Personalized Cancer Vaccines

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Neoantigens & Cancer Immunotherapy

Hammer Lab @ Mount Sinai

- Backgrounds in math, compsci, ML, compbio
- Focus: *cancer immunotherapy*
  - Cancer genomics
  - Machine learning for immunology
  - Clinical trial analysis
- github.com/hammerlab

Icahn School of Medicine at Mount Sinai

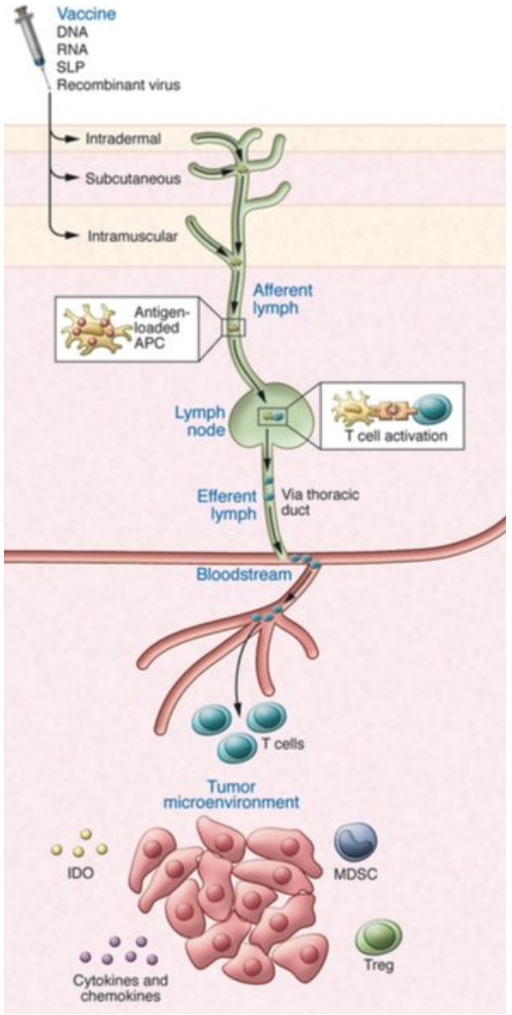
PARKER INSTITUTE for CANCER IMMUNOTHERAPY

Flavors of Cancer Immunotherapy

Checkpoint blockade	Cellular therapies	Vaccines
Disinhibit CD8+ T-cells, antigens responsible for tumor clearance unknown. <u>Success stories:</u> • αCTLA-4 (ipi) • αPD-1 (pembro, nivo) • αPD-L1 (atezo)	Ex-vivo expansion of patient T-cells after receptor engineering and/or selection. <u>Success stories:</u> • CD19 CAR T-cells for B-cell malignancies	Therapeutic vaccines against tumor antigens. Significant interest in personalized “neo-antigen” vaccines. <u>Success stories:</u> • ???

Therapeutic Cancer Vaccines

- Cancer cells differ significantly from their tissue of origin (mutations, expression, dysregulation)
- Can the immune system detect these differences and selectively kill cancers without harming normal tissue?
- Many cancer vaccine trials, only 1 FDA approval



Therapeutic cancer vaccines, Melief, et al.

Complementary w/ Checkpoint Blockade?

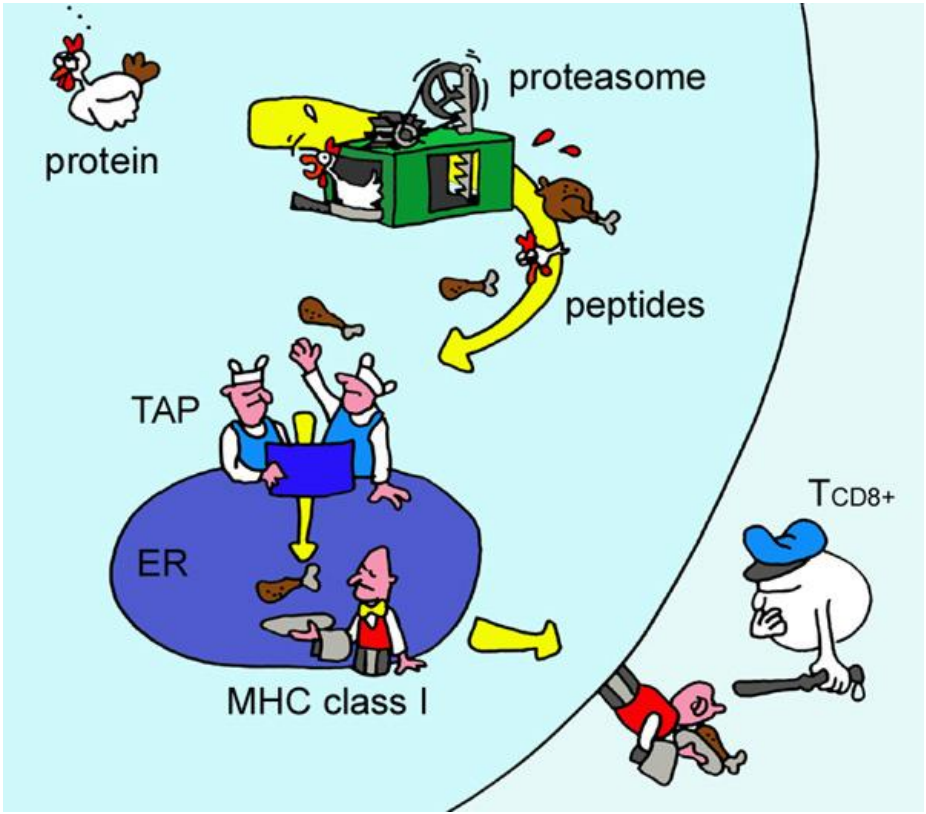
- Tumor specific T-cells inhibited?
  - Checkpoint blockade
- Insufficient tumor specific T-cells?
  - Cancer vaccination

Malignant tumors must have feeble antigenic power as well as sufficient resistance to the normal inhibiting influences *to provide continued growth in the animal in which they originate, otherwise reactions sufficient to destroy them would occur more frequently.*

Ernest Edward Tyzzer
"Tumor Immunity"
The Journal of Cancer Research, 1916

T-cell Vaccines & Antigen Processing 101

- Antigens presented by APCs to T-cells
- Innate activation required “danger signal”
- Protein fragments presented on Class I MHC to cytotoxic (CD8+) T-cells
- Repertoire of CD8+ T-cells undergoes thymic selection to limit self-reactivity



Morten Nielsen

What's In a Cancer Vaccine?

- Antigen
  - Tumor Lysate
  - Peptides
  - mRNA
  - DNA
  - Viral vector
  - Bacterial vector
- Adjuvant

Shared Tumor Antigens

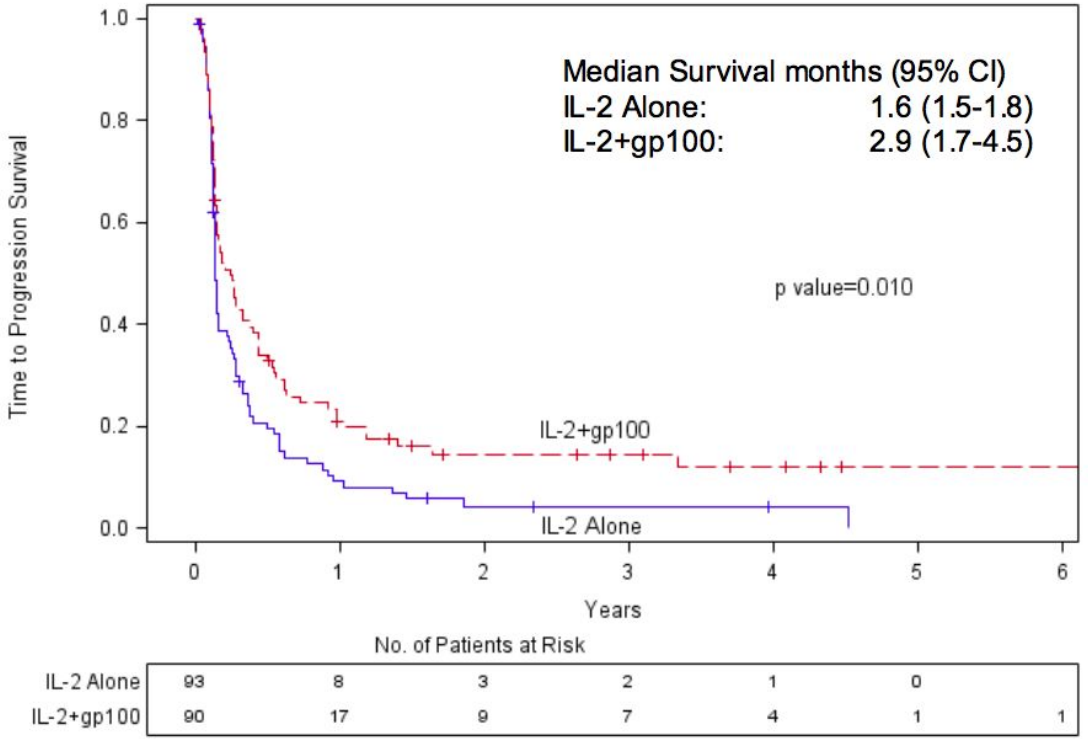
Shared Tumor Antigens

- Overexpressed and/or tissue-specific
  - Abundant on tumor cells but also present in some normal cells
  - Examples: Her2, Survivin, Telomerase, gp100

- Cancer/Testis Antigens
  - Expressed in testis and placenta
  - Thought to be excluded from tolerance
  - Examples: MAGE-A1, NY-ESO-1

Successful Shared Antigen Vaccine Trial

- Stage III or IV melanoma
- Patients with HLA-A2
- Treated with high dose IL-2
- +/- gp100 (209-217) peptide
  - Specific to melanocytes
  - Adjuvant: montanide



A Phase III Multi-institutional Randomized Study of. Immunization with gp100:209-217(210M) Peptide.Followed by High Dose IL-2 vs High Dose IL-2 Alone in Patients with Metastic Melanoma (2009)

A Less Successful Trial…

- MAGRIT: Phase III MAGE-A3 vaccine trial
- ~14k lung cancer patients screened
- ~4k had MAGE-A3 positive samples
- 2,272 patients enrolled
- Randomly assigned (2:1) to receive vaccine or placebo for 27 months
- No difference in Progression Free Survival

MAGRIT, a double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of the recMAGE-A3 + AS15

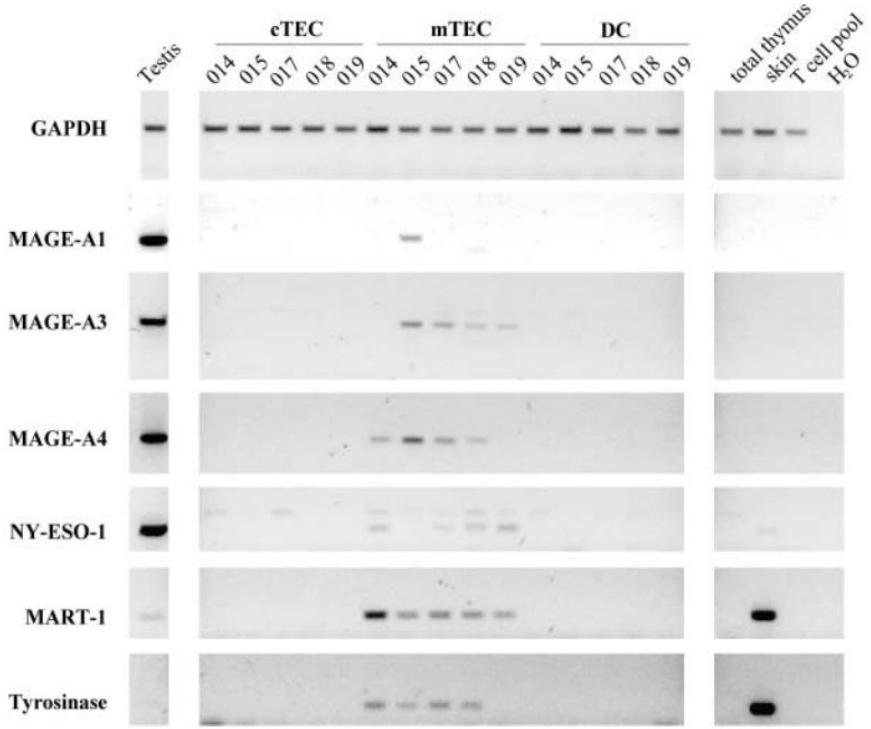
Shared Antigens Mostly Unsuccessful

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

Cancer/Testis Antigens Subject to Negative Selection

- Medullary thymic epithelial cells (mTECs) express commonly studied cancer/testis antigens
- Might explain failure of MAGE vaccine trials

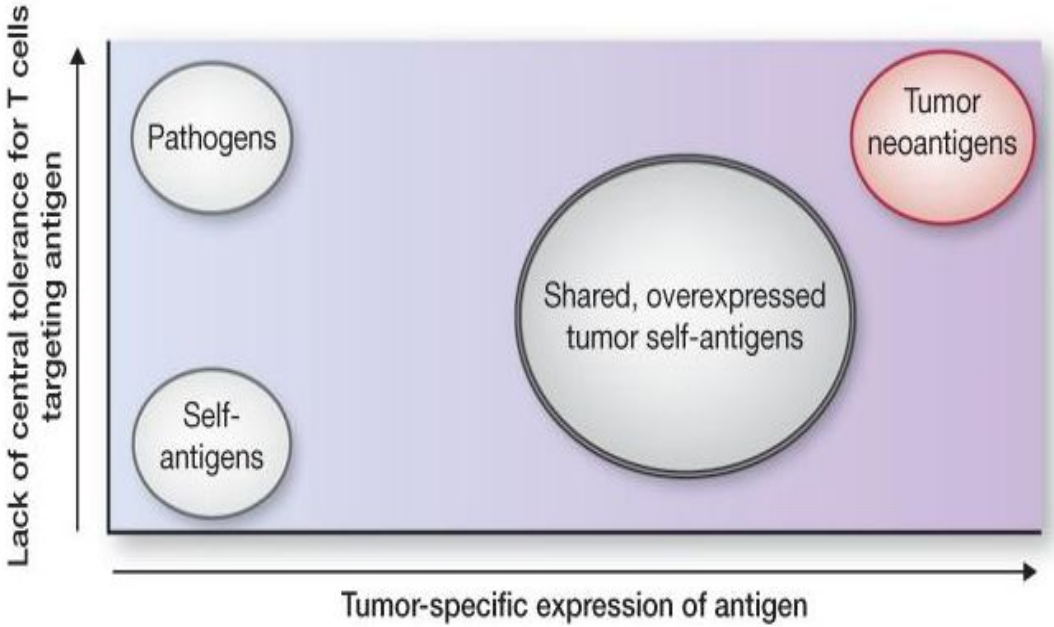


Medullary Epithelial Cells of the Human Thymus Express a Highly Diverse Selection of Tissue-specific Genes Colocalized in Chromosomal Clusters

Neoantigens

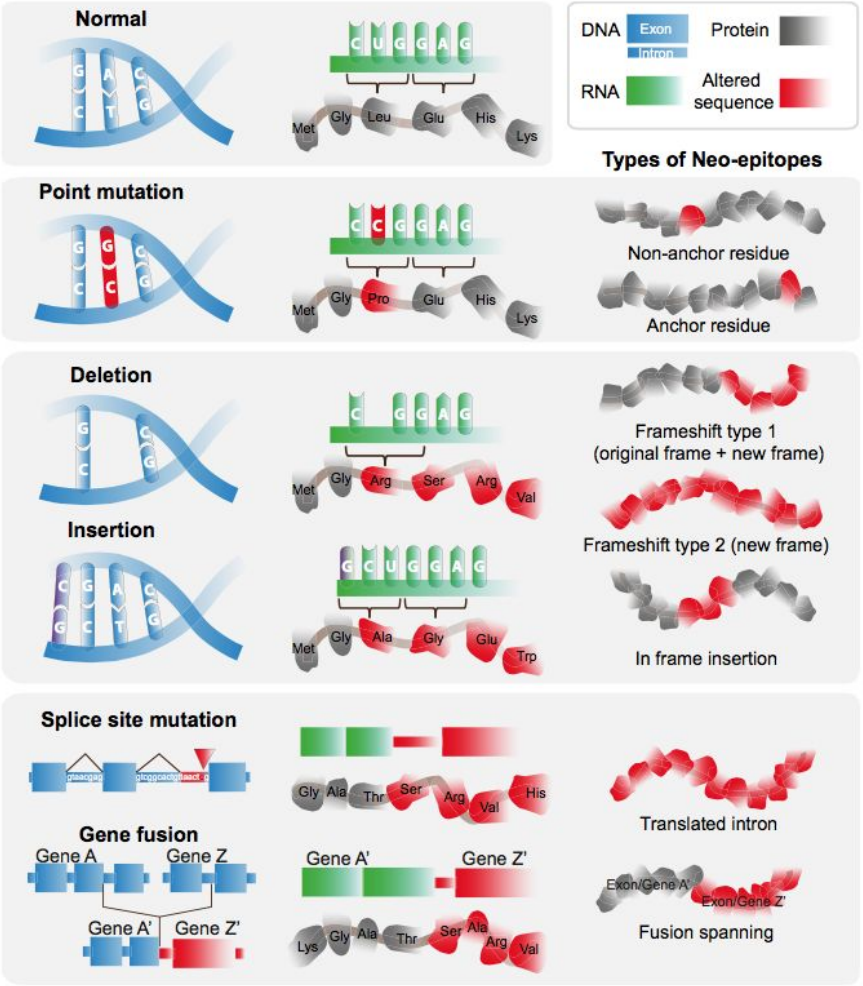
Tumor Specific Neoantigens

- No overlap with normal
  - mutations
  - abnormal splicing
  - abnormal post-translational modifications
- Unlikely to be shared between patients
- Requires personalization



Detecting Mutations That Change Proteins

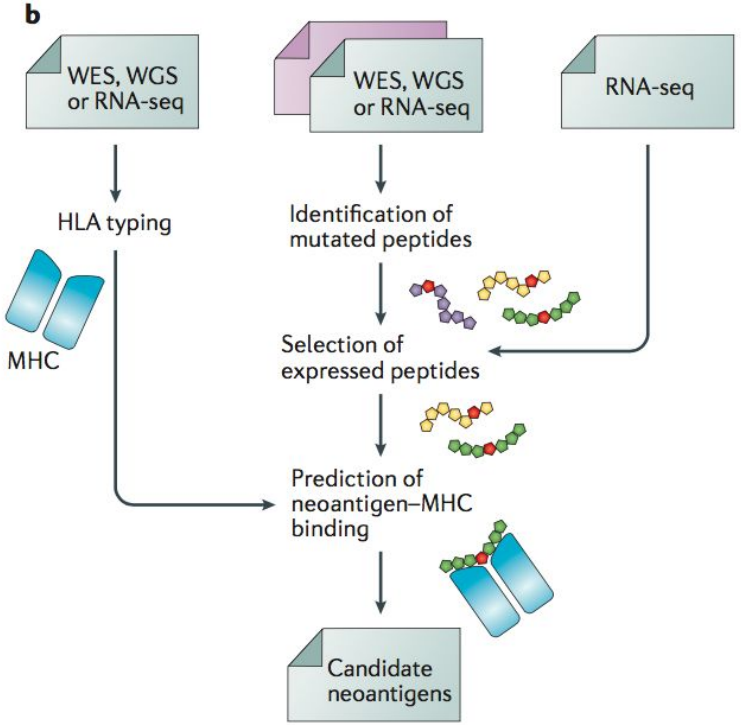
- Exome sequencing
  - SNVs
  - Small indels
  - Exonic splice sites
- Genome sequencing
  - Larger indels
  - Gene fusions
  - Intronic splice sites



Mutated neo-antigens as targets for individualized cancer immunotherapy, Mathias Vohrmer

Typical Neoantigen Pipeline

- DNA tumor + normal sequencing
  - Somatic variant calling
- Tumor RNA sequencing
  - Prioritize expressed variants
- Predict mutant proteins
- MHC binding prediction
  - NetMHC / NetMHCpan

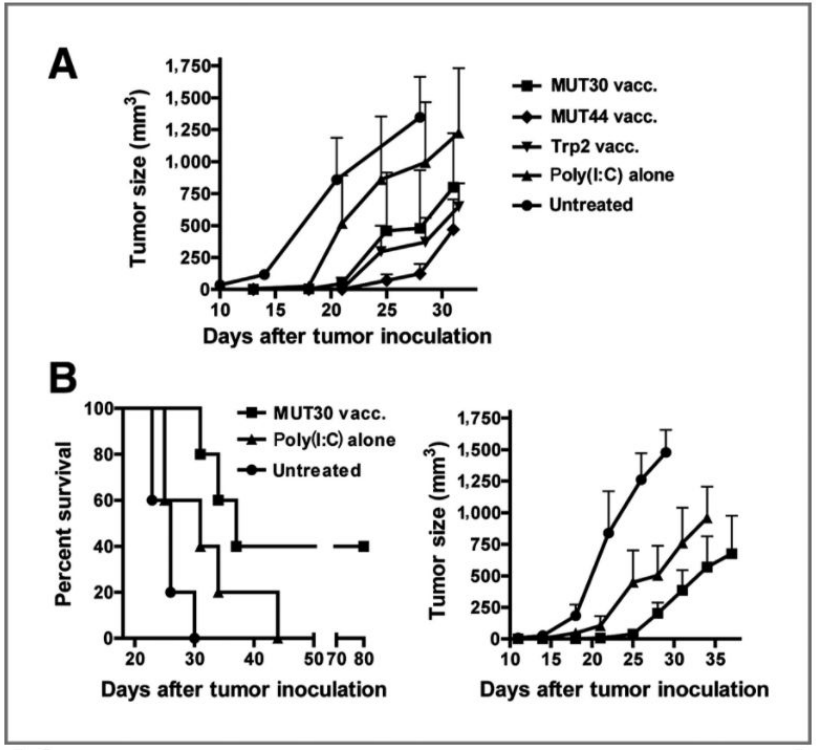


Computational genomics tools for dissecting tumour–immune cell interactions

Preclinical Evidence

John Castle & Ugur Sahin (2012)

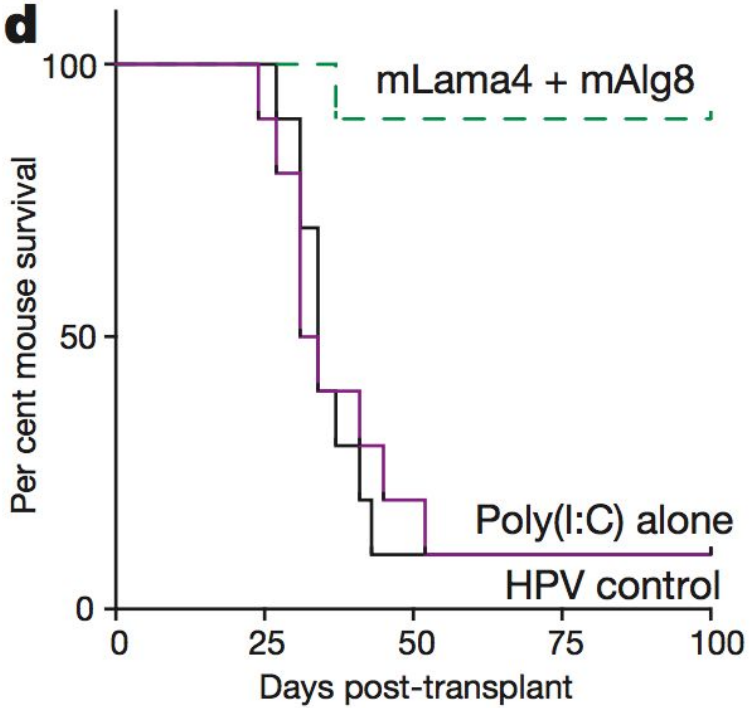
- C57BL/6 mice
- B16.F10 melanoma
- 27mer long peptides
- Poly(I:C) adjuvant
- Single peptide vaccination slows tumor growth



Exploiting the Mutanome for Tumor Vaccination, Castle et al. (2012)

Matt Gubin & Bob Schreiber (2014)

- Taconic 129S6 mice
- MCA-T3 sarcoma cell line
- “mLama4” & “mAlg8” are 8mer neoepitopes
  - Identified with WES + NetMHC
- Long peptide vaccine + Poly(I:C) adjuvant

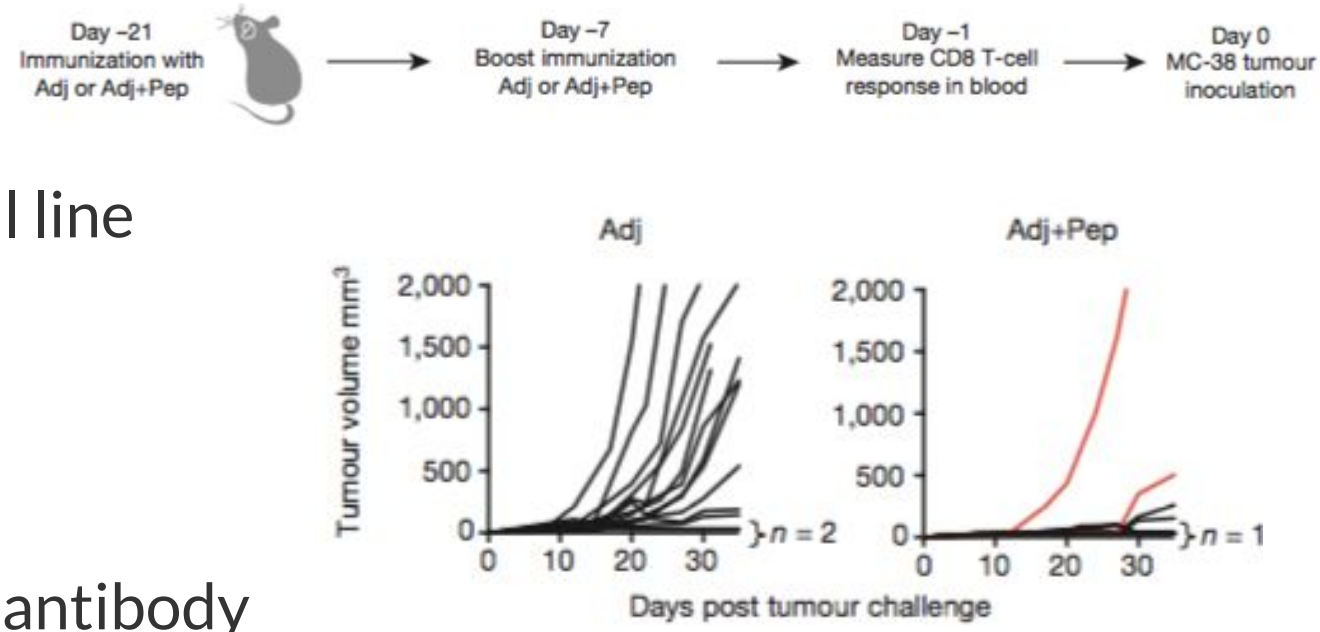


Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens, Gubin et al. (2014)

Mahesh Yadav & Lelia Delamarre (2014)

- C57BL/6 mice
- MC-38 colon cell line
- Vaccine with

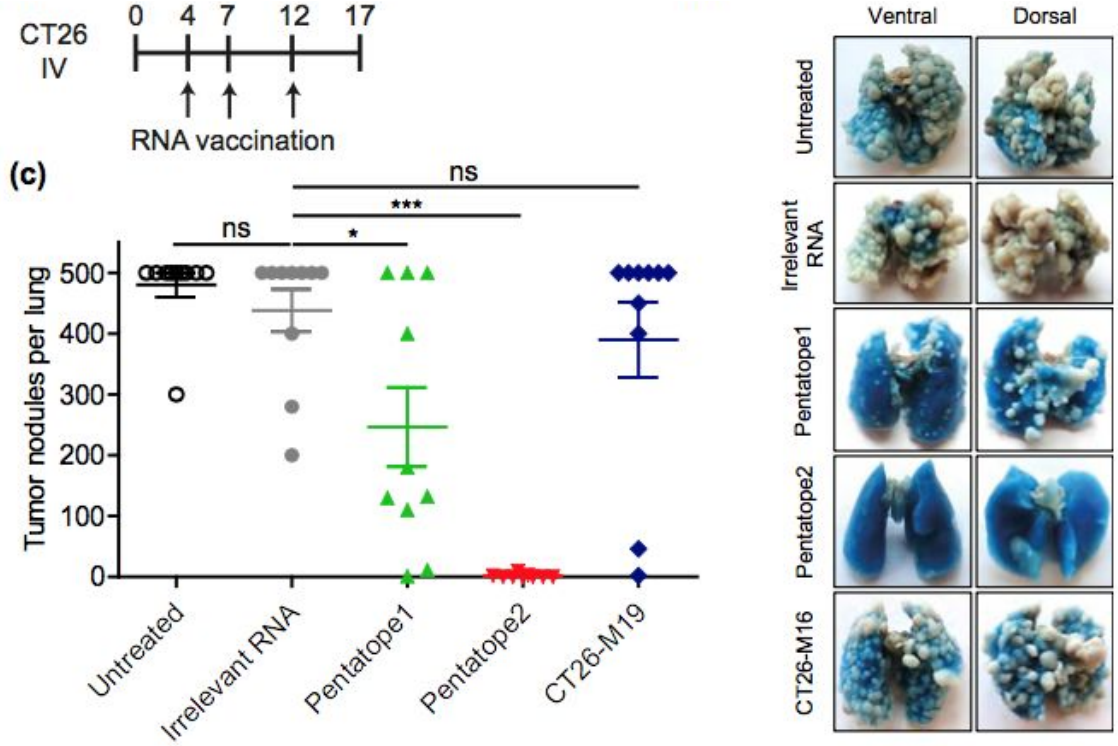
  3x epitopes
  - + Poly(I:C)
  - + anti-CD40 antibody
- Detected by WES + mass spec



Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing, Yadav et al. (2014)

Mathias Vormehr & Ugur Sahin (2016)

- BALB/c mice
- CT26 colon cell line
- mRNA vaccine
- Two groups of 5 epitopes (#2 works)
- Individual epitopes don't work



Mutated neo-antigens as targets for individualized cancer immunotherapy (Figure 3.18), Vormehr (2016)

Ongoing & Upcoming Neoantigen Vaccine Trials

Neon (NEO-PV-01)

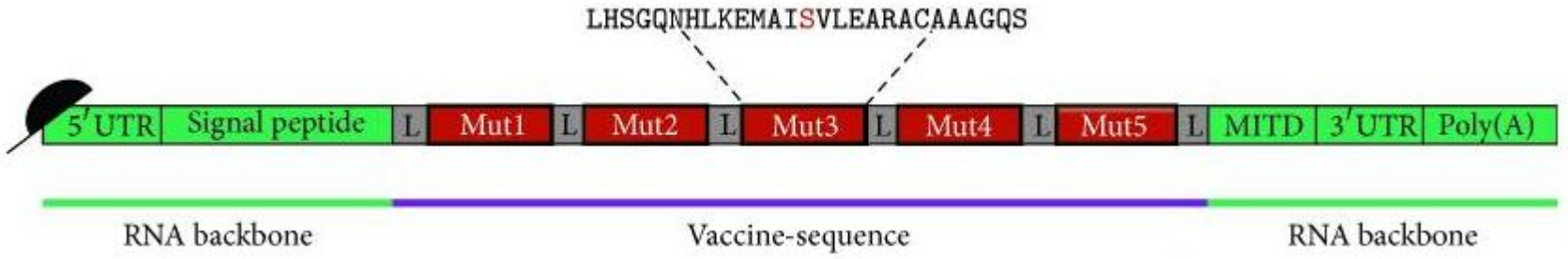
- Synthetic long peptides + Poly-ICLC + anti-PD-1 (nivo)
- In-silico epitope prediction
- Read: *Mass Spectrometry Profiling of HLA-Associated Peptidomes in Mono-allelic Cells Enables More Accurate Epitope Prediction*
- Phase I (NCT02897765) enrolling: 90 patients with {skin, lung, bladder} cancer

Agenus (AutoSynVax)

- Synthetic long peptides + HSP carrier + QS21 adjuvant
- Why heat shock proteins? APCs pick them up via CD91
- In-silico epitope prediction
- Phase I (NCT02992977) enrolling: 20 patients with “advanced cancer”

BioNTech (IVAC MUTANOME)

- Ultrasound guided injection of mRNA into lymph nodes
- Phase I (NCT02035956) ongoing: 15 melanoma patients
- Phase I (NCT02316457) enrolling: 30 TNBC patients



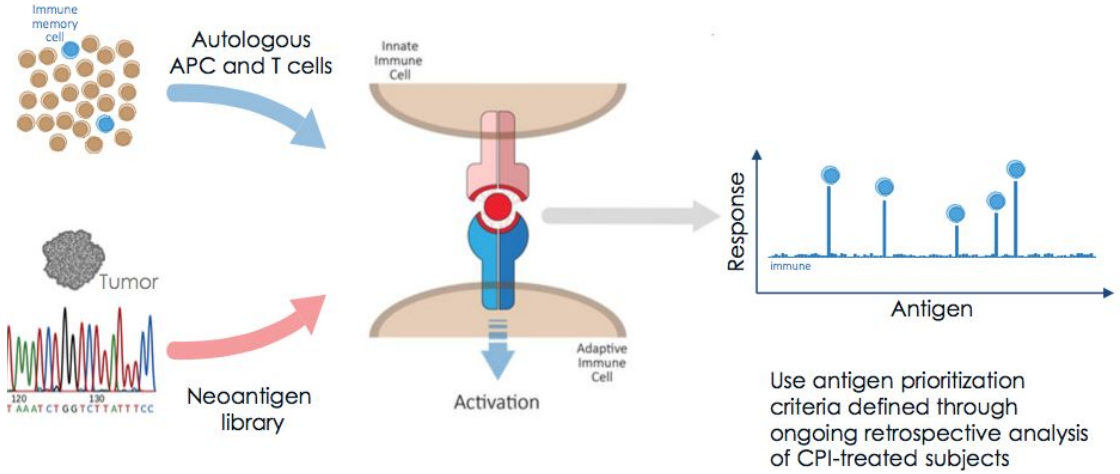
Mutanome Engineered RNA Immunotherapy: Towards Patient-Centered Tumor Vaccination

Caperna

- Launched by Moderna
- mRNA vaccine
- 20 variants
- Status: IND (submitted?)

Genocea (GEN-009)

- WES to identify candidate neoantigens
- Screens mutant peptides with patient APCs & T-cells
- No MHC binding predictions
- Only pre-existing T-cell responses
- *Status*: IND by end of 2017

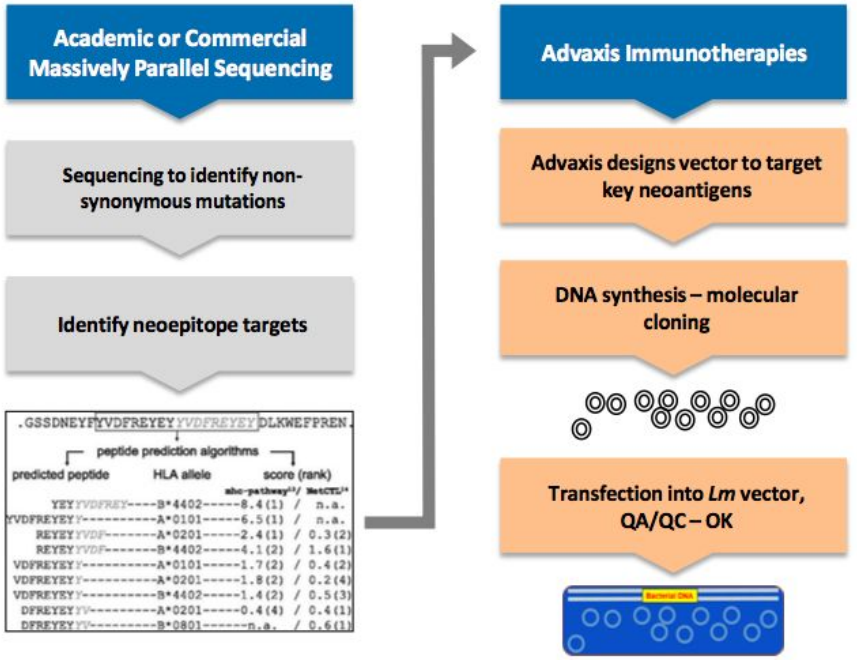


Prioritization of Neoantigens without Predictions: Comprehensive T cell Screening using ATLAS

Advaxis (ADXS-Neo)

ADVAXIS IMMUNOTHERAPIES™

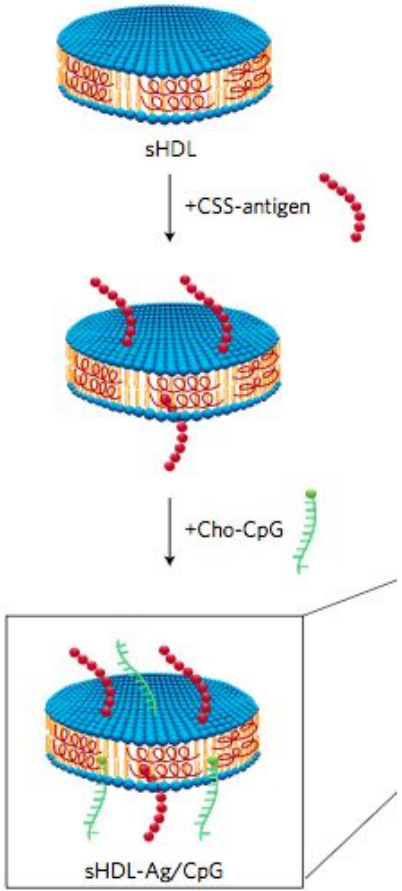
- Listeria vector
- 20+ neoepitopes per plasmid
- Translated neoepitopes secreted into APC cytoplasm
- Status: IND accepted



Advaxis slides from AACR 2016

The Near Future

- Targeted delivery
  - RNA lipoplex from BioNTech
- Enhanced retention time in lymph node
  - Particle size matters
  - PEGylated peptides
- Adjuvant + antigen nanodiscs
- Post-translational modifications
- Fine-grained immune modulation



Designer vaccine nanodiscs for personalized cancer immunotherapy

Thanks!