



Achilles Therapeutics

AI-Powered Precision TIL Therapy

April 2022



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Precision targeting for solid tumors using clonal neoantigen-reactive T cells (cNeT)



Clonal neoantigens: a novel class of cancer target present on all tumor cells

Developed a proprietary AI platform (PELEUS[®]) validated on real world patient data (TRACERx study)



Trackable precision T cell therapies

Able to target multiple tumor antigens with unprecedented precision and tracking in patients



Differentiated, scalable manufacturing

VELOS[™] manufacturing process designed to be closed and automated for commercial scale

NASDAQ:
ACHL



Multiple near-term catalysts

Higher-dose cNeT monotherapy cohort and initial cNeT / PD-1 inhibitor combo cohort data in 2H 2022



Strong cash position

London (HQ) & Philadelphia with ~250 employees and cash runway into 2H 2024 (\$266 M @ Dec. 31, 2021)

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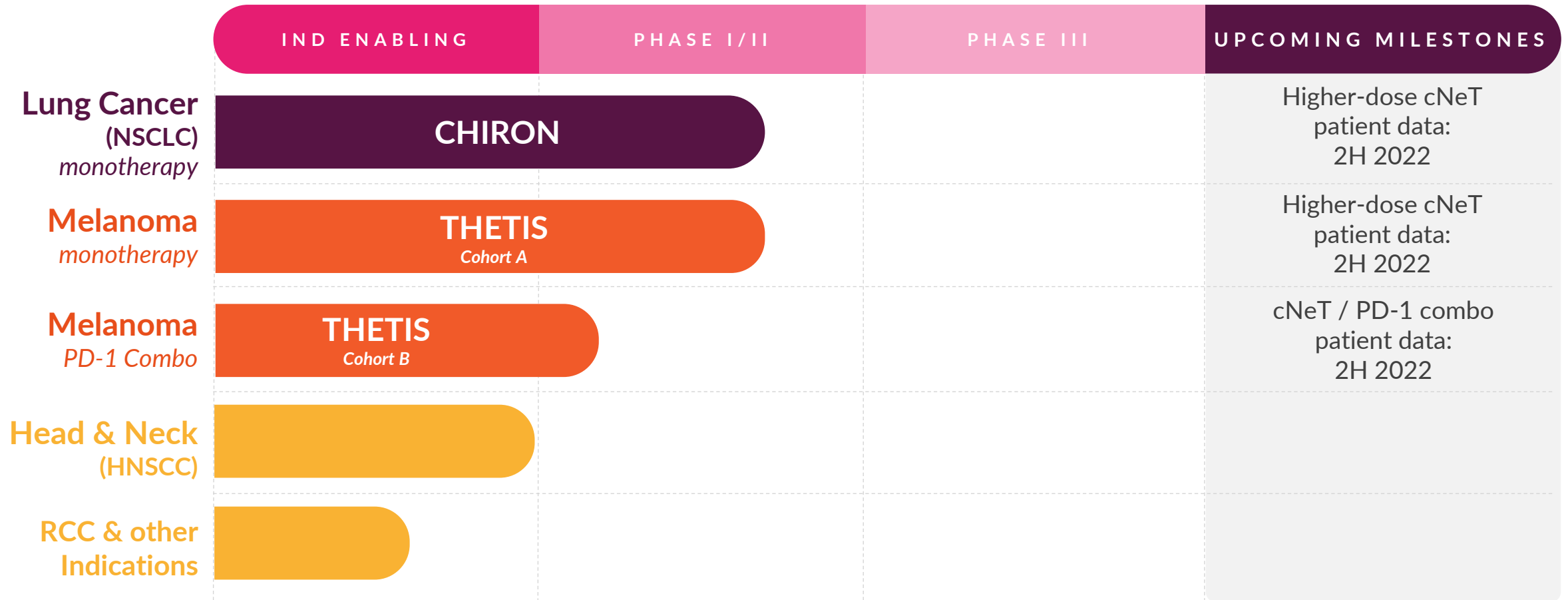


Daniel Hood
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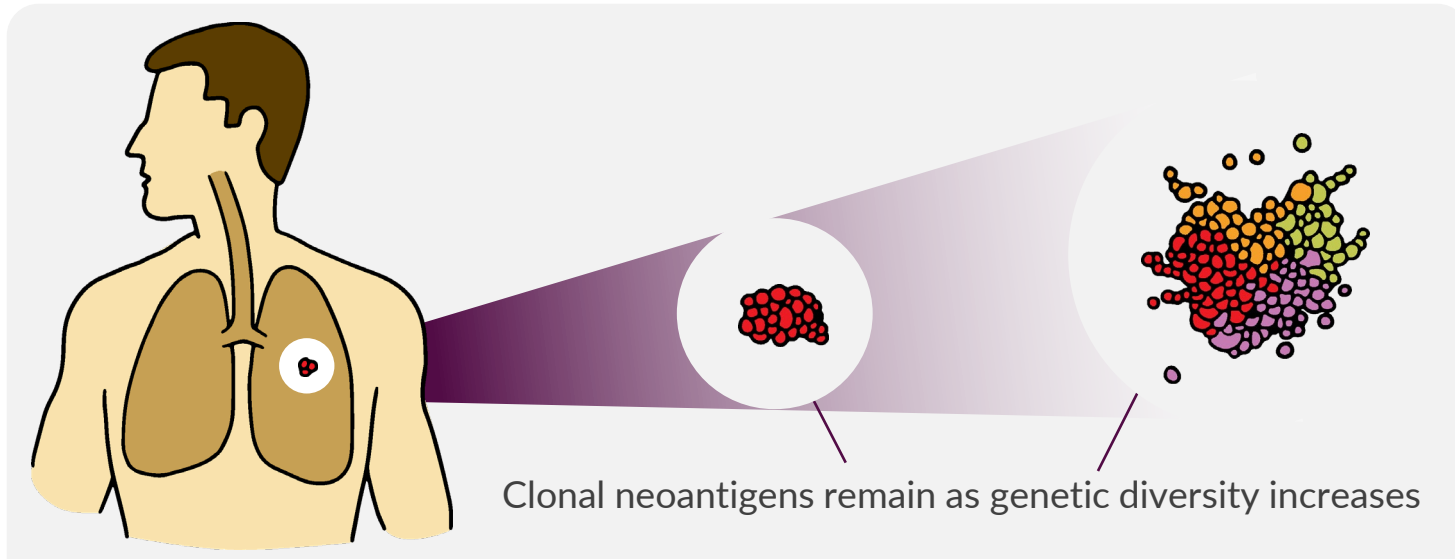
 Intercept
 GILEAD

Experienced leadership with decades in cell therapy drug development

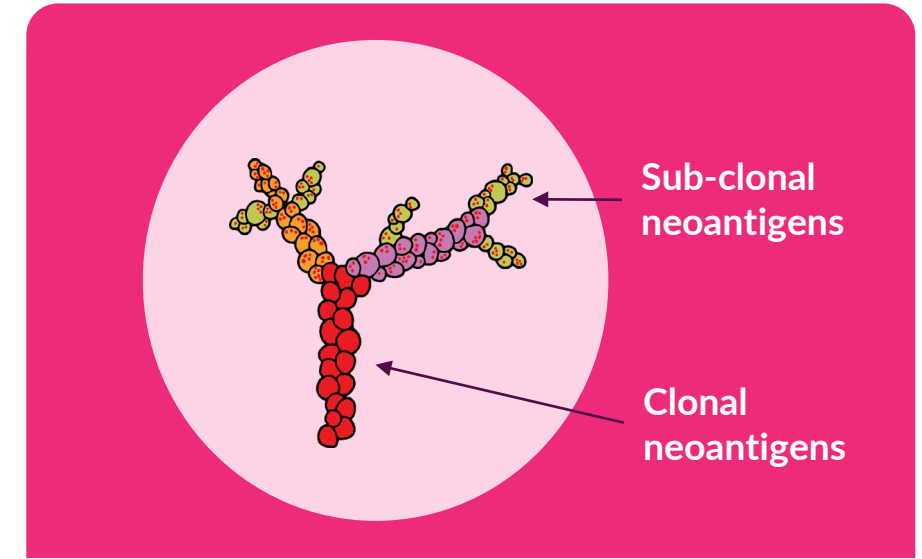
Differentiated pipeline of precision T cell therapies across multiple solid tumors



Ideal cancer targets: clonal neoantigens present on all tumor cells and absent from healthy tissue



- Tumors are constantly evolving and acquiring new mutations
- Genetic diversity enables tumors to develop resistance to standard therapies (e.g., loss of a target) which leads to disease relapse
- Despite increased genetic diversity the original mutations (clonal neoantigens) always remain¹
- Achilles' technology identifies the original (clonal) mutations and enables targeting of multiple antigens present only on tumor cells



Clonal neoantigens are

- Original mutations formed early in tumor evolution
- Expressed on all cancer cells¹ and absent from healthy tissue
- Found in multiple tumor types as tumor evolution principles apply across multiple solid cancers

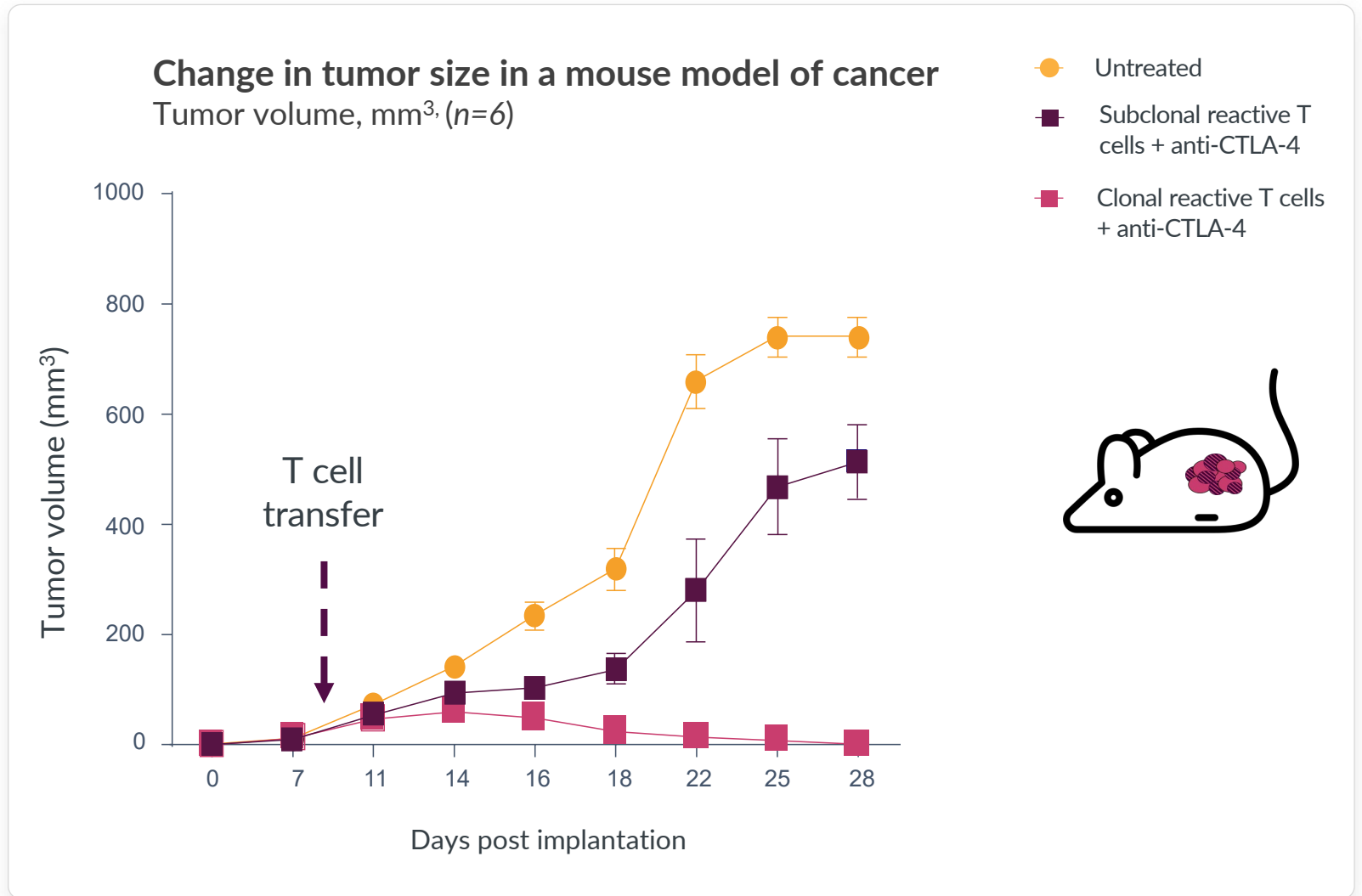
Clonality is key to the eradication of tumors



Mice implanted with tumor cells expressing sub-clonal (on a sub-set of cells) and clonal (on all cells) antigens

Mice were then treated with murine T cells reactive to sub-clonal (■) and clonal antigens (■)

Targeting clonal antigens expressed on every tumor cell leads to complete tumor regression in this model





Clonal neoantigen identification is computationally complex

- Solving the heterogeneity problem requires processing of very large DNA data sets
- The process requires multiple steps and has no universally accepted protocol
- 22 groups using the same DNA sequencing data showed <20% overlap of neoantigen identification¹



Compares tumor DNA to healthy DNA to differentiate clonal and subclonal neoantigens

Achilles has developed an AI-powered solution

- Accurate neoantigen identification requires an advanced computational approach
- AI and machine learning have been developed to enable accurate and rapid processing of very large complex data sets
- Neoantigen predictions are then validated with real-world patient data



TRACER_X

- Commercial rights to the largest longitudinal patient data set¹⁻⁴
- 3,200 tumor regions collected from 795 NSCLC patients over 5 years
- Multi-region data from primary & metastatic sites to confirm clonal status
- Unparalleled network of 15 NHS sites

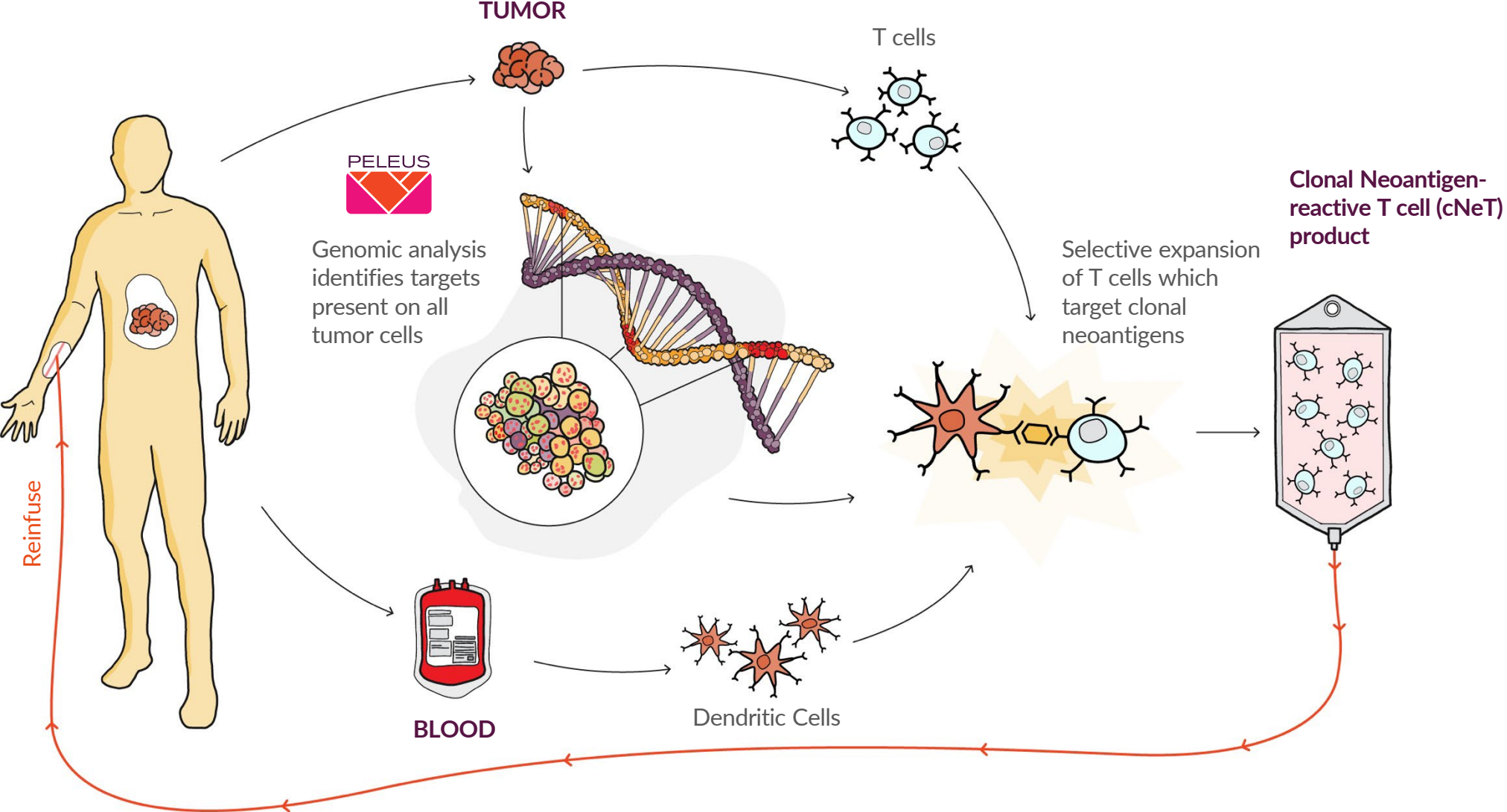


Reactive T cells are identified against clonal neoantigens

- Identification of T cells reactive to predicted clonal neoantigens in patient samples validates the PELEUS platform
- Over 120 patients prospectively analyzed to date across multiple cancer types
- Patient tumor samples validate and train PELEUS AI predictions

VELOS™ process delivers precision clonal neoantigen targeting TIL therapy

Cutting edge personalized genomics and machine learning enable targeting of all cancer cells

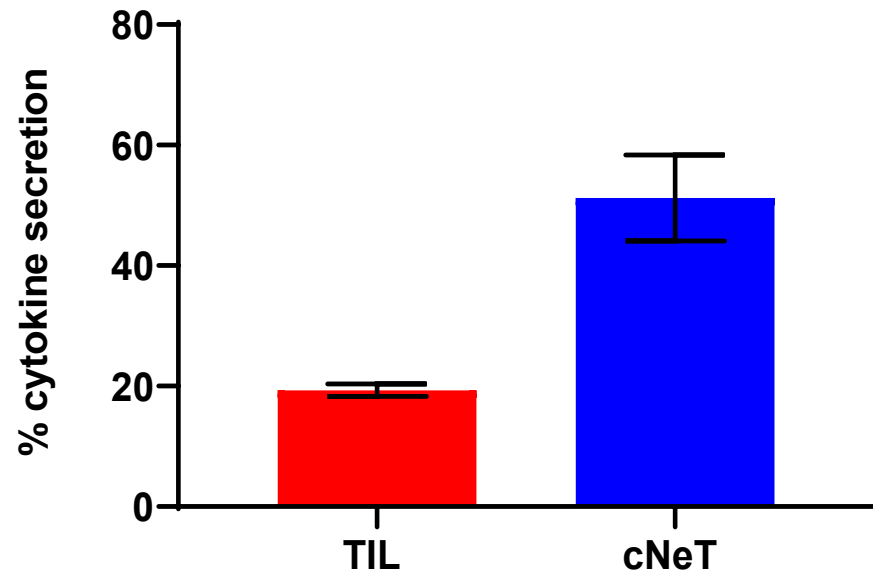


cNeT have improved specificity, function and fitness compared to standard TIL



T cell fitness¹

% cytokine secretion, patient data, n=5



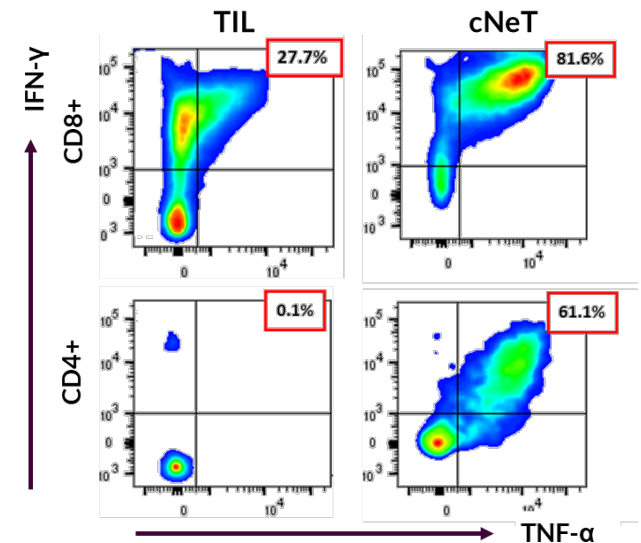
Natural dendritic cell-driven expansion improves T cell fitness

1. Achilles data measuring the ability of T cells to produce inflammatory cytokines in response to the same polyclonal stimulation

T cell specificity and function²

Cytokine secretion measured through flow cytometric analysis, n=1

VELOS selectively expands tumor-derived clonal neoantigen reactive CD4+ and CD8+ T cells with improved specificity and potency



CD4+ and CD8+ T cells can work in concert to deliver robust and durable responses³⁻⁵

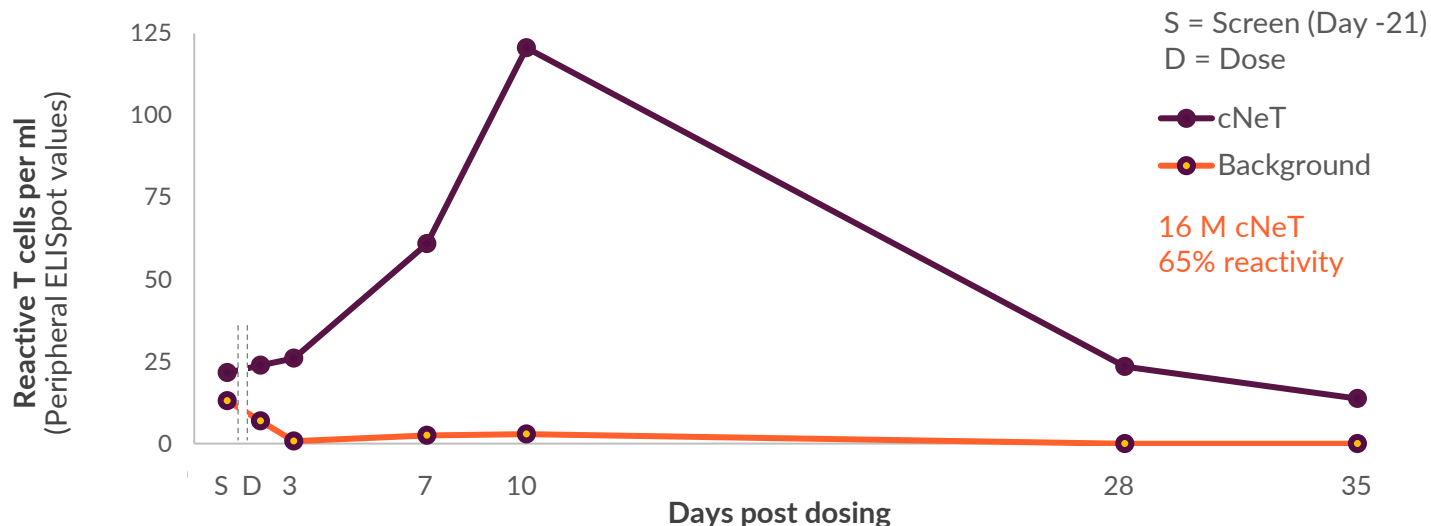
2. Achilles' data measuring the production of inflammatory cytokines in response to clonal neoantigens
3. Hunder et al., NEJM, 2008
4. Church et al., Eur J Immunol, 2014
5. Antony et al. J Immunol, 2005



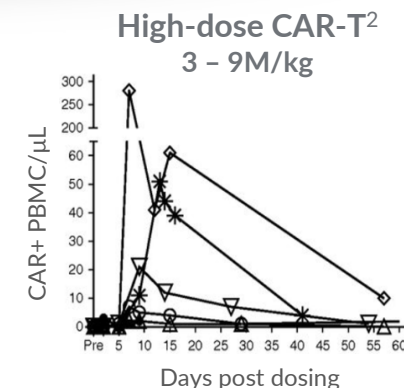
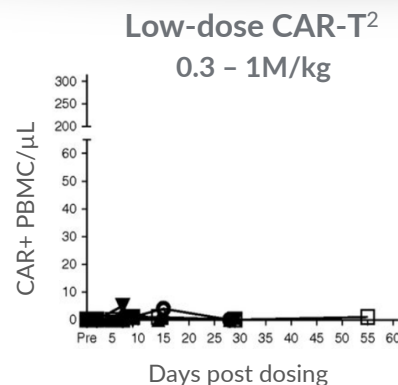
The Achilles cNeT Platform allows:

- Quantification of tumor reactivity and cNeT dose for each product (not possible with TIL therapy)
- Determination if increasing cNeT dose improves cNeT persistence and activity as seen in CAR-T therapy
- Correlation of cNeT dose and persistence with anti-tumor effect
- Product release on cNeT dose and basis for potency assays

Melanoma Patient Case Study¹: Expansion and detection of cNeT post-dosing



cNeT have similar patterns of expansion as seen in CAR-T



Aim to deliver clinical doses of >100M cNeT from our VELOS™ manufacturing process



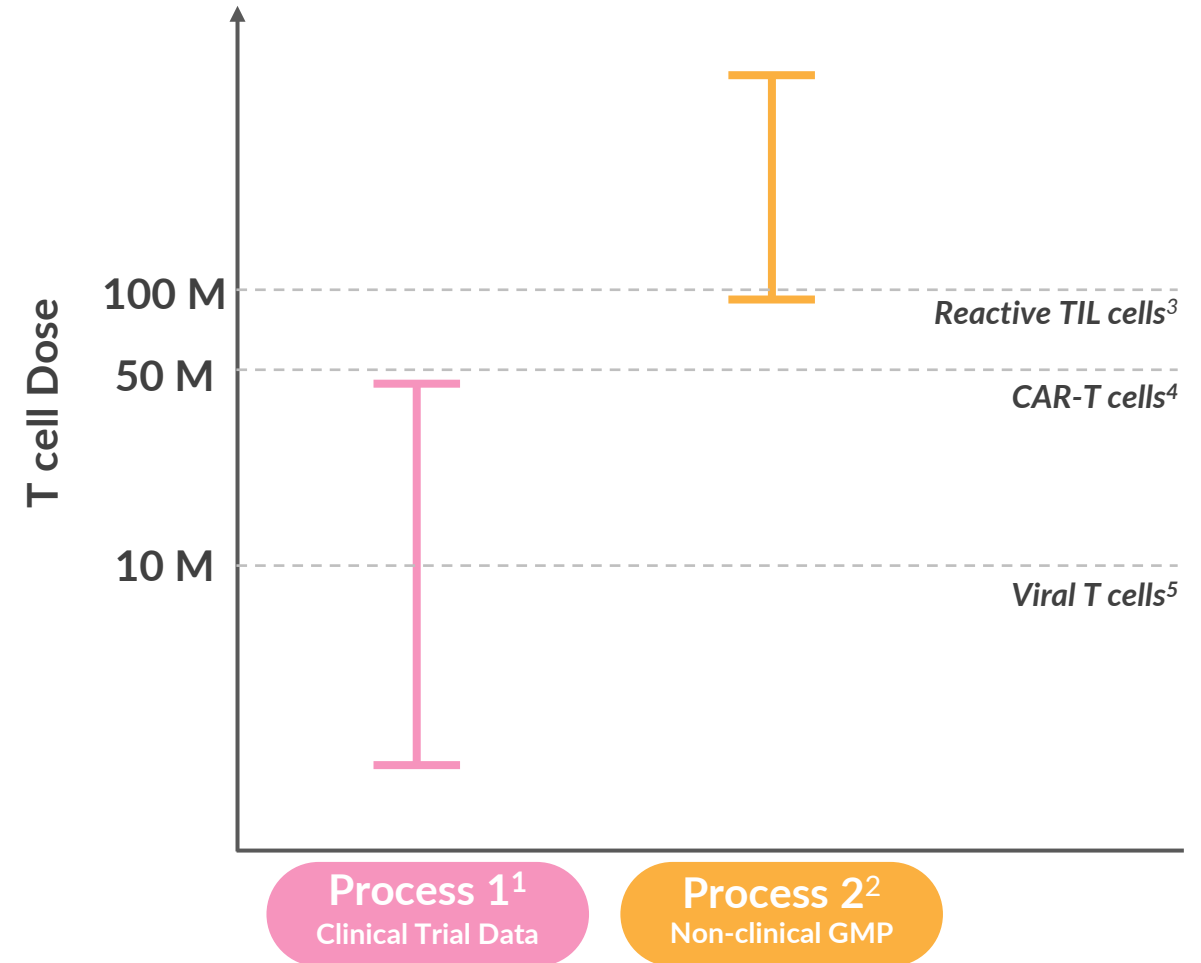
	Process 1	Process 2
Pre-Expansion	T cells are harvested from the tumor	Cytokines boost tumor-reactive cell harvest
Expansion	Dendritic cells loaded with clonal peptides activate and drive cNeT expansion	Optimized DC-driven co-culture followed by short T cell boost increases final cNeT dose

Process 2

- Identical manufacturing timeline to Process 1
- Maintains high functional cell fitness and effector memory phenotype
- Approved in UK, France, Germany & Spain

VELOS Manufactured Cell Doses

Compared to estimated lowest clinically active doses of other T cell therapies



1. SITC 2021 Poster 543
2. ESMO IO 2021 Poster 58P

3. J Clin Invest 2021, Kristensen
4. Blood 2017, Mueller
5. Lancet 2003, Peggs

Achilles has two ongoing Phase I/IIa clinical trials



CHIRON Advanced NSCLC

Monotherapy

- Advanced unresectable or metastatic Stage III-Stage IV NSCLC
- Never-smokers and EGFR/ALK/Ros-1 mut excluded
- Open-label
- n = up to 40
- Option to open Cohort B in combination with a PD-1 inhibitor

Evaluating safety, tolerability and activity (RECIST), biomarkers of clinical activity and bespoke ctDNA assay

Ongoing in UK, EU and US

THETIS Melanoma

Cohort A – Monotherapy

- Recurrent or metastatic malignant melanoma (n = up to 40); Open-label
- Acral, uveal and mucosal melanoma excluded

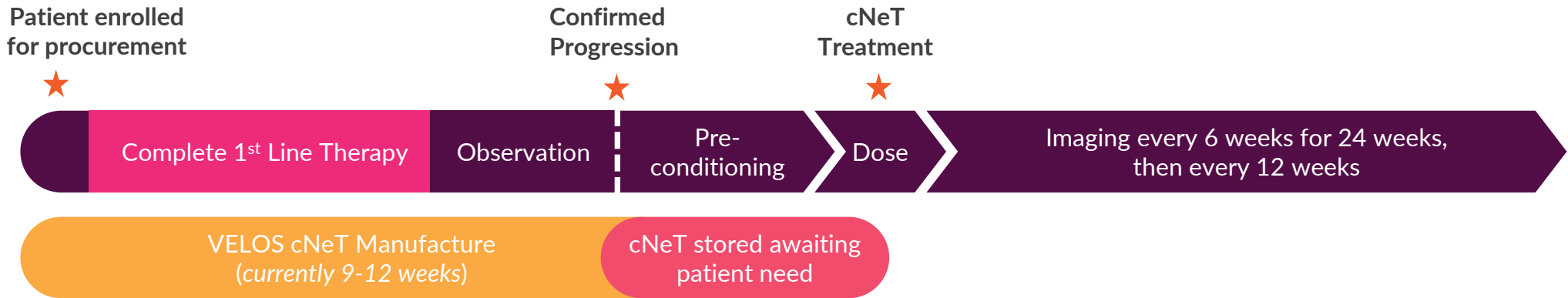
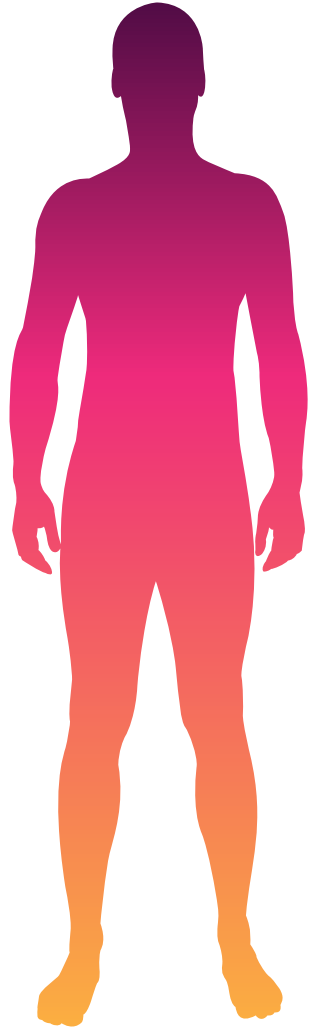
COHORT B – Combination with PD-1 inhibitor (nivolumab)

- n = up to 20 checkpoint refractory patients; Open-label
- CPI dosed 7-13 days prior to cNeT and restarted day 14 post-cNeT

Evaluating safety, tolerability and activity (RECIST)

Ongoing in UK, expanding to EU & US

cNeT therapies can be readily delivered within standard treatment pathways



Manufacturing
Manufactured and cryopreserved for infusion after patient progression

Tolerable pre-conditioning
Lower, more tolerable pre-conditioning (cy/flu)

Low IL-2
Lower dose IL-2 vs existing TIL therapy



Heavily pretreated patients with advanced cancer

- 2.5 median lines of prior therapy
- 14.2m median cNeT dose¹ in monotherapy
- All had progressive disease at time of lymphodepletion
- Five recurrent or metastatic malignant melanoma patients (THETIS)
- Three advanced unresectable or metastatic NSCLC patients (CHIRON)

cNeT tolerability profile

- Tolerability similar to standard TIL products not enriched for cNeT reactivities
- No higher-grade adverse events more commonly associated with the use of higher doses of IL-2
- Three SAEs deemed unlikely related and one ICANS event deemed to be possibly related to cNeT treatment



Activity 6-weeks post treatment

- **Stable disease** in 5 of 8 patients¹
- **Tumor reduction** in 2 of 4 lesions (55% and 90%) in patient with highest cell dose
- **Engraftment** in 5 of 7 patients, with dose associated response
- **2 to 28 reactivities** observed in 7 of 8 cNeT
- Median dose of 14.2 M

Patient	cNeT Dose (M)	Reactivity	Engrafted ²	Best Response
C-03	0.1	0.20%	--	SD
T-12	2	13%	Y	SD
T-09	12	9%	N	SD
C-11	13	41%	Y	SD
T-05	16	65%	Y	PD
C-10	21	3%	N	SD
T-11	42	5%	Y	PD
T-02 ³	287	77%	Y	PD

Median 2.5 lines of prior therapy

Next steps: Explore higher-dose cNeT monotherapy and combination with PD-1 inhibitor

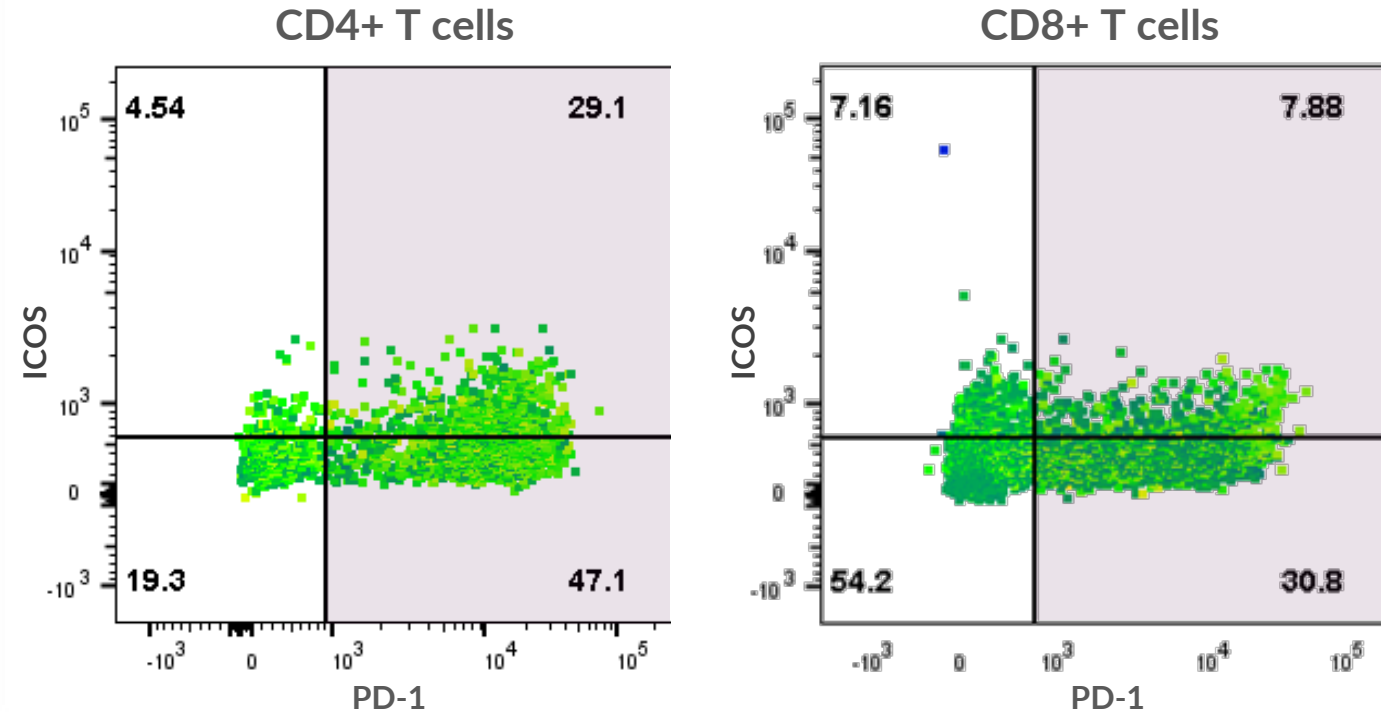


Checkpoint molecules in immune regulation

- Normal immune regulation uses immune checkpoints to inhibit T cells from attacking healthy tissue
- Our data show PD-1 checkpoint is upregulated on a fraction of cNeT which could partially reduce anti-tumor activity¹
- Targeting PD-1 with checkpoint inhibition could further increase cNeT activity

TIL-derived cNeT express elevated levels of PD-1 upon antigen encounter¹

Cell surface marker flow cytometric analysis (n=1)



Scale-up of GMP manufacturing for late stage clinical trials and commercial launch



Royal Free Hospital (UK)

GMP facility supporting FiH studies



Cell & Gene Therapy Catapult (UK)

GMP facility supporting open and closed manufacturing process to support clinical and commercial supply



Center for Breakthrough Medicine (US)

GMP facility in partnership with CBM, a CDMO in Greater Philadelphia



Hayes (UK)

GMP modular facility to support multiple indications for late stage clinical and commercial supply

Online 2019

Peak Dose Capacity 50

2022

200

2023

150-400*

2024

1,000+

*Initial plan of 150-200 doses with potential for expansion



\$266M

CURRENT CASH BALANCE¹

2H 2024

CURRENT CASH RUNWAY

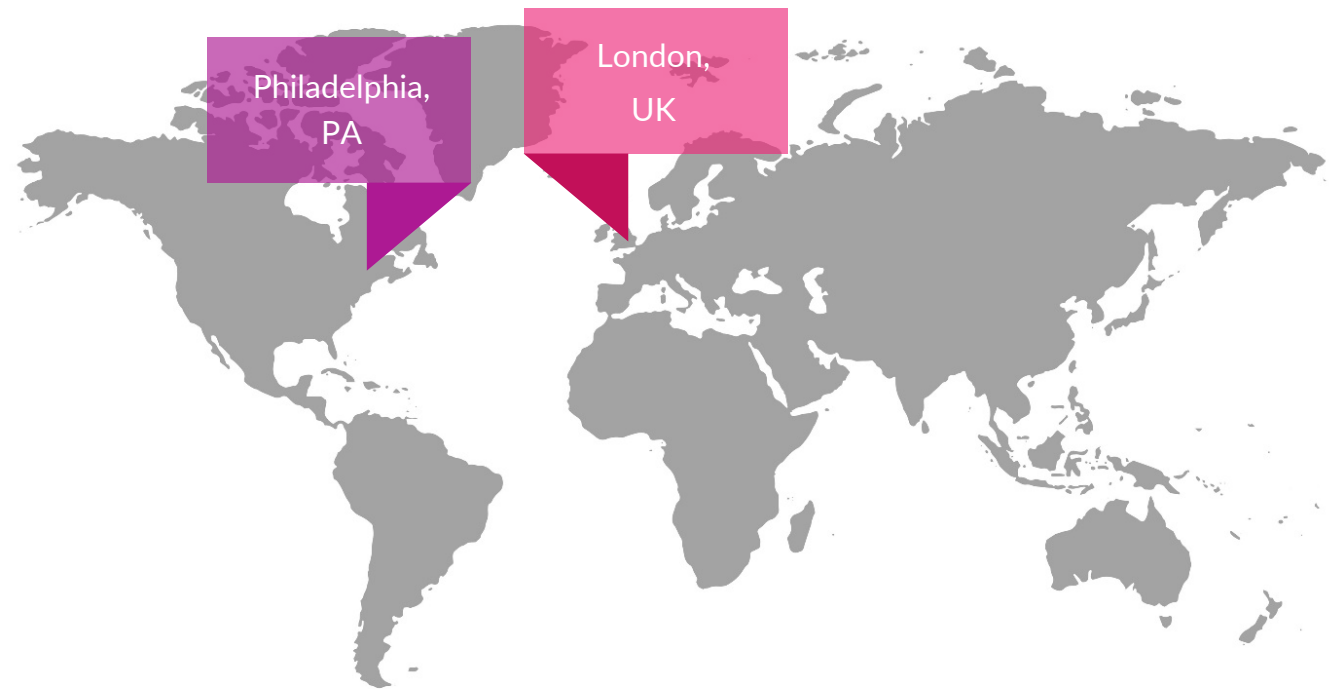
Global Operations

U.S. Headquarters

Philadelphia, PA

Global Headquarters

London, UK



Key anticipated 2022 milestones and updates



	2022			
	Q1	Q2	Q3	Q4
Higher-dose cNeT (Process 2)		First Patient Dose (Process 2)	Add'l Process 2 monotherapy patient data	Add'l Process 2 monotherapy patient data
PD-1 + cNeT combo (Process 1 & 2)	Open CPI combo cohort (melanoma) ✓		First Patient Dose (combo)	Initial combo patient data
Facilities and Manufacturing	Establish US HQ and R&D ✓	Catapult GMP License & US CDMO Partnership ✓		
Tumor Archiving Program (TAP)		Initiate TAP program		

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