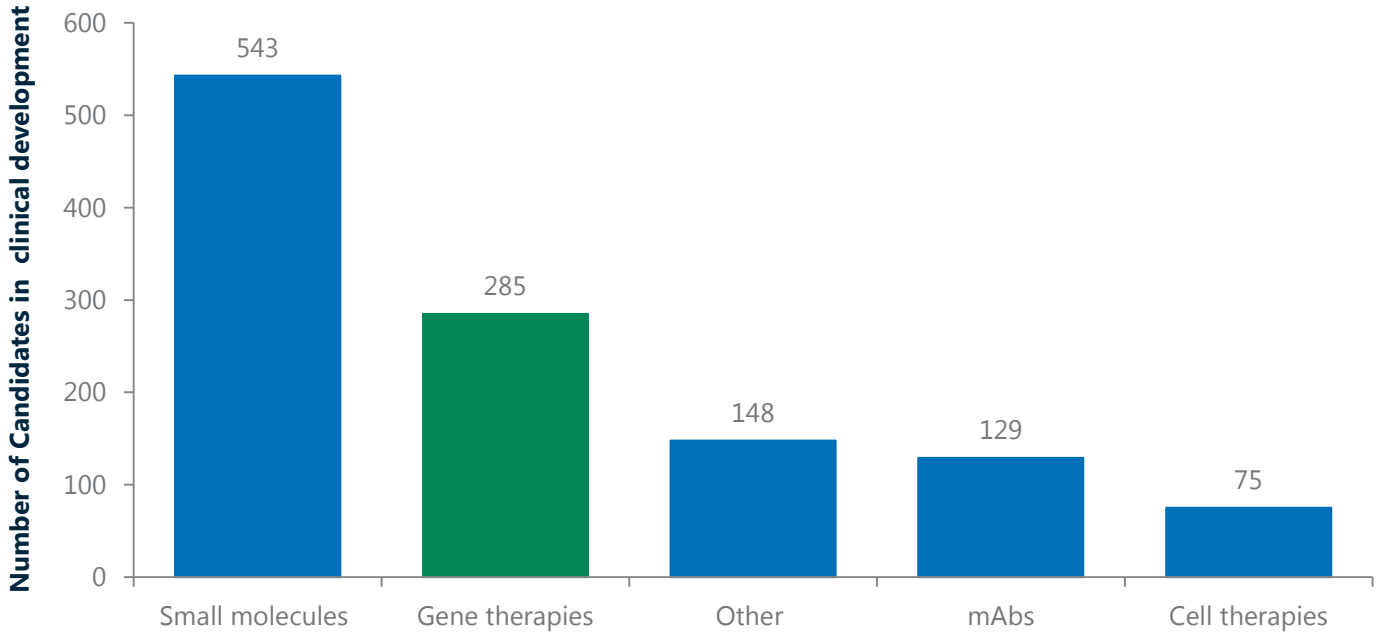
Gene transfer	**Gene disruption**	**Gene-modified cell therapy**	**Gene editing**
Vector delivered genes	Nucleotide technology	Cell therapy / CARs	CRISPR / Homologous Recombination

Executive Summary

Part 2 – The Gene Therapy Ecosystem

To briefly recap, Part 1 of our Gene Therapy report "Global Proprietary Data" provided key valuation and performance stats from MTS' proprietary database of 145 global Gene Therapy companies.

- Gene Therapy companies now represent 20% and 29% by number and market cap, respectively, of precommercial public biotech companies
- The mean valuation of public Gene Therapy companies ($500mm) now significantly exceeds mAbs ($380mm) and small molecule ($290mm) companies
- Within the pre-commercial space, gene therapies are now the #2 modality in clinical development
- We analyzed the subsector and divided it into 4 core approaches



Source: EvaluatePharma as of 11/10/2017; MTS analysis (selected from candidates from precommercial public companies)

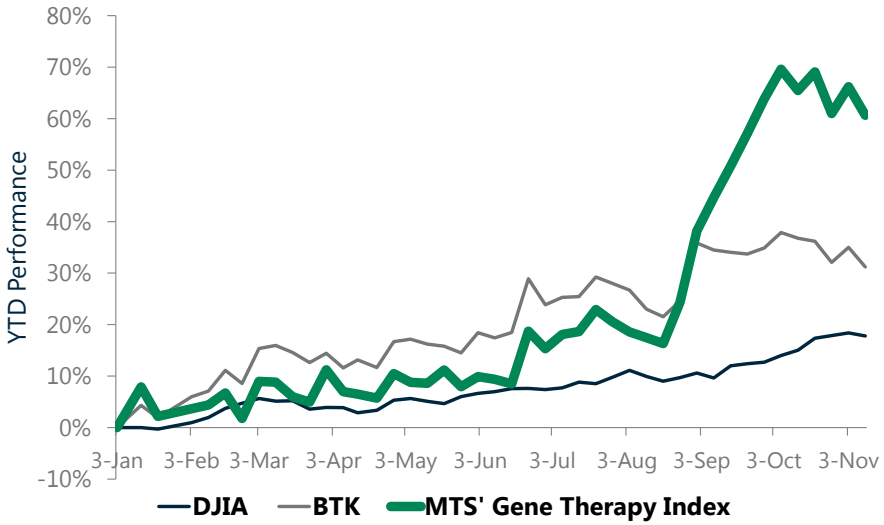
Executive Summary

Part 2 – The Gene Therapy Ecosystem

Since we published Part 1 in August, the performance of the Gene Therapy subsector has been notable and driven by a plethora of significant news flow

- 8/28 - The $11.9bn Gilead buyout of Gene-modified cell therapy company Kite Pharma - the largest M&A for a precommercial biotech in history
- 8/30 - The approval of Novartis' CAR-T product Kymriah - the first FDA approved Gene-modified cell therapy
- 9/20 - Alnylam's successful pivotal trial for Patisiran - the first RNAi drug candidate likely to win FDA approval
- 10/13 – Unanimous recommendation for Spark's Luxturna by an FDA advisory committee
- 10/18 – The approval of Gilead/Kite's CAR-T product Yescarta

Our Gene therapy index is now trading +60% YTD (compared to +31% for the BTK and +18% for the DJIA) and valuations for pure-play Gene Therapy companies are approaching all-time highs



Source: CapIQ as of 11/10/2017

Executive Summary

Part 2 – The Gene Therapy Ecosystem

Today we are publishing Part 2 - "The Gene Therapy Ecosystem," where we describe the Gene Therapy space in detail, highlighting the various technologies and current business models, diving deeper into the unique sensitivities each approach faces in the near-term

The Top Take homes from Part 2 are:

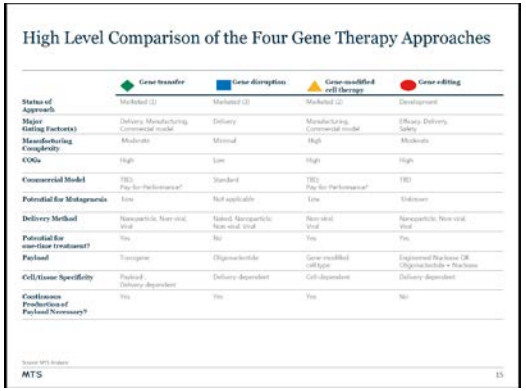
1. **Each Gene Therapy Approach Faces a Unique Set of Hurdles** (Slide 16)

   Given the diversity of technologies within the Gene Therapy subsector, it is not surprising that companies are confronting different clinical, regulatory, manufacturing and commercial hurdles. Companies developing Gene transfer (rAAV, Lentiviral, etc.; see slides #21-30) and Gene-modified cell therapy technologies (CAR, TCR, etc.; see slides #41-53) must address significant challenges around manufacturing. Gene disruption companies (RNAi, ASO, miRNA, etc.; see slides #32-40) are in need of new delivery technologies to expand the number of addressable indications and increase market opportunity. Given the very early-stage of the Gene editing technologies (ZFN, CRISPR, AAV-directed Homologous Recombination, etc.; see slides #55-62), companies in this space are facing more fundamental hurdles around safety and efficacy.

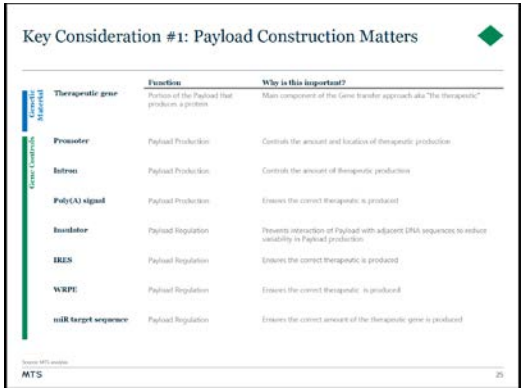
2. **Payload and Delivery Technology are Critical Components of all Gene transfer Therapeutics** (Slide 27)

   Gene transfer therapeutics are designed to permanently replace defective genes within the DNA of cells, restoring cellular function and potentially eliminating disease. This approach is most often used for the treatment of monogenic diseases, where a single disease causing gene has been identified. An example of a Gene transfer therapeutic is Spark's Luxturna for the treatment of inherited retinal disorders. Each Gene transfer therapy contains two components - (1) a payload and (2) a delivery technology – both of which are critical to therapeutic potential (see slide #23). The payload replaces the defective gene with a functional gene and the delivery technology facilitates the targeting of the payload to a specific organ/tissue/cell type. Subtle changes in the payload or delivery technology can have a profound impact on the activity of the therapy.

Slide #16



Slide #27



Executive Summary

Part 2 – The Gene Therapy Ecosystem

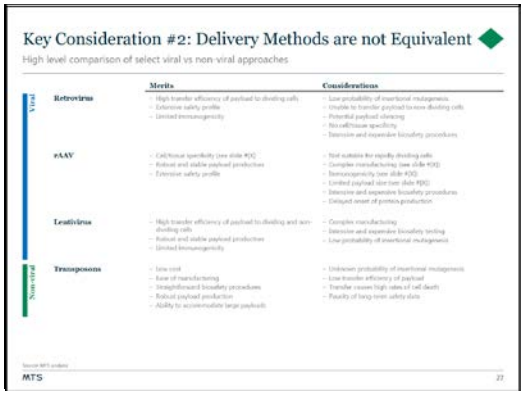
3. **Delivery Technologies for Gene transfer are Principally Viral but Newer Non-viral Approaches may Potentially Offer Advantages.** (Slide 28)

   There are two major classes of Gene transfer delivery technologies: (1) viral and (2) non-viral (see slide #28). Examples of viral delivery technologies include retrovirus, recombinant adeno-associated viruses (rAAV), and lentiviruses, which permanently deliver a payload to cells. Each one of these viral technologies has distinct features which make them more applicable for some applications but not others. A major drawback of viral delivery technologies is the complex manufacturing that currently does not support efficient scale up at reasonable costs and at high reproducibility. This manufacturing hurdle is addressed with a newer non-viral technology known as transposons. Although easier to produce in large quantities at much lower costs, this technology will need to match the organ/tissue targeting specificity and safety profile of viral approaches before it becomes a more mainstream delivery technology for Gene transfer approaches.

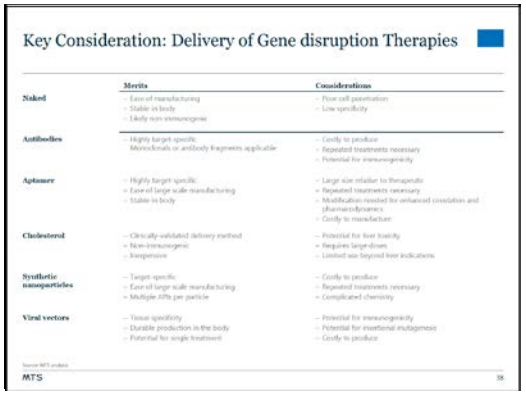
4. **Whilst there is a Plethora of Methods for Delivering Gene disruption Therapeutics, Current Technologies are Still Inadequate to Target Many Tissue and Organ Systems.** (Slide 39)

   Gene disruption therapeutics are designed to alter the production of an gene within the DNA of cells in a non-permanent fashion. This approach is used for the treatment of monogenic and polygenic diseases. An example of a Gene disruption therapeutic is Biogen's Spinraza for Spinal Muscular Atrophy. All Gene disruption technologies require a payload (either a double-stranded or single-stranded oligonucleotide) and a delivery technology (or less commonly are administered "naked"). Delivery technologies for Gene disruption therapeutics include antibodies, aptamers, cholesterol, synthetic nanoparticles and, in theory, viral and non-viral vectors (see slide #38). Each delivery method has its advantages and disadvantages, however none are currently sufficient to efficiently delivery therapy to specific tissues and organ systems, with the exception of the liver. Therefore most applications using Gene disruption therapies must rely on local delivery methods, which limits the universe of addressable indications and impacts market opportunity. When properly targeted to the organ/tissue of interest, like in the case of Biogen's Spinraza, these therapies can be extremely effective.

Slide #28



Slide #39



Executive Summary

Part 2 – The Gene Therapy Ecosystem

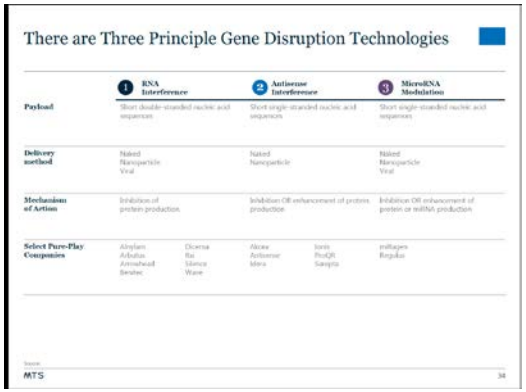
5. **Gene disruption Approaches Employ One of Three Core Technologies.** (Slide 35)

   The three core technologies that make up the Gene disruption approach are RNA Interference (RNAi), Antisense Interference (ASO) and MicroRNA Modulation (see slide #35 for a summary). RNAi uses short double-stranded DNA molecules (oligonucleotides) to turn off genes, thereby reducing protein production. In contrast, ASO are single-stranded oligonucleotides designed to inhibit or enhance the production of genes/proteins. Finally, MicroRNA Modulation are short single-stranded oligonucleotides that regulate protein production by inhibiting or enhancing the activity of native small RNAs that are made in the nucleus of all cells. Each one of the technologies have distinct features which make them more applicable for some indications but not others. To date, only ASO therapeutics have been approved by the FDA but this may change in 2018 when Alnylam's RNAi Patisiran is expected to seek marketing authorization.

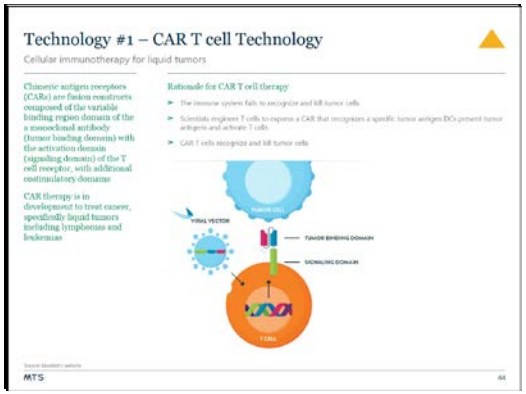
6. **With Two Newly Approved Gene-modified cell therapies on the Market, All Eyes are Now Focused on the Commercial Viability of these Costly therapies.** (Slide 45)

   Two of the first Gene Therapies to hit the market (uniQure's Glybera and GSK's Strimvelis) were flat out commercial failures. Potential reasons for lackluster sales include less than compelling efficacy data for Glybera and the fact Strimvelis is administered in only one clinic worldwide. Whatever the case may be, companies must eventually demonstrate that Gene Therapies can be commercially viable medicines. Recently approved Gene-modified gene therapy offerings from Novartis and Gilead/Kite (Kymriah and Yescarta, respectively; see slide #45 for an explanation of the technology) for the treatment of leukemia are highly efficacious and will be made widely available. The question is, will these be the first Gene Therapies to return meaningful revenue? The answer may lie in whether these companies can innovate around product manufacturing so that there is a significant reduction in the current cost of goods.

Slide #35



Slide #45



Executive Summary

Part 2 – The Gene Therapy Ecosystem

7. **Nowhere is Manufacturing Innovation Needed More Than in the Production of Gene-modified cell therapies.** (Slide 44)

   Gene-modified cell therapy is really a hybrid Gene Therapy approach, meaning it is part Gene transfer and part Cell therapy (see slide #44). It is designed to add a functional gene within the DNA of a specific cell type (T cell, stem cell, etc.). The cell type must be removed from the body and a functional gene within the payload is added via a viral or non-viral delivery technology (see section on Gene transfer slides #20-29). Examples of these therapies are Chimeric Antigen Receptor T cells (CAR) and TCR T cells (TCR), which are used to treat various forms of cancer. Unlike all other Gene Therapy approaches, Gene-modified cell therapies are personalized for each patient, adding significant complexity to manufacturing and distribution. Currently most companies developing these therapies are not set up with efficient process development. Implementation of these measures are critical because Gene-modified cell therapies require not only the manufacture of delivery technologies (vectors) but also cells. The most significant manufacturing challenge surrounds the efficient scale up for commercialization while ensuring product fidelity. The key here may lie in automation, which has the potential to cut manufacturing time and costs, and reduce batch-to-batch variability. Another potential solution to this current manufacturing hurdle is the development of a non-personalized technology, which has the potential to have an on-demand product and significantly reduce production costs (see slide #52).

Slide #43

Executive Summary

Part 2 – The Gene Therapy Ecosystem

8. **While Gene editing may One Day be the Holy Grail of Gene Therapy, There are Many Outstanding Questions Around the Safety and Ease of Use of this New Gene Therapy Approach.** (Slide 58)

Gene editing therapeutics are designed to repair, delete, or add a DNA sequence within a gene, resulting in a permanent change in the genetic make up of the target cell/tissue/organ (see slide #58). This approach will have most utility in the treatment of monogenic diseases, where a single disease causing gene has been identified. Like Gene transfer and Gene modified cell therapies, all Gene editing therapeutics are composed of a payload and delivery technology. Although the delivery technologies are similar to those used by Gene transfer therapies (see slide #28), the payloads contain genes spelling out a class of proteins called nucleases (see slide #58). Each of the four core Gene editing technologies employ a unique nuclease but all perform the same function – they cut DNA in a very efficient manner in order to repair, delete, or add a DNA sequence within an gene. It is this cutting activity of nucleases which presents a potential safety concern, as DNA cuts at off target sites can potentially cause mutations and lead to diseases such as cancer. Until we have a much larger clinical safety database for Gene editing technologies, it is hard to know whether the potential off target activity of nucleases is really a legitimate concern. Nevertheless there are companies developing nuclease-free Gene editing technologies with the goal of potentially providing a safer approach (see slide #61). However before the technologies become more mainstream they will need to demonstrate that they are as efficient in editing genes as the nuclease-dependent approaches.

Slide #58

High Level Comparison of the Four Gene Therapy Approaches

	Gene transfer	Gene disruption	Gene-modified cell therapy	Gene editing
Status of Approach	Marketed (1)	Marketed (3)	Marketed (3)	Development
Major Gating Factor(s)	Delivery, Manufacturing, Commercial model	Delivery	Manufacturing, Commercial model	Efficacy, Delivery, Safety
Manufacturing Complexity	Moderate	Minimal	High	Moderate
COGs	High	Low	High	High
Commercial Model	TBD; Pay-for-Performance?	Standard	TBD; Pay-for-Performance?	TBD
Potential for Mutagenesis	Low	Not applicable	Low	Unknown
Delivery Method	Nanoparticle, Non-viral, Viral	Naked, Nanoparticle, Non-viral, Viral	Non-viral, Viral	Nanoparticle, Non-viral, Viral
Potential for one-time treatment?	Yes	No	Yes	Yes
Payload	Transgene	Oligonucleotide	Gene-modified cell type	Engineered Nuclease OR Oligonucleotide + Nuclease
Cell/tissue Specificity	Payload, Delivery-dependent	Delivery-dependent	Cell-dependent	Delivery-dependent
Continuous Production of Payload Necessary?	Yes	Yes	Yes	No

Source: MTS Analysis

2. Intro to MTS' Gene Therapy Report

Four Distinct Approaches of Gene Therapy

MTS defines Gene Therapy as the use of genetic material (DNA and RNA) to treat a broad range of diseases, from monogenic disorders to complex disease such as cancer

Using this definition, we created a proprietary pure-play Gene Therapy database, which includes 47 public and 98 private companies

We have divided companies within our database into one of the following four Gene Therapy approaches based on lead candidate mechanism of action:

(1) Gene transfer

(2) Gene disruption

(3) Gene-modified cell therapy

(4) Gene editing

Gene Therapy Approaches

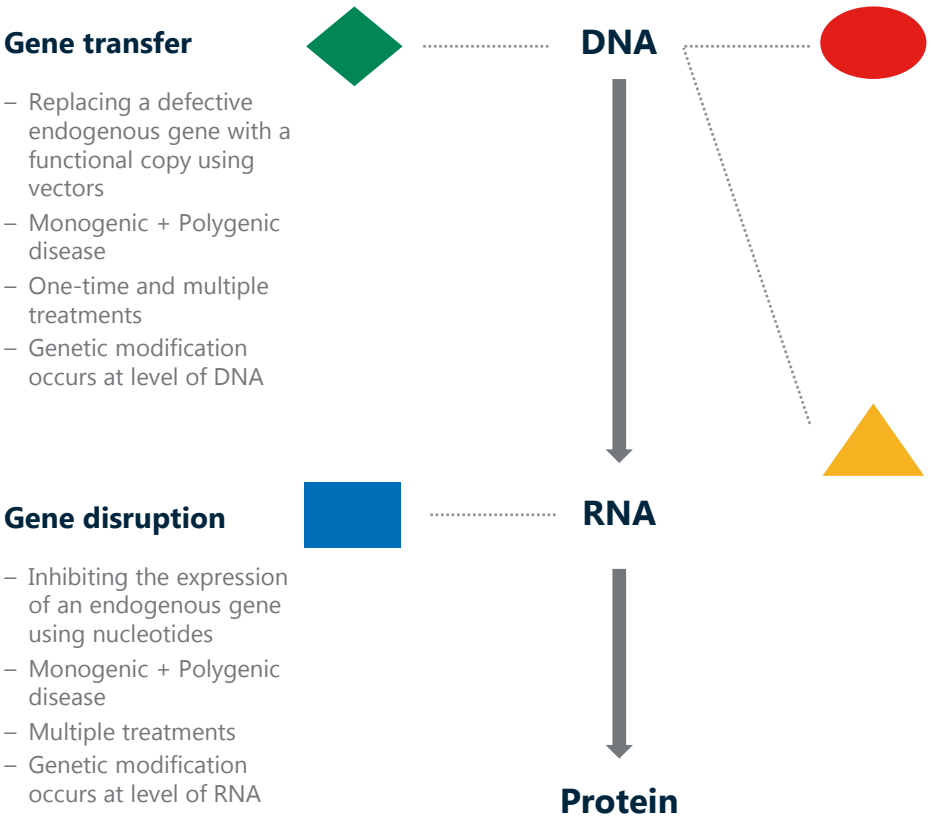
	Marketed or Mid – Late Stage Development			Preclinical
	1	2	3	4
	Gene transfer	**Gene disruption**	**Gene-modified cell therapy**	**Gene editing**
	Vector delivered genes	"Nucleotide technology"	Cell therapy / CAR	CRISPR / Homologous Recombination
	Avexis' AVXS-101 Spark's Luxturna uniQure's Glybera	Alnylam's Patisiran Biogen's Spinraza Sarepta's Exondys	bluebird's LentiGlo Gilead's Yescarta NVS' Kymriah	CRISPR Tx Editas Intellia Sangamo
# Public Companies	**16**	**16**	**11**	**4**
# Private Companies	**39**	**21**	**31**	**7**
# Approved Drugs	**1**	**3**	**3**	**0**

Source: EvaluatePharma as of 11/10/2017, Analysis of MTS' Proprietary Pure-Play Gene Therapy Database

Four Distinct Approaches of Gene Therapy

Relatively Little Expertise "Crosstalk" Between Approaches

Each gene therapy approach is unique and highly specialized, being an expert in one approach does not transfer over to the other approaches



Gene transfer

- Replacing a defective endogenous gene with a functional copy using vectors
- Monogenic + Polygenic disease
- One-time and multiple treatments
- Genetic modification occurs at level of DNA

Gene editing

- Repairing or deleting a DNA sequence of an endogenous gene using CRISPR
- Monogenic disease
- One-time treatment
- Genetic modification occurs at level of DNA

Gene disruption

- Inhibiting the expression of an endogenous gene using nucleotides
- Monogenic + Polygenic disease
- Multiple treatments
- Genetic modification occurs at level of RNA

Gene-modified cell therapy

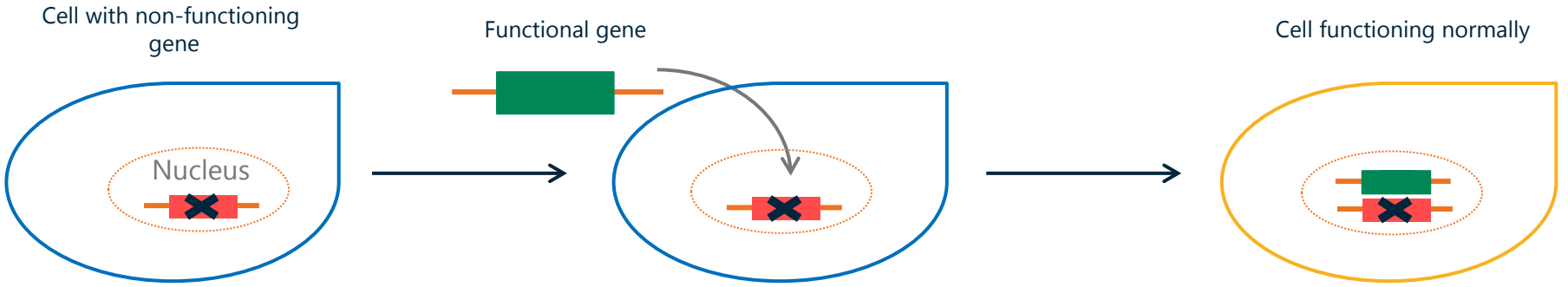
- Adding a functional gene to a cell therapy
- Common cell types targeted include T cells, NK cells and HSCs
- Monogenic + Polygenic diseases
- One-time and multiple treatments
- Change occurs at level of DNA

Source: MTS Analysis

3. Gene transfer Technologies

Select Public Gene Transfer Companies

Replacing a defective endogenous gene with a functional copy



Company	Mkt Cap ($mm)	Product/ Lead Candidate	Phase	Therapeutic Area	Indication	Vector / Transgene(s)

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Select Private Gene Transfer Companies (1/2)

Company	Product/ Lead Candidate	Phase	Indication	Vector / Transgene(s)

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Select Private Gene Transfer Companies (2/2)

Company	Product/ Lead Candidate	Phase	Indication	Vector / Transgene(s)

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Core Components of a Gene transfer Therapeutic

Gene transfer

Replacing a defective endogenous gene with a functional copy; genetic modification of cells occurs in the body; modification results in permanent change to patient's DNA

Two Core Components

- **Payload:** Gene Controls AND Gene
- **Delivery:** Vector

Payload

Gene Controls

DNA sequences that regulate the production of the gene

AND

Gene

DNA sequence coding for the production of a protein

Delivery

Vector

Unit that is required to delivery the payload to cells

Nanoparticle, Non-viral, Viral vectors are used for Gene transfer therapeutics

Source: MTS analysis

Key Consideration #1: Payload Constructs Matters

Despite some success with the Gene transfer approach in clinical trials, reproducibility and stability of therapeutic gene expression from within viral and non-viral constructs remains a challenge

Problems of variability and silencing of therapeutic gene expression from viral and non-viral constructs in the clinic may be masked by several phenomena

- Selective survival of genetically modified cells
- Selective growth advantage of modified cells

Gene controls (shown on the next slide) can be employed to at least reduce position effects and potentially provide more reproducible results

- Promoters are the most important gene controls because they control the amount and location of therapeutic gene expression
- Elements that impact chromatin boundaries, chromatin remodeling and transcriptional activation, such as insulators, have the potential to mitigate variation in therapeutic gene expression but also increase the likelihood of insertional mutagenesis

Source: MTS analysis

Key Consideration #1: Payload Construction Matters

Genetic Material

Gene Controls

Function	Why is this important?

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

Key Consideration #2: Delivery Methods are not Equivalent

The ideal delivery method should provide robust expression of the payload in the target tissue of interest without eliciting an immune response

There are two major classes of Gene transfer delivery methods

- Viral (recombinant viruses – retroviruses and lentiviruses)
- Non-viral (transposons, plasmid DNA, and naked DNA/RNA complexes)

Choosing the appropriate delivery method for a Gene transfer therapeutic is dependent on several important criteria

- Which cell/tissue types are being targeted
- The choice of systemic versus local delivery
- The use of tissue-specific or constitutively active gene controls
- The safety profile associated with the delivered payload

Source: MTS analysis

Key Consideration #2: Delivery Methods are not Equivalent

High level comparison of select viral vs non-viral approaches

	Merits	Considerations
Viral	Please contact Ravi Mehrotra for the full report mehrotra@mtspartners.com	
Non-viral		

Source: MTS analysis

Features of Gene transfer Delivery Methods

Viral vs Non-viral Approaches

Delivery Vector Features	Viral	Non-viral
Maximum Payload Size		
Immunogenicity		
Safety Considerations		
Genome Integration		
Duration of Expression		
Ease of Scale Up for Commercial Applications		

Source: MTS analysis

Current Options for Manufacturing rAAV Vectors

Balancing Safety with Scalability

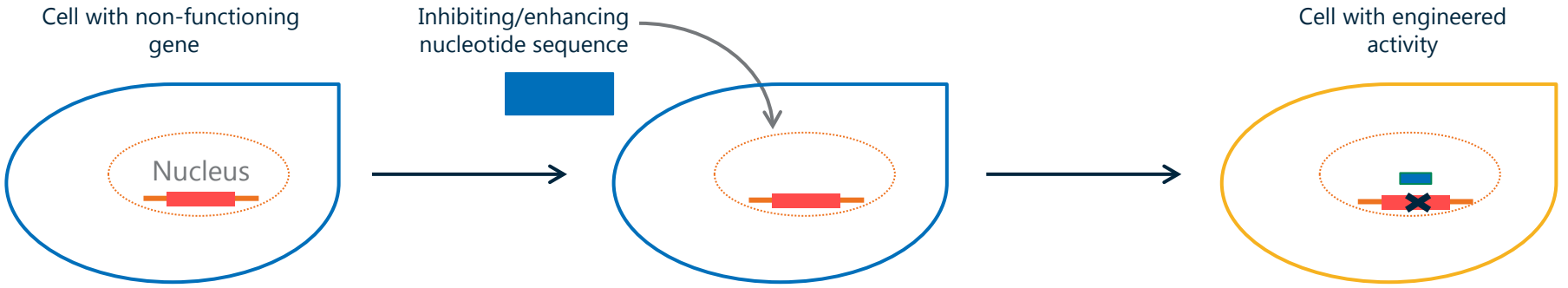
Advantages	Please contact Ravi Mehrotra for the full report mehrotra@mtspartners.com
Challenges	
Efficiency of DNA Delivery	
Scalability	
Safety Concerns	
Cell line	
Production System	

Source: MTS analysis

4. Gene disruption Technologies

Select Public Gene Disruption Companies

Disrupting the expression of an endogenous gene



Company	Mkt Cap ($mm)	Product/ Lead Candidate	Phase	Therapeutic Area	Indication	MoA / Target

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mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Select Private Gene disruption Companies

Company	Product/ Lead Candidate	Phase	Indication	MOA / Target

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mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Core Components of a Gene disruption Therapeutic

Gene disruption

Disrupting the expression of a gene; modification of cells occurs in the body and does not result in permanent change in a patient's DNA

Two Core Components

- **Payload:** Oligonucleotide
- **Delivery:** Vector OR Naked

Payload

Oligonucleotide

Short DNA or RNA sequence complementary to the DNA or RNA sequence of the target gene

Delivery

Vector

Unit that is required to delivery the payload to cells

Antibodies, Aptamers, Nanoparticles, Viral vectors and Non-viral vectors are used for Gene disruption therapeutics

OR

Naked

Source: MTS analysis

There are Three Principle Gene Disruption Technologies

	1 RNA Interference	2 Antisense Interference	3 MicroRNA Modulation
Payload			
Delivery method			
Mechanism of Action			
Select Pure-Play Companies			

Source: MTS analysis

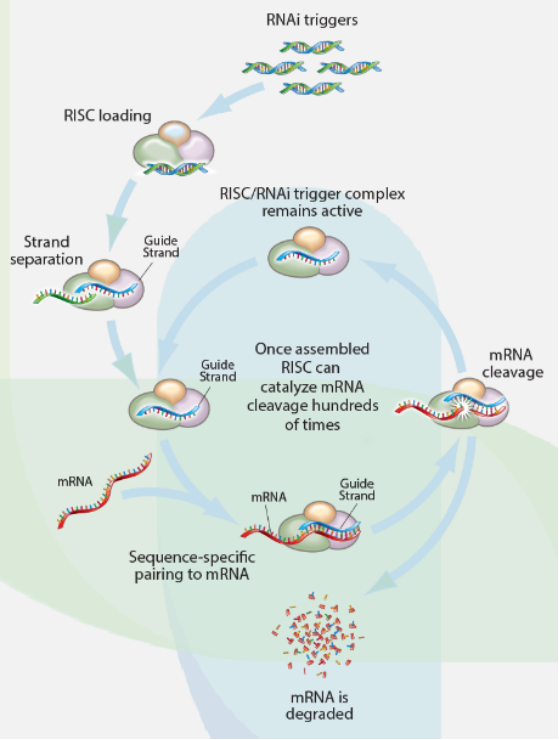
Technology #1 – RNA Interference (RNAi) Technology

This technology uses short double-stranded DNA molecules (oligonucleotides) to turn off gene expression, thereby reducing the production of proteins

RNAi is in development for a wide range of indications, from cancers to infectious disease

Rationale for RNAi therapy

- Altered protein production leads to disease manifestation
- RNAi is delivered to the patient systemically or locally to specific tissues/organs (i.e. eye, skin)
- RNAi enters into cells of the diseased tissue or organ
- RNAi shuts down production of specific proteins that cause disease or disease symptoms



Source: MTS analysis

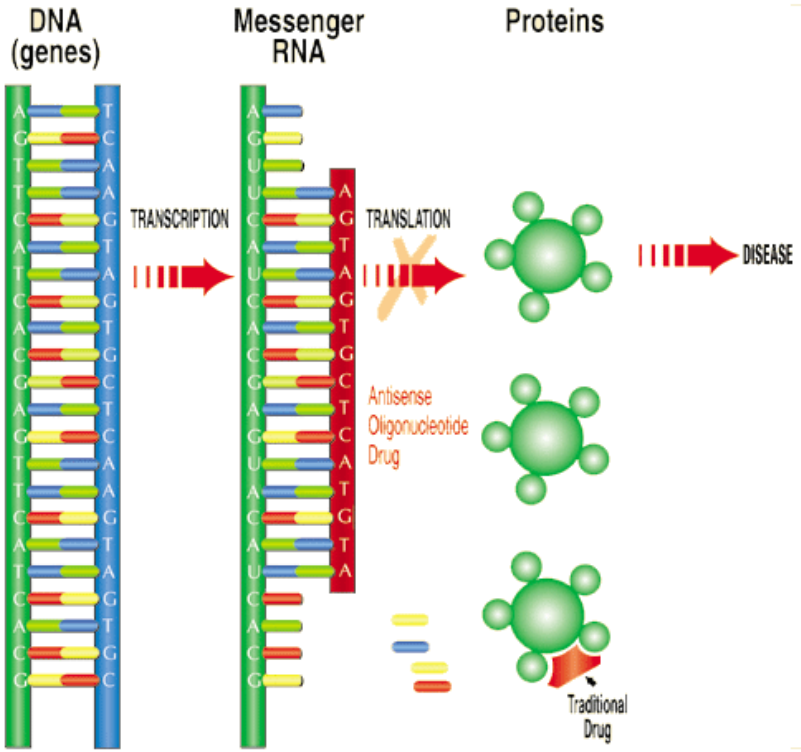
Technology #2 – Antisense (ASO) Technology

This technology uses a single-stranded RNA molecule that is complementary to a messenger RNA (mRNA) designed to inhibit or enhance the translation of the mRNA into protein

Antisense is can be used to treat a wide range of indications

Rationale for ASO therapy

- Altered protein production leads to disease manifestation
- ASO is delivered to the patient systemically or locally to specific tissues/organs (i.e. eye, skin)
- ASO enters into cells of the diseased tissue or organ
- ASO turns off OR enhances production of specific proteins



Source: MTS analysis

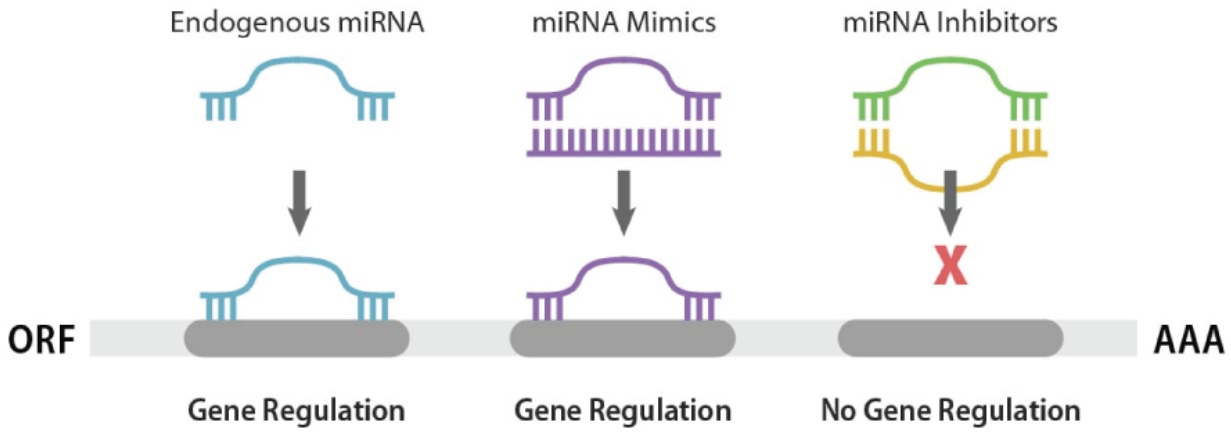
Technology #3 – MicroRNA Modulation Technology

microRNAs are short single-stranded RNA molecules that regulate protein production and play a vital role in influencing the pathways responsible for many disease processes

microRNAs can be modulated by either decreasing the activity (inhibitors aka anti-miRs) or increasing the levels (mimics aka pro-miRs) of expressed microRNAs.

Rationale for MicroRNA Modulation therapy

- Altered miRNA production leads to disease manifestation
- microRNA modulators are delivered to the patient systemically or locally to specific tissues/organs (i.e. eye, skin, eye)
- microRNA modulators enter into cells of the diseased tissue or organ
- microRNA modulators turn off OR enhances production of specific proteins



Source: Regulon's website

Key Consideration: Delivery of Gene disruption Therapies

	Merits	Considerations
Naked		
Antibodies		
Aptamer		
Cholesterol		
Synthetic nanoparticles		
Viral vectors		

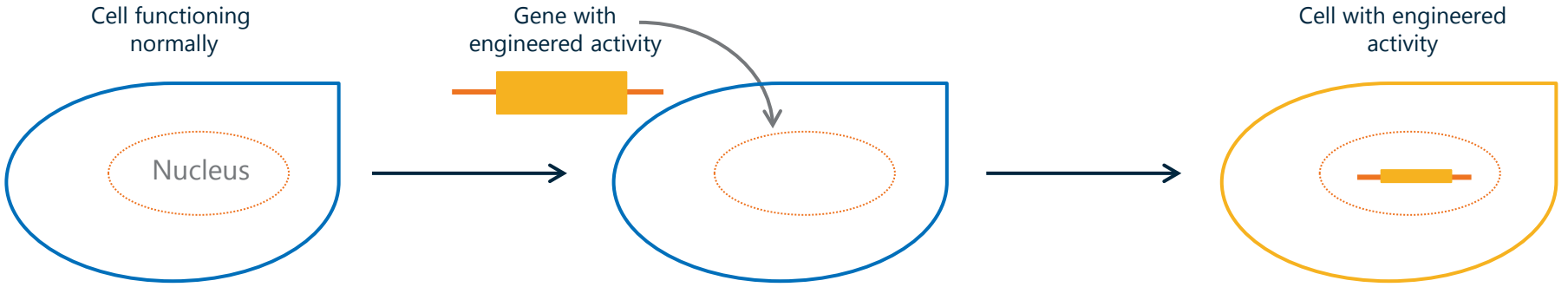
Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

5. Gene-modified cell therapy Technologies

Select Public Gene-modified cell therapy (GMCT) Companies

Introducing a gene with *de novo* (new) activity



Company	Mkt Cap (mm$)	Product/ Lead Candidate	Phase	Therapeutic Area	Indication	Transgene / Cell type

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Select Private GMCT Companies

Company	Product/ Lead Candidate	Phase	Indication	Transgene(s) / Cell type

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Core Components of a GMCT Therapeutic

Gene-modified cell therapy

Transfer of a functional gene into a cell-based therapy; genetic modification occurs outside the body; modification results in a permanent change in the patient's DNA

Three Core Components

- **Payload:** Gene Controls AND Gene
- **Delivery:** Vector + Cell

Payload

Gene Controls

DNA sequences that regulate the production of the gene

AND

Gene

DNA sequence coding for the production of a protein

Delivery

Vector

Unit that is required to delivery the payload to cells

Nanoparticle, Non-viral, Viral vectors are used for Gene transfer therapeutics

AND

Cell type

Tissue-specific cells removed from the patient which will be genetically modified

Common cell types used include T cells, NK cells and HSCs

Source: MTS analysis

There are Six Principle GMCT Technologies

	1 Chimeric Antigen Receptor	2 T cell Receptor	3 Listeria-based	4 Tumor Infiltrating Lymphocyte	5 Natural Killer	6 Hematopoietic Stem Cell
Payload						
Delivery Method						
Cell Type						
Therapeutic Area						
Select Pure-Play Companies						

Please contact Ravi Mehrotra for the full report
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Source: MTS analysis

Technology #1 – CAR-T cell Technology

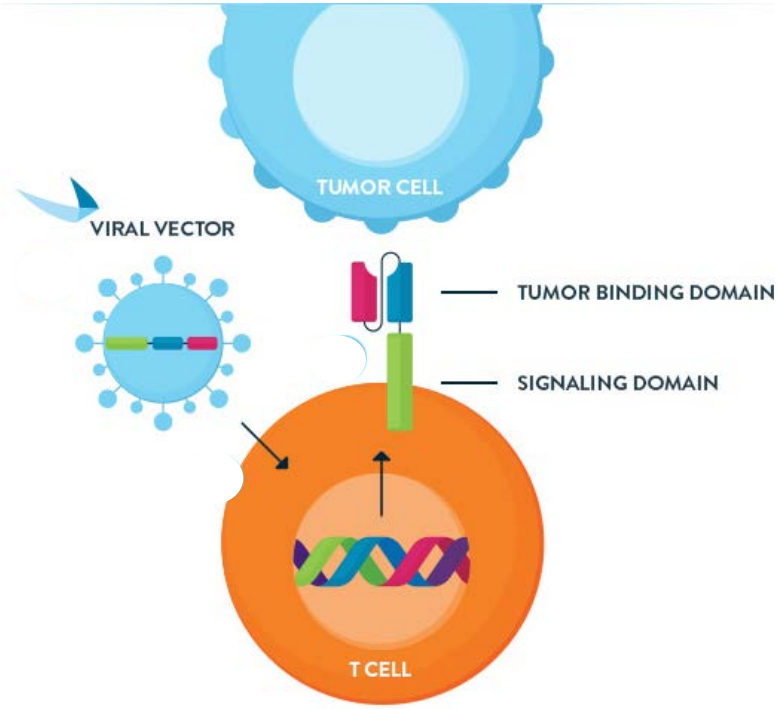
Cellular immunotherapy for liquid tumors

Chimeric antigen receptors (CARs) are fusion constructs composed of the variable binding region domain of the a monoclonal antibody (tumor binding domain) with the activation domain (signaling domain) of the T cell receptor, with additional costimulatory domains

CAR therapy is in development to treat cancer, specifically liquid tumors including lymphomas and leukemias

Rationale for CAR-T cell therapy

- The immune system fails to recognize and kill tumor cells
- Scientists engineer T cells to express a CAR that recognizes a specific tumor antigen DCs present tumor antigens and activate T cells
- CAR-T cells recognize and kill tumor cells



Source: bluebird's website

Technology #1 - Comparison of Select CAR-T Programs

Gene-modified cell technology

Company	Lead Product	Antigen	Off-the-Shelf	Payload Delivery	Phase/ Indication	Originator	Co-Stim Domain	On/Off Switch	Vein-to-Vein Time

Please contact Ravi Mehrotra for the full report
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Source: Company Presentations and filings, MTS analysis

Technology #2 – T Cell Receptor (TCR) Technology

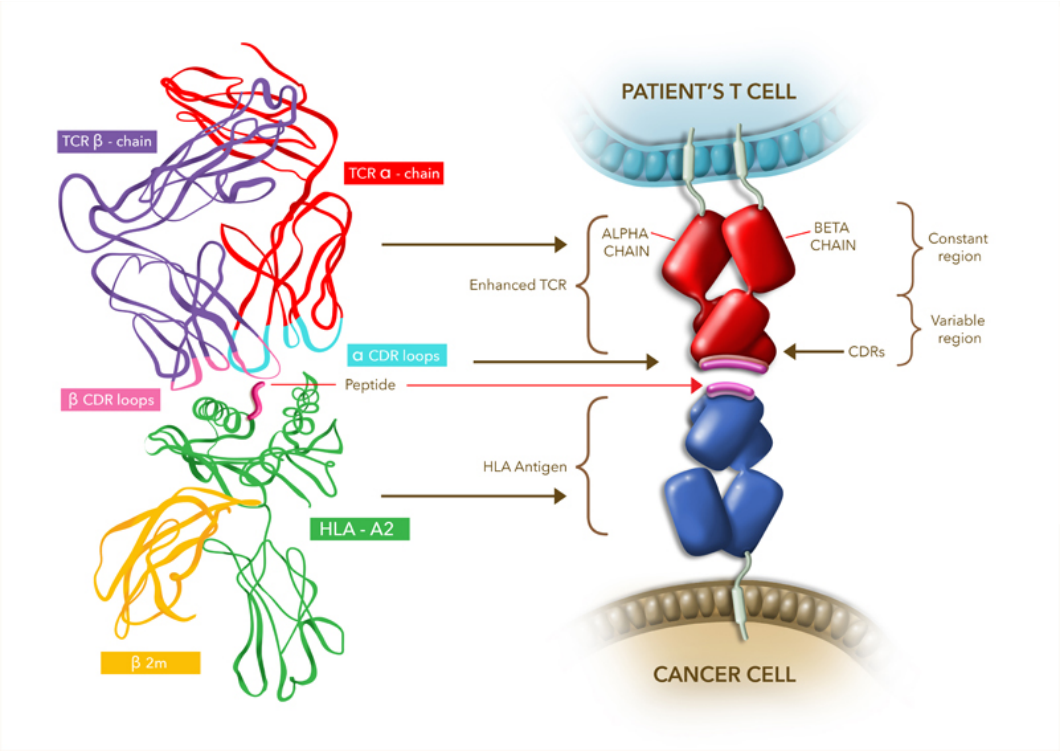
Cellular immunotherapy for solid tumors

T Cell Receptor (TCRs) are constructs composed of the alpha and beta chain of the TCR engineered to target and bind specific cancer peptides presented on the surface of tumor cells

TCR therapy is in development to treat cancer, specifically solid tumors

Rationale for TCR-T cell therapy

- The immune system fails to recognize and kill tumor cells
- Scientists engineer T cells to express a TCR that recognizes a specific cancer peptide-HLA on the surface the
- TCR-T cells recognize and kill tumor cells



Source: Adaptimmune's website

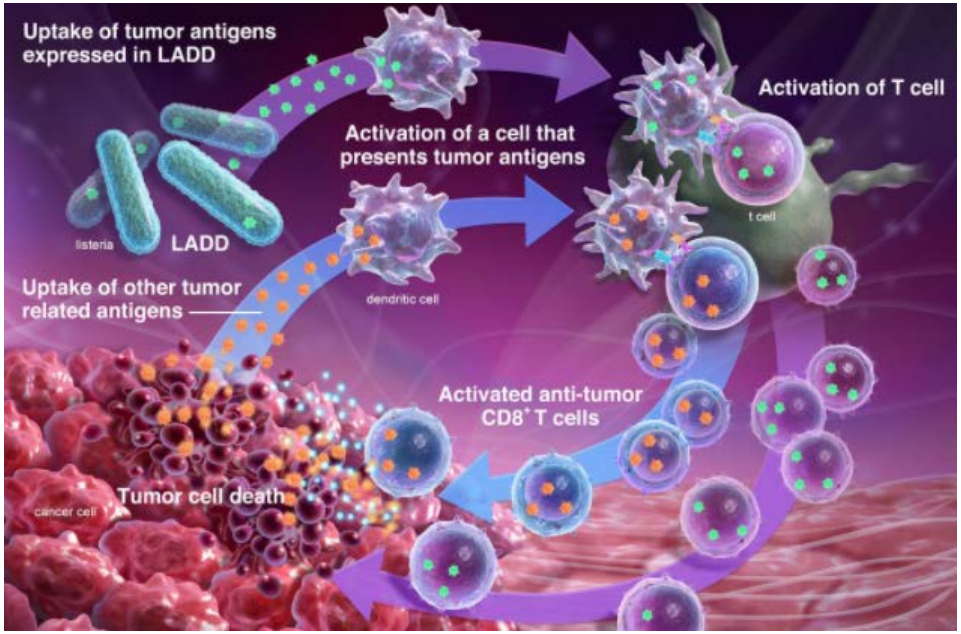
Technology #3 – Lysteria-based Technology

This technology uses a live attenuated Lysteria monocytogenes engineered to express tumor antigens to target dendritic cells (DC) and induce targeted immune responses

Listeria-based therapies are used to treat solid tumors

Rationale for Listeria-based therapy

- The immune system fails to recognize and kill tumor cells
- Scientists engineer Listeria to express tumor antigens and target DC cells
- DCs present tumor antigens and activate T cells
- Tumor specific T cells recognize and kill tumor cells



Source: Aduro's website

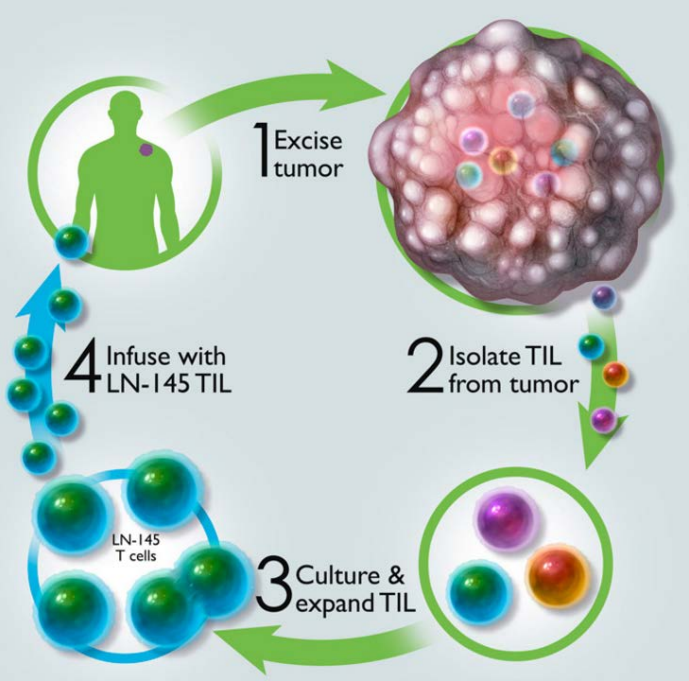
Technology #4 – TIL Technology

This technology uses a patient's own tumor infiltrating lymphocytes (TILs) to attack and kill tumor cells

TIL-based therapies are used to treat solid tumors

Rationale for TIL therapy

- The immune system fails to recognize and kill tumor cells
- TIL cells are isolated from the patient's own tumor following surgical resection
- TILs are expanded to billions in number by simulating them ex vivo away from tumor's immune-suppressing environment
- TIL are then infused back into the patient following a treatment to remove all suppressive influences



Source: Iovance's website

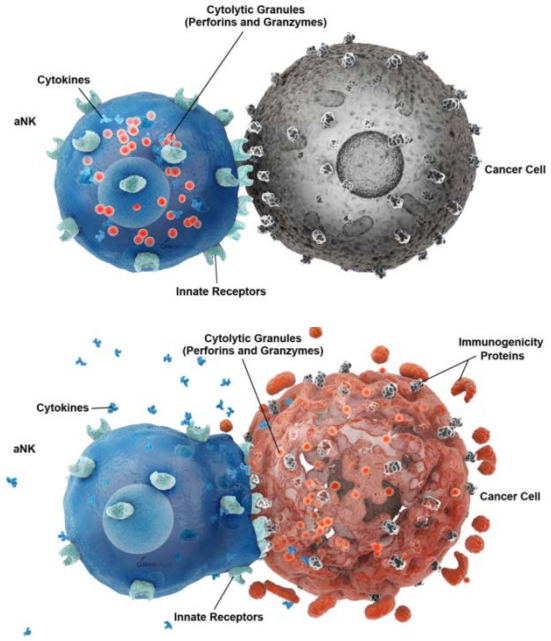
Technology #5 – NK Cell Technology

This technology uses NK cells have the innate ability to rapidly seek and destroy abnormal cells, such as cancer or virally-infected cells, without prior exposure or activation by other support molecules

NK cells are used to treat a broad range of cancers

Rationale for NK cell therapy

- The immune system fails to recognize and kill tumor cells
- NK cells are administered to the patient and become activated when they encounter cancer cell stress ligands
- NK attach to the tumor cell and deposit cell-killing granules into the cytoplasm of the tumor cell
- Cancer cells are killed due to cell membrane digestion and other cell death-causing processes



Source: NantKwest's website

Technology #6 – Genetically-modified HSC Technology

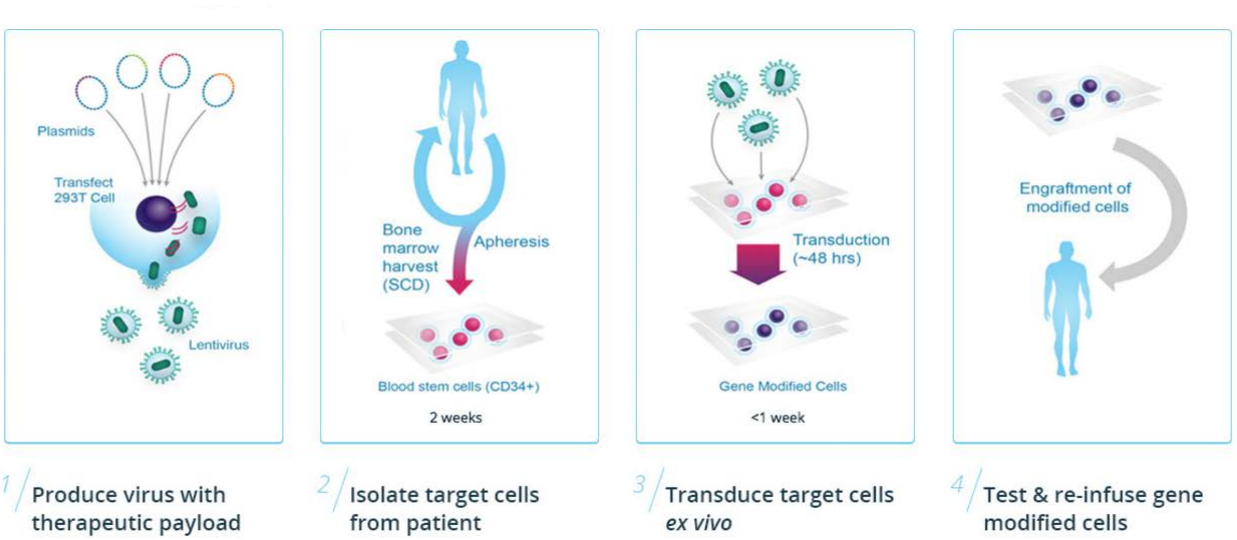
Gene therapy for blood stem cell disorders

HSC therapy involves genetically modifying a patient's own hematopoietic stem cells (CD34+) by adding a functional copy of the gene of interest

HSC therapy is in development to treat a ranged of blood disorders, including sickle cell disease (SCD)

Rationale for HSC therapy

- Patient's carry a mutant gene that prevents the proper production of blood cells
- Patient's HSCs are removed from the body
- A functional gene is transfer into the HSCs outside the body
- Genetically-modified HSCs carrying functional gene are infused into patient



Source: bluebird's website

Key Consideration: Personalized or Off-the-Shelf Therapy?

Personalized (Autologous):

Cell material for personalized therapies is from the patient's own body

Off-the-Shelf (Allogeneic):

Cell material for off-the-shelf therapies is derived from another human being

Personalized **Off-the-Shelf**

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

Considerations for CAR, TCR, TIL and NK Therapy

Obstacles that still need to be addressed before full potential realized

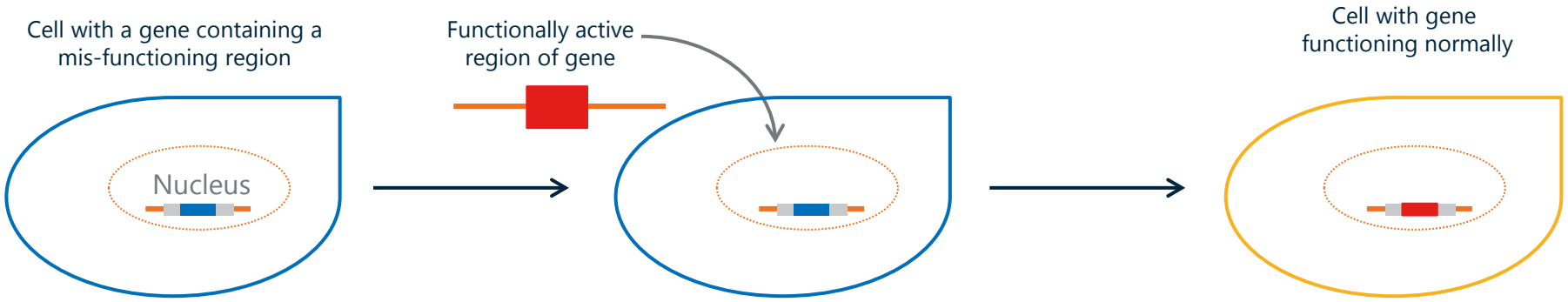
	Considerations	Obstacle	Potential Solutions
Clinical	Immunosuppressive tumor microenvironment	Please contact Ravi Mehrotra for the full report mehrotra@mtspartners.com	
Clinical	Toxicities		
Commercial	Production		
Commercial	Market Opportunity		

Source: MTS analysis

6. Gene editing Technologies

Select Public Gene Editing Companies

Repairing the DNA sequence of an endogenous gene



Company	Mkt Cap ($mm)	Product/ Lead Candidate	Phase	Therapeutic Area	Indication	MoA/Target

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Select Private Gene editing Companies

Company	Product/ Lead Candidate	Phase	Indication	MOA / Target

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: EvaluatePharma as of 11/10/2017, MTS analysis

Core Components of a Gene editing Therapeutic

Gene editing

Repairing or deleting a DNA sequence in an endogenous gene; genetic modification occurs inside the body; modification results in permanent change in patient's DNA

Two Core Components

- **Payload:** Engineered Nuclease OR Nuclease + Oligonucleotide
- **Delivery:** Vector

Payload

Engineered Nuclease

Protein administered to **target and cut** the DNA sequence of a gene of interest

OR

Nuclease

Protein administered to **cut** the gene sequence

Oligonucleotide

Short nucleic acid sequence that targets a nuclease to a specific gene of interest

Delivery

Vector

Unit that is required to delivery the payload to cells

Non-viral and viral vectors are used for Gene editing therapeutics

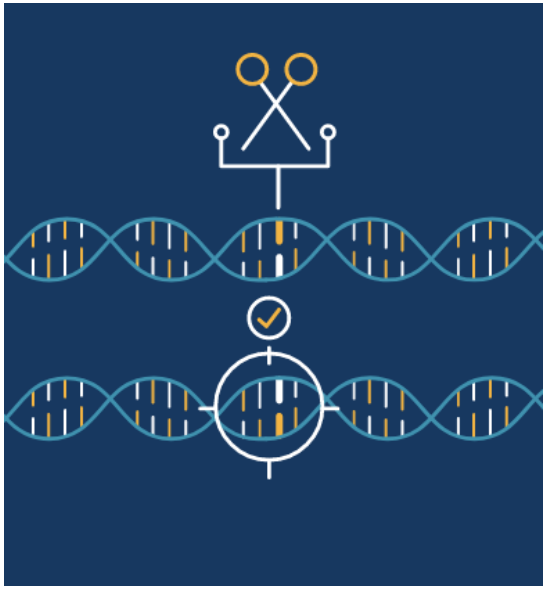
Source: MTS analysis

Three Main Therapeutics Strategies for Gene editing

Disease biology will dictate the strategy used

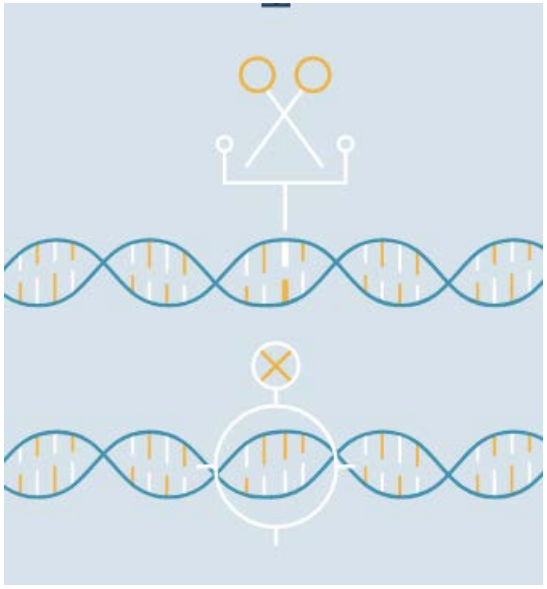
Gene Inactivation

Inactivation is used to prevent the production of a protein. This approach can be used to treat persistent viral infections by inactivating viral genes.



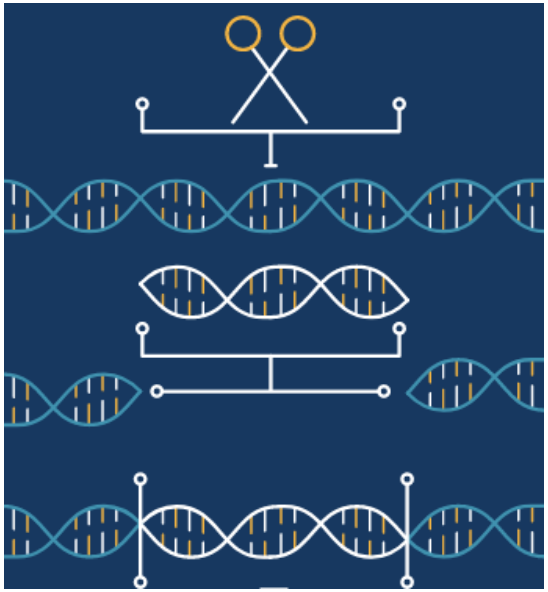
Gene Correction

Correction is used to replace an existing defective protein with a functional one. For example, this strategy could correct CFTR in cystic fibrosis.



Gene Insertion

Insertion is used to add a new protein. This strategy could overcome a genetic defect like hemophilia where not enough functional protein is made



Source: Cellectis' website, MTS analysis

Select Gene Editing Technologies

ZFN

- Sequence-specific restriction enzymes generated by fusing a zinc finger DNA-binding domain to a DNA-cleavage domain (FokI)
- Zinc finger domains can be engineered to target specific DNA sequences and this enables zinc-finger nucleases to target unique sequences within the genome

TALEN

- Sequence-specific restriction enzymes generated by fusing a transcription activator-like effector (TALE) domain to a DNA-cleavage domain (FokI)
- Modification of the TALE domain confers sequence specificity

Meganuclease

- Sequence-specific restriction enzymes that contain the DNA cleavage domain within the DNA binding domain
- MegTALs are hybrid gene editing tools consisting of meganuclease and TALE domain

CRISPR

- CRISPR (pronounced "crisper") stands for Clustered Regularly Interspaced Short Palindromic Repeats, which are naturally occurring sequences found in bacteria
- CRISPR "spacer" sequences are transcribed into short RNA sequences ("CRISPR RNAs" or "crRNAs" or "gRNAs") capable of guiding the system to matching sequences of DNA. When the target DNA is found, Cas9 – one of the enzymes produced by the CRISPR system – binds to the DNA and cuts it

Source: MTS analysis

High Level Comparison of Select Gene Editing Technologies

	ZFN	TALEN	Meganuclease	CRISPR
Ease of Engineering				
Ease of Delivery In vivo				
Payload				
Target Recognition				
Recognition site				
Delivery method				
Select Companies				

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

Nuclease-Free Gene editing Technology

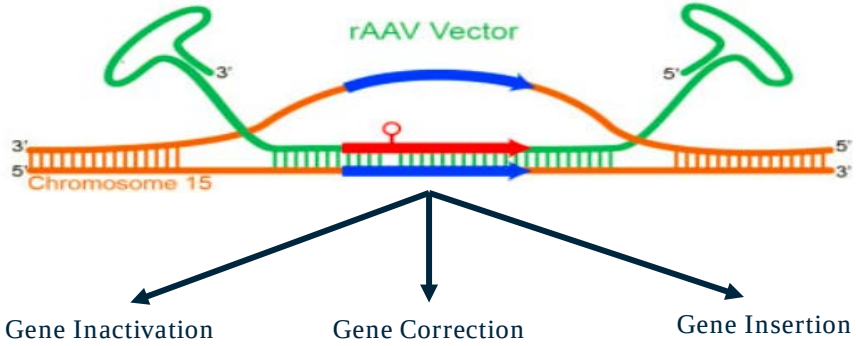
Next-Gen Approach

Nuclease-free gene editing is a novel technology which exploits the natural ability of cells to repair DNA sequences through a process known as homologous recombination

This technology requires the single-stranded vector genome of rAAV, which when modified is able to pair with homologous DNA sequences within the target gene of interest

Nuclease-free technology can be used for all three therapeutic editing strategies

- Gene inactivation
- Gene correction
- Gene insertion



Source: MTS analysis

High Level Merits and Considerations

	Merits	Considerations
ZFN/ TALEN/ Meganucleases		
CRISPR		
Next-Gen Editing		

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

Appendix

Viruses Effectively Delivery Therapeutic Payloads to Cells

Ideal viral vectors for Gene transfer exhibit high reproducibility of virus production and efficiently/selectively target cells in the tissue of interest

All viruses attack their hosts and introduce their genetic material into the host cell as part of their replication cycle

> The viral genetic material contains basic instructions of how to produce more copies of the virus, hijacking the body's normal production machinery to serve the needs of the virus

Some types of viruses insert their genes in the host's genome, meaning they can be engineered to stably introduce genetic materials into cells

> Gene transfer employing viruses remove the viral genes from the virus and replace them with a therapeutic payload

Source: MTS analysis

Tissue / Cell Specificity for Select rAAVs

Tissue	rAAV1	rAAV2	rAAV4	rAAV5	rAAV6	rAAV7	rAAV8	rAAV9

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

rAAV Gene transfer Programs in the Clinic

Sorted by Indication

Primary Indication	rAAV	Product	Company	Phase	Payload

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: Clinicaltrials.gov; EvaluatePharma

Manufacturing Capabilities of Select Companies

Company	Infrastructure	cGMP Compliant	Producer Cell Type	Viral Vector

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

Select CDMO/CROs with Gene and Cell Therapy Capacity

Company	Ticker	Location	GMP	Capabilities	Products

Please contact Ravi Mehrotra for the full report
mehrotra@mtspartners.com

Source: MTS analysis

Introduction to MTS

MTS Health Partners Overview

Investment Banking

- **Privately owned, independent firm, founded in 1999**
- **Aligned strategic and financial advisory services to healthcare companies of all sizes, from global corporations to venture-backed businesses**
- **Extensive experience across a broad range of client and transaction types**
  - Public and private; for-profit and not-for-profit
  - Mergers and acquisitions, restructurings, private placements, IPOs, structured debt financings and general strategic advice
- **Partners averaging 20 years of healthcare experience**
- **Offices in New York, San Francisco, São Paolo and Tokyo**

Life Sciences

- Pharmaceuticals
- Specialty Pharma
- Generics
- Biotechnology
- Orphan / Rare Disease
- Medical Devices / Diagnostics

Healthcare Services

- Managed Care
- Hospitals/Outsourced Services
- PBMs & Pharmacy Services
- Dialysis
- Post-Acute Facilities (SNF, IRF, LTACH)
- Home Healthcare/Hospice
- Healthcare Technology
- Clinical Laboratories
- Healthcare Distribution/Supply
- Pharma Services

Advantages of a Partnership with MTS Advisory Team

Bulge Bracket Capabilities with a Boutique Approach

Distinguished by experienced, attentive and independent counsel in the context of long-term relationships

Aligned

- Economics – compensation model that transcends annual Wall Street bonus cycle
- Culture – private equity mentality allows for **investor-focused perspective**
- "Success" – defined through **achievement of client goals** rather than mere transaction execution

Independent

- **Stability** of franchise and execution in turbulent banking environment
- **Unencumbered by balance sheet conflicts** or commoditized financing solutions
- Advisory team **solely focused on meeting client objectives** without impact from other parts of the organization

Attentive

- **Boutique environment** – ensures personal commitment and focus
- **Team of over 40 professionals**, larger than many bulge-bracket healthcare teams
- **Staffed, resourced similarly to bulge-bracket banks**

Long-Term Partnership

- **Long-term relationships** rather than short-term transactions
- Translates to **unbiased and objective** evaluation and advice

Experienced

- **Senior personnel** – decades of healthcare-focused banking experience
- **Extensive** strategic, operational, financial and capital markets expertise
- **Creative solutions** rather then the "standard" banker playbook

Healthcare-Focused

- Unparalleled network provides **broadest reach** of any healthcare advisor
- **In-depth knowledge** of healthcare industry, trends, transactions, decision-makers and their personalities

Large Firm Scale with Boutique Focus

Senior Life Sciences Team

Mark Epstein
Managing Partner

Completed over 100 private financings for clients raising over $5 billion in private capital

Managing Director / Co-Head Bank of America Private Equity Placements

Prior to BofA, VP and co-head of Direct Private Equity Placements at Merrill Lynch

Andrew Weisenfeld
Managing Partner

Has worked on approximately $50 billion in M&A deal volume across a range of advisory transactions

Managing Director/ Co-Head of BofA Life Sciences Investment Banking

Prior to BofA, Managing Director and Head of Healthcare M&A at JPMorgan

Peter Collum
Partner

Has worked on over $20 billion in M&A deal volume

Director, Bank of America Healthcare Investment Banking from 2003-2009

Prior to BofA, Technical Development Engineer at Hoffmann-La Roche

Andrew Fineberg
Partner

Prior to MTS, Andrew led the Financing Group at Torreya Partners, LLC, a boutique investment bank

Prior to Torreya Partners, Andrew worked at Cowen and Company, a global investment bank as Vice President in the Private Placement Group

Sooin Kwon
Partner

Has worked on over $20 billion in equity and M&A deal volume

Director, BofA Healthcare Equity Capital Markets

Prior to BofA, Equity Research at Merlin Biomed Asset Management and UBS

Worked in Consulting: market research and forecasting

David Low
Partner

Previously, a partner in Lazard's Life Sciences Group, which he joined in 2002

Long career in advising on M&A and equity financing strategies for life sciences companies globally

Worked at Lehman Brothers from 1987-1996 and JPMorgan from 1996 through July 2002

Ravi Mehrotra
Partner

Has nearly two decades of healthcare equity research experience

Previously, at Credit Suisse for 11 years and most recently held the title Global Head of Biotechnology Equity Research

Worked at Cowen 1999-2004 as European head of Biotechnology and Deutsche bank 1997-1999

Entire MTS Team Solely Focused on the Global Healthcare Industry

12 Partners/Senior Advisors

9 Directors / Vice Presidents

29 Associates / Analysts

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