Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

What's Next for Cancer Immunotherapy?

Breelyn A. Wilky, MD

Associate Professor, Director of Sarcoma Translational Research

University of Colorado Anschutz Medical Campus

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Disclosures

- Research Funding: Merck, Pfizer, Agenus
- Other Consulting: Agenus, Lilly, Janssen, Novartis
- I will be discussing non-FDA approved indications during my presentation.

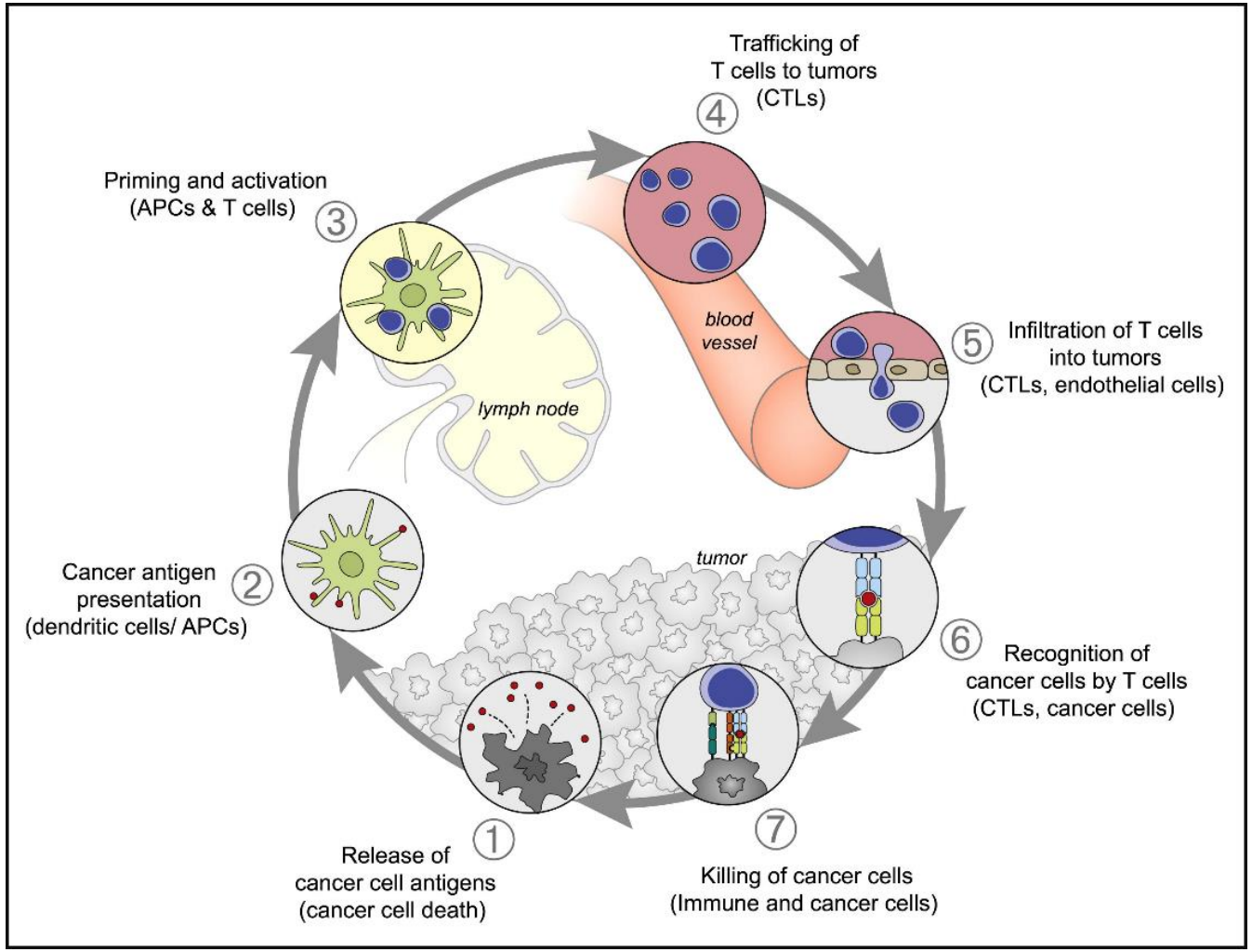
Overview – The Future of Immunotherapy

- Frontier #1 – Better Biomarkers!
- Frontier #2 – Better Preclinical Testing!
- Frontier #3 – Novel Targets and Novel Combinations

Precision Immunotherapy as the Ultimate Goal

Where we've been today …

Promote immature, suppressive DCs and macrophages



Produce suppressive cytokines that prevent migration and infiltration

Loss of neoantigens

Express checkpoint proteins

Chen & Mellman, Immunity, 2013

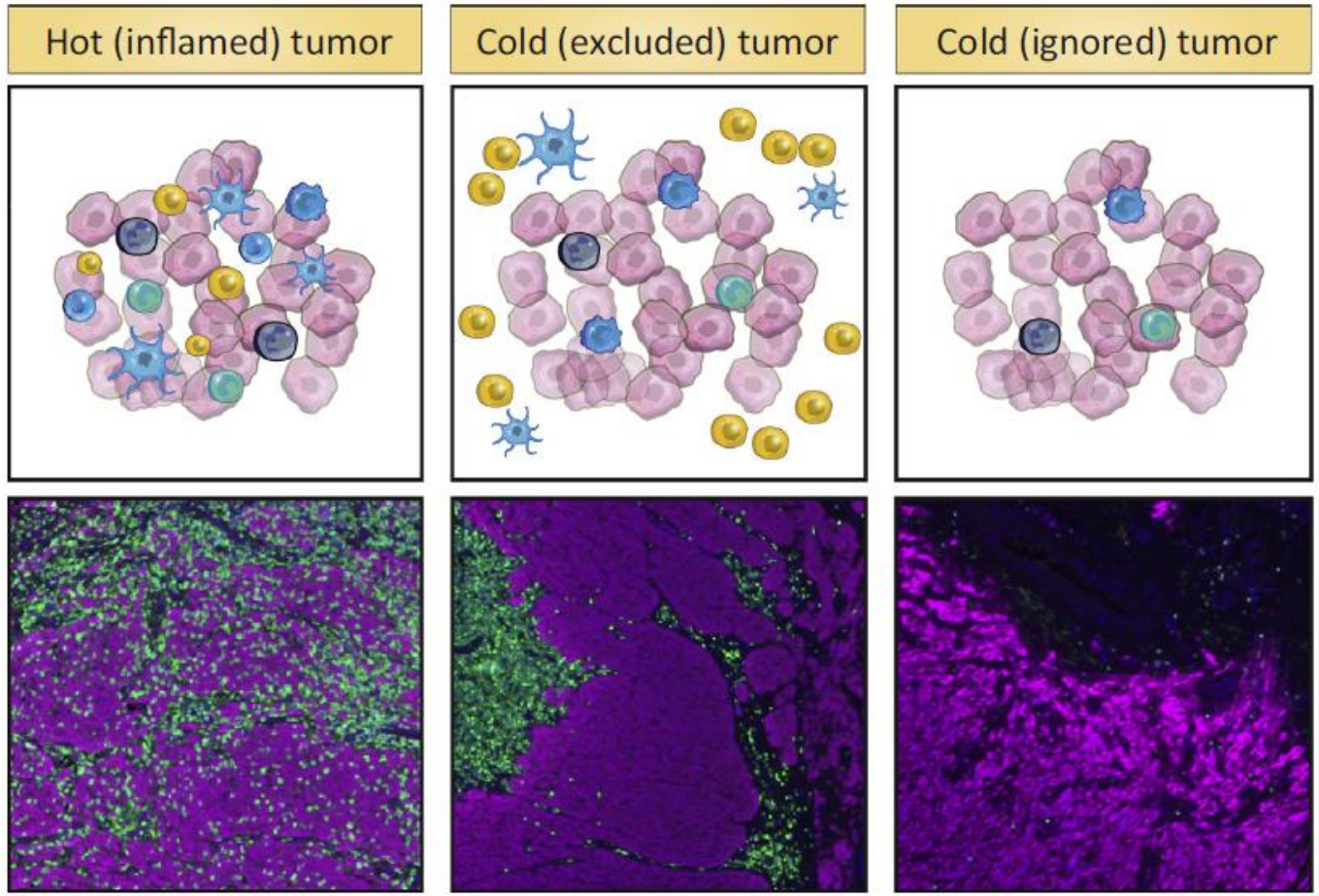
Strategies for Immunotherapy

	Target	Therapeutic Strategies
	Tumor-specific antigens that can be recognized by the immune system	Vaccines, Chemotherapy/Radiation, Oncolytic Viruses, Epigenetic Agents, Microbiome
	Effective antigen presentation/recognition	Macrophage/DC Polarizing Agents, Oncolytic Viruses, Innate Immunity Enhancers
	Antigen-specific T cell production	Adoptive T Cell Therapy, Autologous TIL engineering, selection and expansion
	Improve T cell migration into the tumors	Microenvironment (TKI & Cytokine Inhibitors/Inducers, Chemotherapy, Radiation, Oncolytic Viruses), CTLA-4, Dual Checkpoint/TGF-β traps
	T cells are activated rather than suppressed	Stimulatory Agonists, Engineered T cells, Metabolic Therapies, Microbiome, Bispecific Antibodies
	Counteract immunosuppression	Checkpoint inhibitors, anti-T-regulatory cells, Dual Immunomodulators

Adapted from Jedd Wolchok and others
Wilky & Goldberg, Discov Med, 2017

Understanding Hot and Cold Tumors

- HOT (inflamed) – active immune response but suppressed.
- COLD – (excluded). Immune response is limited by microenvironmental factors
- COLD – (ignored or desert). No recognition of the tumor as foreign by immune system.



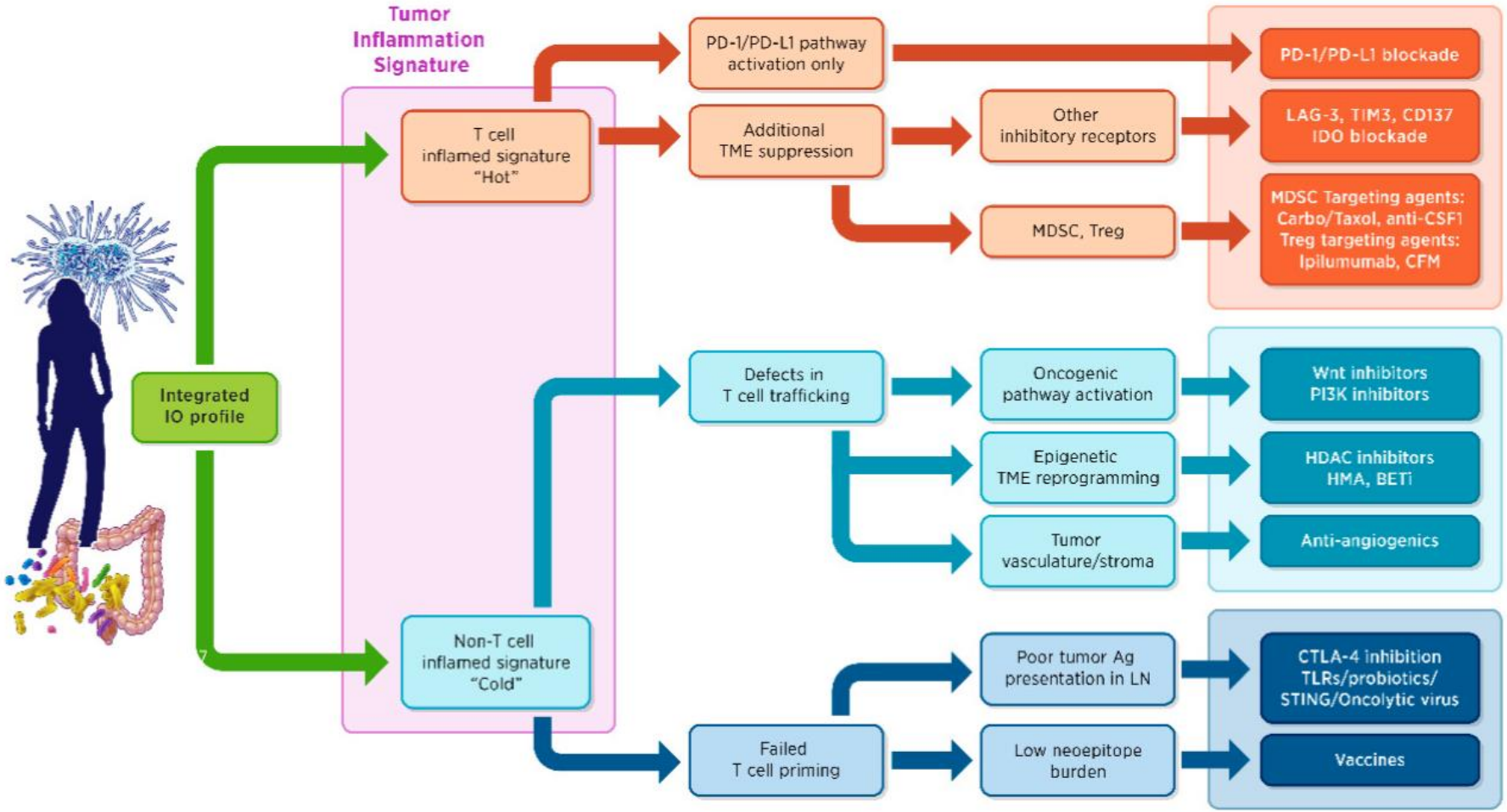
Van der Woode et al, Trends Cancer 2017

Biomarkers of Response/Resistance to Checkpoint Inhibitors

Response	Resistance	Future Directions
High tumor mutational burden	Lack of T cell infiltration	Refining PD-L1 antibody precision
Checkpoint protein expression (PD-L1)	High quantities of T-regs, TAMs, MDSCs	Biomarkers for CTLA-4 response
High quantities of infiltrating CD8+ T cells	Expression of alternative checkpoint proteins	Neoantigen signatures superior to TMB in some tumors
Low circulating neutrophil:lymphocyte ratio	High stromal burden (cancer-associated fibroblasts)	Implementing new technologies to assess immune microenvironment
Higher diversity of gut microbiomes	High suppressive cytokines (VEGF, cofactors, IL-6, TGF-β)	Statistical models to incorporate multiple biomarkers
High expression of immune-related genes (Tumor Inflammation immunosignature)	Genetic mutations (JAK 1/2, PTEN loss, β-catenin/Wnt signaling)	

Sharma et al, Cell 2017
Jenkins et al, Annu Rev Med 2018

Frontier #1 – Improving Biomarkers



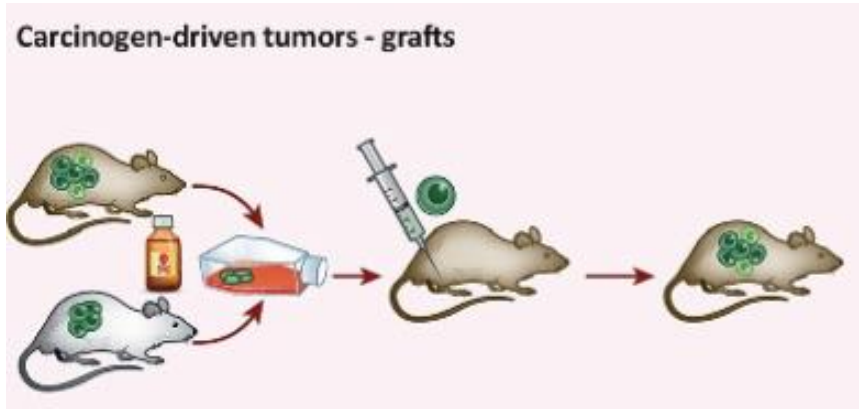
Metabolic reprogramming

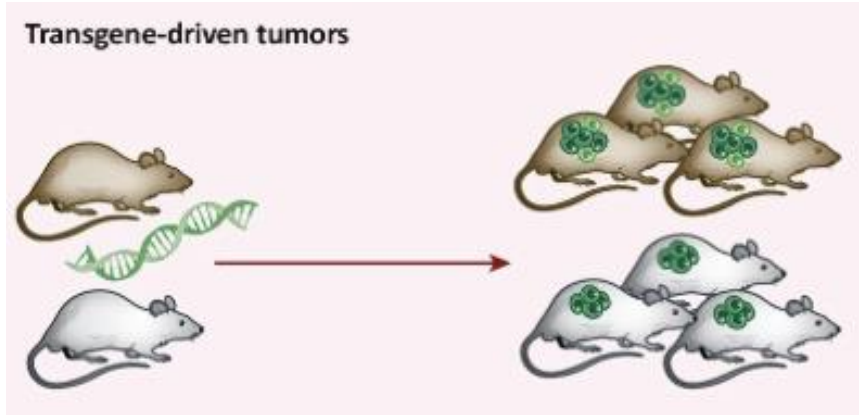
Cesano and Warren, Biomedicines 2018

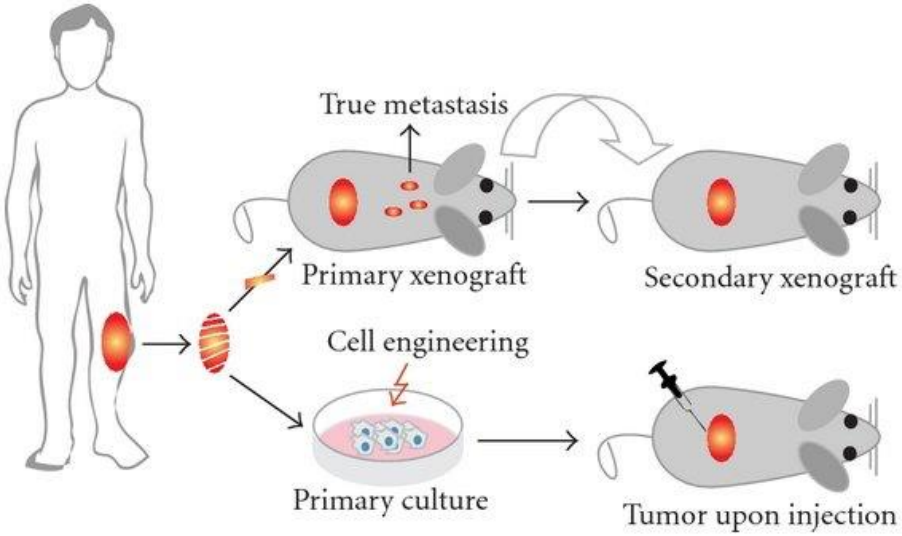
Preclinical models for cancer drug development

Syngeneic/Transgenic mouse models

Mouse immune system and tumors – need mouse-specific antibodies







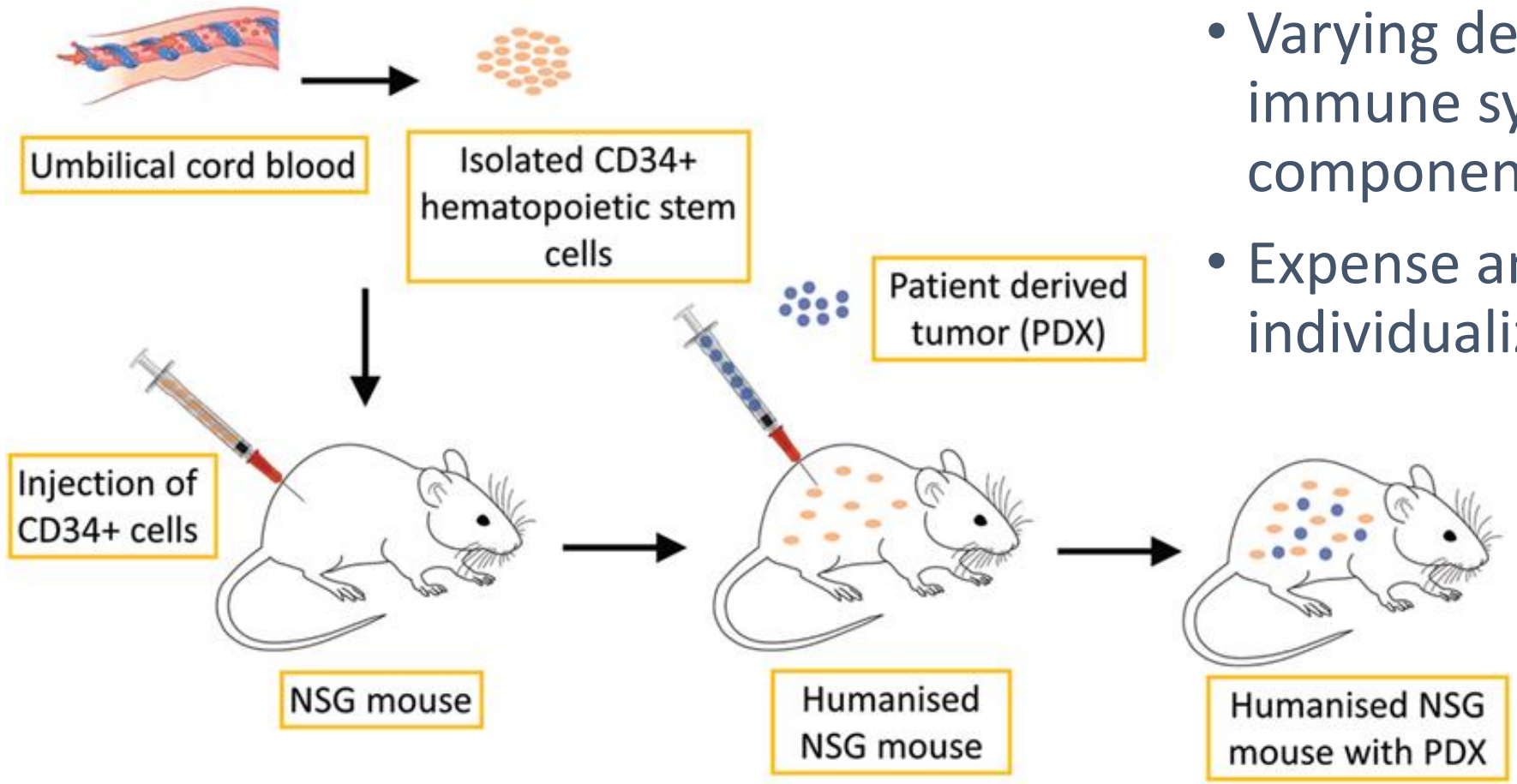
Human cancer xenografts

Requires mice lacking T cells, B cells and NK cells

Human tumors rejected as foreign by mouse immune systems

Buque et al, Trends Cancer 2018

Humanized mouse models for immunotherapy

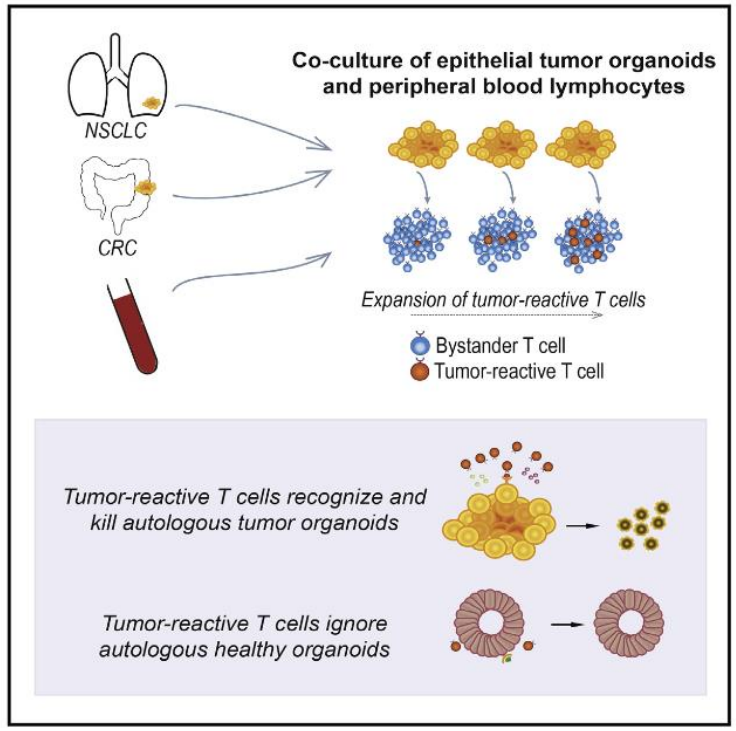


Limitations

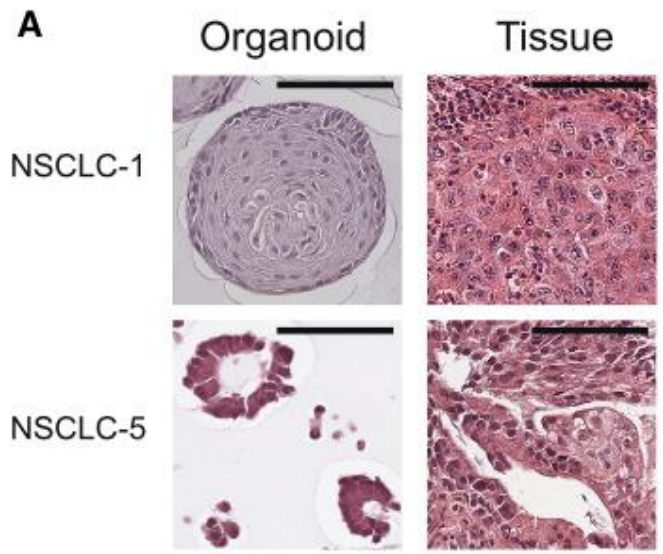
- Varying degrees of human immune system reconstitution/ components (chimeras)
- Expense and time to create individualized models

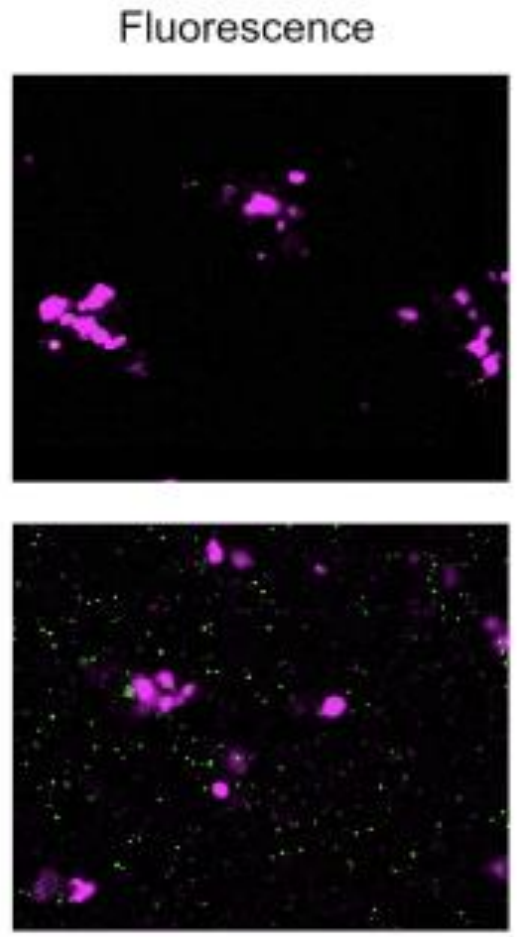
Tratar et al, Front Oncol 2018

Organoids with T cells for immunotherapy



- Organoids from patient tumors co-cultured with peripheral blood lymphocytes
- Can stimulate expansion of tumor-specific T cells that kill tumor cells.



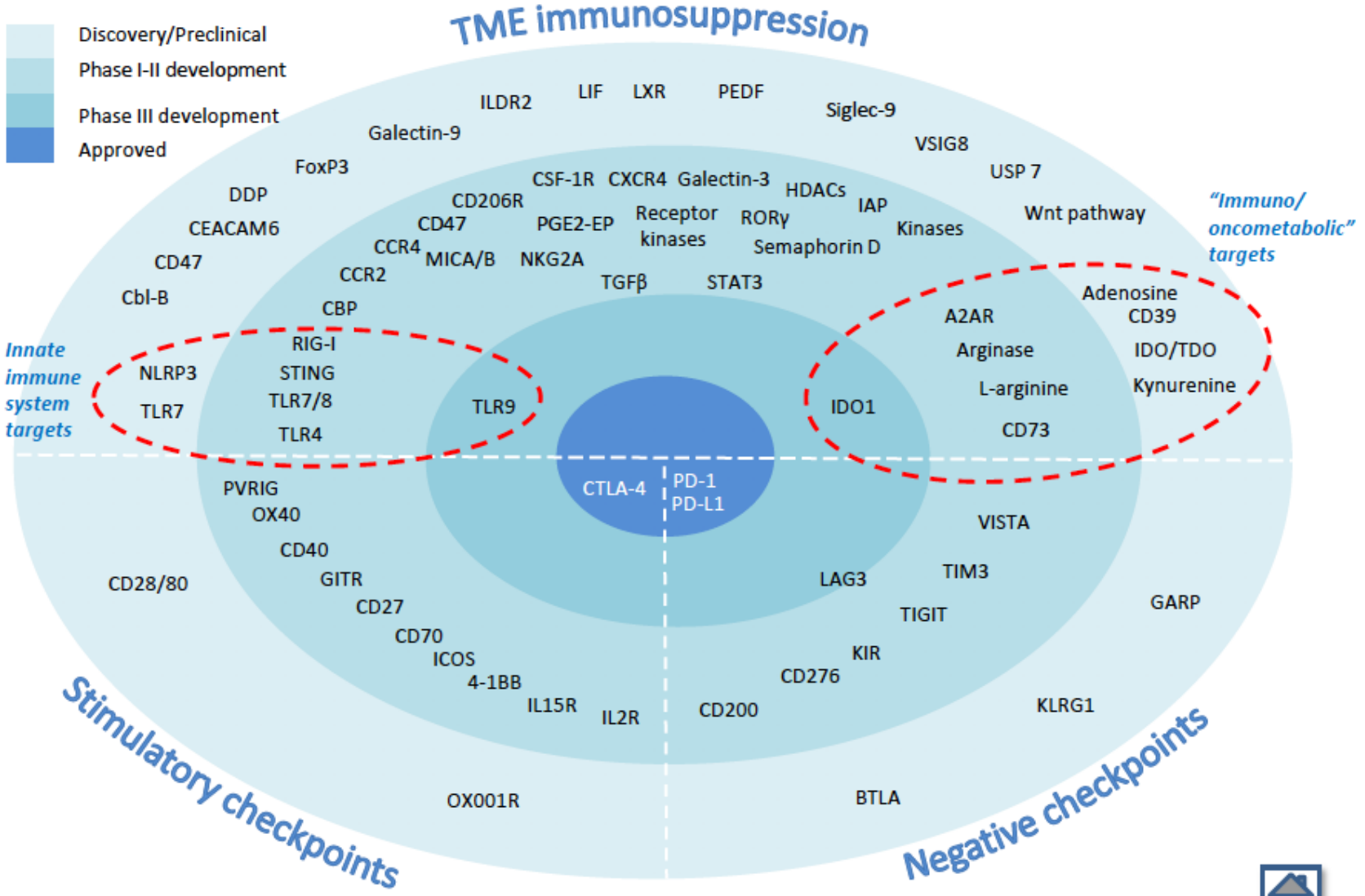


Dijkstra et al, Cell 2018

Frontier #2 – Improving Preclinical Testing of Immunotherapy

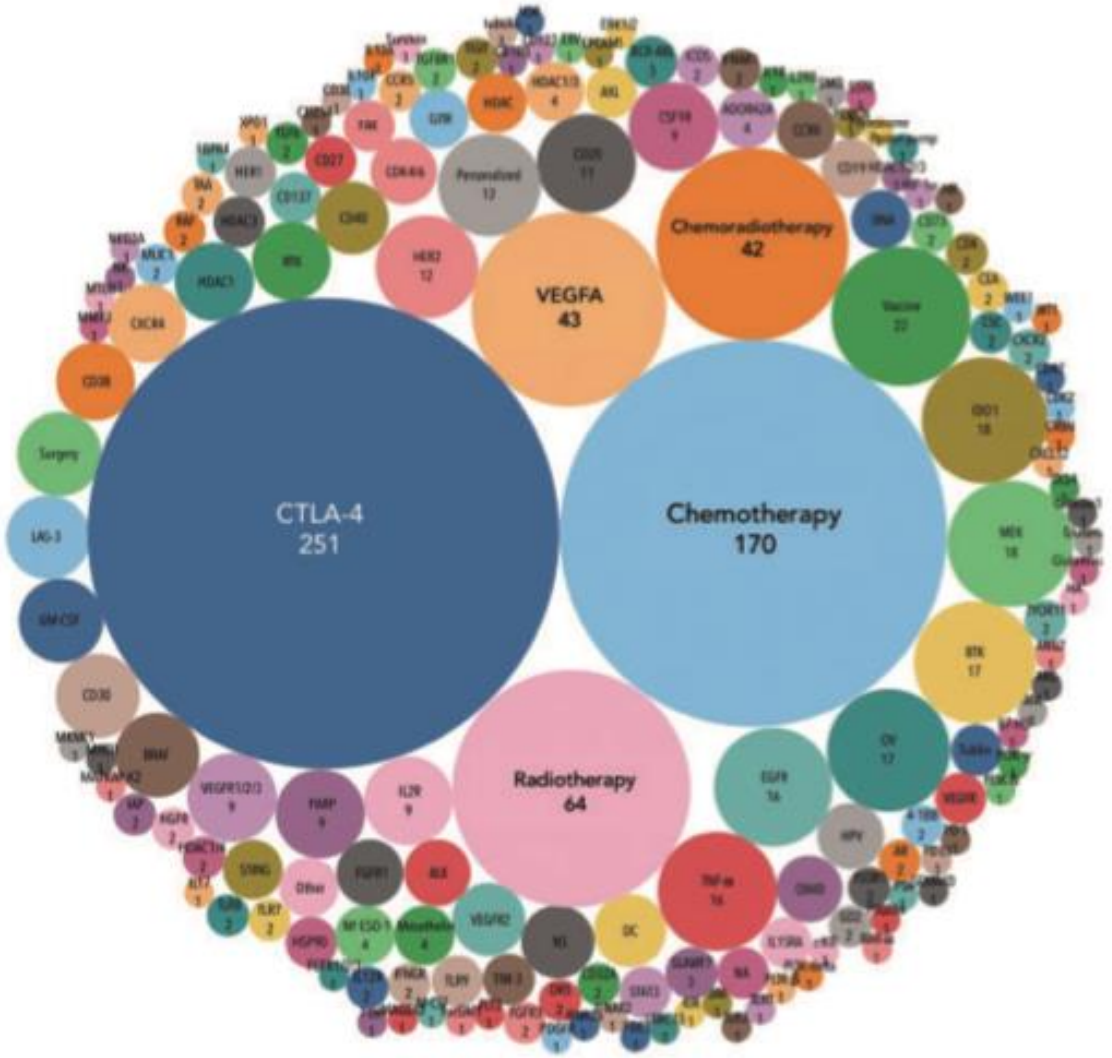
- Enormous funding invested in immuno-oncology drug development
- High costs of therapies, particularly adoptive cellular therapies
- Improved preclinical methods may increase yield of clinical trials
- We need to understand mechanisms and biomarkers for optimal trial design and patient selection
- Prior limitations to study of immune system in preclinical setting are being overcome

The next wave IO drug development target landscape



https://www.researchgate.net/publication/321680036, May 2018

The Age of Immunotherapy Combinations



- Combinations target more than one step in the immune evasion cascade with checkpoint inhibitors as the backbone
- Target Neoantigen + Microenvironment + T-cell activation
- Bypass with adoptive cellular therapies but issues with toxicity, persistence particularly in solid tumors

Tang et al, Annals Oncol, 2018

Designing Therapies with Broader Impact

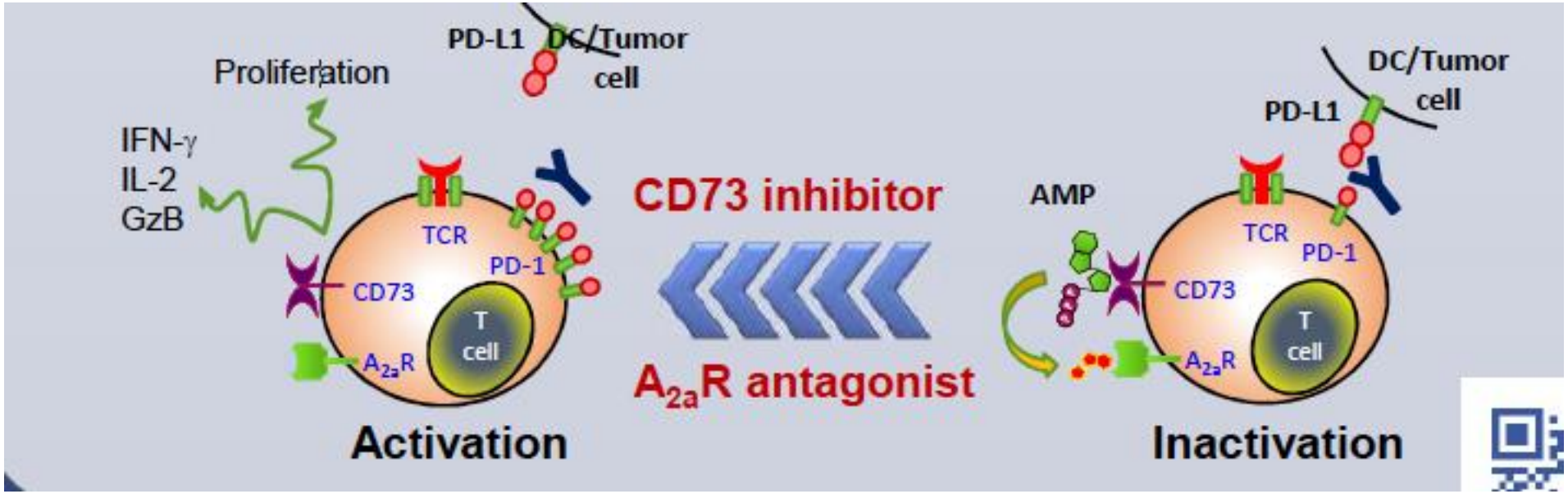
Adenosine Inhibition + PD-L1

ATP → AMP (CD39, **CD73**) → Adenosine →

Hypoxia
Inflammation
TGF-β
Genetic drivers

- Immune suppression of T cells, DCs, and NKs through activation of **$A_{2a}R$** and $A_{2b}R$ even in presence of anti-PD-L1 blockade
- Increased tumor angiogenesis, proliferation, progression

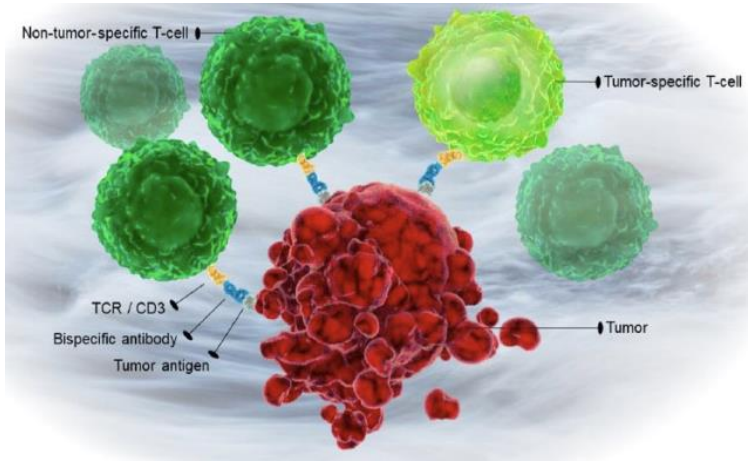
↑ CD73 expression in many solid tumors

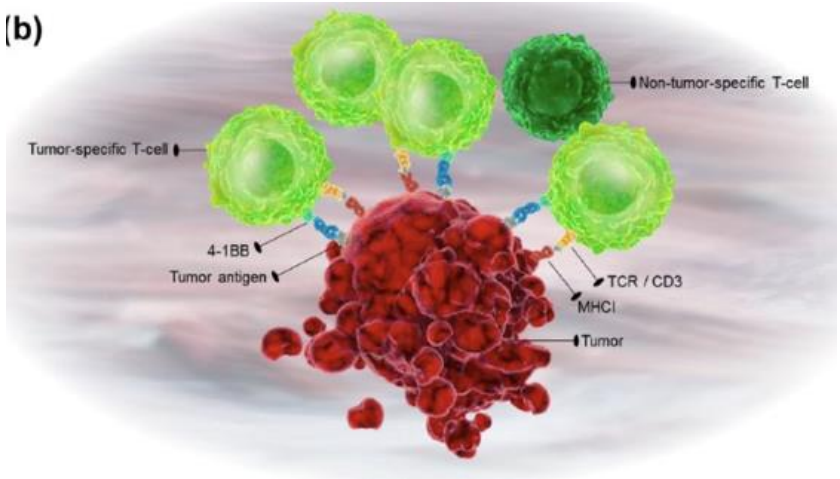


Tan et al, SITC 2017, Poster 494

Designing Dynamic Duos

- **Bispecific Antibodies**





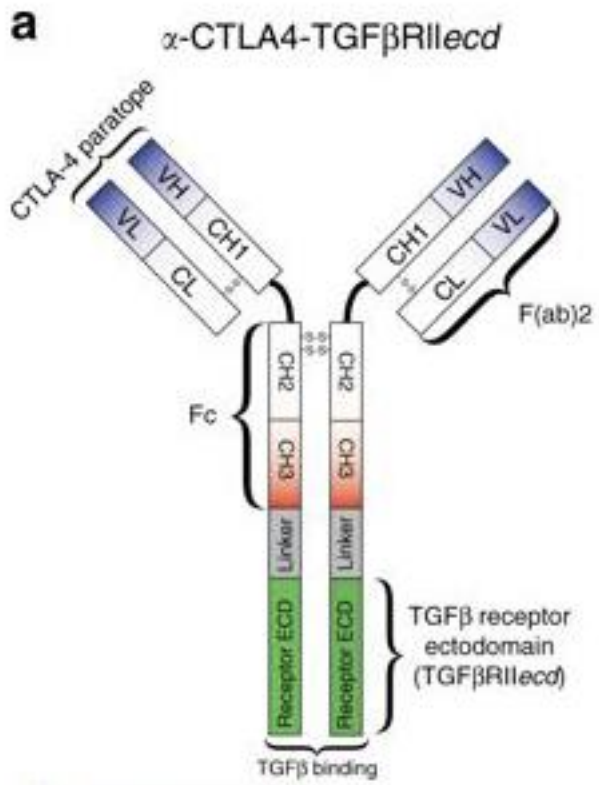


Table 1

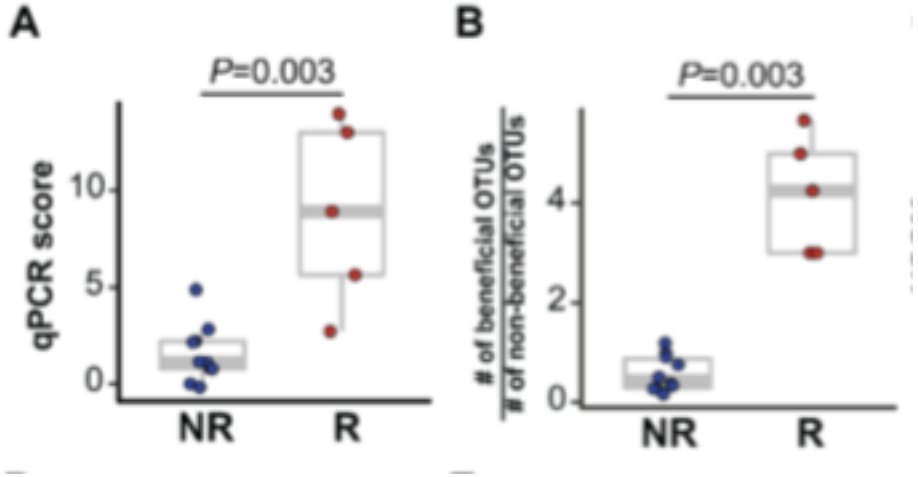
Clinical trials of bispecific antibodies

Name	Target	Disease	Trial	Developer
BiTE (bispecific T-cell engager): T-cell retargeting				
Blinatumomab, AMG103, MT103	CD19 + CD3	Acute lymphoblastic leukemia	Approved[53]	Amgen
Solitomab, AMG110, MT110	EpCAM + CD3	Lung, gastric, colorectal, breast, prostate, and ovarian cancer	Phase I (completed)[53]	Amgen
AMG111, MT111, MEDI565	CEA + CD3	Gastrointestinal adenocarcinomas	Phase I (completed)[53]	Amgen
Pasotuxizumab, AMG112, MT112	PSMA + CD3	Prostate cancer	Phase I[13]	Bayer
AMG330	CD33 + CD3	Acute myeloid leukemia	Phase I[51]	Amgen
AMG420, BI836909	BCMA + CD3	Multiple myeloma	Phase I[6]	Amgen, Boehringer Ingelheim
Quadroma, Triomab: T-cell recruitment				
Catumaxomab	EpCAM + CD3	Malignant ascites	Approved[51]	Fresenius, Trion
Ertumaxomab	HER2 + CD3	Breast cancer	Phase II[2]	Fresenius
FBTA05	CD20 + CD3	B-cell lymphoma	Phase I/II[13]	Fresenius
DART (dual-affinity retargeting): retargeting of T cells to tumors				
PF06671008	P-cadherin + CD3	Solid tumors	Phase I[6]	MacroGenics, Pfizer

Dahlen et al, Ther Adv Vaccines Immunother 2018
Ravi et al, Nature Comm 2018

Enhancing global immune stimulation by targeting the gut microbiome

- Induction of T cell responses against microbial antigens, ? Cross-reactivity against tumor-specific antigens
- Engage pattern recognition receptors that mediate pro-immune or anti-inflammatory effects
- Generating small metabolites with systemic effects

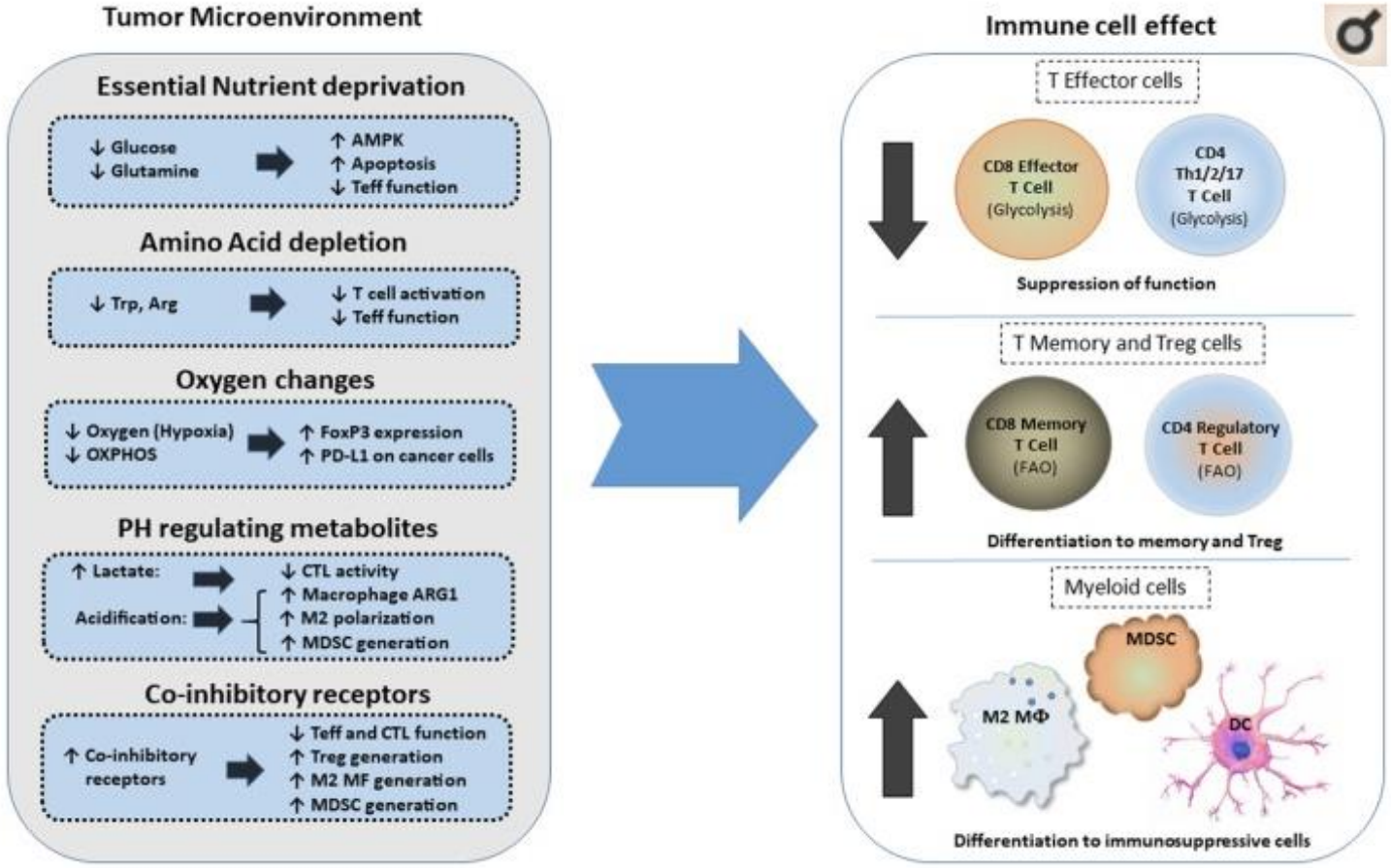


- Fecal microbiota transplants?
- Avoiding antibiotic therapy during immune checkpoint blockade
- Selecting beneficial probiotics?

Zitvogel et al, Science 2018
Matson et al, Science 2018

Targeting T cell Metabolism

- Cancer microenvironment suppresses T cell metabolism, limiting efficacy
  - Hypoxic TMA
  - Preferential glycolysis -> lactate accumulation (Warburg effect)
  - Nutrient deprivation from high metabolic rate in cancer and poor vasculature
  - ARG1 and IDO induced amino acid deprivation



Le Bourgeois et al, Front Oncol 2018

Targeting T cell Metabolism

COMPARTMENT	THERAPY	METABOLISM IMPACT	RELATED IMMUNE IMPACT
Cancer Cells and T cells	Targeting lactate transporters	Reduce lactate in tumor cells	Increase T cell activation and cytotoxic activity
	HIF1 activation	Enhance glycolysis and glutaminolysis	Promote T cell effector functions
T cells	PD-1-blocking antibodies	Increase T cell glycolysis	Reinvigorate T cell function
	Use of IL-2 during ATI process		Maintain proliferative ability and effector functions
	AMPK inhibitors	Decrease FA metabolism	Promote Th1 and Th17 differentiation
	mTOR inhibitors	Decrease glycolysis	Promote T memory cell differentiation
	Compounds promoting FA catabolism	Generate fuel for exhausted T cells	Increase longevity and function of exhausted T cells
	Compounds promoting ROS production	Activate T cell transcription factors	Increase function of T effector cells
	Use of IL-15 or IL-7 during ATI process	Promote mitochondrial metabolism	Increase T memory cells differentiation and longevity *in vivo*
TME	AMPK activation (e.g Metformin)	Increase cellular FA metabolism	Increase $CD8^+$ T cell recruitment and memory differentiation

- Potential synergy with checkpoint blockade, chemotherapies, targeted therapies
- May improve persistence of adoptive cellular therapies

Le Bourgeois et al, Front Oncol 2018

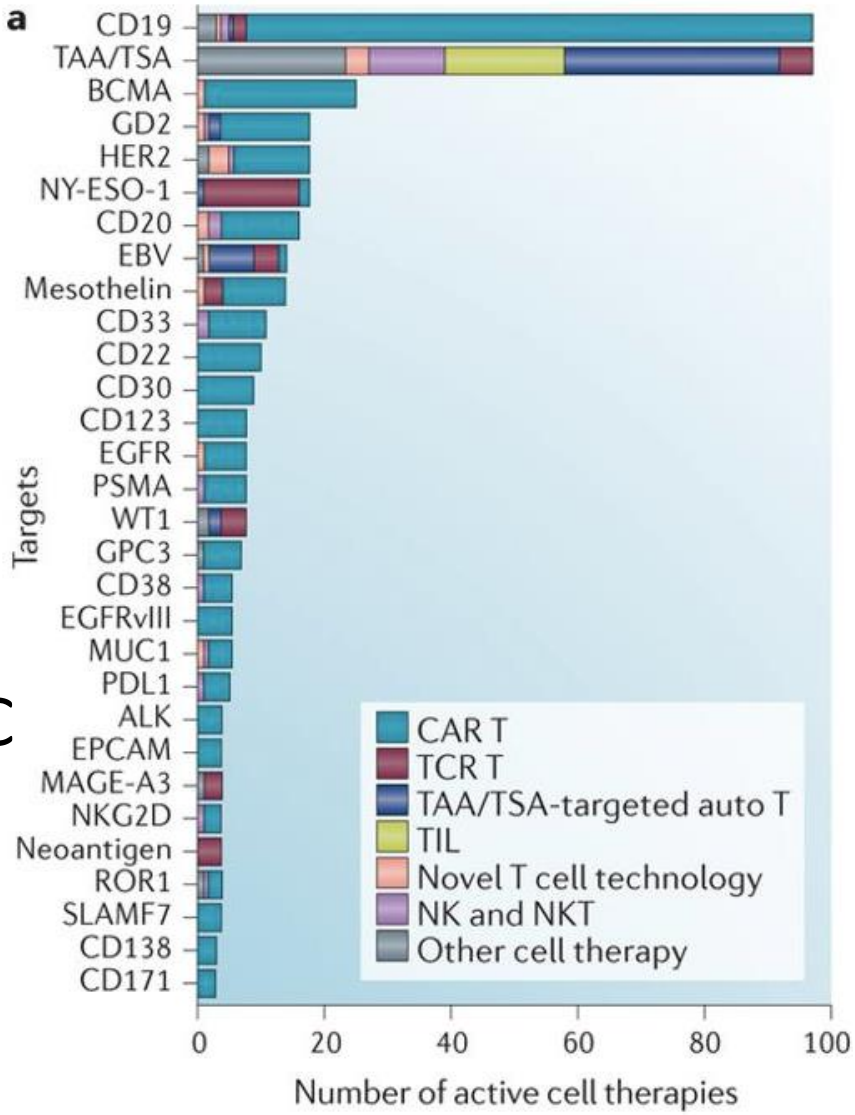
The race forward in adoptive cellular therapies

344 cellular therapies in development in the US, 203 in China

- CAR-T
- Engineered TCR
- Autologous circulating T cells targeting TAA/TSA
- Autologous TIL
- Engineered T cells (CRISPR, γδ T cells)
- NK directed therapies
- Other (macrophages/stem cells)

Next-gen CAR-T strategies

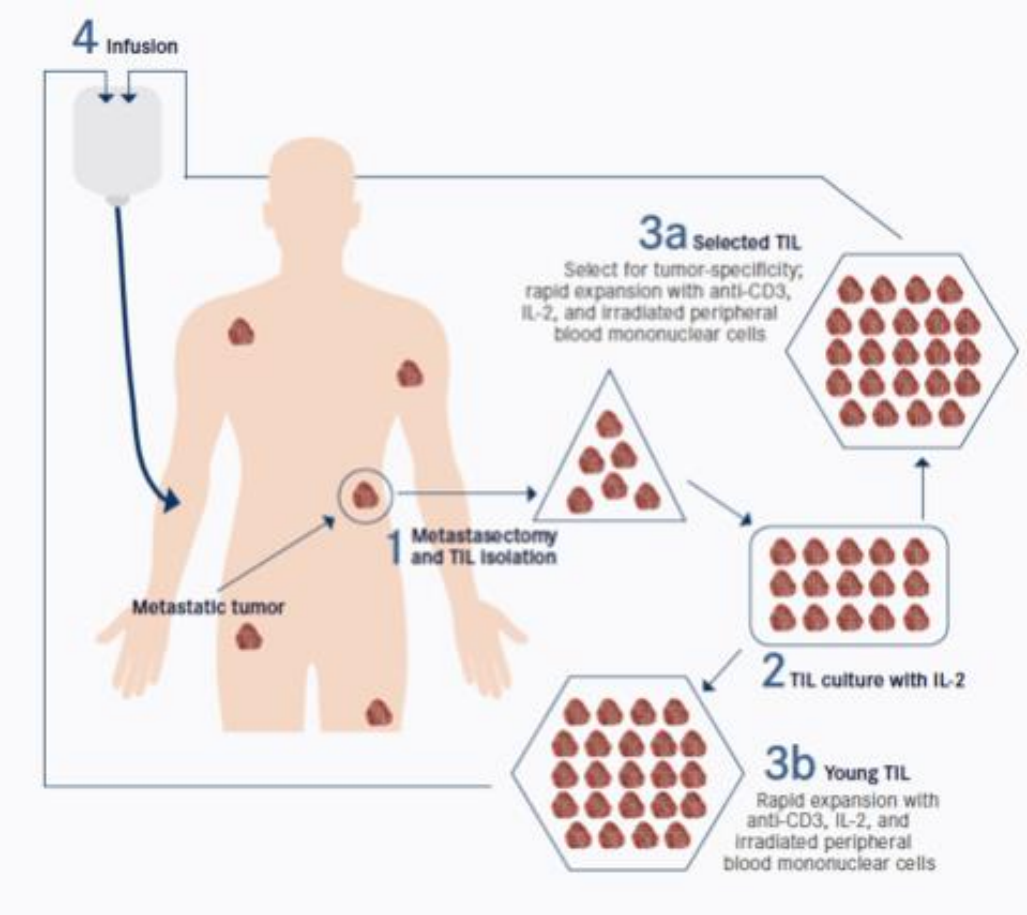
- Bispecific CAR-T (CD19/CD20, CD19/CD22, CD19/BCMA)
- Universal CAR-T (no MHC restriction)
- Suicide switches (apoptosis in CARs in setting of self-reactivity)



Le Bourgeois et al, Front Oncol 2018
June et al Science 2018

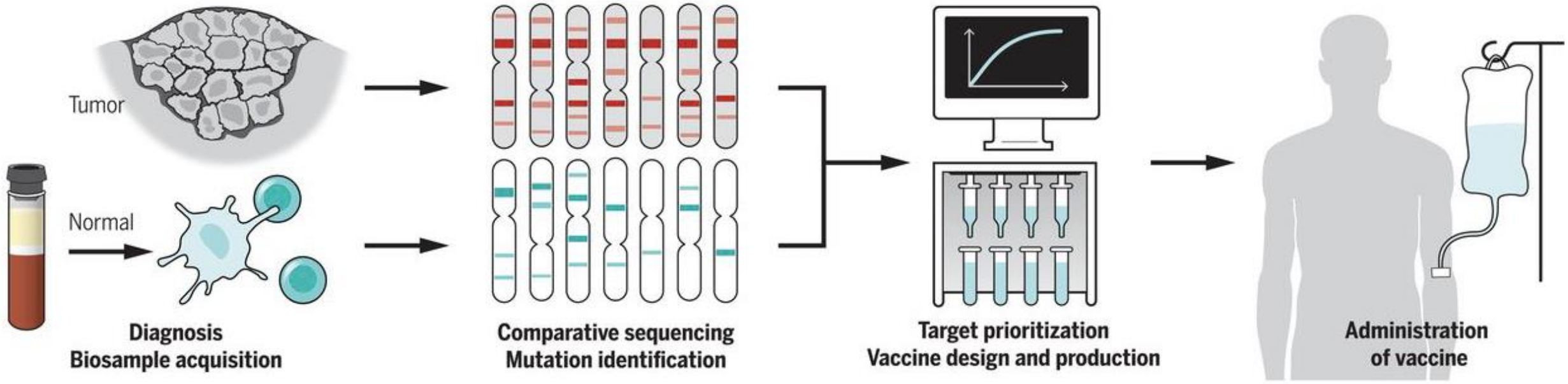
Autologous TIL therapy

- Strategies
  - Selecting tumor-specific antigen clones for expansion (Rosenberg)
- Combination with checkpoint blockade and oncolytic viruses
- Ongoing clinical trials in numerous solid tumors
- Technologies likely to impact include more rapid TCR sequencing and antigen prediction algorithms



Antigen Prediction and Customized Vaccines

- Combinations with checkpoint blockade
- Trials exploring adjuvant and metastatic settings
- Affordability and time to manufacture



Sahin et al, Science 2018

Frontier #3: Multiparameter engineering of the Immune System

- Hundreds of novel drug, targets and technologies – how do we rationally prioritize?
- One size does not fit all for solid tumors
- Engineered TIL may ultimately be more effective strategy for solid tumors than CAR-T, difficulty with targets with manageable therapeutic index with normal tissue
- Metabolism will likely play a key role in the next wave of immune modulatory therapy

The Future: Precision Immunotherapy?

Immunobiomarkers

- Genetic mutational burden
- Neoantigen signature
- IHC for MSI
- PD-L1 expression
- Immunosignature
- Hot vs. Cold tumors
- Gut microbiome
- Antigen Prediction
- TCR sequencing/clonality
- Multiparameter microenvironment
- Avatars and organoids

Induction

Chemotherapy

+

Radiation

+

Targeted therapy (including BITEs, ADC)

+

Surgery

+

Immunomodulator(s)

Consolidation

Engineered TCR/ CAR-T cells

or

Autologous engineered TILs

or

Customized Vaccine

and/or

Checkpoint Inhibitor maintenance

Thank you and Questions!

Breelyn Wilky, MD

University of Colorado Anschutz Medical Campus

Email: breelyn.wilky@ucdenver.edu