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curIOS Therapeutics

mRNA therapies targeting driver antigens in virus-associated cancers

November 2024

Team and Advisors

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MD, DPhil

Physician-Scientist (Medical Oncology)
- Yale Professor, Immuno-Oncology (IO)
- Founder & SAB member for multiple IO companies

David Braun
MD, PhD

Physician-Scientist (Medical Oncology)
- Yale Professor, Immuno-Oncology
- Expert in cancer vaccine clinical trials
- Founder & SAB member for multiple IO companies

Gene Griffin
DVM, MS

Experienced Executive in mRNA and rare disease
- >25 yrs years in drug development
- Prior VP at CureVac, NV and Senior Director at Alexion
- Yale EIR and advisor to Colton Center for Autoimmunity

Rich Brodksy
MS

Business, Marketing and Strategy Leader
- 20+ years of biopharma experience in senior leadership roles including Pfizer and Alexion
- Current Founder and Strategic Lead at Naveos Biopharma Consulting and Yale EIR

Kelly Olino
MD, FACS

Surgeon-Scientist (Surgical Oncology)
- Translational & clinical expert in var. cancers (Merkel cell carcinoma, melanoma, sarcoma and squamous cell cancers)
- IO and clinical trial experience

Alex Frey
MD

Physician-Scientist (Surgical Oncology)
- Yale Surgical Resident
- Co-inventor of multiple CurIOS technologies

Michael Briskin
PhD

Experienced Executive in Immuno-Oncology
- >25 yrs experience in biotech and NewCo development at Phenomic AI, Obsidian, Millenium, Jounce and others
- CSO and SAB Chair experience

YALE VENTURES

Robert Williams, PhD, Blavatnik Fellow

Anjali Ramaswamy, PhD, Blavatnik Fellow

Despite promise as cancer therapies, two key barriers limit the impact of mRNA vaccines

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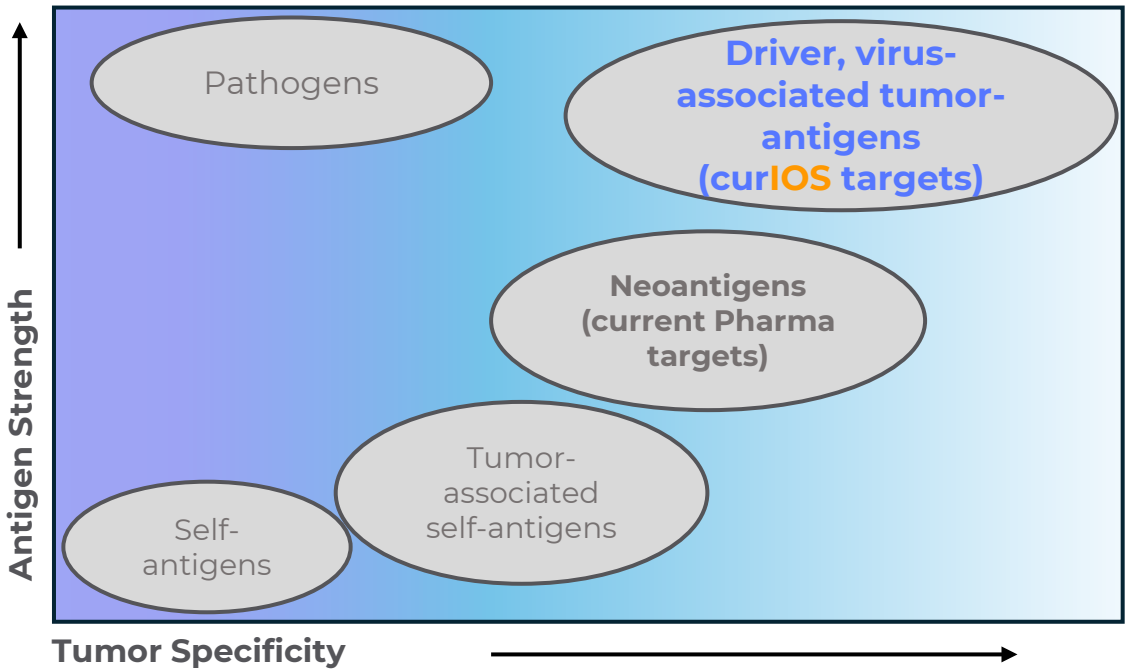
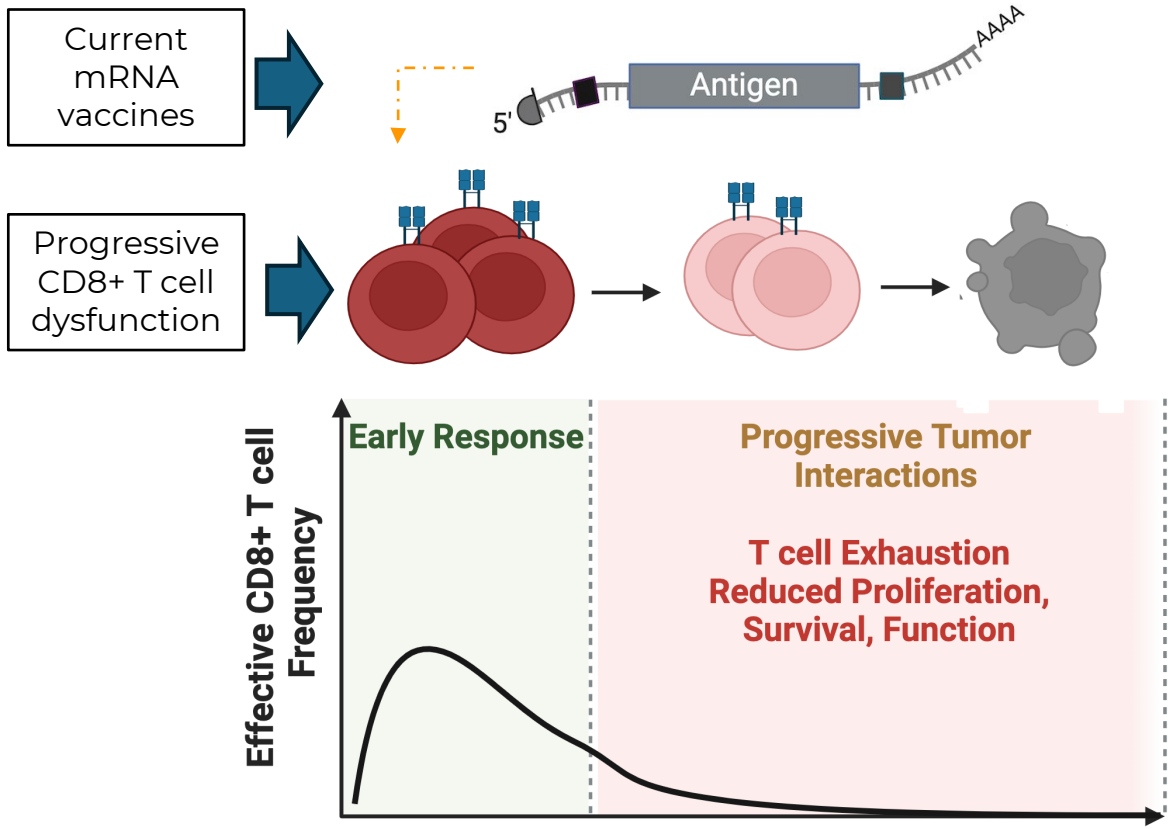
1. Tumor antigen weakness and escape



Most current approaches target neoantigens, but:

- Most predicted neoantigens are poorly antigenic
- Tumors rarely depend on neoantigen expression
- Many tumors lack sufficient neoantigens
- Neoantigen vaccines must be personalized

2. Poorly sustained T cell response



Current vaccines are poorly optimized for sustained CD8+ T cell expansion

The curIOS targeting difference

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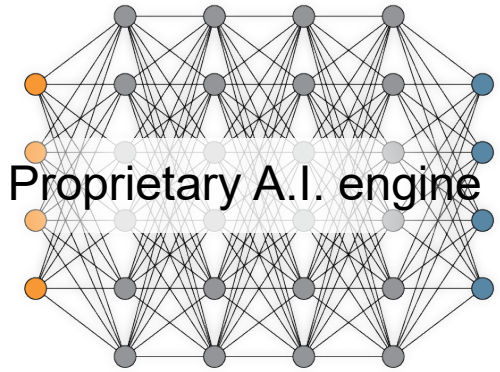
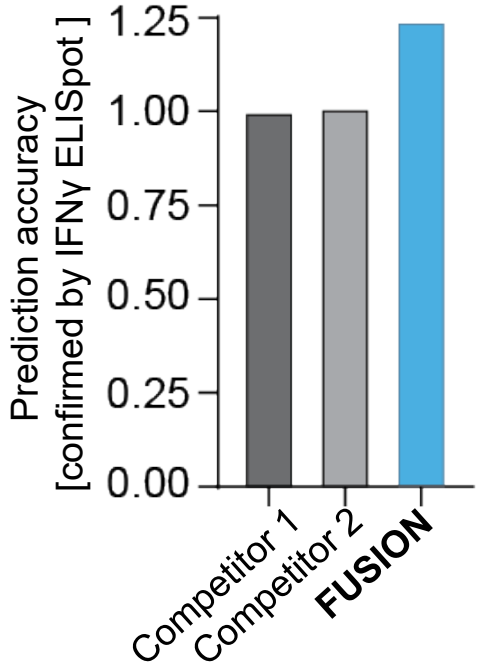
FUSION Platform

A.I. Antigen Discovery

1. Deep neural networks → shared and private **consensus, driver antigens**
2. Works for indication and antigen selection



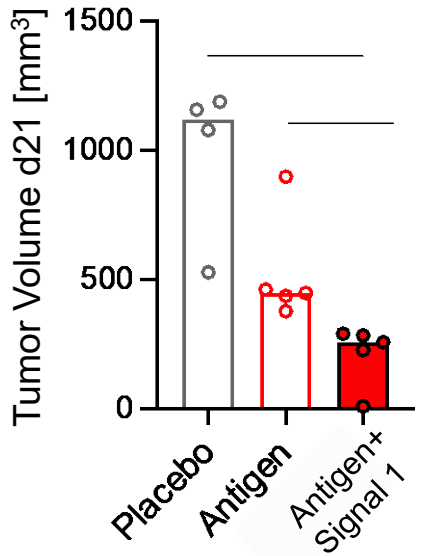


Nearly **25% improvement in prediction of immunogenic antigens** using FUSION compared to state-of-the-art deep learning-based models

COMET Platform

Engineered immune expansion

1. mRNA-based co-expression of proprietary "**Virus Antigen** and **Signal**"
2. Expands antigen-specific T cell compartment
3. Improves infiltration and T-cell effector function



curIOS technology enables development of multiple optimized mRNA cancer vaccines

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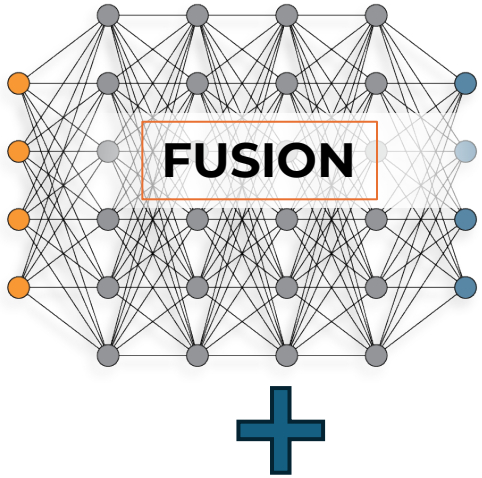
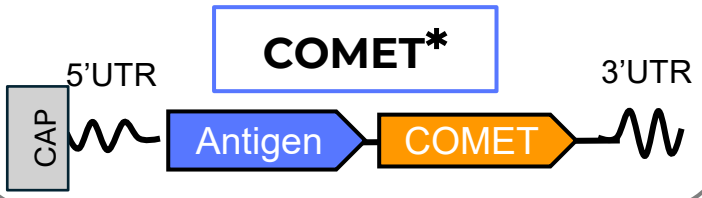
Optimal Antigen Selection



Optimal immune engineering



*Provisional application filed 06/24 for COMET
PCT conversion for MCC asset 12/23

Cancer Applications

Rapid Pipeline Development

Discovery → Lead Selection → Lead Optimization → Preclinical Development

Cur-001	MCPyV	**MCC (lead POC program)**
Cur-002	ERV	**RCC (second indication)**
Cur-003	ERV	Other ERV-driven tumors
Cur-004		Other Solid Tumors

MCPyV = Merkel cell polyoma virus
ERV= Endogenous retrovirus
RCC = Renal cell carcinoma

MCC is an ideal first therapeutic indication for CurIOS

curIOS currently in partnership discussion with two Biotechs

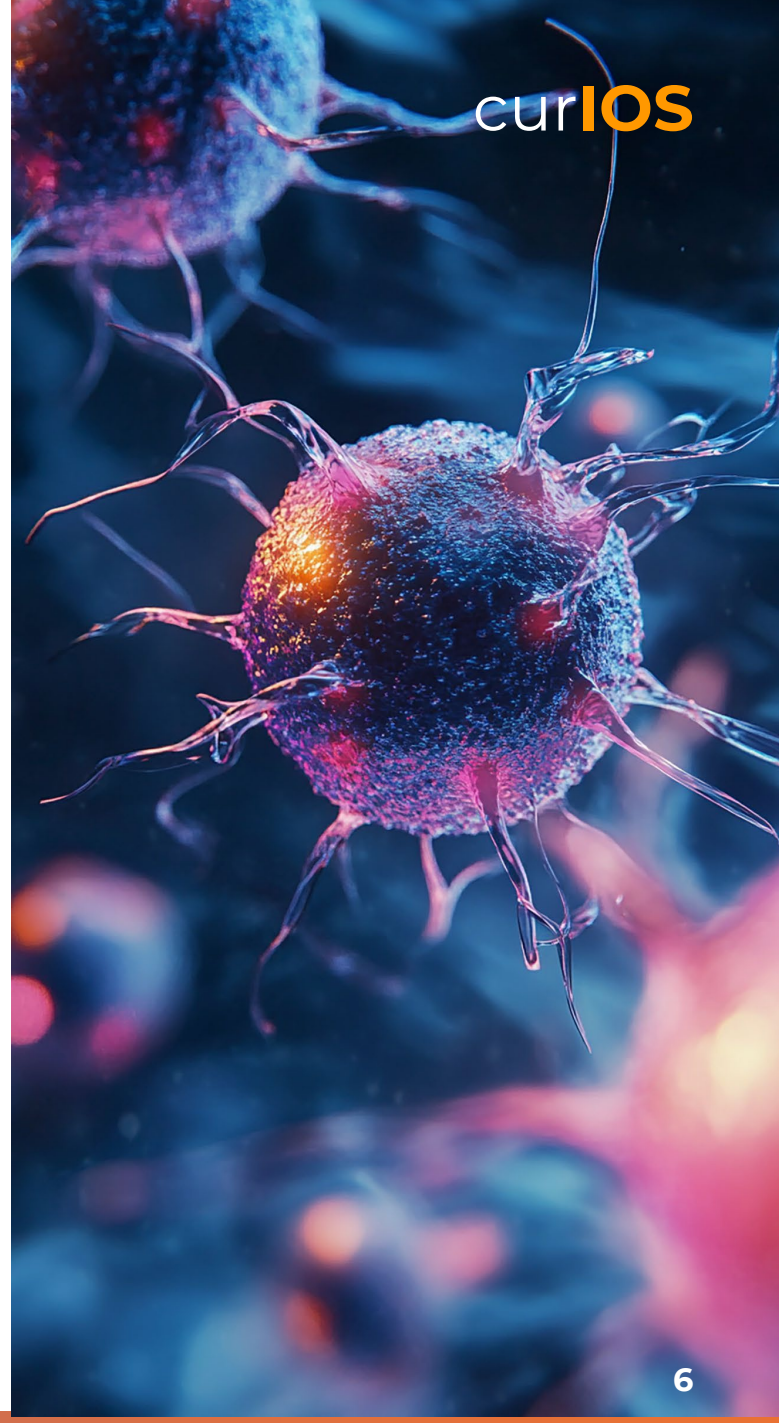
Rare, chronic disease development path
- Ph1b neoadjuvant trial with a path. response efficacy signal feasible at Yale
- Pivotal Ph2 trial as a basis for accelerated approval*
- Clinical-translational expertise, models and relationships of CurIOS team
- Estimated costs to approval ~30-40m USD

Market is significant
- Envisioned use includes initial, intensive followed by intermittent, long-term treatment to prevent recurrence
- US market is up to $600-800 m/yr peak sales and growing rapidly

Scientific risk is low due to MCC-specific biology
- Strong preclinical data
- Conserved, essential, immunogenic antigen target.

Cost-efficient, high likelihood of success POC for vaccine and platforms

*Based on prior Pembrolizumab approval



MCC validation in patient tissues and mouse models

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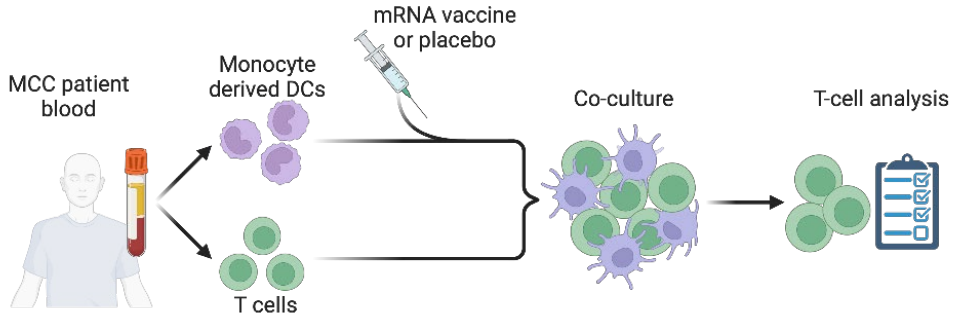
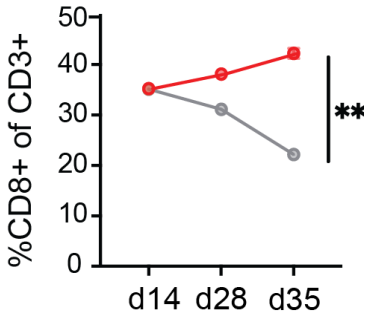
Ex vivo patient validation

human patient tissue

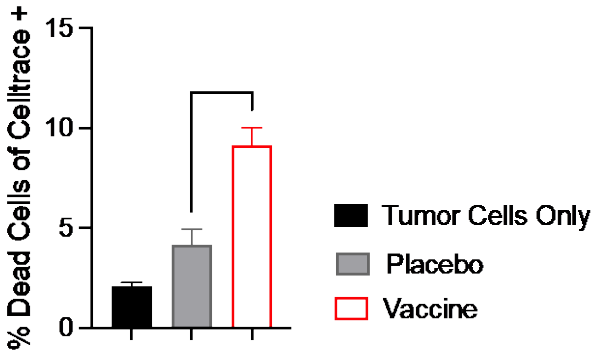
1. CD8+ T-cell expansion: ↑
2. Functionality (IFNγ ELISA): ↑
3. Tumor cell killing: ↑



T cell Expansion



Tumor Cell Killing

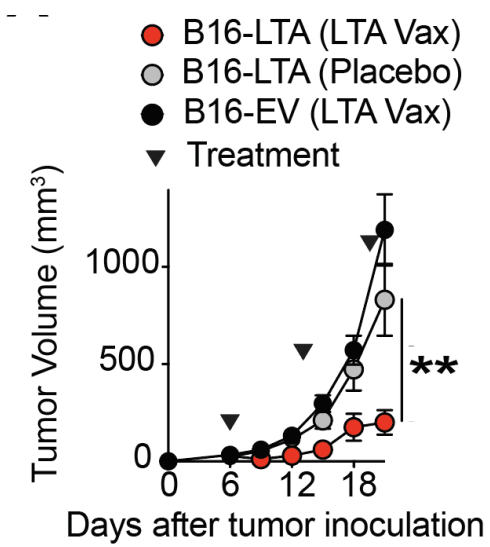


In vivo studies

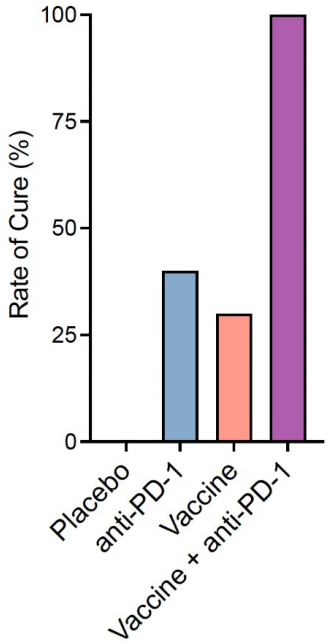
syngeneic murine model

1. cDC1 / T cell expansion: ↑
2. Monotherapy efficacy comparable to SOC
3. Combination therapy improves cure rate

Monotherapy:



Cure Rate:



ERV-associated RCC is a >$3B addressable commercial market

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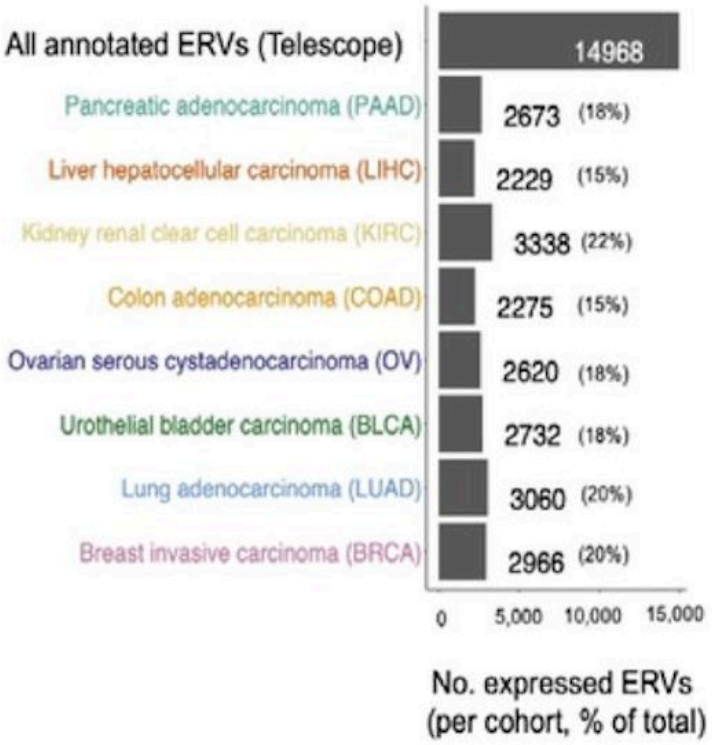
Endogenous Retroviruses (ERVs) in RCC:

- > 85,000 new US cases / yr (440,000 worldwide)
- Development path focused on metastatic disease:
  - Addressable market **$3.4b / yr (US), $17.5b / yr (worldwide)**
- Preclinical and clinical studies support the potency of targeting tumor-associated ERVs
- Differentiated expertise in the Braun lab offers competitive advantage
  - Unique computational pipeline (Nature Medicine)
  - *Recent clinical trial POC in RCC* indication (Nature, accepted)
  - Identification of immunogenic ERVs (Cell, under revision)
- Abundant opportunities for indication expansion



ERV expression is enriched in common cancers

curIOS is positioned to execute on ERV-targeting vaccines in RCC

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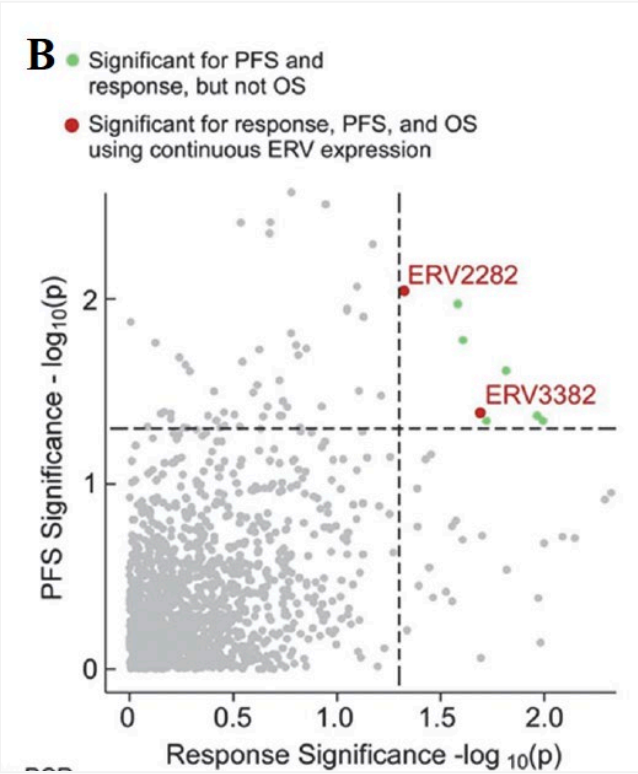
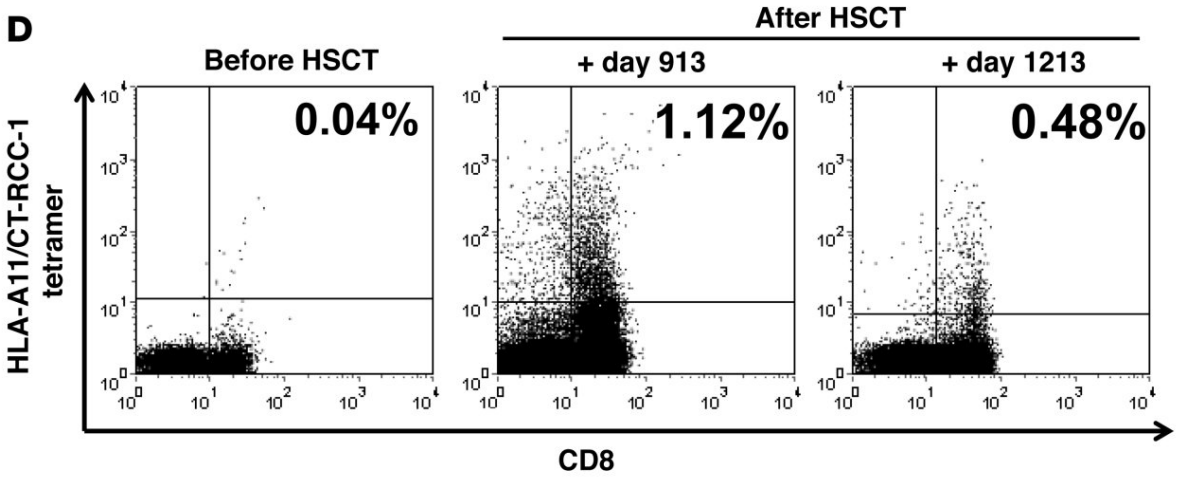
Computational pipeline identifies highly expressed ERVs associated with immunotherapy response



Braun et al., Nature Medicine, 2020 and Nature 2024

ERV-specific T cells can drive clinical rejection of RCC

- Identified CD8⁺ T cells reactive to autologous tumor in long-term survivor
- HLA-A11-restricted T cell clone identified; capable of killing 5/10 HLA-A11⁺ RCC lines
- Target epitope identified and derived from ERVE-4
- Antigen-specific T cells identified after transplant



ERVs are THE target for anti-tumor CD8+ T cells

Blavatnik funds enable completion of critical development activities

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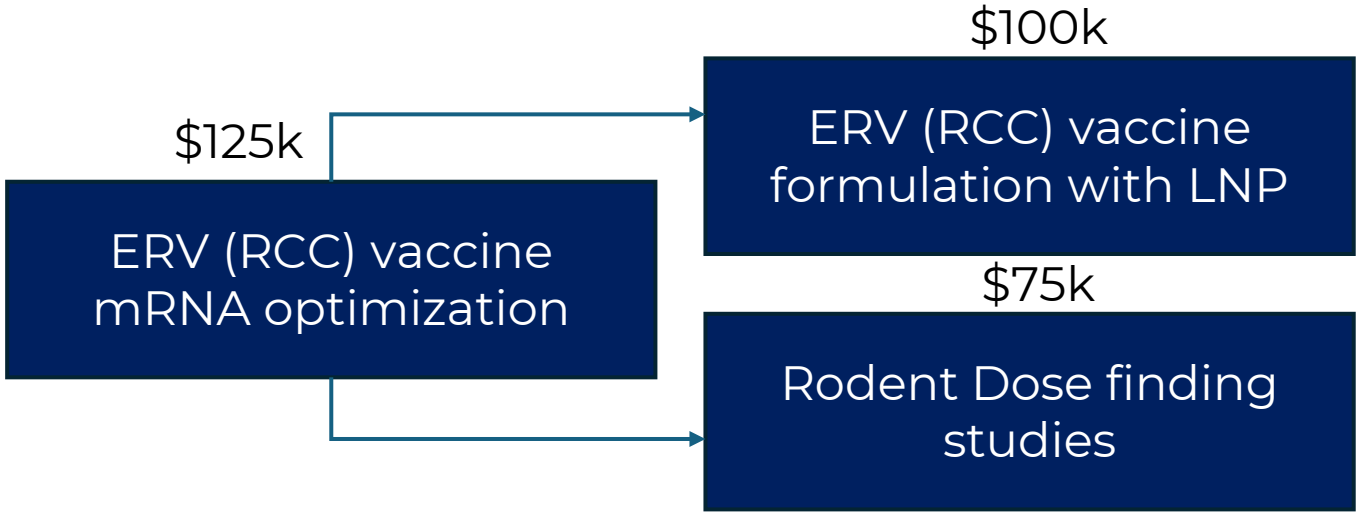
Value inflection Point:
Partner validated candidate vs significant funding event

To achieve key milestones in next 12-18 months internally with $300k Blavatnik Fund Support:



~$5-7M

IND-enabling (Safety and Pharm. Tox and CMC)

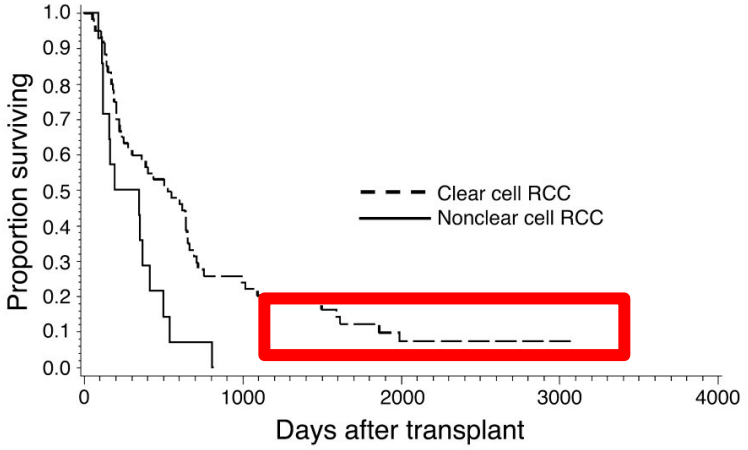
Grant funding, accelerators and/or partnership to support launch:

- NCI SBIR: $400k
- ACS BrightEdge Accelerator: $100k, access to resources
- ACS Accelerator Award: $75k
- Partner identification/licensing

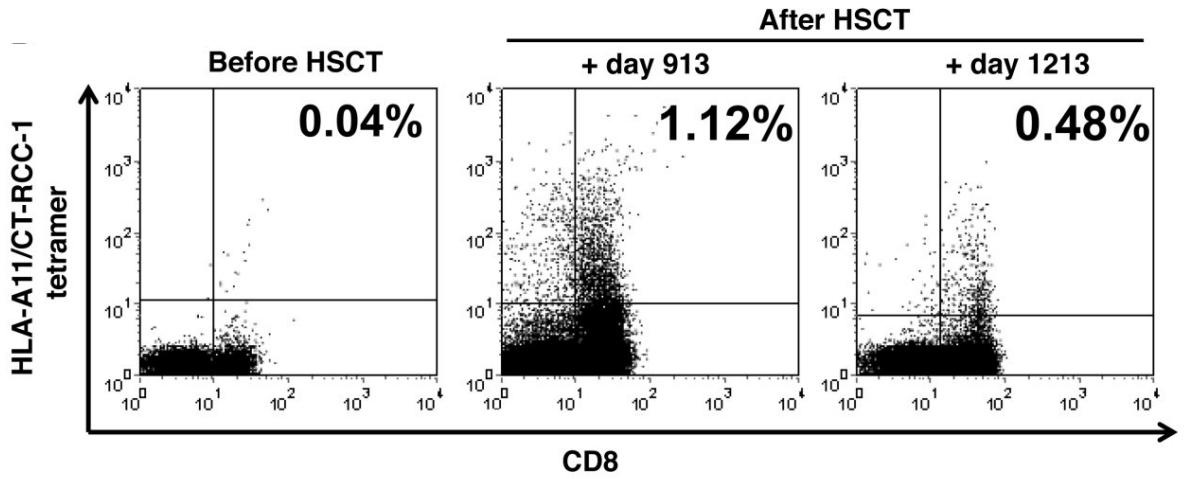
IP:
Current: i) viral antigen platform / MCC (PCT 12/23);
ii) COMET technology (provisional 6/24)
Enabled by this award: i) ERV vaccine; ii) FUSION v2

RCC: ERVE-4-derived peptide is an antigenic target in effective anti-tumor immunity

Allogeneic stem cell transplant
(n = 74)



- Identified CD8⁺ T cells reactive to autologous tumor in long-term survivor
- HLA-A11-restricted T cell clone identified; capable of killing 5/10 HLA-A11⁺ RCC lines
- Target antigen identified as ATFLGSLTWK derived from ERVE-4
- Antigen-specific T cells identified after transplant



[1]Takahashi et al. HCI, 2008

CurIOS' competitive edge in virus-associated cancers

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Company	Stage	Modality	Target Indication	Antigen-specific Immune Enhancement
IMMUNOMIC THERAPEUTICS — AN HLB COMPANY Creative Biolabs Vaccine	Phase 1	DNA vaccine	MCPyV+ MCC	✕
MERCK moderna	Phase 1-3	NeoAg mRNA vaccine	-	✕
BIONTECH	Phase 1,2	mRNA vaccines	HPV+ HNC	✕
EVAXION	Phase 1,2	ERV DNA / peptide	ERVs in Melanoma, NSCLC	✕
curIOS	Preclinical	mRNA vaccine	MCC, RCC, HPV+ cancers	Proprietary FUSION+COMET platforms

Development Strategy:
Rapid path to the clinical and platform proof-of-concept

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2025 | 2026 | 2027 | 2028 | 2029

MCC Phase 1B Start

MCC Phase 2 FDA meeting

FUSION Platform
Virus Antigen Identification

MCC IND Filing

RCC IND Filing

RCC Discovery
- Antigens identified and cloned

New Virus Antigens
- TBD, pending partner

COMET – Preclinical Development
mRNA Preclinical Studies

MCC Preclinical
- MCC mRNA + LNP optimization (internal & external)
- Preclinical efficacy and pharm.
- CMC (GMP plasmid + expansion)
- Safety toxicology

RCC Preclinical
- mRNA construct + LNP optimization

$3-5M Preclinical

COMET – Clinical Development
MCC Phase 1b and
RCC IND Enablement

MCC Clinical Trial
- IND approval
- Phase 1b muti-center (add-on, dose finding) start
- FDA filing for Orphan Drug Designation

RCC Development
- IND enabling studies

$10-15M Phase 1b

COMET – BLA Pathway
MCC Phase 2 Design and
RCC IND

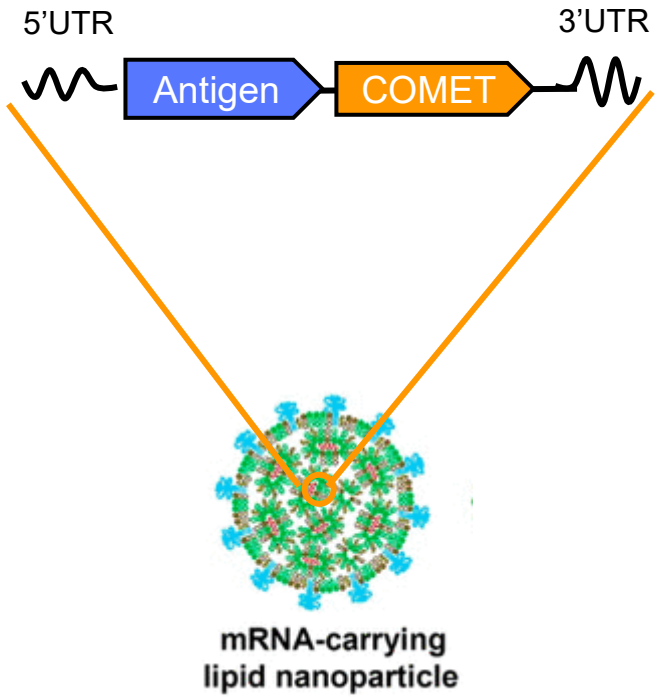
MCC Clinical Trial
- FDA meeting for phase 2 design (add-on design as pivotal)
- Start of MCC phase 2

RCC Clinical Trial
- IND approval

$18-22M Phase 2

Estimated $31-42m total to BLA approval

MCC Asset (Cur-001) Target Product Profile



Parameter	Essential Profile
Modality	mRNA therapy
MoA	Antigen + COMET sequence co-expressed by myocytes and APCs
Delivery Mode	intramuscular
Dosage Form	mRNA-containing LNP in sterile PBS
Regimen	2 doses pre-op, monthly x 1 year post-op, 4x / year afterwards
Primary Product Indication	Minimum Acceptable Result: Stage II-III resectable MCC, neoadjuvant and adjuvant use Ideal Results: All MCPyV+ patients • PD-1 resistant and upfront metastatic with PD-1 combination, earlier stage disease • Consideration in high-risk PPX situations (e.g. CLL patients)
Patient Population	Adults of all ages, excluding solid organ transplant, active immunosuppression
Efficacy	Minimum: Ph1: Safety, pathologic response > 0 Ph2: Rate of recurrence 25% reduced Ideal: Pathologic response 100%, Rate of recurrence 100% reduced?
Risk/Side Effects	Minimum: Injection site reaction, transient fever and chills similar to COVID vaccines Ideal: Injection site reaction

Phase 1b Neoadjuvant trial includes both safety and early efficacy signals

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01

Inclusion:

Resectable, Stage II + III MCC
ECOG 0-1
Goal enrollment: ~10 patients

Exclusion:

Solid organ transplant recipients
Immunosuppression,
autoimmunity or pregnancy

02

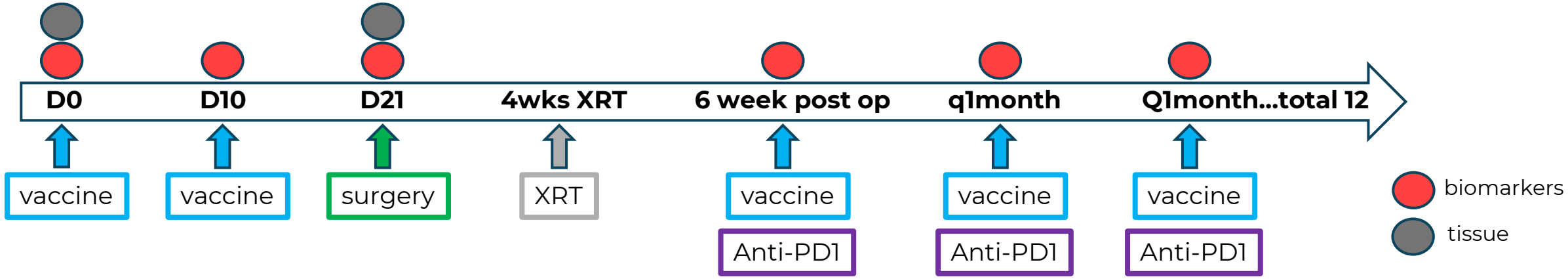
Treatment:

- Neoadjuvant vaccine d0, d10
- SOC surgery +/- radiation
- Adjuvant vaccine (8 doses, q4weeks) + pembrolizumab (up to 1 yr)

03

Outcomes

- Primary: Safety
- Secondary:
  - Pathologic response
  - Recurrence free survival
- Exploratory endpoints:
  - Cytokine array
  - T cells from PBMC
  - scRNAseq
  - ctDNA



Viral MCC has a rising incidence and high unmet need

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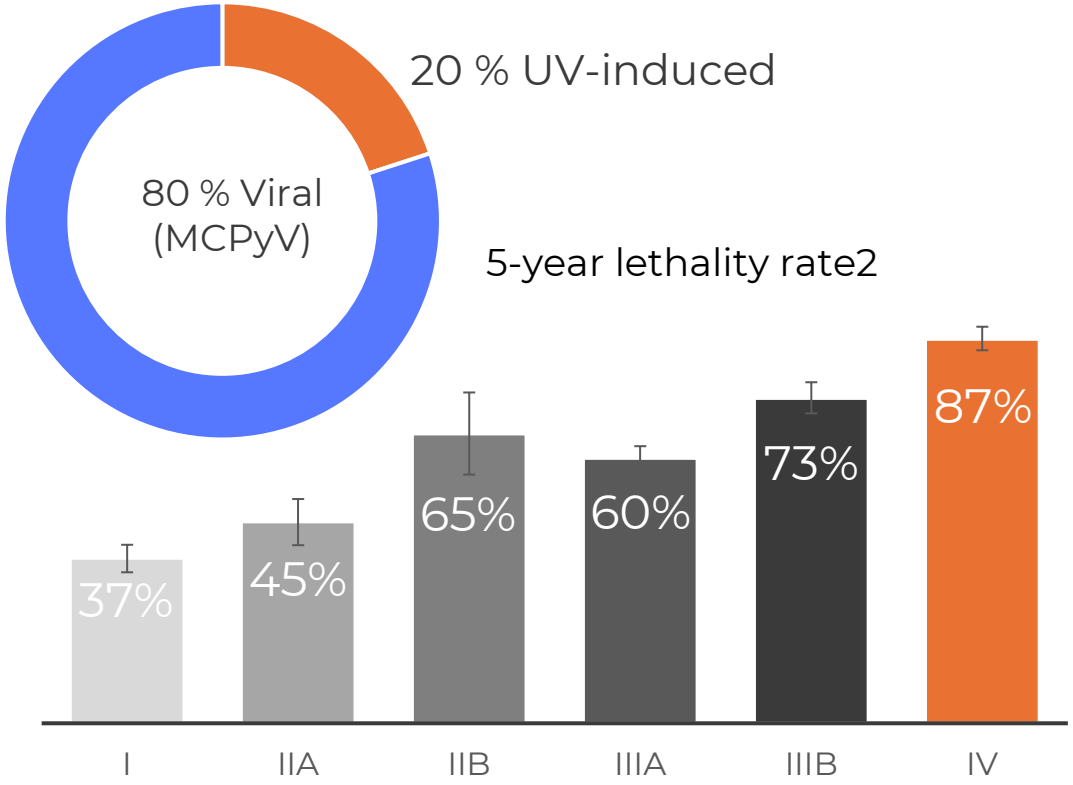
… a growing and deadly problem:

- The most lethal skin cancer (stage-for-stage)
- Rising incidence: 3000 cases today predicted to rise to 5,000 in 2030



…underserved by current SOC:

- Check-point inhibitors (~50% effective) and recurrences are common
- Chemotherapy (~30% response rate but low durability)

… an ideal target for mRNA vaccines:

- Strong antigen dependence[1]
- Highly conserved antigens
- Highly immunogenic antigens[2]

[1]Houben et al., J Virol, 2010
[2] Jing et al., Cancer Immunol Res, 2020
[3] Schadendorf et al, J Clin Oncol, 2017

Most cancers do not respond to available immunotherapies

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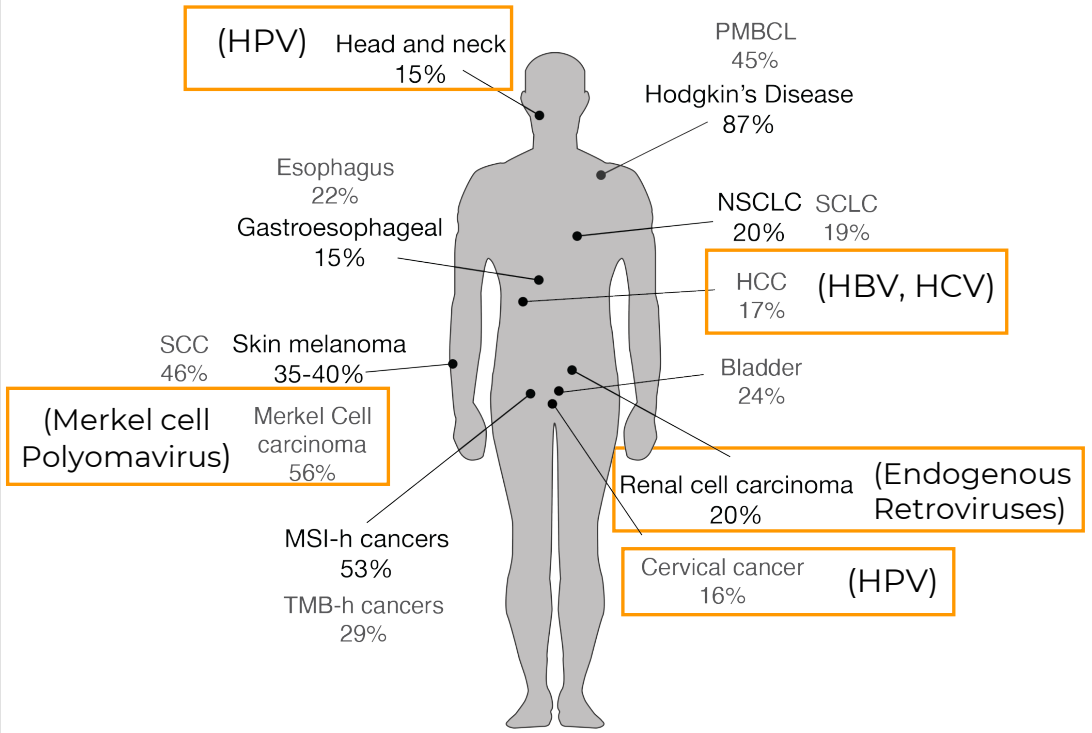
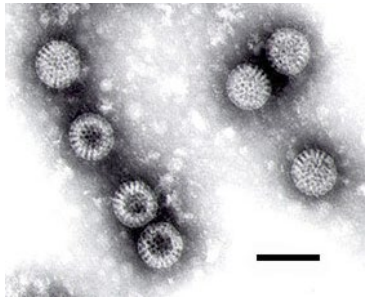
PD-1/PD-L1 Checkpoint Blockade Response Rates

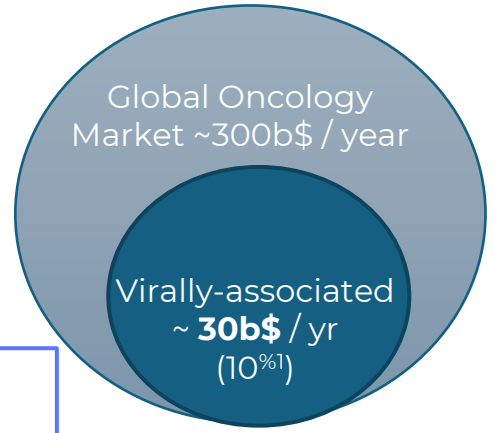


Overall Response Rates < 50%

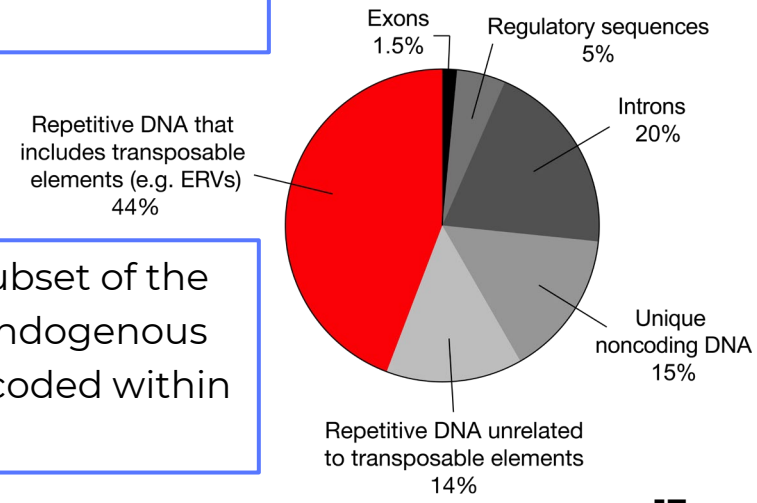
Adapted from Ribas and Wolchok, 2018 and cancerresearch.org, 2023

Virus-associated cancers have high unmet need





Exogenous viral infection is associated with up to **10% of human cancers**



A further, significant subset of the market is associated Endogenous retroviruses (ERVs) encoded within the human genome