



Achilles Therapeutics

Precision T cell therapies to treat solid tumors

June/July 2021



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A clinical stage company developing precision T cell therapies to treat solid tumors



NASDAQ: **ACHL**
Precision TIL therapy



Two open-label Phase I/IIa clinical trials ongoing in NSCLC and melanoma and next program to enter the clinic in 2022



Interim analysis on 10 patients across NSCLC & melanoma expected in Q4 2021; PD-1 combination study in melanoma to start in Q4 2021 and cNeT Process 2 (higher median dose) study to open recruitment in Q4 2021



Designing a closed, automated and scalable manufacturing process to deliver over 1,000 doses annually to supply late stage clinical trials and initial commercial products; GMP modular facility is a blueprint for global commercial supply



Science based on pioneering research led by Profs. Charlie Swanton, Karl Peggs, Mark Lowdell and Sergio Quezada into tumor evolution, immune-regulation and the translation of precision T cell therapies



Team of ~200 employees (HQ in London) fully financed to complete ongoing phase I/IIa clinical trials, expand manufacturing capacity and bring additional programs into the clinic with March 31 *pro forma* cash of \$320M

Our senior management team & board



Senior Leadership Team

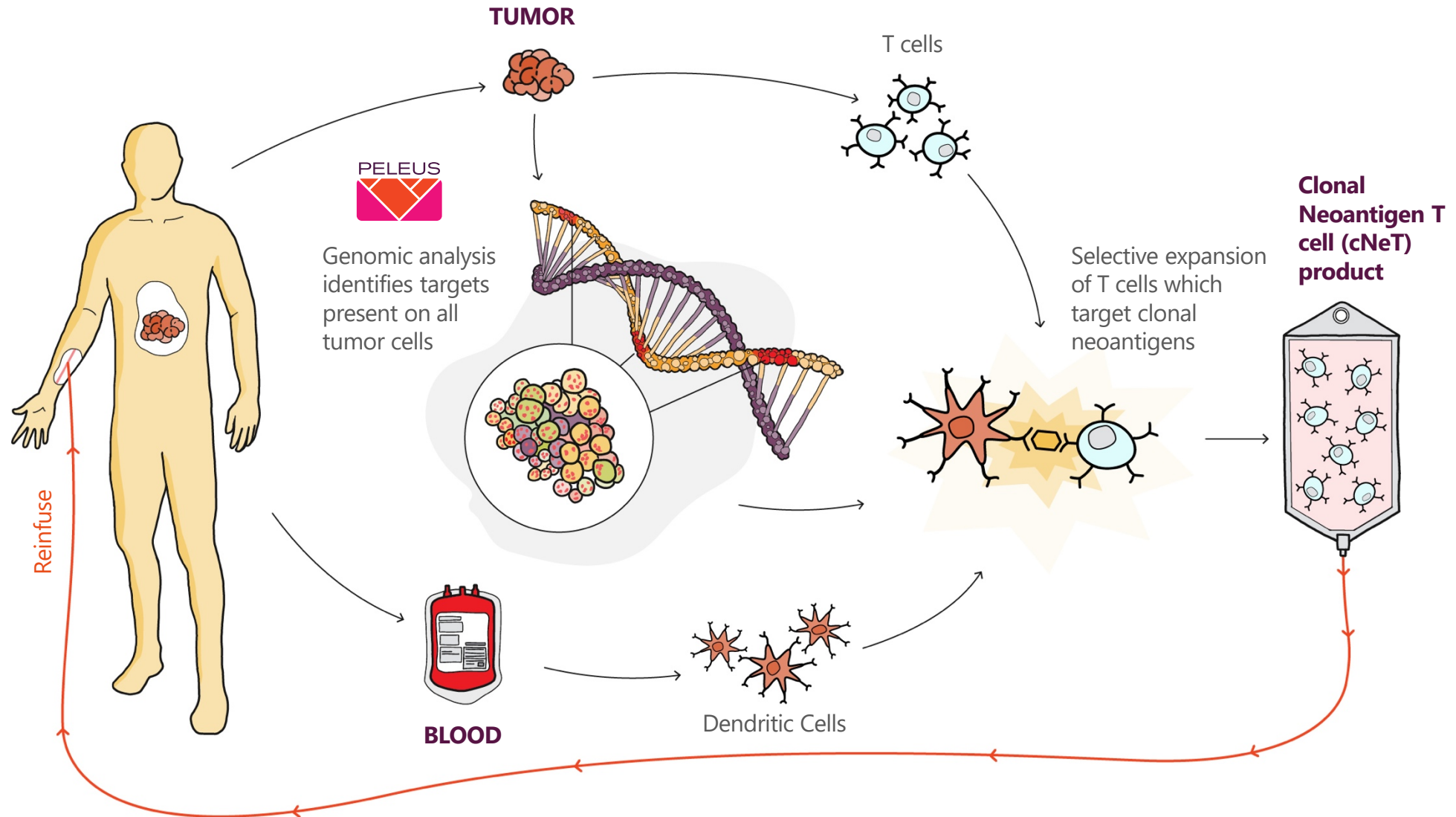
 <p>Iraj Ali CEO & Board Member</p> <p> </p>	 <p>Sergio Quezada CSO & Founder</p> <p> </p>	 <p>Karl Peggs CMO & Founder</p> <p></p>	 <p>Robert Coutts CFO</p> <p> </p>
 <p>Daniel Hood Chief Legal Officer</p> <p> </p>	 <p>Beverley Carr CBO</p> <p> </p>	 <p>Ed Samuel SVP Technical Operations</p> <p> </p>	 <p>Shree Patel SVP Clinical Operations</p> <p></p>

Board of Directors

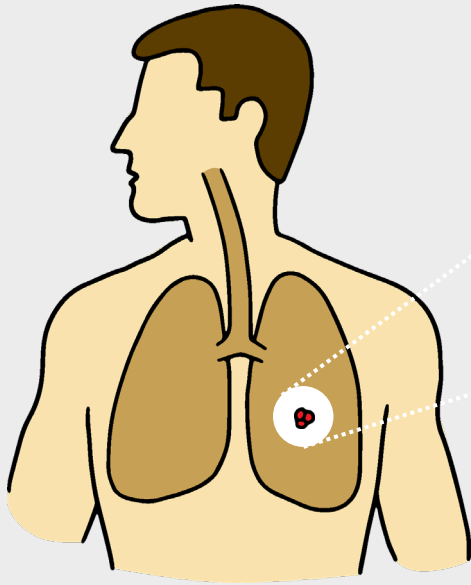
 <p>Edwin Moses Chairman</p> <p></p>	 <p>Carsten Boess Non-Executive Director</p> <p> </p>	 <p>Derek DiRocco Non-Executive Director</p> <p></p>	 <p>Michael Giordano Non-Executive Director</p> <p></p>	 <p>Julie O'Neill Non-Executive Director</p> <p> </p>
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Precision TIL therapy targeting clonal neoantigens

Using cutting edge personalized genomics to target all cells in a patient's tumor



Achilles has developed proprietary technology to **target all tumor cells**



Tumors are **clonal in origin** and originate from a group of cells that are exactly the same



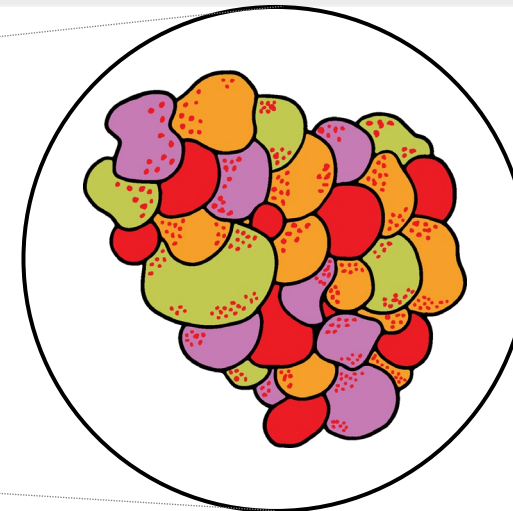
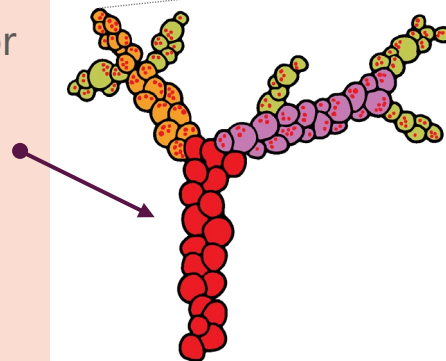
Tumors evolve, developing many new mutations resulting in **heterogeneity** that enables them to evade targeting¹



To kill all of the tumor cells we believe you need to target the **clonal neoantigens formed early in tumor evolution**

Achilles has developed proprietary technology to identify the original tumor mutations **present on all cancer cells, clonal neoantigens**

We are able to identify and **target multiple clonal neoantigens** with our Clonal Neoantigen T cell therapy, cNeT



Clonal neoantigens are present on **primary tumors and all metastases**



TRACERx

A clinical study of tumor evolution

The TRACERx study comprises **multi-region, longitudinal, data from over 780 NSCLC patients** collected over a period of 5 years^{1,2,3,4}

Over **3,000 tumor region samples**, comprising **one of the largest** bioinformatic data sets of its kind

The learnings from TRACERx **can be applied to other solid tumors**



PELEUS®

A proprietary platform to identify clonal neoantigens

We have developed the proprietary **PELEUS** platform, which can identify the patient's unique clonal neoantigens

The PELEUS platform has been built using the **extensive data from TRACERx** combined with our own **proprietary statistical models**

The PELEUS platform is **trained and improved** using new TRACERx data



Our precision TIL therapy specifically targets clonal neoantigens



Tumor associated antigens

Present on some tumor cells and on healthy tissue



Neoantigens

Present on some tumor cells



Clonal neoantigens

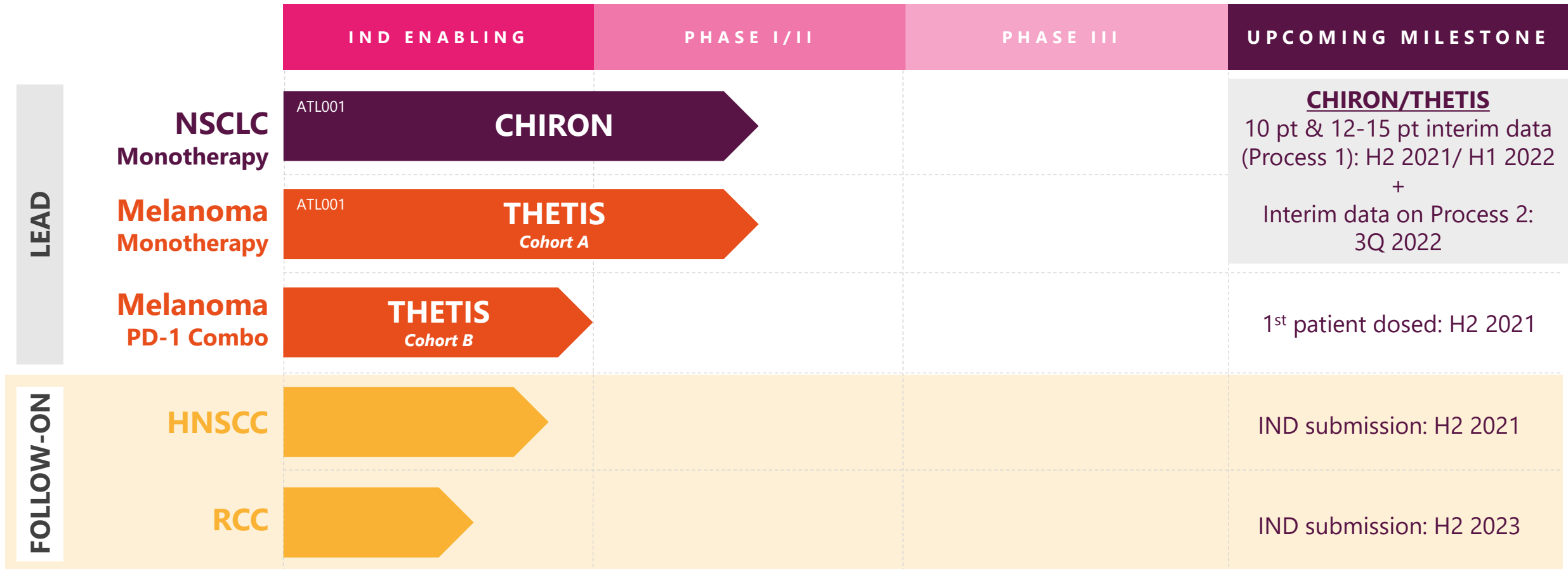
Present on all tumor cells, absent from healthy tissue



Achilles has a unique capability to target clonal neoantigens

Our process can deliver tumor specificity and potency improvements over standard TIL

Our current pipeline



Our proprietary VELOS™ manufacturing process builds on standard TIL therapy but leverages clonal neoantigen targeting to deliver a more precise and potent product



Precision platform

Selective expansion of tumor targeting T cells

- **Prospectively target patient-specific clonal neoantigens** shown to correlate with anti-tumor activity^{1,2}
- Able to quantify the **active component (cNeT)** in each product and **track post dosing** in blood or tissue
- **Enable a mechanistic understanding of cNeT therapy** (e.g., dose response) and a path to a **robust potency assay**

Potent product

Potent polyclonal product

- VELOS process delivers a **polyclonal product** able to target **multiple cancer antigens** present **on all tumor cells**
- Products contain both **T helper (CD4+)** and **cytotoxic T cells (CD8+)** subtypes
- Natural dendritic cell process **reduces the need for IL-2** in the VELOS process and post-dosing

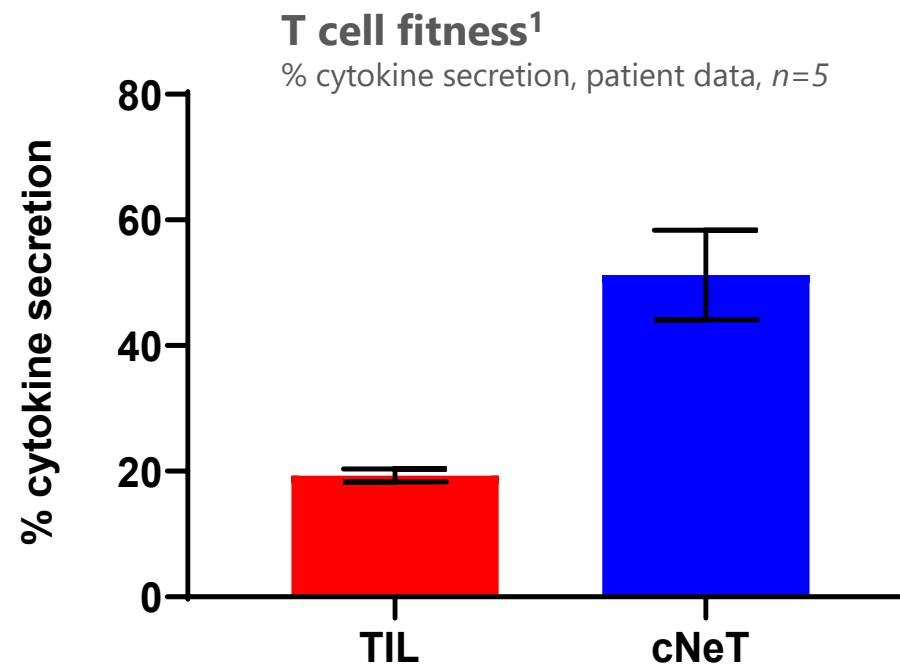
VELOS

Manufacturing
process

cNeT have demonstrated improved T cell fitness compared to standard TIL



- Natural dendritic cell-driven expansion delivers **significant improvement in T cell fitness** for cNeT compared to standard TIL
- The fitness of all T cells can be assessed through the non-specific activation of the CD3+ T cell co-receptor



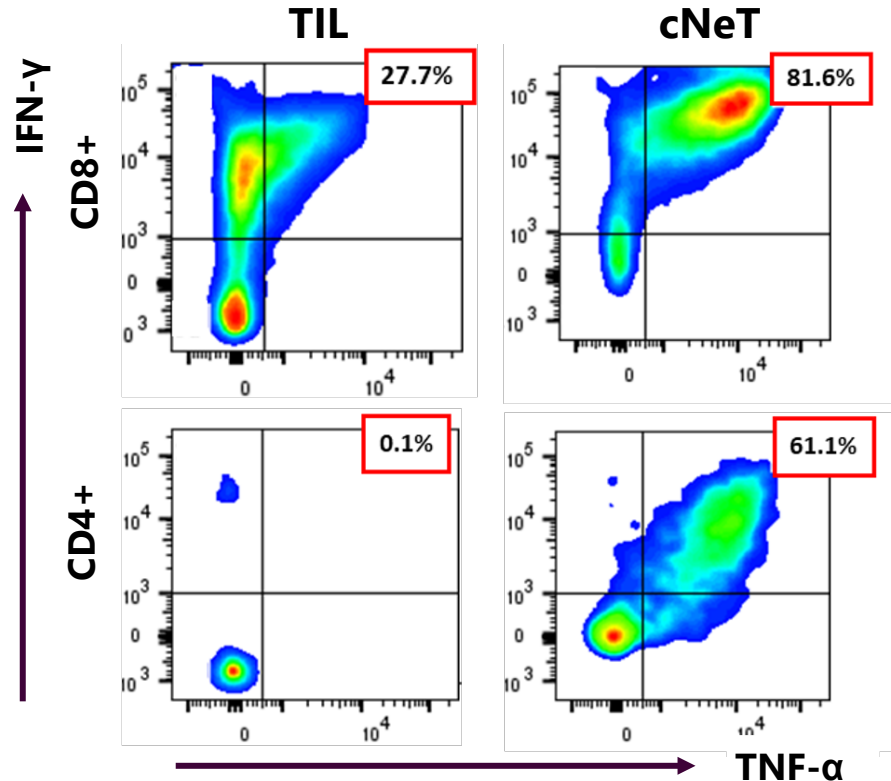
cNeT have demonstrated improved specificity and potency compared to standard TIL



VELOS™ manufacturing process has been shown to produce both **CD4+ and CD8+ T cell** populations. There is a strong body of pre-clinical data which shows **CD4+ and CD8+ T cells** can work in concert to deliver **robust and durable responses**¹⁻³

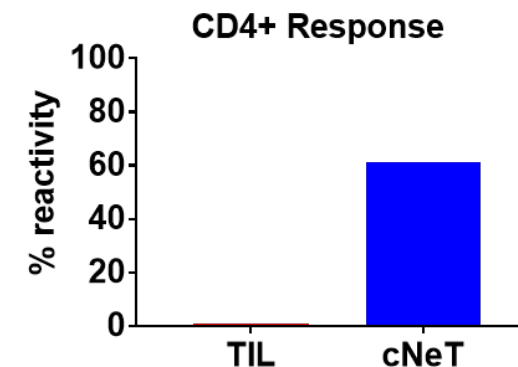
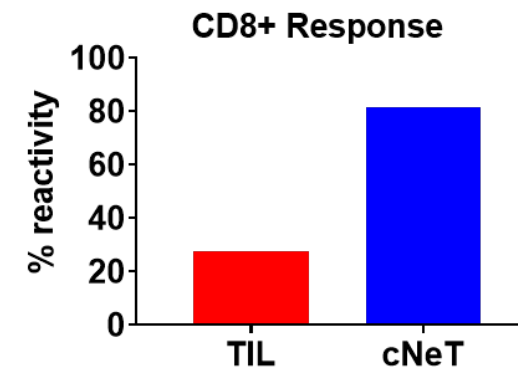
T cell specificity and potency⁴

Cytokine secretion measured through flow cytometric analysis, $n=1$



T cell specificity and potency⁴

% reactivity, $n=1$



Our cNeT platform delivers a route to developing a robust potency assay

Patient case study Presented at AACR 2021



Characterization and tracking of cNeT correlated to patient outcomes offers insight into mechanism



For each patient we can identify the **specific (clonal) tumor antigens** we will be targeting



Cells can be **tracked post-dosing** in the patient's blood revealing cNeT expansion kinetics



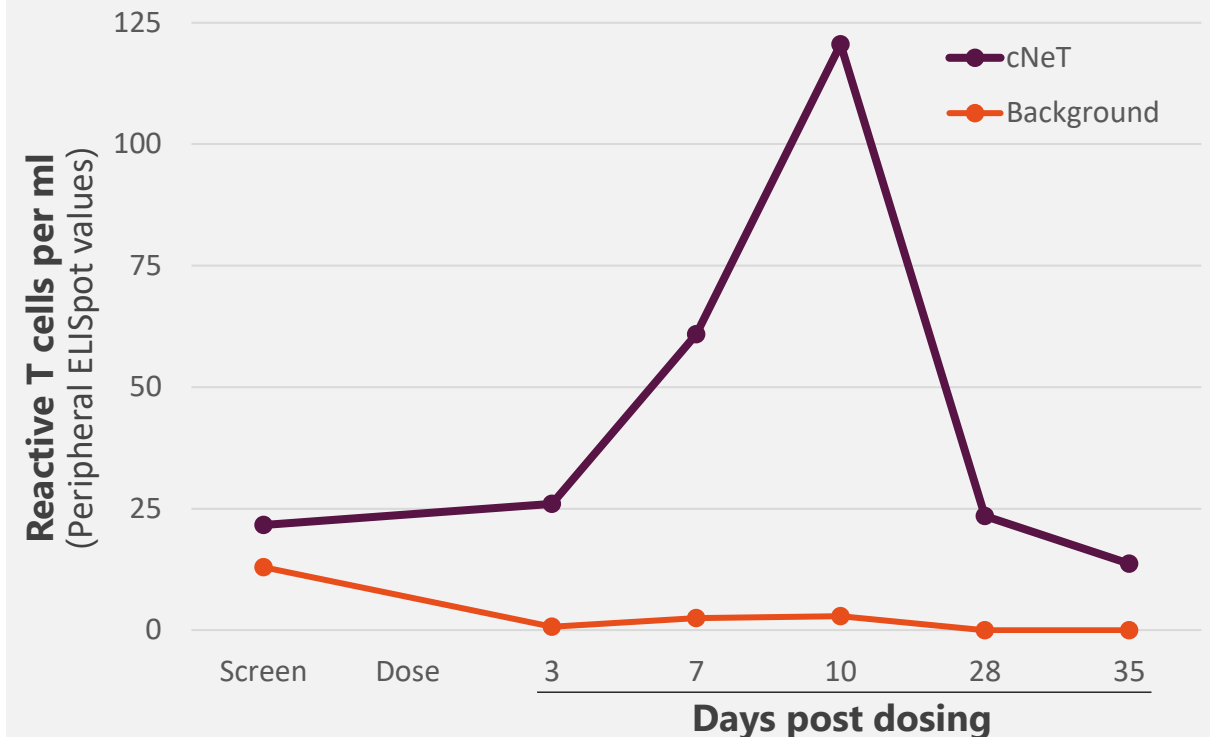
Correlating cNeT kinetics with clinical activity provides a **path to potency assay**



Data for this patient show **increasing absolute levels of cNeT** in the blood but with **limited persistence**

Estimated cNeT per ml

Expansion and detection of cNeT post dosing THETIS patient, $n=1$



Achilles has two ongoing Phase I/IIa clinical trials



CHIRON

Advanced non-small cell lung cancer
(Stage III-Stage IV)
Open-label

- Up to 40 patients with advanced unresectable or metastatic NSCLC
- Never-smokers and EGFR/ALK/Ros-1 mutations excluded
- cNeT monotherapy with option for PD-1 inhibitor combination cohort
- Evaluating safety, tolerability and activity (RECIST), biomarkers of clinical activity and bespoke ctDNA assay
- Ongoing in UK, EU and US

THETIS Cohort A

Recurrent or metastatic malignant melanoma; monotherapy
Open-label

- Up to 40 patients with metastatic or recurrent melanoma (monotherapy)
- Acral, uveal and mucosal melanoma excluded
- Evaluating safety, tolerability and activity (RECIST)
- Ongoing in UK, EU and expanding to US

THETIS Cohort B

Combination with checkpoint
inhibitor
Open-label

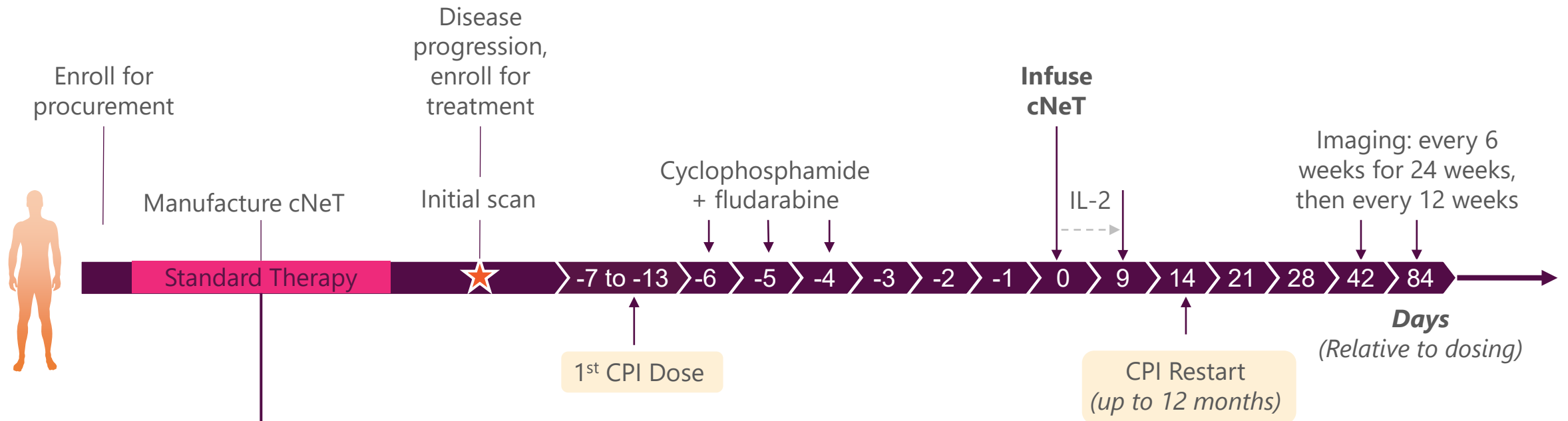
- Up to 20 checkpoint refractory patients in combination with PD-1 inhibitor (nivolumab)
- Checkpoint dosed prior to cNeT dosing (~7-13 days) and restarted at day 14 post-dosing
- Opening in Q4 2021

CHIRON and THETIS trial design

cNeT therapies can be readily delivered within standard treatment pathways



Key: Cohort B only



- **Option to procure tissue before, after and during systemic therapy**
- cNeT can be manufactured during checkpoint therapy

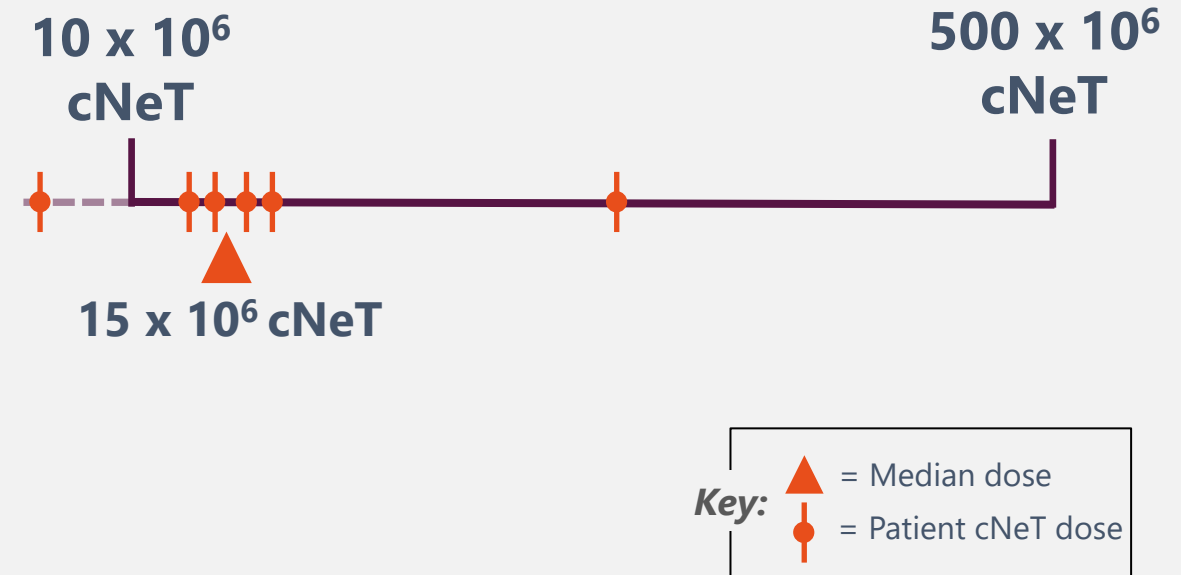
- **Well-tolerated pre-conditioning and IL-2 regimens** (vs. existing TIL therapy)
- Lower cyclophosphamide and IL-2 dose delivered over a longer period



Patient summary

- Data from first six dosed patients following scan 6 weeks post-cNeT infusion
 - 3 in CHIRON, 3 in THETIS
- Median 2.5 lines of prior therapy
- All had progressive disease at time of lymphodepletion
- Median dose at the low end of prospectively targeted therapeutic range
- cNeT doses manufactured using VELOS Process 1
 - Generated doses of 0.1M to 278M cNeT with high specificity and fitness

Prospectively Targeted Therapeutic cNeT range (VELOS Process 1)





Tolerability

- **IDSMC** recommended that both clinical trials **continue as planned** with no modification
- **Tolerability similar to standard TIL** products not enriched for cNeT reactivities
 - Most higher-grade AEs from lymphodepletion regimen
- **No grade 3 or 4 IL-2 related toxicities**
- **Two SAEs observed**
 - One deemed unlikely related to cNeT
 - One deemed possibly related to cNeT

Activity

- **Stable disease** at 6 weeks post-dosing in 4 of 6 patients and progressive disease in 2 of 6¹
- **Tumor reduction** in 2 of 4 lesions of approx. 55% and 90% in patient that received the highest cell dose
- **Evidence of engraftment** in 3 of 6 patients, with highest dose associated with highest engraftment
- **Ability to characterize** infused cells at level of individual cNeT reactivities, in contrast to standard TIL
 - **Basis for potency assay**
 - **Documented polyclonality** of infused products and engrafted cells (up to 28 reactivities)

Key Next Steps

Explore higher cNeT monotherapy doses and combination with PD-1 inhibitor
Incorporate additional cytokines to boost TILs extracted & cNeT generated (VELOS Process 2)

VELOS Process 2 is expected to yield higher cNeT doses

Targeting pre-expansion and expansion steps provides a consistent boost in TIL and cNeT



Pre-Expansion

Expansion

Process 1

T cells are harvested from the tumor

Dendritic cells loaded with clonal peptides activate and drive cNeT expansion

Process 2

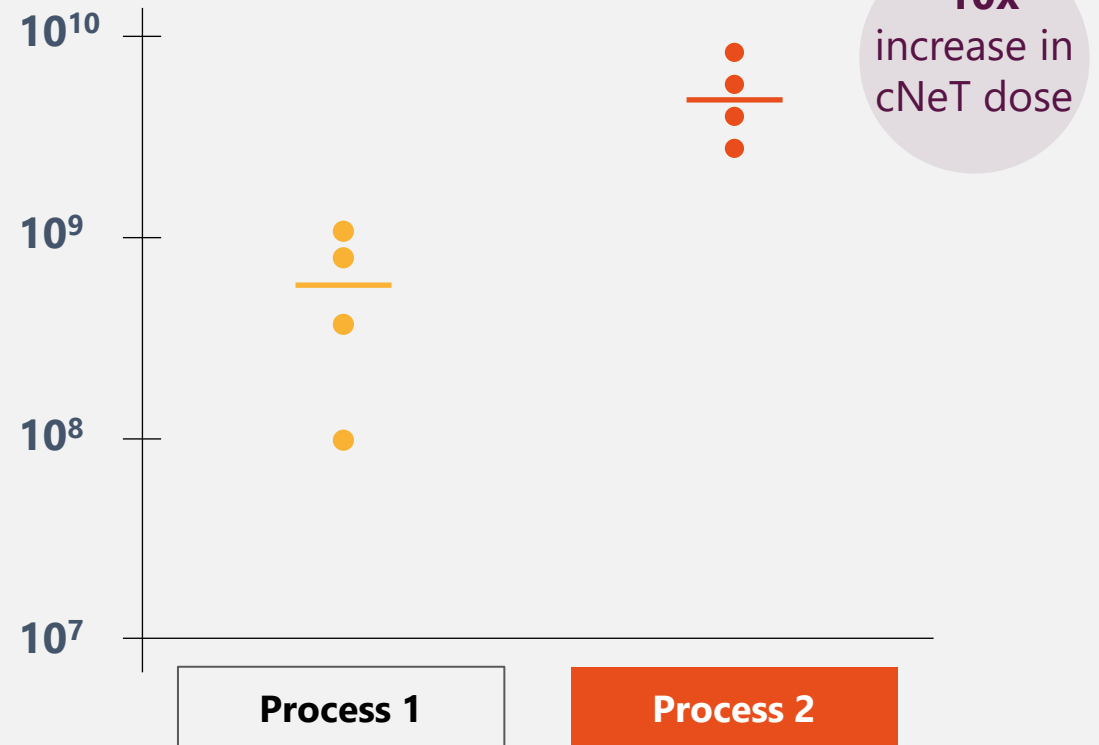
Additional cytokines boost the harvest of tumor reactive cells

Optimized DC-driven co-culture followed by short T cell boost increases final cNeT dose

Timelines for both processes are identical

cNeT dose by process*

cNeT reactivity as measured by our potency assay (IFN γ /TNF α positive cells)



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



Royal Free Hospital



GMP facility operated by Achilles staff to support FiH studies

Cell & Gene Therapy Catapult



Supports both open and fully closed manufacturing process

Hayes



- GMP modular facility utilizing PODS
- Support multiple indications for late stage clinical studies and commercial supply
- Includes in-house peptide manufacturing

Online

2019

Peak Dose Capacity

50

2021

200

2023

1,000



End-to-end closed process enables operation in simplified (lower cost) GMP facility

Tumor collection device



Tumor is collected in our bespoke device to **close the process from procurement**

Closed tumor processing



Closed processing at our GMP facilities reduces COGs, **eliminates human operator steps and drives scale-up**

Targeting a 6 to 8 week process at commercial stage from sample collection to patient dosing



Alternative starting materials (e.g. blood)

Manufacture of cNeT from
blood and other sources



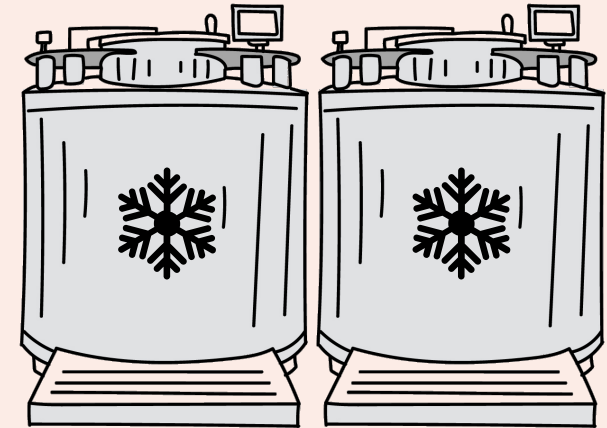
Gene-edited products

Targeted gene knock-down
in cNeT

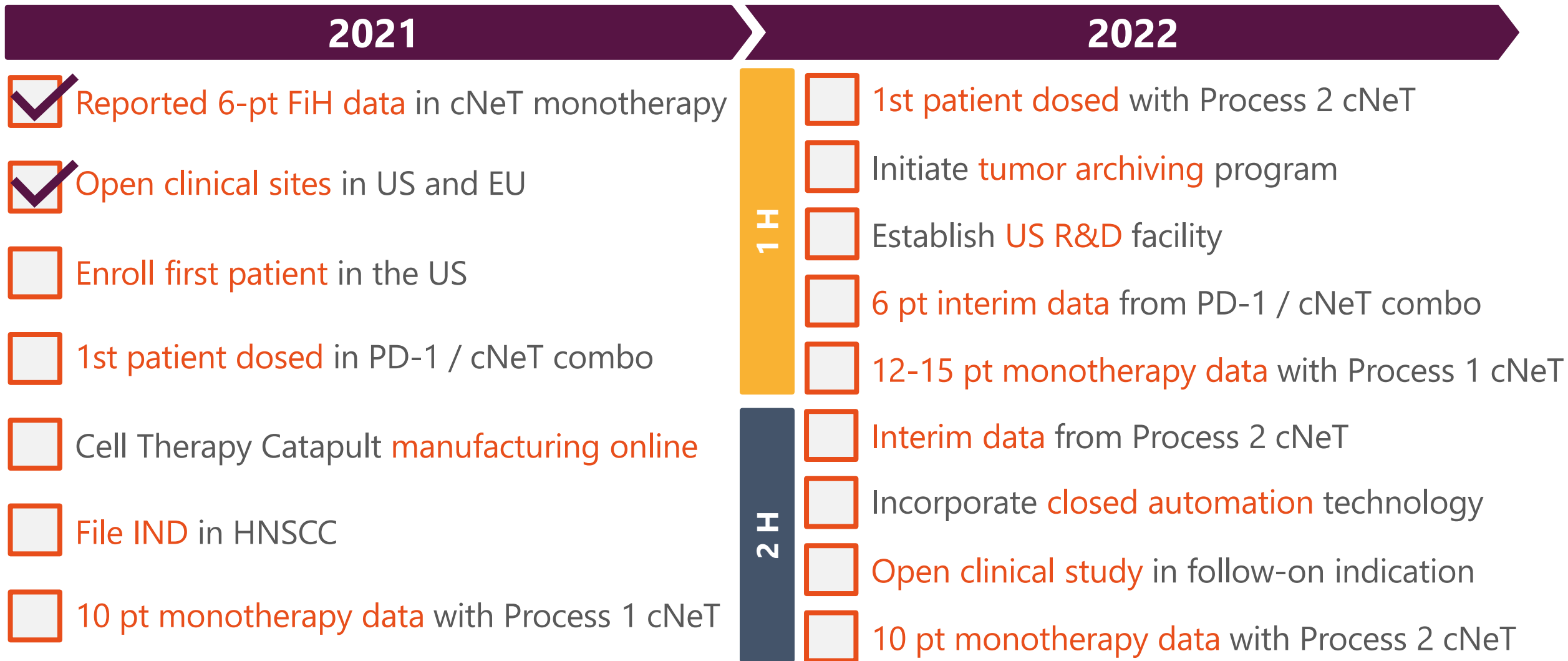


Early tumor sample archiving

Banking of tumor from earlier
stage patients









Key anticipated milestones

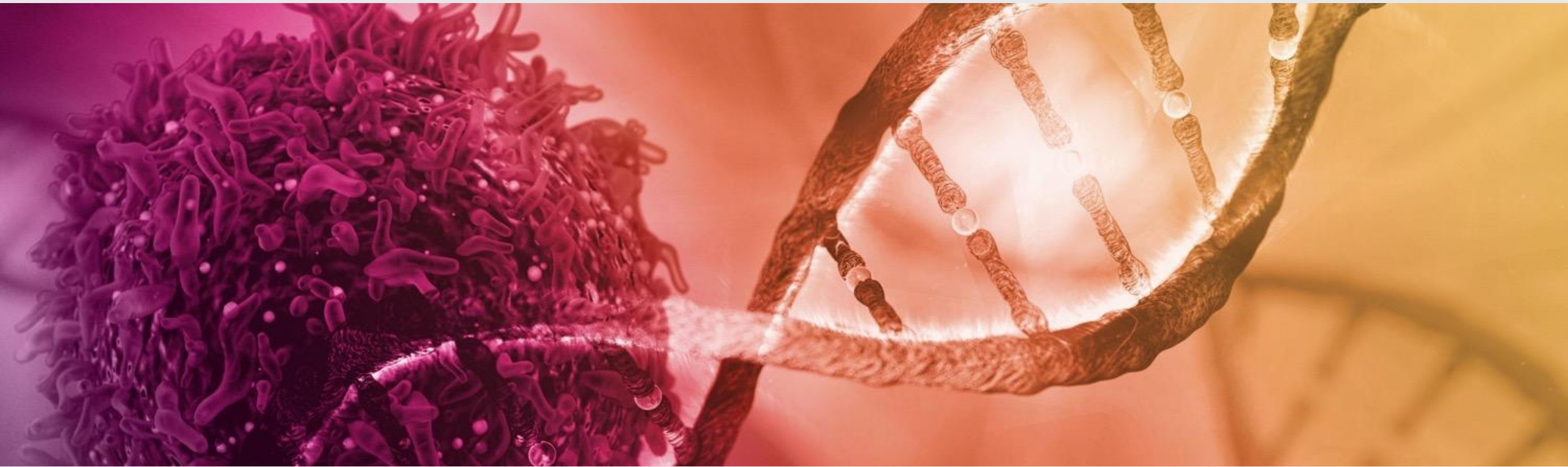


Business is financed to complete phase I/IIa CHIRON and THETIS studies (2H 2023)

Achilles is building a transformative oncology business



-  Two ongoing clinical trials with near-term data readouts and plans to add new indications
-  Exclusive access to TRACERx, which gives the unique capability to address clonal neoantigens
-  cNeT platform can deliver target multiple cancer antigens present in all tumor cells
-  Technology allows us to develop a potency-based release assay
-  Robust and commercially scalable manufacturing process designed to be fully closed and automated
-  Cash to complete planned I/IIa clinical trials, expand manufacturing capacity, and broaden pipeline



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