MNEMO THERAPEUTICS

A new class of tumor targets for next-generation cancer immunotherapies

Non-Confidential Presentation

January 2025

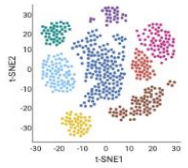
Mnemo Therapeutics: an integrated end-to-end novel target discovery and validation platform

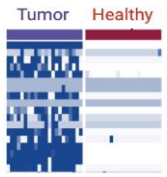
Discovering druggable targets, developing immunotherapies

Discovery Hub

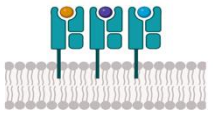
A first-in-class, end-to-end validated, proteogenomic dark genome and alternative splicing target discovery platform

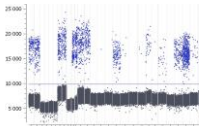
Target identification





Transcriptional & proteomic validation





Target Library

A unique target portfolio of pan-cancer and tumor-specific actionable targets for immuno-therapy

Peptide Major histocompatibility Complex (pMHC) E-antigen

TCR-mimic scFv

Immunotherapy Modalities

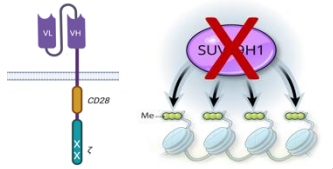
Unique opportunities for developing multi-modality immunotherapies

T-cell engagers

- Lead TCR-scFv(1) binders for TCE development

(1) single chain variable fragment

Cell therapy



- High efficacy and persistence-enhancing CAR-T asset

Vaccination

- Validated peptide lists for indication-specific, off-the-shelf dark antigen vaccines

Company Overview

Proprietary Technology Platform

Differentiated end-to-end target discovery platform for immuno-oncology, from discovery to validation

Key Facts

Founded December 2018

Institutional investors:

CASDIN CAPITAL · HILLHOUSE · Redmile Group · Sofinnova partners

Non-dilutive funding from bpifrance

Strategic academic partnership: institut Curie

Assets

- Lead binders for a highly recurrent pMHC E-antigen in glioblastoma (GBM)
- Portfolio of multi-solid cancer targets
- Validated cancer E-antigens for high coverage cancer vaccine development
- Epigenetic reprograming technology for highly persistent, exhaustion-resistant CAR-T cells

Mnemo Team

Dieter Weinand
Chairman of the Board

Benoit Durand-Barracand
Chief Executive Officer

Sebastian Amigorena, PhD
Scientific Co-Founder and CSO

MNEMO'S UNIQUE TECHNOLOGIES AND TARGETS ARE PROTECTED BY:

(as of September 2024)

11 Patent families worldwide

44 Patent pending

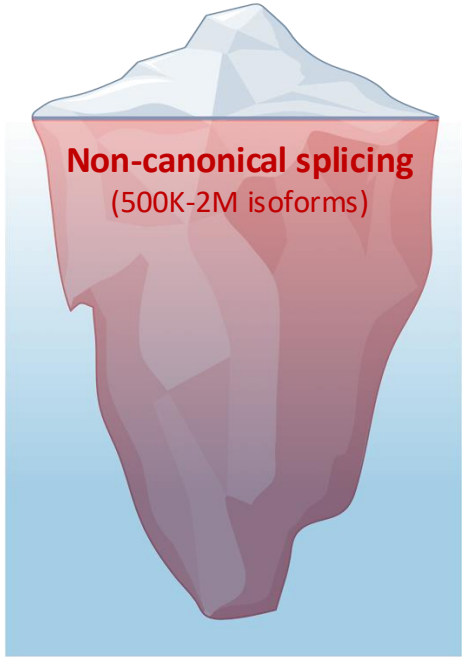
8 Patent granted

Alternative and non-canonical splicing are a source of unexploited druggable and tumor-specific isoforms

Alternative splicing expands the cellular proteome by 10 to 100-fold

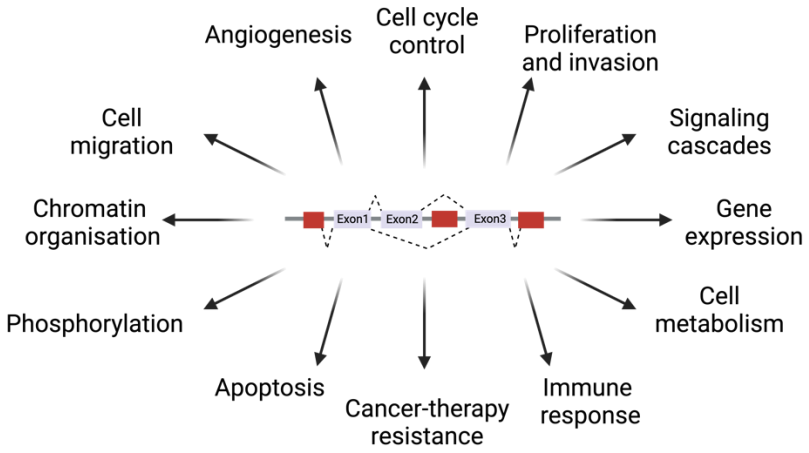
Canonical splicing
(30-100K isoforms)

Alternative splicing
(200-300K isoforms)



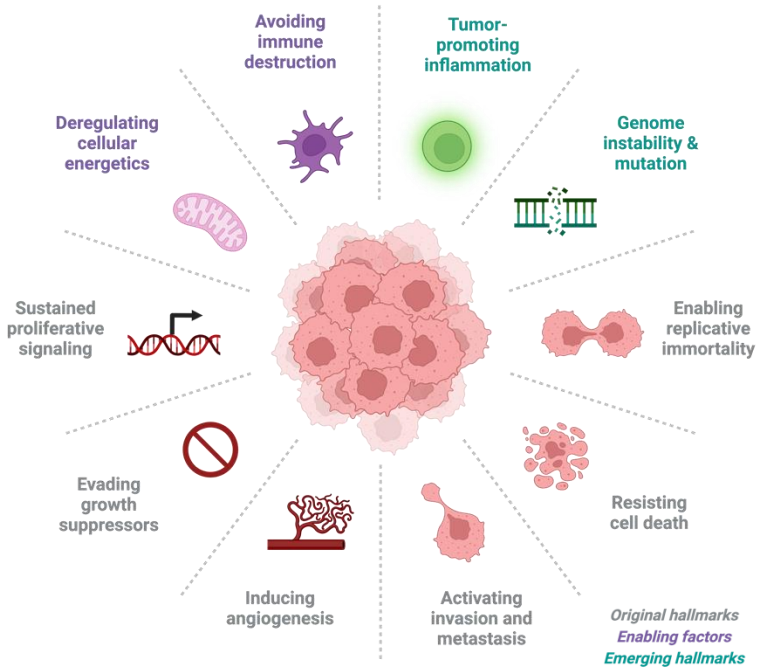
Splicing targets are druggable and can be tumor specific

Alternative splicing regulates cell functions



Alternative splicing and disease (2016). Genetics – Research & issues

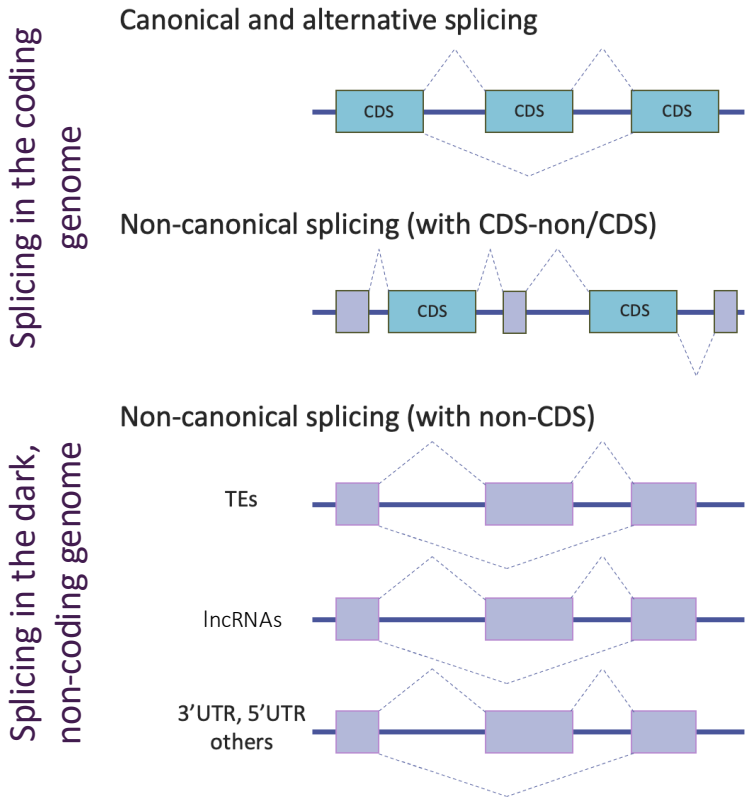
Alternative splicing is deregulated in cancer, revealing tumor-specific protein isoforms

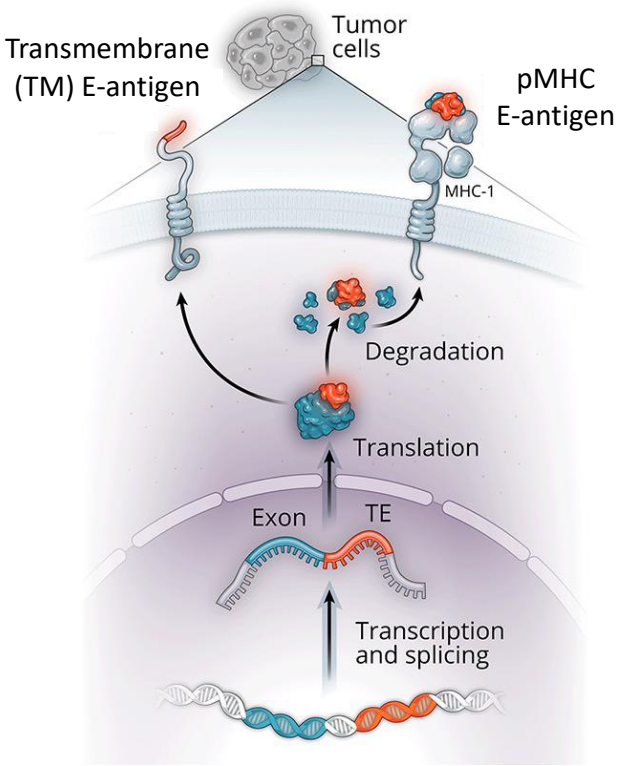


Hanahan and Weinberg (2011). Hallmarks of Cancer: The Next Generation. Cell.

Mnemo's unique dark genome splicing platform discovers a new class of tumor-specific targets for immunotherapy: E-antigens

- E-antigens are a product of epigenetic dysregulation and non-canonical splicing
- They are highly **tumor specific** (including high unmet medical need indications) and **shared between patients**, due to recurrent splicing defects in tumors
- E-antigens include new **transmembrane** isoforms (TM E-antigens) and **new peptides presented by HLA (pMHC E-antigens)**





CDS – coding sequence

E-antigens represent a new class of tumor-specific targets shared among large populations of cancer patients

E-antigens are optimal tumor targets:

- More tumor-specific than conventional Tumor Testis Antigen (TTAs)
- More recurrent in patients than mutational or frame-shift antigens

Mnemo's pMHC E-antigens

Peptides presented at cell surface

	Coding Genome		Non-coding Genome
			
	Point Mutations	**Tumor Associated Antigens**	**E-Antigens**
Tumor specific	+	–	+
Tumor coverage	+	+	+
Patient recurrence	–	+	+
Immunopeptidomics (pMHC only)	–	+	+
T-cell responses in cancer patients (pMHC only)	+	+	+

Two recent publications from the Amigorena lab describe pMHC E-antigens in cancer derived from dark genome and non-canonical splicing

Non-canonical splicing junctions produce peptides presented by HLA (E-antigens)
E-antigens are protective in mice, and immunogenic in cancer patients

ONLINE COVER: Tumor-infiltrating Lymphocytes on JET Patrol. This month's cover depicts T lymphocytes specific for tumor neoantigens near a cancer cell (yellow) displaying neoantigen peptides on a subset of its cell-surface MHC molecules. JETs (Junctions between Exons and Transposable elements) are a new class of cancer-associated neoantigens made by tumor cells as a result of noncanonical mRNA splicing linking exons to transcripts from transposable elements. Merlotti *et al.* identified recurrent JETs in human lung tumors and the presence of $CD8^+$ T cells specific for JET-encoded epitopes in cancer patients. In a companion paper, Burbage *et al.* used mouse models to demonstrate that tumor-specific expression of JETs is under epigenetic control.

Credit: Alexis Finkbeiner/Mnemo Therapeutics

Also see:

- Bonté et al (2022) Cell Reports
- Arribas et al (2024) Cell

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

CANCER IMMUNOLOGY

Epigenetically controlled tumor antigens derived from splice junctions between exons and transposable elements

Marianne Burbage[1*†], Ares Rocañín-Arjó[1†], Blandine Baudon[1], Yago A. Arribas[1], Antonela Merlotti[1], Derek C. Rookhuizen[1], Sandrine Heurtebise-Chrétien[1], Mengliang Ye[1], Alexandre Houy[2], Nina Burgdorf[1], Guadalupe Suarez[1], Marine Gros[1], Benjamin Sadacca[1,3,4], Montserrat Carrascal[5], Andrea Garmilla[1], Mylène Bohec[6], Sylvain Baulande[6], Bérangère Lombard[7], Damarys Loew[7], Joshua J. Waterfall[3,4], Marc-Henri Stern[2], Christel Goudot[1], Sebastian Amigorena[1*]

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

CANCER IMMUNOLOGY

Noncanonical splicing junctions between exons and transposable elements represent a source of immunogenic recurrent neo-antigens in patients with lung cancer

Antonela Merlotti[1†‡], Benjamin Sadacca[1,2,3†‡], Yago A. Arribas[1†], Mercia Ngoma[1‡], Marianne Burbage[1], Christel Goudot[1], Alexandre Houy[2], Ares Rocañín-Arjó[1], Ana Lalanne[4,5], Agathe Seguin-Givelet[6,7], Marine Lefevre[8], Sandrine Heurtebise-Chrétien[1], Blandine Baudon[1], Giacomo Oliveira[9,10], Damarys Loew[11], Montserrat Carrascal[12], Catherine J. Wu[9,10,13], Olivier Lantz[1,4,5], Marc-Henri Stern[2], Nicolas Girard[6], Joshua J. Waterfall[2,3§*], Sebastian Amigorena[1§*]

Click on each thumbnails to access online links

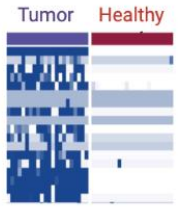
Discovery hub and targets

A best-in-class discovery hub for dark genome and unannotated splicing antigens

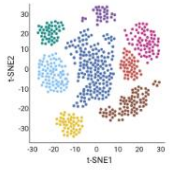
Mnemo has validated its end-to-end discovery workflow, which integrates transcriptomic, proteomic and wet lab techniques

Target discovery

Bulk RNAseq



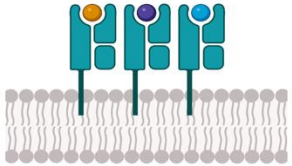
scRNA Seq



- Identify E-antigen transcripts

MS Immunopeptidomic validation

Immunopeptidomics



- Validate transcript expression
- Assess surface expression by proteomics

Target nomination

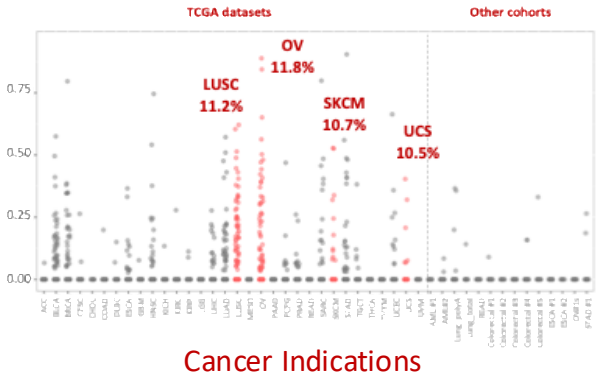
pMHC E-antigen

- Nominate lead candidates

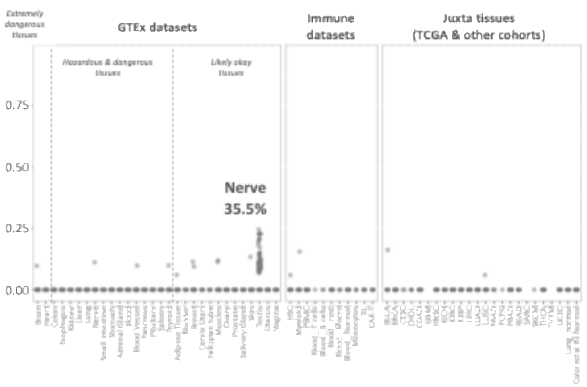
Mnemo's pMHC targets show high tumor-specificity in high proportions of patients and are not expressed in healthy tissues

RNA expression profiles of "conventional" surface targets exhibit medium / no tumor specificity

NY-ESO-1
A*02:01

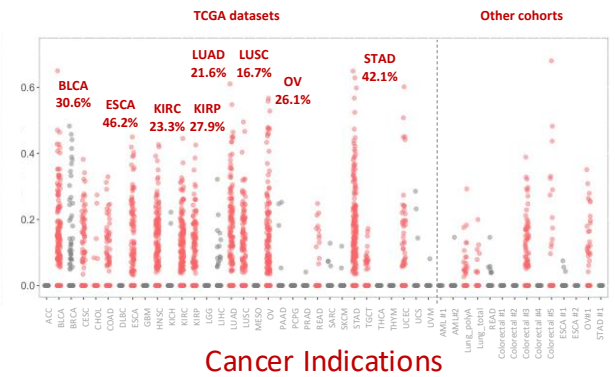


Cancer Indications

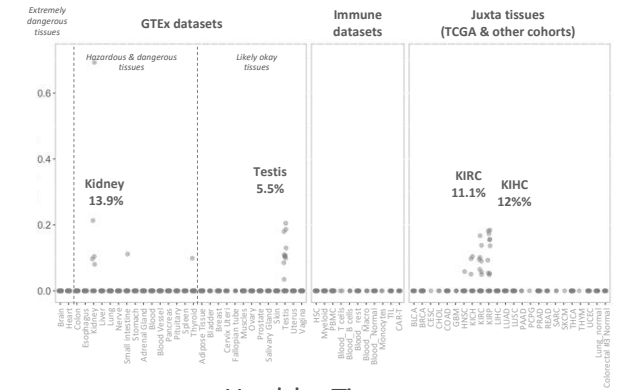


Healthy Tissues

MNO-P7
A*03:01

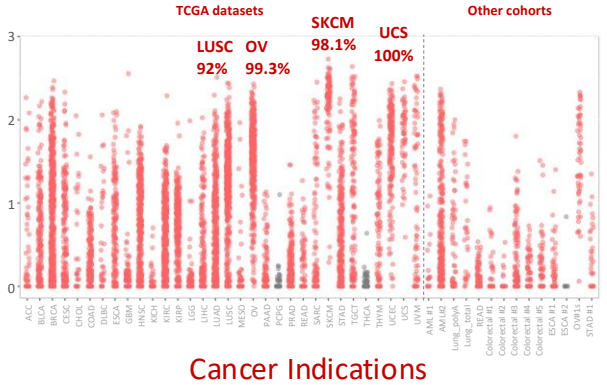


Cancer Indications

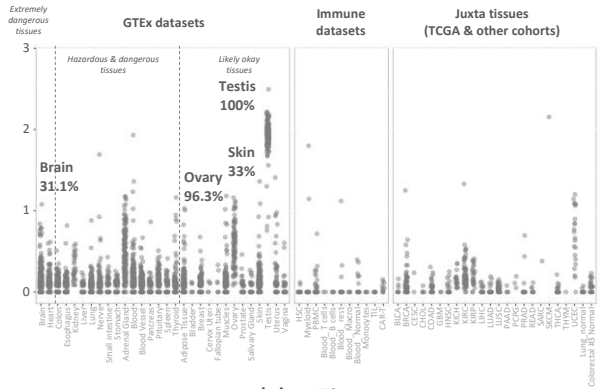


Healthy Tissues

PRAME
A*02:01

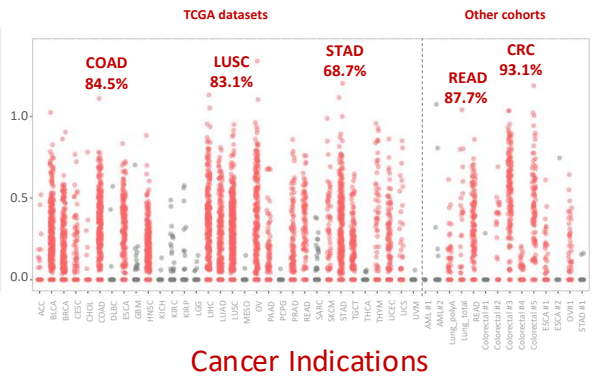


Cancer Indications

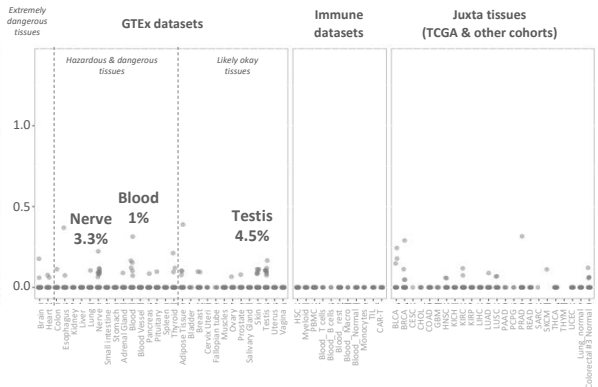


Healthy Tissues

MNO-P12
A*03:01/11:01



Cancer Indications

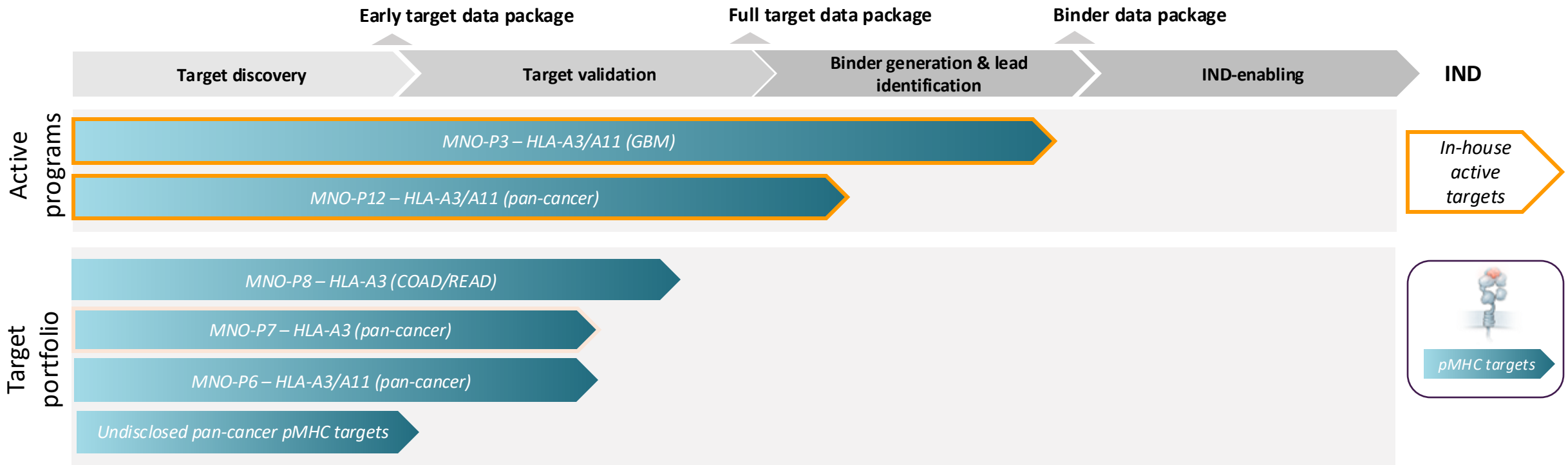


Healthy Tissues

Active programs for TCE development

A pipeline of tumor-specific targets in multiple cancer indications

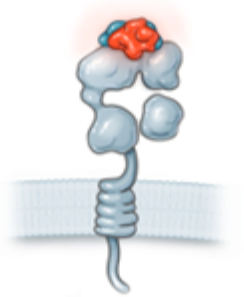
- Active programs focus on highly tumor-specific, highly recurrent targets in major cancer indications with strong medical needs



MNO-P3 is a highly specific pMHC target for glioblastoma, druggable by immunotherapies

MNO-P3

HLA-A*03 and HLA-A*11



- *First-in-class Dark Genome pMHC target in Glioblastoma*
- *High recurrence in GBM patients: 25-30% US & EU and 40-50% CN*
- *dPCR-based assay & HLA-typing for patient selection*
- *One lead binder with in vivo efficacy*

Early target data package

Extended target data package

Extended binder data package
Full target data package

Target discovery	Target validation	Binder generation & lead identification	TCE modality selection & IND-enabling

*MNO-P3 – HLA-A*03 (GBM)*

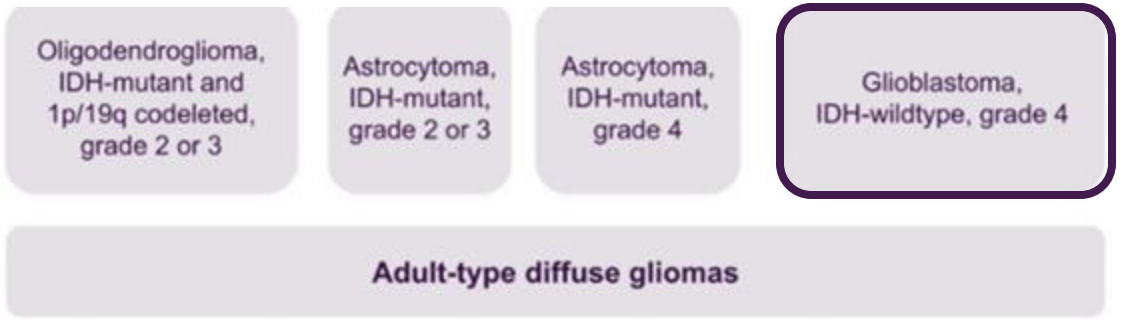
IND in 2026

MNO-P3 is a first-in-class pMHC target in glioblastoma

Glioblastoma has one of the highest levels of unmet need across all of oncology

- More than 79,000 incident cases of GBM in 2023[1], expected to rise to 86,900 cases by 2028, especially A*11 high markets (Asia)
- Average survival lower than 8 months

MNO-P3 is expressed in aggressive non-curable Grade-4 gliomas



- Glioblastoma is an important unmet medical need for immunotherapies
- Bispecific antibodies and CAR-Ts are under early clinical investigation
- Paucity of high quality targets hampers clinical response
- Manufacturing costs remain a limiting factor for clinical development

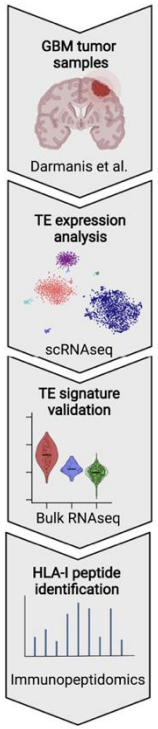
➢ **Mnemo's MNO-P3 program offers an off-the-shelf first-in-class therapeutic solution**

[1] 16 countries covered in GlobalData's epidemiology forecast, Global Data Reports 2023; Alsajjan & Mason, 2023, Curr Oncol; Ajeeb & Clegg, 2023, Adv Drug Deliv Rev Testa et al, 2024, Cancers

MNO-P3 expression is highly brain tumor-specific

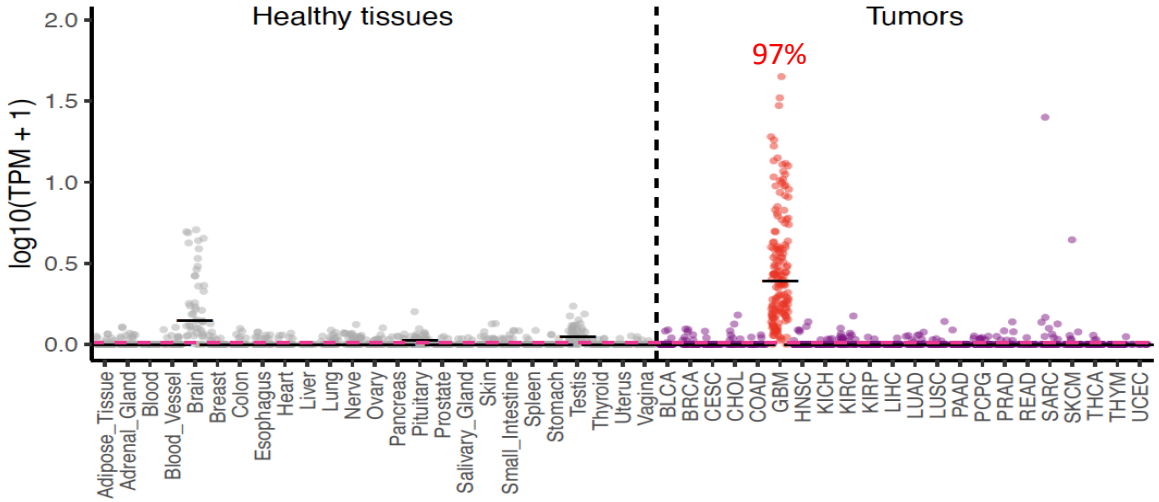
- Dark Genome-derived peptide, expressed in >97% of GBM tumors with very low healthy brain tissue expression
- MNO-P3 is presented by multiple HLA alleles: HLA-A*03:01 (25-30% US & EU) and HLA-A*11:01 (40-50% CN)

Bonté *et al.*
Cell Rep. (2022)



MNO-P3 identification

Bulk RNAseq



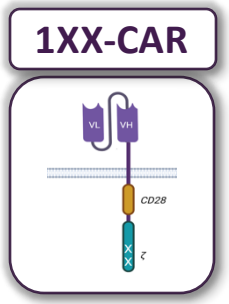
Immunopeptidomics

Dataset	Sample type	MNO-P3 detection
Shraibman et al (A*03)	**GBM sample**	**Yes**
Bartok et al (A*03)	**SKCM cell line**	**Yes**
Daoy-HLA-A*11	**MB cell line**	**Yes**
HLA Ligand Atlas	*Normal brain tissue*	*No*

- MNO-P3 is expressed in aggressive non-curable Grade-4 gliomas (GBM)
- Safe profile with very low healthy tissue expression
- MNO-P3 expression is only detected in neoplastic cells in single-cell RNA-seq GBM datasets
- MNO-P3 peptide is detected in brain tumour and not in healthy samples

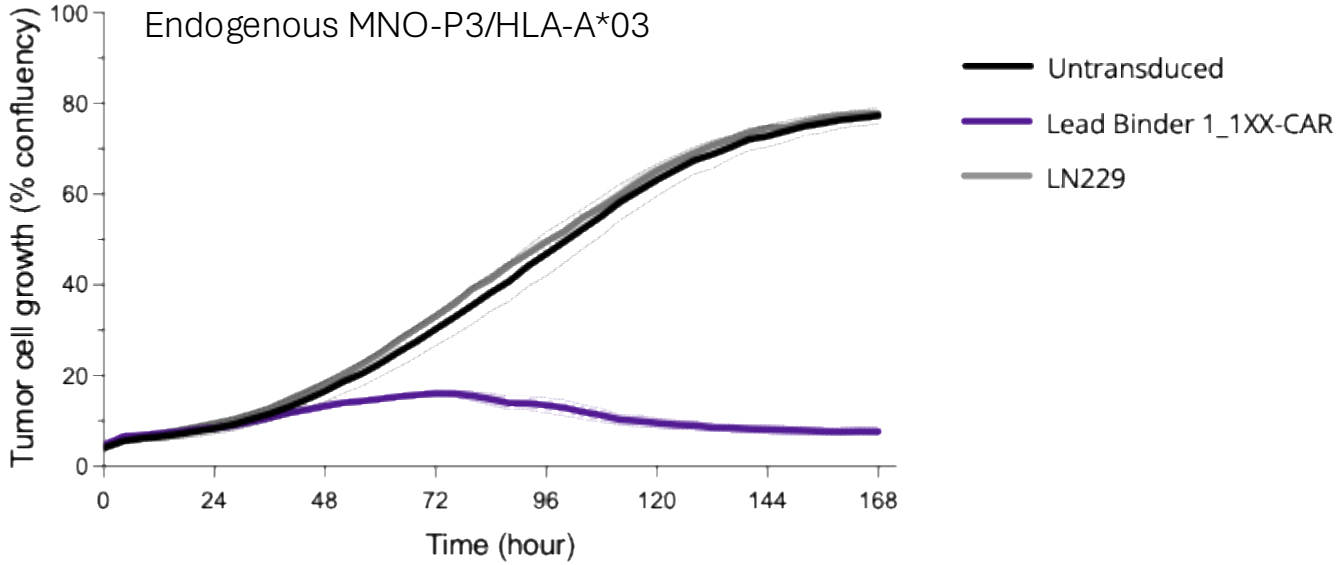
MNO-P3 targeting CAR T cells promote rejection of GBM cell lines in vitro and in vivo

1XX-CAR



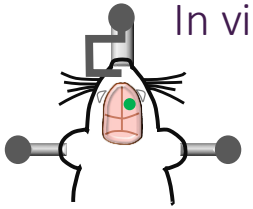
CAR long CTL assay with low E:T ratios
7 days, Fluorescence live imaging

Tumor cell growth



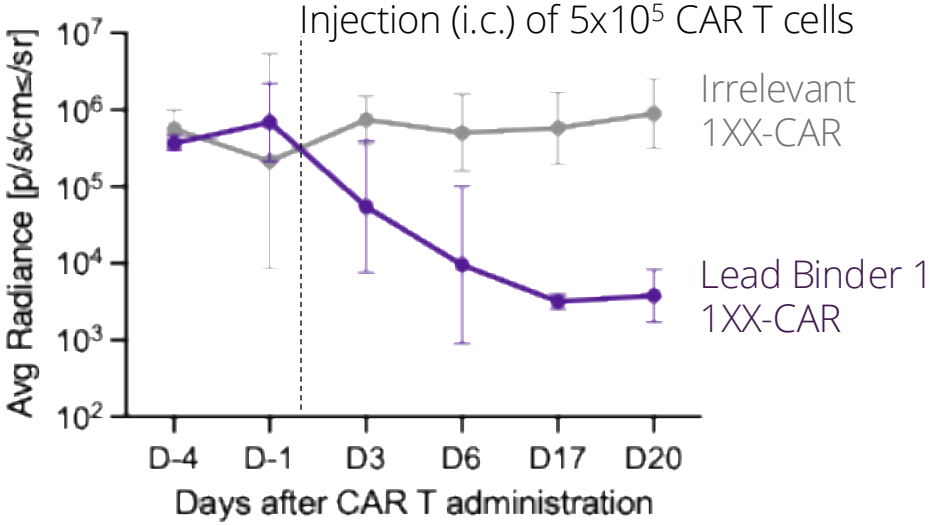
➢ *100% killing of target cells in vitro*

In vivo validation (preliminary results)



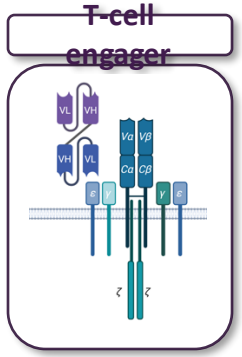
NSG mice
(n=3-4/group)

D-7: Intracranial injection of
GBM cell line LN229
(MNO-P3^{pos} / HLA-A3^{pos})

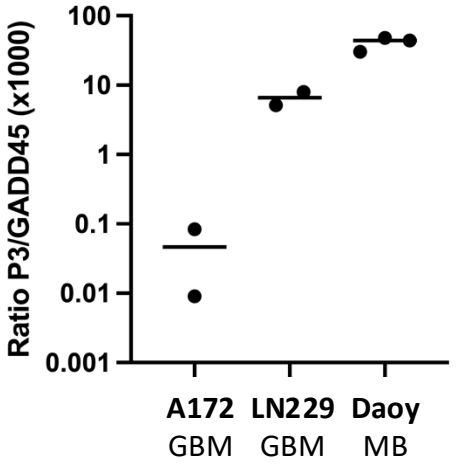


➢ *In vivo rejection of intracranial GBM tumors*

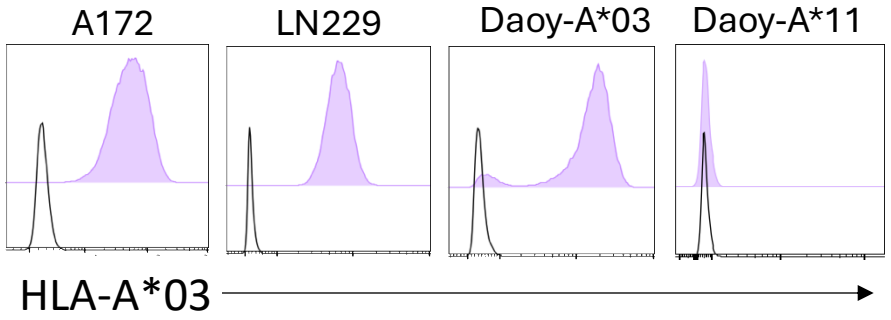
MNO-P3 targeting BiTEs promote specific cytotoxicity of brain tumor cell lines



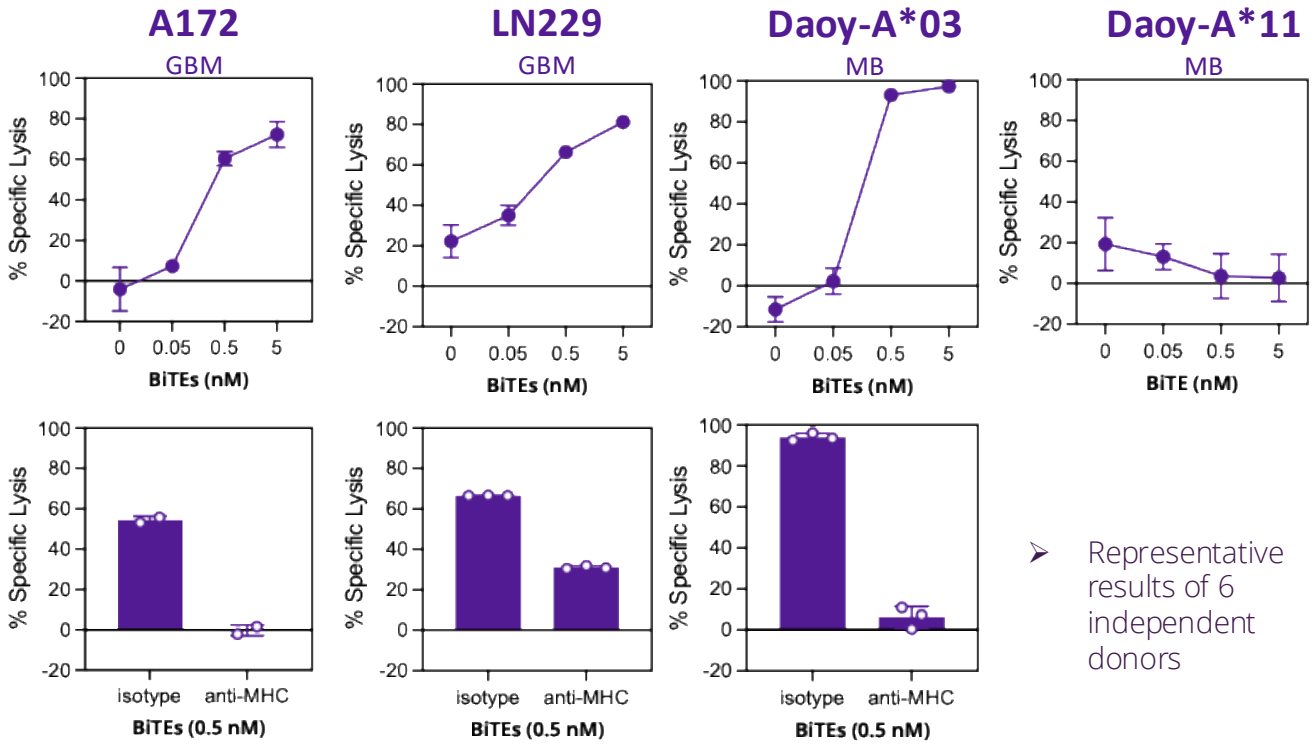
MNO-P3 expression validated in brain tumor cell lines by Digital PCR



HLA-A*03 expression by flow cytometry



Lead Binder 1-BiTE cytotoxicity
48h Bioluminescence assay, E:T ratio 5:1



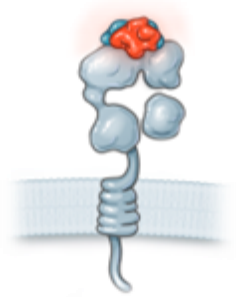
- Representative results of 6 independent donors

- MNO-P3/HLA-A*03 targeting BiTEs promote specific cytotoxicity of brain tumor cells with both peptide pulsing and endogenous MNO-P3 expression
- Lead binder cytotoxicity is dose-dependent and HLA-specific
- Similar results with Lead Binder 2
- "Novel clinical TCE format" under evaluation

MNO-P12 is a highly tumor-specific pan-cancer target

MNO-P12

HLA-A*03 and HLA-A*11



- *Dark Genome derived pMHC target*
- *Highly tumor-specific in multiple solid tumors (70-90% recurrence in LUSC, COAD, READ…)*
- *>600,000 (EU & US) and >1,100,000 (Asia) patient cases per year (A*03/A*11)*
- *PCR-based companion assays (quantitative and single cell level) in development*
- *TCR-mimic scFv clones identified by phage display screens*

Early target data package

Extended target data package

Extended binder data package
Full target data package

Target discovery → **Target validation** → **Binder generation & lead identification** → **TCE modality selection & IND-enabling**

*MNO-P12 – HLA-A*03 (Pan-cancer)*

IND in 2027

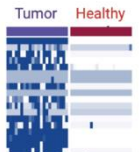
LUSC - Lung Squamous Cell Carcinoma; COAD - Colon adenocarcinoma; READ - Rectum adenocarcinoma

MNO-P12 is a highly tumor-specific pMHC target for multiple cancers

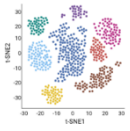
- MNO-P12 is a peptide derived from a *lncRNA* invovled in cancer progression
- MNO-P12 is presented by multiple HLA alleles: HLA-A*03:01 (25-30% US & EU) and HLA-A*11:01 (40-50% CN)

Discovery Hub

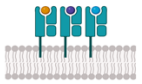
Bulk RNAseq



scRNAseq



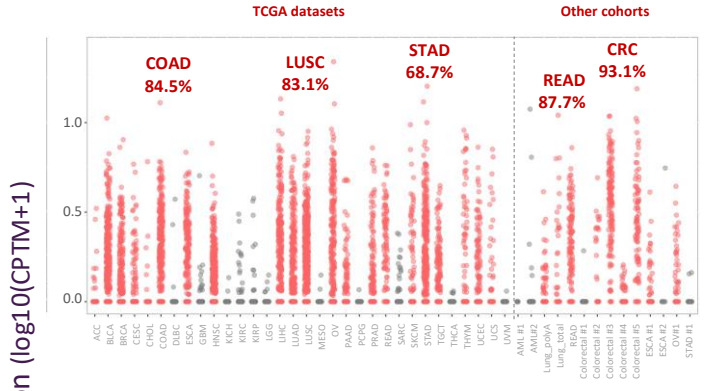
Immuno-peptidomics



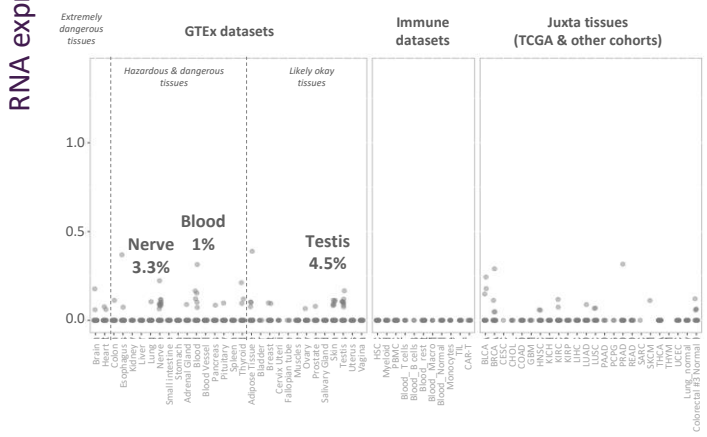
Identification of MNO-P12

RNA expression profile

Expression in tumors

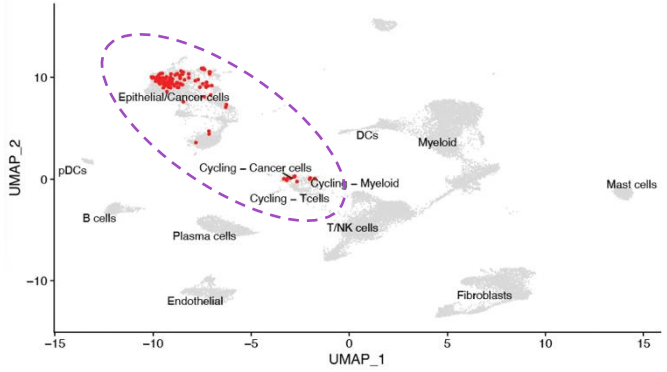


Expression in healthy tissues



Single-cell RNAseq (scRNAseq)

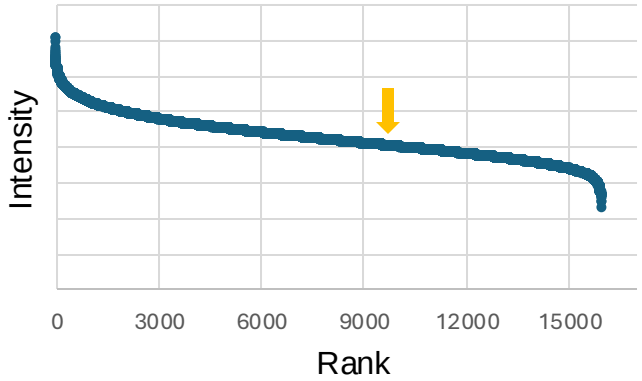
100% of MNO-P12 expressing cells are malignant



(n=6/33 positive samples) Maynard *et. al,* Cell 2020

Immunopeptidomics

Relative intensity of MS-detected MNO-P12



- MNO-P12 splicing junction is highly recurrent in multiple cancer indications, (Lung / Gastro-intestinal / Ovarian cancers…)
- MNO-P12 transcript has been found in malignant cells only by scRNAseq in Lung Cancer and Melanoma
- MNO-P12 peptide is presented by HLA-A*03 on the surface of tumor cells and can be detected by mass spectrometry

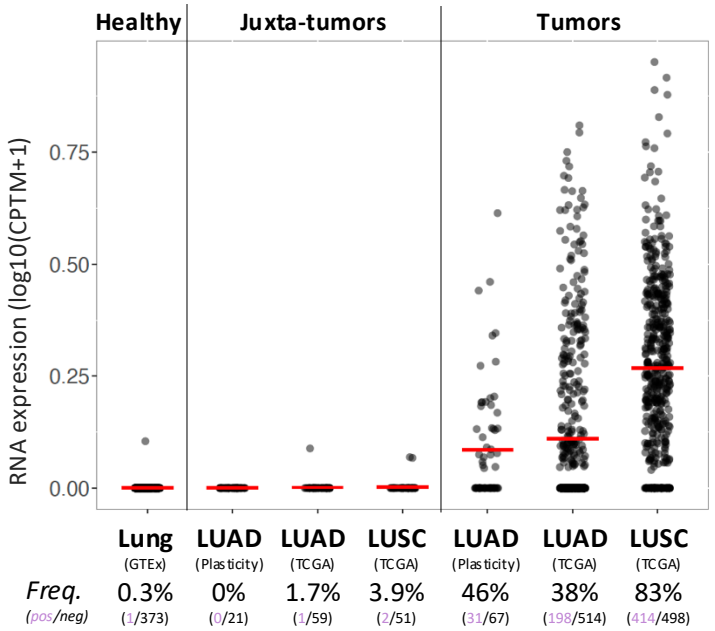
Expression of MNO-P12 splicing junction is highly tumor-specific

- MNO-P12 splicing junction was assessed in healthy lung (n=5), LUAD (n=8) and LUSC (n=9) patient samples

RNA-seq

Expression

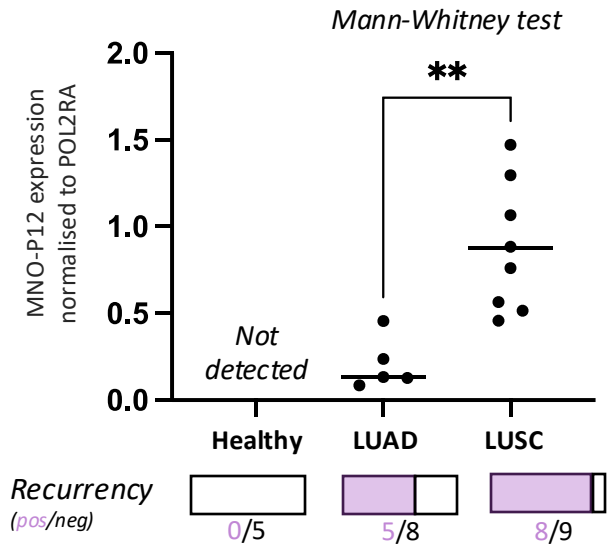
(Each dot is a sample
Mean of all samples is represented)



RT-qPCR

Expression

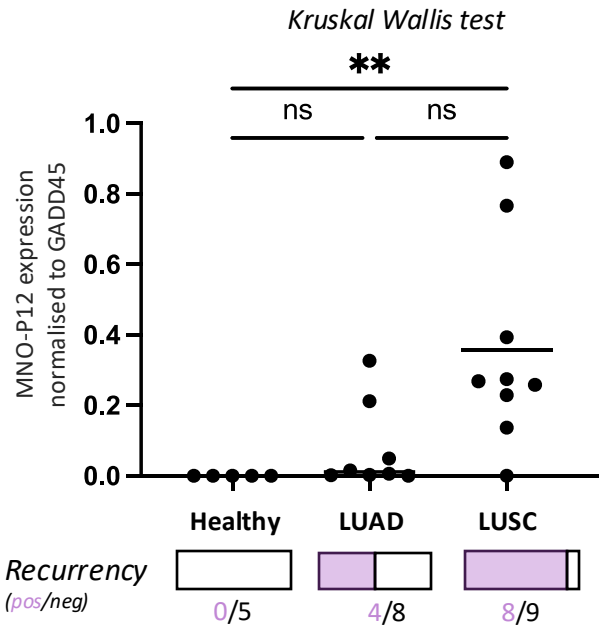
(Normalised to housekeeping gene
Mean of biological replicates represented)



RT-ddPCR

Expression

(Normalised to housekeeping gene
Mean of biological replicates represented)



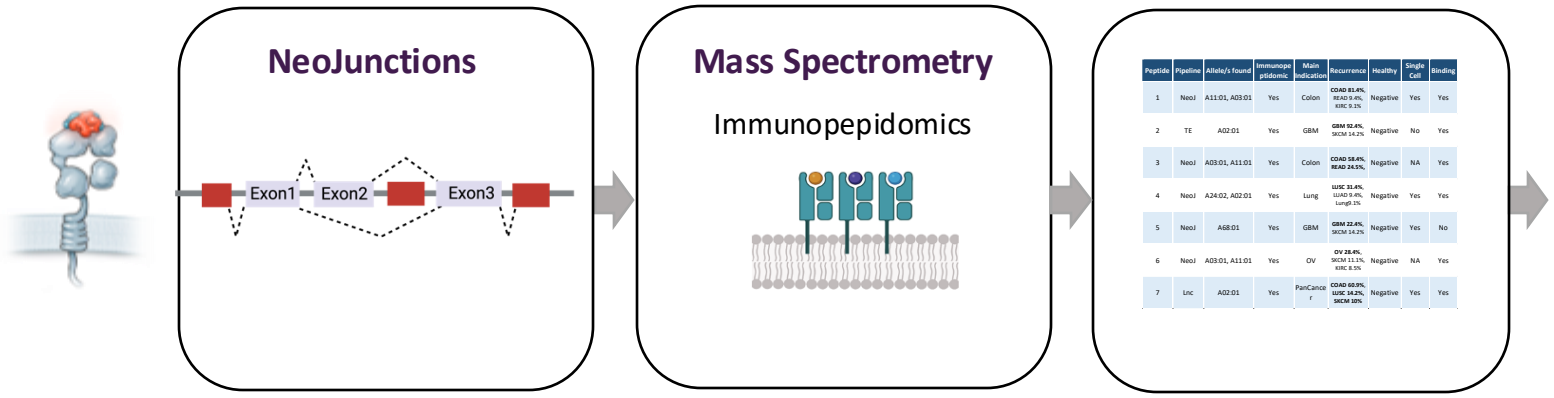
- MNO-P12 junction expression is tumor-specific, not detected in healthy samples
- MNO-P12 junction expression is increased in LUSC over LUAD tumor samples

Cancer Vaccines

Mnemo's novel pMHC E-antigens can also be used to develop cancer vaccines

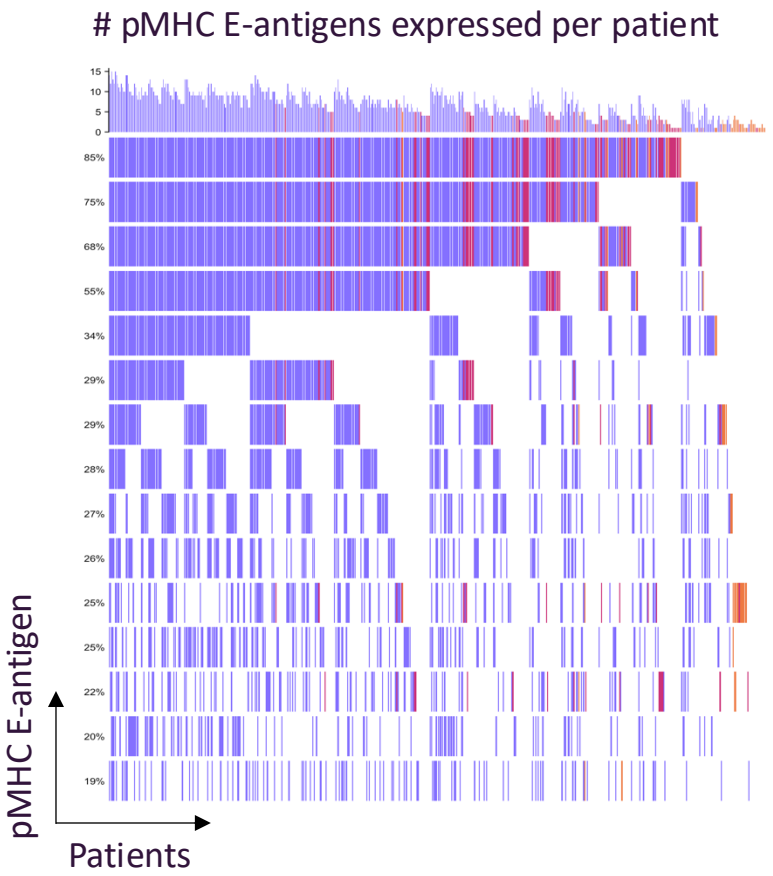
- pMHC E-antigens are highly recurrent and tumor-specific
- E-antigens are all MS-validated
- Novel and proprietary peptide bank generated across cancer indications and HLA alleles
- High patient coverage with a small pool (10-20) of pMHC E-antigens in main HLA alleles

Identification of tumor-specific transcripts → **HLA-presented antigens** → **Bank of multi-allelic public dark genome validated antigens**



Peptide	Pipeline	Allele/s found	Immunopeptidomic	Main indication	Recurrence	Healthy	Single Cell	Binding
1	NeoJ	A11:01, A03:01	Yes	Colon	COAD 81.4%, READ 9.4%, KIRC 9.1%	Negative	Yes	Yes
2	TE	A02:01	Yes	GBM	GBM 92.4%, SKCM 14.2%	Negative	No	Yes
3	NeoJ	A03:01, A11:01	Yes	Colon	COAD 58.4%, READ 24.5%,	Negative	NA	Yes
4	NeoJ	A24:02, A02:01	Yes	Lung	LUSC 31.4%, LUAD 9.4%, Lung9.1%	Negative	Yes	Yes
5	NeoJ	A68:01	Yes	GBM	GBM 22.4%, SKCM 14.2%	Negative	Yes	No
6	NeoJ	A03:01, A11:01	Yes	OV	OV 28.4%, SKCM 11.1%, KIRC 8.5%	Negative	NA	Yes
7	Lnc	A02:01	Yes	PanCancer	COAD 60.9%, LUSC 14.2%, SKCM 10%	Negative	Yes	Yes

Dark genome cancer vaccine with high patient coverage in lung, ovarian, and colon cancer

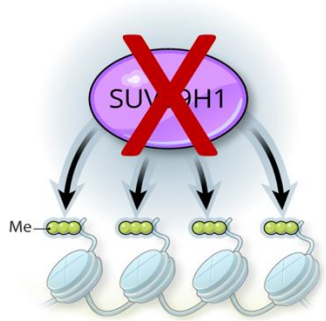


CAR-T cells

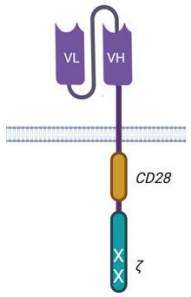
Mnemo's technology for CAR-T epigenetic reprograming enhances long-term protection in pre-clinical solid tumor models

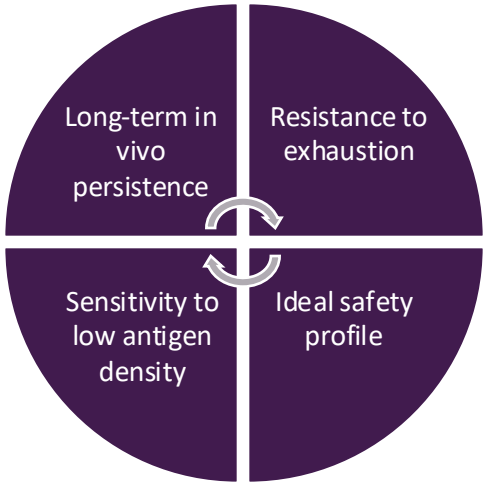
Mnemo's Approach

SUVi

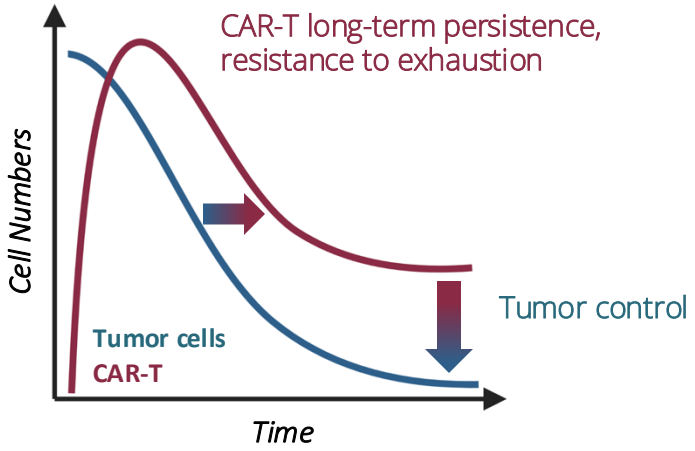


1XX-CAR



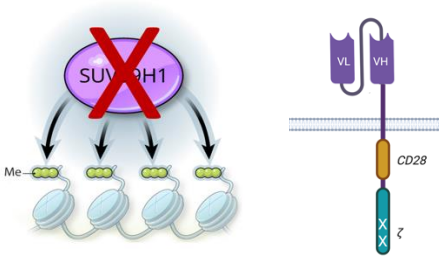


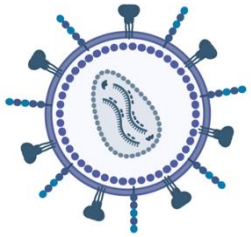
- Ablation of SUV39H1, a histone methyl transferase, enhances CAR-T cell persistence and activity in vivo, and prevents CAR-T exhaustion in solid tumors
- Best-in-class combination with the powerful 1XX-CAR



1XX-SUVi can be used in:

- Autologous setting
- Allogeneic (off-the-shelf) setting
- In vivo cell engineering
- NKs, iPSCs, TILs





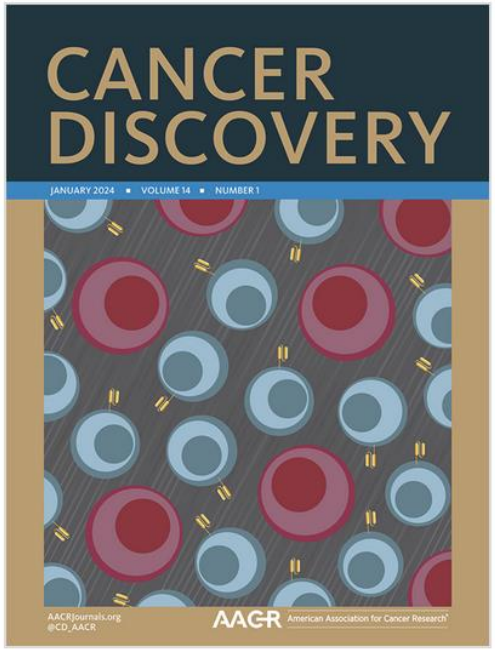
Strong IP position and FTO / Advanced Preclinical and Pre-IND Studies

Two recent publications from Amigorena and Sadelain labs demonstrate robust CAR-T epigenetic reprograming by SUV39H1 deletion

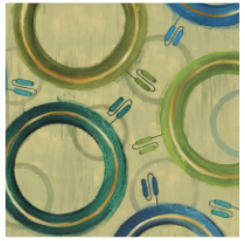
On the cover of Cancer Discovery Jan 2024 issue:

Volume 14, Issue 1

1 January 2024



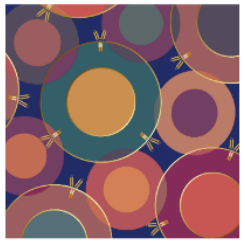
Long-Term CAR-T Function in Solid Tumors Is Enhanced by SUV39H1 Ablation



Limited chimeric antigen receptor (CAR) T cell expansion and persistence contributes to the failure of adoptive T cell therapies in patients with cancer. López-Cobo, Fuentealba, and colleagues demonstrate that CAR T cell stem/memory differentiation and persistence can be epigenetically enhanced via ablation of *SUV39H1*, a histone methyltransferase. *SUV39H1* gene-edited BBz-CAR T cells showed early reprogramming into stem-like populations with decreased expression of dysfunction genes, increased long-term *in vivo* persistence, and also protected mice against tumor relapses and rechallenges in solid tumor models, encouraging the use of SUV39H1 inactivation in adoptive cell therapy products. ■

Lopez-Cobo et al (2024) *See article, p. 120.*

SUV39H1 Disruption Promotes CAR T Cell Efficacy



Chimeric antigen receptor (CAR) T cells have demonstrated clinical success, but many patients will eventually relapse, in part, due to poor T cell function and persistence. Jain, Zhao, and colleagues showed that genetic disruption of *SUV39H1*, which encodes a histone-3, lysine-9 methyl-transferase, leads to enhanced early expansion, long-term persistence, and antitumor efficacy in leukemia and prostate cancer models. Moreover, upon multiple rechallenges, *SUV39H1*-edited CAR T cells had improved expansion and tumor rejection while also having limited exhaustion and reduced inhibitory receptors. Together, these results suggest that CAR T cell epigenetic programming could lead to improved anti-cancer adoptive cell therapies. ■

Jain et al (2024) *See article, p. 142.*

Executive summary

Executive summary

➢ Mnemo has a cutting-edge end-to-end validated platform, providing multiple partnering opportunities

Discovery Hub

A first-in-class, end-to-end validated, proteogenomic Dark Genome target discovery platform

Tumor targets

A unique target portfolio of pan-cancer and tumor-specific actionable dark genome targets for immunotherapy

Immunotherapy Modalities

Unique opportunities for developing T-cell engagers, cancer vaccines and CAR T cells

Assets:

- End-to-end validated, proteogenomic dark genome target discovery platform
- Lead and backup binders for a highly recurrent pMHC E-antigen in GBM
- Portfolio of multi-solid cancer targets
- Validated cancer E-antigens for high coverage cancer vaccine development
- Epigenetic reprograming technology for highly persistant, exhaustion resistant, CAR-T cells

MNEMO THERAPEUTICS

Thank you!

www.mnemo-tx.com

Q1 2025

Some figures of this deck have been created with Biorender