Machines of Loving Hype

Let's get specific about "curing cancer with AI"

(secretly, personalized TCR therapies for NUT carcinoma and beyond)

Alex Rubinsteyn
September 3rd, 2025

A.I. execs like to dream

Anthropic CEO Dario Amodei believes AI can achieve a century of medical advancements in just 10 years

From breakthroughs in biology and medicine to major shifts in governance and economic development, Amodei sees a future where AI accelerates human progress at a substantial rate

AI could cure all disease in a decade, says Google DeepMind CEO— Perplexity's Aravind Srinivas agrees

Demis Hassabis, co-founder and CEO of Google DeepMind, envisions AI models potentially curing all diseases within the next decade. His claims received support from rival Aravind Srinivas, CEO of Perplexity AI, who praised Hassabis as a genius.

OpenAI, SoftBank and Oracle announce $500 billion AI infrastructure project in US; Sam Altman says it can cure cancer

SoftBank, OpenAI, and Oracle are launching a $500 billion joint venture named Stargate to fund AI infrastructure in the U.S. The initiative, praised by President Trump, aims to deploy $100 billion immediately for projects like data centers and cancer research.

Livemint

Updated • 22 Jan 2025, 08:42 AM IST

Dario Amodei

Machines of Loving Grace[1]

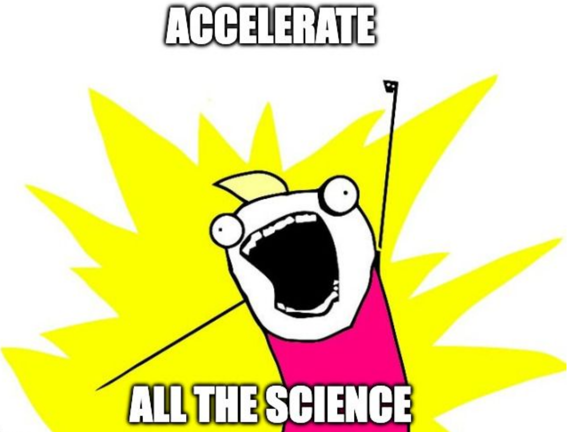
How AI Could Transform the World for the Better

Dario’s vision

Elimination of most cancer. Death rates from cancer have been dropping ~2% per year for the last few decades; thus we are on track to eliminate most cancer in the 21st century at the current pace of human science. Some subtypes have already been largely cured (for example some types of leukemia with CAR-T therapy), and I’m perhaps even more excited for very selective drugs that target cancer in its infancy and prevent it from ever growing. AI will also make possible treatment regimens very finely adapted to the individualized genome of the cancer—these are possible today, but hugely expensive in time and human expertise, which AI should allow us to scale. Reductions of 95% or more in both mortality and incidence seem possible. That said, cancer is extremely varied and adaptive, and is likely the hardest of these diseases to fully destroy. It would not be surprising if an assortment of rare, difficult malignancies persists.

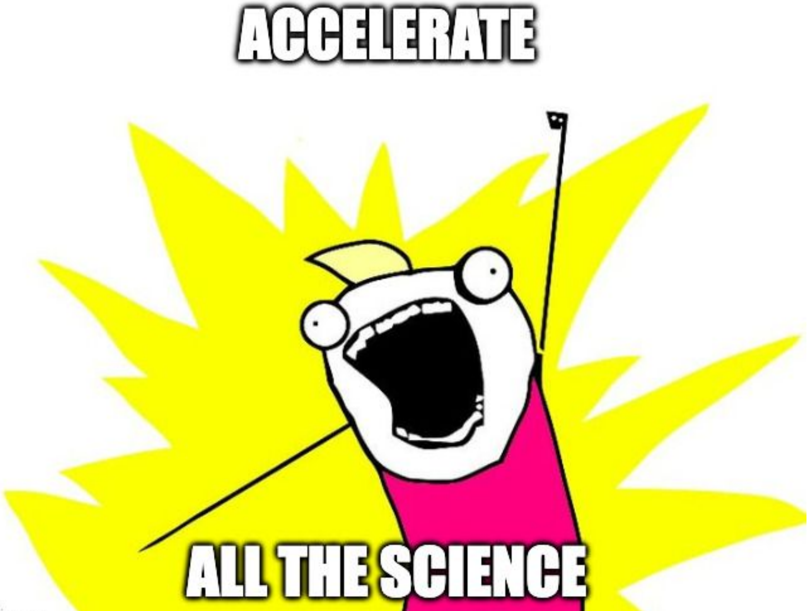
“Compressed 21st century” is vague

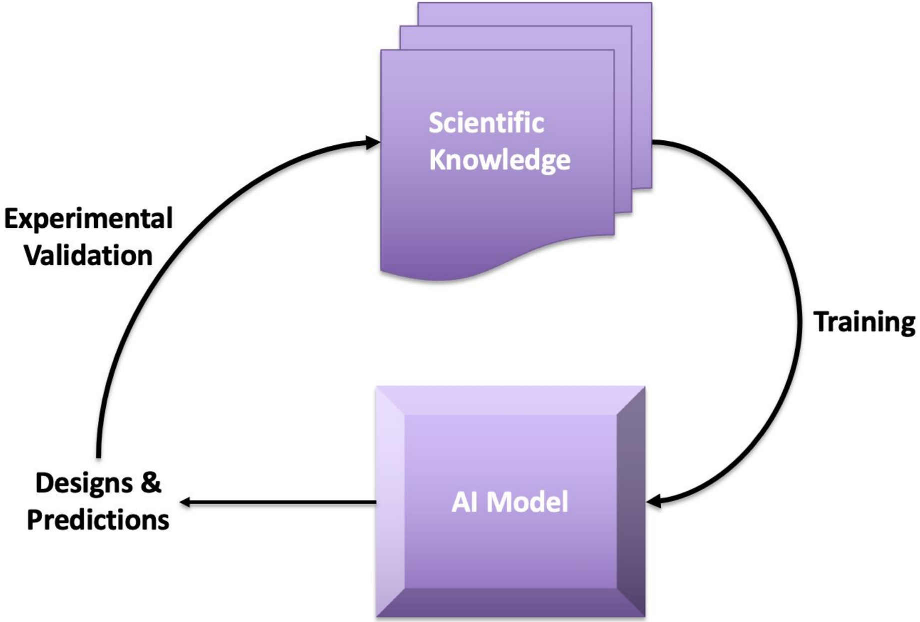
To summarize the above, my basic prediction is that AI-enabled biology and medicine will allow us to compress the progress that human biologists would have achieved over the next 50-100 years into 5-10 years. I’ll refer to this as the “compressed 21st century”: the idea that after powerful AI is developed, we will in a few years make all the progress in biology and medicine that we would have made in the whole 21st century.



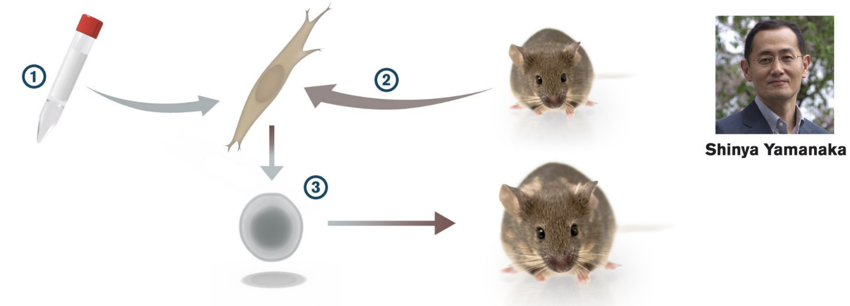
[14] I didn't want to clog up the text with speculation about what specific future discoveries AI-enabled science could make, but here is a brainstorm of some possibilities:
– Design of better computational tools like AlphaFold and AlphaProteo – that is, a general AI system speeding up our ability to make specialized AI computational biology tools.
– More efficient and selective CRISPR.
– More advanced cell therapies.
– Materials science and miniaturization breakthroughs leading to better implanted devices.
– Better control over stem cells, cell differentiation, and de-differentiation, and a resulting ability to regrow or reshape tissue.
– Better control over the immune system: turning it on selectively to address cancer and infectious disease, and turning it off selectively to address autoimmune diseases. ↩

In theory, a self-improving virtuous cycle





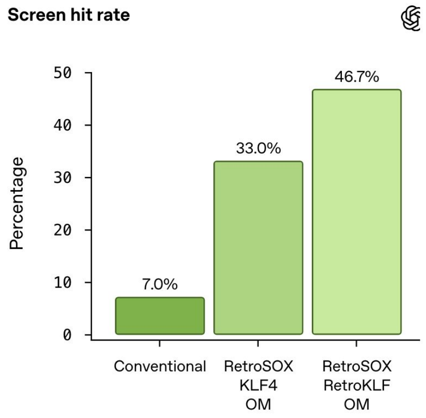
Example: OpenAI designing Yamanaka factors

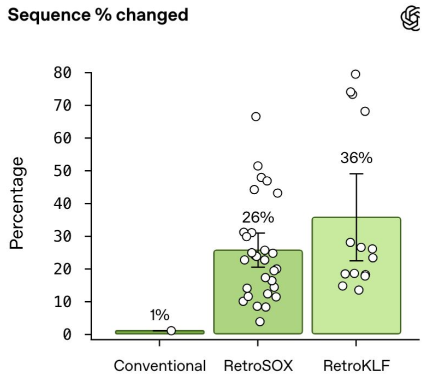


Shinya Yamanaka studied genes that are important for stem cell function. When he transferred four such genes (1) into cells taken from the skin (2), they were reprogrammed into pluripotent stem cells (3) that could develop into all cell types of an adult mouse. He named these cells induced pluripotent stem (iPS) cells.

We are excited to share that we've successfully leveraged GPT-4b micro to design novel and significantly enhanced variants of the Yamanaka factors, a set of proteins which led to a Nobel Prize for their role in generating induced pluripotent stem cells (iPSCs) and rejuvenating cells. They have also been used to develop therapeutics to combat blindness, reverse diabetes, treat infertility, and address organ shortages.

Figure 2: Visualization of the 3D structure of the Yamanaka factors KLF4 (left) and SOX2 (right). Notice that the majority of these proteins are unstructured, with flexible arms that attach to other proteins. Source: AlphaFold Protein Structure Database (left, right)





Synthesizing prior work?

Stem Cell Reports
Resource
OPEN ACCESS

Directed Evolution of Reprogramming Factors by Cell Selection and Sequencing

Veeramohan Veerapandian,[1,2,3] Jan Ole Ackermann,[1,2] Yogesh Srivastava,[1,2,3] Vikas Malik,[1,2,3] Mingxi Weng,[1,2,4] Xiaoxiao Yang,[1,2] and Ralf Jauch[1,2,4,*]

Stem Cell Reports
Resource
OPEN ACCESS

KLF4 N-Terminal Variance Modulates Induced Reprogramming to Pluripotency

Shin-Il Kim,[1,2] Fabian Oceguera-Yanez,[1] Ryoko Hirohata,[1] Sara Linker,[1,3,6] Keisuke Okita,[1] Yasuhiro Yamada,[1,2] Takuya Yamamoto,[1,2] Shinya Yamanaka,[1,2,4] and Knut Woltjen[1,2,5,*]

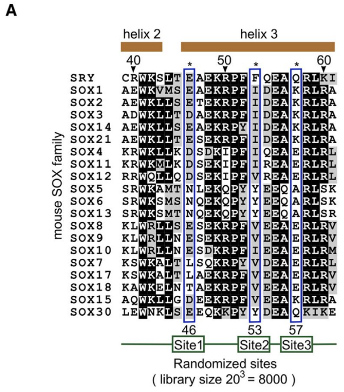
Stem Cell Reports
Report
OPEN ACCESS

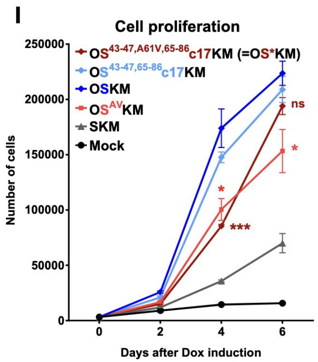
An acidic residue within the OCT4 dimerization interface of SOX17 is necessary and sufficient to overcome its pluripotency-inducing activity

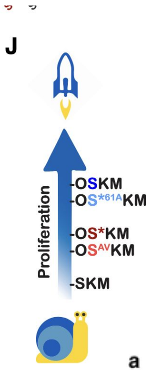
Sik Yin Ho,[1,2,7] Haoqing Hu,[1,3,7] Derek Hoi Hang Ho,[1,3] Allan Patrick Stephane Renom,[1] Shi Wing Yeung,[1,3] Freya Boerner,[1,3,4] Mingxi Weng,[1,5] Andrew Paul Hutchins,[6] and Ralf Jauch[1,3,8,*]

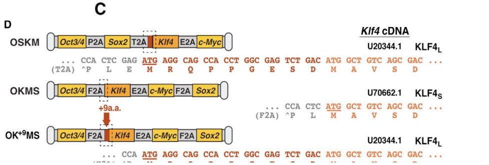
The evolutionally-conserved function of group B1 Sox family members confers the unique role of Sox2 in mouse ES cells

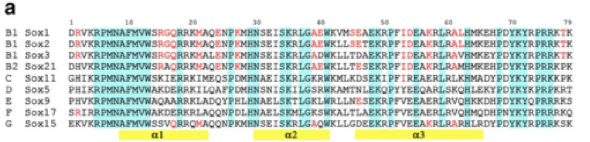
Hitoshi Niwa[1,2*], Akira Nakamura[3], Makoto Urata[4], Maki Shirae-Kurabayashi[5], Shigehiro Kuraku[6], Steven Russell[7] and Satoshi Ohtsuka[1,8]

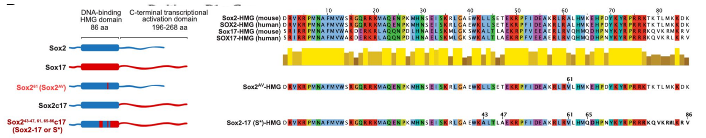


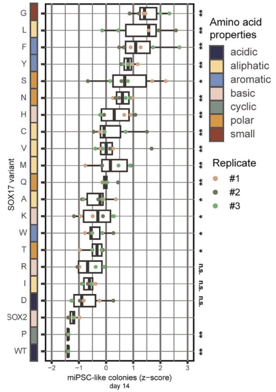


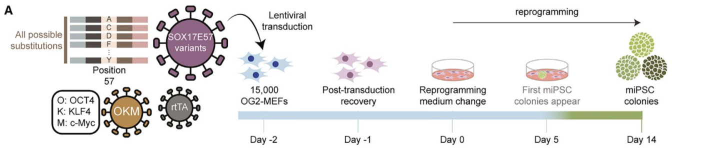








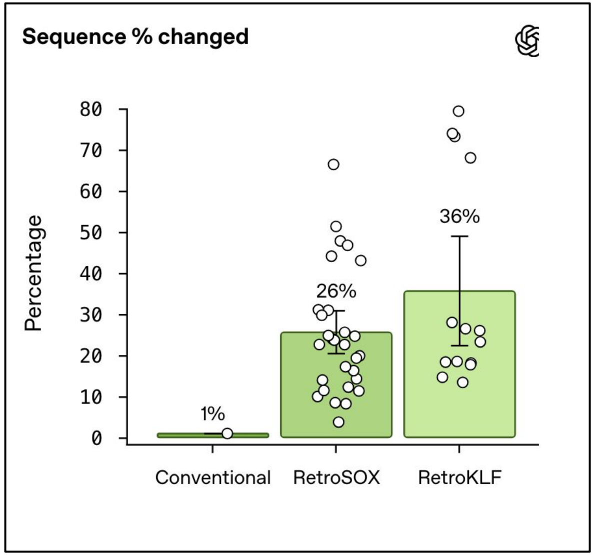


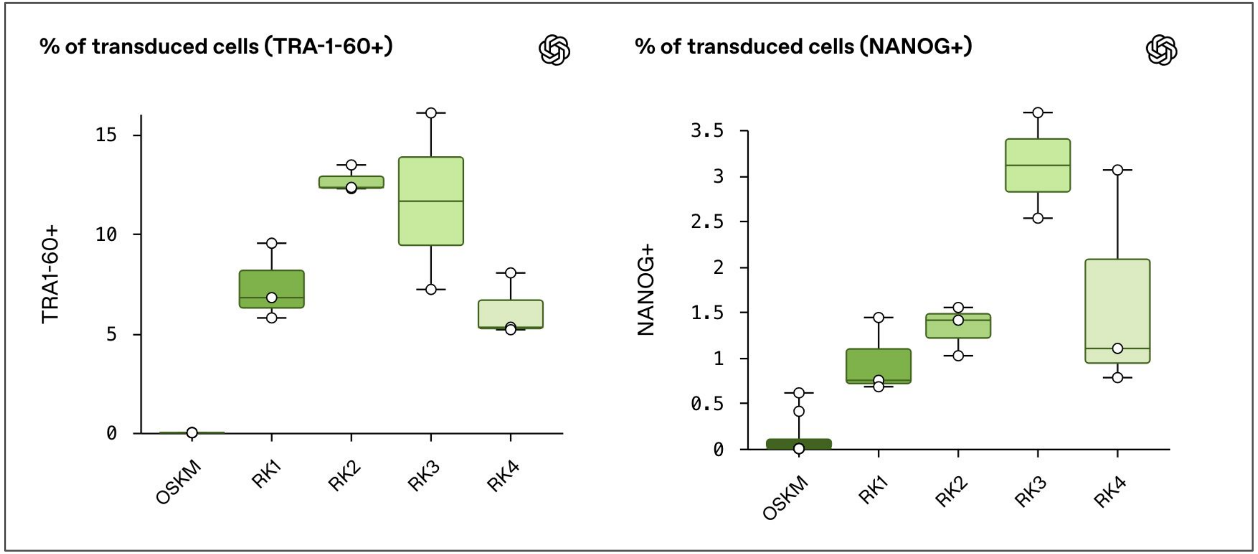


Synthesizing prior work? (they say no)

rico meinl @ricomnl · 14h

@iskander the sequences are not derived from/have no overlap with existing studies



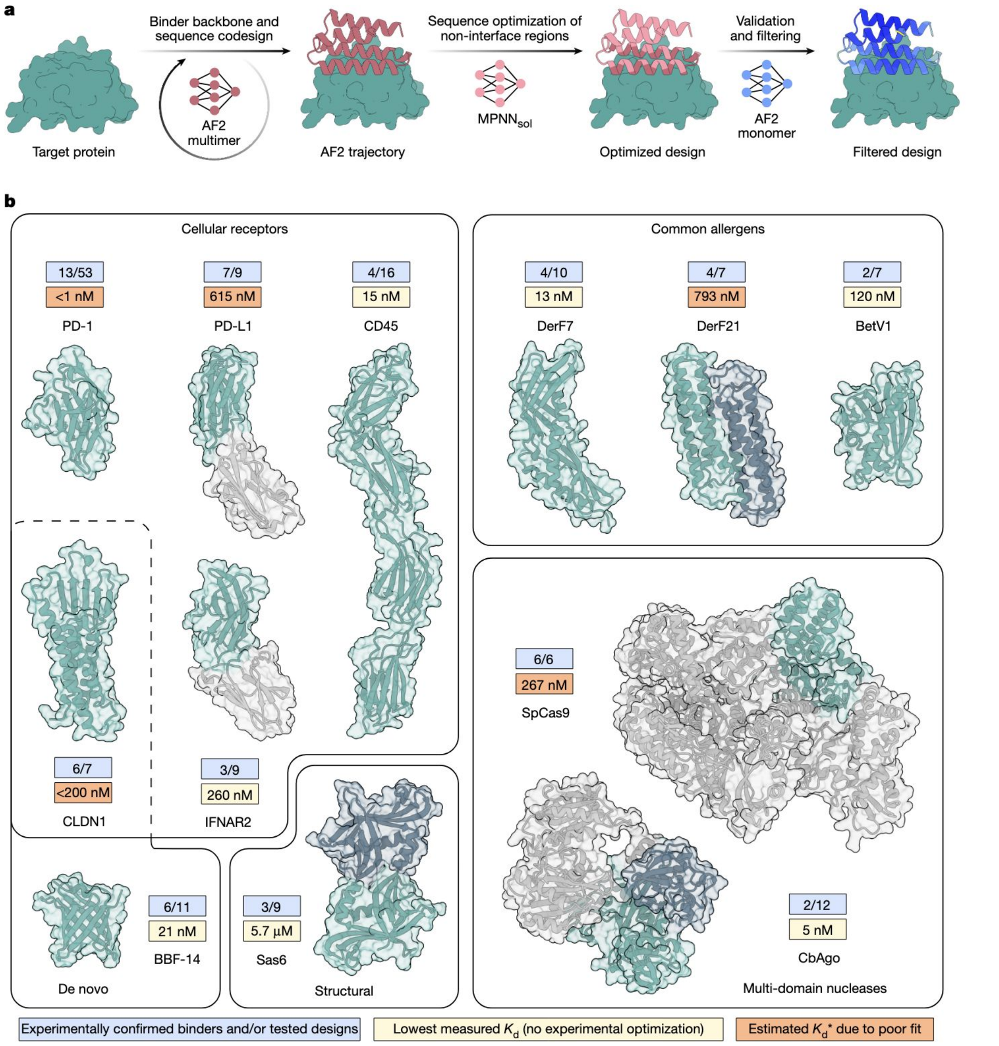


An example you can actually use: BindCraft

One-shot design of functional protein binders with BindCraft

https://doi.org/10.1038/s41586-025-09429-6
Received: 7 December 2024
Accepted: 17 July 2025
Published online: 27 August 2025
Open access
Check for updates

Martin Pacesa[1,10]✉, Lennart Nickel[1,2,10], Christian Schellhaas[1,2,10], Joseph Schmidt[1], Ekaterina Pyatova[1], Lucas Kissling[3], Patrick Barendse[4], Jagrity Choudhury[5], Srajan Kapoor[5], Ana Alcaraz-Serna[6], Yehlin Cho[7], Kourosh H. Ghamary[8], Laura Vinué[8], Brahm J. Yachnin[8], Andrew M. Wollacott[8], Stephen Buckley[1], Adrie H. Westphal[4], Simon Lindhoud[4], Sandrine Georgeon[1], Casper A. Goverde[1], Georgios N. Hatzopoulos[9], Pierre Gönczy[9], Yannick D. Muller[6], Gerald Schwank[3], Daan C. Swarts[4], Alex J. Vecchio[5], Bernard L. Schneider[2], Sergey Ovchinnikov[7]✉ & Bruno E. Correia[1]✉



BindCraft: less hype, more details

BindCraft design protocol

The input and design settings for running the BindCraft pipeline are organized into user-friendly JSON files. To initiate design trajectories, a target PDB format structure needs to be specified, along with the desired minimum and maximum length of the binders, and the desired number of final filtered designs. A target hotspot can be specified as either individual residues or entire chains, or can be omitted completely in which case a binding site is selected according to the combined design loss.

The binder hallucination process is performed using the ColabDesign implementation of AF2. The design process is initialized with a random sequence for the binder, which is predicted in single sequence mode, and a structural input template for the target. This is passed through the AF2 network to obtain a structure prediction and calculate the design loss. The design loss function is composed of several terms, with default weight values indicated in parentheses:

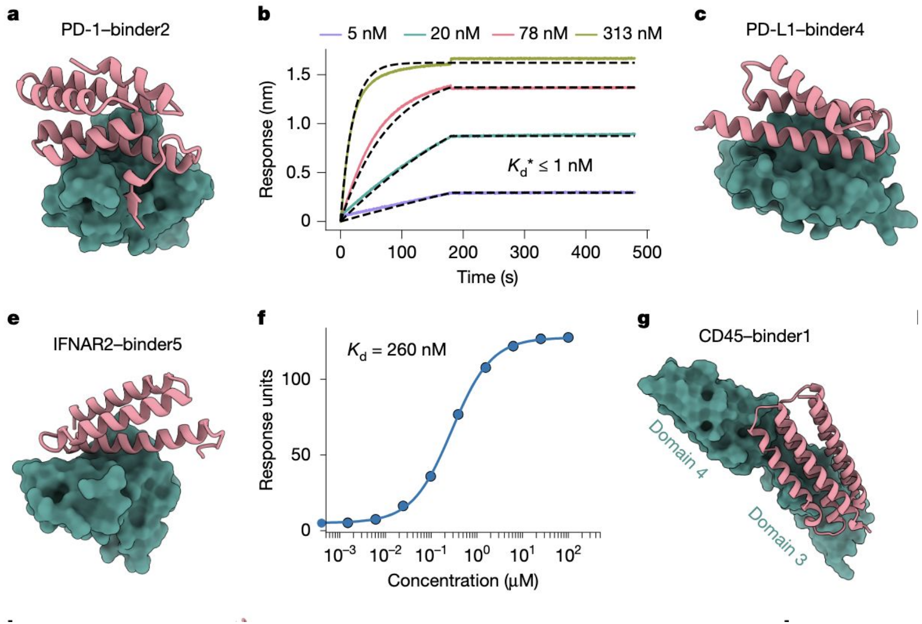
(1) binder confidence pLDDT (weight 0.1)
(2) interface confidence i_pTM (weight 0.05)
(3) normalized predicted alignment error (pAE) within the binder (weight 0.4)
(4) normalized predicted alignment error (pAE) between binder and target (weight 0.1)
(5) residue contact loss within binder (weight 1.0)
(6) residue contact loss between the target and binder: if hotspots are specified, the rest of the target is masked from this loss (weight 1.0)
(7) radius of gyration of binder (weight 0.3)
(8) 'helicity loss': penalize or promote backbone contacts every one in a three-residue offset to promote the hallucination of helical or non-helical designs (weight −0.3)
(9) optional 'N&C termini loss' increases the proximity of the N and C termini of the binder to allow splicing into protein loops (weight 0.1).

Successful binder design trajectories are subjected to $MPNN_{sol}$ sequence optimization to improve stability and solubility[12]. To this end, we preserve binder residues in a 4 Å radius around the target interface, and design 20 new sequences for the remaining binder core and surface residues using the soluble weights of ProteinMPNN[6], with a temperature of 0.1 and 0.0 backbone noise. These optimized sequences are then repredicted using the AF2 monomer model, with three recycles and two template-based models[49] in single sequence mode, to ensure robust and unbiased complex assessment. Each of the two resulting models is then energy minimized using Rosetta's FastRelax protocol[52] with 200 iterations, and interface scores are computed using the InterfaceAnalyzer mover[53] with side-chain and backbone movement enabled.

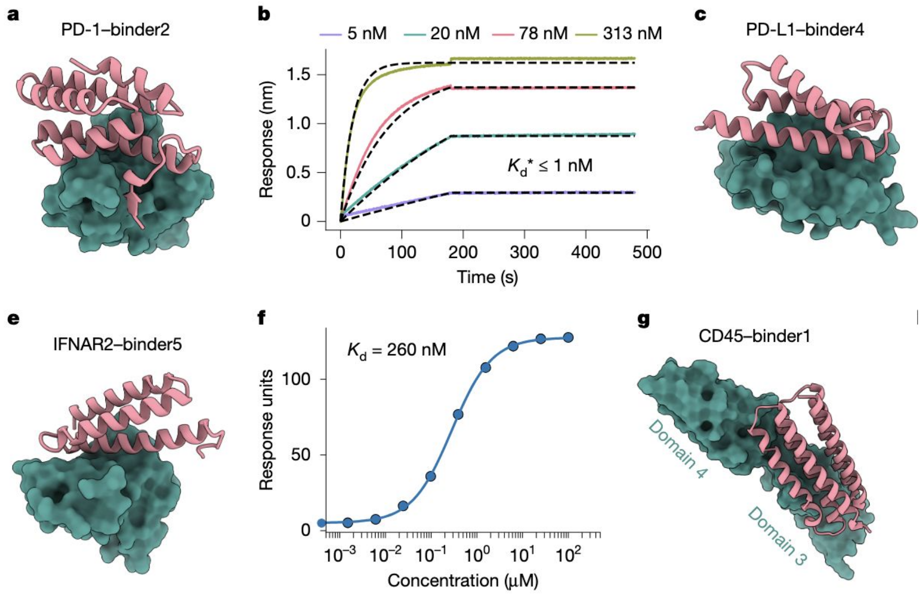
Designs are finally filtered using a set of predefined filters to ensure the selection of high quality designs for experimental testing. Filters were initially defined based on experimental observations from previous binder design studies[2–5] and refined over the course of this work. These include:

(1) AF2 confidence pLDDT score of the predicted complex (>0.8)
(2) AF2 interface predicted confidence score (i_pTM) (>0.5)
(3) AF2 interface predicted alignment error (i_pAE) (<0.35)
(4) Rosetta interface shape complementarity (>0.60)
(5) number of hydrogen bonds at the interface (>3)
(6) number of unsaturated hydrogen bonds at the interface (<4)
(7) hydrophobicity of binder surface (<35%)
(8) r.m.s.d. of binder predicted in bound and unbound form (<3.5 Å)
(9) fewer than three lysines and methionines at the binder interface.

BindCraft: new collective capability unlocked



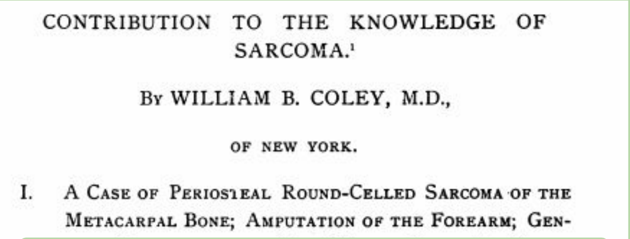
BindCraft: new collective capability unlocked



…how much could it have accelerated previous cancer therapy breakthroughs?

Cancer immunotherapy

Short history of cancer immunotherapy



CONTRIBUTION TO THE KNOWLEDGE OF SARCOMA.[1]

By WILLIAM B. COLEY, M.D.,

OF NEW YORK.

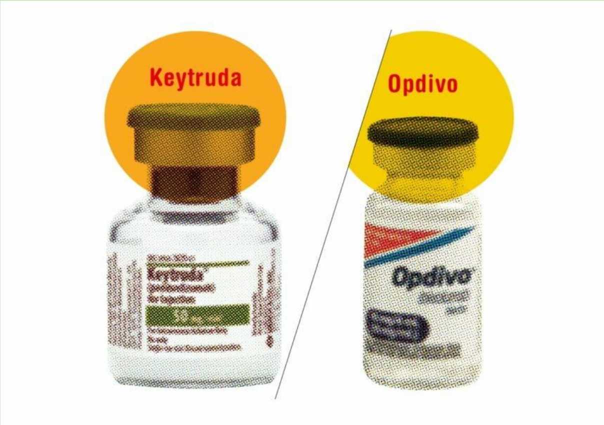
I. A Case of Periosteal Round-Celled Sarcoma of the Metacarpal Bone; Amputation of the Forearm; Gen-

1850s - 1890s
Infection & fever =>
tumor regression?

1893
Coley's Toxins
(complete response in
~10% of sarcomas)

20th century

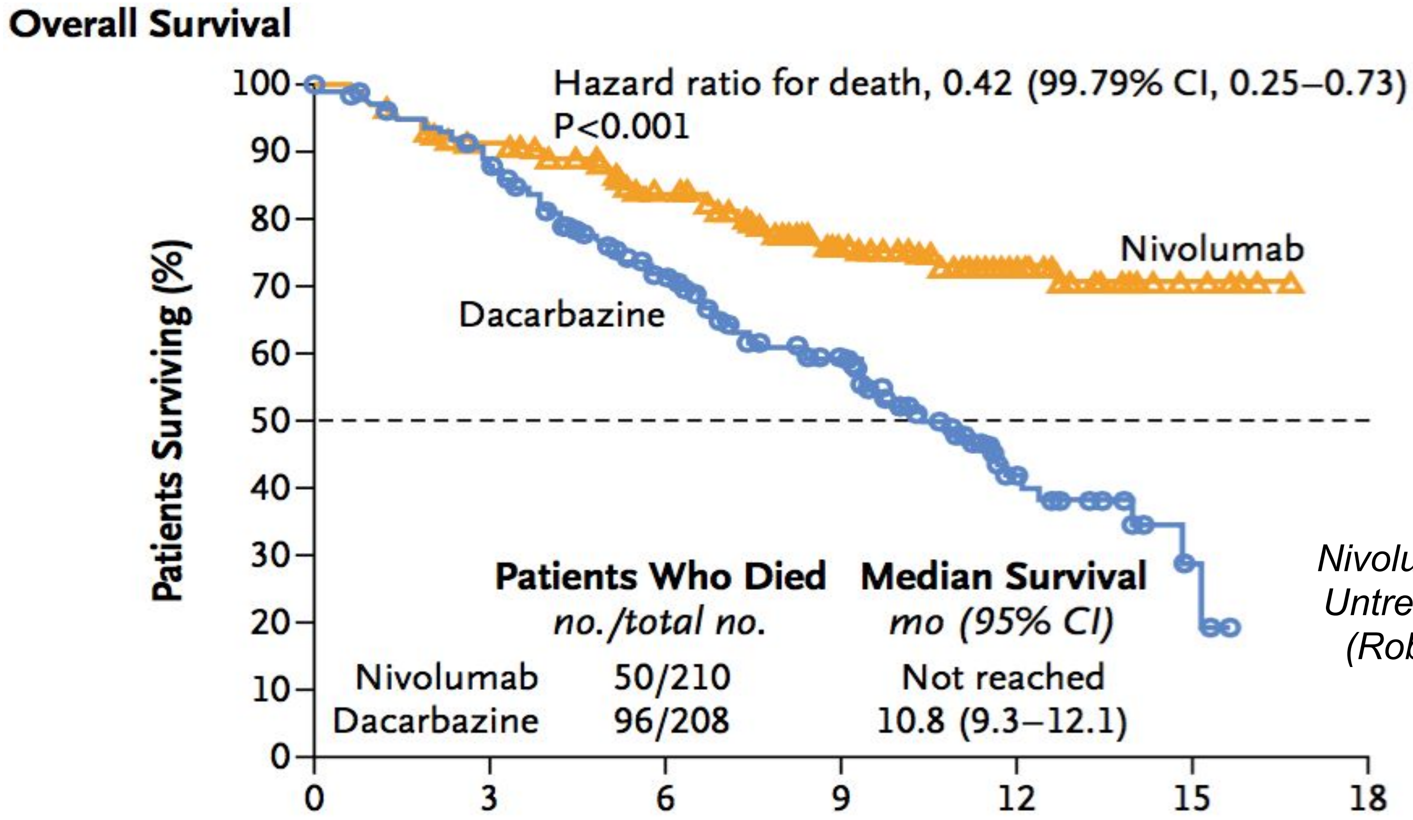
Dark Age of
radiation and
chemotherapy



2010s - now

150+ immunotherapy
approvals

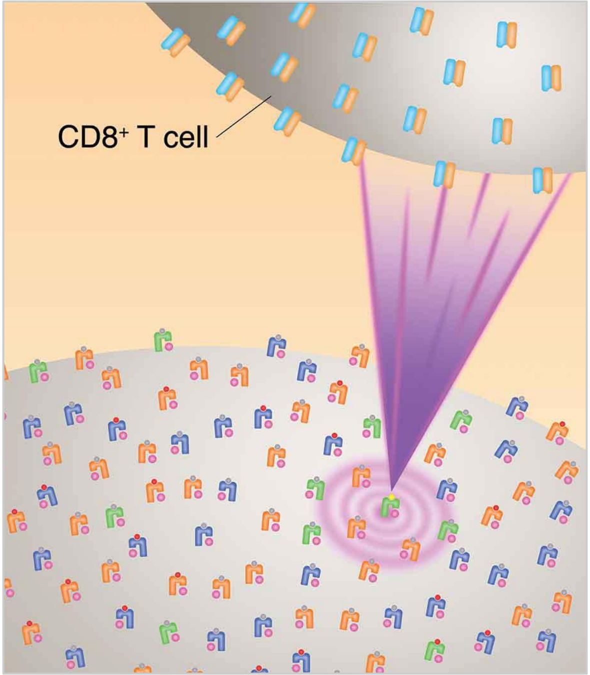
Immunotherapy vs. chemotherapy



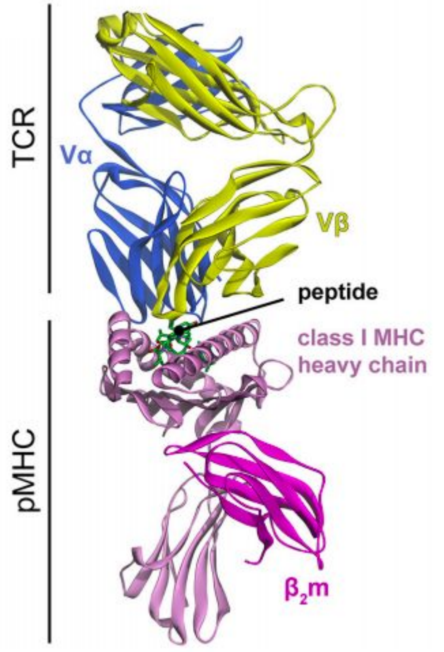
Nivolumab in Previously Untreated Melanoma… (Robert NEJM 2015)

How do cytotoxic T-cells recognize their targets?

- Cells present peptide fragments of their protein contents bound to MHC-I
- CD8+ T-cells selected in thymus to recognize non-self
- CD8+ T-cells “licensed” to kill by APCs, integrating innate danger signals



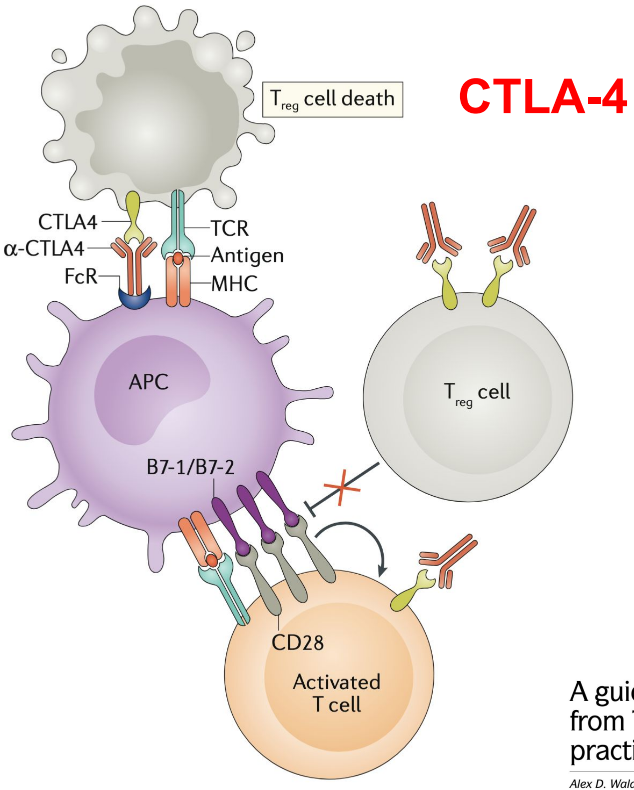
Lost in the crowd: identifying targetable MHC class I neoepitopes for cancer immunotherapy



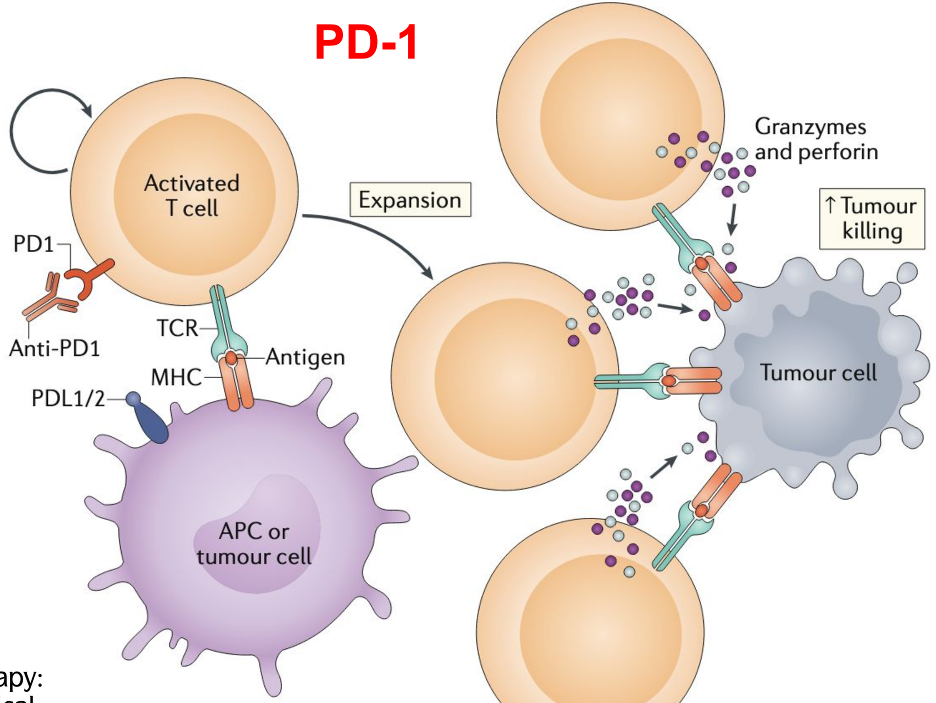
Using Global Analysis to Extend the Accuracy and Precision of Binding Measurements with T cell Receptors and Their Peptide/MHC Ligands

Meet the checkpoints

CTLA-4



PD-1



A guide to cancer immunotherapy: from T cell basic science to clinical practice

Alex D. Waldman[1,2], Jill M. Fritz[1,2] and Michael J. Lenardo[1,2]

It took ~30 years to “develop” checkpoint blockade

A new member of the immunoglobulin superfamily—CTLA-4

Jean-François Brunet, François Denizot, Marie-Françoise Luciani, Magali Roux-Dosseto*‡, Marie Suzan, Marie-Geneviève Mattei† & Pierre Golstein

Centre d’Immunologie INSERM-CNRS de Marseille-Luminy, Case 906, 13288 Marseille Cedex 9, France
* INSERM U.119, 27, Boulevard Leï Roure, 13009 Marseille, France
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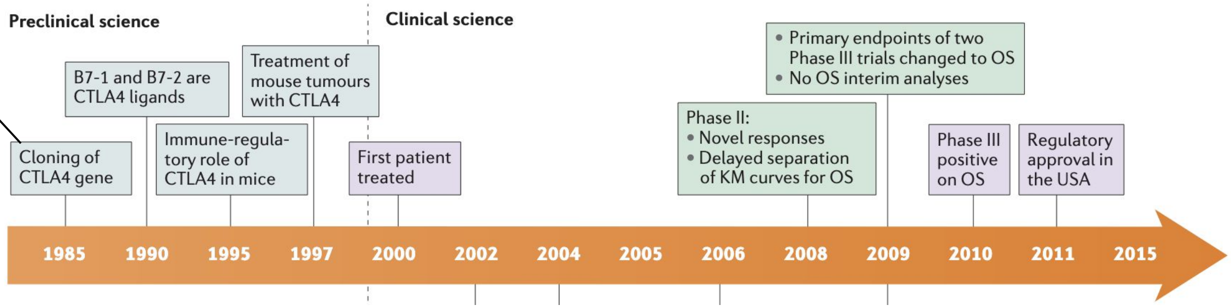
‡ Present address: UA CNRS 1175, Faculté de Médicine Secteur Nord, 13326 Marseille Cedex 15, France



1992
PD1
discovered

2014
aPD1 approval

Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death.

Y Ishida [1], Y Agata [1], K Shibahara [1], T Honjo [1]

First Approval of PD-1 Inhibitor: Pembrolizumab in Unresectable or Metastatic Melanoma

By Matthew Stenger
October 15, 2014

…then 10+ years to figure out when to use it (>150 approvals so far)

FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer

On July 26, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

FDA also granted regular approval to pembro
for patients with locally recurrent unresectabl
PD-L1 (Combined Positive Score [CPS] ≥10)
FDA granted accelerated approval to pembro

FDA approves neoadjuvant and adjuvant pembrolizumab for resectable locally advanced head and neck squamous cell carcinoma

On June 12, 2025, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for adults with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, as a single agent as neoadjuvant treatment,
t in combination with radiotherapy (RT) with or without
as a single agent.

SCC in 6 years and the first overall perioperative approval

FDA approves pembrolizumab for HER2 positive gastric or gastroesophageal junction adenocarcinoma expressing PD-L1 (CPS ≥1)

On March 19, 2025, the Food and Drug Administration granted traditional approval to pembrolizumab (Keytruda, Merck) with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥1).

Pembrolizumab previously received accelerated approval for this indication on May 5, 2021, based on interim analysis of the trial described below.

…but only took ~3 months to discover aCTLA-4 antibody (ipi)

WHAT IS CLAIMED IS:

1. A human sequence antibody that specifically binds to human CTLA-4.

2. A therapeutically-effective human sequence antibody that specifically binds to human CTLA-4.

3. The therapeutically-effective human sequence antibody of claim 2, wherein the antibody binds CTLA-4 on the cell surface of normal human T cells.

(26) Publication Language:

(30) Priority Data:
60/150,452 24 August

(63) Related by continuation (CON
(CIP) to earlier application:
US
Filed on 24 /

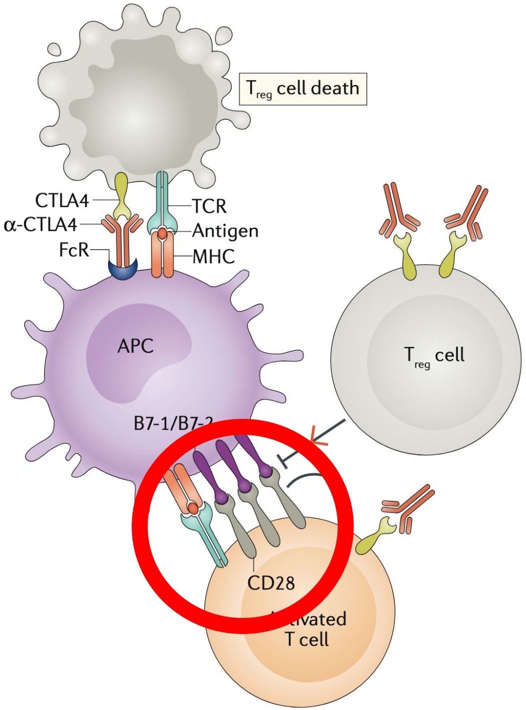
(71) Applicant *(for all designated States except US)*: **MEDAREX, INC.** [US/US]; 1545 Route 22 East, Annandale, NJ 08801 (US).

NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

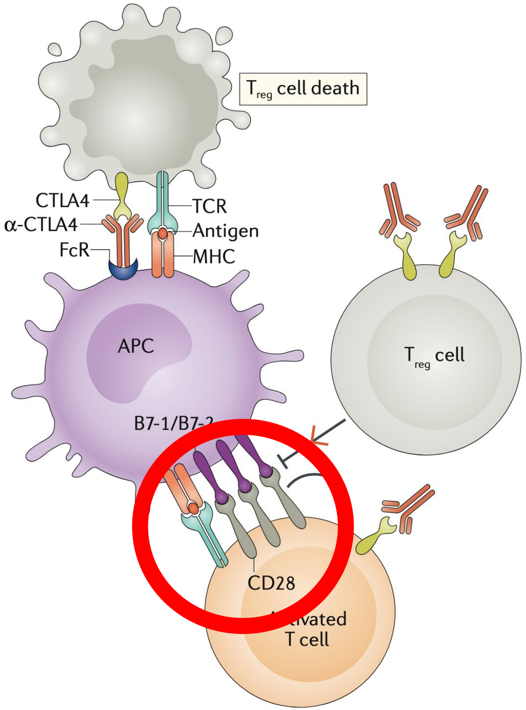
[Continued on next page]

(54) Title: HUMAN CTLA-4 ANTIBODIES AND THEIR USES

PD-1 and CTLA-4 work, which other targets would AI have chosen?



PD-1 and CTLA-4 work, which other targets would AI have chosen?



Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P., Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A., Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

SUMMARY

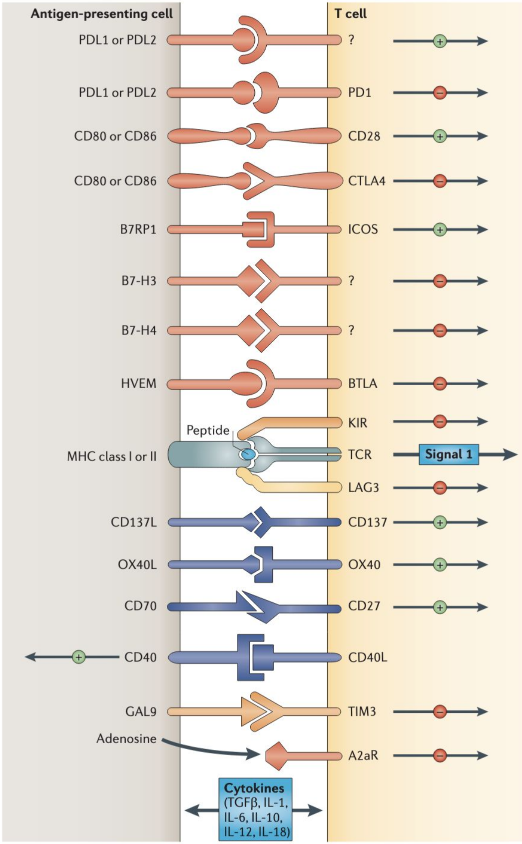
Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure, and disseminated intravascular coagulation. Severe and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti–interleukin-2 receptor antagonist antibody. Prolonged cardiovascular shock and acute respiratory distress syndrome developed in two patients, who required intensive organ support for 8 and 16 days. Despite evidence of the multiple cytokine-release syndrome, all six patients survived. Documentation of the clinical course occurring over the 30 days after infusion offers insight into the systemic inflammatory response syndrome in the absence of contaminating pathogens, endotoxin, or underlying disease.

Oops!

Fine, not CD28, what else?

The blockade of immune checkpoints in cancer immunotherapy

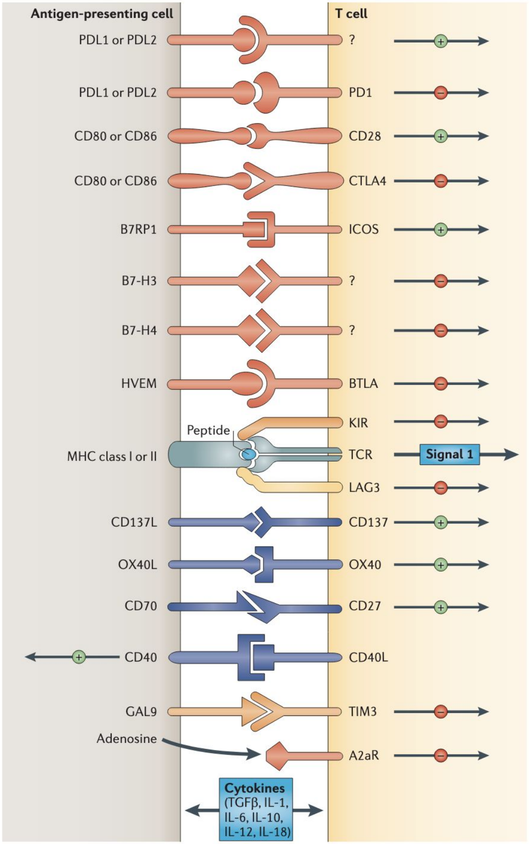
Drew M. Pardoll



Fine, not CD28, what else?

The blockade of immune checkpoints in cancer immunotherapy

Drew M. Pardoll



Hundreds of trials later, pretty much only CTLA-4, PD-1/PDL1 work

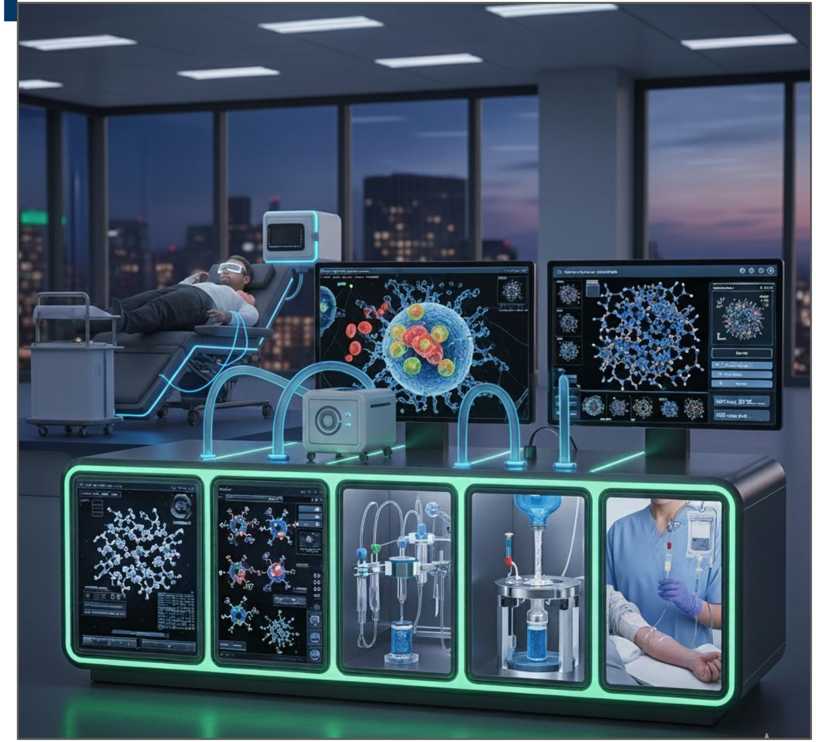
Summary (so far)

- Scientific discoveries take decades to unspool into validated therapies
- “Binders on demand” is cool but doesn’t fix the rate-limiting steps
- Unclear if AI systems would escape the trap of chasing targets similar to ones already known to work
  - e.g. both PD-1 & PDL-1 are safe but only CTLA-4 (not CD28) is safe
  - “non-canonical” checkpoint trials (e.g. OX40/OX40L) have almost all failed

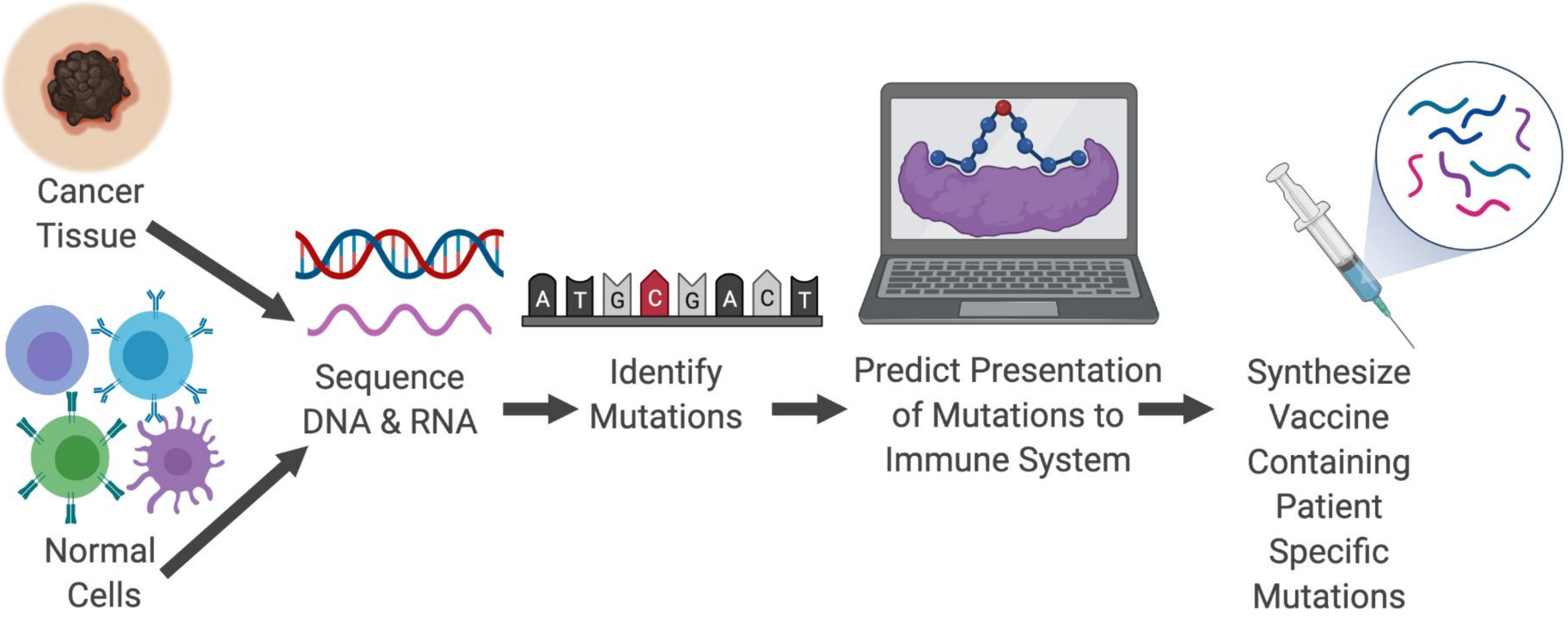
Personalized cancer immunotherapy

Sci-Fi vision to ⌘F-Delete the cancer

- Profile patient and their cancer
- Discover tumor-specific cellular targets
- Design novel therapy to “⌘F-Delete” cancer cells while sparing healthy cells
- Synthesize therapeutic on demand
- Administer to patient

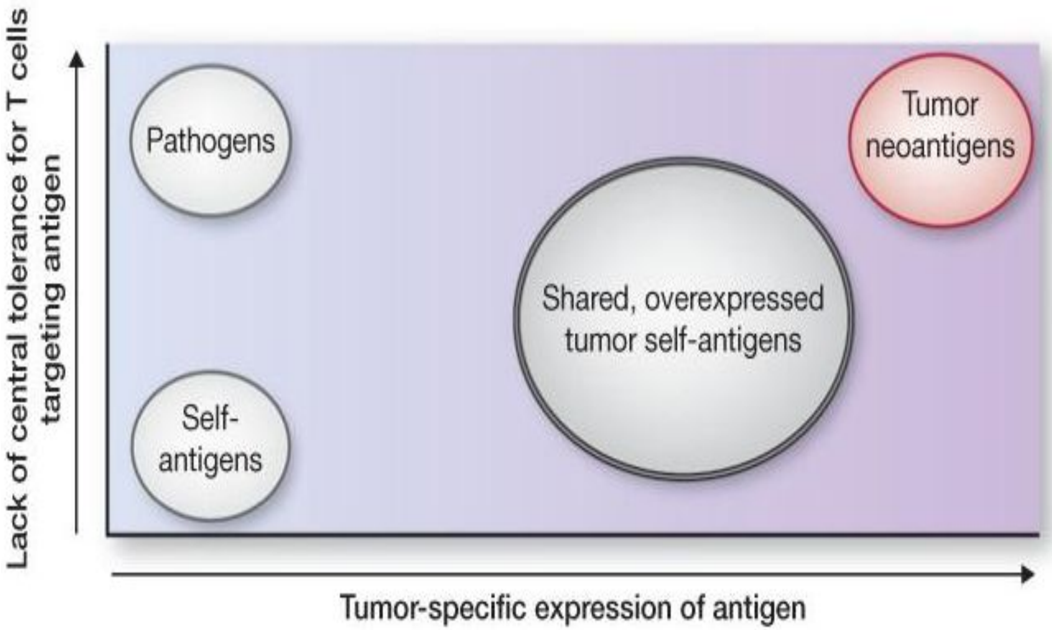


We already do this: therapeutic neoantigen-targeting vaccines



The Pitch for “neoantigens”

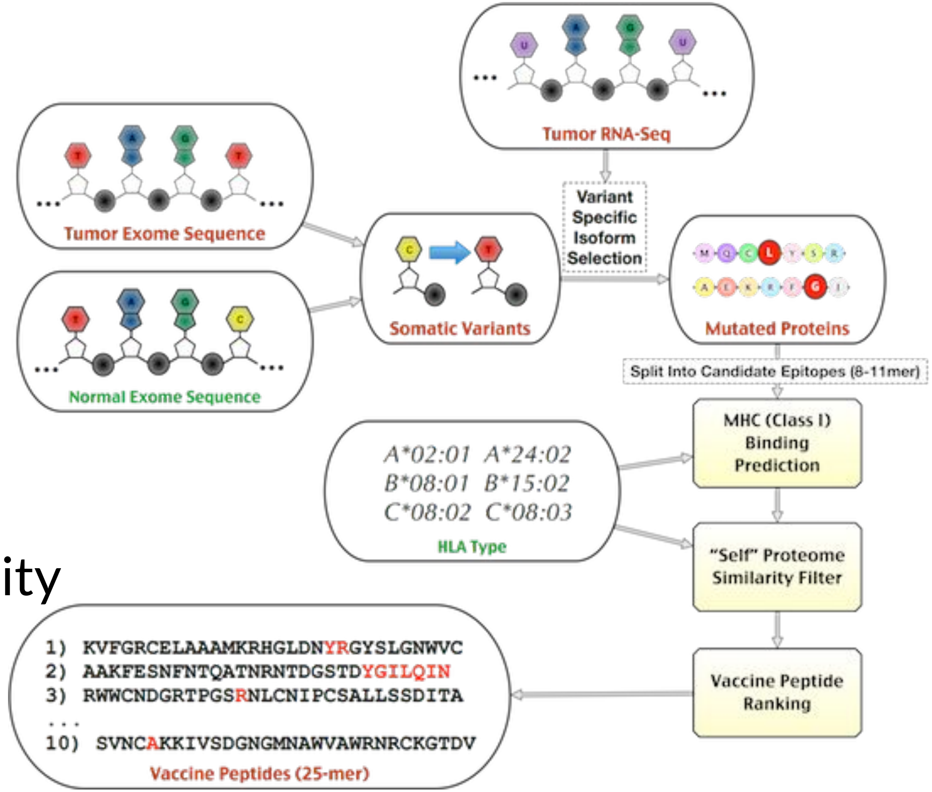
- No overlap with normal tissue!
    - Safe
    - Immunogenic
- …but unlikely to be shared between patients



Getting Personal with Neoantigen-Based Therapeutic Cancer Vaccines

Example neoantigen vaccine pipeline

- Tumor + normal exome seq
  - Somatic variant calling
- Tumor RNA
  - Phase co-expressed variants
  - Mutant protein sequence
  - Quantify mut. allele expression
- Rank by expression and MHC-I affinity
- Select manufacturable peptides
- www.github.com/openvax/



Do neoantigen vaccines actually work?

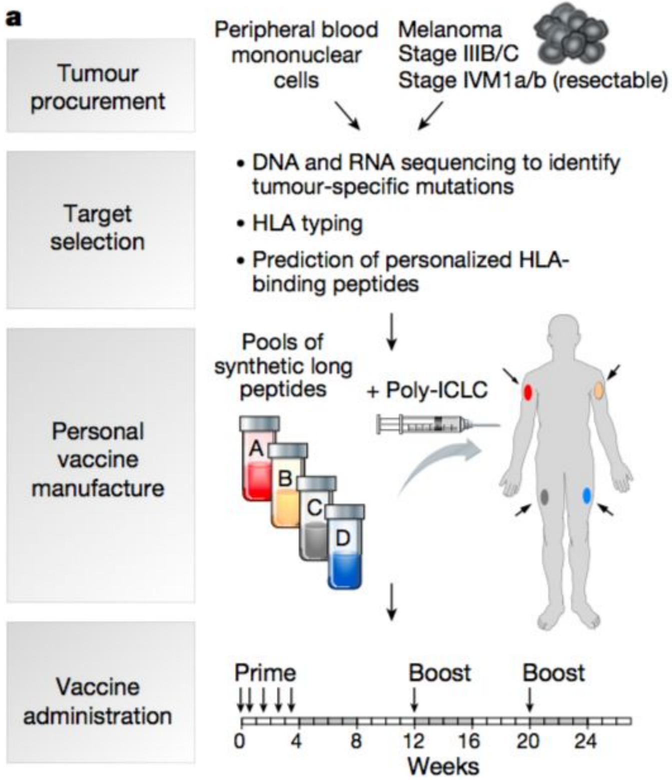
Peptides + poly-ICLC @ DFCI (2017)

An immunogenic personal neoantigen vaccine for patients with melanoma

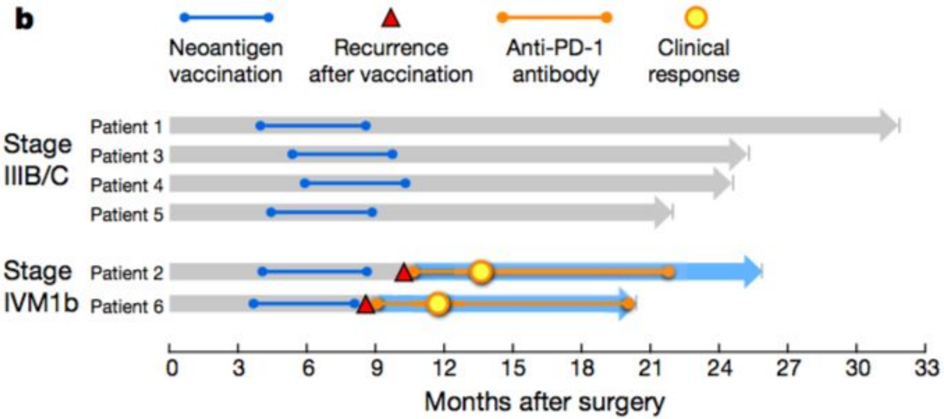
Patrick A. Ott[1,2,3]*, Zhuting Hu[1]*, Derin B. Keskin[1,3,4], Sachet A. Shukla[1,4], Jing Sun[1], David J. Bozym[1], Wandi Zhang[1], Adrienne Luoma[5], Anita Giobbie-Hurder[6], Lauren Peter[7,8], Christina Chen[1], Oriol Olive[1], Todd A. Carter[4], Shuqiang Li[4], David J. Lieb[4], Thomas Eisenhaure[4], Evisa Gjini[9], Jonathan Stevens[10], William J. Lane[10], Indu Javeri[11], Kaliappanadar Nellaiappan[11], Andres M. Salazar[12], Heather Daley[1], Michael Seaman[7], Elizabeth I. Buchbinder[1,2,3], Charles H. Yoon[3,13], Maegan Harden[4], Niall Lennon[4], Stacey Gabriel[4], Scott J. Rodig[9,10], Dan H. Barouch[3,7,8], Jon C. Aster[3,10], Gad Getz[3,4,14], Kai Wucherpfennig[3,5], Donna Neuberg[6], Jerome Ritz[1,2,3], Eric S. Lander[3,4], Edward F. Fritsch[1,4]†, Nir Hacohen[3,4,15] & Catherine J. Wu[1,2,3,4]

- 6 (stage III & IV) melanoma patients
- Up to 20 mutated peptides per vaccine
- Adjuvant: Poly-ICLC

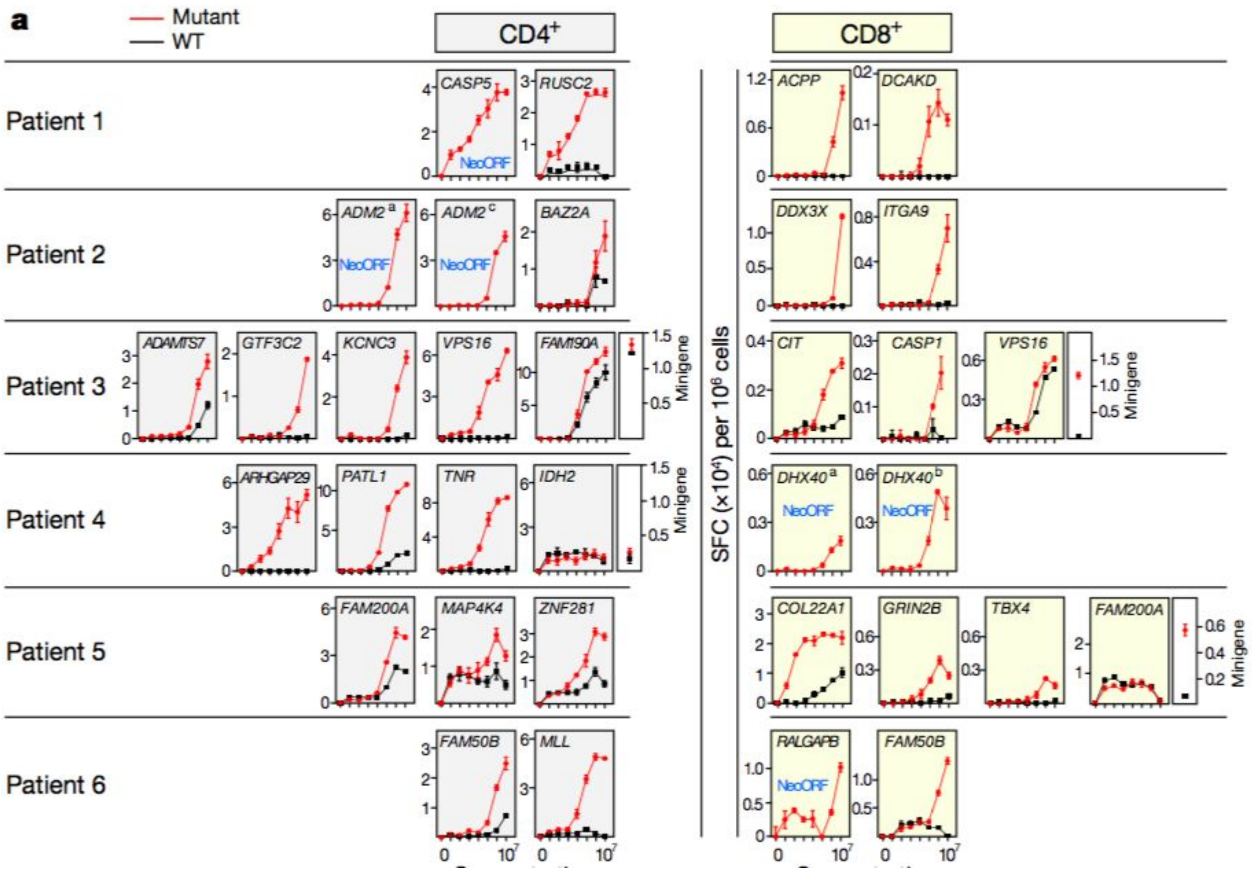
Does it work? (2017 DFCI melanoma trial)



Of six vaccinated patients, four had no recurrence at 25 months after vaccination, while two with recurrent disease were subsequently treated with anti-PD-1 (anti-programmed cell death-1) therapy and experienced complete tumour regression, with expansion of the repertoire of neoantigen-specific T cells.



…kinda? Some (mostly CD4+) T-cell responses

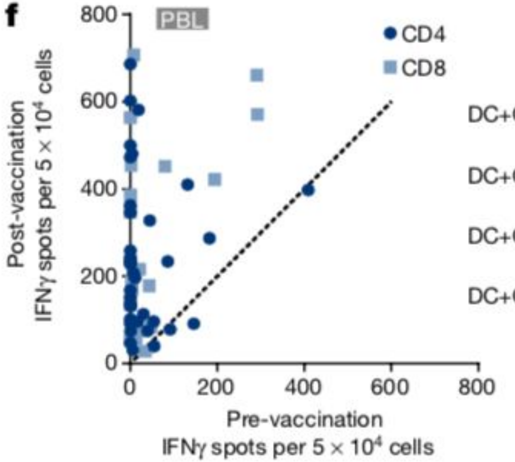


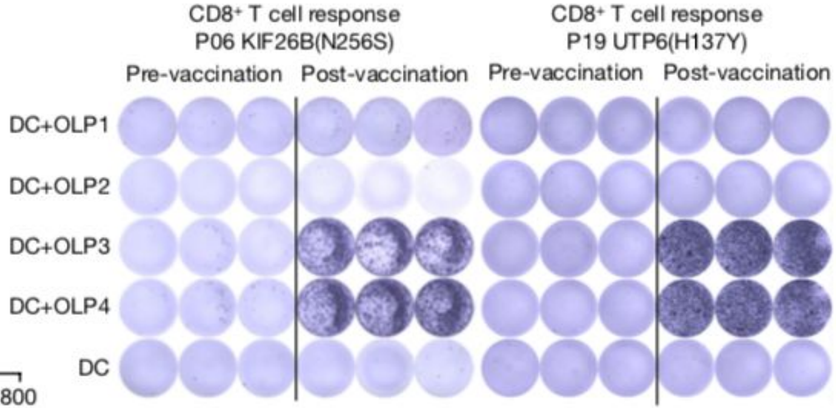
Does it work? mRNA vaccine edition

- ~20% mutations had ex vivo CD4+ responses
- ~25% mutations had CD8+ responses **after in vitro stimulation** (i.e. no ex vivo response)

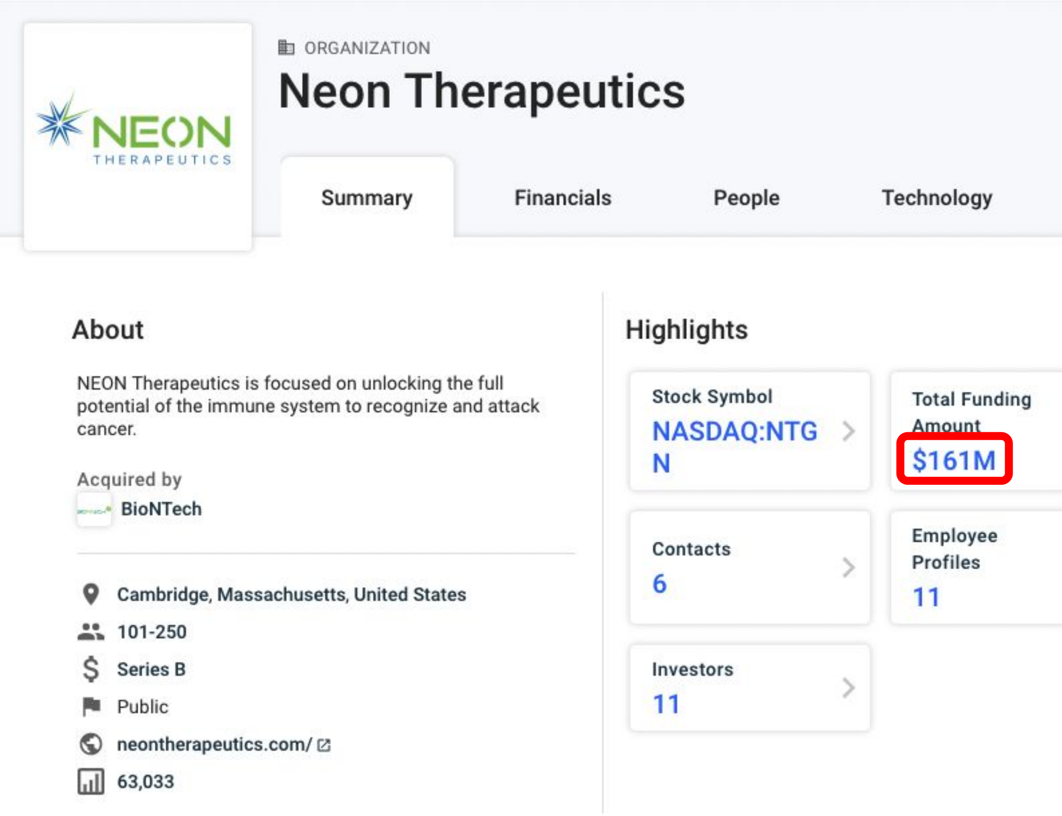
Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

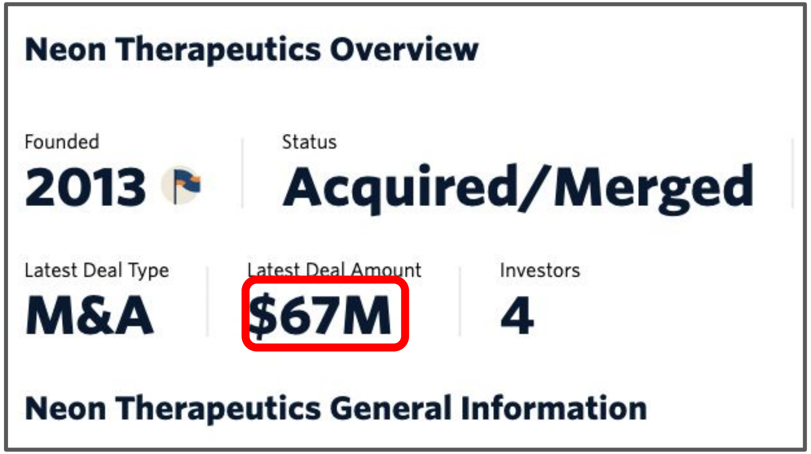
Ugur Sahin[1,2,3], Evelyna Derhovanessian[1], Matthias Miller[1], Björn-Philipp Kloke[1], Petra Simon[1], Martin Löwer[2], Valesca Bukur[1,2], Arbel D. Tadmor[2], Ulrich Luxemburger[1], Barbara Schrörs[2], Tana Omokoko[1], Mathias Vormehr[1,3], Christian Albrecht[2], Anna Paruzynski[1], Andreas N. Kuhn[1], Janina Buck[1], Sandra Heesch[1], Katharina H. Schreeb[1], Felicitas Müller[1], Inga Ortseifer[1], Isabel Vogler[1], Eva Godehardt[1], Sebastian Attig[2,3], Richard Rae[2], Andrea Breitkreuz[1], Claudia Tolliver[1], Martin Suchan[2], Goran Martic[2], Alexander Hohberger[3], Patrick Sorn[2], Jan Diekmann[1], Janko Ciesla[4], Olga Waksmann[4], Alexandra-Kemmer Brück[1], Meike Witt[1], Martina Zillgen[1], Andree Rothermel[2], Barbara Kasemann[2], David Langer[1], Stefanie Bolte[1], Mustafa Diken[1,2], Sebastian Kreiter[1,2], Romina Nemecek[5], Christoffer Gebhardt[6,7], Stephan Grabbe[3], Christoph Höller[5], Jochen Utikal[6,7], Christoph Huber[1,2,3], Carmen Loquai[3]* & Özlem Türeci[8]*





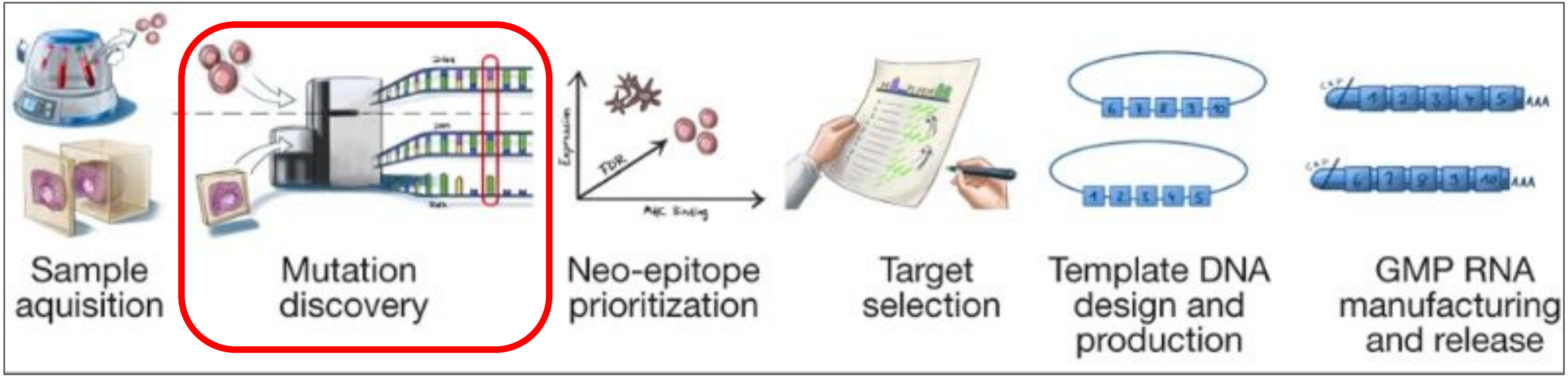
Does it work? Startup valuation edition





Problem #0: neoantigen field all look under the same street light

BioNTech (Sahin, …, Türeci 2017)

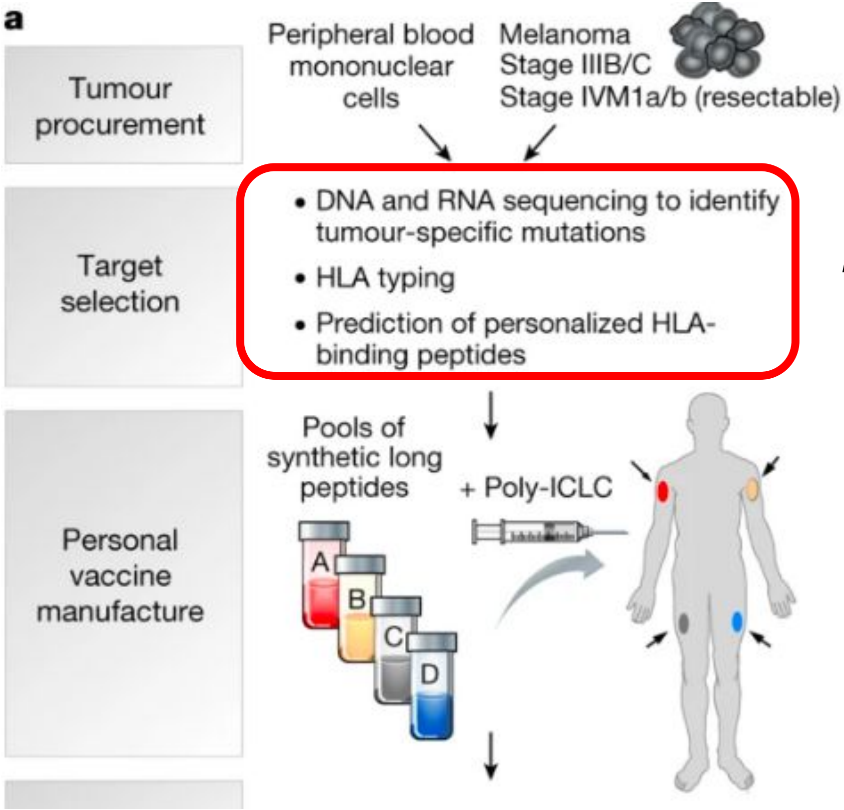


Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

- Tumor/normal WES
- SNVs only

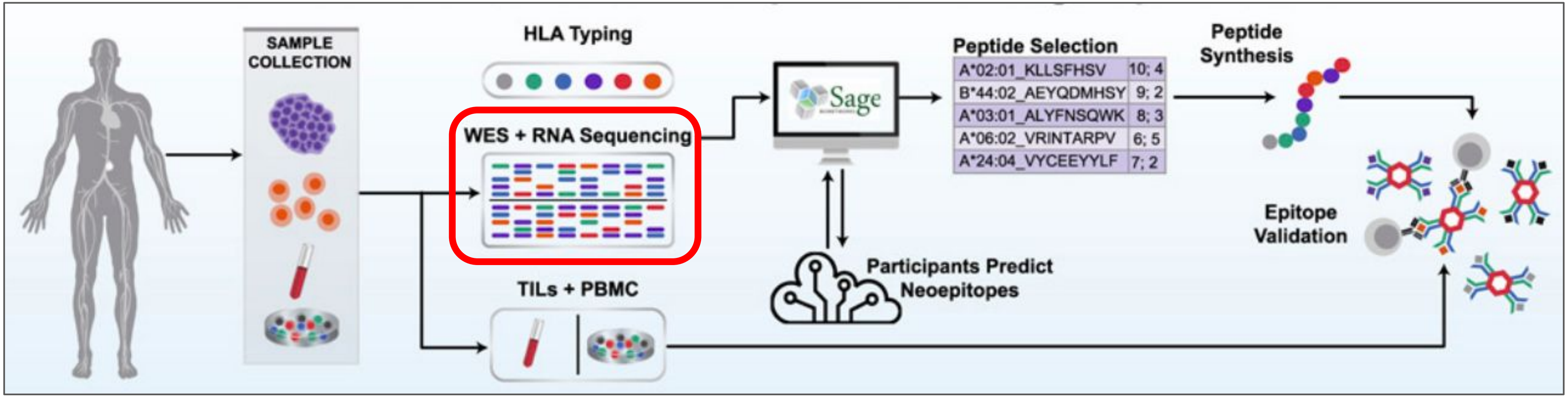
DFCI (Ott, …, Wu 2017)

- Tumor/normal WES
- SNVs and small indels
  - Mutect
  - Indelocator
  - Strelka



An immunogenic personal neoantigen vaccine for patients with melanoma

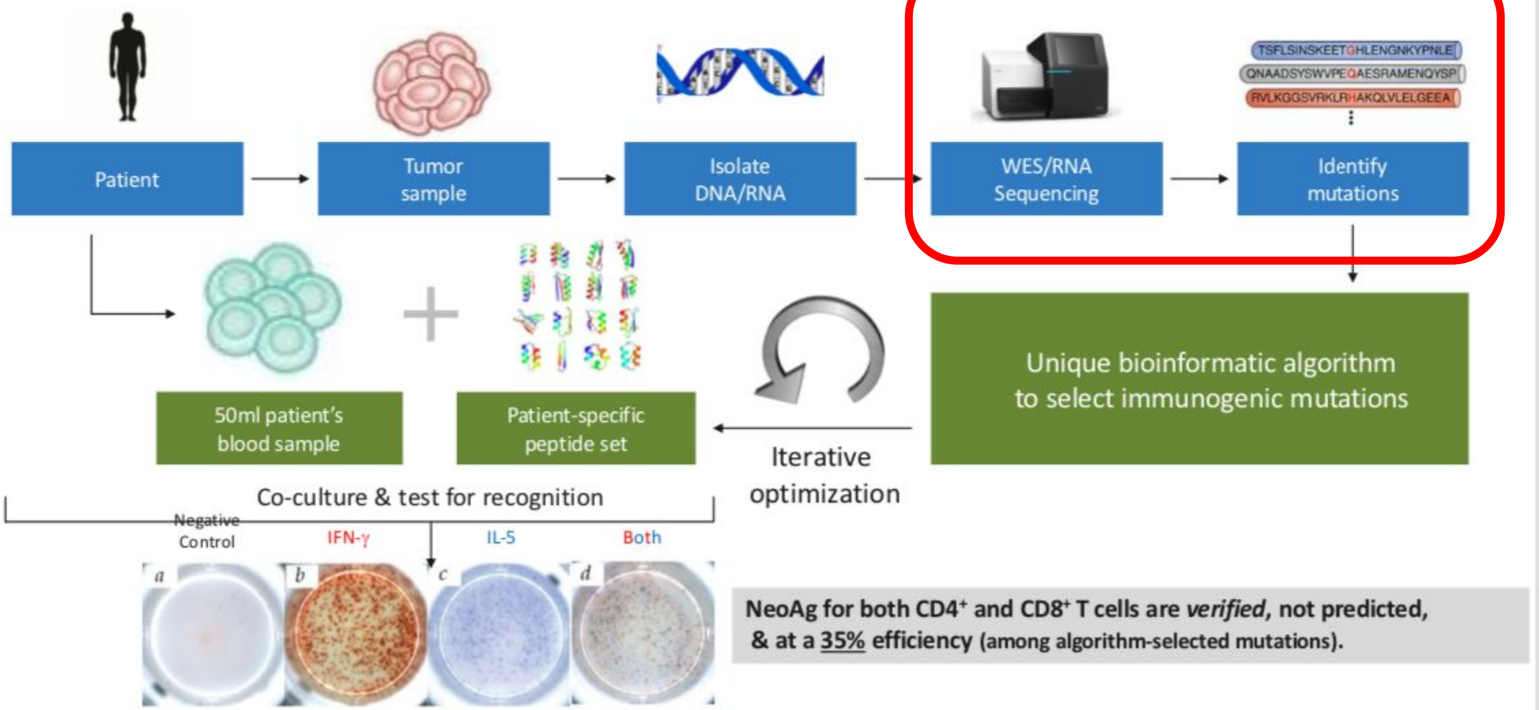
TESLA (Wells, …, Defranoux 2020)



Key Parameters of Tumor Epitope Immunogenicity Revealed Through a Consortium Approach Improve Neoantigen Prediction

- Tumor/normal WES
  - Variant calling: SNVs and small indels
- Tumor mRNA-seq
- *Task*: prioritize variants, some T-cell response validation

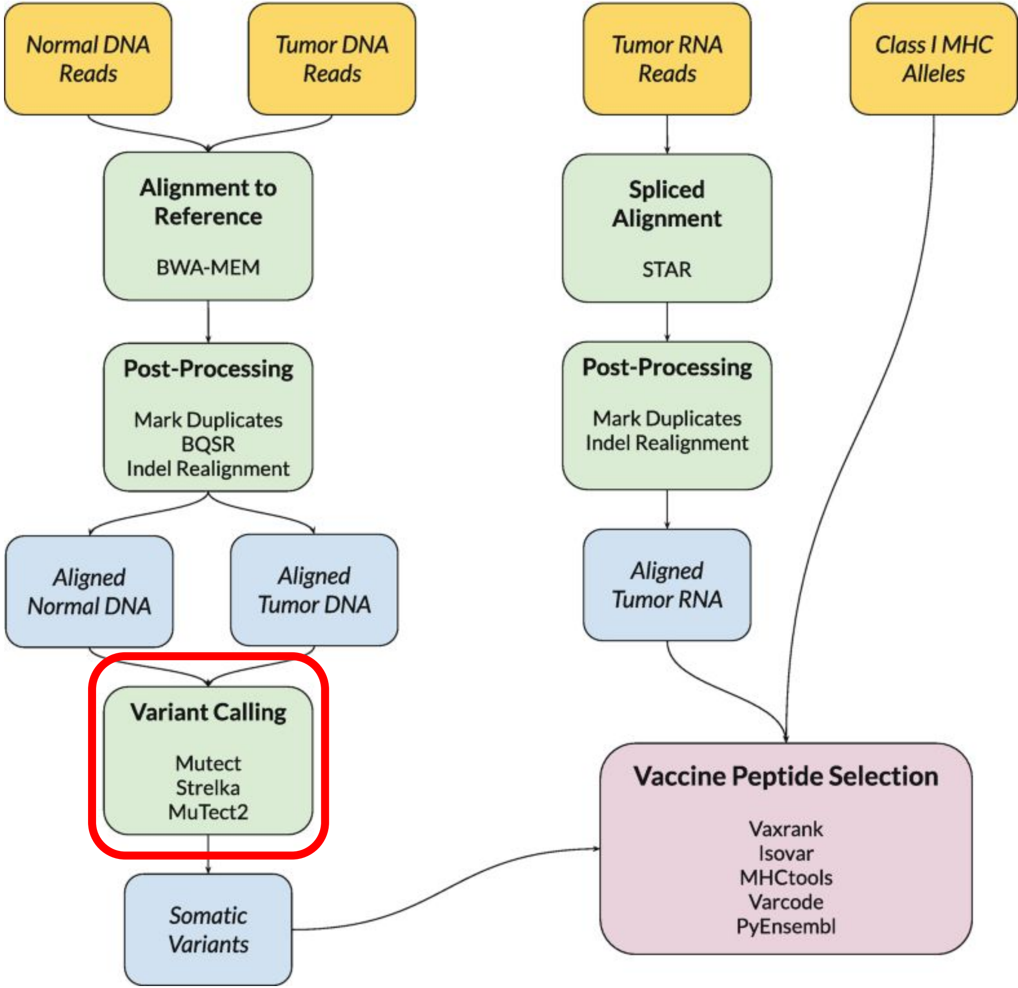
Cell therapy: LJI's Identify-Prioritize-Validate (IPV)



NeoAg for both CD4⁺ and CD8⁺ T cells are *verified*, not predicted, & at a 35% efficiency (among algorithm-selected mutations).

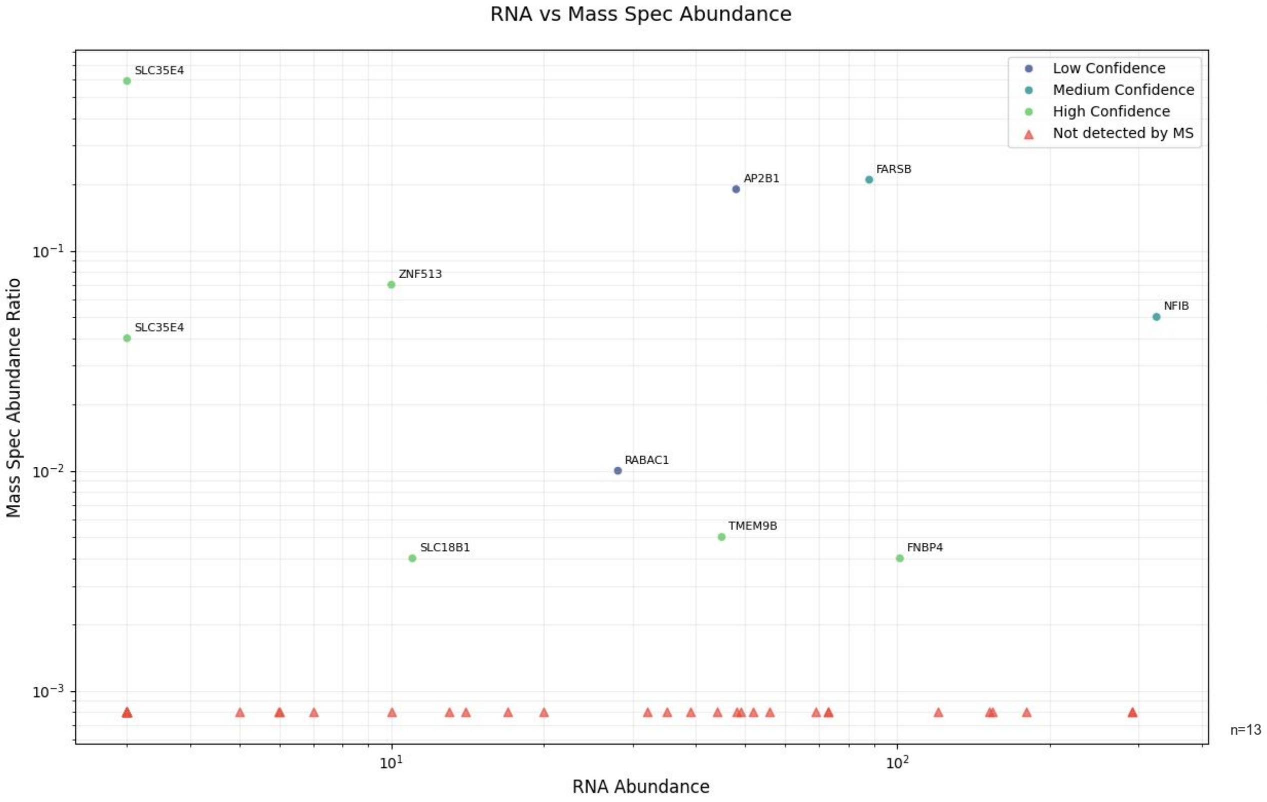
OpenVax (Mount Sinai)

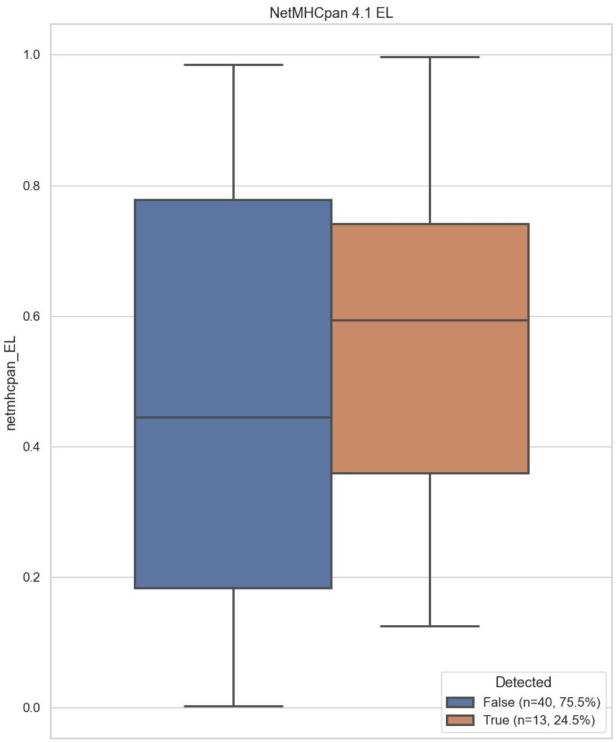
- **SNVs & small indels**
- Inputs:
  - Tumor & normal exome
  - RNA-seq
- Outputs:
  - Vaccine peptides w/ multiple predicted neoantigens
- Special features: variant phasing & *some* splice variants



Problem #1: predicted targets aren't really on the tumor

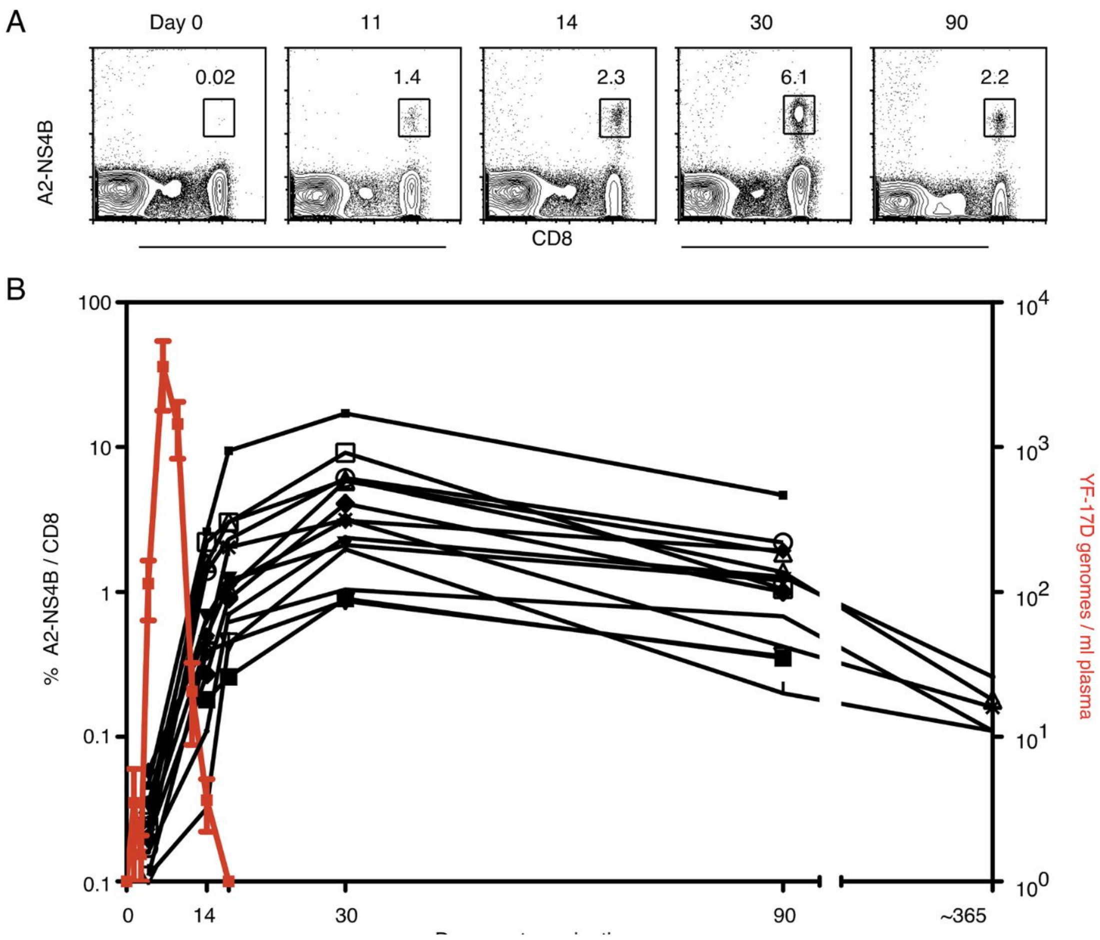
Targeted mass spec of patient tumor





Problem #2: most existing vaccine platforms are weak

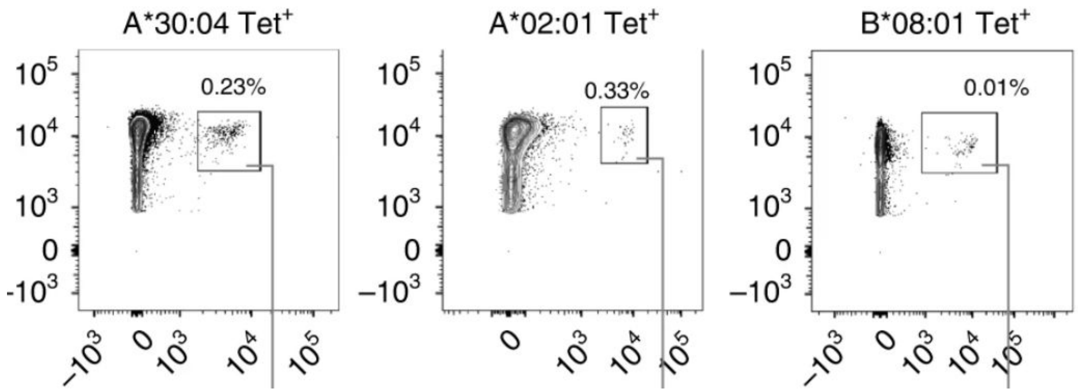
Example of success: CD8+ T-cell responses to live attenuated YFV vaccine



The Yellow Fever Virus Vaccine Induces a Broad and Polyfunctional Human Memory CD8+ T Cell Response

Strongest *ex vivo* CD8+ T-cell response to neoantigen vaccination I could find…

- Gritstone Bio's GRANITE trial (NCT03639714)
  - Microsatellite stable colorectal cancer
- *Prime*: ChAd68
- *Boost*: self-amplifying mRNA
- **…with both anti-PD-1 and anti-CTLA-4**



Individualized, heterologous chimpanzee adenovirus and self-amplifying mRNA neoantigen vaccine for advanced metastatic solid tumors: phase 1 trial interim results

The FDA loves poly-ICLC as a personalized vaccine adjuvant

Biological: NeoVax

At each vaccination time point, patients will receive up to 20 synthetic long peptides co-administered with 1.5 mg of **poly-ICLC** divided into a maximum of four injections (pools). Each pool (of vaccine + poly IC:LC) will be administered to one of the four limbs (right axilla, left axilla, right inguina, left inguina) by subcutaneous injection.

Other Name: Synthetic long peptides plus **poly-ICLC**

Drug: **Neoantigen** Vaccine with **Poly-ICLC** adjuvant

Neoantigen Vaccine with **Poly-ICLC** adjuvant will be administered on days 1, 8, 15 and 22. 2 to 5 subcutaneous injections will be administered in the upper thighs, arms and/or back.

Drug: 0.3 mg per peptide vaccine + 0.5mg **Poly-ICLC**

Other Name: **Hiltonol®** (**Poly-ICLC**)

Drug: Retifanlimab

500 mg will be administered as a 30 minute IV. Infusion (-5 min/+15min) on Day 1 of each 28 day cycle every 4 weeks.

Other Name: INCMGA00012; MGA012

Drug: 6MHP

6 melanoma helper vaccine comprised of 6 class II MHC-restricted helper peptides

Other Name: 6 melanoma helper peptide vaccine

Drug: NeoAg-mBRAF

BRAF 586-614 (V600E) peptide to which a histidine has been added to the N-terminus, resulting in BRAF 585-614 (V600E).

Other Name: BRAF 585-614 (V600E)

Drug: **PolyICLC**

polyICLC, local adjuvant

Drug: CDX-1140

CDX-1140, local adjuvant

Biological: **Neoantigen** Peptide Vaccine

- Each pool of vaccine study drug + poly IC:LC will be administered to one of the four limbs (A - Right Arm, B - Left Arm, C - Right Leg, D - Left Leg) by subcutaneous (SC) injection.

Drug: **Poly ICLC**

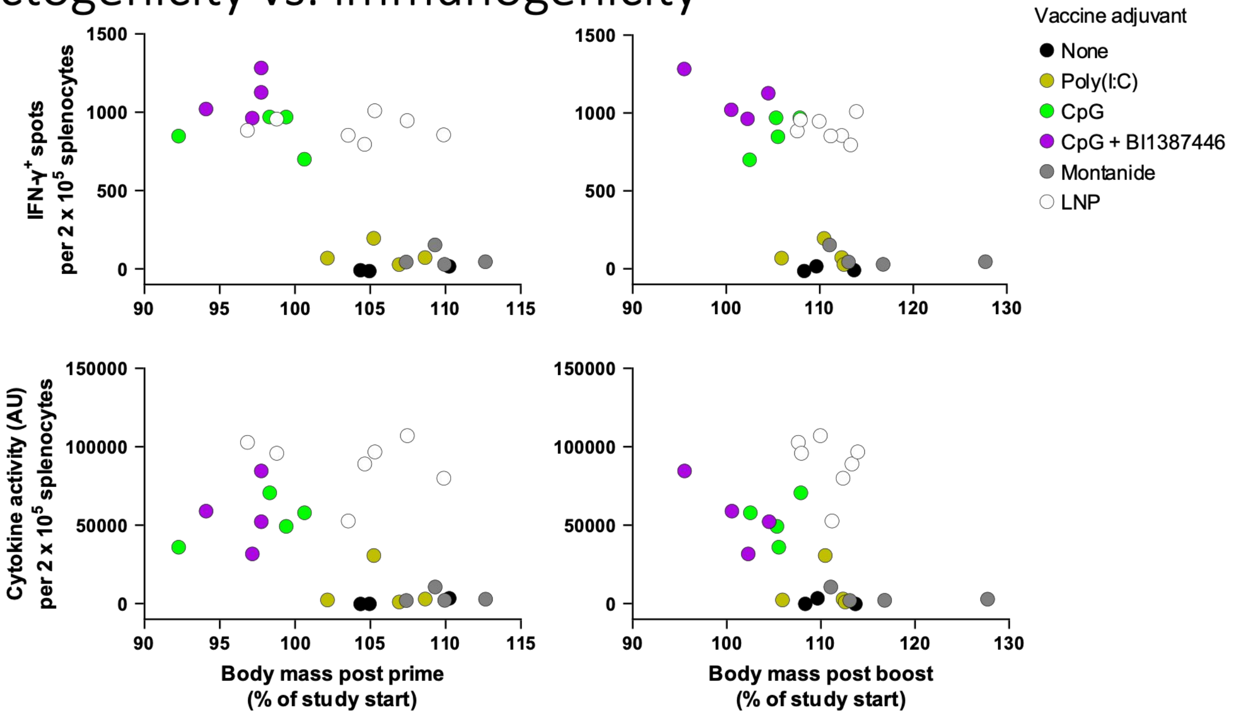
- Each pool of vaccine study drug + poly IC:LC will be administered to one of the four limbs (A - Right Arm, B - Left Arm, C - Right Leg, D - Left Leg) by subcutaneous (SC) injection.

Other Names:

- **Poly-ICLC**
- **Hiltonol**

OISTER: vaccine bake-off at PIRL

Reactogenicity vs. immunogenicity



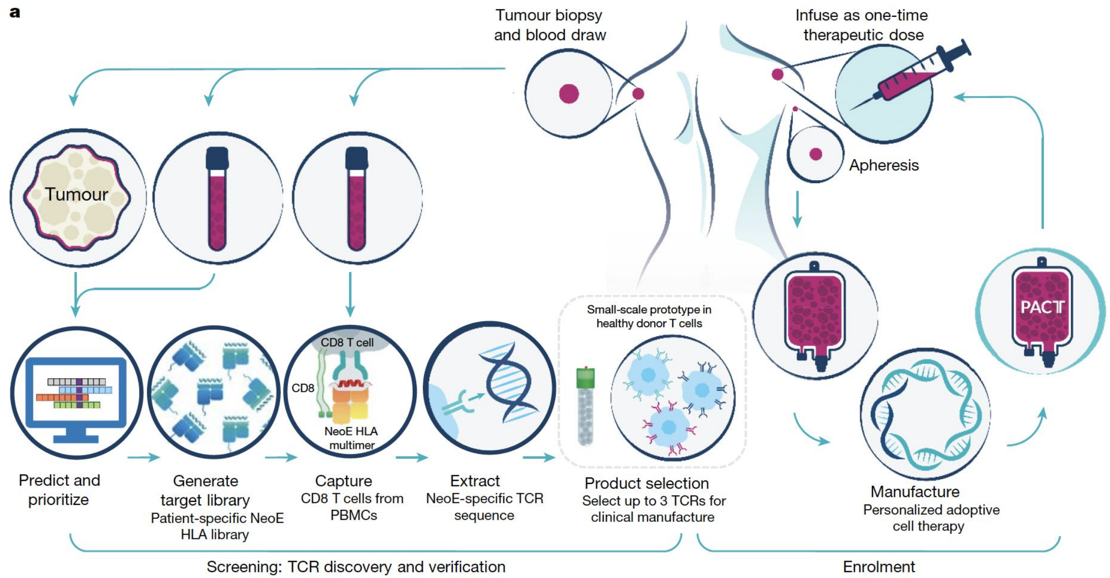
Unpublished / PIRL / Figure created by Jess Alley

Attempted solution #1: TCR-T cell therapy against neoantigens

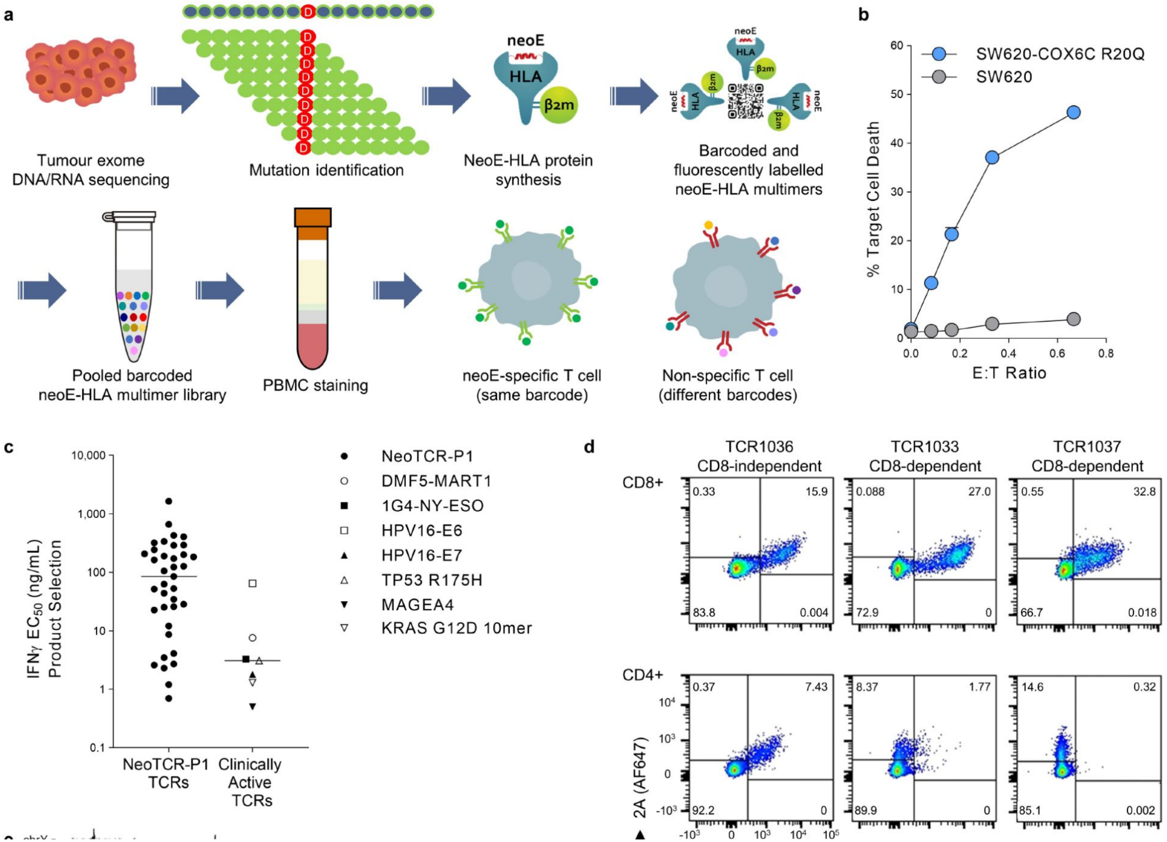
PACT Pharma Neoantigen Personalized TCR-T

Article

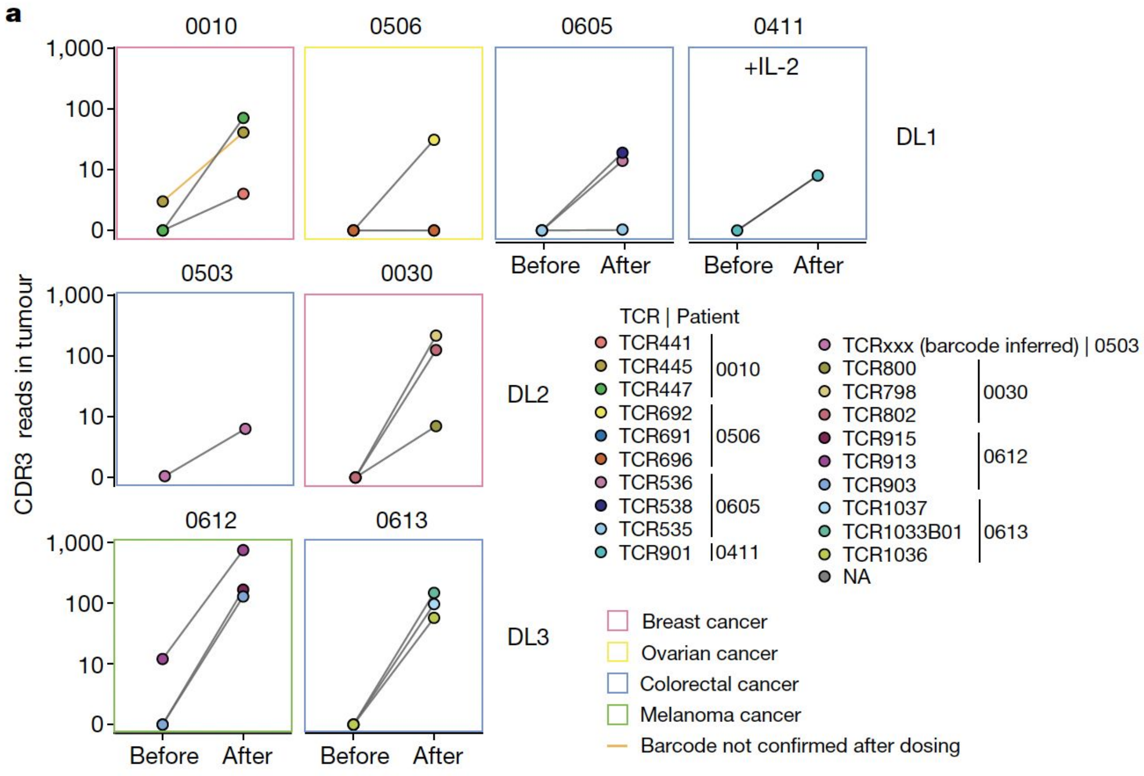
Non-viral precision T cell receptor replacement for personalized cell therapy



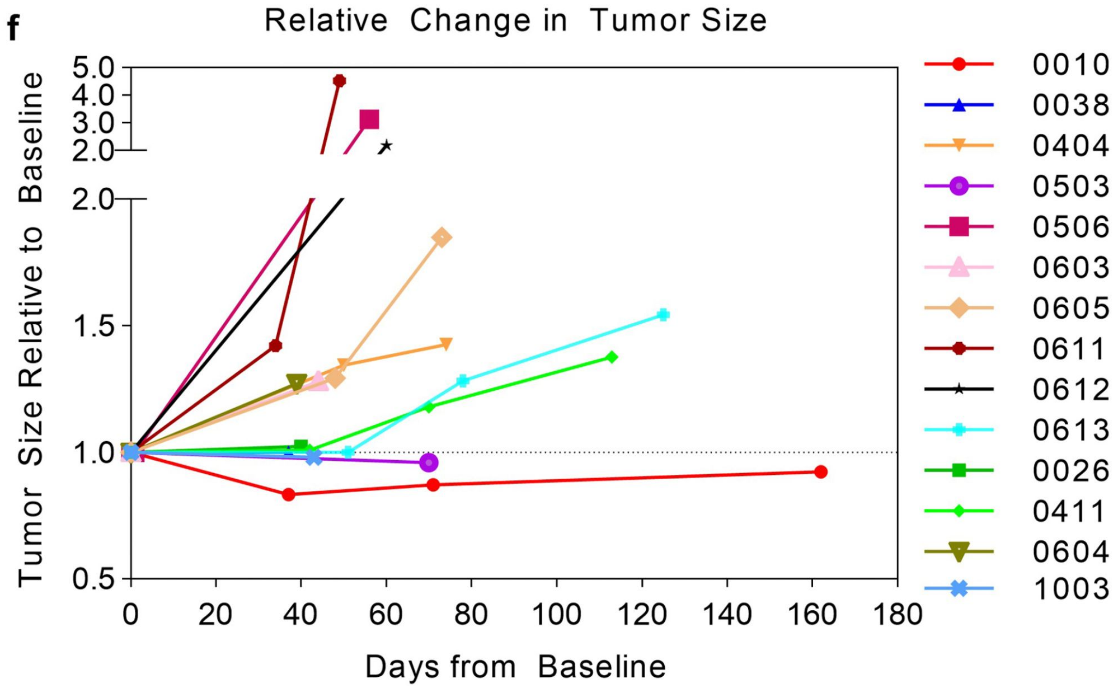
Single chain peptide-MHC trimers for TCR Discovery



TCRs in the tumor!



But…


f
Relative Change in Tumor Size
Tumor Size Relative to Baseline
5.0
4.0
3.0
2.0
2.0
1.5
1.0
0.5
0
20
40
60
80
100
120
140
160
180
Days from Baseline
0010
0038
0404
0503
0506
0603
0605
0611
0612
0613
0026
0411
0604
1003

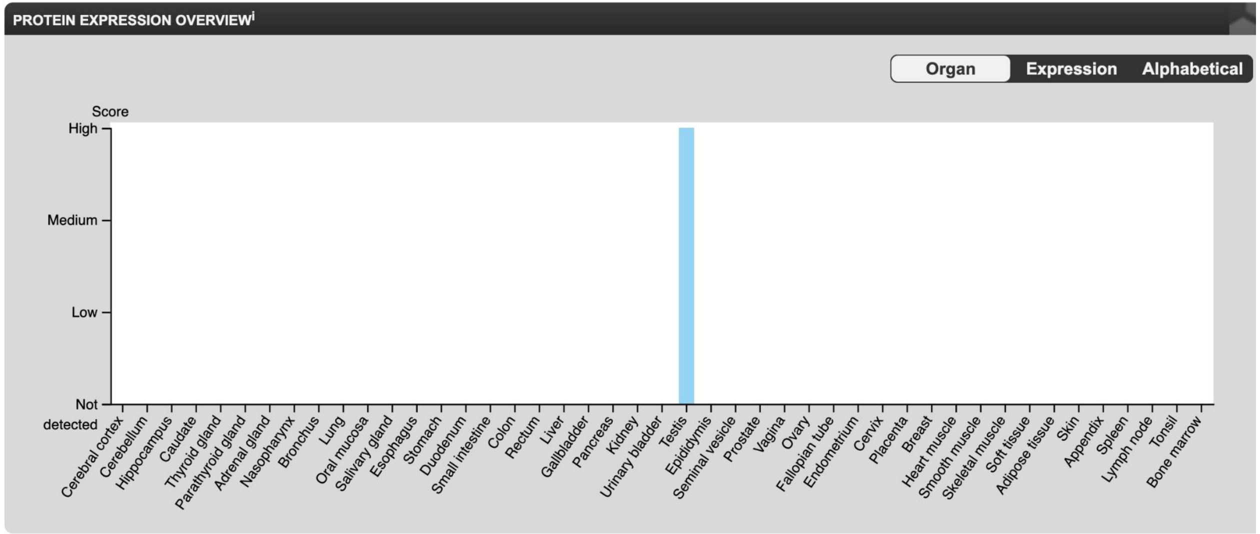
And then…

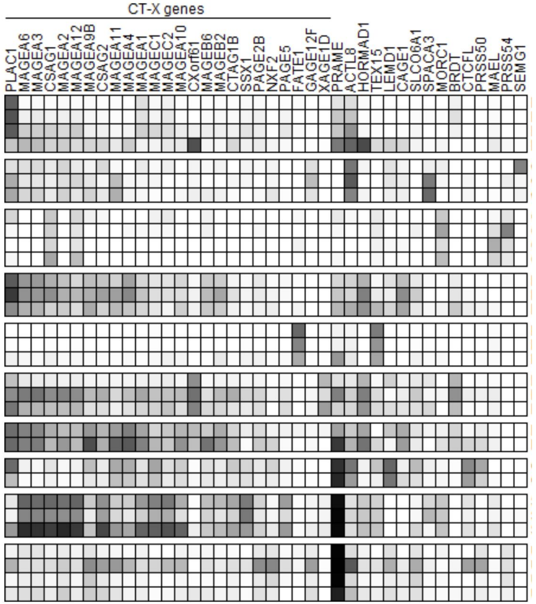
CDMO AmplifyBio closes doors amid tough market for early-stage cell and gene therapy development

By **Fraiser Kansteiner** · Apr 7, 2025 10:38am

Attempted solution #2: TCR-T cell therapy against recurrent cancer testis antigens

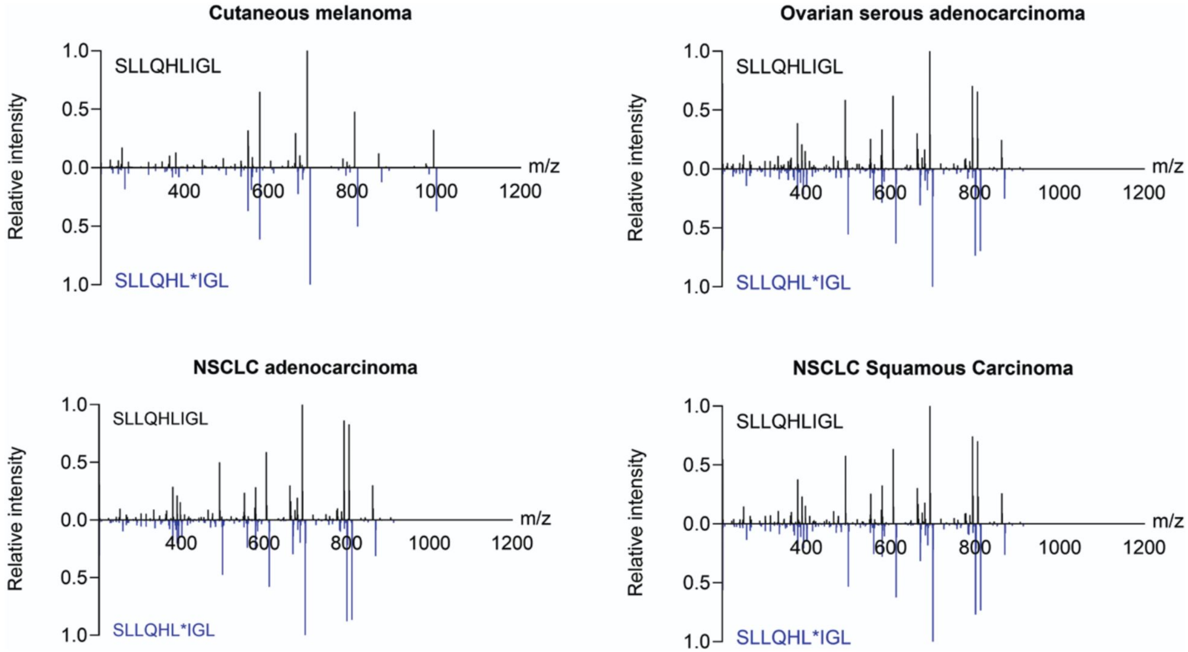
Cancer/testis antigens





Tumor subtype-specific cancer-testis antigens as potential biomarkers and immunotherapeutic targets for cancers

Get rid of informatic uncertainty: target recurrent validated epitopes across samples



TCR-T against a CTA epitope (MAGE-A4)

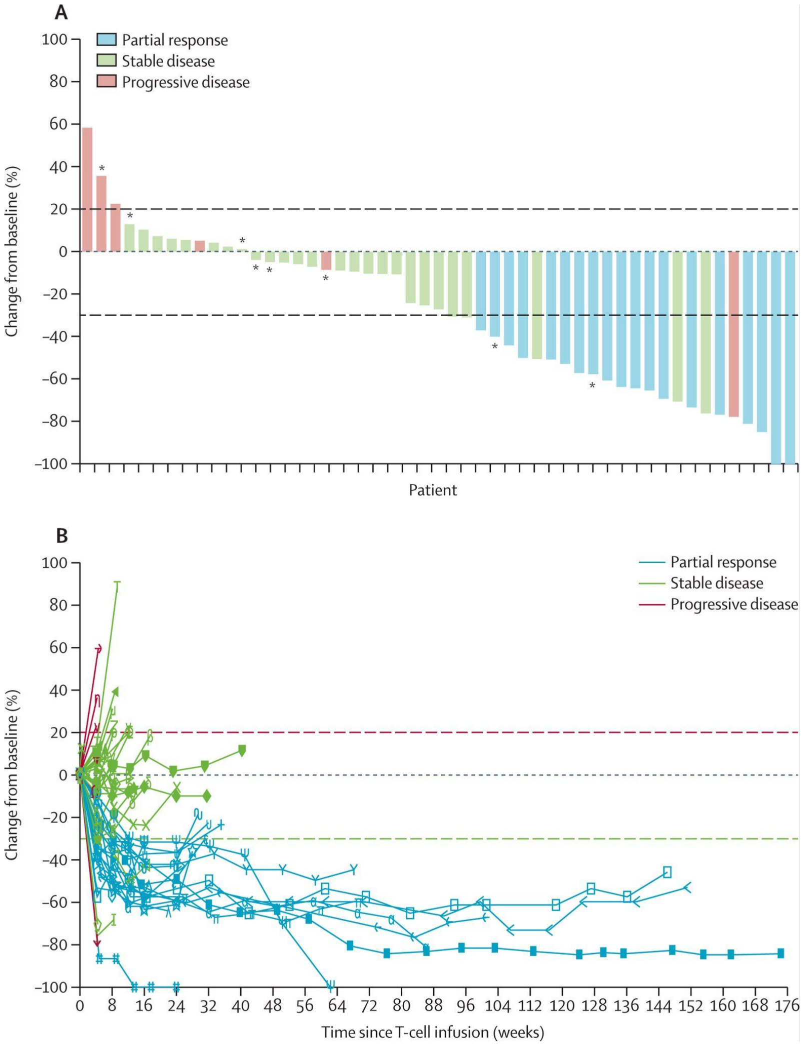
FDA Grants Accelerated Approval to Afamitresgene Autoleucel (TECELRA) for Treating Advanced Synovial Sarcoma

On August 2, 2024, the *FDA* made history by granting accelerated approval to *afamitresgene autoleucel* (TECELRA), the first-ever engineered cell therapy for a solid tumor.

This groundbreaking treatment, developed by *Adaptimmune*, LLC, offers new hope for adults battling unresectable or metastatic synovial sarcoma who have already undergone chemotherapy.

Afami-cel, as it's commonly known, represents a paradigm shift in cancer care, utilizing the patient's own genetically re-engineered immune cells to target and destroy cancer cells.

This precision medicine approach, tailored for specific HLA types and tumors expressing the MAGE-A4 antigen, marks the first significant advancement in synovial sarcoma treatment in over a decade.



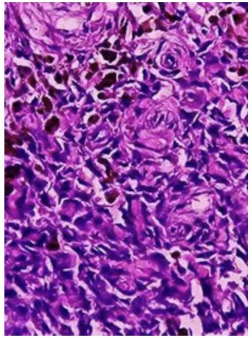
And another TCR-T success! (targeting NY-ESO-1)

Lete-Cel Generates Durable Responses in Synovial Sarcoma and Myoxid/Round Cell Liposarcoma

Author(s): Courtney Flaherty
Fact checked by: Chris Ryan

Listen 00:00 12:13

Patients with metastatic myxoid/round cell liposarcoma or synovial sarcoma expressing NY-ESO-1 and HLA achieved an ORR of 42% with lete-cel.



MdBabul– stock.adobe.com

Treatment with letetresgene autoleucel (lete-cel; GSK3377794) generated durable responses in patients with previously treated advanced or metastatic myxoid/round cell liposarcoma (MRCLS) or synovial sarcoma (SyS) expressing NY-ESO-1, meeting the primary efficacy end point of the ongoing phase 2 IGNYTE-ESO trial (NCT03967223).[1]

Results from the primary analysis of IGNYTE-ESO presented during the 2024 CTOS Annual Meeting showed that in the overall population (n = 64), lete-cel produced an overall response rate (ORR) of 42% (95% CI, 29.9%-55.2%) by central independent review assessment, including a complete response (CR) rate of 9% and partial response (PR) rate of 33%. Stable disease (SD) was achieved by 47% of patients, and 9% experienced progressive disease (PD). One patient was not evaluable (NE).

But…

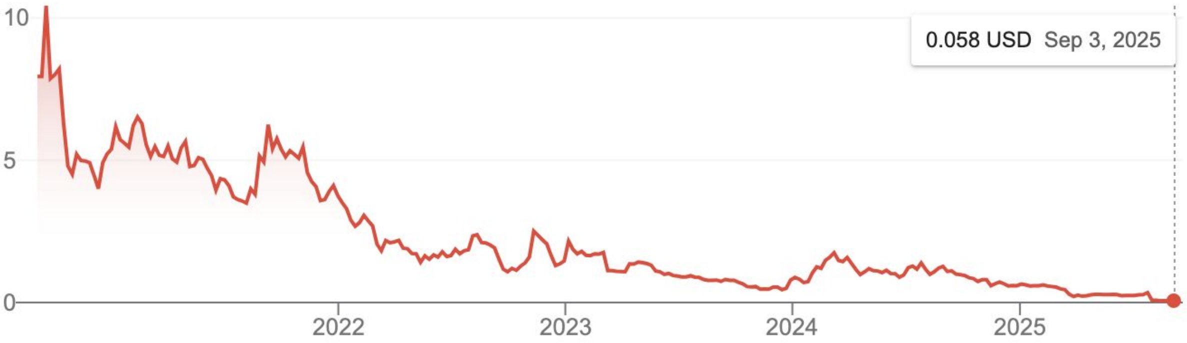
Market Summary > Adaptimmune Therapeutics PLC - ADR

0.058 USD

-7.88 (-99.27%) ↓ past 5 years

Sep 3, 9:53 a.m. EDT • Disclaimer

1D | 5D | 1M | 6M | YTD | 1Y | 5Y | Max



Attempted solution #3: <u>soluble TCR bispecific</u> against recurrent cancer testis antigens

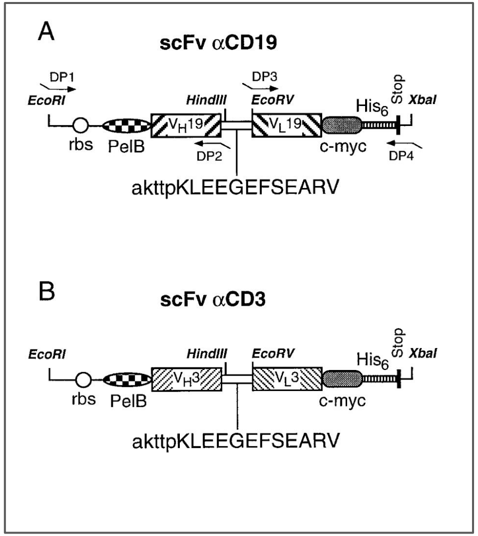
Idea: T-cell glue instead of CAR-T

BISPECIFIC CD3 × CD19 DIABODY FOR T CELL-MEDIATED LYSIS OF MALIGNANT HUMAN B CELLS

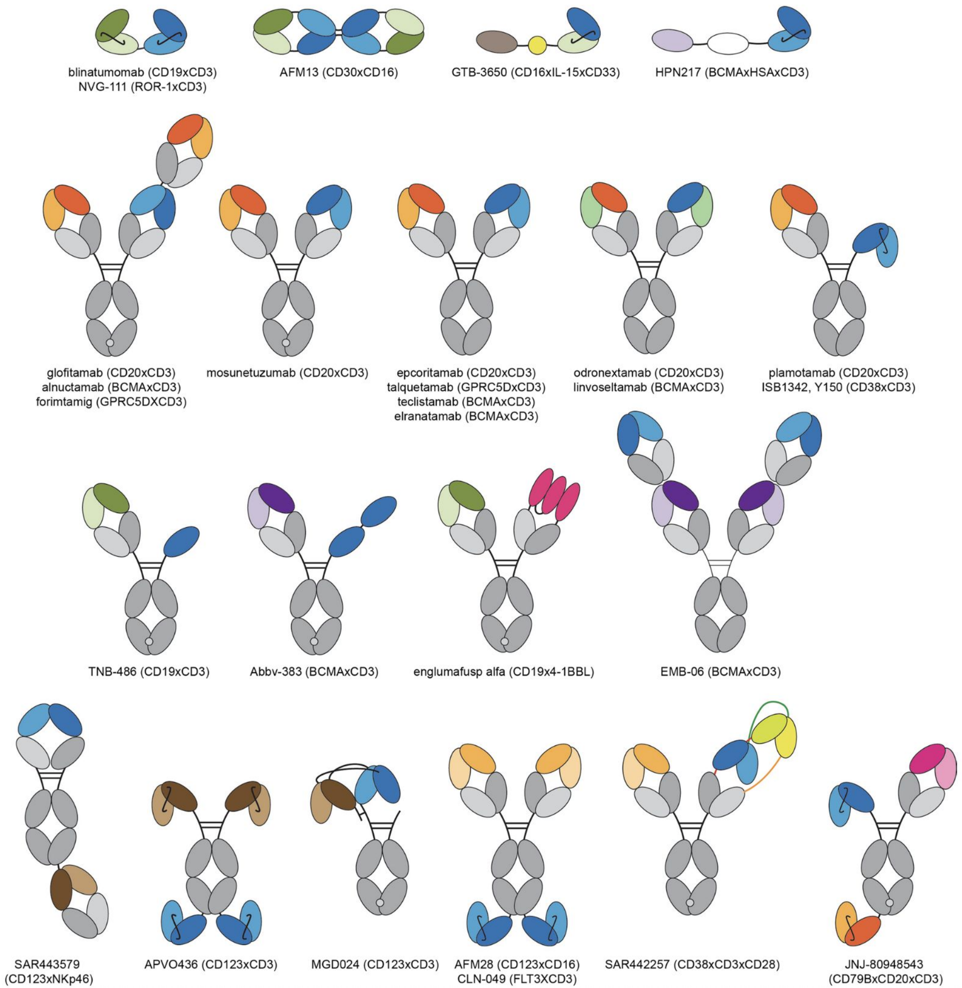
Sergey M. KIPRIYANOV[1], Gerhard MOLDENHAUER[2], Gudrun STRAUSS[2] and Melvyn LITTLE[1]*

[1]*Recombinant Antibody Research Group, Diagnostics and Experimental Therapy Program, German Cancer Research Center (DKFZ), Heidelberg, Germany*

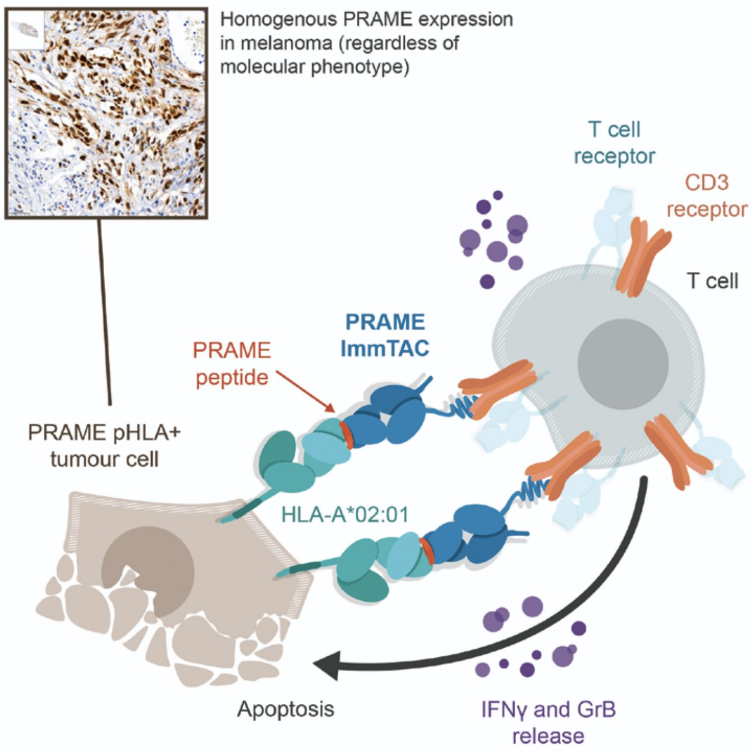
[2]*Department of Molecular Immunology, Tumor Immunology Program, DKFZ, Heidelberg, Germany*



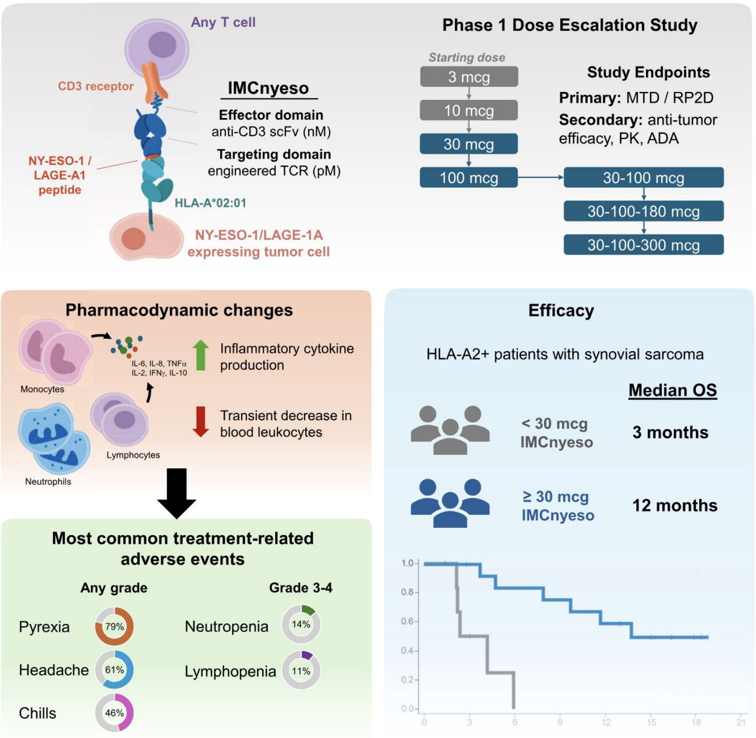
T-cell engagers: alternative to CAR-T (easier to make, slightly less effective)

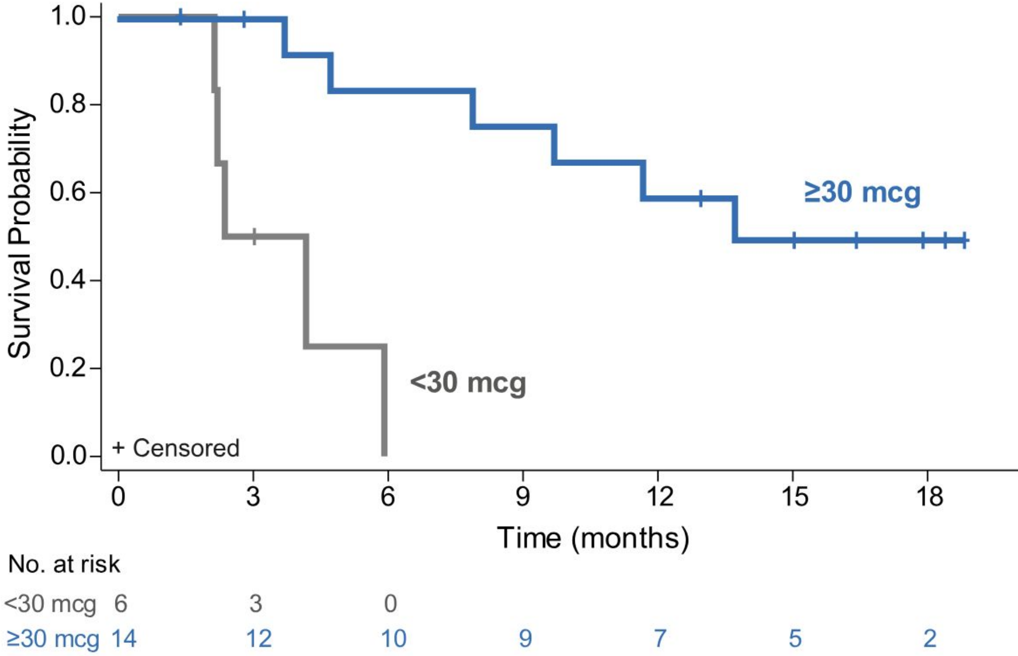


Twist: what about TCR instead of scFV?



Kinda works? (targeting NY-ESO-1)





Challenge: can you make TCR TCEs personalized?

- Cell therapy manufacturing is horrible
- Recombinant protein manufacturing is better but still too slow / finicky for personalized therapies
- **…what about mRNA encoding of soluble T-cell engagers?**

There’s a precedent: BNT142
mRNA encoded bispecific T-cell engager

Preclinical efficacy and pharmacokinetics of an RNA-encoded T cell–engaging bispecific antibody targeting human claudin 6

CHRISTIANE R. STADLER, URSULA ELLINGHAUS, LEYLA FISCHER, HAYAT BÄHR-MAHMUD, MARTIN RAO, CLAUDIA LINDEMANN, ANUHAR CHATURVEDI, CAROLINE SCHARF, IMKE BIERMANN, [...], AND UĞUR ŞAHIN +11 authors Authors Info & Affiliations

First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors.

Authors: Timothy A. Yap, Alberto Hernando Hernando-Calvo, Emiliano Calvo, Victor Moreno, Raul Marquez, Kyriakos P. Papadopoulos, Javier Garcia García - Corbacho, ... SHOW ALL ... , and Ugur Sahin | AUTHORS INFO & AFFILIATIONS

Putting the pieces together

- Select CTA derived pMHCs based on tumor CTA expression
    - Use pMHCs which are recurrent in public mass spec data
- Discover autologous TCRs from patients using PACT process
    - Single chain peptide-MHC-B2M trimers used to pull down reactive T-cell clones
- Encode CTA recognizing TCRs as part of a personalized therapeutic
- Synthesize as mRNA -> administer IV

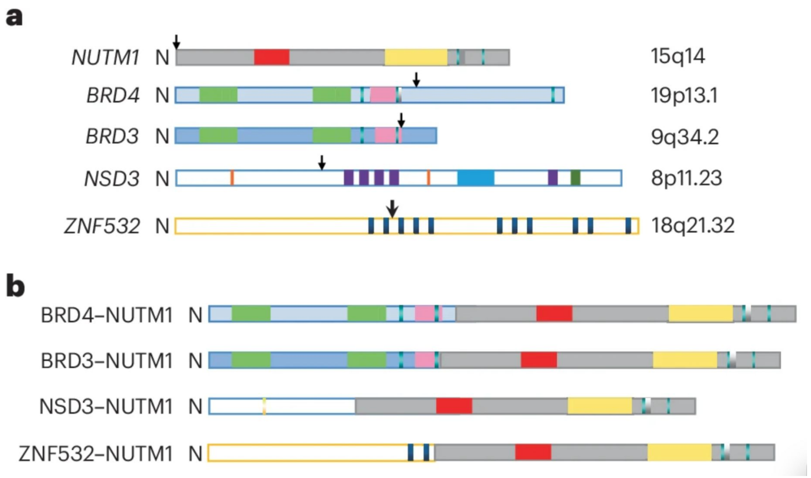
What’s good model cancer to start with?

Want a cancer with:

- Homogeneous biology / oncogenic event
- Consistently high expression of CTAs
- No good standard of care

NUT carcinoma

From: Hiding in plain sight: NUT carcinoma is an unrecognized subtype of squamous cell carcinoma of the lungs and head and neck



Intensive Treatment and Survival Outcomes in NUT Midline Carcinoma of the Head and Neck

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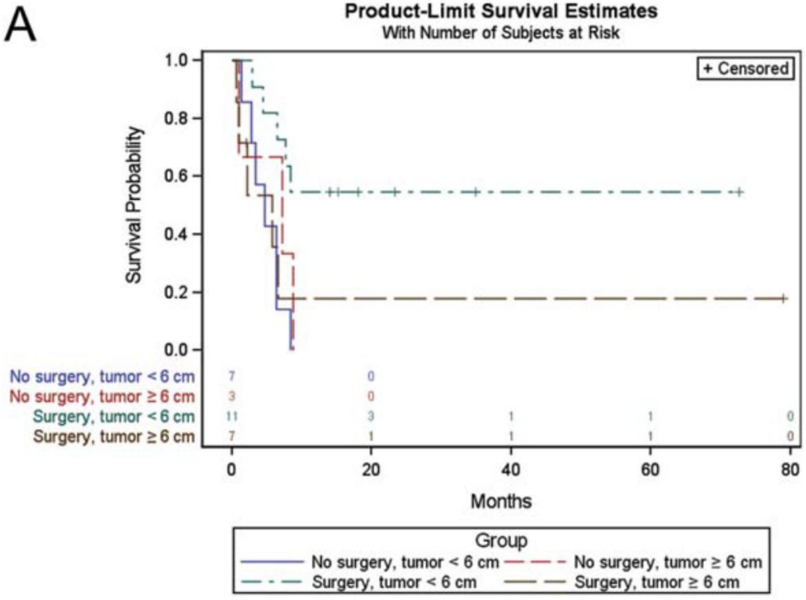
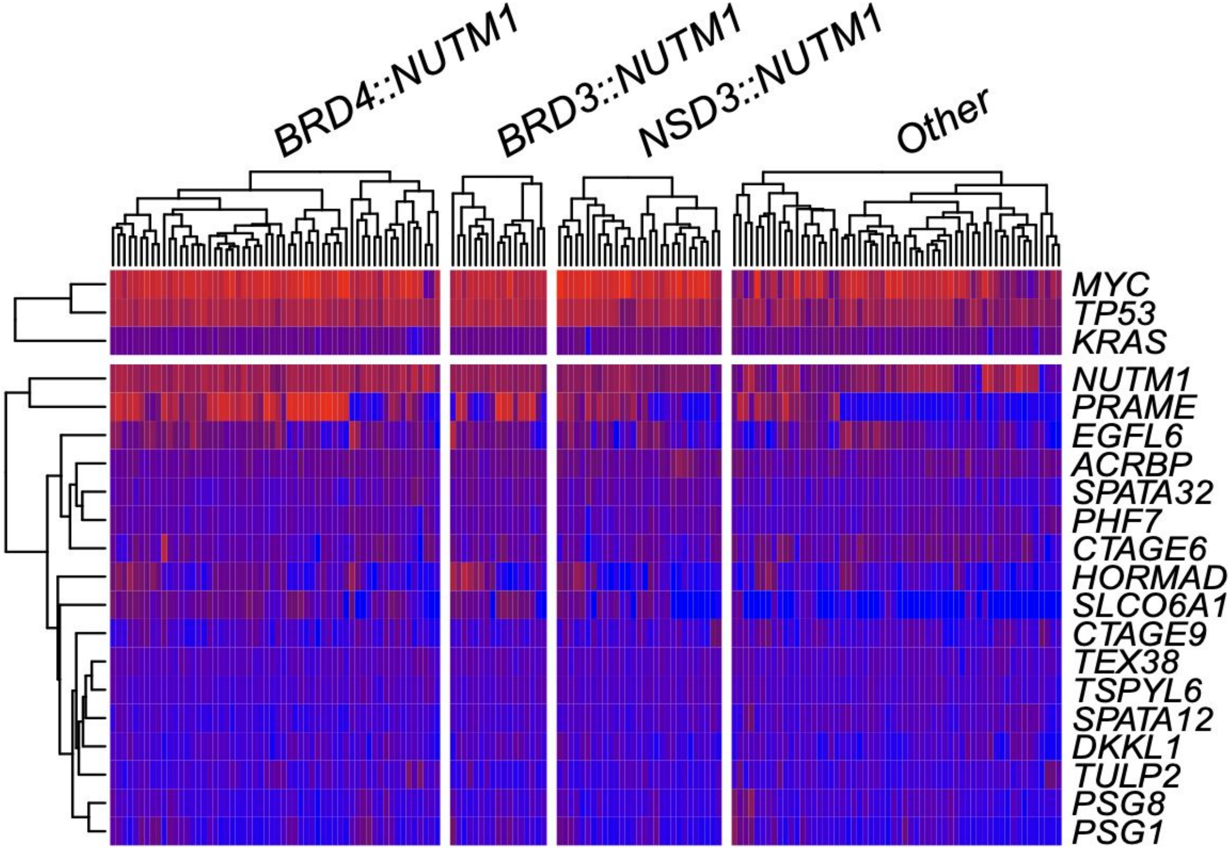
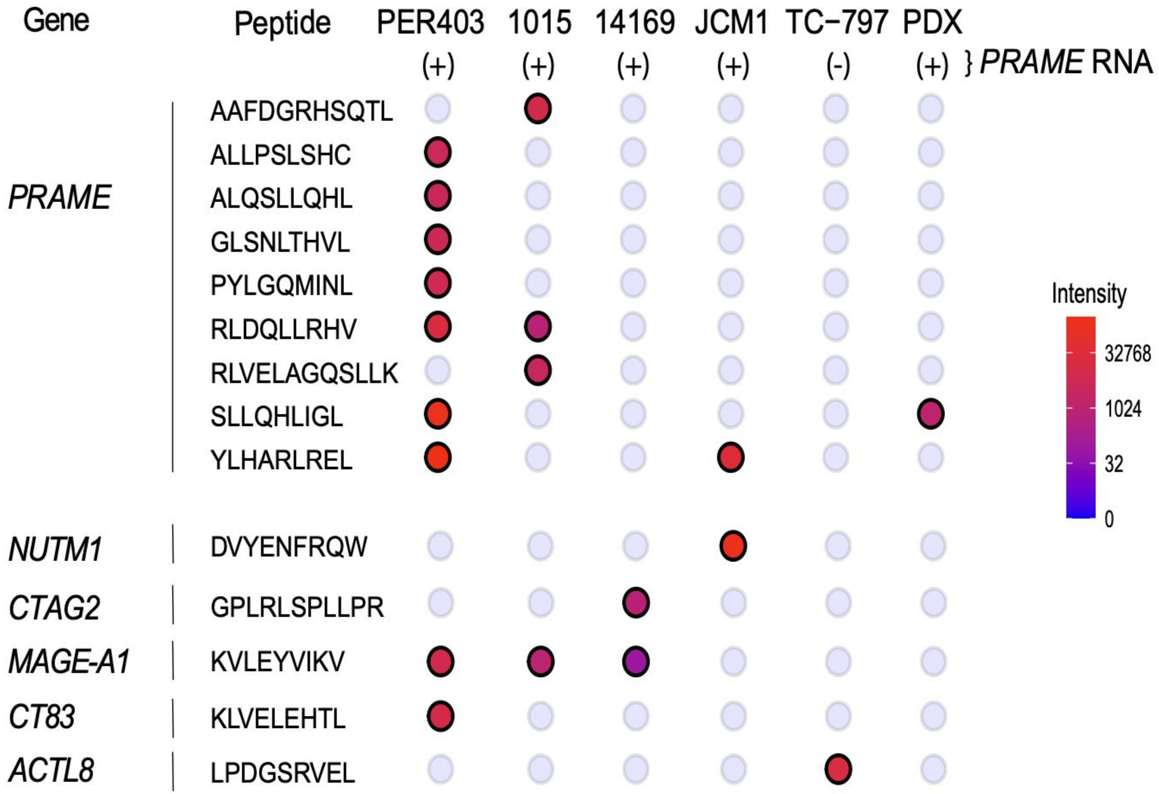


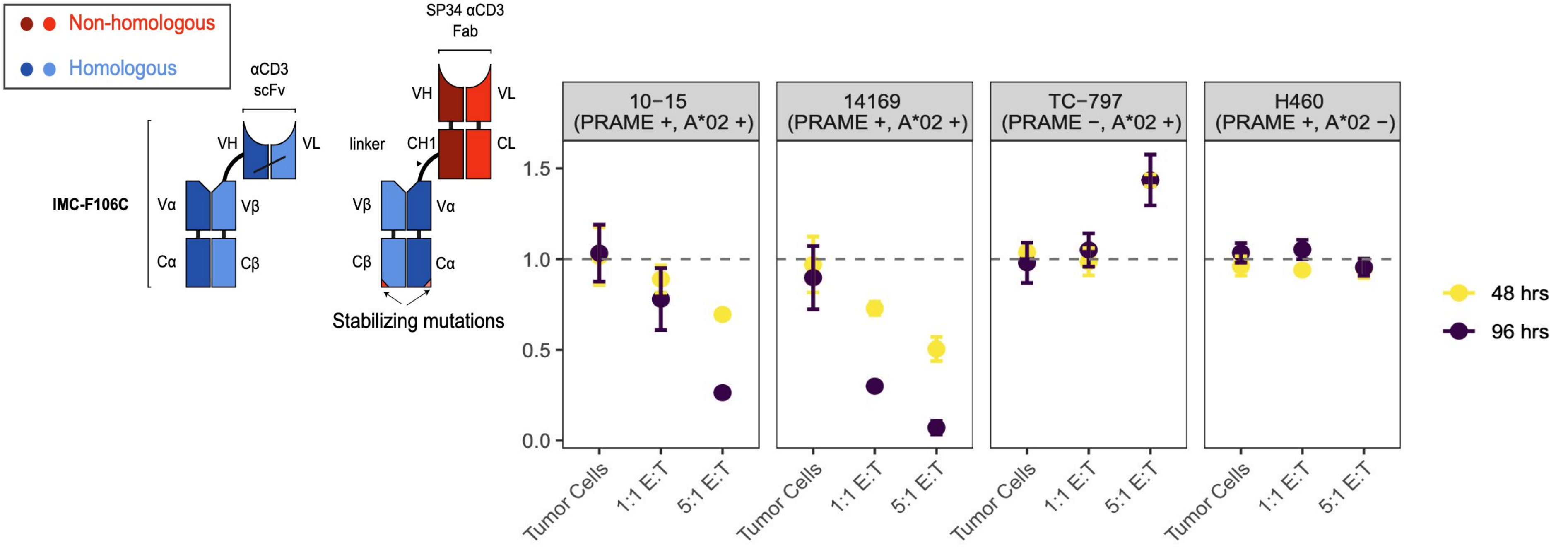
CTA expression in NUT carcinoma



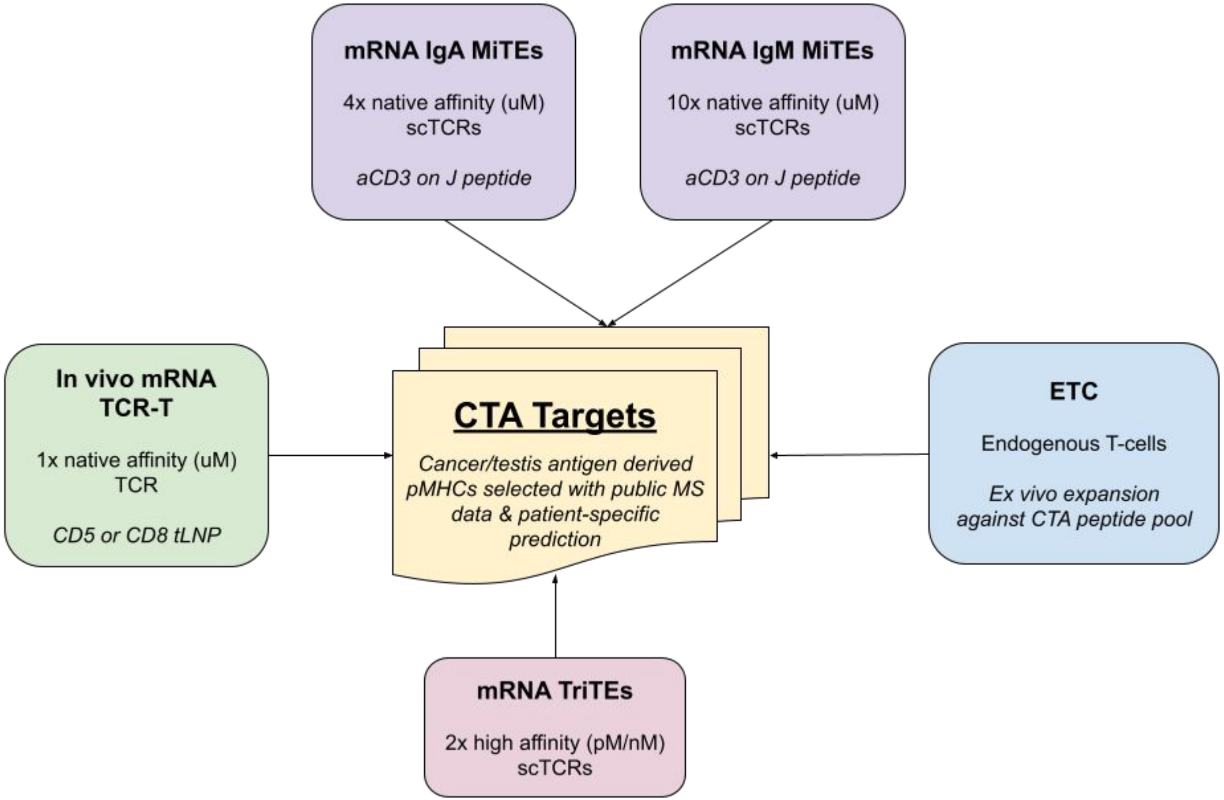
We see lots of PRAME pMHCs with MS



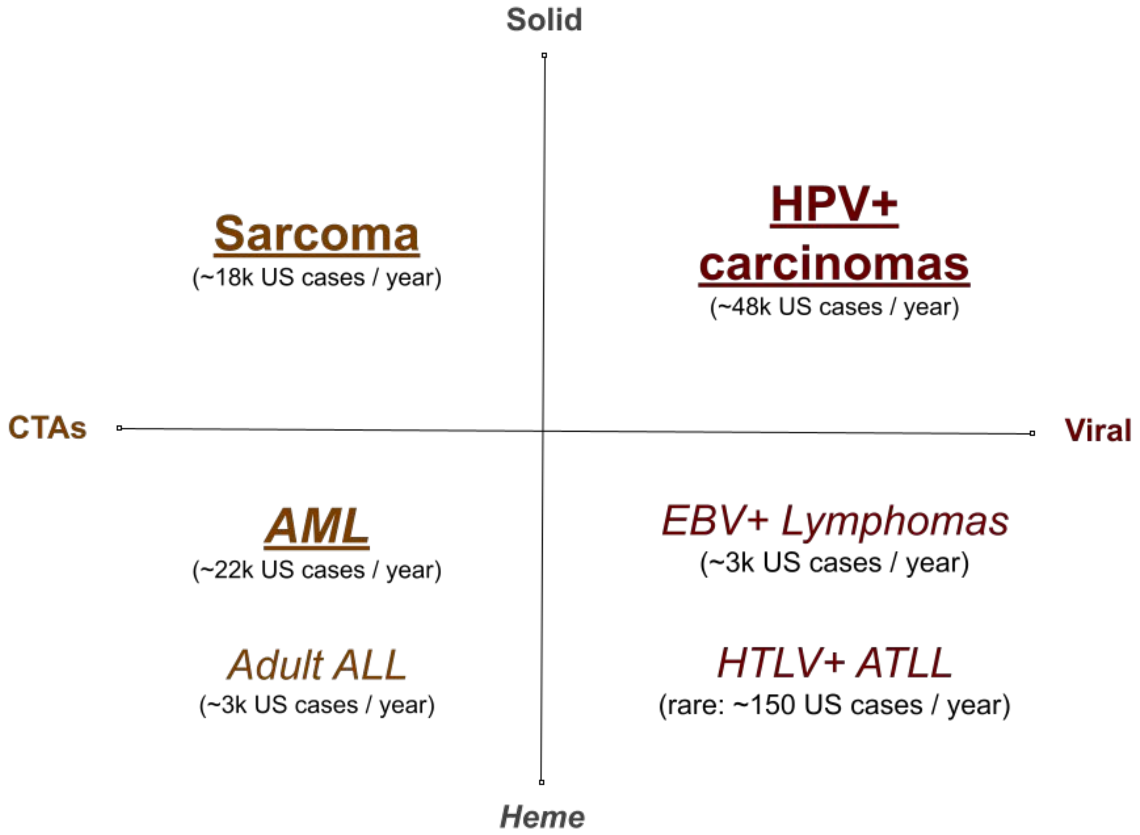
Sanity check: does a PRAME TCE work?



Therapies we’re investigating for CTA targets

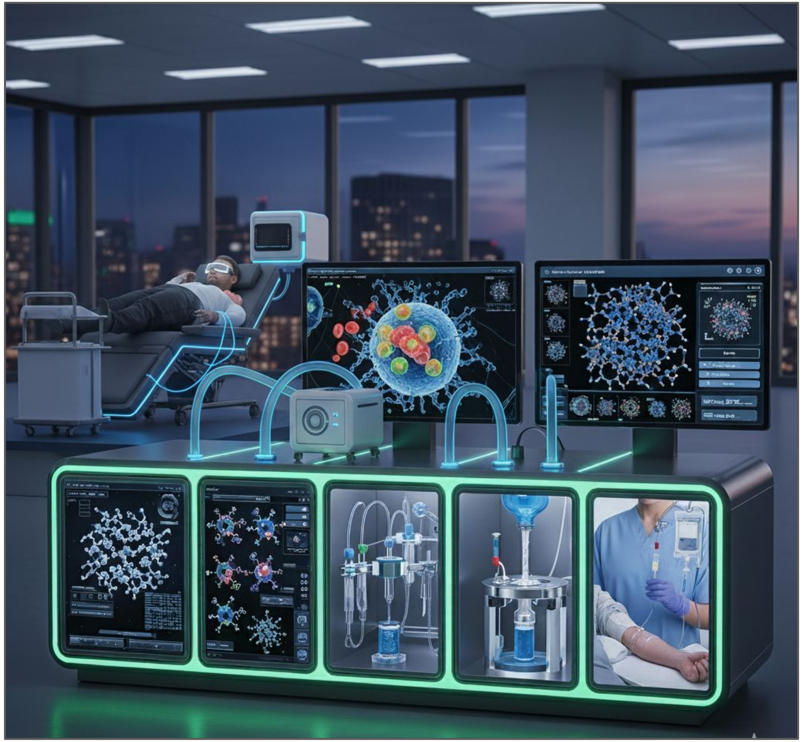


Another possible antigen category: viruses!



Summary

- We can already find very confident tumor-specific pMHC targets on 5-10% of cancers
  - Strong regulatory precedent for fully personalized immunotherapies
  - Personalized TCR discovery already works
  - Proof of concept mRNA TCE safe
- **<u>AI role</u>: TCR generation x cross reactivity prediction**



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Extra

Question: what's the antigen?

If disinhibiting CD8+ T-cells causes them to preferentially kill cancer cells, what MHC presented antigens are responsible for cancer recognition?

- Shared antigens
  - **Tumor associated antigens**: over-expressed proteins in cancer
  - **Cancer-testis antigens:** genes specific to reproductive cells which are never expressed in normal tissue but may occur in cancer
- "Neo"-antigens
  - Non-self proteins whose tumor specificity is assured from genomically templated mutations
- Misc: splice variants, post-translational modifications, &c (...cellular chaos!)

Can we target tumor antigens directly?

Flavors of antigen-specific therapies targeting MHC presented T-cell epitopes:

- **Therapeutic vaccination**
    - Inject antigen (+ adjuvant) to generate anti-tumor T-cell response in vivo
- **Cell therapies**
    - **TCR-T**: Engineer TCR which recognizes tumor antigen into patient T-cells
      ETC (endogenous T-cell therapy): Antigen-specific *ex vivo* expansion of patient T-cells → infuse
- **Dendritic cell vaccination**
    - Perform first step of vaccine (getting antigenic peptides loaded on antigen presenting cells) *ex vivo*; infuse APCs (hybrid between vaccine and cell therapy)

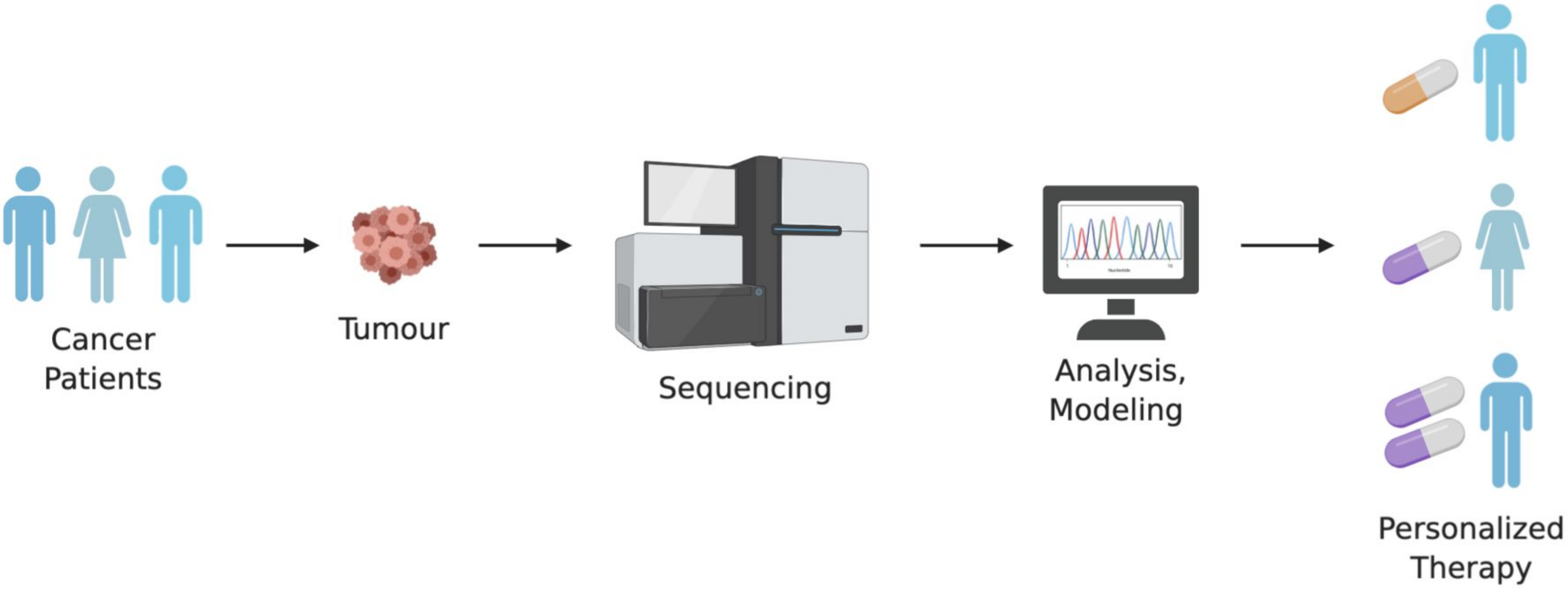
Shared antigen vaccines unsuccessful

Cancer type	Vaccine	Total patients	Patients responding
Melanoma	Tyrosinase + GMCSF	16	0
Melanoma	Peptides in IFA or on DC	26	3
Melanoma	MART-1 + IL-12	28	2
Prostate	Peptides	10	0
Melanoma	Peptides on PBMC + IL-12	20	2
Breast and prostate	Telomerase	7	0
Cervix	HPV16 E7	17	0
Colorectal	Peptides in IFA	10	0
Multiple	NY-ESO-1	12	0
Multiple	Ras in DETOX adjuvant	15	0
Multiple	Peptides in IFA	14	0
Prostate	Vaccinia-PSA	33	0
Prostate	Vaccinia-PSA	42	0
Colorectal	Vaccinia-CEA	20	0
Colorectal	Vaccinia-CEA and B7-1	18	0
Multiple	Avipox-CEA(IGMCSF)	60	0
Multiple	Avipox-CEA	15	0
Multiple	Vaccinia + avipox-CEA	18	0

Cancer immunotherapy: moving beyond current vaccines

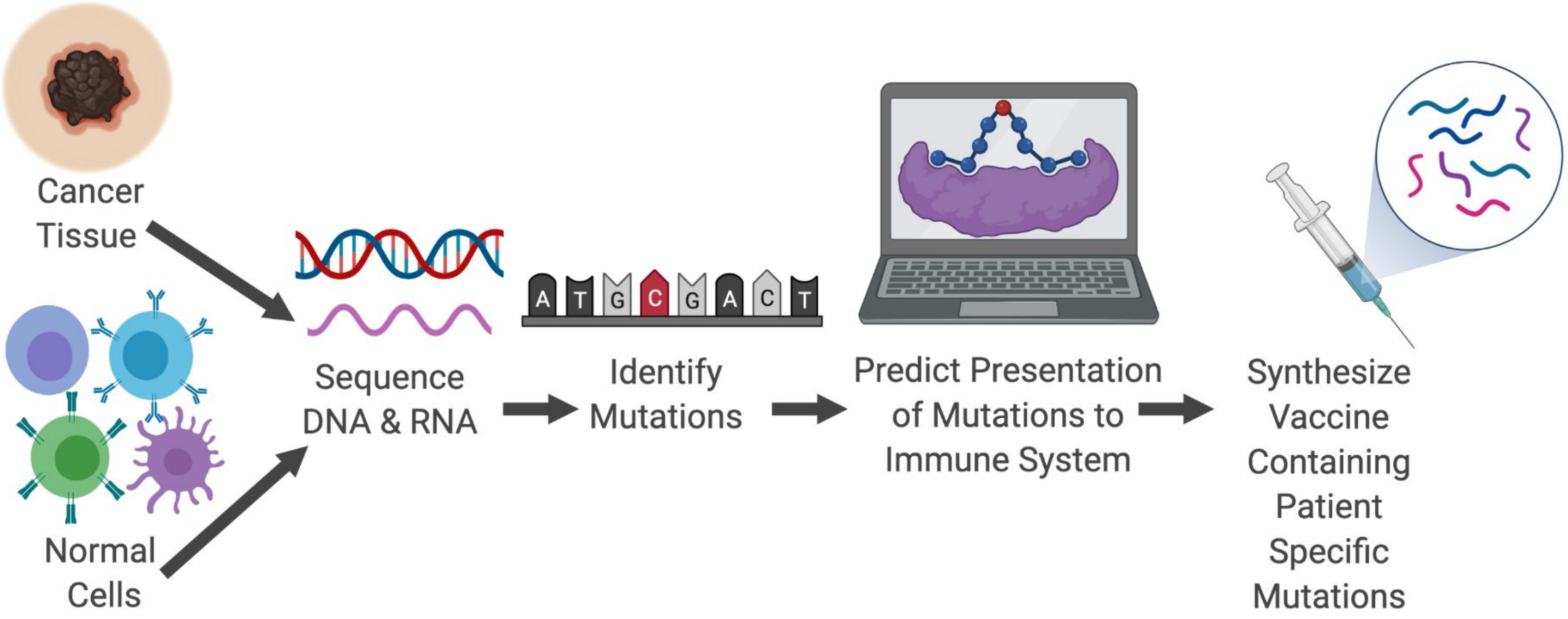
Personalized cancer immunotherapy

“Traditional” personalized medicine



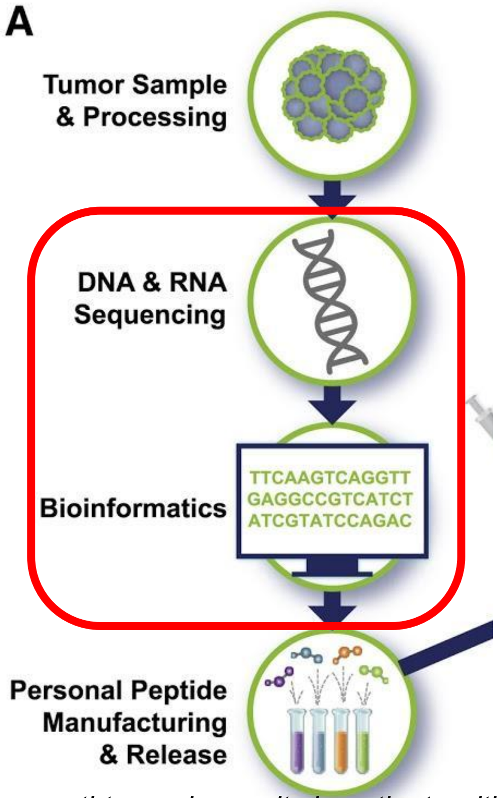
https://en.wikipedia.org/wiki/Personalized_medicine

Neoantigen vaccines: extremely personalized medicine



Neon (Ott, …, Srinivasan 2020)

- Tumor/normal WES
- Variant calling: SNVs and small indels
  - VarDict
  - Strelka
  - Mutect2
  - VarScan2
  - Atlas Indel2
  - Seurat
  - Platypus



A personal neoantigen vaccine, NEO-PV-01, with anti-PD1 induces broad de novo anti-tumor immunity in patients with metastatic melanoma, NSCLC, and bladder cancer

Cell therapy: NCI’s Rosenberg lab

- Preliminary screening of “all” coding mutations using tandem minigenes
    - WES
    - SNVs + small indels
- Identify specific reactive neoantigens using peptides