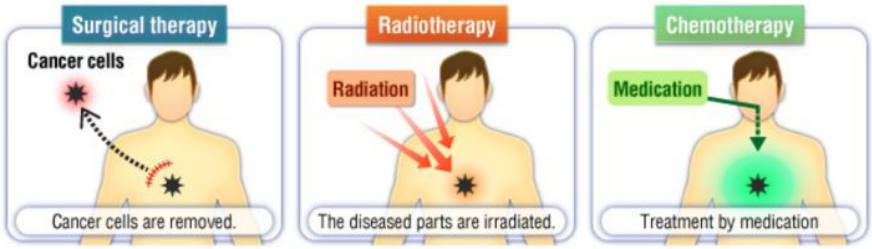
State of the Art Immunotherapy

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

Ezra E.W. Cohen, MD

UC San Diego
Moores Cancer Center

Current approaches to cancer treatment



Can the immune system help control cancer?

Yes!

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La Jolla Institute for Immunology | Life Without Disease.

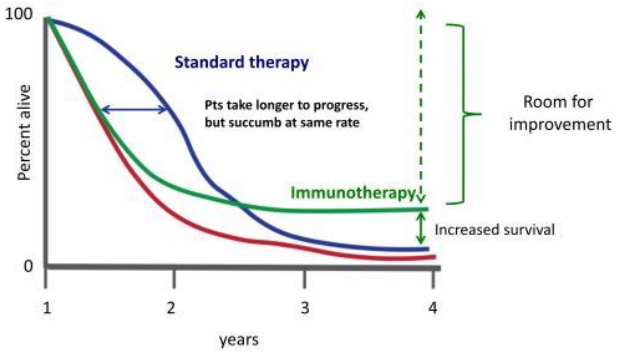
The immune system exists to protect us from infection

Effective defense requires *both* innate and adaptive immunity

Innate arm:

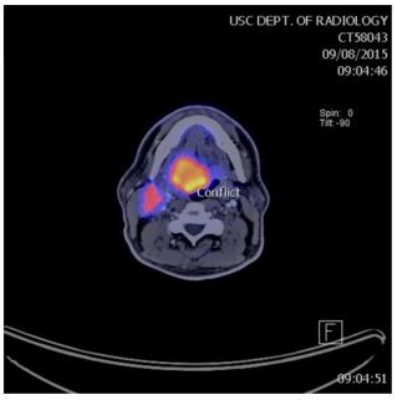
Adaptive arm:

Why Immunotherapy?



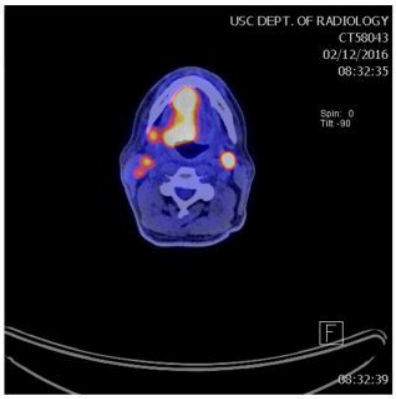
Case Presentation

- RR 55 y/o man diagnosed initially with T2N2c HPV+ BoT in September 2015
- Treated with cetuximab/RT [hearing loss]
- Completed without interruption or dose reduction

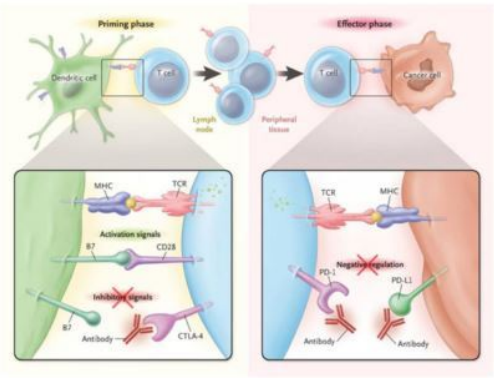


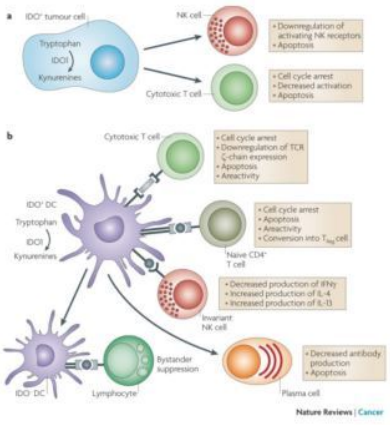
Case Presentation

- Post-CRT PET revealed evidence of persistent disease with bilateral lymphadenopathy
- Confirmed in-field failure
- Confirmed by biopsy



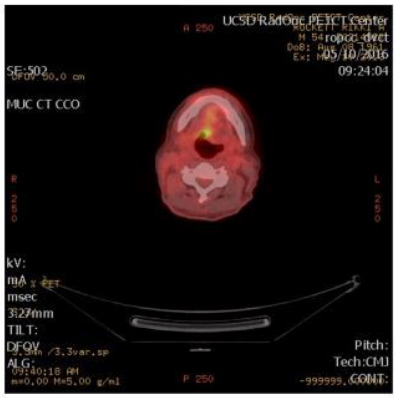
PD-1 Antibody + IDOi Clinical Trial





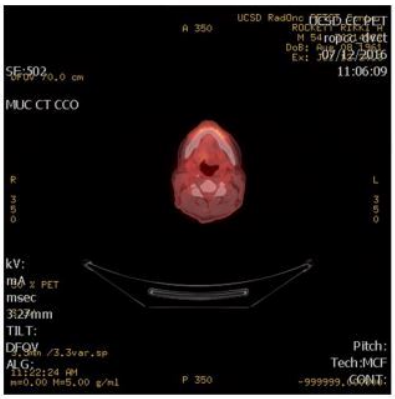
Case Presentation

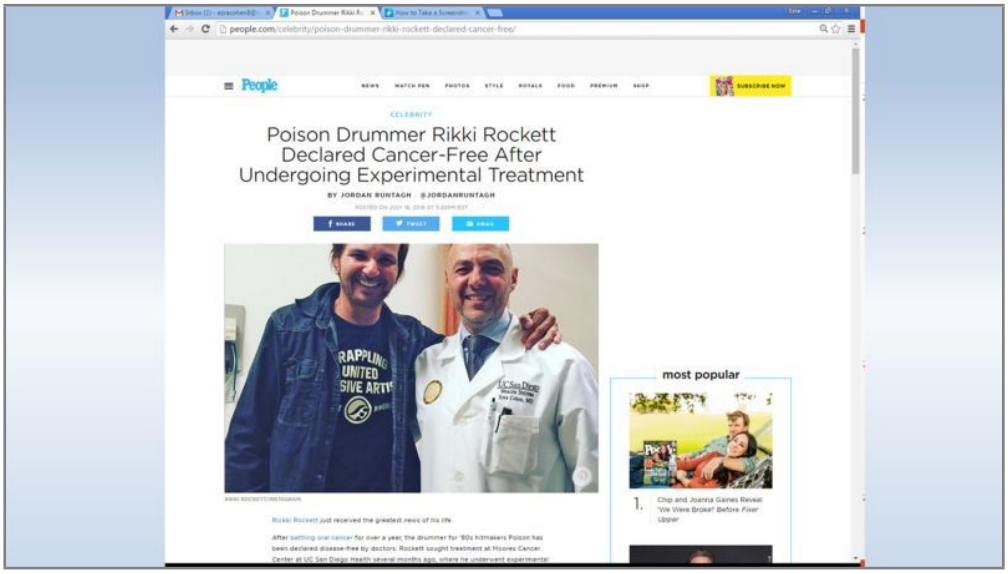
- Started on clinical trial of pembrolizumab [anti-PD1] plus epacadostat [Indoleamine-pyrrole 2,3-dioxygenase 1 inhibitor] on March 9th
- First scans on therapy [May 10th] revealed deep PR
- Not requiring pain medication, swallowing significantly improved



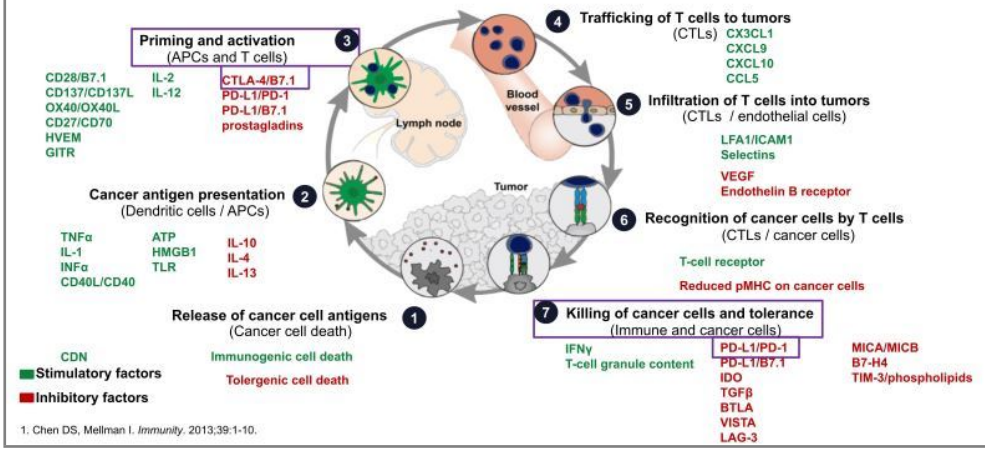
Case Presentation

- Next scans [July 12th] reveal CR
- Essentially asymptomatic
- No drug-related adverse events



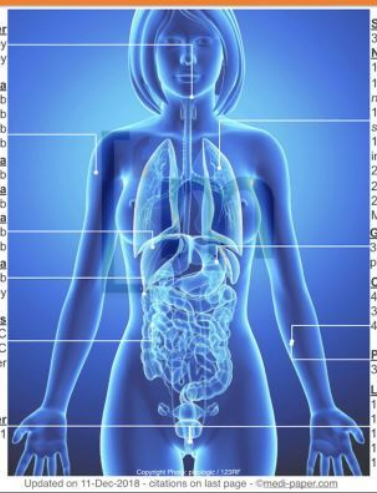


The Cancer-Immunity Cycle: Stepwise Events in Anticancer Immune Response[1]



1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10.

U.S. FDA Approved Immune-Checkpoint Inhibitors[1-7]



Squamous Cell Head & Neck Cancer
1L/2L nivolumab after platinum chemotherapy
1L/2L pembrolizumab after platinum chemotherapy

Malignant Melanoma
Adjuvant/1L ipilimumab
1L nivolumab ± ipilimumab
Adjuvant nivolumab
1L pembrolizumab

Merkel Cell Carcinoma
2L avelumab

Cutaneous Squamous Cell Carcinoma
1L cemiplimab

Hepatocellular Carcinoma
2L nivolumab after sorafenib
2L pembrolizumab after sorafenib

Adv. Renal Cell Carcinoma
1L nivolumab plus ipilimumab
2L nivolumab after anti-angiogenic therapy

MSI-H or dMMR Cancers
2L nivolumab in CRC
2L nivolumab plus ipilimumab in CRC
2L pembrolizumab in any MSI-H/dMMR cancer

Cervical Cancer
2L pembrolizumab CPS≥1

Small Cell Lung Cancer
3L nivolumab

Non-Small Cell Lung Cancer
1L pembrolizumab TPS≥50%
1L pembrolizumab + pemetrexed & platinum-salt in *non-squamous* NSCLC
1L pembrolizumab + carboplatin & (nab-)paclitaxel in *squamous* NSCLC
1L atezolizumab + bevacizumab, paclitaxel & carboplatin in *non-squamous* NSCLC
2L pembrolizumab TPS≥1%
2L nivolumab
2L atezolizumab
Maintenance durvalumab after chemoradiation

Gastric & GEJ Carcinoma
3L pembrolizumab after fluoropyrimidine- and platinum-chemotherapy +/- HER2 therapy & CPS≥1

Classical Hodkin Lymphoma
4L pembrolizumab
3L nivolumab after auto-HSCT and BV
4L nivolumab and after auto-HSCT

PMBCL
3L pembrolizumab

Locally Adv. or Met. Urothelial Cancer
1L/2L nivolumab after platinum chemotherapy
1L/2L pembrolizumab
1L/2L atezolizumab after platinum chemotherapy
1L/2L avelumab after platinum chemotherapy
1L/2L durvalumab after platinum chemotherapy

Updated on 11-Dec-2018 - citations on last page - ©medi-paper.com

Phase III KEYNOTE-040 Study (NCT02252042)

Key Eligibility Criteria
- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 mo of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification Factors
- ECOG PS (0 vs 1)
- p16 status[b] (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R 1:1

Pembrolizumab 200 mg IV Q3W for 2 y

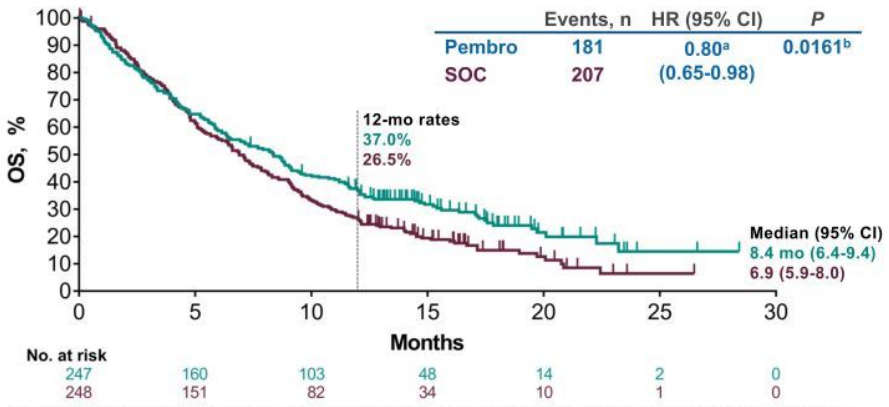
Methotrexate 40 mg/m² QW[e]
OR
Docetaxel 75 mg/m² Q3W
OR
Cetuximab 250 mg/m² QW[f]

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.
[c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

Soulières D, et al. Presented at: AACR Annual Meeting 2018. Abstract CT115.

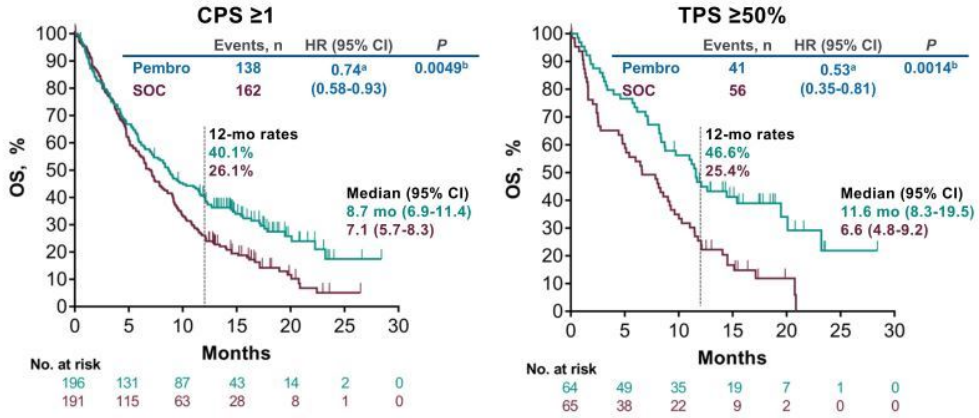
Overall Survival: ITT



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Soulières D, et al. Presented at: AACR Annual Meeting 2018. Abstract CT115.

Overall Survival by PD-L1 Expression



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Soulières D, et al. Presented at: AACR Annual Meeting 2018. Abstract CT115.

Best Overall Response[a]
(RECIST v1.1, Blinded Independent Radiology Review)

	ITT		CPS ≥1		TPS ≥50%	
Best Response, (%)	Pembro N = 247	SOC N = 248	Pembro n = 196	SOC n = 191	Pembro n = 64	SOC n = 65
ORR	36 (14.6)	25 (10.1)	34 (17.3)	19 (9.9)	17 (26.6)	6 (9.2)
CR	4 (1.6)	1 (0.4)	4 (2.0)	1 (0.5)	3 (4.7)	1 (1.5)
PR	32 (13.0)	24 (9.7)	30 (15.3)	18 (9.4)	14 (21.9)	5 (7.7)
SD	56 (22.7)	65 (26.2)	46 (23.5)	53 (27.7)	15 (23.4)	15 (23.1)
PD	108 (43.7)	97 (39.1)	77 (39.3)	72 (37.7)	22 (34.4)	23 (35.4)
NonCR/nonPD[b]	2 (0.8)	1 (0.4)	2 (1.0)	0	1 (1.6)	0
Not evaluable or assessable[c]	45 (18.2)	60 (24.2)	37 (18.9)	47 (24.6)	9 (14.1)	21 (32.3)

[a]Best overall response did not change with the updated analysis.[b]Patients without measurable disease at baseline per RECIST v1.1 by independent radiology review who did not experience CR or PD. [c]Not evaluable: patients who had ≥1 postbaseline tumor assessment, none of which were evaluable (n = 9); not assessable: patients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy (n = 96). Data cutoff date: May 15, 2017.

Soulières D, et al. Presented at: AACR Annual Meeting 2018. Abstract CT115.

Novel Immunotherapies

Vaccines
NK cells
CAR-T cells

UC San Diego Health

Steve

Personalized Cancer Vaccines

Ezra

Tumor types with NeoAg verified by our method

- ✓Head and Neck
- ✓Colorectal
- ✓Pancreatic Ductal
- ✓Neuroendocrine
- ✓Liver (HCC)
- ✓Gastric-Esophageal
- ✓Appendiceal
- ✓Kidney
- ✓Prostate
- ✓Breast
- ✓Bile Duct
- ✓Ovarian
- ✓Astrocytoma
- ✓Glioblastoma

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OCTOBER 14, 2018

The San Diego Union-Tribune

SUNDAY

$2.77

MOORES GIVES FIRST PERSONALIZED CANCER VACCINE

Researchers hope to remove guesswork with precise targeting method

BY PAUL SISSON

UC San Diego Moores Cancer Center

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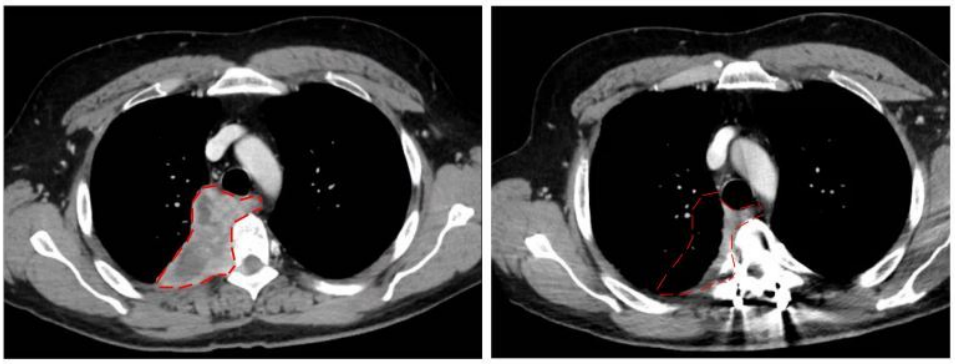
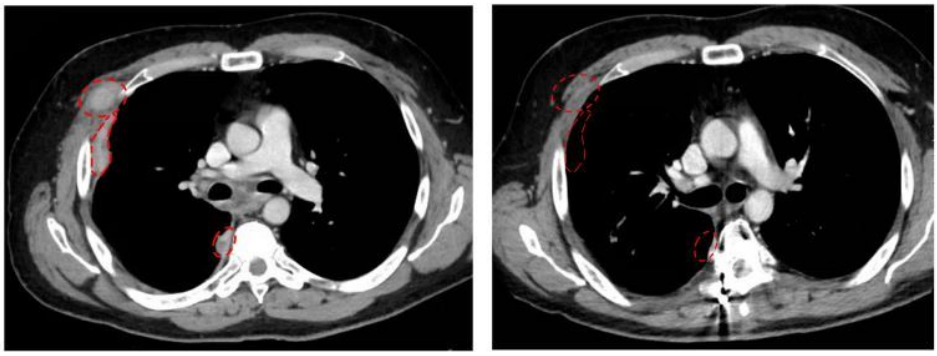
Personalized Vaccine Patient #4 - HNSCC



3/29/2019 6/07/2019

Ezra

Personalized Vaccine Patient #4 - HNSCC

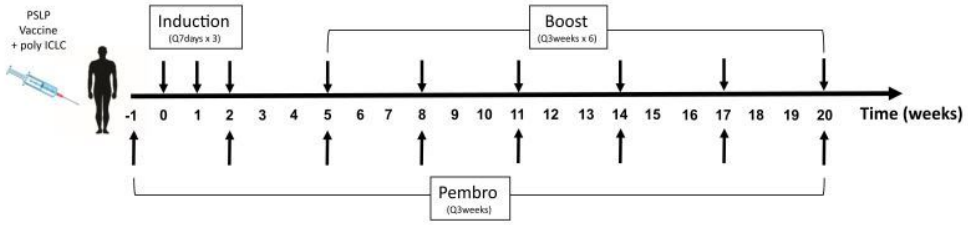


3/29/2019 6/07/2019

Ezra

New protocol: Arm C

Strategy: *make the tumor appear as a viral infection*



1st two patients (54 y.o. man with Colorectal Cancer and 60 y.o. woman with Pancreatic Cancer) began treatment in November

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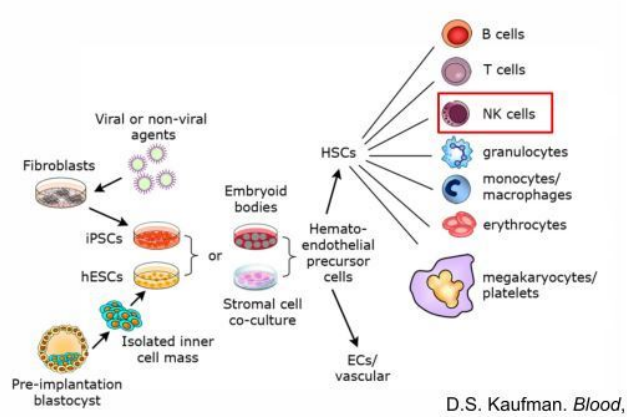
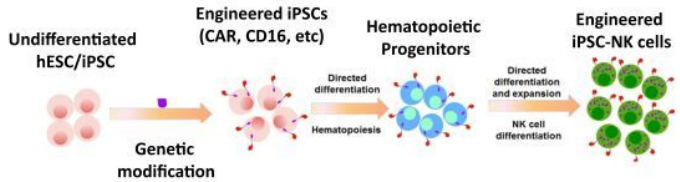
Development of functional lymphocytes from human pluripotent stem cells



D.S. Kaufman. *Blood*, 2009

Human iPSCs as a platform for engineered cellular therapies



Summary of NK Cell Products being moved in to clinical trials

- **FT500**: First-of-kind cancer immunotherapy
  - Multi-dose administration in solid and liquid tumors, including in combination with checkpoint inhibitor therapy
  - **Clinical trial started in February 2019 at UCSD**
  - **1st iPSC therapy in the US. 1st iPSC-blood cells and cancer therapy anywhere**
- **FT516**: Engineered with high-affinity, cleavage-resistant CD16 to enhance ADCC
  - Clinical trial started November 2019 (UMN), soon to open here.
  - Multi-dose administration to augment monoclonal antibody therapy
- **FT596**: Engineered with anti-CD19 chimeric antigen receptor and IL15RF
  - IND Approved
  - Multi-dose administration for treatment of B-cell malignancies

UC San Diego

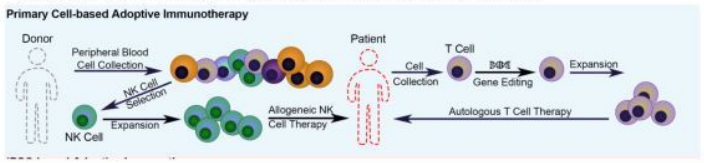
University of Minnesota

iPSC-derived NK cells now in clinical trials (FT500) with Fate Therapeutics

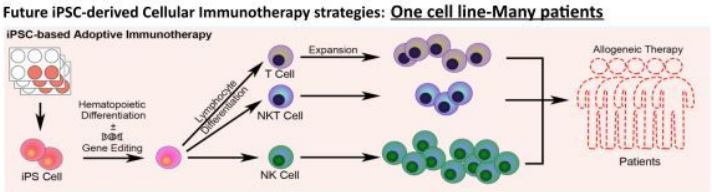
UCSD Moores Cancer Center
February, 2019

Current and Future Cellular Immunotherapy Strategies

Current Cellular Immunotherapy strategies: One donor-One patient

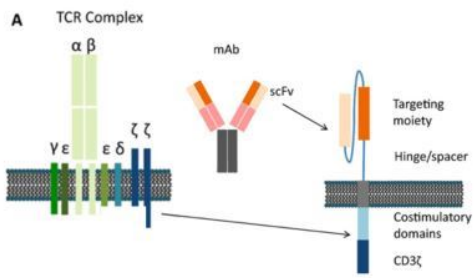


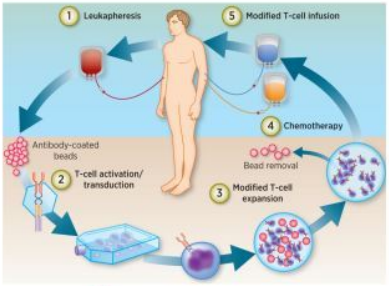
Future iPSC-derived Cellular Immunotherapy strategies: One cell line-Many patients



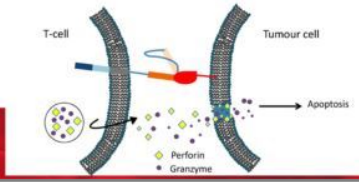
Zhu, et al. *Stem Cells* 2018

CAR modification enables re-direction of T cell effector function





- T cells have robust anti-tumour activity
- requires recognition of peptide-MHC complex
- cancers develop mechanisms to evade T cells



Whilding et al. *Biochem Society Trans*, 2016.
Maus et al. *Clin Cancer Res*, 2016.

CAR T-cell toxicities

- B-cell depletion (normal B cells are targeted as well)
  - Appears to be well tolerated in patients with no long term effects
- CAR T-cell specific toxicities
  - Cytokine Release Syndrome (CRS)
  - Immune-effector Cell Associated Neurotoxicity Syndrome (ICANS)
  - Treatment with tocilizumab (anti-IL6R antibody) +/- steroids
    - Reversible in the majority of cases

CRS spectrum

Fever
Flu-like symptoms
↓
Low Blood Pressure
↓
Shock/Organ failure

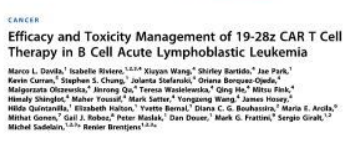
High remission rates achieved by CD19 CAR-T cells in B-cell ALL

Measurable residual disease-negative complete remission (MRD-negative CR) rates of 70-85% are achievable with CD19 CAR-T cells

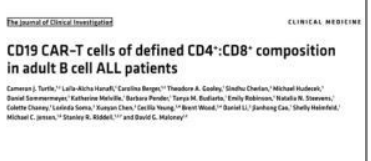
T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial


ORIGINAL ARTICLE

Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia


CANCER

Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia


The Journal of Clinical Investigation

CD19 CAR–T cells of defined CD4+:CD8+ composition in adult B cell ALL patients

Factors associated with long remissions (disease-free survival, DFS) are relatively unknown

Conclusions

- The era of cancer immunotherapy is here
- Anti-PD1/PDL1 now has an established role in multiple cancers
  - Checkpoint blockade and other immune modulators are being tested in every cancer
- Immunotherapy can potentially cure patients even with metastatic disease

Conclusions

- Next BIG questions:
  - How to treat PD1/PDL1 refractory patients?
  - What biomarkers better define benefit?
  - How to impove IO?
  - How to extend cellular therapy to solid tumors?
  - How to integrate vaccines?