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Elcano Therapeutics
Boston, MA

Overview
Elcano Therapeutics is a Venrock-incubated newco whose goal is to engineer precise, potent, and durable gene therapies. Viral gene therapies have recently transformed the treatment of several serious diseases: Luxturna from Spark Therapeutics has restored sight to children with inherited blindness, and Zolgensma from AveXis (a Venrock portfolio company) has produced profound clinical benefit in children with severe spinal muscular atrophy. These viral gene therapy companies have also been the targets of acquisition activity from big pharma: Spark was acquired by Roche in 2019 for $4.8B, and AveXis was acquired by Novartis in 2018 for $8.7B.

Despite the transformative benefit that existing viral therapies have yielded for patients, there remain key limitations to their use broadly across diseases: today's viral vectors are not cell-type-specific, often not durable and can only be used in some tissues such as liver and brain. One way around these limitations involves isolating cells and manipulating them outside the body (current oncology approach for CAR-T cells – Juno); this too is problematic because it takes time, drives up costs and leaves cells in a less activated state, reducing therapeutic efficacy.

Elcano's platform bypasses these limitations and potentially enables the next major wave of gene therapy. Elcano scientific co-founder Michael Birnbaum, a professor of biological engineering at MIT, discovered that lentivirus (most gene therapies use AAV today) can be modified to specifically target (and infect) desired cell types, while avoiding others. Additionally, Lentivirus (unlike AAV) durably integrates into the target cells.

The Elcano technology could therefore enable durable, safer, and more potent therapies for a broad range of serious indications: 1) cancers such as multiple myeloma and non-Hodgkin lymphoma and 2) genetic diseases such as sickle cell and hemophilia. A long-term goal of the company is to engineer immune cells to secrete antibodies.

An earlier stage, next generation precise, potent and durable gene therapy platform utilizing HSV-1 rather than lentivirus is the subject of a collaboration between Michael Birnbaum and Michael Fischbach (Stanford Professor and Venrock friend, co-founder of Fererederation Bio). The primary advantage to HSV-1 would be therapeutic payload capacity (150 Kb v. lenti 7-8 Kb and AAV 4.5 Kb). This platform will also be brought into Elcano, although the initial product candidates will be based on the more mature lentiviral approach.

Team
To lead the Elcano scientific operations, we have recruited two experienced drug-hunters, Kevin Friedman and Molly Perkins, who previously worked together at Bluebird Bio (a

lentivirus gene therapy company) and developed a cell therapy for multiple myeloma that is expected to gain FDA approval this March.

- Kevin Friedman: Chief Scientific Officer
    - Previously VP at Bluebird Bio, served as oncology R&D lead
    - Invented and led development of multiple myeloma therapy ide-cel
- Molly Perkins: VP of Research
    - Previously Director of Oncology R&D at Bluebird Bio
    - Led preclinical research of a multiple myeloma cell therapy

Michael Fischbach introduced Bryan to Michael Birnbaum in early 2019. We have spent the last ~18 months working with the scientific founders to identify key technical risks, areas of differentiation, and target indications. Venrock teammate Kole Roybal has also started collaborating academically with Michael Birnbaum to drive the expansion of the technology to hematopoietic stem cells.

- Michael Birnbaum: Scientific co-founder
    - Professor of Biological Engineering, MIT
- Michael Fischbach: Scientific co-founder
    - Professor of Bioengineering, Stanford
    - Federation Bio co-founder, Achaogen BoD member
- Kole Roybal: Scientific co-founder
    - Professor of Microbiology and Immunology, UCSF
    - Co-founder at Arsenal and Cell Design Labs

Deal
The current proposal is for Venrock to invest $7.5MM for 35% ownership (~$13.5 premoney) with a >30% pool. While real milestones (definition of complete initial product candidate) to enable a Series A will take $10-15MM and 18 months, over 9 months there will be material platform exploration and de-risking. Our thought is to fund through ~12 months such that we get our ownership with reasonable capital at risk while providing optionality for another round in 6-9 months, either based on the strong financing market, Elcano progress or both.

Market Sizing
The Elcano platform could potentially address a range of high unmet need, prevalent indications, providing the company multiple paths to success. Each of these indications represents a $1B+ peak annual sales opportunity.

Therapeutic area	Indication	Total new cases/yr (US)	Elcano est. peak sales potential (US)
Oncology	Non-Hodgkin lymphoma	77,000	$1.2B
	Multiple myeloma	32,000	$1.4B
Genetic disease	Hemophilia A	400	$1.4B

	Sickle cell disease	2,000	$1.7B

Competition

There are a Kajillion gene therapy efforts. Viral gene therapy companies today generally fall into two categories: adeno-associated virus (AAV) and lentivirus (LV) companies. While AAV can be more easily administered directly into the body (in vivo), it has a small payload capacity, suffers from limited tropism and generally infects only the liver or brain at appreciable amounts. It is also not durable in cell types that divide. Examples of AAV companies include AveXis, Spark, RegenX, and Encoded.

In contrast, LV cannot currently be administered in vivo due to widespread infection across cell types, and as a result cells must be isolated from the body and treated with LV ex vivo before being returned to the patient. This increases the cost of LV-based therapies, and it reduces the health of the cells that are returned to the patient because of the harsh ex vivo processing conditions. The benefit of LV is that its effects are durable, even in dividing cell types. As a result, the competitive landscape looks like this:

	AAV	**Standard LV**	**Elcano LV**
Easily administered?	**Yes**	No	**Yes**
Durable in dividing cells?	No	**Yes**	**Yes**
Cell-type-specific?	No	No	**Yes**

Elcano is able to achieve durability and easy administration by engineering viruses to be cell-type-specific: viral vectors that are not targeted to a specific tissue will either go very predominantly to liver or brain, or they need to be administered – laboriously - outside the body.

The company's most direct competitor is Sana Biotechnology, a high-profile start-up that raised a $700M series A round and is also engineering LVs to be cell-type-specific. Despite being exceedingly well-financed, our competitive intel has led us to believe that Sana's LV modifications are not robust and result in low viral titers. In fact, scientific founder Michael Birnbaum invented his own method of LV engineering (the Elcano platform) after failing to achieve encouraging results with the technology on which Sana is based.

Pros

- **Broad platform potential**: New modalities don't come around often in biotech, and this has the chance to be one, unlocking a variety of high unmet need indications.
- **Team**: The founding leadership team has strong experience in the cell therapy space, having previously invented and progressed a drug from early preclinical development through the clinic.

Cons

- **Early science**: Key aspects of the platform remain to be de-risked (serum neutralization, producing virus at scale, immunogenicity to the virus, etc.). And then we have to create actual products.
- **Early stage Company:** Need IP licenses, team, space, etc.
- **Competition**: A potential direct competitor (Sana) is well-financed, and other smaller companies are also increasingly interested in cell-type-specific viral therapies.

Glimmer of Greatness

Leaders in the first wave of viral gene therapy have developed transformative medicines for patients with serious diseases – and produced great returns for investors. The next major frontier in gene therapy is cell-type-specific targeting, which will enable therapies that are both durable and easily administered. With card-carrying drug-hunters at the helm and a robust technology platform, Elcano has the potential to become a dominant player in this next wave of gene therapy.