bluebird bio, Inc. (BLUE) — Overweight

Taking Flight With Gene Therapy. Initiating At OW

CONCLUSION

We are initiating coverage on BLUE, one of the pioneers in gene therapy. The company has an evolving platform which currently leverages its capabilities with lentivirus vector, which can uniquely target dividing cells and handle large transgenes (for larger proteins). BLUE's lead clinical program is Lenti-D which appears to have established proof of concept in early clinical testing and is now in a Phase II/III clinical trial. LentiGlobin is an earlier stage clinical gene therapy product for beta-thalassemia and sickle cell anemia, with new data on two patients being presented this weekend at the EHA conference. Beyond these clinical programs, the gene therapy arena offers a vast array of opportunity, and companies such as BLUE are just in the early stages of unlocking the potential of this exciting platform. Our PT is $34.

- **CCALD the tip of the iceberg:** Accurately diagnosing this disease can be difficult, but with the growing adoption of newborn screening, we believe the diagnosis and treatment paradigm will be transformed. As such, we model Lenti-D achieving 60% penetration in CCALD, at a price of $1.3M, and peak W/W revenue of $123M in 2020.

- **Beta thal and sickle up next:** BLUE has already reported a strong vector copy number update which bodes well for a favorable clinical effect update this weekend. We are optimistic this datapoint will help unlock value for this program, but regardless of the results we believe the long-term outlook for the company is strong. This weekend represents a modest binary event for the company, but one which we're comfortable stepping in front of given downside support to shares from other programs and a high likelihood of having a positive update.

- **Addressing mutagenic transformation risk:** BLUE has characterized the insertion site for lentivirus vs prior attempts in the field using gamma-retrovirus. It is clear that lenti's propensity to integrate into proto-oncogenic sites is substantially lower (likely negligible), and positive outcomes with patients treated to date support that. If it turns out leukemic transformations are seen with longer follow-up, we believe the CCALD program may still be viable given the limited alternatives, and BLUE could further optimize lentivirus either for non-integration or with addition of a suicide gene. These or other modifications may represent new opportunities for BLUE to pursue regardless as the gene therapy field advances.

- **Thoughts on the stock:** BLUE is among a handful of leaders/opportunities in emerging gene therapy space and has unique lentivirus capabilities. While there is active investor debate over who the 'winner' is, we believe the field is vast enough to accommodate multiple winners.

RISKS TO ACHIEVEMENT OF PRICE TARGET

BLUE or the gene therapy field may face development or regulatory setbacks.

COMPANY DESCRIPTION

BLUE is one of the pioneers in gene therapy.

PRICE: US$25.27
TARGET: US$34.00
DCF through 2022 using 11% disc rate, 8% terminal growth & 36x terminal multiple.

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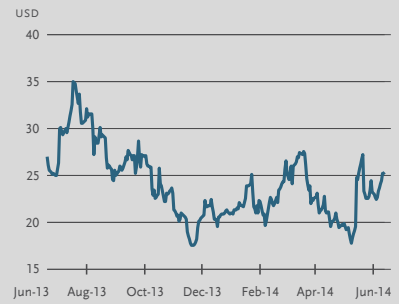
Changes	Previous	Current
Rating		Overweight
Price Tgt		US$34.00
FY14E Rev (mil)	—	24.3
FY15E Rev (mil)	—	21.0
FY14E EPS	—	(1.74)
FY15E EPS	—	(1.84)

52-Week High / Low	US$36.25 / US$17.00
Shares Out (mil)	24.5
Market Cap. (mil)	US$619.1
Avg Daily Vol (000)	236
Net Cash Per Share	US$7.80
Yield	0.00%
Fiscal Year End	Dec

Price Performance - 1 Year



Source: Bloomberg

YEAR	REVENUE (m)						EARNINGS PER SHARE ( )					
	Mar	Jun	Sep	Dec	FY	FY RM	Mar	Jun	Sep	Dec	FY	FY P/E
2013A	1.1	6.3	6.4	6.4	20.2	30.6x	(19.94)	(2.13)	(0.26)	(0.34)	(2.02)	NM
2014E	6.3A	6.0	6.0	6.0	24.3	25.5x	(0.44)A	(0.44)	(0.43)	(0.43)	(1.74)	NM
2015E	—	—	—	—	21.0	29.5x	—	—	—	—	(1.84)	NM

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bluebird bio (BLUE): Snapshot

- **Leader in lentivirus-based gene therapies treating ultra-rare diseases, with the potential to have one of the first gene therapies approved in the US (See page 46).**
  - BLUE has access to one of the largest lentiviral vector patent estates (from Cell Genesys).
  - BLUE's therapies have the potential to cure rare, monogenic inherited diseases through a single administration, potentially reducing the long-term healthcare costs assumed by patients, payors, and providers.

- **By using the patient's own cells to treat diseases, BLUE is improving the existing practice of transplanting cells from a donor, which already has proof-of-concept in the diseases BLUE is looking to cure.**
  - BLUE is taking a modified approach to allogeneic hematopoietic stem cell transplant (HSCT)by making use of the patient's own cells, instead of a donor's cells, which eliminates the risk of graft-versus-host disease. Ultimately, we expect BLUE's approach to replace allogeneic HSCT and be used in those cases where allogeneic HSCT is not applicable (**See page 29**).
  - HSCs differentiate into a variety of cell types, so BLUE can easily expand its gene therapy platform with little additional investment.
  - Infrastructure is in place for BLUE's approach, since the administration of BLUE's therapies is consistent with existing stem cell transplant practices.

- **Significant upside potential offered by CELG partnership to develop CAR-T cell therapies for hematologic malignancies/solid tumors as well as expansion of gene therapy platform (See pages 64-68).**
  - Offers potential to expand gene therapy beyond ultra-orphan patient populations, and enables BLUE to remain competitive in the constantly evolving field of gene therapy.

BLUE: Company Description

bluebird bio (BLUE) is focused on the development of gene therapies for life-threatening genetic and orphan diseases. The company employs lentiviral vectors to deliver its gene therapies and currently has 2 clinical-stage programs in development. The most advanced pipeline candidate, Lenti-D, recently entered into a Phase 2/3 trial (ALD-102 or the "Starbeam Study") for the treatment of childhood cerebral adrenoleukodystrophy (CCALD). BLUE plans to conduct an observational study (ALD-103) of CCALD patients treated by allogeneic hematopoietic stem cell transplant (HSCT). The second pipeline candidate, LentiGlobin, is currently in clinical trials for the treatment of hemoglobinopathies– beta thalassemia (BT) and sickle cell disease (SCD). LentiGlobin is in a Phase 1/2 study (HGB-205) in France for the treatment of BT and SCD. A second Phase 1/2 trial (HGB-204 or the "Northstar Study") with LentiGlobin has been initiated in the US for the treatment of BT. The company plans to initiate a Phase 1/2 study (HGB-206) with LentiGlobin in the US during 2H14 for patients with SCD. Finally, BLUE has partnered with CELG in the development of a chimeric antigen receptor-modified T cell (CAR-T) program for oncology.

BLUE is supported by a strong IP portfolio, related to lentiviral vector use and development, as well as significant funding from investors and pharmaceutical companies. During its IPO in June 2013, the company raised $116M, which is expected to fund R&D (see breakdown below), SG&A, potential future development programs, as well as in-licensing or acquiring complementary gene therapy businesses, technologies, or products. **BLUE has ~$200M of cash on hand, and with approximately $50-70M of operating expenses per year, the company has enough to fund current operations through at least the end of 2015.**

- $11.8M to evaluate the safety and efficacy of the Phase 2/3 trial (ALD-102) for Lenti-D in CCALD.
- $12.7M for the Phase 1/2 trial (HGB-204) in the US for LentiGlobin in BT.
- $2.5M for the Phase 1/2 trial (HGB-205) in the EU with BT and SCD.

BLUE: Our Investment Thesis

1. **BLUE has significantly de-risked pipeline programs, since proof-of-concept has been achieved in CCALD, SCD, and BT with hematopoietic stem cell transplantation (HSCT).**
   - Patients with CCALD, SCD, and BT rely upon HSCT to effectively manage their diseases. Although outcomes improve with allogeneic HSCT, BLUE's gene therapy + autologous hematopoietic stem cell approach is a winning combination which helps eliminate many of the risks associated with allogeneic HSCT and gets these patients closer to being cured.

2. **The use of lentivirus as the viral vector may offer benefits that can outweigh the potential risks.**
   - Lentivirus can accommodate larger genes than adeno-associated virus (AAV), which may allow this vector to treat diseases which cannot be targeted by AAV.
   - Lentivirus integrates the therapeutic transgene into the patient's DNA, which can enable a sustained therapeutic effect.

3. **The company is currently focused on industrializing their gene therapy manufacturing and production.**
   - Investing in the development of mid-to large-scale manufacturing systems designed to be both reproducible and sustainable, with a view towards supporting product candidates, if approved, at a commercial scale.
   - This will be key for the company to stand out against the competition, especially in SCD, BT, and cancer, where other gene therapies are emerging.

4. **Partnership with CELG to discover, develop and commercialize novel, disease-altering gene therapies in oncology.**
   - Broadens application of gene therapy beyond ultra-orphan populations.

5. **Ability to evolve the gene therapy platform to remain competitive.**
   - Given the expertise of BLUE's management and scientists, the company has the ability to pursue additional approaches (ex: CRISPR, ZFN, TALENs, suicide genes, and non-integrating lentiviral vectors), which could further mitigate the potential risks of gene therapy (see page 8).

We believe BLUE is poised for success given its extensive expertise in viral vector design, a broad intellectual property estate, an experienced management team, and a world-class group of scientific advisors and key opinion leaders.

BLUE Valuation: Price Target $34/share

Our $34 PT represents ~35% upside from BLUE's current share price of $25.27(as of 6/12).

- **We arrive at our PT via a DCF analysis of estimated free cash flow (modeled through 2022)**
  - 11% discount rate reflects clinical/commercial risk for Lenti-D and LentiGlobin and regulatory prospects.
    - 8% terminal growth (36x terminal multiple) reflects the long-term outlook for BLUE's current pipeline programs and the potential gene therapy additions to the pipeline.
    - Assumptions:
      - Lenti-D for CCALD is approved in 2018, with 60% penetration in CCALD, a price of $1.3M/patient, and $182M peak revenue in 2022.
      - Lenti-Globin for beta-thalassemia approved in 2020 at a price of $1M/patient, and revenue of $60M in 2022. Potential to unlock the sickle cell disease (SCD) indication for Lenti-Globin beyond 2022, which is a larger market than beta-thalassemia.

- **Thoughts on the stock:** Good entry point for the stock especially with preliminary data from the HGB-205 study in beta-thalassemia patients to be presented at the European Hematology Association (EHA) on June 14. Additional data from HGB-205 as well as preliminary data from the Northstar study are expected by YE14. SCD and BT could represent ~$500M-1B opportunities.

BLUE: Investment Risks

- **Clinical Trial Risks**
  - Pipeline programs may fail to generate compelling data.
  - If mutagenic transformation is seen, this could unfavorably shift risk/benefit platform.
  - Data from 2 patients with beta-thalassemia will be presented this weekend (June 14).

- **Competitive Risks**
  - Mutagenic transformation could negatively impact BLUE and prove to be a positive for those companies that are focused on targeted therapies, especially if BLUE is not able to incorporate these targeted therapies into its platform.

- **Regulatory Risks**
  - Regulatory risks center around data from trials, safety profile of BLUE's therapies, and contract manufacturing company (CMC) controls.
  - BLUE's therapies may fail to gain regulatory approval.

- **Manufacturing and Commercialization Risks**
  - Although BLUE has proven expertise in the purification process and ensuring potency, the company is now focused on manufacturing their therapies on a clinical and ultimately commercial scale. Currently, the company relies on 3rd parties to conduct the majority of vector productions, product manufacturing, and clinical development.
  - Insertional mutagenesis with lentivirus presents a low risk, and BLUE is exploring add-on approaches to further mitigate this risk.
  - Competitive programs may emerge for CCALD, BT, SCD, and cancer, which could impede the commercial prospects for BLUE's gene therapies.

BLUE: Upcoming Catalysts Which Could Unlock Value

1. **Data from a Phase 1/2 study (HGB-205) in France will be presented this weekend (June 14 at 10:15AM) at the European Hematology Association (EHA).**

   - BLUE will be hosting a conference call Monday, June 16 at 8AM to discuss the initial results.
   - The preliminary data that has been released (vector copy number in 2 beta-thalassemia patients was 1.5 and 2.1; **see more on vector copy number on page 25**) suggests a positive effect of the therapy, but there is much more to BLUE than this one datapoint.

2. **Progress with the Phase 2/3 (Starbeam) study of Lenti-D in CCALD.**

   - Enrollment is expected to be complete by 2015, and European sites will be opened up in 2H14.
   - Pivotal data could be expected in 2017.

3. **Additional progress with Lenti-Globin for beta-thalassemia and sickle cell disease (SCD).**

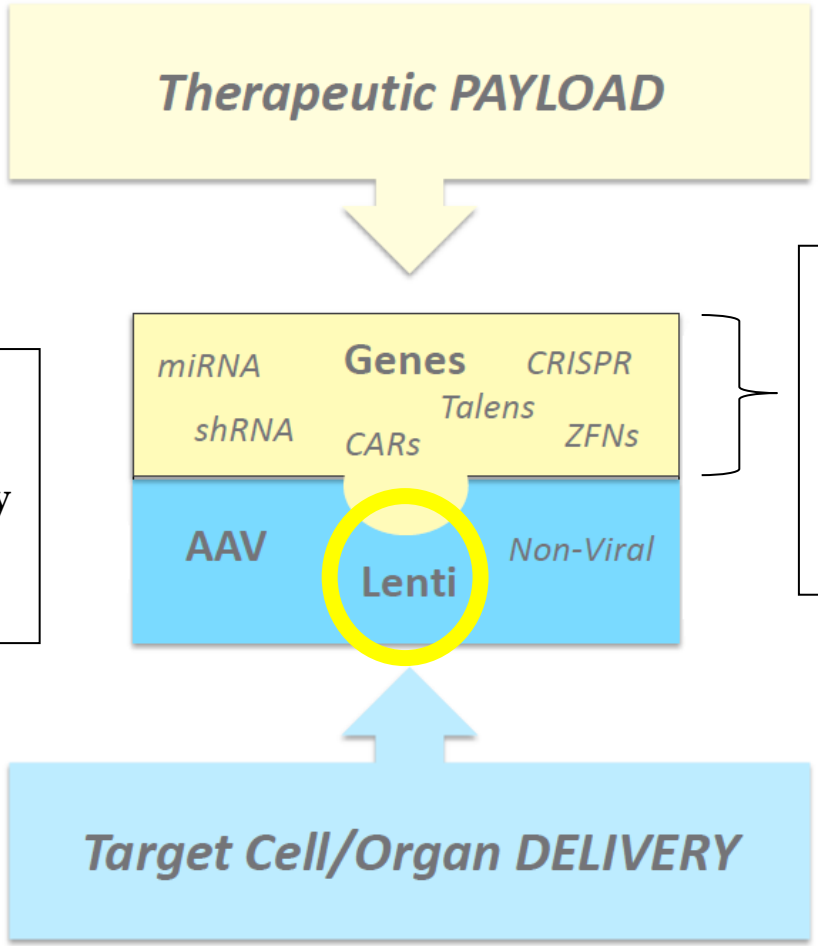
   - Additional data for both of these indications can be expected by YE14.
   - BLUE plans to initiate a Phase 1/2 study (HGB-206) in SCD in the US during 2H14.

4. **Longer-term follow-up of treated patients.**

5. **Increasing interest in the gene therapy field.**

6. **Expansion of BLUE's pipeline (and any updates on the Car-T program partnered with CELG).**

BLUE's Forward-Looking Gene Therapy Approaches Offer Significant Upside



Lentivirus integrates the therapeutic transgene into the patient's genome, thereby enabling a sustained therapeutic effect.

These are targeted therapies, which BLUE could potentially incorporate into its platform.

Source: BLUE Corporate Presentation

Gene therapy is a constantly evolving field, and BLUE is determined to remain competitive over the long term by pursuing opportunities in synergistic platforms.

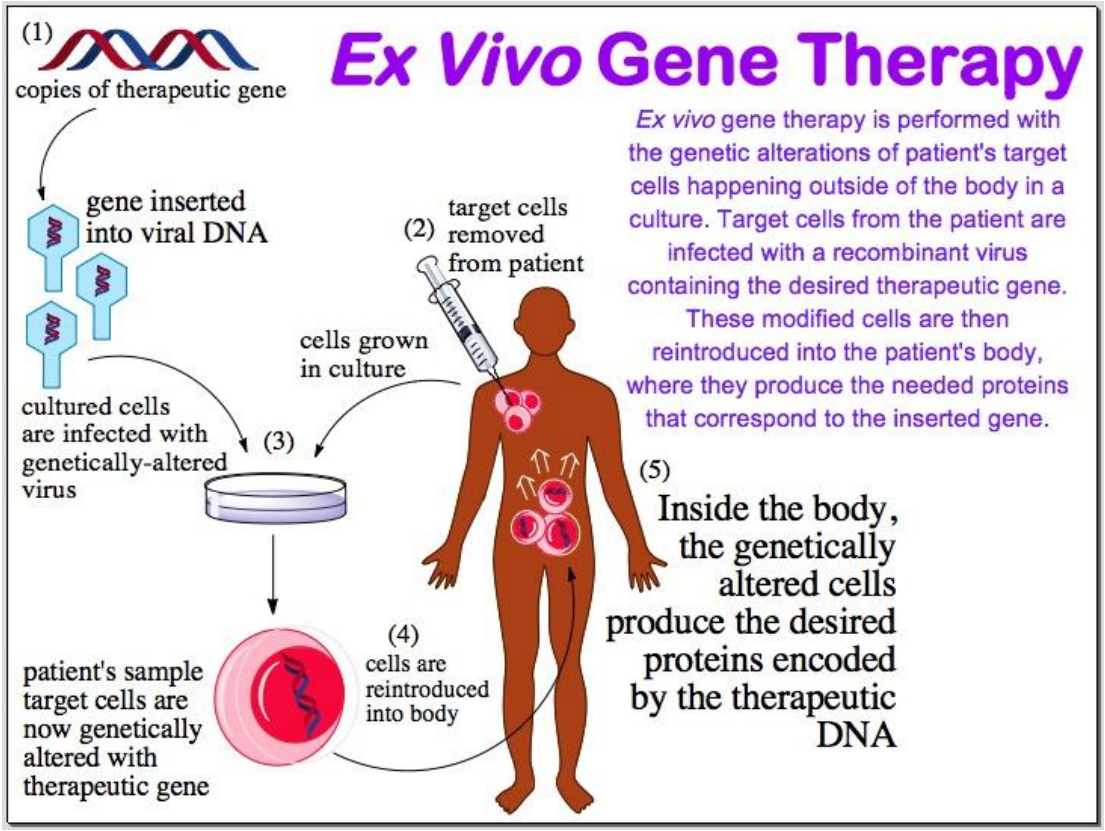
Gene Therapy Has Gone Viral!

Gene therapy has undergone a revival within the last few years, as gene therapy-focused companies are conducting IPOs, partnering with large-cap pharma companies, and generating positive clinical trial data. As the platform becomes increasingly de-risked, we expect to see even greater activity within the next 5-10 years in this exciting and potentially transformative space.

- The goal of gene therapy is to modify the genetic material of a patient's cells for therapeutic purposes.
- Genes produce proteins that perform a vast array of functions, through a process called **gene expression**.
  - A mutation, or alteration, in a gene can cause proteins to be overproduced, underproduced, or completely missing, which may lead to the manifestation of a disease.
- Gene therapy introduces a working copy of the defective gene (known as the **transgene**) into a patient's own cells, using a **viral vector** as the delivery vehicle.
  - Viral vectors are engineered so as to enable only the expression of the desired transgene (**viral vectors are noninfectious and can't reproduce themselves**).
    - The delivery of a gene by a virus is known as **transduction**. The delivery of the viral vector may be performed by **injecting the virus into the body** (***in vivo***) or by **exposing the patient's cells to the virus outside the body**, then reintroducing these cells to the body (***ex vivo***).
  - **Most common viral vectors: Adenovirus, retrovirus (lentivirus), and adeno-associated virus (AAV).**

Gene therapy has the potential to change the way patients are treated by correcting the underlying genetic defect that is the *cause* of their disease, rather than offering solutions that only address their *symptoms,* thereby providing transformative disease modifying effects with life-long clinical benefits based on a single therapeutic administration.

BLUE's Delivery Approach– *Ex Vivo* Gene Therapy



Source: www.gene-therapy.yolasite.com

Lentivirus is an optimal vector for *ex vivo* gene therapy given its ability to integrate into the patient's genome, thereby providing a sustained therapeutic effect in dividing cells (like hematopoietic stem cells).

Unlike *in vivo* gene therapy (employed by QURE), which directly injects the therapeutic gene into the patient, BLUE takes the *ex vivo* approach to gene therapy delivery. With this approach, certain cells (specifically hematopoietic stem cells, see next page) are removed from the patient, and are then treated with a vector (BLUE uses lentivirus) carrying the therapeutic gene.

Hematopoietic Stem Cells (HSCs)– The Cells Targeted By BLUE

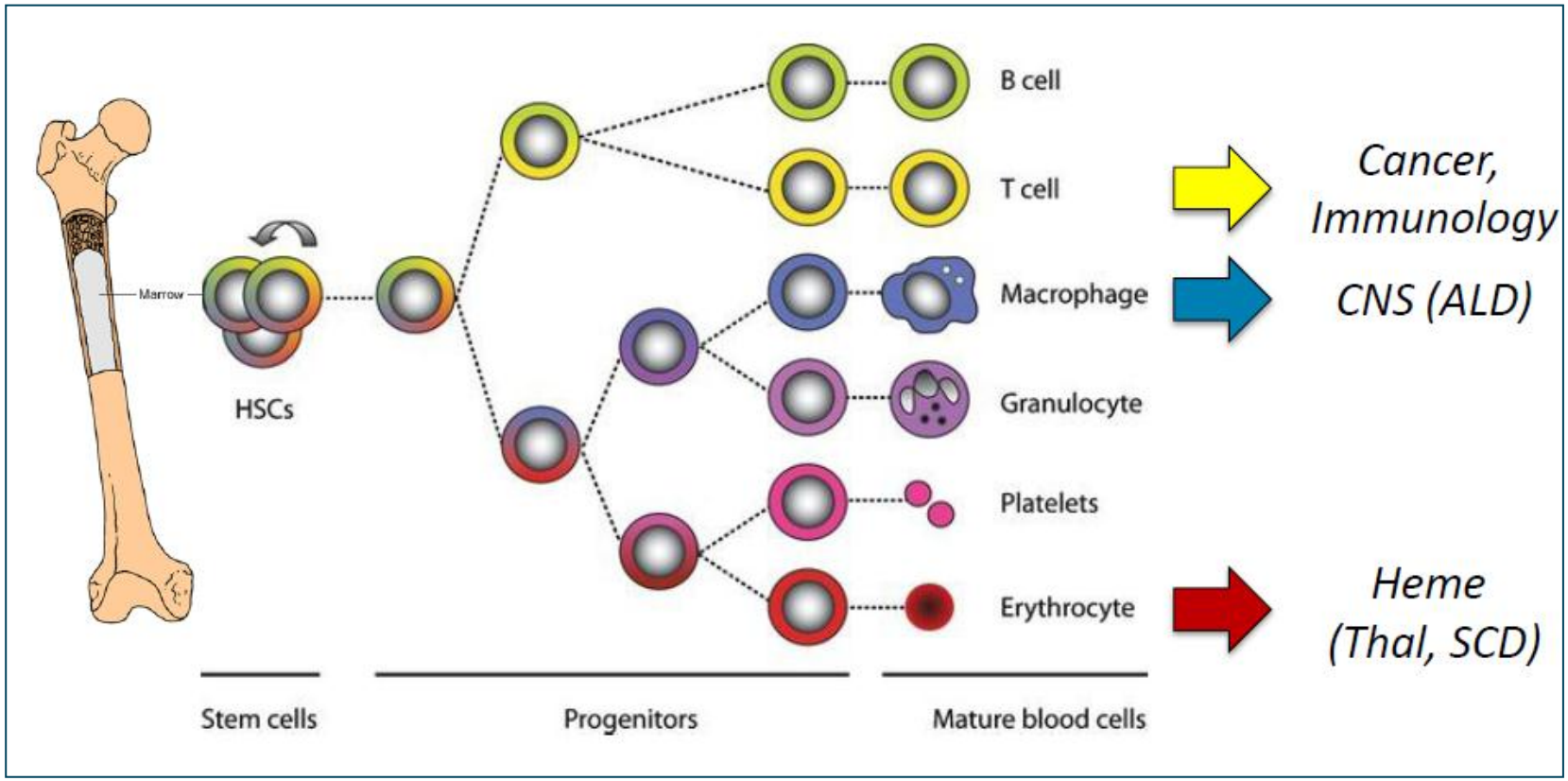
Hematopoietic stem cells are specific types of stem cells which form blood and immune cells. These cells are primarily found in the bone marrow– the tissue inside bones– and are responsible for the constant renewal of blood and the cells that support the immune system (see next page). HSCs can also migrate from the bone marrow and circulate in the blood.

What Makes Stem Cells Ideal For Gene Therapy

- Stem cells are:
  - Capable of cell division, which allows for renewal and repair.
  - Unspecialized or partially specialized, meaning that they are not yet programed to carry out one specific function in the body. Mature (adult) stem cells ultimately differentiate into tissue- or organ-specific cells with special functions.
  - Immune evasive– if a patient receives a product of his own stems cells (known as **autologous** stem cells), these cells are less likely to experience an immune response.

Because stem cells are capable of cell division, they are ideal for ensuring sustained expression of a therapeutic transgene when targeted by gene therapy. Stem cells can also be used to treat a variety of diseases, since they have the ability to differentiate into different cell types. Finally, autologous stem cells are familiar to the body so they are less likely to induce an immune response.

HSCs Differentiate Into The Relevant Cells For BLUE's Indications



Source: BLUE Corporate Presentation

HSCs differentiate into a variety of blood and immune cell types. As a result, HSCs are very effective vehicles for delivering a therapeutic gene to correct diseases where marrow-derived cells play a critical role, such as adrenoleukodystrophy (ALD), beta-Thalassemia (BT), sickle cell disease (SCD), and cancer. Lentivirus (BLUE's vector of choice) is an integrating vector, which effectively targets these dividing cells, thereby preventing dilution of the transgene.

Two Methods Of Extracting HSCs From The Patient

There are existing hospital infrastructure and standard protocols in place for stem cell transplant procedures, which reduce BLUE's investment in these processes. However, because HSCs have a limited window of stability after extraction, patients must be close to a transplant facility.

Extraction Directly From The Bone Marrow

Although the bone marrow has been the traditional site of HSC extraction, use of this procedure is fading.

The process:

- The patient is first put under anesthesia.
- A special syringe is used to puncture a large bone (most commonly the iliac crest of the pelvis) and draw out the bone marrow.
- The HSCs are then isolated from the other cells in the bone marrow.

Although BLUE seems to prefer extracting HSCs from the blood, both extraction methods are used and it is up to the physician's discretion to determine which method is optimal/safest for each patient.

Extraction From The Blood

In recent years, the blood has become the standard extraction source of HSCs, given the following **advantages**:

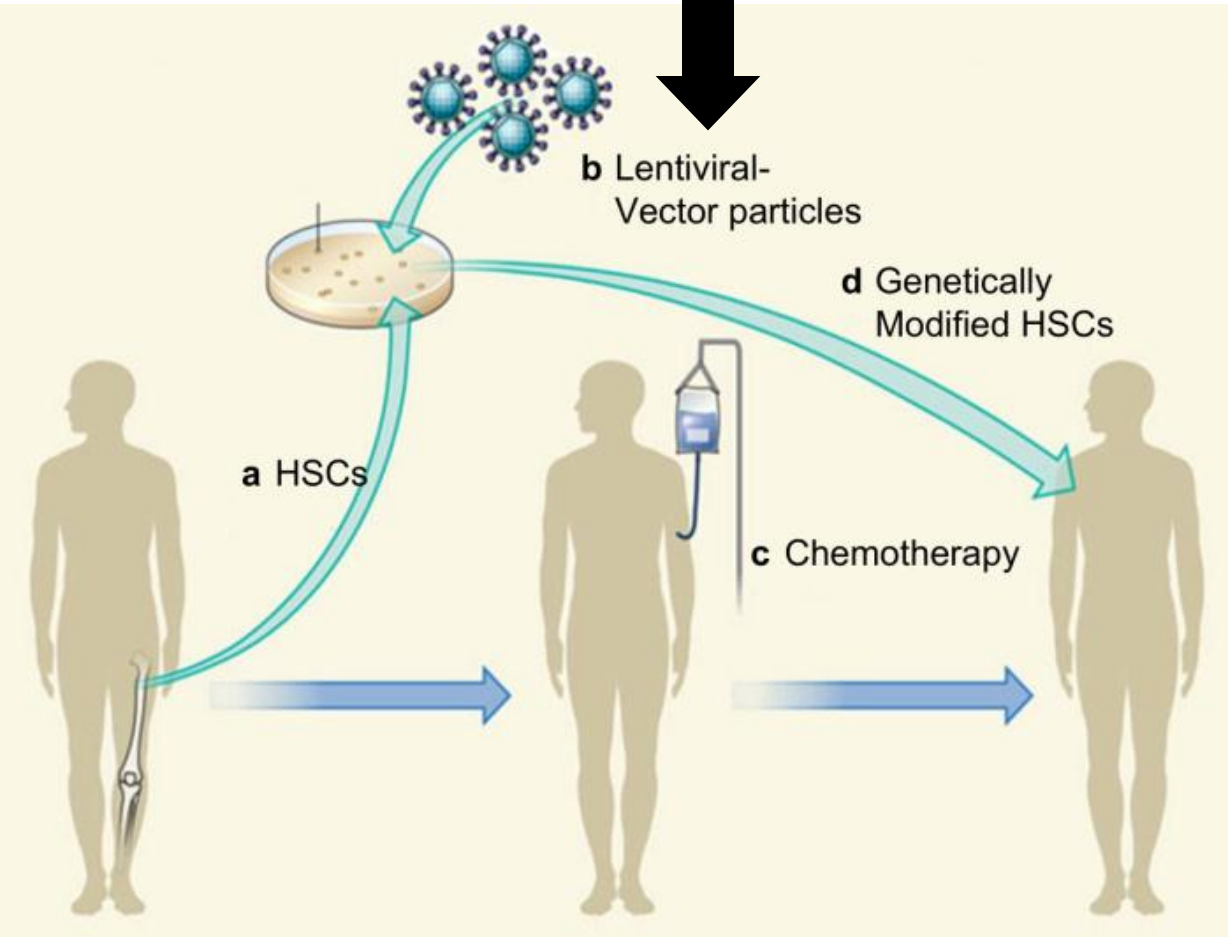
- Less invasive, no anesthesia is required since pain is minimal.
- More HSCs can be harvested from the blood than from the bone marrow.
- HSC transplantation which relies on blood extraction results in a higher survival outcome than that with standard bone marrow extraction. Recovery time is also faster.

The process:

- A few days before the HSC harvest, the patient is injected with cytokines (most commonly granulocyte colony-stimulating factors), which induce the HSCs to migrate from the bone marrow and into the blood.
- The cells are then collected with an IV tube that is inserted into the patient's vein.
- Through the tube, the blood is passed through a filtration system, which pulls out cells with a protein (CD34) which is found on the surface of HSCs.
- The remaining cells are returned to the patient's circulatory system.

So The HSCs Have Been Extracted…Now What?

Enter the viral vector!



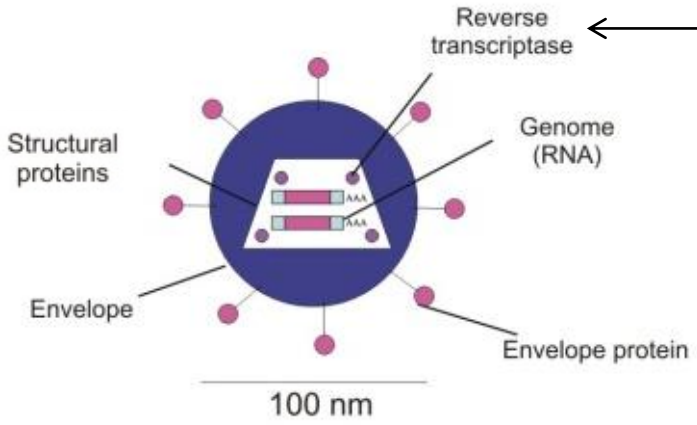
Source: www.intechopen.com

Lentivirus– BLUE's Vector Of Choice

Description

- Lentivirus is a member of the retrovirus family of viruses.
  - These viruses store their genetic material in RNA.
- Unlike AAV, lentivirus incorporates its DNA directly into a cell's chromosome upon infection.
  - When lentivirus enters a target cell, it uses **reverse transcriptase*** to make viral DNA from RNA.
- **With a larger genome than AAV**, lentivirus has the capacity to incorporate therapeutic genes as large as 9kb.
- **HIV** is an example of a lentivirus.

Basic Representation Of Lentivirus



Source: www.intechopen.com

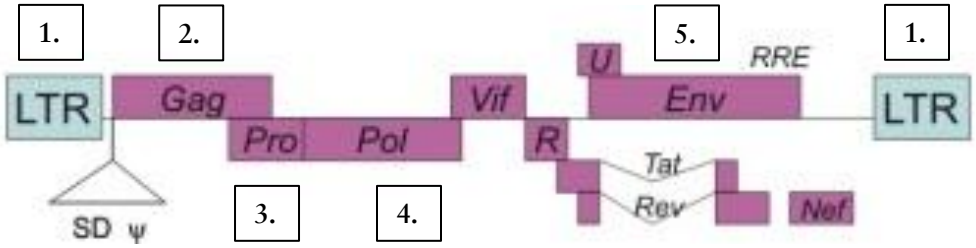
***Reverse transcriptase** is an enzyme used to generate DNA from an RNA template.

As an **integrating virus**, lentivirus poses different safety risks than AAV (not necessarily more, just different). The extensive research from BLUE and other academic centers/companies has identified these risks and made great strides in improving the safety profile of this class of viruses. However, the ability to integrate offers the benefit of sustained transgene expression.

Getting To Know Lentivirus Better

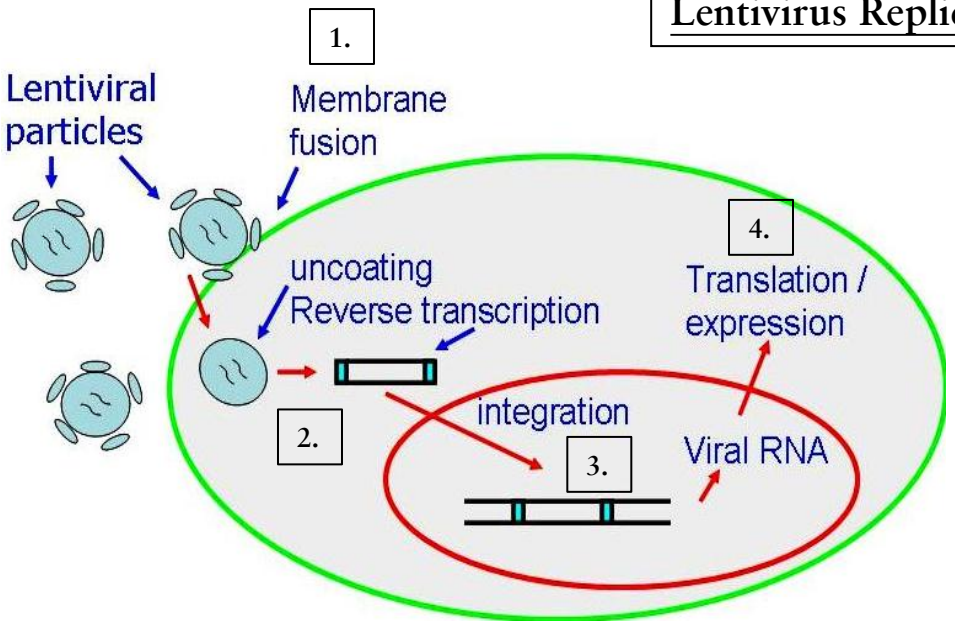
Key Components Of The Lentivirus Genome

- *LTRs* (1), or long terminal repeats, act as a promoter, or "control center," for the expression of viral genes.
- *Gag* (2), *pro* (3), *pol* (4), and *env* (5) genes encode for the structural proteins of the capsid, protease, reverse transcriptase, and envelope proteins, respectively.
- The remaining genes perform regulatory functions (*tat* and *rev*) as well as alter cellular function.



Sources: www.intechopen.com, www.gentarget.com

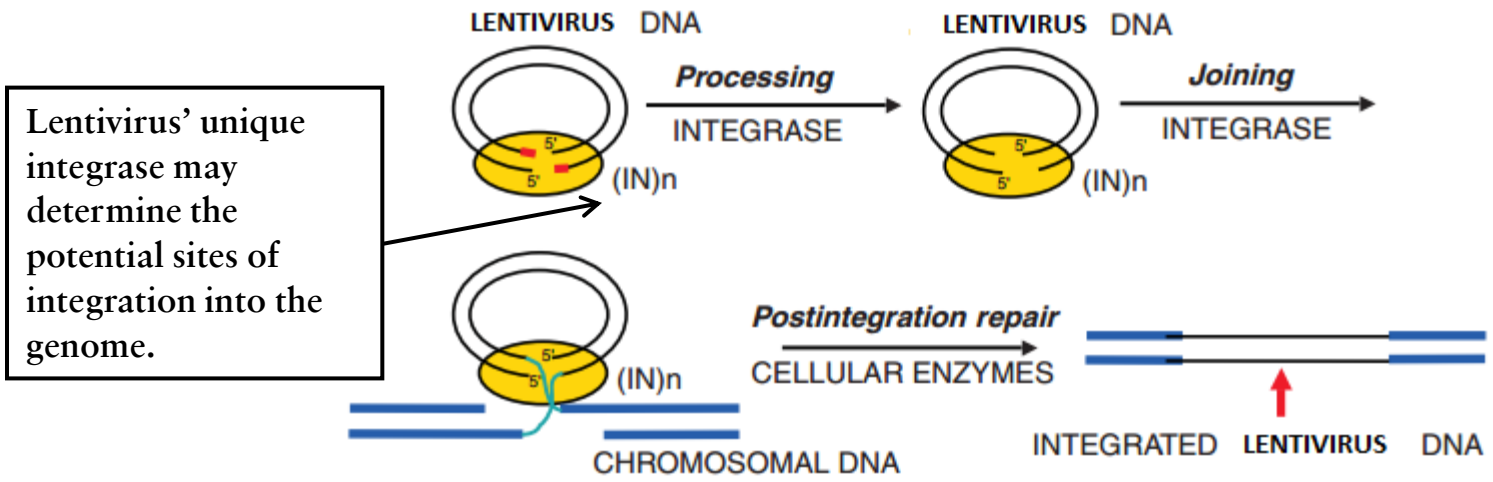
Lentivirus Replication Cycle



1. Lentivirus envelope protein interacts with a receptor on the cell surface, and the membranes fuse.
2. The viral genome (RNA) is released in the cell and reverse transcription results in a DNA copy of this genome.
3. Viral DNA enters the nucleus, and is **incorporated into the host genome via a viral enzyme known as "integrase" (see next page).**
4. Once in the host genome, expression of the viral genes and proteins results outside of the nucleus.

Sources: www.intechopen.com, www.gentarget.com

Understanding How Lentivirus Integrates



- The viral enzyme known as **integrase** catalyzes both the cleavage of viral DNA and the joining of the cleaved viral DNA to host cell DNA.

- After viral DNA is joined to the host DNA, post-integration repair is conducted by the cell's own DNA repair proteins.

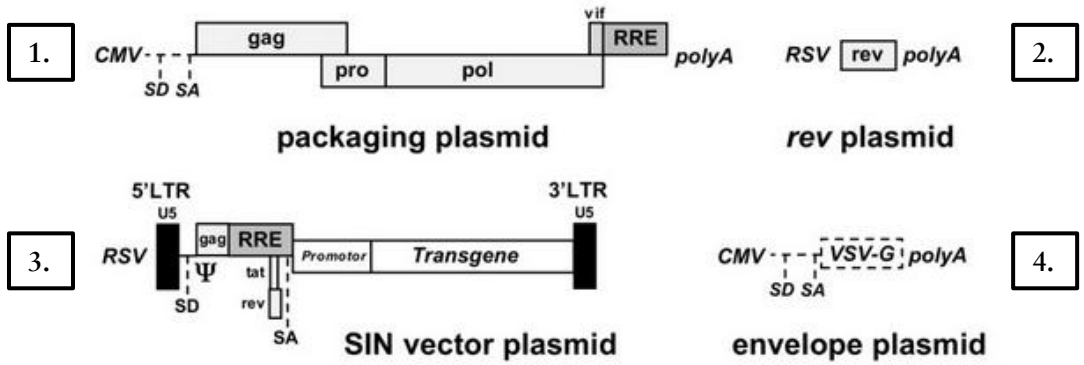
Sources: Daniel, R; Smith. Human Gene Therapy (2008)

Turning Lentivirus Into A Safe Vector For Gene Delivery

Source: www.intechopen.com

*What is a **plasmid**?
A plasmid is a small, double-stranded DNA molecule that is used as a tool for transferring and manipulating genes.

The 4 Components That Make A Lentiviral Vector

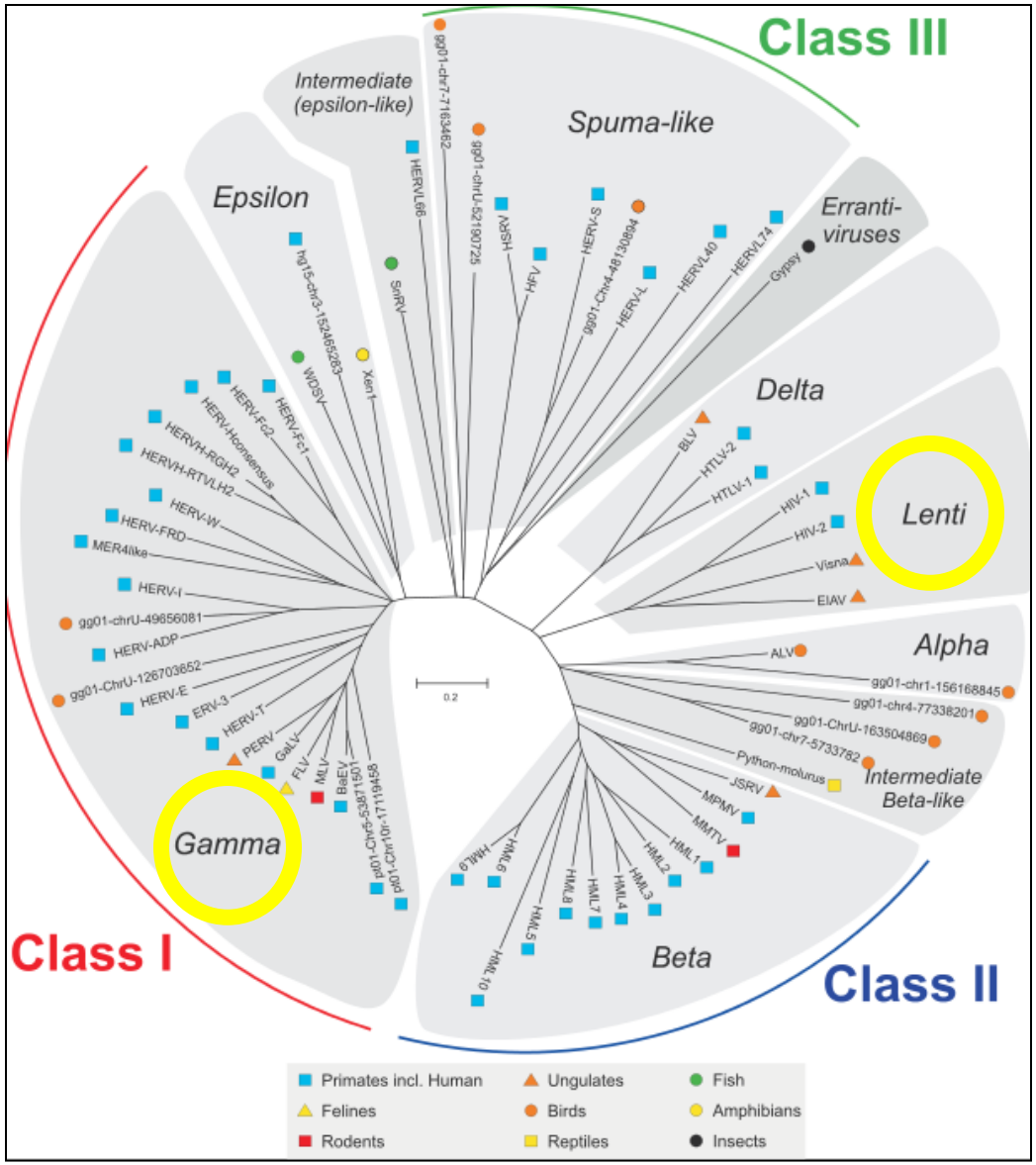


These 4 plasmids transduce the manufacturing cells (mammalian 293T cells, *see page 24*) and come together to form the therapeutic lentiviral vector.

To form a lentiviral vector, ~ 1/3 of the viral genome has been deleted (specifically the virulence factors), and the vector system has been divided into 4 plasmids (described below). **Separating various components of the lentivirus into 4 distinct plasmids is an important safety step designed to prevent the resulting lentiviral vector from being able to replicate and cause infection on its own.**

1. The **packaging plasmid** contains the *gag* and *pol* genes, which encode the viral core proteins and reverse transcriptase, respectively.
2. The ***rev* plasmid** encodes for the regulatory enzyme which is essential for production of protein from the therapeutic transgene.
3. The **SIN (self-inactivating) vector plasmid** contains the therapeutic transgene.
4. The **envelope plasmid** encodes the envelope protein and determines what receptor the virus binds to when entering a cell.

The Retrovirus Family– Lentivirus Emerges As A Safe Option For Gene Therapy



Source: Wikipedia

Gammaretrovirus and lentivirus (highlighted to the left) have been the most common vectors used in gene therapy. In the next few pages, we explain the differences between these two classes of retroviruses, and how lentivirus' integration profile makes it a safe vector for gene therapy.

Lentiviral Vectors Are An Improvement On Gammaretroviral Vectors

In many early gene therapy trials (before 1996), researchers employed gammaretroviral vectors because of the sustained transgene expression these vectors offered. However safety concerns (specifically, **insertional mutagenesis***) arose with these vectors, which prompted researchers to discover and improve upon other classes of retroviruses. Lentivirus in particular has emerged as a safe and effective vector for gene therapy.

Safety Concerns Associated With Gammaretroviral Vectors….

1. **Insertional mutagenesis**: Because retroviruses integrate their DNA into the host genome, there is risk of transgene integration into inopportune sites. Based upon pre-clinical and clinical studies, traditional **retroviruses are likely to promote unwanted expression of cellular genes given their tendency to integrate within certain regulatory regions of genes, which can inappropriately activate the cell to divide uncontrollably and lead to cancer through a process called insertional mutagenesis.**

2. **Accidental formation of virulent viruses**: Because retroviruses are potent viruses, the formation of replication-competent viruses has been a safety concern for this class of viruses.

…And How Lentivirus Has Mitigated These Risks

1. Lentiviral vectors reduce the likelihood of insertional mutagenesis due to their more **targeted integration preferences**. So far, no pre-clinical or clinical studies have shown lentiviral vectors to be associated with insertional mutagenesis or tumor formation (Themis et al., 2005).

2. Unlike traditional retroviruses, **lentivirus has efficiently adapted to self-inactivating (SIN) vector technology** (see previous page). With this technology, one of the LTRs has been deleted, rendering the other LTR inactive so the virus cannot replicate. The use of SIN lentiviral vectors has almost eliminated the possibility of forming replication-competent viruses.

*__Insertional mutagenesis__ refers to the mutation caused by the random insertion of additional DNA bases to a host's existing DNA. Random insertion can lead to tumor formation.

BLUE Has Made Even Further Improvements To Lentivirus Vector Technology

Over the past 21 years, BLUE has developed multiple iterations of proprietary viral vectors, with the goal of achieving the highest level of potency, efficiency, and safety. The company currently employs a **modified, non-replicating version of the Human Immunodeficiency Virus Type 1** (**HIV-1**) as its viral vector for all current pipeline programs. This virus is the most common of the HIV subtypes and has been stripped of all the components required for self-replication and infection of cells beyond the target cells (HSCs).

Further Reducing Insertional Mutagenesis Risk

- BLUE is making use of **sequencing technologies and integration site analysis** to identify possible integration sites within HSCs and monitor **oligoclones**, which are cell lines that have disproportionate replication and represent a potentially increased risk of turning into cancer.
  - As an example, BLUE did see an oligoclone in an early hemoglobinopathy patient but this has since dissipated.
  - This polyclonal phenomenon with intermittent oligoclones was described as the "stochastic model of hematopoiesis" and suggests that risk of leukemic transformation is minimal as these oligoclones pop up and disappear without detrimental effect.

Lowering The Potential For Replication-Competent Vector Formation

- Through the development of proprietary vector manufacturing processes and techniques over the last 2 decades, BLUE has been able to produce a more purified and concentrated product.

Although lentiviral vectors represent a substantial improvement over traditional retroviral vectors, risks still remain, but BLUE has made great strides in eliminating these risks and ensuring its lentiviral vectors are safe and efficacious.

The Difference Between Lentiviral and Gammaretroviral Integration Profiles

Retroviral vector- based gene therapy has been studied in diseases such as X-SCID, ADA-SCID, and CGD. Because use of this vector led to insertional activation of proto-oncogenes, contributing to the development of leukemia, there has been extensive characterization of the integration profile of this class of vectors.

Gammaretroviral Integration Profile

- Strong propensity to integrate at a gene's **promoter** (a particular region of the DNA which initiates transcription). **>20% of integration events during gammaretrovirus infection take place near the promoter region. The remaining integration sites occur in a random manner.**
- Rather than integrating in sites which regulate the production of a particular protein, gammaretrovirus integrates near genes **controlling cell growth and proliferation.**
- Gammaretrovirus has a strong tendency to integrate within proto-oncogenic sites such as **BMI1**, **LMO2**, and **MECOM**. BMI1 regulates stem cell proliferation, overexpression of LMO2 has been linked to leukemia, and MECOM is involved in the activation of cell cycle genes and has been associated with leukemia.

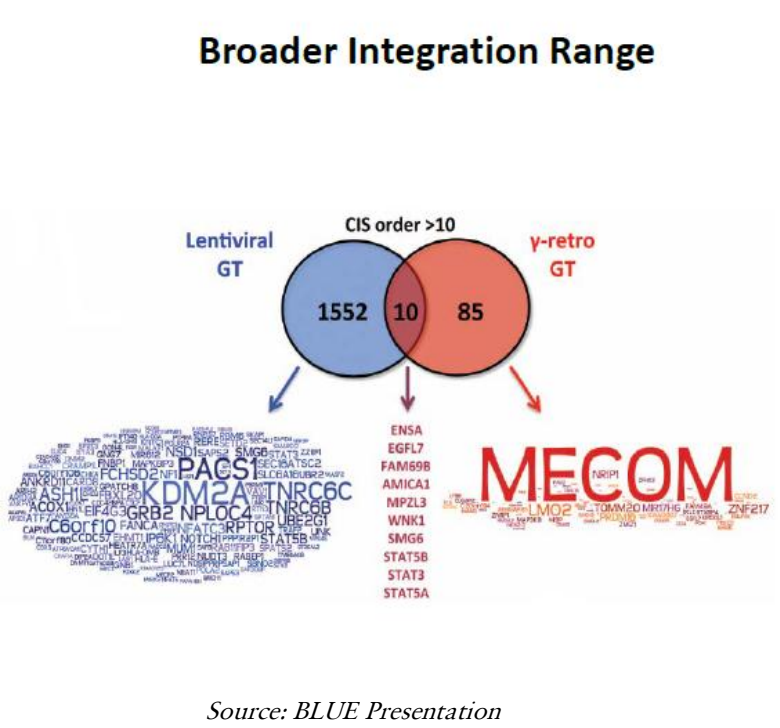
Lentiviral Integration Profile

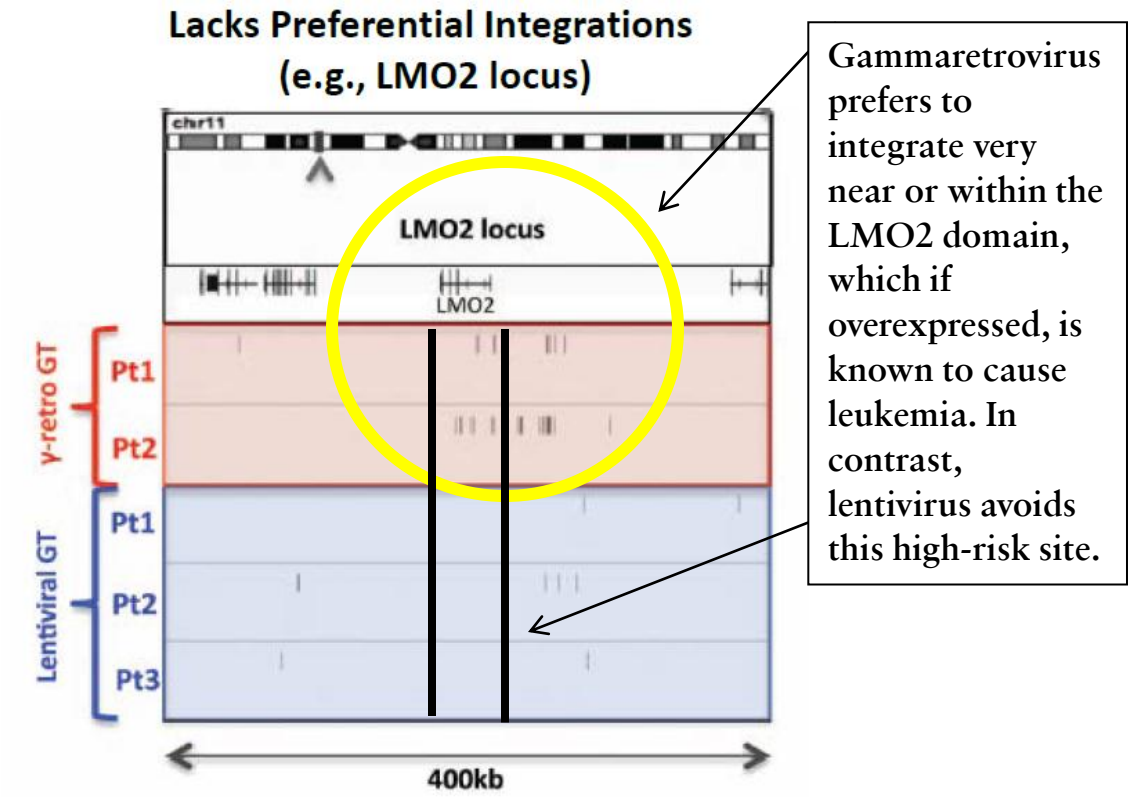
- Favors integration in the bodies of transcription units, which encodes **a specific protein to be created via the process of translation. >70% of lentivirus integration occurs in this manner.**
- Based upon extensive insertion site analysis, lentivirus **avoids integration near promoters and genes that regulate the cell's growth.**
- In BLUE's beta-thalassemia clinical trial, the lentivirus seemed to preferentially integrate within the **HMGA2 gene**– but this site is **not associated with oncogenesis** and the patient had no adverse clinical reactions.

Although the lentiviral integration profile may be less likely to result in insertional activation, other factors such as cell type and the pathological changes in the cells as a result of transduction may explain the lack of insertional mutagenesis during lentivirus integration.

Lentivirus' Integration Profile Makes It A Safer Vector Than Gammaretrovirus

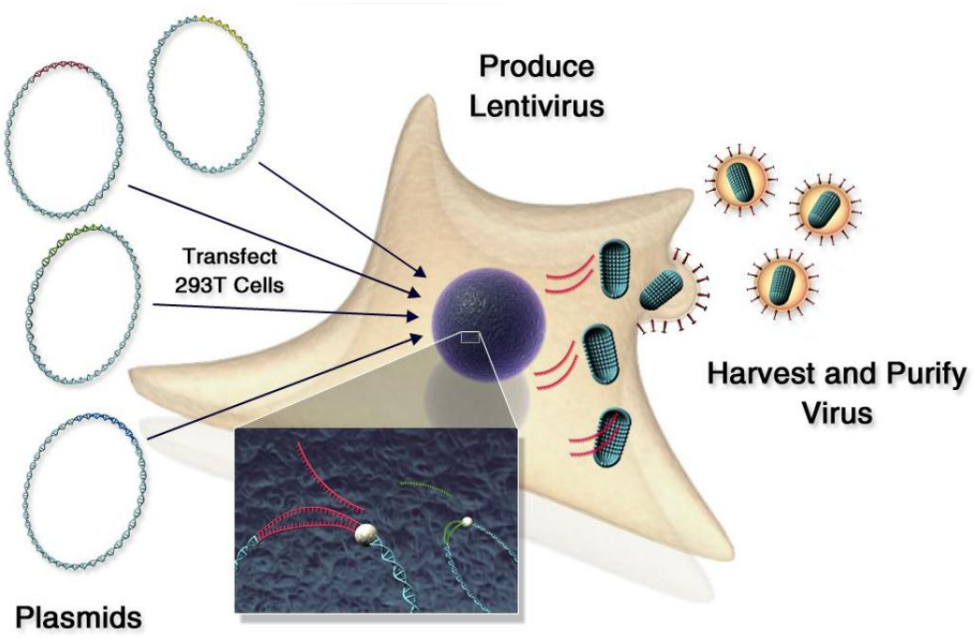
The data below is based upon Wiskott-Aldrich Syndrome patients who have been treated with gammaretrovirus- and lentivirus-based gene therapy.





Lentivirus has the ability to integrate into more sites than gammaretrovirus (flexibility and freedom offer greater safety), and avoids the higher-risk sites that gammaretrovirus inserts its DNA (such as promoter regions and proto-oncogenic sites like BMI1, LMO2, and MECOM).

BLUE's Process For Manufacturing Its Vectors



BLUE transfects mammalian (293T) cells with the 4 plasmids carrying the components necessary to make a lentiviral vector.

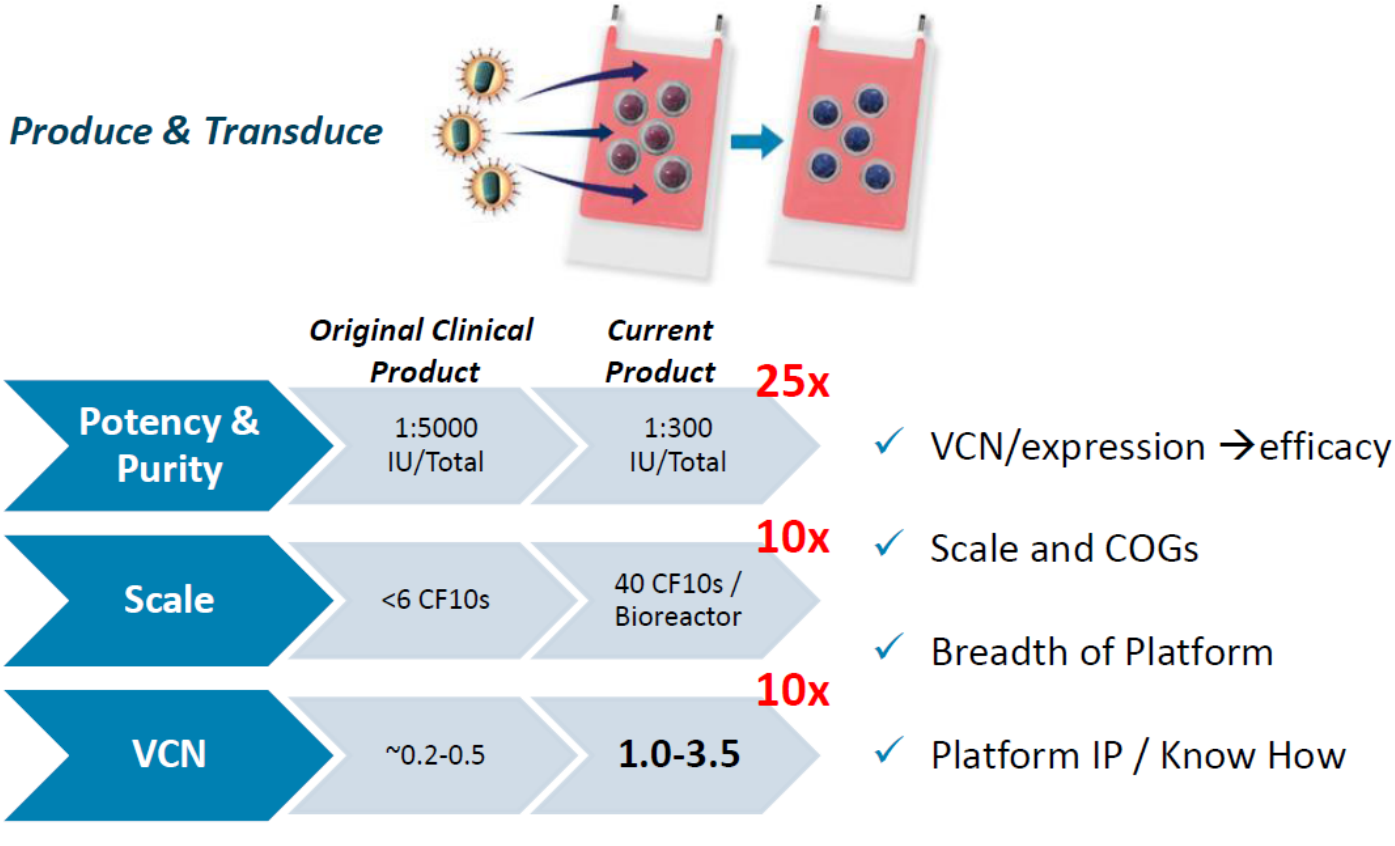
- Unlike QURE, which utilizes insect cells in the manufacture of its viral vectors, BLUE employs mammalian cells (293T cells).
- 293T cells are a specific cell line originally derived from human embryonic kidney (HEK) cells grown in tissue culture.
- These cells are easy to grow, transfect very readily, and support high-level expression of lentiviral proteins.
- Although mammalian-cell based vector production is more time/labor intensive, these cells are the optimal cells to use for efficient and high-titer lentiviral vector transduction.

Source: BLUE Presentation

BLUE Has Improved Its Vector Technology

Focused on improving the potency, purity, safety, and scale of its lentiviral vectors, BLUE has gone through various iterations of its vectors. Since its original lentiviral vector, the company has greatly improved a key metric– vector copy number (VCN)– which is the number of vector copies per cell following gene transfer. The higher this number, the more potent and efficacious its therapy can be.

Source: BLUE Presentation



Potency and purity increased 25 times compared to original product. The number viral particles that transduce the 293T cells (known as infectious units, or IU) increased from 1 in every 5000 viral particles to 1 in 300 viral particles.

The original product utilized <6 10-tray cell factories (CF10s), while the current product utilizes 40 CF10s/Bioreactor, representing a 10-fold increase in scale.

Increased vector copy number 10 times compared to original product

BLUE's success here is key because a gene therapy will only be as good as the viral vector delivering the gene.

Lentivirus + HSCs = A Winning Combination

Advantages Of Lentivirus

- Lentiviral vectors can **transduce HSCs more efficiently than other vectors.**
- By integrating the therapeutic transgene into the target cell's DNA, lentiviral vectors enable **stable, sustained expression of the transgene** since the target cells (HSCs) are dividing cells.
- Lentiviral vectors have the potential to be more flexible vehicles for gene therapy delivery since they can **accommodate larger genes than AAV.**
- Low immunogenicity is associated with lentiviral vectors, since these vectors are **less likely to induce inflammation and innate immune responses**, compared to AAV.

Because HSCs divide continually over the course of a patient's life and lentivirus integrates its DNA (the therapeutic transgene) into the HSCs' DNA, this type of gene therapy is expected to provide long-term expression of the transgene and a sustained therapeutic effect.

Putting It All Together– Getting BLUE's Gene Therapy To The Patient

1. **Extract HSCs**: HSCs are extracted from the blood (following mobilization with cytokines) or bone marrow. The process is carried out using existing hospital infrastructure and standard protocols in place for stem cell transplant procedures. Approximately 200-300M cells are removed from the patient.

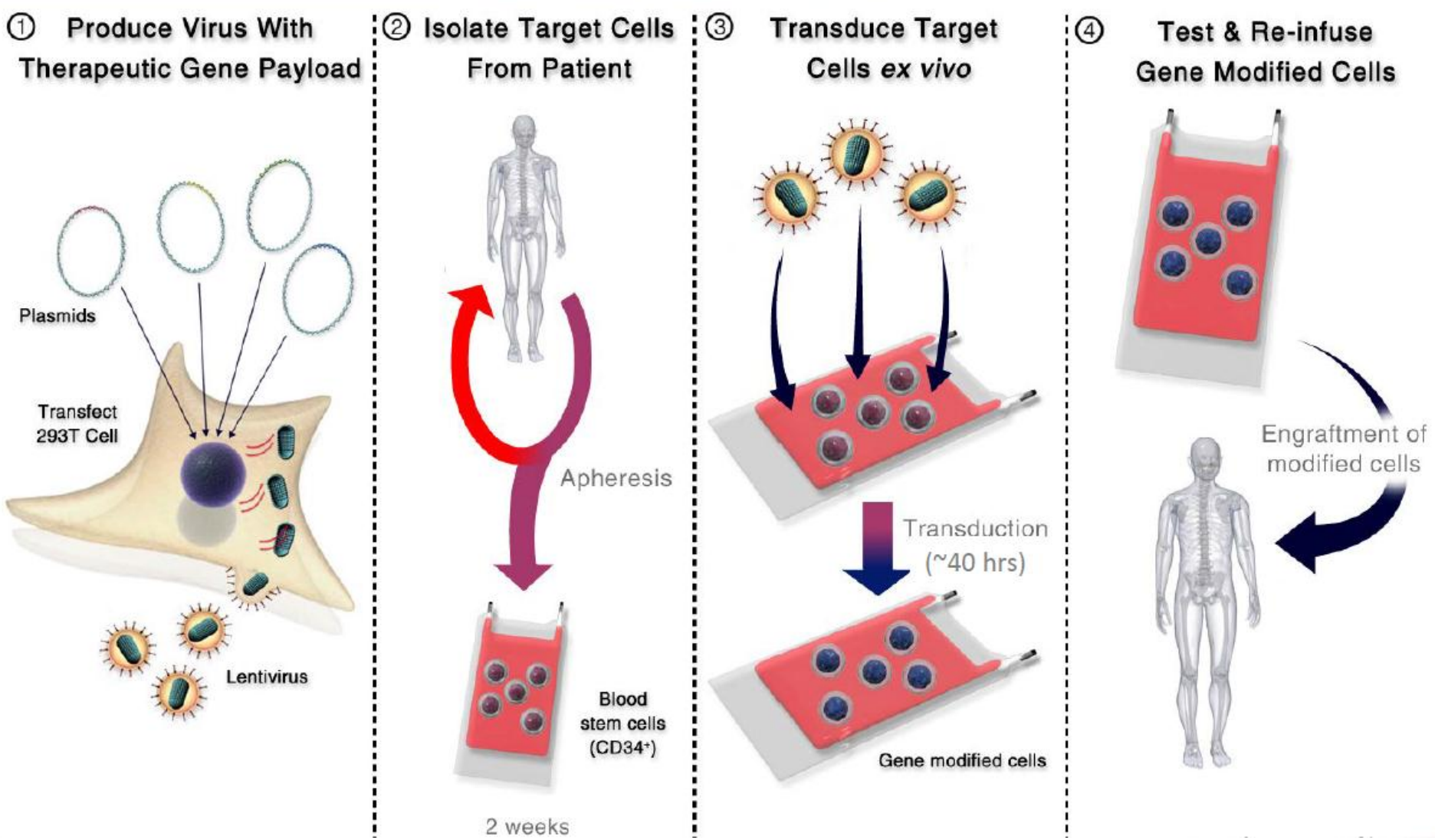
2. **Prepare HSCs**: The isolated HSCs are treated with a mixture of growth factors and additional processes proprietary to BLUE that enable an efficient transduction process.

3. **Transduce HSCs With The Viral Vector**: The isolated, purified and pre-treated HSCs are exposed to lentiviral vectors containing the appropriate transgene for up to 40 hours to facilitate transduction and insertion of the therapeutic DNA into the HSCs' existing DNA (creating autologous, gene-modified cells).

4. **Purify The Product**: Once transduction is complete, the genetically-modified HSCs are washed and re-suspended into cell culture media to remove any remnants of the viral vector or residual impurities. A portion of the harvested cells is removed for quality control testing.

5. **Deliver HSCs Back To The Patient**: Prior to re-administering the modified HSCs, the patient undergoes a standard myeloablation procedure (which is used in allogeneic HSCT) to remove all endogenous bone marrow cells. The modified HSCs (approximate 3M cells) are then re-infused back into the patient (~1-2 months after initial extraction) and begin re-populating a portion of the bone marrow as permanently modified HSCs in a process known as **engraftment**. The engrafted HSCs will go on to give rise to "daughter cells" carrying the functional gene. **There is no need for immunosuppression, since the patient's own cells are used.**

Conceptualizing BLUE's Gene Therapy Delivery Process



Source: BLUE Presentation

Hematopoietic Stem Cell Transplant (HSCT) = Adoptive Gene Therapy

Allogeneic hematopoietic stem cell transplants (HSCTs), which rely upon cells from a well-matched donor rather than the patient's own (autologous) cells, have been used to treat many diseases (including all the diseases BLUE is targeting) for decades.

How allogeneic HSCT works:

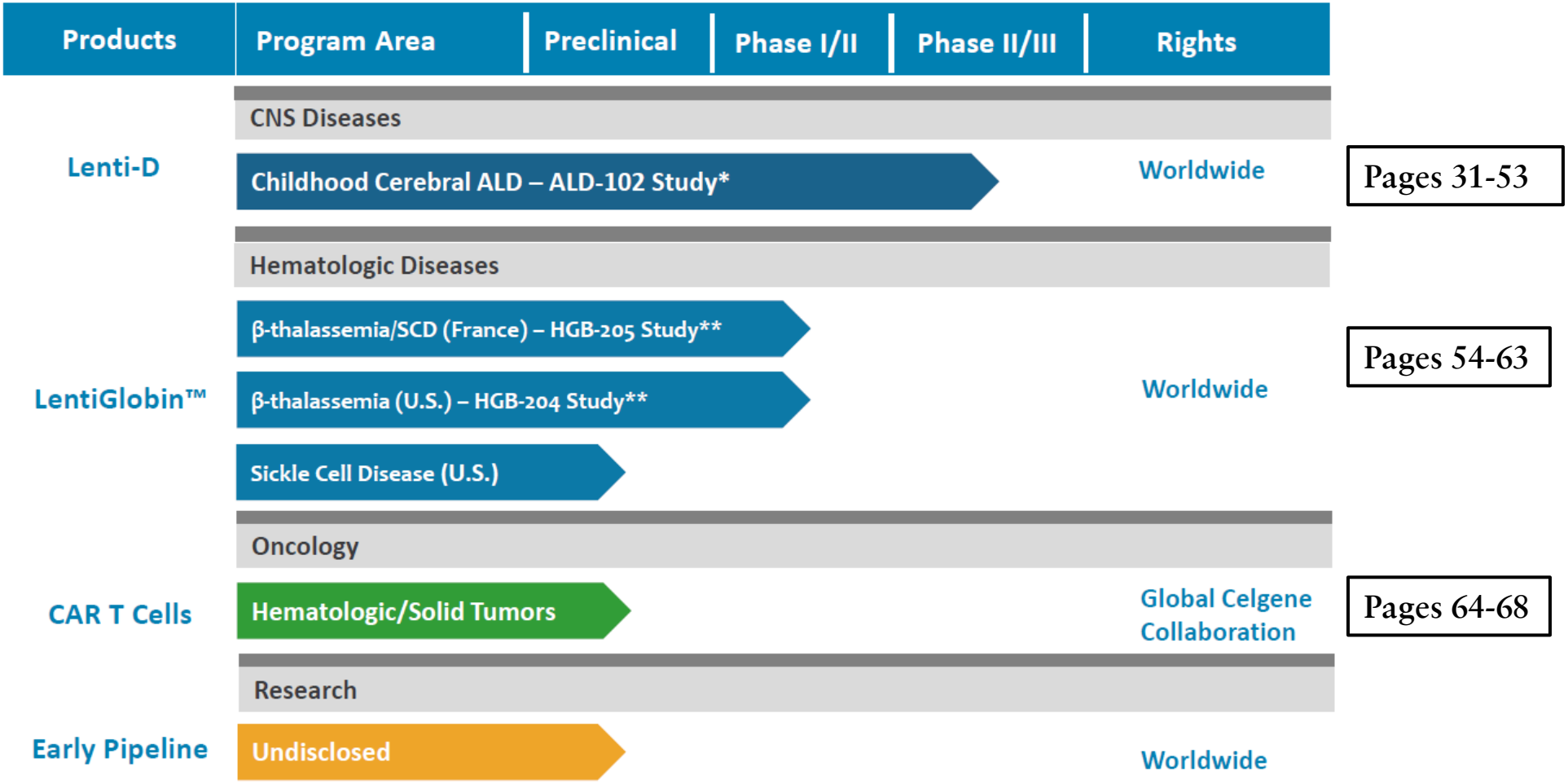
- The HSCs from a donor, who is capable of producing an enzyme/protein that the recipient lacks, are infused into the recipient, with the expectation that the recipient will now be able to make the missing enzyme/protein.

There are limitations:

- It is difficult to find an appropriate, genetically- matched donor (**15% of CCALD patients have a sibling with matching tissue type**).
- Allogeneic HSCT comes with a high risk of transplant-related rejection (graft vs. host disease) and mortality.

Although allogeneic HSCT has proven to be beneficial in many diseases (including all of BLUE's indications), it is a far less precise and riskier procedure than the approach taken by BLUE. By using the patient's own (autologous) cells rather than a donor's cells (allogeneic), BLUE eliminates the complications of graft vs. host disease and/or immunosuppression.

Taking Flight With The bluebird Pipeline



Source: BLUE Corporate Presentation

BLUE has a de-risked pipeline, with the ability to expand into new indications with its lentiviral + autologous stem cell approach without significant investment.

Overview Of Childhood Cerebral Adrenoleukodystrophy (CCALD)

- CCALD is a phenotype of adrenoleukodystrophy (ALD), a rare, X-linked, genetic metabolic storage disease affecting males.
  - CCALD presents in boys between the ages of 4 and 10. It is characterized by inflammation in the brain and rapid deterioration to a vegetative state.
- This disease is caused by a **mutation in the ABCD1 gene**, which, when fully functional, is responsible for producing the **adrenoleukodystrophy protein** (**ALDP**).
- Patients with this disease do not produce enough ALDP to prevent accumulation of very long-chain fatty acids (VLCFA) in their tissues, especially in the brain and adrenal glands.
  - In the absence of ALDP, VLCFAs accumulate in the brain (in the case of CCALD), causing damage to the **myelin sheath**, a protective and insulating membrane that surrounds nerve cells.
  - Over time, the damage caused by fatty acid accumulation in the brain leads to decreased motor coordination, cognitive function, and eventual death.
- The current standard of care is **allogeneic hematopoietic stem cell transplant** (**HSCT**), but this treatment comes with significant mortality and morbidity risks.

BLUE chose to target CCALD first because HSCT has been shown to positively impact the natural history of this type of ALD.

ALD Phenotypes

The worldwide incidence of ALD is ~1 in 20,000 births, and is classified based on the age of onset and the site of central nervous system damage.

- CCALD (Childhood Cerebral Adrenoleukodystrophy): This is the most severe form of ALD, accounting for about **30-40% of patients diagnosed with ALD**. Symptoms present between the ages of 4 and 10, and patients experience inflammation in the brain which destroys the myelin sheath. **In the absence of therapeutic intervention, boys suffering from CCALD typically experience rapid degeneration into a vegetative state and ultimately death within a decade of diagnosis.**

- AMN (Adrenomyeloneuropathy): AMN affects adults over 21 and is the most common form of ALD, accounting for **40-45% of all patients diagnosed with ALD**. This disease is characterized by little to no inflammation in the brain and a slower progression of symptoms compared to CCALD. AMN typically affects the spinal cord and occasionally the peripheral nerves. However, **approximately 30% of men with AMN will experience cerebral involvement at some point.**

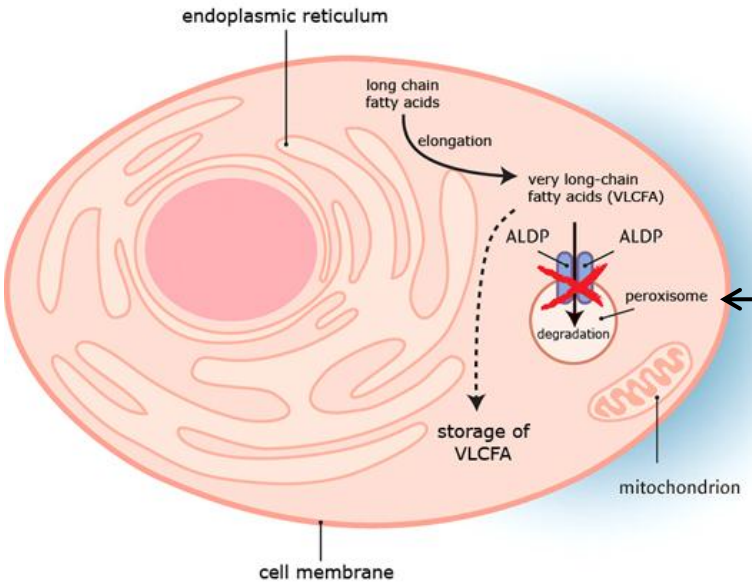
- ACALD (Adult Cerebral ALD): This disease typically develops in males 15 years and older and accounts for ~5% of all patients diagnosed with ALD. ACALD is characterized by a very severe progression of neurologic symptoms that parallels the course of CCALD. **Although no formal studies have been conducted, HSCT has shown benefit in ACALD.**

- Addison's Disease: This disease is characterized by impaired adrenal function and is seen in **~70% of patients with ALD** (Listernick R, *Pediatric Annals*, 2009). As a result, any patients with Addison's disease should be screened for ALD.

Source: BLUE S-1

Understanding The Cause Of CCALD

The Inner Workings Of A Human Cell

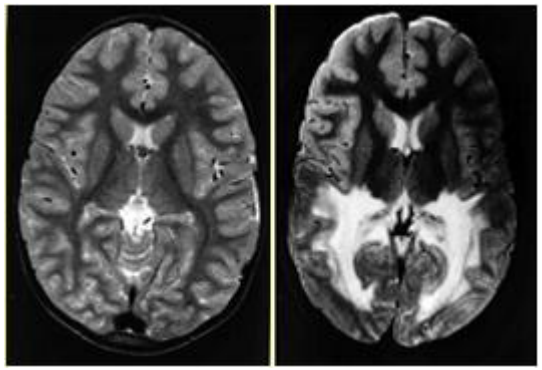


- In healthy individuals, ALDP breaks down very-long chain fatty acids (VLCFAs) to smaller fatty acids in the **peroxisome** of a human cell. These fatty acids are then transported to the mitochondria for further processing.

What is a peroxisome?

A peroxisome is an organelle (a specialized unit within a cell that has a specific function) which is involved in the breakdown (catabolism) of VLCFAs.

Comparison Of A Normal Brain And The Brain Of An ALD Patient



- In patients with CCALD, the gene (ABCD1) which encodes for the proper production of ALDP, is dysfunctional and therefore does not produce ALDP.
  - As a result, VLCFAs build up in the brain, adrenal glands, and peripheral nervous system, which damage the myelin sheath and lead to "**white matter**" in the brain, characteristic of neurologic deterioration.

Source: www.x-ald.nl

Understanding The Clinical Manifestation Of CCALD

35% of boys between the ages of 4 and 10 with ALD develop CCALD, which is characterized by severe neurological issues (progressive cerebral demyelination) as well as endocrine deficiencies.

- The endocrine deficiencies result in impaired adrenal function, and is characterized by a condition known as **Addison's disease**. Patients may experience increased skin pigmentation, fatigue, and weight loss. This component of CCALD can be **fairly well managed by corticosteroids and/or hormone replacement therapy**. Addison's disease in young boys may be an early signal of the development of neurological issues indicative of CCALD.

- The early neurological signs of CCALD include behavioral changes, deterioration in vision, and impaired hearing. In the absence of rigorous screening processes for this disease, these **symptoms are often misdiagnosed as ADHD, learning disorders, autism, multiple sclerosis, and epilepsy**.

  - Demyelination (destruction of the protective myelin sheath around neurons) reduces the ability of nerves to relay information to the brain. As more fatty acids accumulate in the brain, damage to myelin sheath becomes increasingly worse, causing the neurological consequences of CCALD to rapidly progress.

  - Although there are currently no cures for CCALD, allogeneic stem cell transplant has proven effective in slowing or halting the progression of damage to the brain. However, without treatment, the prognosis of untreated patients is poor, with severe disability and death expected within 2-4 years of the onset of severe neurological symptoms.

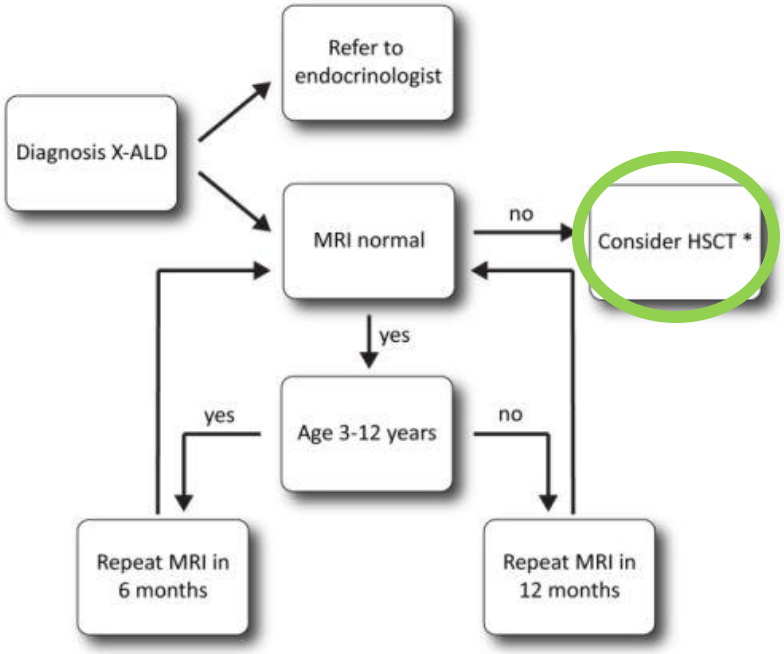
Accurately Diagnosing And Treating CCALD Can Be Difficult

Approximately 20-50% of CCALD patients may have a disease so advanced at the time of diagnosis, that a beneficial outcome from treatment would be unlikely. Early diagnosis is often difficult (CCALD is often misdiagnosed as ADHD, autism, MS, and epilepsy), and the disease can rapidly progress, which limits the window to provide a therapeutic benefit.

Current Tests To Diagnose CCALD Do Not Catch The Disease Early

By the time most of the tests show positive results, the patient is already symptomatic and disease may have progressed too far.

1. **Blood test:** Captures levels of VLCFAs in the blood.
2. **Neurologic examination:** Measures vision, hearing, speech, and fine motor skills.
3. **MRI with Gadolinium enhancement:** Gadolinium is a contrast agent used in brain magnetic resonance imaging (**MRI**) studies. Gadolinium enhancement (or a gadolinium positive results) helps detect the "white matter" characteristic in the brain of ALD patients, suggests that neuroinflammation is present, and that the blood-brain barrier has been compromised.
4. **Loes** (MRI severity) **Score**: This is a 34-point scale which measures the extent of CNS disease burden. Determines the extent of myelin damage (or the presence of "white matter") in the brain.
   - **Very early stage**: MRI score 1-3
   - **Early stage**: MRI score 4-8
   - **Late stage**: MRI score 9-13
   - **Very late stage**: MRI score greater than 13



* If there is no gadolinium enhancement present, consider arrested cerebral ALD and repeat the MRI in 3 months.

Source: www.x-ald.nl

Case Studies Indicate It Is Easy To Misdiagnosis ALD Without Screening For The Disease

KOLs report that misdiagnosis of ALD as MS, ADHD, autism, and epilepsy leads to the failure to screen for the disease in a timely manner so as to identify patients before symptoms progress too far. BLUE is focused on increasing physician awareness of CCALD and its early signs (ex: Addison's disease, behavioral changes, learning disabilities, and MRI abnormalities), so physicians will screen for the disease and not let it go undiagnosed or misdiagnosed.

Comparing The Signs And Symptoms Of ALD and ADHD

	Degenerative Disorders (eg, ALD)	Developmental/Behavioral Disorders (eg, ADHD)
Family History	Sibling with unexplained death or neurologic abnormality (such as multiple sclerosis), or alternatively, lack of a suggestive family history; Addison's disease	Learning disabilities, attention disorders, behavior problems often reported in family members
Disease Course	Onset or marked worsening of symptoms; preschool and early school years often normal	Behavioral/developmental symptoms chronic, often noticed when child begins school; ADHD diagnosis requires onset of symptoms before age 7
Comorbidity	Symptoms of multiple externalizing and internalizing disorders (ie, depression, anxiety) common; neurological signs such as seizures often present; adrenal insufficiency often present	Symptoms of multiple externalizing and internalizing disorders (ie, depression, anxiety) *less* common; adrenal insufficiency lacking

Source: Ievers CE. J Dev Behavior Pediatrics, 1999

Newborn Genetic Screening Could Improve Therapeutic Outcomes

CCALD is characterized by very rapid disease progression, with MRI abnormalities preceding disease onset, neuroinflammation, and compromised blood brain barrier by months. The only available treatment for cerebral disease is allogeneic bone marrow transplant, which can arrest demyelination, and has little benefit when the disease is well-advanced. As a result, early testing is key for accurately diagnosing the disease and improving therapeutic outcomes.

- A newborn genetic screening test is being developed that is simple and inexpensive.
- This process enables early detection of CCALD and offers the opportunity to identify patients for proactive disease monitoring and early disease intervention.
- Newborn genetic screening is already available in several states (e.g., Connecticut and New York) and is expected to be widely adopted in the US within the next 5 years.
  - **Within the first few months of the adoption of newborn genetic screening in New York, 5 boys were diagnosed with the disease, giving them the opportunity to receive treatment options that they may not have been able to take advantage of if the disease had been undiagnosed or misdiagnosed.**
  - Beyond the state level, the Stop ALD Foundation has submitted a Senate bill, requiring newborn screening for adrenoleukodystrophy.

Since treatment outcomes improve the earlier CCALD is detected, the widespread adoption of newborn genetic screening could transform the diagnosis and treatment paradigm for CCALD, potentially unlocking a broader patient population. BLUE would benefit from this genetic screening, since patients could be accurately diagnosed and treated before symptoms even present.

Current CCALD Treatment Options Highlight Great Unmet Need

- **Hematopoietic stem cell transplant** (HSCT).
  - Demonstrated to be successful in arresting disease progression in a small subset of pre-symptomatic patients with demonstrable early signs of cerebral demyelination.

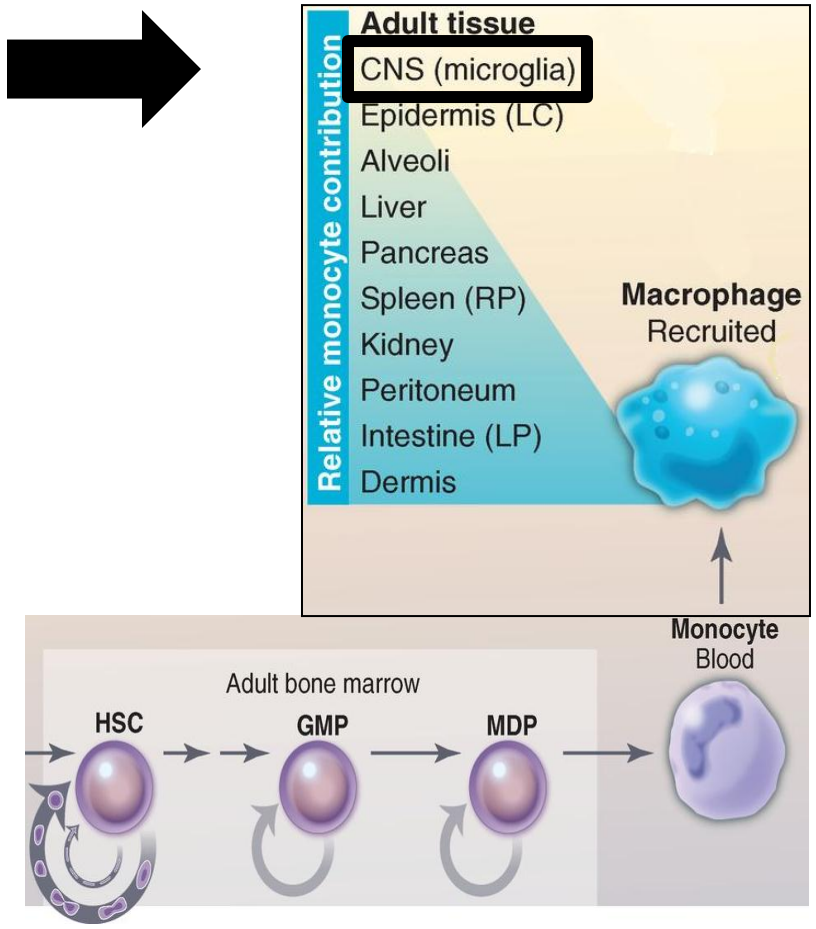
- **"Lorenzo's Oil"** (glyceryl trioleate-trierucate oil).
  - A natural supplement, extracted from rapeseed and olive oils, which normalizes the accumulation of the very long chain fatty acids in the brain, thereby halting the progression of ALD.
  - Not FDA-approved for the treatment of CCALD, and is currently only available to patients taking part in a clinical trial under the direction of the Kennedy Krieger Institute.
  - Lorenzo's oil does not alter the clinical progression of patients with neurological symptoms, and has shown little benefit in patients over the long term.

- **Dietary adjustments and statins.**
  - While dietary adjustments and statins lower VLCFAs, they do not prevent neurologic deterioration in CCALD patients. Also, dietary adjustments are difficult for patients to maintain.

A clear unmet need exists for CCALD patients, given that HSCT is a limited treatment option since it cannot be used as a preventative therapy, given the associated risks, and has limited efficacy in those patients whose disease has progressed too far (indicated by a Loes score greater than 9).

How HSCT Is Able To Treat CCALD– A Brain Disease

- HSCs differentiate into a number of different cells.
- One such type of cell is a **macrophage.**
- These cells are responsible for protecting the body against infection and **inflammation.**
- Macrophages can further differentiate into additional cell types, based upon the tissue location.
  - Upon penetration into the brain/CNS through the peripheral blood, these **macrophages differentiate into microglia cells.**
  - Microglia cells are ubiquitously distributed throughout the CNS and have a **key role in the defense against inflammation and neurodegeneration** (Kreutzberg, 1996).
- Following HSCT, transplant-derived macrophages migrate to the brain and differentiate into **microglia cells, which are specifically attracted to sites of neuronal damage.**
- Long-term follow-up has confirmed that HSCT can arrest the neuroinflammatory demyelinating process of ALD (provided the procedure is conducted at an early stage of the disease).
- However, there is generally a delay before progression of demyelination arrests after HSCT, **given the relatively slow replacement of brain microglia from bone marrow derived cells.**



Source: www.nature.com

Extensive Study Of HSCT For CCALD Provides Proof-Of-Concept For BLUE

In 2004, an extensive study was published in *Blood* which explored the outcomes of 94 boys with CCALD who underwent HSCT at 43 transplant centers. The researchers concluded that HSCT is an effective treatment for CCALD, but only if it is performed at an early stage of the disease. The following are key takeaways from the 17-year study:

- The average estimate of **5-year survival after HSCT was 56%**, while the survival prospects for boys who **do not receive HSCT after symptoms present was less than 40% and approaches 0% after 15 years.**

- The Loes score (or MRI severity score, see page 35) is predictive of survival after HSCT.
  - The Loes Score grades the extent of cerebral damage (demyelination), and correlates with neurocognitive dysfunction.
  - Those boys with a **Loes Score <9 before HSCT, had an 84% chance of survival 5 years after HSCT**, while those with a **Loes Score >9 had only a 42% chance of survival.**
  - As a result, researchers concluded that HSCT is most beneficial in the early stages of CCALD. However, researchers opposed HSCT as a preventative measure in those boys who have no evidence of demyelination yet (Loes score of 0) given the risks associated with the procedure.

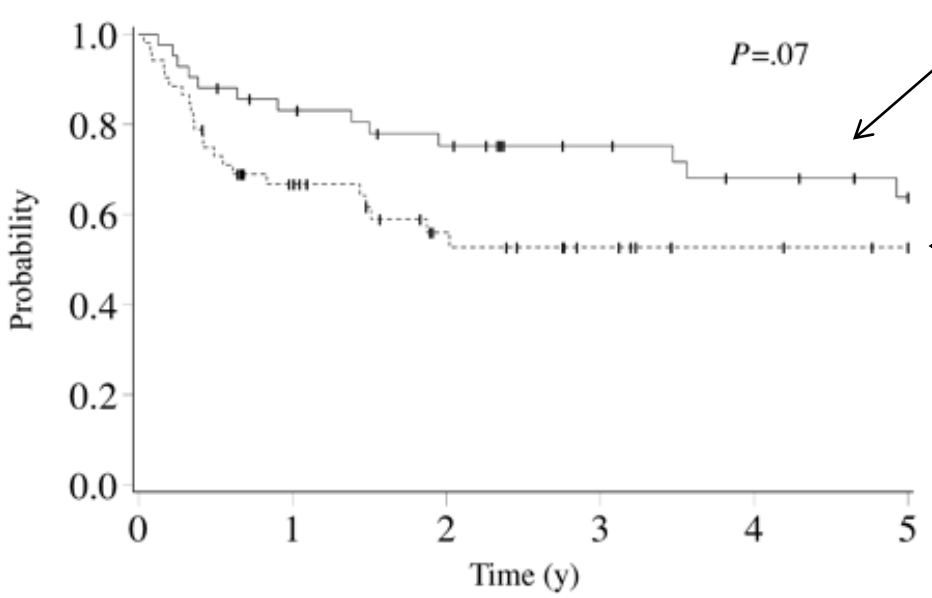
- The leading causes of death in the study were attributed to disease progression and graft vs. host disease.

Source: C. Peters, Blood, 2004

HSCT With A Related Donor Improves Outcomes

Kaplan-Meier Survival Estimate For CCALD After Related and Unrelated Donor HSCT

Source: C. Peters, Blood, 2004



5-year survival probability for related donor HSCT was 64%.

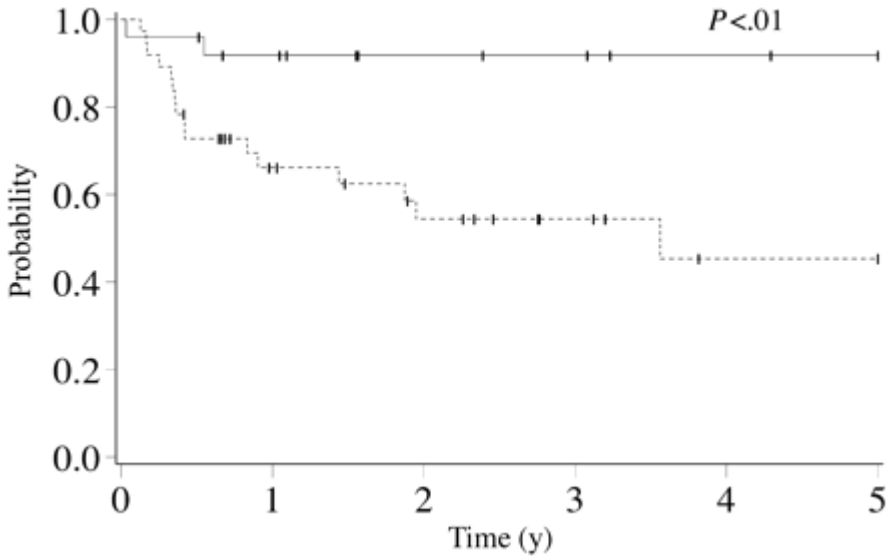
5-year survival probability for unrelated donor HSCT was 53%.

The study highlighted that survival outcomes improve when a more favorable donor (i.e., a relative) is used. Unrelated donor HSCT comes with a higher risk of mortality and disease progression. Since survival outcomes improve when the procedure is carried out with a relative, we would expect survival outcomes to even further improve by employing BLUE's method of autologous HSCT, in which the **patient's own cells are used**, therefore mitigating graft vs. host disease.

Early Treatment With HSCT Significantly Improves Outcomes

Kaplan-Meier Survival Estimate Based On Severity Of CCALD Disease Progression

Source: C. Peters, Blood, 2004



Survival estimate is 92% for those patients whose disease is caught early and treated with HSCT.

Survival estimate is 45% for those patients whose disease has progressed.

Although survival improved with early HSCT treatment, patients still underwent complications, such as GVHD.

The earlier CCALD is treated with HSCT, the more favorable the outcomes. However, given the risks associated with allogeneic HSCT, the procedure is not recommended as a preventative measure. While BLUE has the opportunity to effectively treat both early and late stage CCALD, the ultimate goal of BLUE's gene therapy is to prevent the onset of CCALD symptoms, so no damage will occur to the brain. With the potential wide adoption of newborn genetic screening for CCALD, we expect this will be a feasible goal to attain within the next 5 years.

The Risks Associated With Allogeneic HSCT

- Since it is difficult to find a related donor for HSCTs (**15% of CCALD patients have a sibling with a matching tissue type**), most of these procedures are done with an unrelated donor. Because a unrelated donor's cells do not recognize the recipient's cells upon transplantation, the donor's cells wage an immune response on the host's cells, rejecting their new, foreign environment. This is known as graft vs. host disease (GVHD).
  - To combat GVHD, glucocorticoids (ex: prednisone) are administered to suppress the donor cells' rejection of the recipient's tissue.
  - Extended use of glucocorticoids compromise the recipient's immune system and put the recipient at risk of developing life-threatening opportunistic infections.
- The 2004 article in *Blood* reported that unrelated donor HSCTs resulted in:
  - **30% risk of graft vs. host disease.**
  - **12-16% incidence of life-threatening infection.**
  - **14% incidence of transplant-related mortality within 3 years after HSCT.**
  - **10-30% risk of engraftment failure.**

Source: C. Peters, Blood, 2004

These risks are more closely associated with allogeneic HSCT than with autologous HSCT. Using a patient's own cells for HSCT lowers the risk of GVHD and eliminates the need for extended immunosuppression regimens, and improves engraftment.

To Summarize– Great Unmet Need Exists For CCALD, Despite HSCT

- Allogeneic HSCT works, but it comes with significant risks of GVHD and mortality.
  - **BLUE's autologous approach could greatly improve safety.**
- Case studies of allogeneic HSCT in CCALD benchmark efficacy for BLUE's autologous gene therapy approach.
  - **Survival outcomes improve for CCALD patients treated with HSCT.**
  - **However, disease progression can continue even after HSCT.**
  - **BLUE's approach has the potential to shorten the time to halting disease progression after administration of its gene therapy, which in turn improves the patient's outcomes.**

Although HSCT provides a benchmark for BLUE's autologous gene therapy approach, BLUE may offer a safer and more efficacious approach for CCALD patients.

Lorenzo's Oil May Benefit Asymptomatic ALD Patients, But Not Over The Long-Term

Some Good…

- In a study of 89 ***asymptomatic*** ALD patients treated with Lorenzo's Oil, researchers concluded that the therapy is useful in those males who have normal brain MRIs and have not yet shown neurologic symptoms (H. Moser, *JAMA Neurology*, 2005).
  - After being following for ~7 years, 74% of the patients did not experience disease progression.
  - However, those that **did develop MRI and neurological abnormalities** (33%), **had the CCALD form of ALD**.
- Researchers noted that given the rapid progression of this disease and the current reliance on imprecise testing methods, it is difficult to catch those patients who have ALD before symptoms present.

…And The Bad

- A number of studies confirm that Lorenzo's oil should **not be prescribed to ALD patients who are already symptomatic.**
  - For example, in a 2-year trial with Lorenzo's Oil in 14 males, researchers reported "no evidence of a clinically relevant benefit from treatment with Lorenzo's oil in ALD patients" (P. Aubourg, *NEJM*, 1993).
  - Although a few asymptomatic patients experienced an initial decline in VLCFAs, this decline was not sustained beyond 2 years, and none of the 14 males showed an improvement in their disease.
- Furthermore, studies highlight that **Lorenzo's Oil induces adverse effects.**
  - In a study of 22 patients treated for at least a year with Lorenzo's Oil, no patients benefited from the therapy (no neurological function improvement nor arrested disease progression), but most all suffered from adverse events. 55% of patients experienced thrombocytopenia, 55% experience elevated liver enzyme levels, and 14% had gastrointestinal complaints (B M van Geel, *J Neurol Neurosurg Psychiatry*, 1999).

Given the severity of CCALD and the difficulty of achieving an early diagnosis, benefit with Lorenzo's Oil may be hard to achieve, and any benefit obtained is only sustained in the short-term. BLUE's therapy has the potential to provide a life-long cure for CCALD.

BLUE's Lenti-D Product Candidate– Offering Hope For CCALD Patients

Lenti-D: How It Works

- Lenti-D delivers a functional copy of the ABCD1 gene to a patient's own (autologous) HSCs *ex vivo* via a **modified, non-replicating version of the Human Immunodeficiency Virus Type 1 (HIV-1)** .
- The isolated, genetically modified HSCs are returned to the patient, which in turn differentiate and correct the aberrant expression of ALDP that results in excess VLCFA in the brain.
- Based upon initial data, Lenti-D stabilizes the cerebral damage (demyelination) and inflammation characteristic of CCALD.
- Clinical benefits of Lenti-D are expected to become **evident within 20-24 months of transplant**.

Key Details And Milestones For Lenti-D

- BLUE has secured US and EU orphan drug designation for Lenti-D.
- Phase 2/3 (ALD-102 or "Starbeam") clinical trials are ongoing, and the first patient was transplanted in October 2013.
- EU sites are expected to be opened up in mid-2014.
- **Enrollment is expected to be complete by 2015.**

Lenti-D has the potential to be a one-time therapy intended to stabilize CCALD symptoms and prevent disease progression. Pivotal data can be expected in 2017, and we model a commercial launch in 2018.

BLUE's Retrospective Study (ALD-101) Verifies HSCT Improves CCALD Outcomes

- Because CCALD is such a rare disease and allogeneic HSCT has not been subject to extensive, systematic analysis in controlled clinical studies, the FDA recommended BLUE complete a non-interventional, retrospective study to assess the natural history of CCALD.
- BLUE completed ALD-101 in March 2013 and, in assessing the natural course of the disease in **137 patients** (**72 were untreated, 65 were treated with allogeneic HSCT**), BLUE concluded the following:

1. **Untreated CCALD patients experience bleak outcomes.**
   - In the untreated cohort, the median overall survival was 7.7 years, and the estimated probability of survival at 5 years was 55%.

2. **Baseline disease severity, as assessed by a neurological/neuropsychological exam and Loes score, are good predictors of survival.**
   - Treating CCALD early improves survival outcomes. The table below compares the **mortality rates*** (determined by the number of deaths that occurred at any time through the observation period after CCALD diagnosis) of untreated and treated patients based on baseline disease severity.

	Mortality Rate*			
	Normal neurological exam	Abnormal neurological exam	Loes score ≥ 1 ≤ 9	Loes score > 9
Untreated cohort	42%	85%	46%	76%
Treated cohort	12%	29%	13%	28%

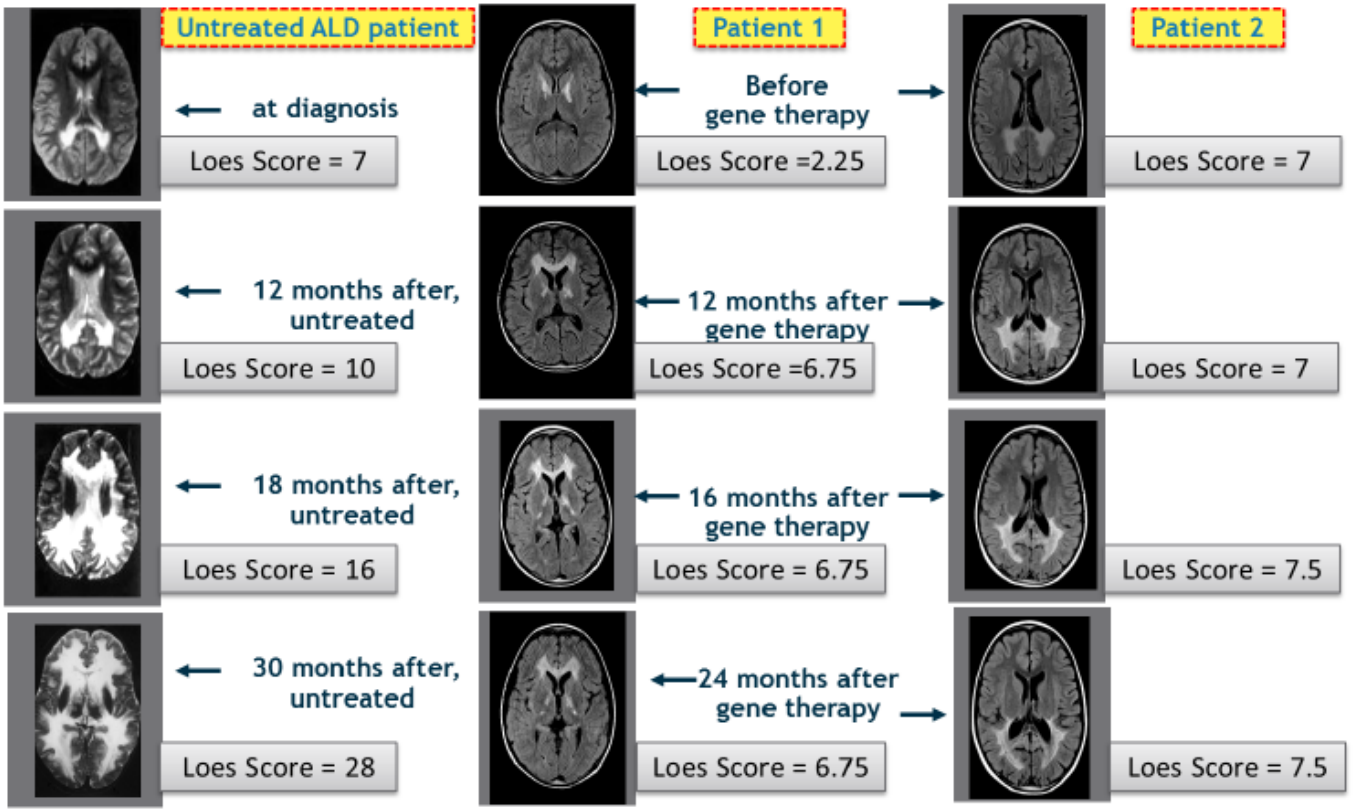
Source: BLUE S-1

3. **Although allogeneic HSCT offers the potential for disease stabilization, the procedure is associated with clinically significant morbidity and mortality.**
   - 71% of the patients treated with HSCT were transplanted with unrelated donor cells. As a result:
     - Engraftment failure occurred in 18% of patients treated with HSCT.
     - The rate of graft vs. host disease was 54%.
     - The 2- and 5-year survival rates post- allogeneic HSCT were 82% and 74%, respectively.

Proof-Of-Concept For Lenti-D Has Been Established In The Short Term…

TG04.06.01 Clinical Trial Results Using A Precursor To BLUE's Lenti-D Product

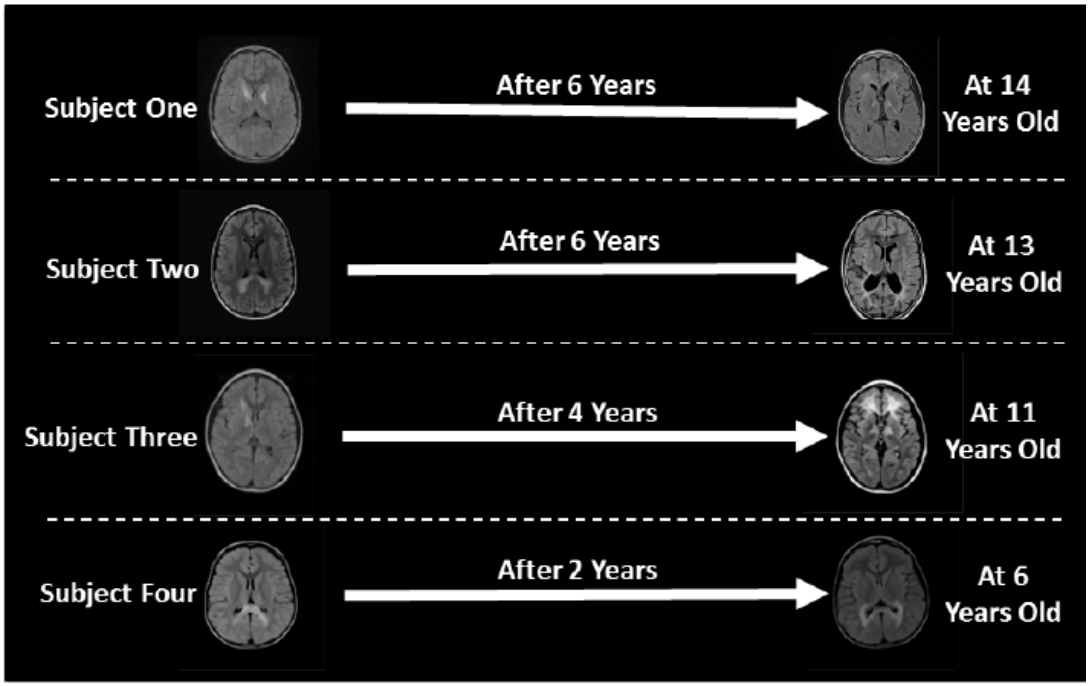
Source: BLUE Corporate Presentation



*Loes Score is a continuous scale 0 to 34 points based on the volume of myelin loss manifested on brain MRI. The higher the number the more myelin is destroyed.

In 2009, short-term clinical results for 2 CCALD boys treated with a **precursor to Lenti-D** were published in *Science.* This small study in France is ongoing through a collaboration with the French Institute of Health and Medical Research (INSERM), and longer-term efficacy results were released in March 2013 (see next page).

...And In The Long Term



Source: BLUE S-1

- **Efficacy results comparable to (if not better than) allogeneic HSCT.**
  - For example, the ALD-101 study suggested that the expected mortality rate is ~20% in the 2 years following allogeneic HSCT.
  - All 4 boys were alive two years or more after treatment with gene therapy and all experience multi-year disease stabilization.
- **None of the patients experienced any gene therapy-related adverse events.**
  - All 4 boys achieved successful engraftment within 15 days post-transplant and none experienced graft vs. host disease.

Although this is a limited study, which utilizes a **precursor to Lenti-D**, it serves as a useful benchmark of Lenti-D's potential long-term efficacy and safety.

Starbeam Study (ALD-102) Design

Number of subjects enrolled	N=15
Description	This is a Phase 2/3 trial designed to assess the safety and efficacy of Lenti-D in preserving neurological function and stabilizing cerebral demyelination in subjects with CCALD.
Primary endpoint	Proportion of subjects who have no **major functional disabilities** (**MFDs**)* at **24 months post transplant.**
Secondary endpoints	Change from baseline in neurological exam and Loes score, resolution of gadolinium enhancement, and overall survival.
Safety evaluations	Success of HSC engraftment, incidence of transplant-related mortality through 100 and 180 days post-transplant, detection of vector-derived replication of the lentivirus, and determination of the functional gene's insertion location.
Post-trial requirements	In accordance with the FDA, BLUE will monitor study participants **for up to 15 years to ensure maintenance of efficacy and safety.**

*MFDs include:
1. Loss of communication
2. No voluntary movement
3. Cortical blindness
4. Tube feeding
5. Wheelchair required
6. Total incontinence

The first subject was transplanted in Oct. 2013 and enrollment is expected to be complete in 2015. If this study is successful, BLUE believes it could form the basis of a BLA to the FDA. **Clinical data from this trial needs to be robust, with patient survival approaching 100% and minimal neuronal progression.**

What Lenti-D Needs To Do To Be Viable

- **A high percentage of HSCs need to express the therapeutic gene.**
  - Given the relatively slow replacement of brain microglia from bone marrow derived cells, if more HSCs express the therapeutic gene, the period during which cerebral demyelination continues to progress after HSCT could be shortened.
- **The vector copy number (VCN) needs to be high.**
  - VCN is the number of vector copies per cell following gene transfer. The higher this number, the more potent and efficacious the therapy can be.
  - As BLUE has improved its manufacturing processes, this number has increased from 0.3-0.6 to 1.0-3.0 (refer back to page 25).
  - **Preliminary data from 2 beta-thalassemia patients in the French HGB-205 study will be presented this weekend (on June 14) at the European Hematology Association (EHA)– ahead of the conference, BLUE released that the VCN in achieved in 2 patients was 1.5 and 2.1.**
  - According to BLUE management, if Starbeam achieves or beats these VCNs, the trial has a high likelihood of efficacy.

Given the proof-of concept data established for Lenti-D and the preliminary data on vector copy number from the beta-thalassemia trial in France (HGB-205), we believe that Lenti-D is well-positioned to deliver positive results for CCALD patients.

The Market Opportunity For Lenti-D In CCALD

Although CCALD affects a small patient population, there may be more patients affected by this disease than expected. If newborn genetic screening is widely adopted within the next 5 years, BLUE could greatly benefit from this because newborns could be treated before symptoms present (**~80 baby boys are born with CCALD each year in the US and EU**). BLUE is also working with KOLs to improve the diagnosis of CCALD and is promoting the widespread adoption of newborn genetic screening for the disease.

CCALD Patient Population And Lenti-D Penetration

- The current global incidence of CCALD is 123 patients, and we believe this number should rise with the increased adoption of newborn screening. We assume Lenti-D reaches 60% penetration into the global CCALD patient population by 2022.

Pricing Model

- According to BLUE management, cost of Lenti-D will be incremental to the transplant procedure (which can range from $100-500k, depending on the complexity of procedure). We believe a $1.3M price point for the therapy would be reasonable.

Assuming an average price of $1.3M, the peak global market for Lenti-D could be $180M+ per year, based upon our research. Considering the annual cost of orphan drugs, this price point for a 1-time therapy should be seen as reasonable.

Future Applications For Lenti-D

- BLUE chose to target CCALD first given the positive effect of allogeneic HSCT on the natural history of the disease.

- However, ACALD and AMN (other phenotypes of the broader ALD patient population) offer potential applications for Lenti-D.

  - Allogeneic HSCT has shown some early reported success in ACALD patients, suggesting autologous gene therapy with Lenti-D may be safe and efficacious in these patients. ACALD accounts for 5% of ALD.

  - No known allogeneic studies have been conducted in AMN patients, given that only 40% of these patients present serious cerebral symptoms. A natural history study would have to be conducted to provide evidence of the potential benefit from a gene therapy + HSC treatment. Currently, HSCT is not recommended in AMN patients without cerebral involvement given the risk of the procedure.

BLUE is interested in expanding Lenti-D to treat ACALD, but wants to get proof of concept in CCALD first.

Diving Into BLUE's Next Indications: Beta-Thalassemia And Sickle Cell Disease

Beta-Thalassemia (BT)

- BT is a rare, inherited blood disorder caused by a dysfunctional beta-globin protein, which in turn leads to inadequate hemoglobin production.
  - A reduction in hemoglobin deprives the body's cells of oxygen and creates a shortage of red blood cells.
- BLUE is targeting **BT major**, the severe form of the disease.
- Symptoms include severe anemia, splenomegaly, and iron overload in major organs.
- Patients require chronic blood transfusion regimens to maintain a steady state of hemoglobin levels.
  - However, over time, these transfusions lead to severe iron overload that causes serious damage to many organs.
- Allogeneic stem cell transplantation carries a significant risk of morbidity and mortality
- **Approximately 288,000 individuals have BT major, with an estimated 15,000 in the US and EU.**

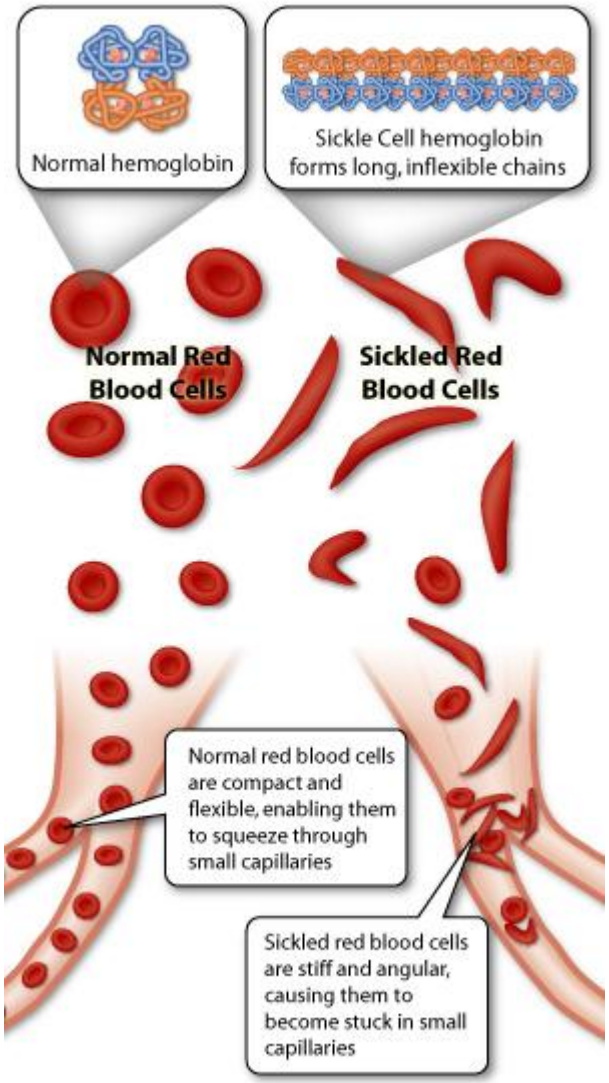
Sickle Cell Disease (SCD)

- SCD is a hereditary blood disorder resulting from a dysfunctional beta-globin protein that causes hemoglobin proteins to distort red blood cells into a crescent shape and break down prematurely.
- Symptoms include anemia, vaso-occlusive crisis, and strokes.
- Patients typically receive life-long chronic blood transfusion regimens, which may ameliorate symptoms but have safety and efficacy limitations.
- Allogeneic transplants have been shown to be effective, but there are few match donors.
- **Global incidence of SCD is approximately 250,000 - 300,000 births annually, and the global prevalence of the disease is estimated to be about 20-25M.**

BT and SCD represent larger opportunities for BLUE than CCALD– however its gene therapy (Lenti-Globin) will go up against an entrenched treatment paradigm (regular blood transfusions and iron chelation) as well as competition from other gene therapies.

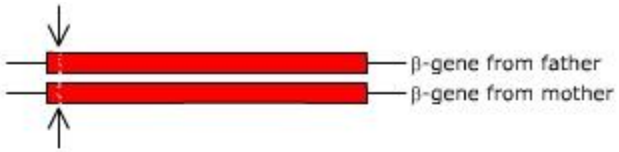
Understanding SCD And BT

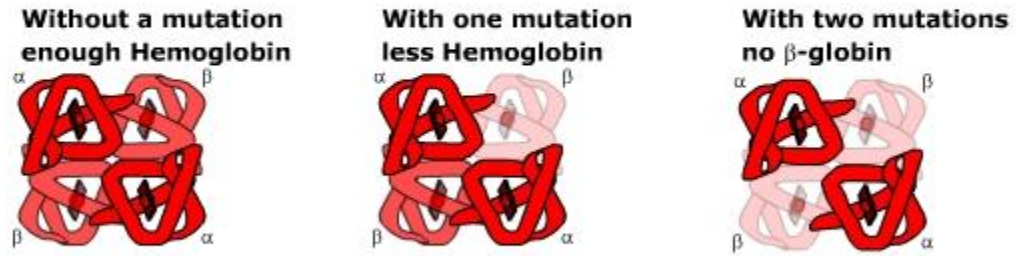
Sickle Cell Disease



Beta-Thalassemia

With a mutation on one of the two ß-globin genes, a carrier is formed with lower protein production, but enough hemoglobin





Both SCD and BT are caused by mutations in the hemoglobin beta (HBB) gene, which regulates the production of the beta-globin protein, a component of hemoglobin found in red blood cells. In SCD, the flow of blood through the capillaries is blocked given the crescent shape of the red blood cells. In BT, there is insufficient formation of hemoglobin which results in a shortage of red blood cells (causing anemia) able to transport oxygen.

Sources: http://jura.wi.mit.edu/bio/education/HS2010/, http://www.hbpinfo.com/en/mainframe/id/gfx/beta.jpg

The Current And Developing Therapies For BT

The Current Standard Of Care

- Chronic blood transfusions, which address the patient's anemia.
- To manage the iron overload associated with these chronic transfusions, patients often undergo iron chelation therapy.
  - NVS and ApoPharma are the leading providers of iron chelation therapy. They are seeking to develop improvements to their product profile and accessibility.
- Some BT patients receive HSCT, but only if a well-matched donor is found, since the **mortality risk of allogeneic HSCT in adults with BT exceeds 20%.**

The Gene Therapies In Development

- **SGMO/BIIB**
  - Employing ZFNs to "turn-on" fetal hemoglobin. No clinical studies have been initiated, but an IND will be submitted during 2014.
- **Memorial Sloan Kettering**
  - Received approval for its IND in 2012 and is actively recruiting for a Phase 1/2 gene therapy trial.
- **GSK**
  - Pursuing an agreement with San Raffaele Telethon. No clinical trials have been initiated.
- **St. Jude**

And The Non-Gene Therapies In Development

- **Acceleron's ACE-536 (partnered with CELG).**
  - A Phase 2 trial in beta-thalassemia intermedia patients (a less severe version of BT than BLUE is targeting) is currently ongoing. Results are expected YE14. ACE-536 is a ligand trap that inhibits members of transforming growth factor beta, which are proteins that are involved in RBC regulation.

Other gene therapies in development utilize a similar ex vivo autologous approach, but employ different vectors and different cell processing techniques.

Current And Developing Therapies For SCD

The Current Standard Of Care

- Chronic blood transfusions or hydroxyurea (a generic drug).
  - Ongoing studies are evaluating the efficacy and safety of hydroxyurea and data from these studies will influence its future utilization.
- To manage the iron overload associated with these chronic transfusions, patients often undergo iron chelation therapy.
- Some SCD patients receive HSCT, but only if a well-matched donor is found (less than 10% of SCD patients have a well-matched donor).

The Gene Therapies In Development

- **UCLA.**
  - Received funding from the California Institute of Regenerative Medicine to pursue a Phase 1/2 gene therapy study for SC. No clinical trials have been initiated.
- **SGMO/BIIB.**
  - Phase I expected to begin in 2015, with potential launch in 2020.
- **St. Jude.**

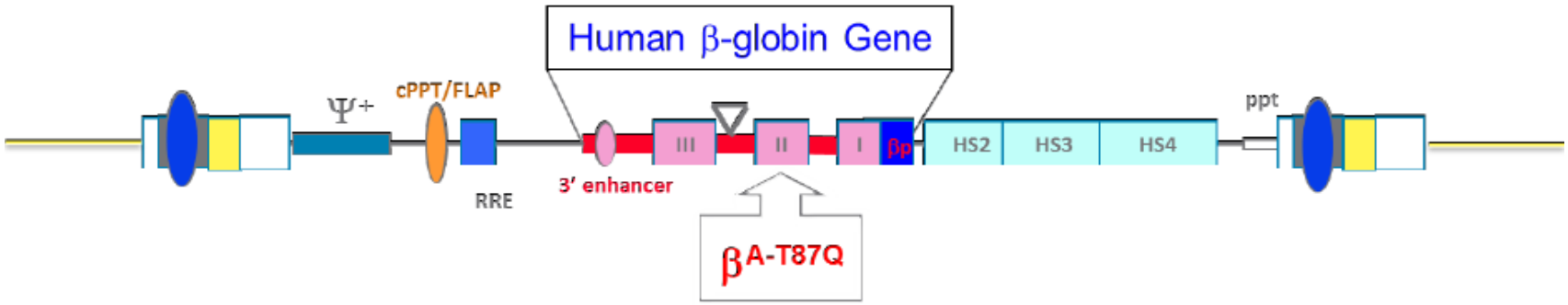
And The Non-Gene Therapies In Development

- **Mast Therapeutics' MST-188.**
  - An inflammatory inhibitor, currently in Phase 3, with data expected in 2015.
- **HemaQuest's HQK-1001.**
  - A Fetal hemoglobin regulator, which is entering Phase 3 in 2H14.
- **Merck's Vorinostat.**
  - Induce fetal hemoglobin, currently in Phase 2.
- **PFE/GlycoMimetics' GMI-1070.**
  - A pan-selectin inhibitor, currently in Phase 2.

LentiGlobin Could Be Disruptive In BT And SCD

With the development of LentiGlobin, BLUE is looking to achieve a dramatic clinical impact for patients with BT and SCD.

- The current treatment options and non-gene therapy programs in development have only a modest and incremental effect upon the BT and SCT disease course.
- LentiGlobin has the potential to disrupt the current standard of care for both BT and SCD, as a one time therapy with the potential to both cure and ultimately prevent both of these diseases.



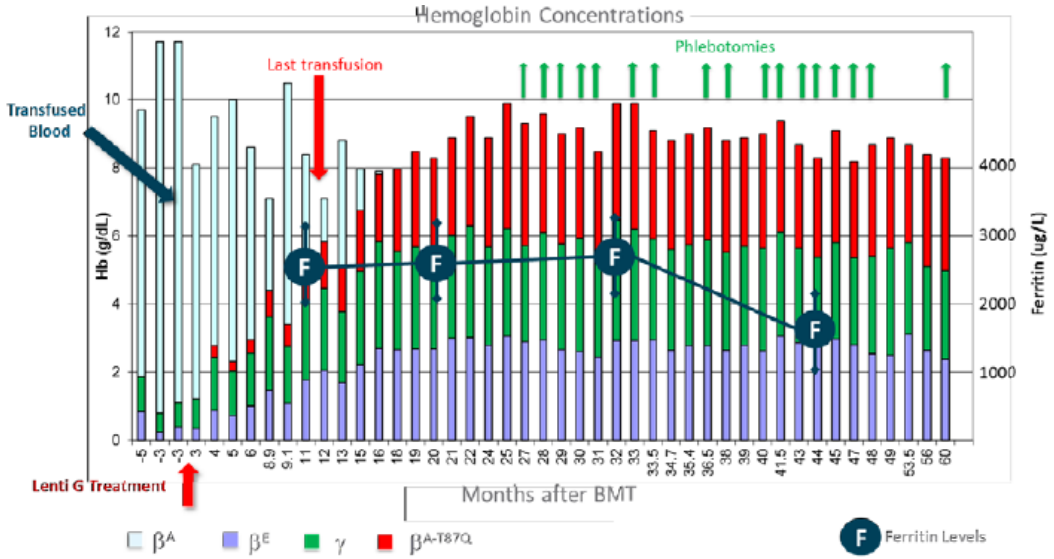
- Biomarker for transgene expression via blood sample
- Provides anti-sickle properties (published Science 2001)

Source: BLUE Corporate Presentation

French Collaborators' LG001 Study Provides Proof Of Concept For LentiGlobin

Between 2006 and 2011, LG001 (a Phase 1/2 study) was conducted by BLUE's French scientific collaborators in 3 BT subjects with a **precursor to LentiGlobin** (**called HPV569**). 2 subjects underwent successful engraftment, and while only one experienced remarkable results, BLUE reiterates that the vector used was a precursor to LentiGlobin, and vast improvements have been made.

- Following infusion with HPV569, 1 subject has been transfusion-independent for 5 years, a testament to the therapeutic potential of this gene therapy.
- Another subject achieved higher levels of therapeutic hemoglobin, but these levels gradually declined. As a result, this subject remains transfusion dependent.



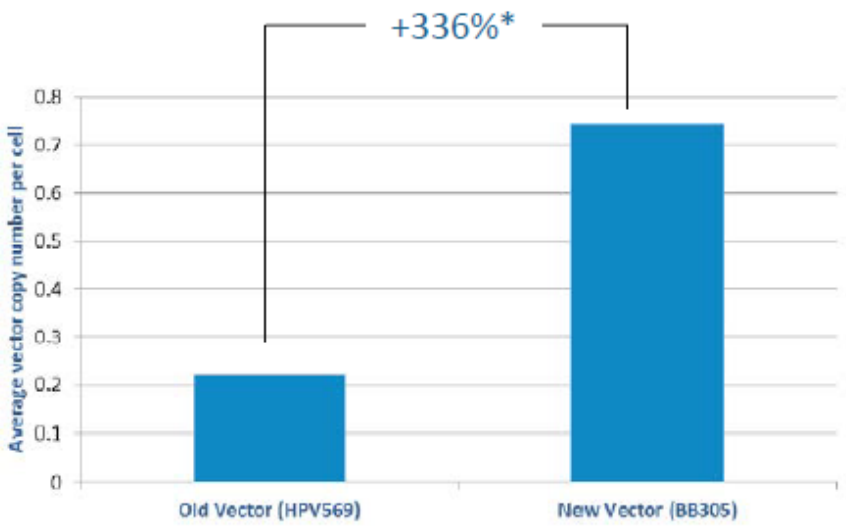
Source: BLUE Corporate Presentation

An extension study is now being conducted (HGB-205) in France with the new LentiGlobin vector in patients with both BT and SCD. All 3 subjects from the LG001 study will also participate in a follow-up study LTF-303 to evaluate the long-term safety and efficacy post-transplant.

LentiGlobin Product An Improvement To HPV569 Precursor

A preclinical evaluation of LentiGlobin showed that transduction efficiency was higher with LentiGlobin as compared to the HPV569 vector used in the LG001 Study. These improvements were introduced into the vector manufacturing and transduction processes– the transgene remains the same.

- LentiGlobin resulted in higher expression of the therapeutic globin protein compared to that of HPV569.



*Source: bluebird bio, Inc . unpublished data

Improvements to the precursors vector (HPV569) have resulted in LentiGlobin which has:

1. **25 to 30-fold reduction in non-infectious viral particles.**
2. **3x vector copy number increase (the number of vector copies per cell following gene transfer).**

BLUE expects that LentiGlobin will achieve a higher frequency of gene-therapy modified HSCs in the patients treated in the HGB-205 and Northstar clinical trials as compared to what was achieved in the LG001 study.

HGB-205 Study Design

Number of subjects enrolled	N=7
Description	This is a Phase 1/2 trial designed to assess the safety and efficacy of LentiGlobin in patients with BT or SCD.
Primary endpoint—All Patients	Red blood cell transfusion requirements per month and per year, post transplant and the number of total in-patient hospitalization days.
Secondary endpoint– SCD patients	Number of vaso-occlusive crises or acute chest syndrome events at 6, 12, and 24 months.
Safety evaluations	Success of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived lentivirus, and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.
Study duration	Subjects will remain on the study for 24 months.

This is a small study which was initiated in France in 2013. **Initial data from two BT patients will be presented this weekend (on June 14) at the European Hematology Association in Milan.** Additional data can be expected by YE14.

Northstar Study (HGB-204) Design

Number of subjects enrolled	N=15
Description	This is a Phase 1/2 trial designed to assess the safety and efficacy of LentiGlobin in increasing hemoglobin production and eliminating/reducing transfusion dependence in BT patients following treatment.
Primary endpoint	Clinically meaningful increase in endogenous hemoglobin production that would be expected to diminish transfusion requirements.
Secondary endpoints	Red blood cell transfusion requirements per month and per year, post transplant.
Safety evaluations	Success of HSC engraftment, incidence of transplant-related mortality post-treatment, overall survival, detection of vector-derived lentivirus, and characterization of events of insertional mutagenesis leading to clonal dominance or leukemia.
Study duration	Subjects will remain on the study for 26 months, and then will be enrolled in a long-term follow-up for 2 years to assess safety and efficacy.

The first BT patient was transplanted in March 2014 and preliminary data could be expected by YE 2014. BLUE plans to initiate a Phase 1/2 study (HGB-206) with LentiGlobin in SCD patients during 2H14.

The Market For LentiGlobin In BT And SCD Could Be Big

The market opportunity for LentiGlobin in BT and SCD is much larger than that of Lenti-D in CCALD. By targeting these diseases, BLUE has the potential to establish a leadership position in a major therapeutic class by disrupting the current standard of care.

SCD and BT Patient Populations

- Global incidence of SCD is ~250-300k births annually (global prevalence is 20-25M).
- In the US, SCD is a standard part of newborn screening, and incidence is >1600 births annually (US prevalence is 100k).
- Global prevalence of BT major is 288k, with 15k patients in the US and EU.

Pricing Model

- BT is a smaller market than SCD and SCD is concentrated in populations of African, Middle Eastern, and South Asian descent.
- We model commercial availability of LentiGlobin for beta-thalassemia in 2020, at a price of $1M.

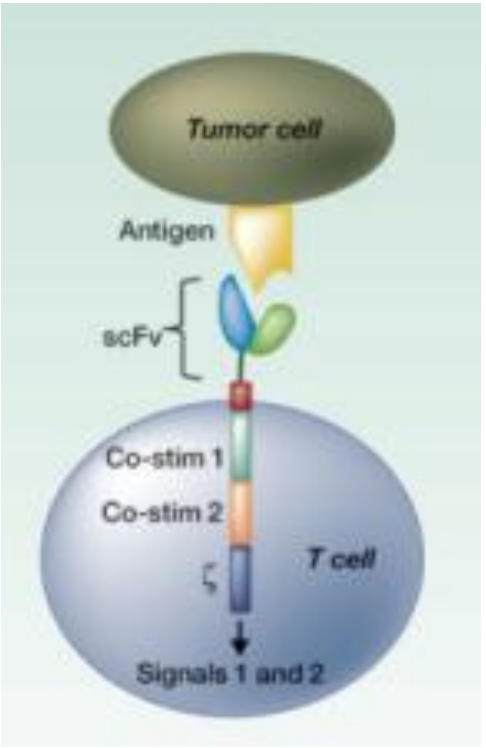
LentiGlobin could potentially be a $500M-$1B therapy, especially if it works well in SCD, which is the larger market opportunity.

And In Preclinical Development With Partner CELG– Car-T Therapy

Brief Background On Car-T Therapy

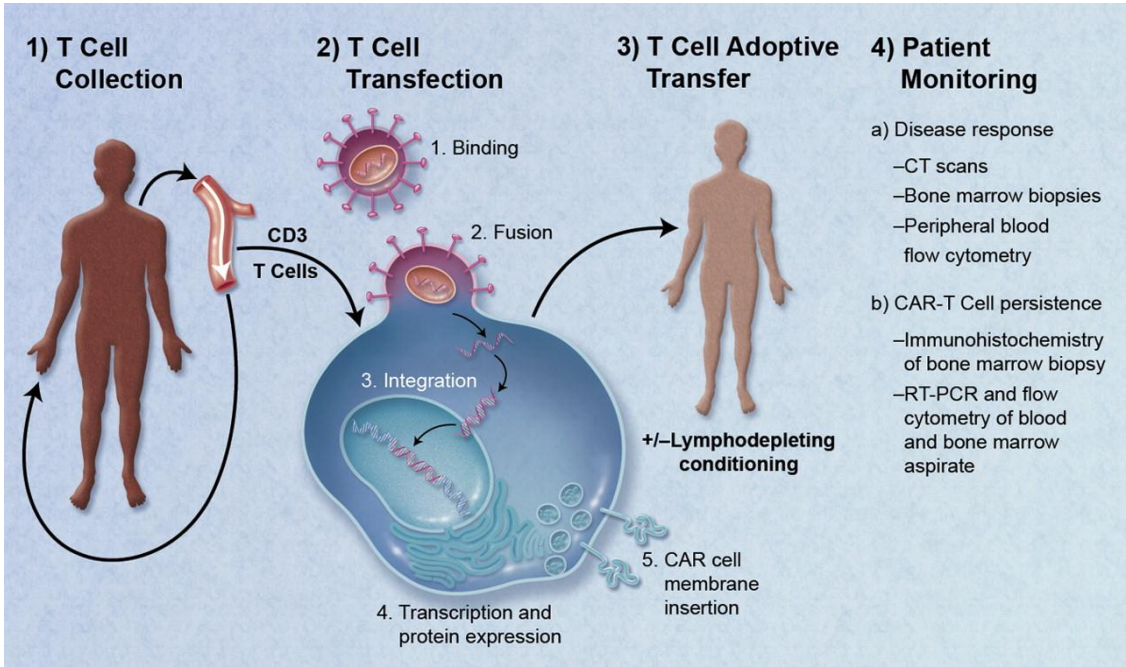
- *Chimeric antigen receptor (*CAR)-T therapy applies gene therapy to genetically modify a patient's own *T cells* to target and destroy cancer cells.
- Defining the key terms:
  - **T cells:** These cells are the "killers" of the immune system– they play a central role in cell-mediated immunity.
  - **Antigen:** Typically presented on surface of cells foreign to the body (like on viruses, bacteria, or tumor cells) which evoke an immune response.
  - **CD19:** Known as **C**luster of **D**ifferentiation **19**, CD19 is a an antigen commonly found on the surface of B-cells (white blood cells) and signal tumor cells that arise from these cells. CD19 is an ideal target for CARs because its expression is restricted to normal and malignant B cells.
  - **Chimeric:** The term refers to the fact that CARs combine distinctly different domains of an antibody with intracellular signaling domains to form a **single chimeric protein**. The 2 components of the chimeric antigen receptor are:
    1. **scFV** (single-chain **v**ariable **f**ragment): A piece of a monoclonal antibody which resides outside the T-cell membrane. scFV (known as the ligand binding domain) guides the cell to its target antigen (ex: CD19).
    2. **Co-stim 1** and **Co-stim 2**: These are the signaling domains inside the T-cell, which engage when the T-cell binds to the tumor cell's antigen. Co-stim 1 and Co-stim 2 tell the T-cell to become fully active– able to proliferate and attack cancer cells.

Anatomy Of The Interaction Between A CAR-T Cell And A Tumor Cell



Source: www.cancer.gov

Licensed To Kill– T-Cells On A Mission



1. A patient's T cells are harvested.
2. These autologous T cells are genetically modified (likely with a viral vector such as lentivirus- enter BLUE's expertise) to express a *chimeric antigen receptor* that targets CD19.
3. The cells are then infused back to the patient.
4. Patients are monitored to ensure the therapy's efficacy and safety.

Source: Wikipedia

Car-T therapy has resulted in durable responses and by partnering this program with CELG, BLUE is well-aligned to expand beyond orphan diseases and tap into the larger cancer patient population, while maintaining expertise in lentiviral vectors and HSCT.

What Makes Car-T Therapy So Exciting– Proof Of Concept Has Been Established

There are currently 20+ clinical trials ongoing evaluating Car-T therapy across a range of B-cell malignancies. During the 2013 ASH annual meeting, exciting data were presented by UPenn and the National Cancer Institute (NCI).

UPenn Clinical Trial Results

- In a study of 20 patients (16 children and 4 adults), all signs of cancer disappeared (a complete response was achieved) in most patients treated.
  - **14 patients (82%) achieved a complete response.**
  - Although 3 of the patients relapsed, **11 of the 17 evaluable patients who had complete responses have remained cancer free.**
- No serious adverse events occurred and the therapy was generally well tolerated.
- According to the investigators, Car-T therapy has promise as a salvage therapy for patients who relapse after allogeneic HSCT, give the low risk of GVHD.
- This trial is currently entering Phase 2.

Sources: Grupp SA. ASH 2013; Lee DW. ASH 2013.

NCI Clinical Trial Results

- In a study of 8 pediatric ALL and NHL patients (both pre- and post- HSCT), **5 of the patients (62.5%) have had complete responses.**
  - 6 of the 8 patients had successful expansion of Car-T cells that met the assigned dose level.
  - Transduction efficiencies ranged from 18-87%.
  - Expansion was insufficient to meet the target dose for 2 patients, but each received products that were 3% and 14% of the target dose.
  - The therapy was well tolerated.

A barrier to the speedy development of Car-T has been its manufacture– manufacturing the therapy is time-intensive. However, academic institutions and companies have made great strides in producing Car-T on a clinically (and ultimately commercially) viable scale.

The Car-T Competition Will Be Stiff, And Everyone Is Keeping Quiet

Although much of the research has been limited to academic institutions (Baylor College of Medicine, University of Pennsylvania, and Memorial Sloan Kettering Cancer Center) the following are key biotech/pharma players with platforms harnessing lymphocytes to target tumors (TCR, Car-T, and bispecific antibodies):

- **Novartis/U. Penn** (potentially in the lead)
- **Cellectis**
- **Adaptimmune**
- **Kite Therapeutics**
- **Juno Therapeutics**
- **Jounce Therapeutics**
- **Bellicum**
- **Sangamo**
- **Lentigen**
- **Affimed**
- **Emergent Biosolutions**

Terms Of The CELG Partnership In Car-T Therapy Development

- BLUE received an up-front payment of $75M.
- BLUE will be responsible for conducting and funding all R&D performed up through completion of the initial Phase 1 clinical study, after which time CELG has the option to obtain an exclusive WW license to develop and commercialize the product.
- As a result of the license, CELG would be obligated to pay development and regulatory milestones as well as a percentage of net sales as a royalty.
- Max payment is $225M in connection with this program, and royalties would range from the mid-single digits to mid-teens.
- The collaboration will expire in 2016, but CELG has the option to extend for another 2 years.

And Beyond The Pipeline– Many Future Opportunities Are Open To BLUE

Source: BLUE S-1

LENTIVIRAL PLATFORM				AAV PLATFORM		
Central Nervous System	Hematology	Oncology	Immunology	Hemophilia B	Ocular	Central Nervous System
ALD	ß-thalassemia	Hematologic Tumors				
Lysosomal Storage Disorders	Sickle Cell Disease	Solid Tumors				
Other Central Nervous System	Hemophilia A					

Additional Indications That Can Be Treated With Allogeneic HSCT

- Diamond Blackfan Anemia
- Schwachman Diamond Syndrome
- Epidermolysis Bullosa
- Wiskott Aldrich
- MPS Type 1
- SCID
- Fanconi Anemia
- Hemophagocytic Lymphohistiocytosis
- Leukocyte Adhesion Deficiency

BLUE is committed to becoming a leader in gene therapy and to achieve this, the company plans to expand its expertise beyond *ex vivo* gene therapy with lentiviral vectors. BLUE will likely explore *in vivo* gene therapy with lentivirus as well as adeno-associated virus (AAV) in many new indications. The indications that can be treated with allogeneic HSCT may give us clues to future potential programs for BLUE's lentiviral gene therapy approach.

Regulatory Environment Increasingly Focused On Gene Therapy

The FDA's Cellular, Tissue, and Gene Therapies Advisory Committee has been tasked with establishing clinical and manufacturing guidelines to facilitate the industry's development of gene therapy products as well as codify the regulatory review process for cell and gene therapies.

- In February 2014, the committee met to discuss the design of early-stage clinical trials, to ensure the appropriate evaluation of a gene therapy's safety, tolerability, and feasibility.
  - Specific topics of discussion included:
    - Clinical trial objectives
    - Study population
    - Use of a control group and blinding procedures
    - Dose selection and escalation schedule
    - Treatment plans
    - Monitoring
    - Follow-up activities
- The guidance documents have not yet been finalized, but should be expected in 2H14.
- The committee will have follow-up meetings on July 29-30, and again on November 5-6.

These discussions are very important and highlight a shifting regulatory environment as the FDA is becoming more engaged with facilitating the development and review of gene therapies. We believe this may bode well for BLUE, which will likely submit a BLA after the completion of its Starbeam Study (Phase 2/3) for CCALD.

BLUE IP and Exclusivity

BLUE's patent portfolio includes the following:

- ~191 patents/patent applications owned by the company or exclusively in-licensed from academic institutions and third parties related to lentiviral vectors and vector systems
- ~58 patents/patent applications that have been non-exclusively in-licensed or optioned from academic institutions and third parties related to lentiviral vectors and vector systems
- ~18 patents/patent applications that are owned or have been exclusively in-licensed from academic institutions and third parties, including 8 that are co-owned with MIT, related to vector manufacturing or production
- ~7 patents/patent applications that have been non-exclusively in-licensed from academic institutions related to vector manufacturing and production
- ~22 patents/patent applications that are owned or have been exclusively in-licensed from academic institutions and third parties related to therapeutic cellular products

BLUE holds one of the most extensive lentiviral vector patent estates and "know-how"– which gives the company a competitive advantage.

BLUE Management Team– Leaders In The Field Of Gene Therapy

Nick Leschly	**President & Chief Executive Officer**	• Joined bluebird bio in 2010 • Formerly a partner of Third Rock • Also worked at Millennium Pharmaceuticals, leading early-stage drug development programs
Mitchell Finer, PhD	**Chief Scientific Officer**	• Joined bluebird bio in 2010 • Founder of Cell Genesys, Abgenix, and Avalanche Biotechnologies
David Davidson, MD	**Chief Medical Officer**	• Joined bluebird bio in 2012 • Previously senior medical director at Genzyme, where he led Genzyme's gene therapy and Pompe disease ERT programs
Jeffrey Walsh	**Chief Operating Officer**	• 25 years of experience in finance, business development, and strategic planning • Previously chief business officer of Taligen Therapeutics
Richard Smith, PhD	**VP Investor Relations**	• Joined bluebird bio in 2013 • Previously VP of IR at Pharmasset and was an equity research analyst at JP Morgan from 2004 to 2008
Cyrus Mozayeni, MD	**VP Business Development**	• Joined bluebird bio in 2010 • Previously direct of strategic/business development at PPD Dermatology

Source: bluebird bio

Program	Indication	Type	Event	Expected Timing
Lenti-D	CCALD	Clinical	Initiate enrollment in EU sites	2014
		Clinical	Complete Enrollment in Starbeam Study	2015
		Regulatory	File BLA	2016/2017
LentiGlobin	Beta-Thalassemia	Clinical	Prelim. data from HGB-205 in France at EHA	June 14
		Clinical	Additional data from Northstar and HGB-205	YE14
	Sickle Cell Disease	Clinical	Initiate enrollment in HGB-206	2H14
		Clinical	Prelim. Data from HGB-205 and HGB-206	2015

Source: PJC and Company reports

Discounted Cash Flow (DCF) Analysis	
Assumed Discount Rate (%)	*11.0%*
Discounted Net Cash Flow (2014-'22)	-$93
Terminal Growth Rate (%)	*8%*
Implied Terminal Year FCF Multiple	**36.0x**
NPV of FCF	$1,047
Terminal value as % of total	*108.9%*
Net Cash	159
Shares Outstanding 2018E (million)	35.7
Price Target	**$34**
Current Price	$25.27
Mkt Cap, Current Share Count	$610
Implied Mkt Cap, Price Target	$815
Implied Multiple on 2020 Rev	**3.0x**

Source: Company Reports and Piper Jaffray.

BLUEPrice Target Sensitivity Analysis					
		Discount Rate			
		10.0%	11.0%	12.0%	13.0%
Terminal Growth	5%	$22	$17	$13	$11
	6%	$27	$20	$16	$12
	7%	$37	$25	$19	$14
	8%	$55	**$34**	$23	$17
	9%	$110	$51	$31	$22
Growth rate in 2022:			31.5%		

Source: Company Reports and Piper Jaffray.

BLUEPotential Upside From Current Levels					
		Discount Rate			
		9.0%	10.0%	11.0%	12.0%
Terminal Growth	5.0%	(14%)	(34%)	(48%)	(57%)
	6.0%	8%	(20%)	(39%)	(51%)
	7.0%	45%	(0%)	(26%)	(43%)
	8.0%	118%	**34%**	(8%)	(32%)
	9.0%	337%	101%	23%	(14%)

Source: Company Reports and Piper Jaffray.

BLUE Quarterly P&L	2012A	1Q13A	2Q13A	3Q13A	4Q13A	2013A	1Q14A	2Q14E	3Q14E	4Q14E	2014E
Collaboration revenue	0.1	1.0	6.2	6.3	6.3	19.8	6.3	6.0	6.0	6.0	24.3
Research and license fees	0.7	0.1	0.1	0.1	0.1	0.4	0.1	0.0	0.0	0.0	0.1
Product revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Other product-associated revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenue	**0.7**	**1.1**	**6.3**	**6.4**	**6.4**	**20.2**	**6.3**	**6.0**	**6.0**	**6.0**	**24.3**
Operating Expenses:											
COGS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
% product sales	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
R&D	17.2	5.3	7.2	8.7	9.8	31.0	11.5	12.0	12.0	12.0	47.5
% Revenue	*2326%*	*469%*	*114%*	*136%*	*152%*	*153%*	*181%*	*200%*	*200%*	*200%*	*195%*
General and administrative	6.8	2.3	3.3	3.8	4.7	14.1	5.5	5.5	5.5	5.5	22.0
% Revenue	*925%*	*206%*	*52%*	*60%*	*73%*	*70%*	*87%*	*92%*	*92%*	*92%*	*91%*
Total Operating Expenses	**24.1**	**7.6**	**10.5**	**12.5**	**14.5**	**45.1**	**17.0**	**17.5**	**17.5**	**17.5**	**69.5**
Operating Income (GAAP)	**(23.3)**	**(6.5)**	**(4.2)**	**(6.2)**	**(8.0)**	**(24.9)**	**(10.7)**	**(11.5)**	**(11.5)**	**(11.5)**	**(45.2)**
Interest income	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.6	0.7	0.8	2.1
Interest expense/other	0.0	(0.1)	(0.4)	0.0	0.0	(0.4)	0.1	0.1	0.1	0.1	0.4
Pretax Income (loss)	**(23.7)**	**(6.5)**	**(4.6)**	**(6.1)**	**(8.0)**	**(25.3)**	**(10.6)**	**(10.8)**	**(10.7)**	**(10.6)**	**(42.7)**
Net Income as Reported/GAAP	(3.6)	(6.5)	(4.6)	(6.1)	(8.0)	(25.3)	(10.6)	(10.8)	(10.7)	(10.6)	(42.7)
Diluted EPS (as reported/GAAP)	**($13.79)**	**($19.94)**	**($2.13)**	**($0.26)**	**($0.34)**	**($2.02)**	**($0.44)**	**($0.44)**	**($0.43)**	**($0.43)**	**($1.74)**
Weighted average shares outstanding	0.3	0.3	2.2	23.6	23.8	12.6	24.1	24.4	24.6	24.9	24.5

Source: Company reports and PJC Estimates

Joshua Schimmer: 212-284-9322

Current disclosure information for this company can be found at http://www.piperjaffray.com/researchdisclosures.
Proprietary to Piper Jaffray & Co. June 12, 2014

BLUE Revenue Model	2012A	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
W/W ALD Incidence	350	350	350	365	385	400	410	420	440	460	470
W/W CCALD Incidence	35%	35%	35%	35%	35%	35%	35%	40%	45%	45%	45%
W/W AMN Incidence	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%	40%
CCALD Patients	123	123	123	128	135	140	144	168	198	207	212
AMN Patients	140	140	140	146	154	160	164	168	176	184	188
Lenti-D Penetration into CCALD	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*20%*	*45%*	*55%*	*60%*
CCALD Patients treated with Lenti-D	0	0	0	0	0	0	7	34	89	114	127
Lenti-D Penetration into AMN	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*3%*	*4%*	*7%*
AMN Patients treated with Lenti-D	0	0	0	0	0	0	0	0	5	7	13
Lenti-D Price	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$1.3	$1.3	$1.3	$1.3	$1.3
W/W Lenti-D Revenue	$0	$0	$0	$0	$0	$0	$9	$44	$123	$158	$182
US/EU Beta-Thalassemia Major Prevalence	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000	15,000
LentiGlobin Penetration	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0.2%*	*0.3%*	*0.4%*
Patients treated with LentiGlobin	0	0	0	0	0	0	0	0	30	45	60
LentiGlobin Price	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$1.0	$1.0	$1.0
LentiGlobin Revenue	$0	$0	$0	$0	$0	$0	$0	$0	$30	$45	$60
TOTAL REVENUE	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$9.3**	**$43.7**	**$152.7**	**$202.6**	**$242.1**

Source: Company reports and PJC Estimates

BLUE P&L (MM)	2012A	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Collaboration revenue	0.1	19.8	24.3	20.0	20.0	20.0	23.0	25.0	25.0	25.0	25.0
Research and license fees	0.7	0.4	0.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Product revenue	0.0	0.0	0.0	0.0	0.0	0.0	9.3	43.7	152.7	202.6	242.1
Other product-associated revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenue	**$0.7**	**$20.2**	**$24.3**	**$21.0**	**$21.0**	**$21.0**	**$33.3**	**$69.7**	**$178.7**	**$228.6**	**$268.1**
COGS	0.0	0.0	0.0	0.0	0.0	0.0	0.5	2.2	7.6	10.1	12.1
% product sales	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
R&D	17.2	31.0	47.5	48.0	48.0	48.0	50.0	50.0	60.0	65.0	70.0
General and administrative	6.8	14.1	22.0	25.0	25.0	35.0	60.0	65.0	85.0	90.0	95.0
Total Operating Expenses	**$24.1**	**$45.1**	**$69.5**	**$73.0**	**$73.0**	**$83.0**	**$110.5**	**$117.2**	**$152.6**	**$165.1**	**$177.1**
Operating Income (GAAP)	**($23.3)**	**($24.9)**	**($45.2)**	**($52.0)**	**($52.0)**	**($62.0)**	**($77.1)**	**($47.5)**	**$26.1**	**$63.4**	**$91.0**
Interest income	0.1	0.0	2.1	3.0	3.0	4.0	4.0	5.0	5.0	6.0	7.0
Interest expense/other	0.0	(0.4)	0.4	0.5	0.5	0.5	1.0	1.0	1.0	1.0	1.0
Pretax Income (loss)	**(23.7)**	**(25.3)**	**(42.7)**	**(48.5)**	**(48.5)**	**(57.5)**	**(72.1)**	**(41.5)**	**32.1**	**70.4**	**99.0**
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*15%*	*25%*
Taxes	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**10.6**	**24.7**
Net Income as Reported/GAAP	(3.6)	(25.3)	(42.7)	(48.5)	(48.5)	(57.5)	(72.1)	(41.5)	32.1	59.9	74.2
Diluted EPS (as reported/GAAP)	**($13.79)**	**($2.02)**	**($1.74)**	**($1.84)**	**($1.62)**	**($1.83)**	**($2.02)**	**($1.12)**	**$0.80**	**$1.45**	**$1.73**
Weighted average shares outstanding	0.3	12.6	24.5	26.3	29.9	31.4	35.7	37.2	40.2	41.4	42.8

Source: Company reports and PJC Estimates

BLUE Cash Flow Statement	2012A	2013A	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Net income	**(4)**	**(25)**	**(43)**	**(49)**	**(49)**	**(58)**	**(72)**	**(42)**	**32**	**60**	**74**
Depreciation/amortization	0	1	1	1	1	1	2	2	2	2	3
Stock based comp	1	6	7	9	10	13	16	17	17	18	20
Remeasure of warrants	(0)	0									
Loss on disposal	0	0									
Change in NWC	2	61	(8)	(8)	(10)	(15)	(15)	(5)	(5)	(5)	0
Net Cash Provided by Operating Activities	**(21)**	**43.5**	**(43)**	**(47)**	**(48)**	**(59)**	**(69)**	**(28)**	**46**	**75**	**97**
Capital expenditures	0	(9)	(4)	(5)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Free Cash Flow	**(21)**	**35**	**(47)**	**(52)**	**(52)**	**(63)**	**(73)**	**(32)**	**42**	**71**	**93**
Net Cash From Financing	**60**	**106**	**1**	**2**	**75**	**2**	**100**	**2**	**2**	**2**	**3**
Cash and Cash Equivalents	**67**	**206**	**159**	**109**	**133**	**72**	**99**	**70**	**114**	**187**	**283**

Sources: Company Reports and Piper Jaffray

IMPORTANT RESEARCH DISCLOSURES

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R: Resuming Coverage
T: Transferring Coverage
D: Discontinuing Coverage
S: Suspending Coverage
OW: Overweight
N: Neutral
UW: Underweight
NA: Not Available
UR: Under Review

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			IB Serv./Past 12 Mos.	
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SELL [UW]	15	2.62	0	0.00

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Analyst Certification — Joshua E. Schimmer, MD, Sr Research Analyst
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