Enabling affordable and accessible advanced medicines

Advanced medicines are curing disease

Let's make them affordable and accessible

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Clinical success and approval of gene therapy products

- Kymriah® – CAR-T cells, Pediatric Leukemia
- Yescarta® – CAR-T cells, Adult Lymphoma
- Tecartus® – CAR-T cells, Mantle Cell Lymphoma
- Breyanzi® – CAR-T cells, Adult Lymphoma
- Abemca® – CAR-T cells, Multiple Myeloma
- Carvykti® – CAR-T cells, Multiple Myeloma
- Zynteglo® – Stem Cells, β–Thalassemia
- Strimvelis ® – Stem Cells, SCID (Bubble Boy Syndrome)
- Many others in clinical development and several on the verge of approval

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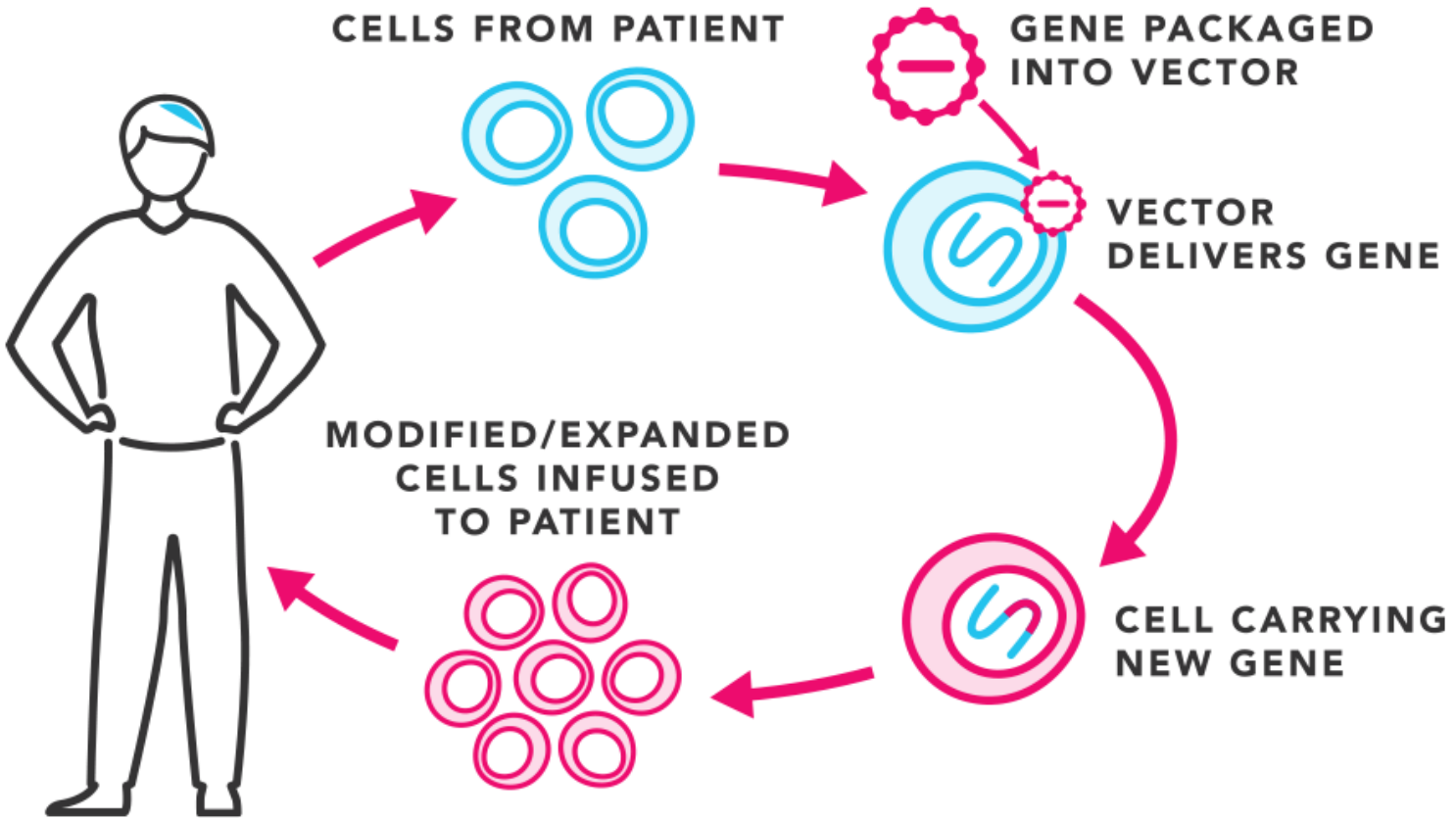
All approved products are autologous



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But their high price is not sustainable and restricts access

- $475,000 Kymriah®, $375,000 Yescarta®, $2,800,000 Zynteglo®
- These prices do not include clinical costs
- Such pricing is not sustainable for insurance companies or health systems
- Such pricing is not feasible in low- and middle-income countries (LMIC)
- Such pricing is restricting access, particularly for underserved populations
- Also significantly restricts access in low- and middle-income countries

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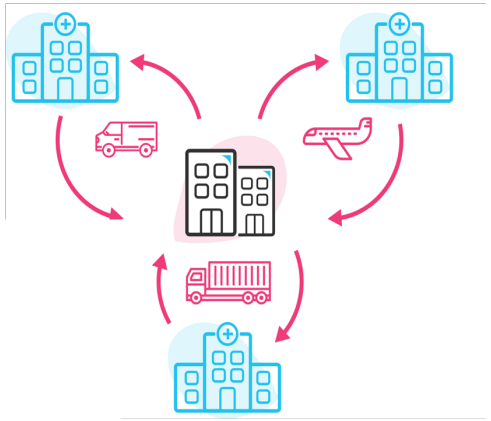
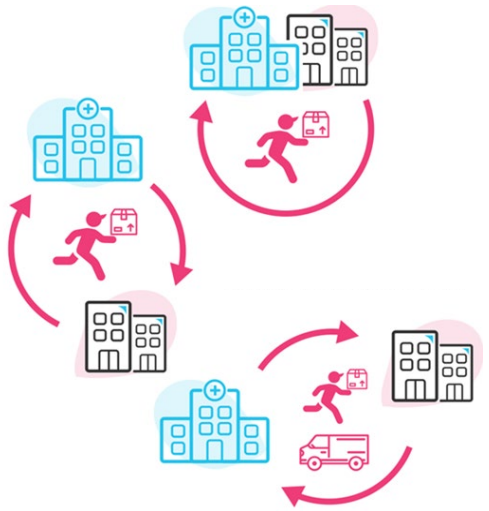
Why such a high price?



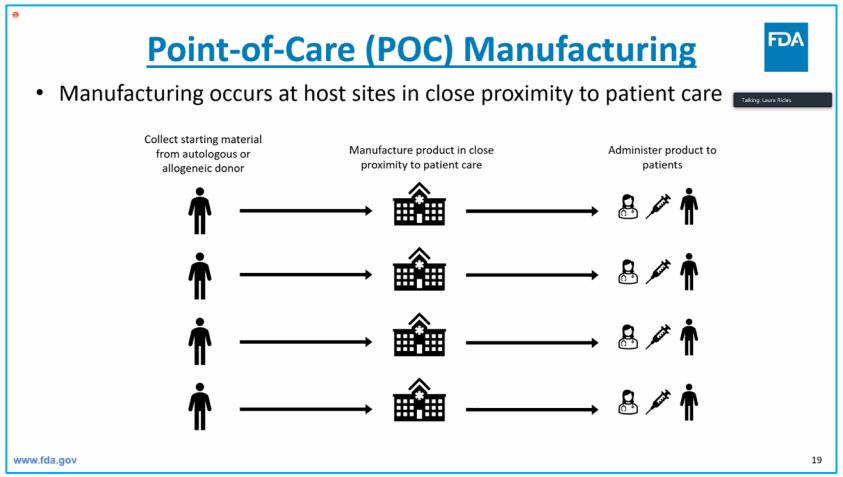
Complex logistics	Patient Result
• Complex logistics between hospital and central manufacturing facility is very expensive • High number of oversight personnel needed to ensure chain of custody & identity at one regional facility hub • Infrastructure cost for each company creating and owning its own centralized manufacturing facility – high facility cost and payback	• Vein to vein times are at least 3-4+ weeks, including insurance approval delays • This results in therapy not reaching many patients in time • Access limited for patients on Medicare since not financially viable • Limited access for patients in geographic regions not close to large academic medical centers

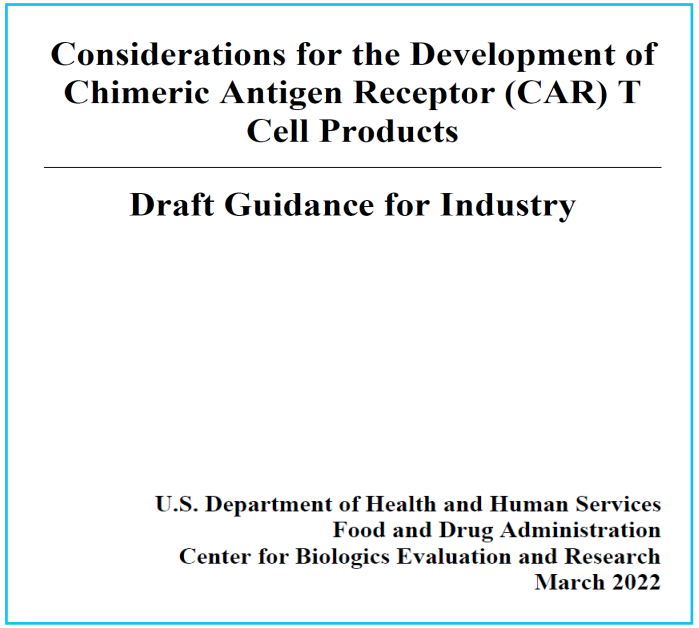
How to reduce cost and enable affordable access



POC Manufacturing	Improved Technologies
• POC manufacturing is significantly more economical for autologous therapies – 1/10 cost • Reduces vein to vein times <1-7 days and better scheduling for patients • Freshly manufactured cells are better than frozen cells • Larger hospitals are competent to manufacture cell products – no need for expensive company manufacturing facilities which drives up product cost	• Simple and robust manufacturing significantly lowers cost while maintaining the benefits of autologous gene-modified cells • Lowering the cost of vector and materials needed to produce cells • Improving vector and ancillary technologies allow for targeting and surface programing of T cells • Short ex vivo, matrix hybrid and in vivo gene delivery technologies

Regulatory authorities are supportive of decentralized point-of-care manufacturing





Outstanding manufacturing and clinical results when CAR-T cells are manufactured at the point-of-care (POC)

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-27312-6 OPEN

Check for updates

Multiple site place-of-care manufactured anti-CD19 CAR-T cells induce high remission rates in B-cell malignancy patients

Michael Maschan[1,11], Paolo F. Caimi[2,9,11], Jane Reese-Koc[2], Gabriela Pacheco Sanchez[3], Ashish A. Sharma[3], Olga Molostova[1], Larisa Shelikhova[1], Dmitriy Pershin[1], Alexey Stepanov[1,4], Yakov Muzalevskii[1], Vinicius G. Suzart[2], Folashade Otegbeye[2], David Wald[2], Ying Xiong[5], Darong Wu[5], Adam Knight[5], Ibe Oparaocha[5,6], Beatrix Ferencz[5], Andre Roy[5], Andrew Worden[5], Winfried Kruger[5], Michael Kadan[5], Dina Schneider[5], Rimas Orentas[5,6,7,8], Rafick-Pierre Sekaly[3], Marcos de Lima[2,10,12]✉ & Boro Dropulić[5,6,12]✉

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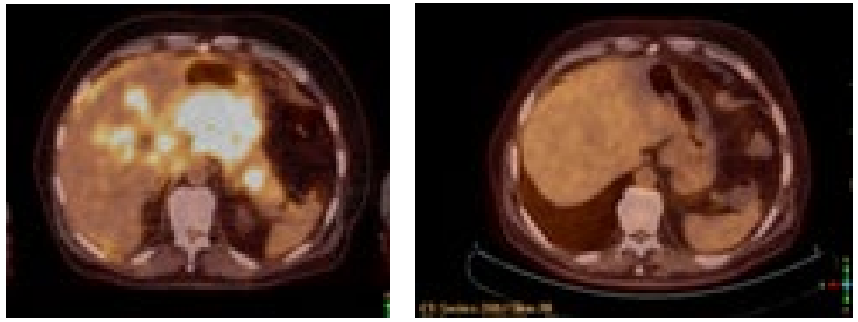

Prior to CAR-T 90 day post CAR-T

Tumor elimination in a 69yo patient with Follicular Lymphoma after therapy with anti-CD19 CAR-T cells

8-day vein-to-vein time
All patients treated with great outcomes

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Point-of-care manufacturing of CAR-T cells are producing excellent clinical results in patients with leukemia and lymphoma

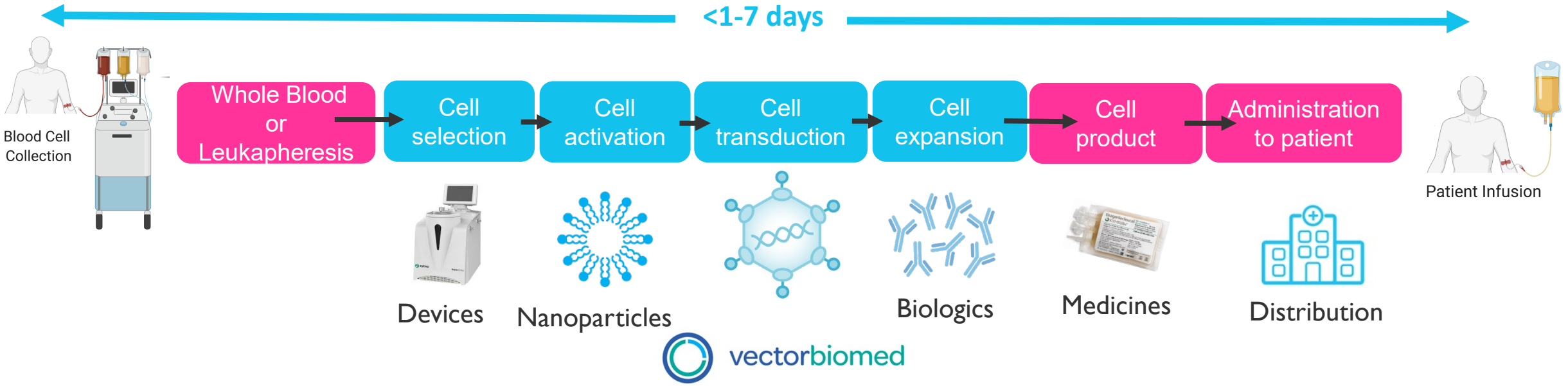
Remarkable results compared to drugs or transplantation at
~35% overall response rate (ORR) for standard of care

1. **Case Western Reserve University (CWRU)**
   - Single anti-CD19 CAR (B cell lymphomas)
   - 14 out of 17 **adult** patients had an 82% ORR
2. **Dimitry Rogachev National Research Center** in Moscow, Russian Federation
   - Single anti-CD19 CAR (B cell leukemias)
   - 19 out of 21 **pediatric** patients had a 90% ORR

   Nature Communications 2021
3. **Medical College of Wisconsin**
   - Bi-specific anti-CD19 and anti-CD20 CAR (B cell lymphomas)
   - 13 out of 14 patients had a 92% CRR
   - After 2 years (n = 14) only 1 relapse to date!

   Nature Medicine 2020

We are focused upon developing low-cost CAR-T cell products and manufacturing solutions



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- **Short and simple processes** – short improves COGS, simple improves robustness, of process
- Decreased vein-to-vein times – better for patients, especially with advanced disease
- Fresh in, fresh out manufactured cells – better quality of cells for patients
- Freedom-to-operate (FTO) clinical products – no third-party IP that increases cost

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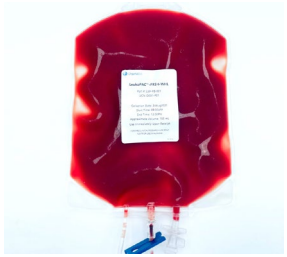
A robust and economical ex vivo CAR-T cell manufacturing process

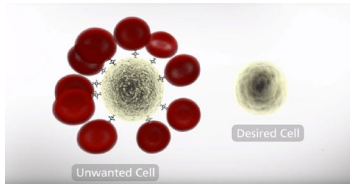
Whole Blood

OR



Leukopak

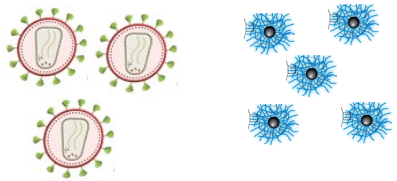
Negative Selection



+

Sepax-C-Pro

Vector + Activation



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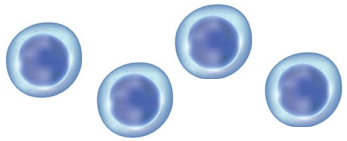
Purified T cells



G Rex

1-7 Days

Incubator

Formulation

Sterility

+

dPCR

+

Release Testing

CAR-T cells Ready for Infusion

Material Cost about $15,000/dose including vector

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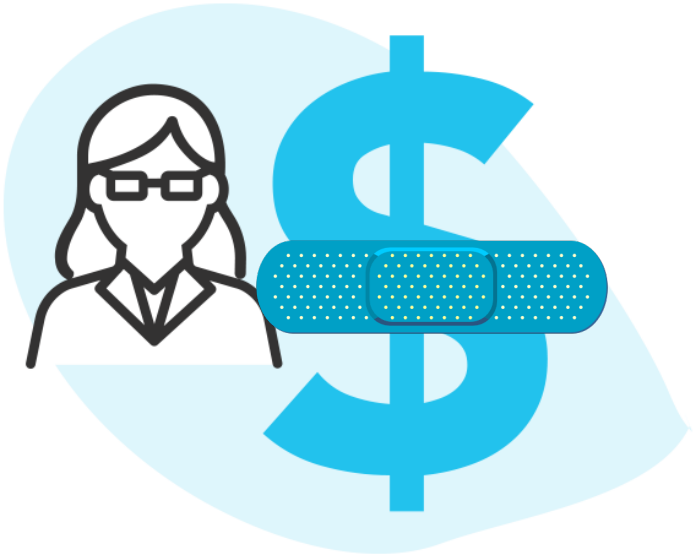

A price that is affordable, sustainable and expands access

- Cost of materials for manufacturing CAR-T cells is about $15,000/dose
- Labor cost for each unit is about $5,000/dose if site is manufacturing 100 doses per year, costs decreases with more usage of facility
- Facility maintenance cost is about $5,000/dose if site is manufacturing 100 doses per year, cost decreases with more usage of facility
- **Total product cost for hospital per dose is about $25,000/dose** if site manufactures 100 doses per year, cost decreases with more usage of facility
- Such a product could be reimbursed at a price that is affordable for Medicare, Medicaid and most private payers and health systems
- **Medicare reimburses total cost of CAR-T cell therapy at $247,938**

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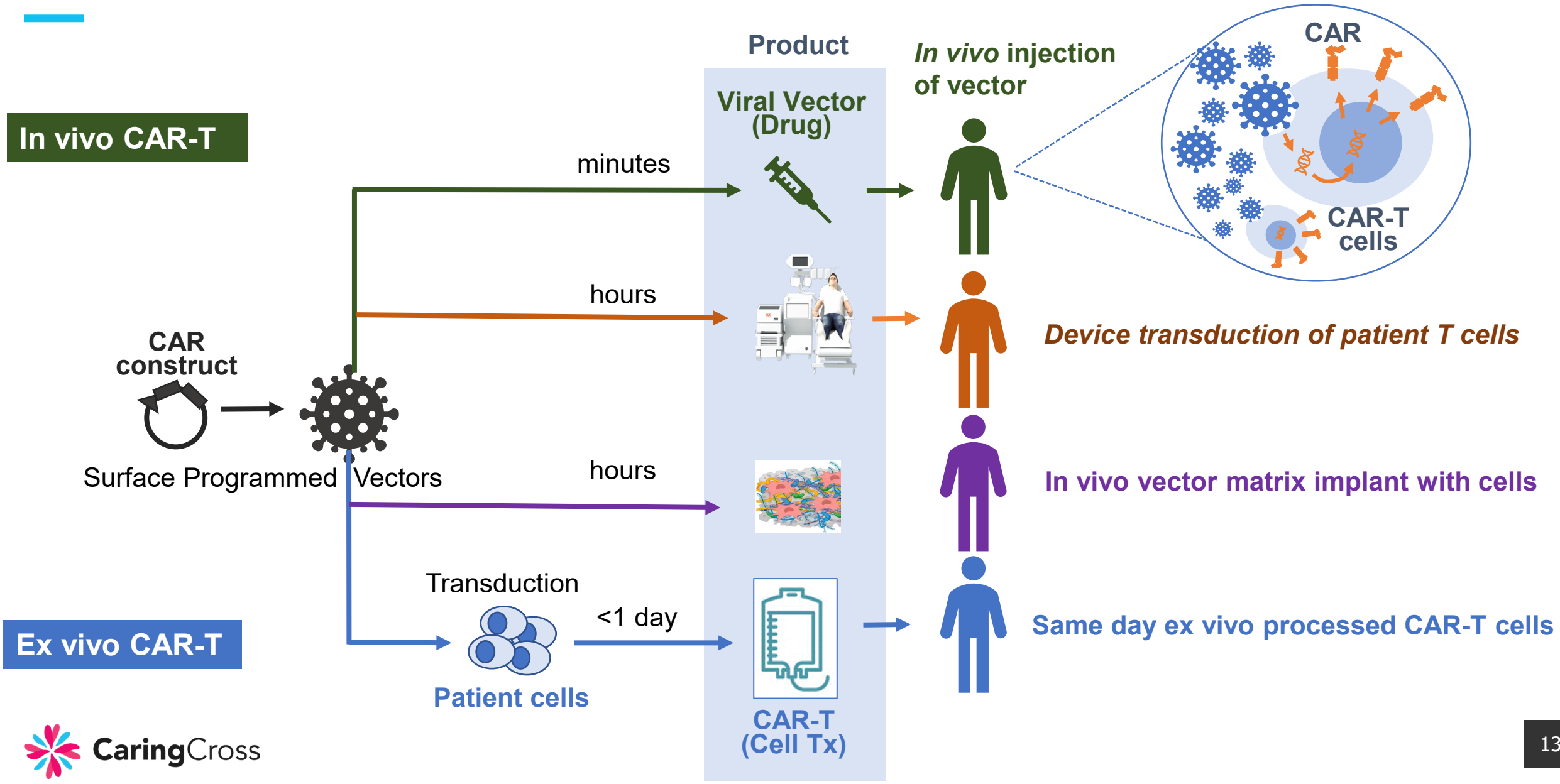
Innovative gene delivery technologies for optimization of therapies



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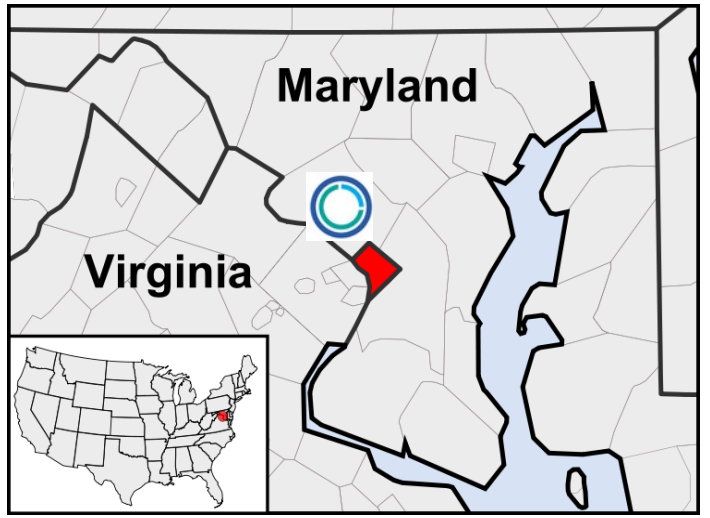
Making improved vector technologies broadly accessible

- Vector BioMed - CDMO
  - Public Benefit Corporation – spin out from Caring Cross
  - Mission is to serve the industry and scientific community with rapid and affordable Lentiviral vector manufacturing solutions
- Affordable contract GMP Lentiviral vector manufacturing organization **– efficient technology → lower cost and price → broad access**
- First LV clinical trial at UPenn; team developed vector used in the production of Kymriah® - first FDA approved gene therapy product
- **Surfaced Reprogrammed and Targeted Lentiviral vectors**

NIMBL
The National Institute for Innovation in Manufacturing Biopharmaceuticals

- **Open process LV and AAV vector manufacturing methods for phase I/II clinical trials**



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Combining technologies with FTO candidates with POC manufacturing model – e.g. cancer and infectious diseases

NATURE MEDICINE

nature medicine | LETTERS
https://doi.org/10.1038/s41591-020-1081-3

Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial

Nirav N. Shah[1], Bryon D. Johnson[1], Dina Schneider[2], Fenlu Zhu[1], Aniko Szabo[3], Carolyn A. Keever-Taylor[1], Winfried Krueger[2], Andrew A. Worden[2], Michael J. Kadan[2], Sharon Yim[1], Ashley Cunningham[4], Mehdi Hamadani[1], Timothy S. Fenske[1], Boro Dropulić[2], Rimas Orentas[2,5] and Parameswaran Hari[1]

Chimeric antigen receptor (CAR) T cells targeting CD19 are a breakthrough treatment for relapsed, refractory B cell malignancies. Despite impressive outcomes, relapse with CD19⁻ disease remains a challenge. We address this limitation through a first-in-human trial of bispecific anti-CD20, anti-CD19 (LV20.19) CAR T cells for relapsed, refractory B cell malignancies. Adult patients with B cell non-Hodgkin lymphoma or chronic lymphocytic leukemia were treated on a phase 1 dose escalation and expansion trial (NCT03019055) to evaluate the safety of 4-1BB–CD3ζ LV20.19 CAR T cells and the feasibility of on-site manufacturing using the CliniMACS Prodigy system. CAR T cell doses ranged from 2.5×10^5–2.5×10^6 cells per kg. Cell manufacturing was set at 14 d with the goal of infusing non-cryopreserved LV20.19 CAR T cells. The target dose of LV20.19 CAR T cells was met in all CAR-naive patients, and 22 patients received LV20.19 CAR T cells on protocol. In the absence of dose-limiting toxicity, a dose of 2.5×10^6 cells per kg was chosen for expansion. Grade 3–4 cytokine release syndrome occurred in one (5%) patient, and grade 3–4 neurotoxicity occurred in three (14%) patients. Eighteen (82%) patients achieved an overall response at day 28, 14 (64%) had a complete response, and 4 (18%) had a partial response. The overall response rate to the dose of 2.5×10^6 cells per kg with non-cryopreserved infusion ($n = 12$) was 100% (complete response, 92%; partial response, 8%). Notably, loss of the CD19 antigen was not seen in patients who relapsed or experienced treatment failure. In conclusion, on-site manufacturing and infusion of non-cryopreserved LV20.19 CAR T cells were feasible and therapeutically safe, showing low toxicity and high efficacy. Bispecific CARs may improve clinical responses by mitigating target antigen down-

of relapse is downregulation of the CD19 antigen and development of a CD19⁻ clone[9–11]. Biopsies obtained at relapse from patients with B cell NHL after anti-CD19 CAR T cell therapy revealed that approximately 30% of patients were CD19⁻, demonstrating the impact of clonal selection that occurs with single targeting of the CD19 antigen[12,13]. Simultaneous targeting of more than one B cell antigen has been proposed as a therapeutic strategy to reduce the risk of relapse mediated by antigen-negative clonal escape[14–16]. Preclinical studies found that tandem, bispecific CD20–CD19 lentiviral CARs can mitigate downregulation of not only the targeted receptors but also at least one non-targeted B cell receptor (that is, CD22)[17]. These data provided support for the clinical development of a phase 1 trial for tandem bispecific anti-CD20, anti-CD19 4-1BB–CD3ζ lentiviral (LV20.19) CAR T cells (Extended Data Fig. 1) for patients with relapsed, refractory B cell malignancies, including NHL and chronic lymphocytic leukemia (CLL).

Twenty-six patients with B cell NHL or CLL met eligibility criteria and underwent apheresis for LV20.19 CAR T cell production (Extended Data Fig. 2). Four patients did not meet their target doses, three of whom were treated per clause, allowing infusion outside of specified cohorts. Patient and disease characteristics for the remaining 22 patients are detailed in Table 1 (top). The median age at CAR T cell infusion was 57 years (range, 38–72 years), and the median number of lines of prior therapy was 4 (range, 2–12) (see Supplementary Table 1 for detailed patient history). Patients with mantle cell lymphoma (MCL) were particularly heavily pretreated, with a median of 8 prior lines, and all patients had experienced treatment failure with Bruton's tyrosine kinase (BTK) inhibitors. Most patients (82%) were refractory to their last line of treatment. Baseline CD19 and CD20 expression on tumor cells from biopsy material taken before infusion with LV20.19 CAR T cells is listed in

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Trispecific CD19-CD20-CD22–targeting duoCAR-T cells eliminate antigen-heterogeneous B cell tumors in preclinical models

Dina Schneider*†, Ying Xiong*, Darong Wu, Peirong Hu, Leah Alabanza, Brittany Steimle, Hasan Mahmud, Kim Anthony-Gonda, Winfried Krueger, Zhongyu Zhu, Dimiter S. Dimitrov‡, Rimas J. Orentas§, Boro Dropulic†||

A substantial number of patients with leukemia and lymphoma treated with anti-CD19 or anti-CD22 monoCAR-T cell therapy relapse because of antigen loss or down-regulation. We hypothesized that B cell tumor antigen escape may be overcome by a chimeric antigen receptor (CAR) design that simultaneously targets three B cell leukemia antigens. We engineered trispecific duoCAR-T cells with lentiviral vectors encoding two CAR open reading frames that target CD19, CD20, and CD22. The duoCARs were composed of a CAR with a tandem CD19- and CD20-targeting binder, linked by the P2A self-cleaving peptide to a second CAR targeting CD22. Multiple combinations of intracellular T cell signaling motifs were evaluated. The most potent duoCAR architectures included those with ICOS, OX40, or CD27 signaling domains rather than those from CD28 or 4-1BB. We identified four optimal binder and signaling combinations that potently rejected xenografted leukemia and lymphoma tumors in vivo. Moreover, in mice bearing a mixture of B cell lymphoma lines composed of parental triple-positive cells, CD19-negative, CD20-negative, and CD22-negative variants, only the trispecific duoCAR-T cells rapidly and efficiently rejected the tumors. Each of the monoCAR-T cells failed to prevent tumor progression. Analysis of intracellular signaling profiles demonstrates that the distinct signaling of the intracellular domains used may contribute to these differential effects. Multispecific duoCAR-T cells are a promising strategy to prevent antigen loss–mediated relapse or the down-regulation of target antigen in patients with B cell malignancies.

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Multispecific anti-HIV duoCAR-T cells display broad in vitro antiviral activity and potent in vivo elimination of HIV-infected cells in a humanized mouse model

Kim Anthony-Gonda[1]*, Ariola Bardhi[2]*, Alex Ray[2], Nina Flerin[2], Mengyan Li[2], Weizao Chen[3], Christina Ochsenbauer[4], John C. Kappes[4,5], Winfried Krueger[1], Andrew Worden[1], Dina Schneider[1], Zhongyu Zhu[1], Rimas Orentas[1†], Dimiter S. Dimitrov[6‡], Harris Goldstein[2‡], Boro Dropulić[1‡]

Adoptive immunotherapy using chimeric antigen receptor–modified T cells (CAR-T) has made substantial contributions to the treatment of certain B cell malignancies. Such treatment modalities could potentially obviate the need for long-term antiretroviral drug therapy in HIV/AIDS. Here, we report the development of HIV-1–based lentiviral vectors that encode CARs targeting multiple highly conserved sites on the HIV-1 envelope glycoprotein using a two-molecule CAR architecture, termed duoCAR. We show that transduction with lentiviral vectors encoding multispecific anti-HIV duoCARs confer primary T cells with the capacity to potently reduce cellular HIV infection by up to 99% in vitro and >97% in vivo. T cells are the targets of HIV infection, but the transduced T cells are protected from genetically diverse HIV-1 strains. The CAR-T cells also potently eliminated PBMCs infected with broadly neutralizing antibody-resistant HIV strains, including VRC01/3BNC117-resistant HIV-1. Furthermore, multispecific anti-HIV duoCAR-T cells demonstrated long-term control of HIV infection in vivo and prevented the loss of $CD4^+$ T cells during HIV infection using a humanized NSG mouse model of intrasplenic HIV infection. These data suggest that multispecific anti-HIV duoCAR-T cells could be an effective approach for the treatment of patients with HIV-1 infection.

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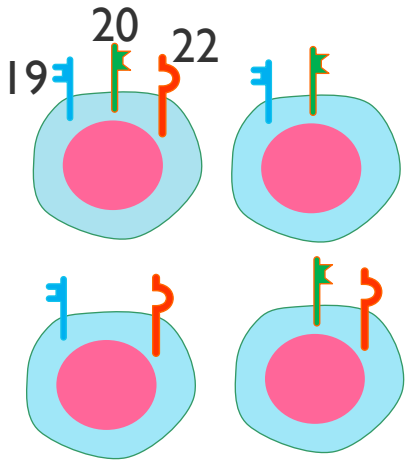
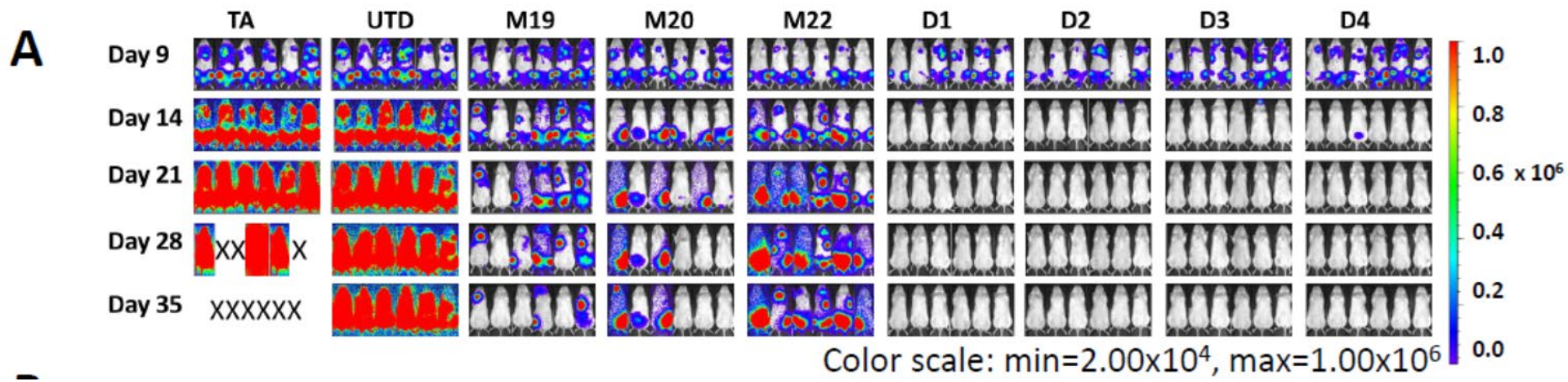
Multitargeting CARs prevent single CAR relapse due to antigen loss





Triple-targeting of tumor cells prevents relapse due to loss of one or two tumor antigens

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Summary

- Autologous gene therapies like CAR-T cell therapy are effective and curative in many cases
- But their current high cost are not sustainable and limits access, particularly for underserved in high need
- We develop and accelerate technologies and methods for low-cost manufacture of CAR-T cell and other CGT products – highly experienced team that has 25+ year history in developing such products
- Improved technologies include short ex vivo, matrix enhanced in vivo, device in vivo and injectable in vivo
- A pipeline of Freedom-To-Operate products – lead candidates target HIV, Leukemia/Lymphoma, Multiple Myeloma and Sickle Cell Disease/Beta Thalassemia
- Create new companies - our first company is Vector BioMed, a public benefit corporation (CDMO) that efficiently manufactures Lentiviral vectors at a lower cost with significant discount for Caring Cross vectors
- Implementing a point-of-care (POC) network of hospitals to manufacture these products in a very short time – short decreases cost, improves product quality and expands access to patients

Thanks to all our partners!

Let’s Impact the Lives of All Needing Curative Medicines

CaringCross