# VivoVec: Our proprietary technology platform for in vivo gene delivery to T cells.

VivoVec™ particles are biologically-generated lipid nanoparticles ~100 nm in size that we believe represent the most sophisticated lipid nanoparticles in development for biotechnological application. VivoVec particles comprise an outer lipid envelope surrounding an approximately 10 kb RNA sequence encased in a protein capsid shell. Within that shell are incorporated additional components that enable integration of the payload information into the host cell genome. VivoVec particles serve solely as information delivery devices for human T cells - no component of the particle is incorporated intact into a target cell. Rather, the information in the RNA component is converted into a DNA fragment that is integrated into the target cell genome.

## VivoVec mechanisms of action

VivoVec particles possess multiple mechanisms of action:

1. **T cell binding:** The surface of VivoVec particles is comprised of multiple ligands for proteins located on the surface of T cells, enabling VivoVec particles to mimic the interactions of the natural T cell activation process mediated by antigen presenting cells. The interaction between T cells and antigen presenting cells comprises a complex structure designated the "Supra Molecular Activation Complex" or SMAC. We thus term our 2nd generation surface engineered particle surfaces as "LentiSMAC™" technology. Both 1st generation and LentiSMAC VivoVec particles bind T cells as the primary target cells for gene delivery, passing along the genetic payload, which we've termed VivRNA.

2. **T cell activation:** T cells must be in an appropriate metabolic state to support the biochemical events required for successful reverse transcription and genomic integration. Both 1st generation and LentiSMAC VivoVec surface engineering are designed to drive T cells out of a resting state into one which supports these events. LentiSMAC engineering accomplishes this efficiently while also helping to direct T cell differentiation down memory pathways that we believe will enhance the therapeutic attributes of VivoVec-based products.

3. **Genome integration:** The information encoded in the VivRNA payload is copied into a piece of DNA through a complex multi-step mechanism. The DNA fragment generated by reverse transcription is delivered to the target cell nucleus and freed from the capsid shell where it then binds to chromatin and is integrated into the genome of the target cell. During this process, all components of the viral particle are effectively degraded by host cell disposal mechanisms leaving only the information that was encoded in the original RNA payload, now copied into a piece of DNA, in the host cell.

4. **Expression of the payload cassette and re-programming of cellular function:** Once the payload cassette is integrated into the target cell genome, the promoter included in the payload becomes active, resulting in the expression of proteins that modify the function of the T cell to enhance its cancer fighting activity.

## VivoVec is based on 3rd generation lentiviral vector technology

The VivoVec platform is built on 3rd generation lentiviral vector gene delivery technology. Lentiviral vector technology is well known among lab researchers as the most efficient way to introduce genes into primary cells of all types, including T cells. This 3rd generation lentiviral technology was chosen as the foundational technology for VivoVec because it satisfies five key criteria:

1. **In vivo-compatible gene delivery** platform technology that enables GMP drug products to be manufactured at scale
2. **Enables efficient, specific delivery** to T cells and/or other immune cells with cancer-fighting capability relative to non-immune tissues
3. **Provides stable/durable expression** of the target gene through multiple cycles of T cell division
4. **Well-understood mechanism of action** with the potential for continued advances in performance
5. **Established history** of safe application in humans

These technical criteria were derived from our deep experience developing engineered cell products for human translational application, including products derived from hematopoietic stem cells and T cells. The selection of lentiviral vector technology as the best platform among those evaluated to meet these criteria reflects our analysis of the technical performance of multiple alternative platforms (summarized in the table below), as well as a laser focus on what cancer patients and their physicians need: safe, effective, practical, and affordable therapies.

**The following table contrasts lentiviral vector technology against the current class of in vivo gene delivery platforms:**

| Attribute | Synthetic LNP + RNA | Synthetic LNP/ retrotransposon | Synthetic LNP + DNA | Adenovirus | AAV | Lentiviral vectors |
|---|---|---|---|---|---|---|
| **Scalable CMC** | (++) | (+) Multiple RNAs required for retrotransposon activity | (-) Multiple DNAs + DNA if transposase or CRISPR-targeted | Yes, depending on dose, but not if in combination with e.g., RNA-encoded DNA integrating enzyme transposase/ CRISPR | Depends on dose. | **Yes,** more than two decades experience with lentiviral vector CMC |
| **Engineerable surface properties** | Yes, but limited by lipid properties required for endosomal escape | Yes, but limited by lipid properties required for endosomal escape | Yes, but limited by lipid properties required for endosomal escape | Yes, but no current capsids with highly specific delivery properties | Somewhat, but no current capsids with highly specific delivery properties | **Yes** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Immune-stealth payload** | If modified RNA. | LNP immunogenicity depends on composition. RNA/DNA hybrids can be highly immunogenic depending on subcellular location | LNP immunogenicity depends on composition. DNA payload can be immunogenic depending on packaging. | Highly immunogenic capsid and DNA payload | Immunogenic capsid and DNA payload | Protein encapsulated RNA genome is protected from cytosolic immunosurveillance |
| **Efficient T-cell delivery** | (+) | (+) | (+) | (++) | (+) | **(+++)** Gold standard |
| **Specific T-cell Delivery** | With appropriate lipids and appended surface ligands | With appropriate lipids and appended surface ligands | With appropriate lipids and appended surface ligands | (-) Possibly with appropriate knob | No | **Yes**, with appropriate fusion glycoprotein and surface ligands |
| **DNA double strand break** | No DSB or integration, but short duration expression | No | No if transposase. Yes if CRISPR/other editing agent | No if transposase. Yes if CRISPR/other editing agent | No | **No** |
| **Specific genomic integration site** | No integration | Not currently. Also no current systems with high integration efficiency and/or high expression | Not for current transposons. No current technology with high integration efficiency and high expression | Not alone. No current technology with high integration efficiency and high expression | No | **Semi-random, with a predilection for introns.** However, notable for 20-year history of safe clinical use in human *ex vivo* gene therapy |
| **Durable expression** | No | Maybe, but integration of many partial cassettes with current technology | No unless transposase co-delivery | No, unless transposase co-delivery | No, episomal cassette | **Yes**, integrated cassettes are all full length and passed to daughter cells |

Our analysis establishes that lentiviral vector technology is differentiated from other technologies in the following critical attributes:

- **Lentiviral vectors have been manufactured at scale for more than 20 years for clinical use in ex vivo gene delivery:**
  - The lentiviral manufacturing process can be readily scaled with improved yield in a suspension format producing a final drug product suitable for direct administration to patients.
  - Lentiviral vectors have been used in the clinic for ex vivo gene delivery to human T cells for more than 20 years with **no** adverse events related to the vector technology.

- **Lentiviral vectors have protein encapsidated RNA genomes:**
  - Capsid protomers self-assemble to form the viral capsid (effectively a capsule) that shields the RNA from immunosurveillance and protects it from immune-mediated targeting and destruction as the encapsidated genome travels from cytosol to nucleus.

- The viral capsid shields a critical step in lentiviral gene delivery— reverse transcription— from immunosurveillance. This step involves copying information from the original RNA genome of VivoVec particles into a DNA fragment (the form that is integrated into the target T cell's genome). During this process, the capsid shields the formation of highly immunogenic RNA/DNA hybrids that would otherwise be susceptible to targeting and degradation by endogenous cellular processes.

- **The mechanism through which lentiviral vectors integrate their genetic payload cassette into the genome of T cells is well understood:**
  - Lentiviral transduction results in stable integration of a DNA cassette into the genome of target cells that is passed on to all progeny cells.
    - The mechanism of cassette integration by lentiviral vectors has an extremely high degree of fidelity in that essentially every cassette integrated into the genome of a T cell is full length. As such, the therapeutic gene is expected to be delivered in its active form every time it is integrated into a T cell genome.
    - An attribute of lentiviral integration known as position effect variegation allows T cells with optimal CAR expression to be naturally selected from a large transduced population. This selection potentially increases the efficacy of therapeutic T-cells toward patient-specific tumor properties.
  - **NO** DNA double strand breaks are created in the process of integrating the DNA version of the lentiviral vector payload cassette.
    - In contrast, all current CRISPR-based approaches to gene insertion generate double strand breaks.
    - Double stranded breaks are prone to repair via mechanisms that generate translocations, a highly deleterious type of genetic alteration. Thus, lentiviral vectors have a potentially significant safety advantage over CRISPR-based approaches.
  - There is substantial literature supporting the capacity of lentiviral vectors to safely deliver gene cassettes to T cells without causing insertional oncogenesis.

- **The surface properties of lentiviral vectors are readily engineerable and can be iteratively modified to achieve improved particle performance.**
  - Umoja scientists have developed proprietary methods to modify the surface of lentiviral particles to enable them to efficiently deliver genes to T cells in vivo. These proprietary methods of surface engineering comprise our VivoVec technology platform.
  - VivoVec particles display T cell binding ligands that endow the particles with unique T cell binding properties intended to render T cells susceptible to efficient gene delivery.
  - We have developed 2$^{nd}$ generation surface engineering approaches to promoting physiologic particle-T-cell interactions which we term LentiSMAC.

## VivoVec particle manufacturing

VivoVec particles are produced using 3rd generation packaging systems for lentiviral vectors that have been developed, matured, and safely used in human clinical application for over 20 years, that are combined with our proprietary methods for VivoVec particle surface engineering. The 3rd generation lentiviral vector packaging technology applies a deep knowledge of the life cycle of human immunodeficiency virus (HIV) **(Figure 1)**.

**Figure 1**: Life cycle of human immunodeficiency virus

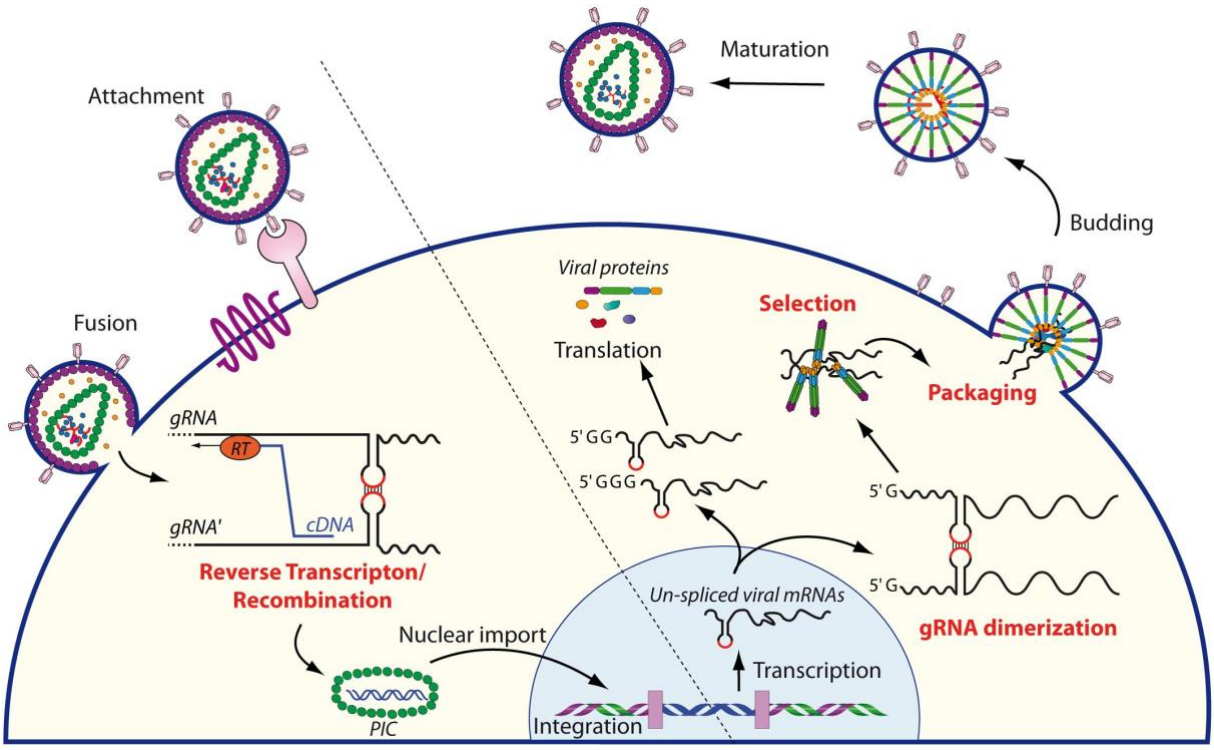


*Figure 1 Legend: HIV viral particles replicate by binding to T cells through their natural spike protein, gp120. This binding causes them to fuse with the membrane of the T cells, allowing the capsid to enter the cytoplasm. The capsid transits across a network of proteins to the nuclear membrane where it binds to nuclear pores and eventually transits into the nucleus of the cell. During the journey from cell membrane to nucleus, the information in the RNA genome is converted into a piece of DNA through a process known as reverse transcription that is carried out by the enzyme reverse transcriptase (RT), a type of RNA-dependent DNA polymerase. Once a full-length copy of the genome has been generated in DNA form, this DNA fragment is integrated into the genome of the host cell by HIV IN, a type of integrase. Once integrated, the genome is initially dormant, but upon activation, the genome is transcribed into RNA copies of the HIV genome and protein components of the HIV particle. These components spontaneously assemble into capsid-encased genomes which are able to bind to the underside of the cell's plasma membrane and eventually bud off the cell as de novo generated HIV particles.*

To adapt the lentiviral life cycle for generation of vector particles that are safe for use as information delivery devices, elements of the HIV genome that are required for viral replication are removed — including all structural components and enzymes that enable replication of the HIV genome or generation of HIV particles — from the RNA that is normally packaged into a lentiviral particle. The space created in the RNA by removing these genes is filled with new genes encoding information intended to reprogram the function of the T cell to enhance its cancer fighting properties. VivoVec particles that contain these synthetic RNAs are unable to generate new particles, and thus act as one-time delivery devices for integrating new information — for Umoja's purposes, new gene expression programs — into target cells.

To produce VivoVec particles, our engineers have developed cells that separately express the components required to make lentiviral particles as well as the modified RNA genome **(Figure 2)**. This modified RNA genome only encodes the necessary information to be delivered to reprogram T cells to enhance their cancer fighting potency – it cannot make any native lentiviral proteins. By separating the expression of the structural protein components required to form lentiviral particles from the genome that is packaged, we can generate VivoVec particles that function solely as safe and efficient devices for in vivo gene delivery to T cells.

**Figure 2:** VivoVec packaging process

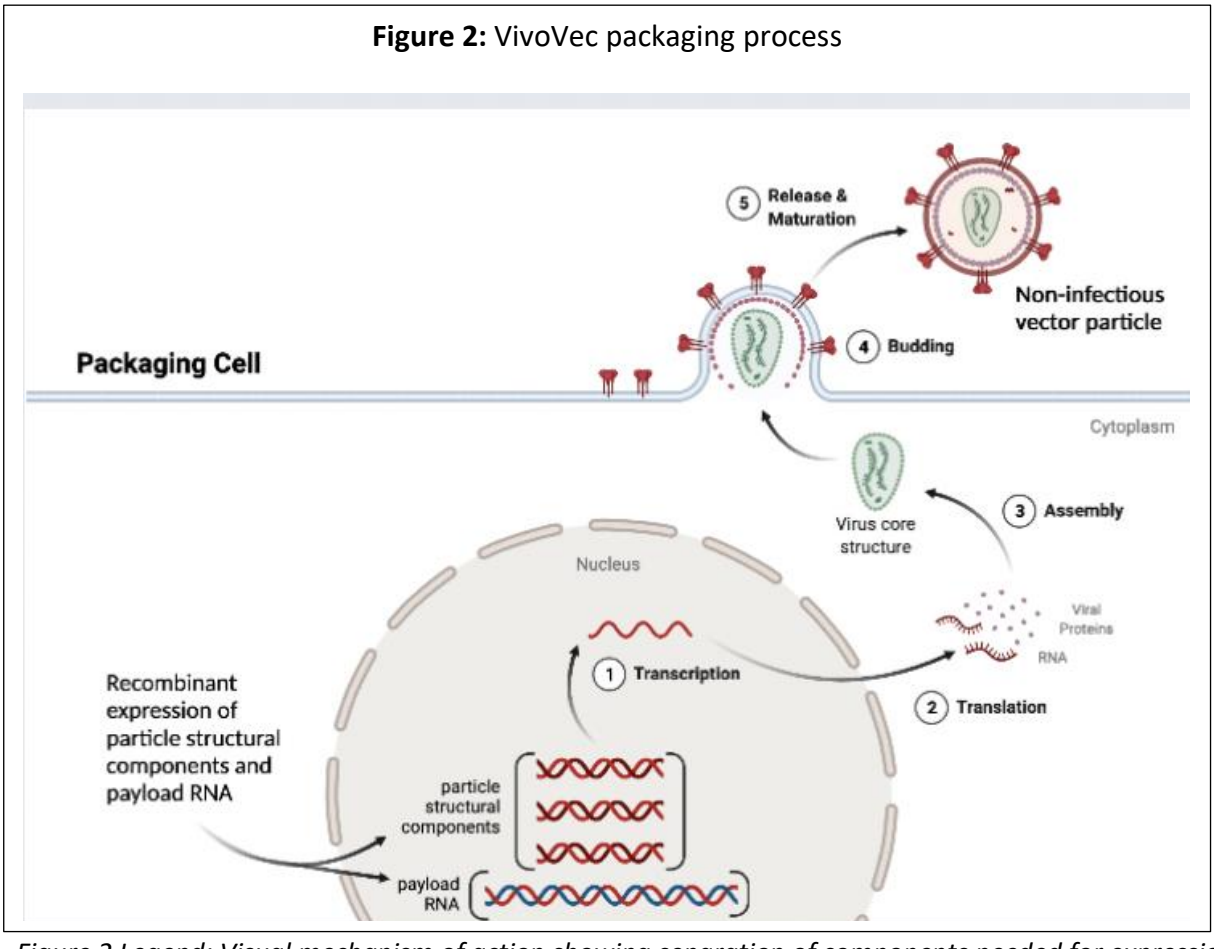


*Figure 2 Legend: Visual mechanism of action showing separation of components needed for expression of VivRNA, the genetic RNA payload delivered by VivoVec particles, and components needed for*

*packaging VivRNA into lentiviral particles sufficient for in vivo delivery of the payload to T cells. This helps ensure that VivoVec particles cannot replicate on their own, permitting controlled therapeutic dosing. Expressed recombinant genetic instructions (shown in steps 1 and 2, cannot be packaged into viral particle without being grown in specialized packaging cells (steps 4 and 5) which are only used in Umoja's controlled cell therapy manufacturing facilities and do not exist as part of the natural repertoire of human cells. Adapted from "HIV Replication Cycle", by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.*

## The VivoVec manufacturing process

A critical additional aspect of Umoja's VivoVec technology platform is the development of a manufacturing process capable of producing drug-quality vector particles at a scale sufficient to provide VivoVec drug products to any patient that would potentially benefit from a product incorporating VivoVec technology.

Umoja scientists have developed specialized cells for VivoVec production which are handled in advanced large scale automated cell culture and purification vessels to achieve the scale necessary for generation of thousands of doses of a VivoVec drug product **(Figure 3)**. Our engineers have incorporated data monitoring and capture technologies to closely monitor the expansion, health and VivoVec particle production by these cells in real time, allowing us not only to consistently obtain optimized manufacturing runs, but also to learn from every run.

**Figure 3:** Large Scale VivoVec Manufacturing Process

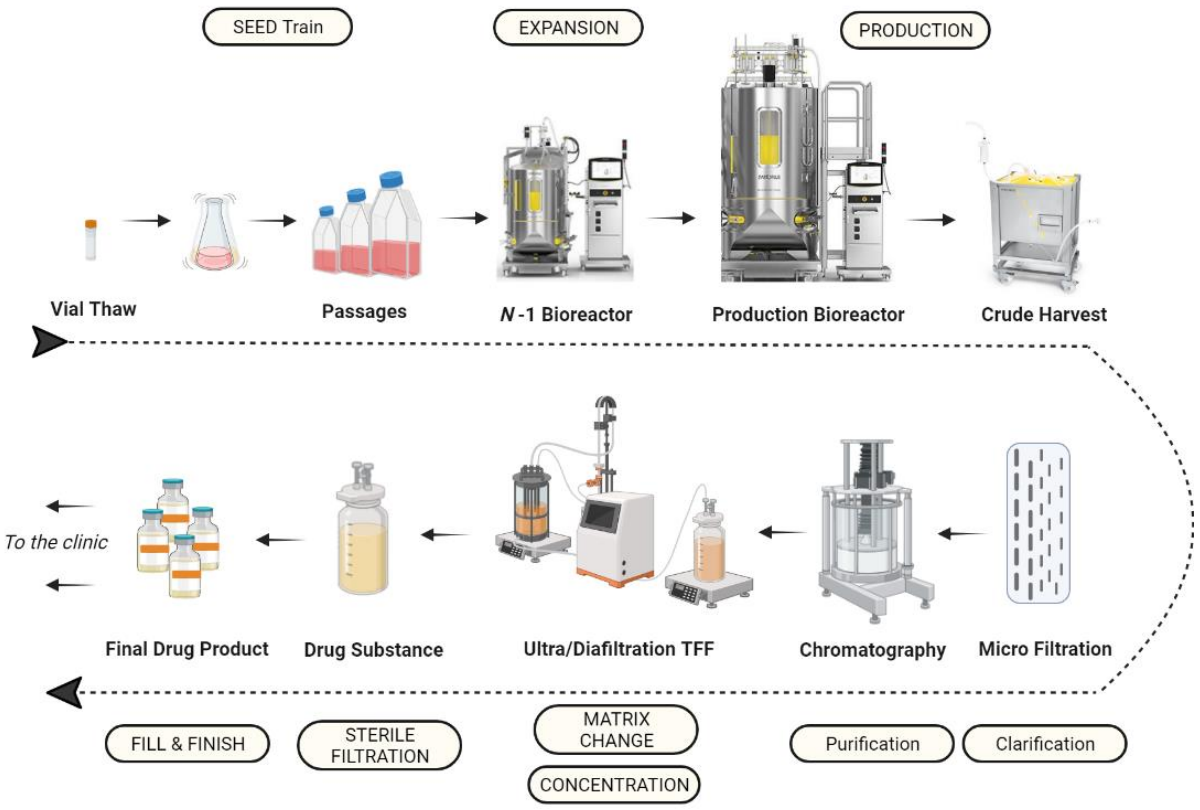


*Figure 3 Legend: Depiction of Umoja's proprietary scalable cGMP manufacturing process for VivoVec gene therapy particles. Optimization of manufacturing is a critical early step for development of biologic drugs like gene therapies where in many ways, the process is a critical aspect of the product. Umoja researchers have developed methods for mass-production of consistent batches of VivoVec therapeutics. Created with BioRender.com. Bioreactor and harvest images from [https://www.sartorius.com/en](https://www.sartorius.com/en).*

Manufacturing of VivoVec drug products for all of our, and our partners, early-stage clinical trial work will take place in our Louisville, CO manufacturing facility **(Figure 4)**. We believe it is critical to control every aspect of the process through which we generate VivoVec particles, in order to achieve optimal quality and potency.

**Figure 4:** Umoja Vector Particle Manufacturing Facility in Louisville, CO


*Figure 4 Legend: Groundbreaking at Umoja's cGMP-grade manufacturing facility in Louisville, CO took place in 2021 and construction is expected to be completed and the facility fully-on line for production of clinical-grade supply in early 2023.*