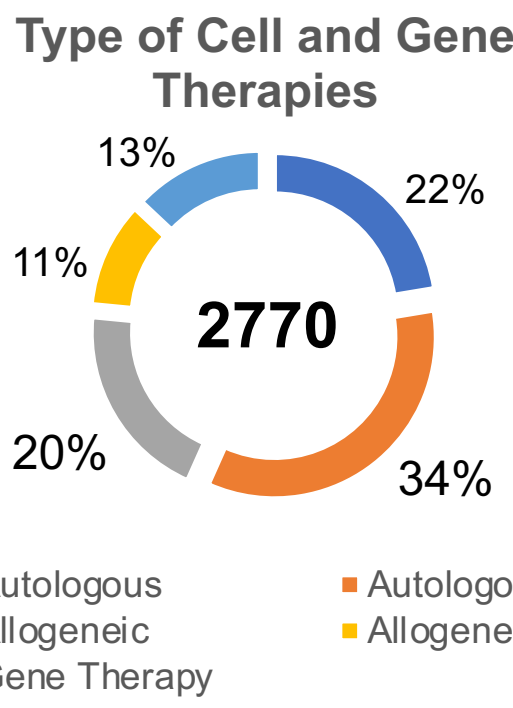
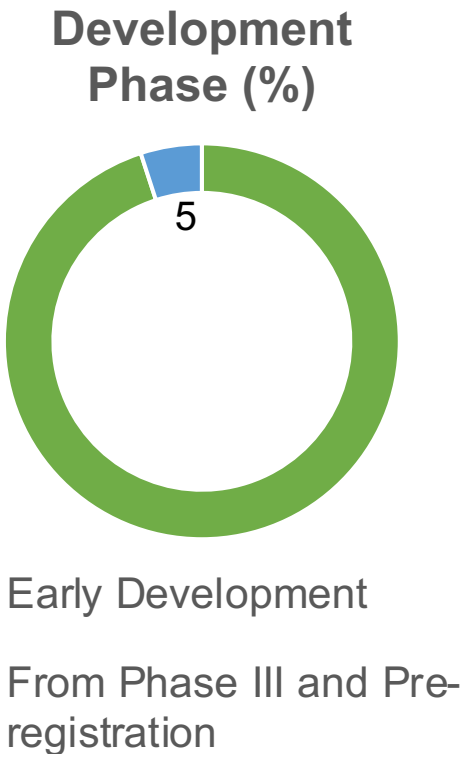
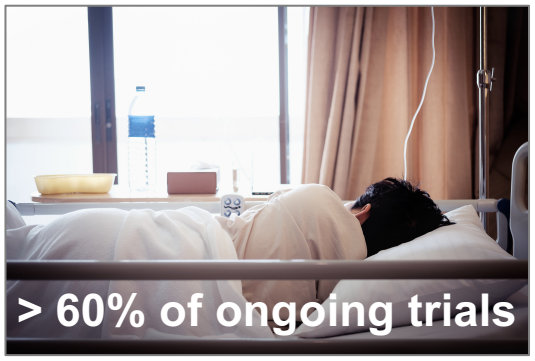
Cell and Gene Therapies in «Pills»





Oncology:



30 trials on non-small cell lung cancer

Clinicaltrial.gov & Globaldata Nov 2021

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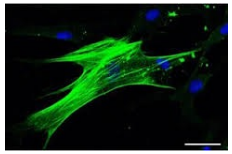
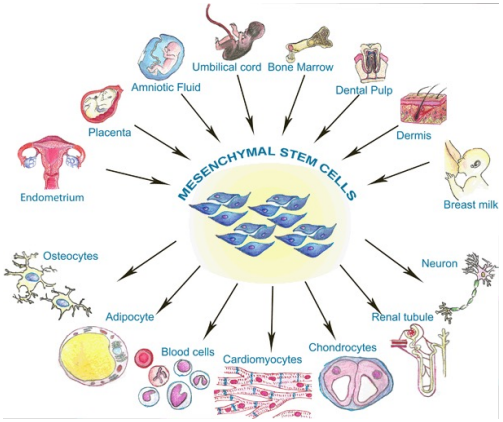
Treating Mesothelioma By Cell and Gene Therapies

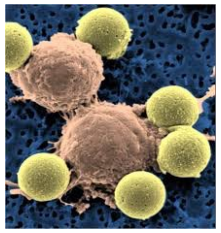
Massimo Dominici, Chiara Chiavelli & Giulia Grisendi

Mesenchymal Stromal/Stem Cells (MSC)





Chimeric Antigen Receptor (CAR) - Lymphocytes



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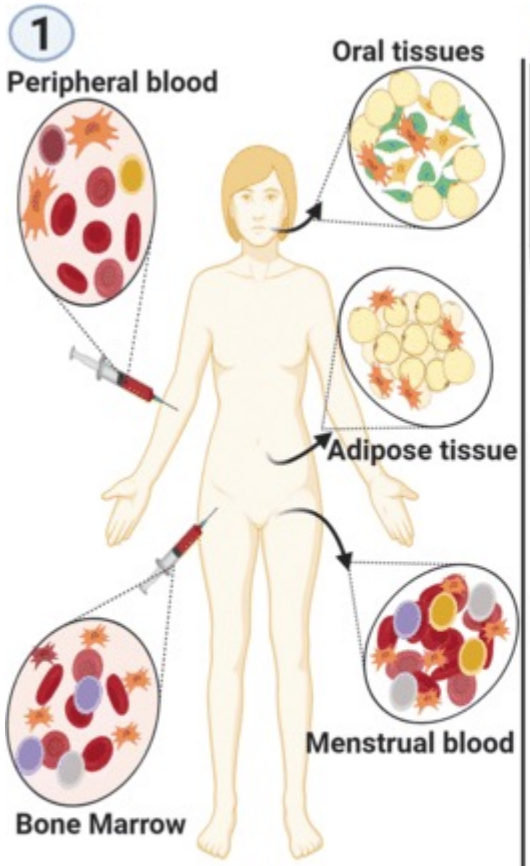
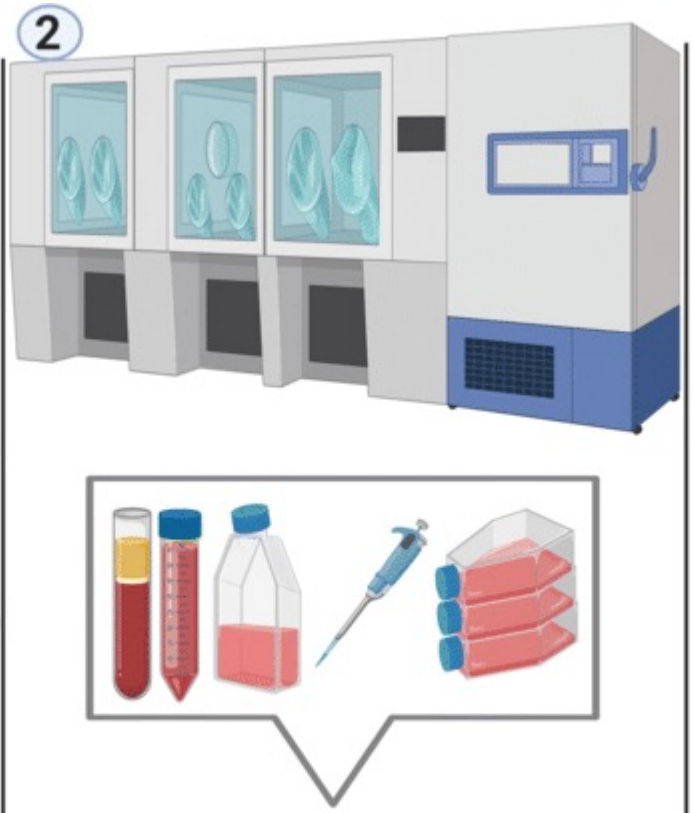
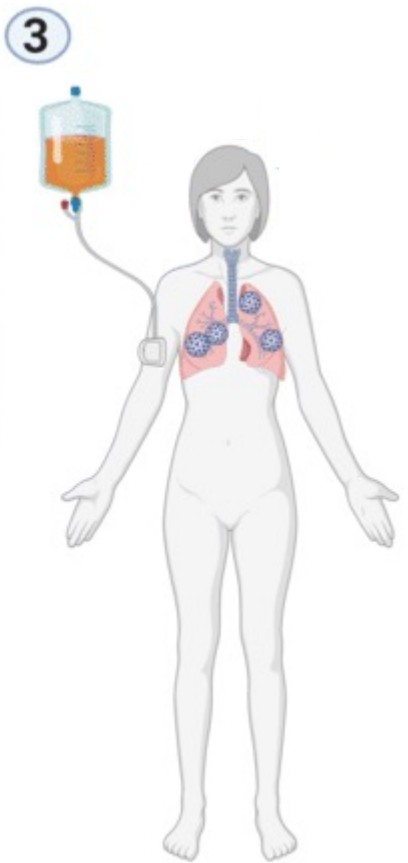
Use of engineered MSC to target solid malignancies



Mesenchymal stem cell sources in adults

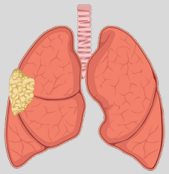


Cleanroom and Cell preparation process



Mesenchymal stem cell therapy for Mesothelioma

Modified from Golchin A. 2021 (Stem Cell Reviews and Reports)



Use of engineered MSC to target solid malignancies

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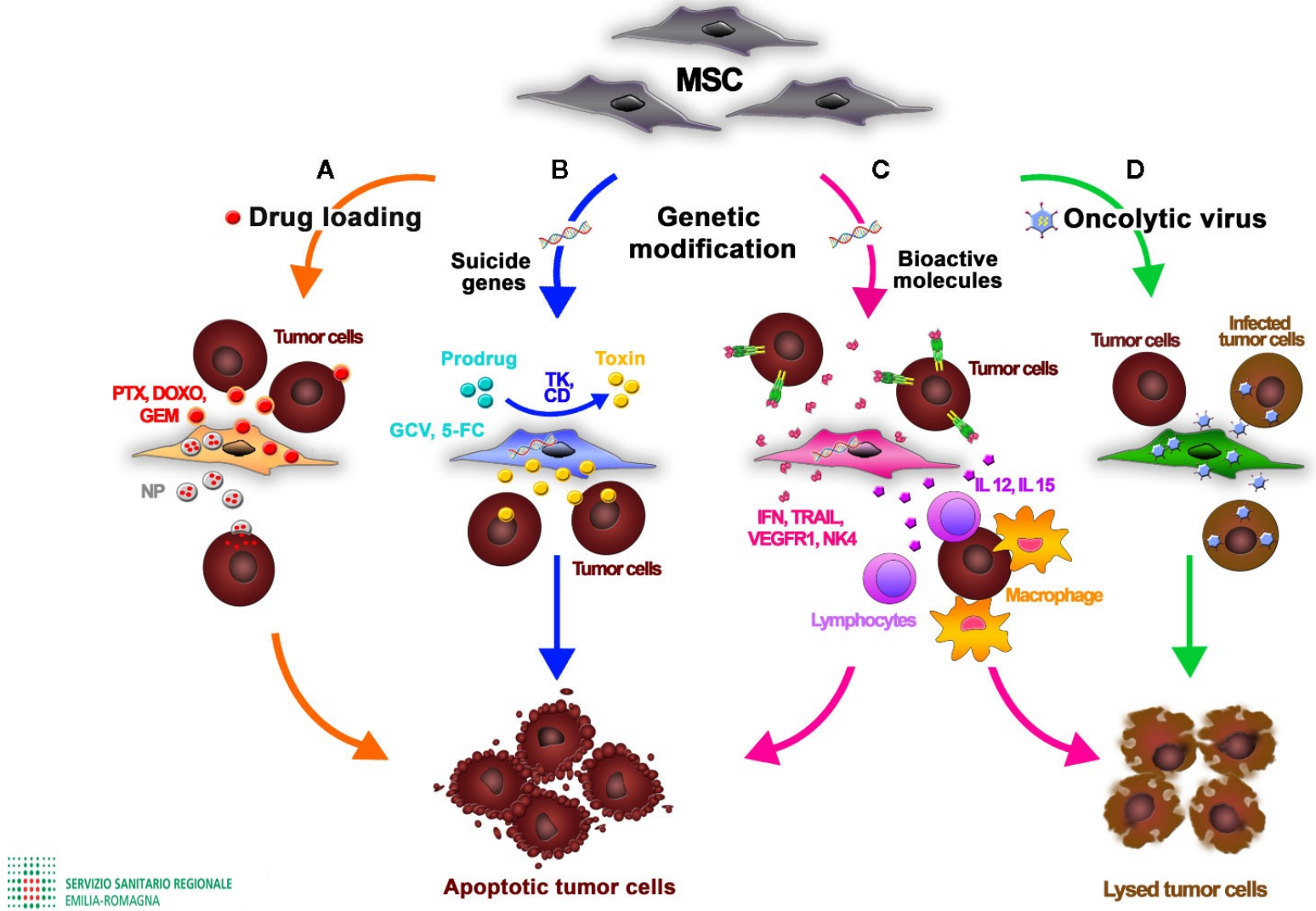

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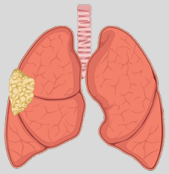
Golinelli G et al. 2020 (Front Pharmacol.)



MSC-based in vivo pre-clinical studies for MPM

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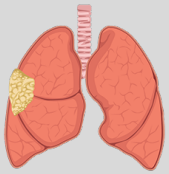
AUTHOR AND JOURNAL	TUMOR CELLS LINE	MSC DOSE AND DELIVERY	ADMINISTRATION NUMBER	RESULTS
Sage E. et al. (S.M. Janes)	MSTO intra pleural (80.000)	MSC sTRAIL 1.000.000 iv. And intra plural	5 (day 5; 9; 12;15;18)	No effect i.p. administration Tumor reduction (BLI) i.v.
Lathorp M.J	HEMSO intra peritoneally (1.000.000)	MSC-mbTRAIL 300.000 via intra peritoneum	Twice a week for 3 weeks starting from day 21	Slight reduction of tumore volume Reduction of sistemic inflammation
Cocce et al.	MSTO s.c. (1.000.000)	AD-MSC 5.000.000 s.c. close to tumor (MATRIGEL)	4 (day 0, 7,14,21 starting fromm 100 mm3 tumor volume)	Control of tumor growth comparable to Nab-PTX, reduction of tumor cell number



Systemic but not topical TRAIL-expressing MSC reduce tumor growth in malignant mesothelioma

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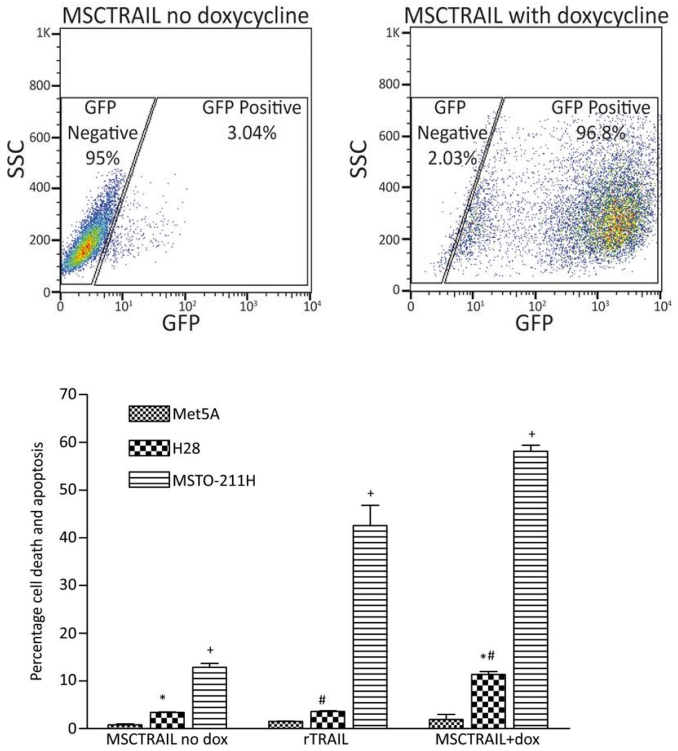
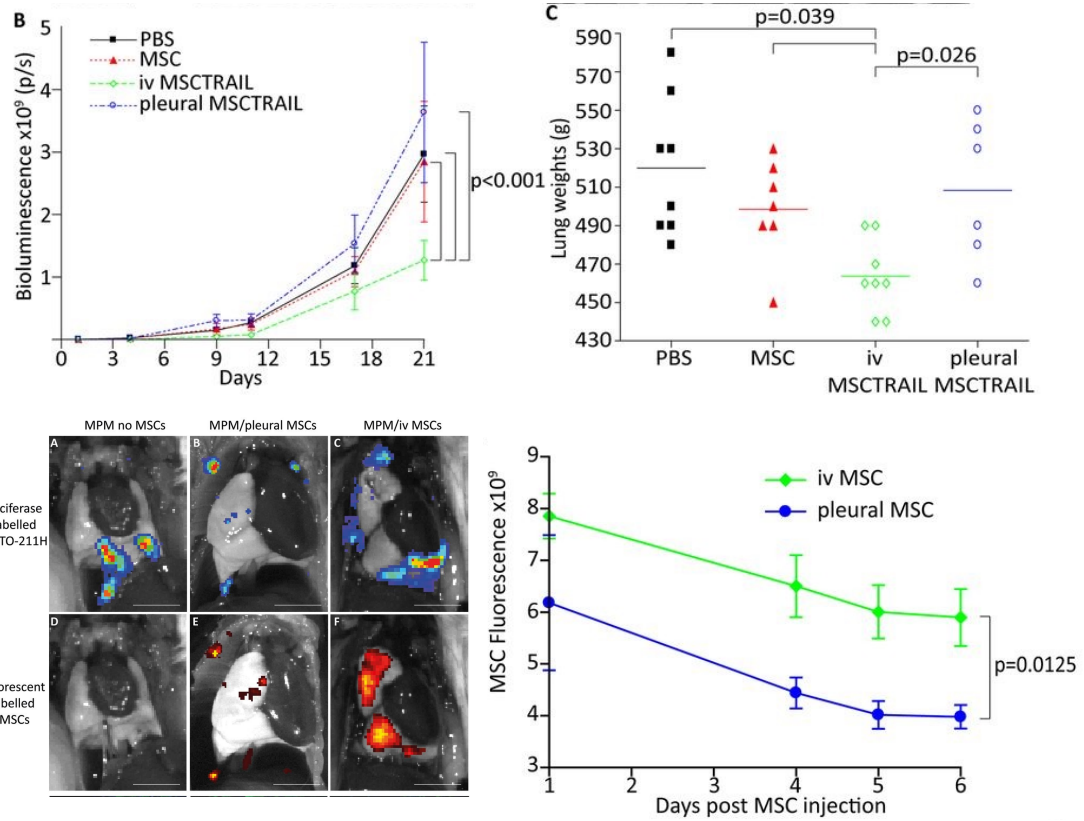
In vitro data



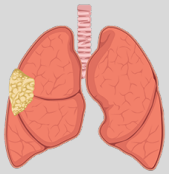
MSC transduction with TRAIL-IRES-eGFP under the control of a tetracycline-dependent. Human MPM exhibit variable in vitro sensitivity to rTRAIL and MSCTRAIL.

In vivo data



MSC-TRAIL reduce the growth of MPM when delivered i.v.
Human MSCs home to MPM when delivered both i.p. and i.v. but i.v.-delivered MSCs incorporate into tumors in greater numbers than intrapleural- delivered MSCs.

Sage E.K. et al. 2014 (Lung Cancer)



Antitumor effects of TRAIL-expressing MSC in a mouse xenograft model of human mesothelioma

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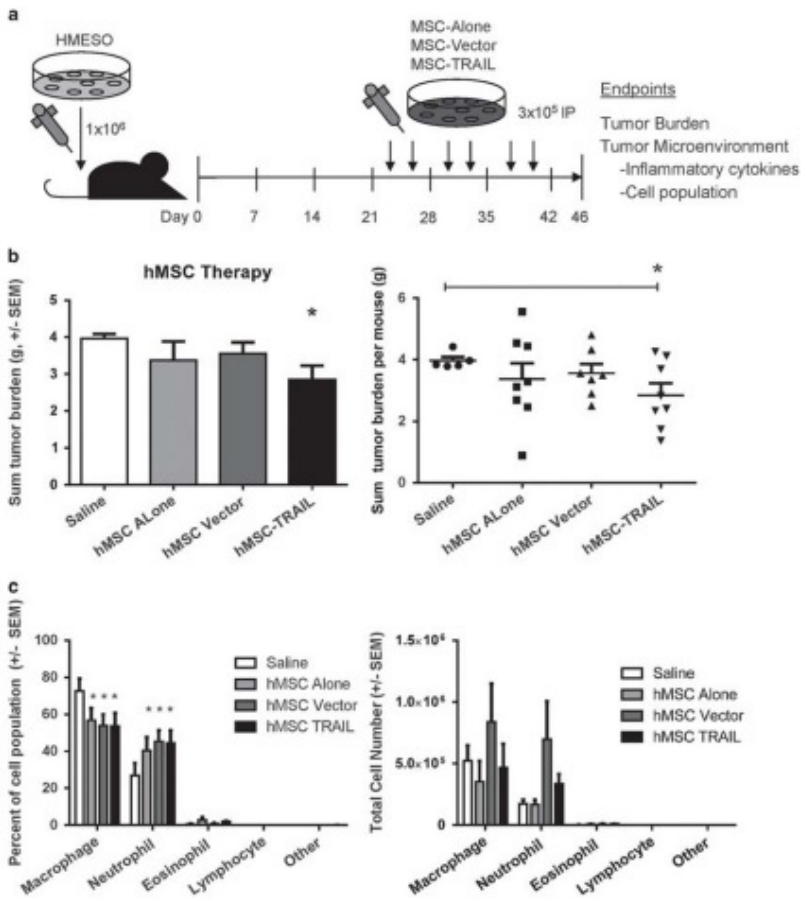
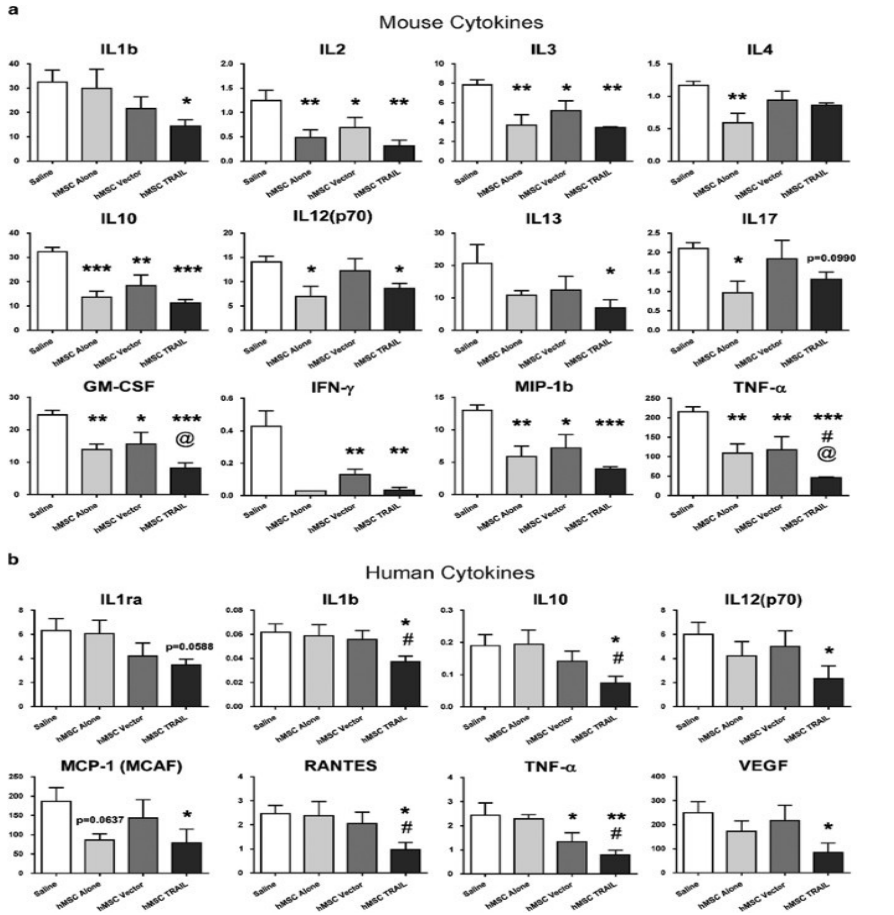
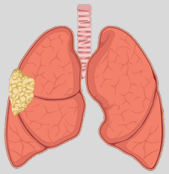


TRAIL-expressing hMSCs inhibit tumor growth when administered intraperitoneally to mature tumors. hMSC administration significantly increased the percentage of neutrophils within the PLF cell population.



hMSC administration further significantly decreased the levels of multiple PLF cytokines and chemokines (both mouse and human) in this model significantly reducing the inflammatory tumor environment in vivo.

Lathrop MJ et al 2015 (Cancer Gene Therapy)



Inhibition of Human Malignant Pleural Mesothelioma Growth by MSC

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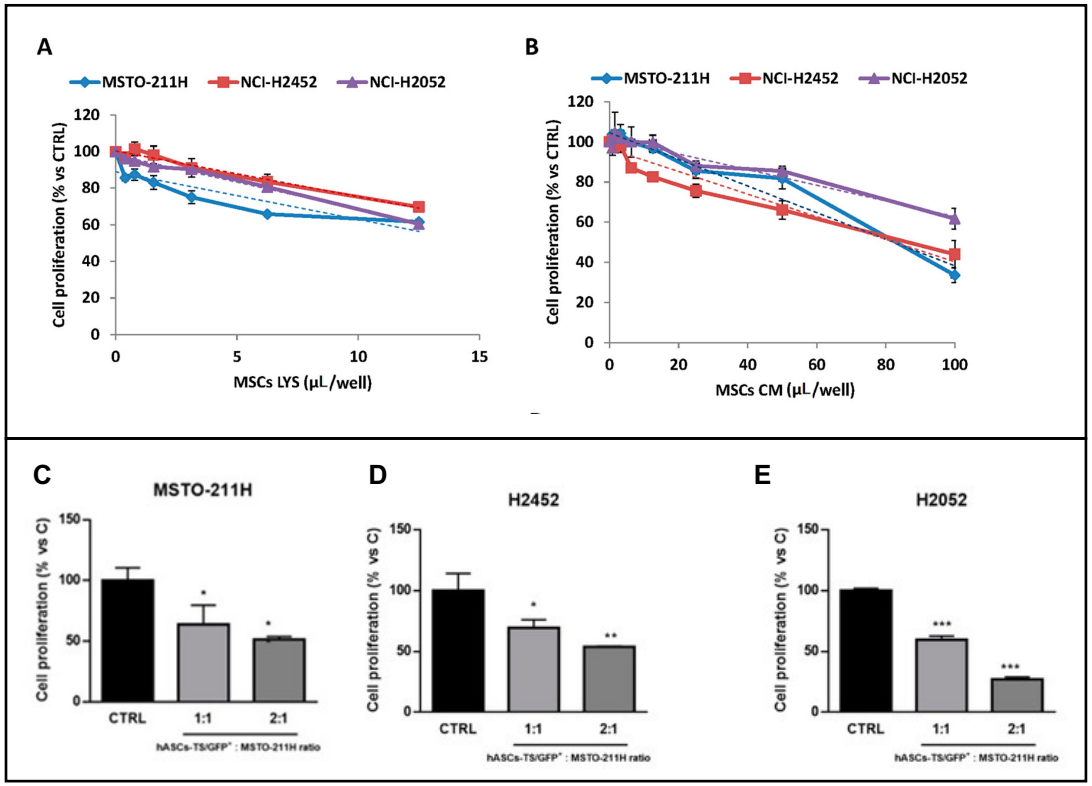

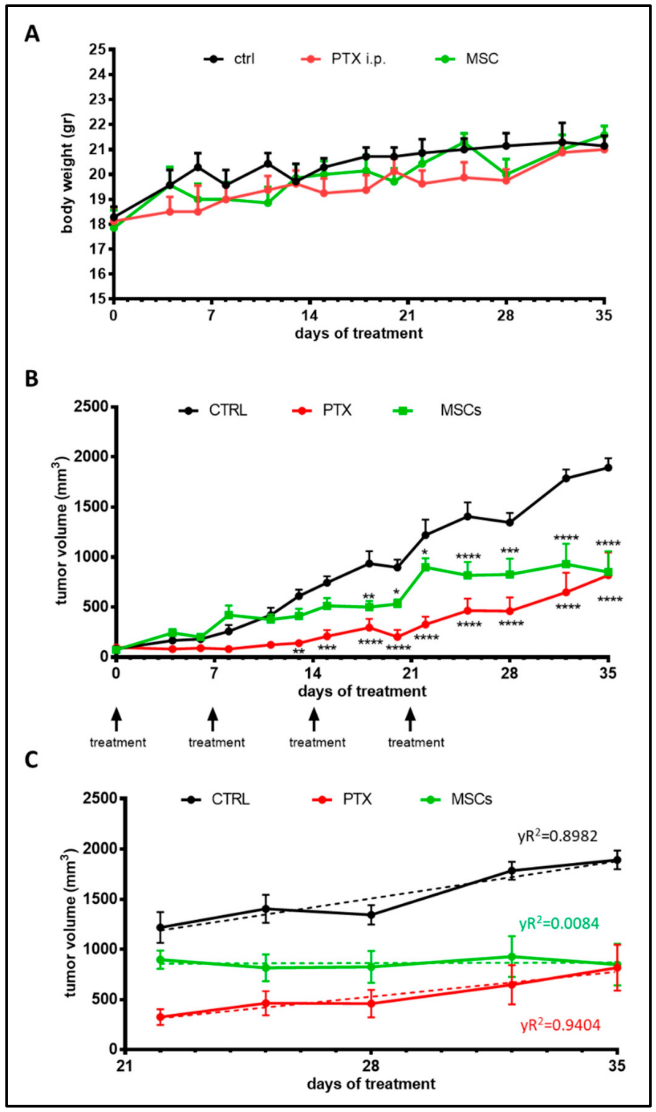

MSCs lysate and secretome inhibited MPM cell proliferation in vitro. Specific co-culture experiments showed that the proliferation of MPMcells was significantly impaired by the interaction with hASCs cells. The efficacy of MSC was confirmed in vivo by a significant inhibition of tumor growth, similar to that produced by systemic administration of paclitaxel. No tumor progression was observed after the last MSC treatment, while tumors started to grow again after stopping chemotherapeutic treatment..

Coccè V et al. 2021 (Cells)

MSC Towards Clinics

RIGENERAND
Steps Ahead In Cell Technology

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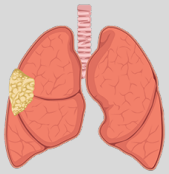

CAR T Cell Therapy against MPM

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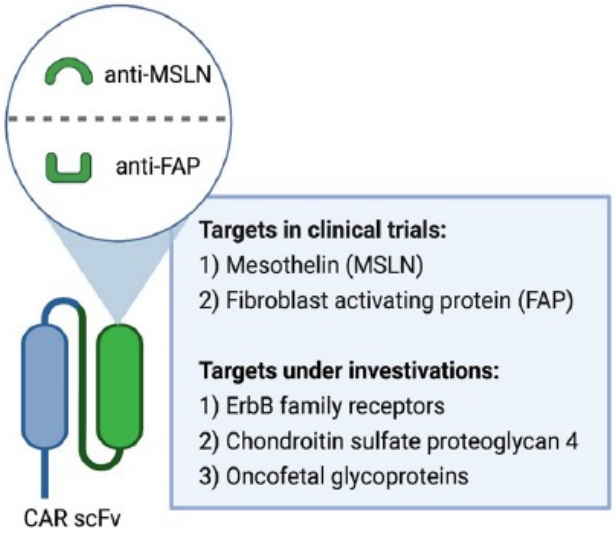
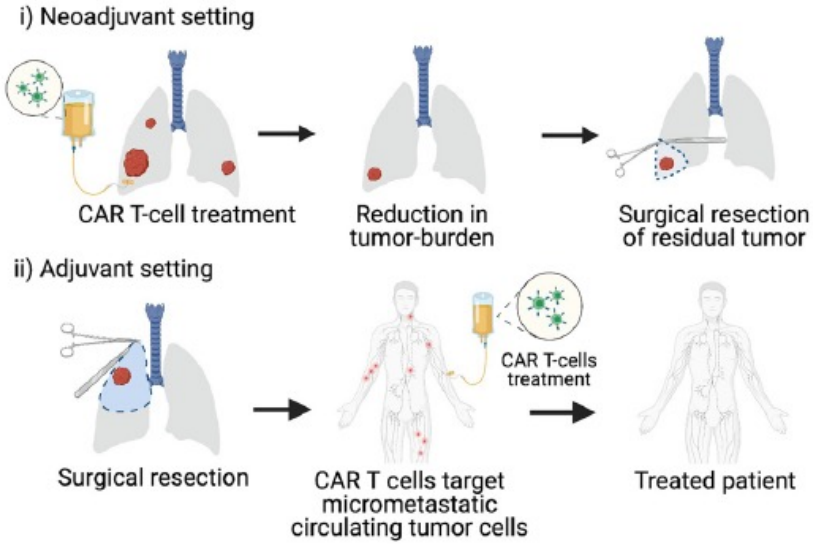
Antigen Targets in MPM

Mesothelin (MSLN) is an ideal cell-surface antigen to target. It is involved in tumor invasion and is expressed in 85% to 90% of MPM compared with lower levels in mesothelia.

FAP is expressed in the tumor stroma of multiple epithelial tumors, including all histologic subtypes of mesothelioma, with limited expression in normal adult tissue.





Surgery and CAR T treatment

Chintala NK et al. 2021 (*Lung Cancer*)

CAR T Cell Activity in MPM: Strategies to Overcome the Barriers

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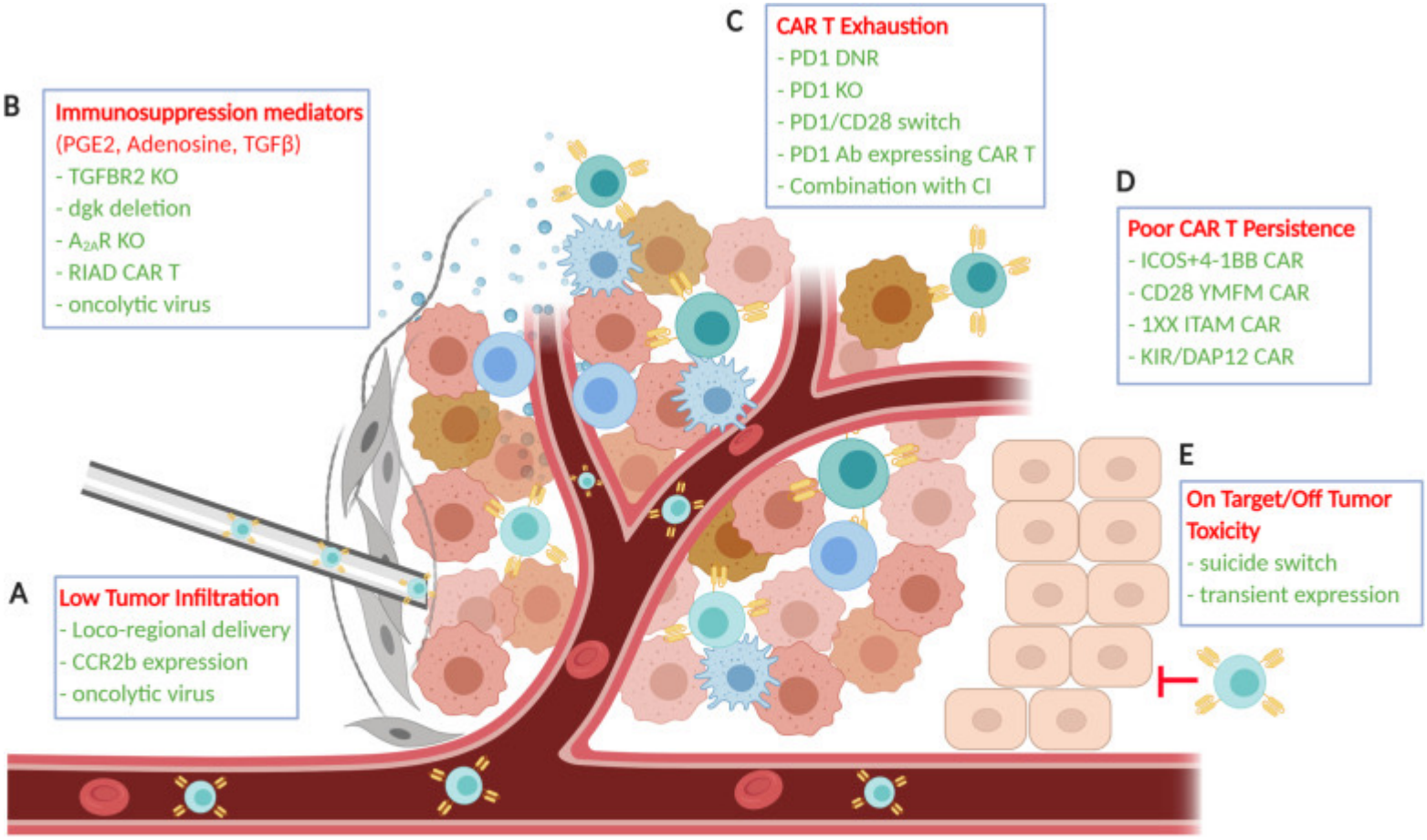

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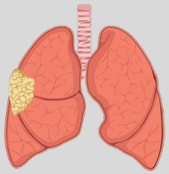
Castelletti L et al. 2021 (*Biomark. Res*)



CAR T Cell Therapy Clinical Trials for MPM

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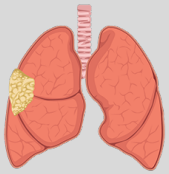
NTC, PHASE	TARGET ANTIGEN	CAR T CELL PRODUCT	DELIVERY	COMBINATORY THERAPY	CLINICAL SITE
NCT01355965 PhI	Mesothelin	mRNA transduced, mouse scFv	IV		University of Pennsylvania
NCT02159716, PhI	Mesothelin	Lentiviral transduced, mouse scFv	IV	w and w/o cyclophosphamide pretreatment	University of Pennsylvania
NCT03054298, PhI	Mesothelin	Lentiviral transduced, human scFv	IV/IPL		University of Pennsylvania
NCT02414269, PhI/II	Mesothelin	iCasp9M28z	IPL	w and w/o cyclophosphamide preconditioning, w and w/o pembro	Memorial Sloan Kettering Cancer Center
NCT04577326, PhI	Mesothelin	M28z-1XXPD1DNR	IPL	Cyclophosphamide	Memorial Sloan Kettering Cancer Center
NCT01583686, PhI/II	Mesothelin	Anti mesothelin CAR	IV	Fludarabine, cyclophosphamide, aldesleukin	National Cancer Institute
NCT03608618, PhI	Mesothelin	mRNA transduced PBMC	IP	Cyclophosphamide	MaxCyte
NCT03907852, PhI/II	Mesothelin	TRuC	IV	w and w/o cyclophosphamide preconditioning, w and w/o pembro	TCR2 Therapeutics
NCT04489862, PhI	Mesothelin	Anti–PD-1 nanobodies	IV	Cyclophosphamide	Wuhan Union Hospital
NCT03615313, PhI/II	Mesothelin	Anti–PD-1 antibody	IV	Fludarabine, cyclophosphamide	Shanghai Cell Therapy Research Institute
NCT01722149, PhI	FAP	FAP-specific redirected T cells	IPL	Neoadjuvant chemotherapy	University Hospital of Zurich

IV:intravenous, IP:intraperitoneal, IPL:intrapleural



A Phase I Trial: Mesothelin CAR T with Pembrolizumab

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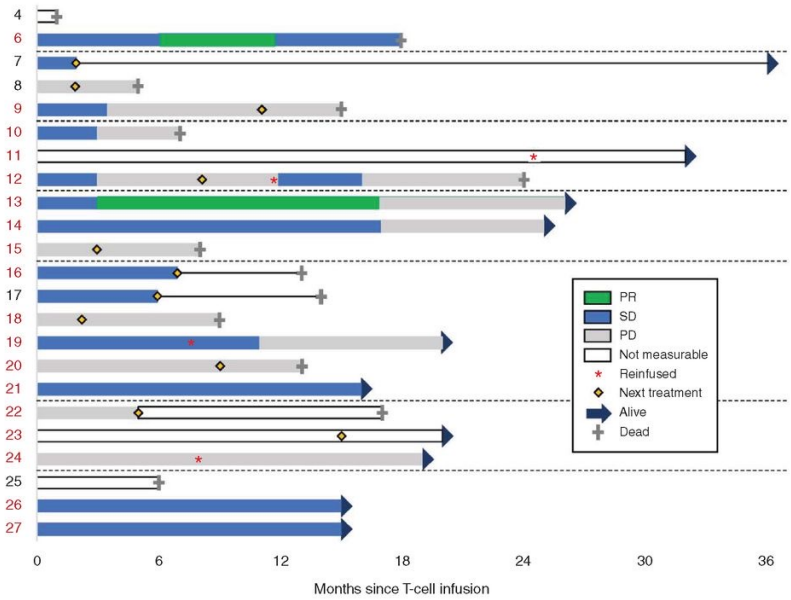
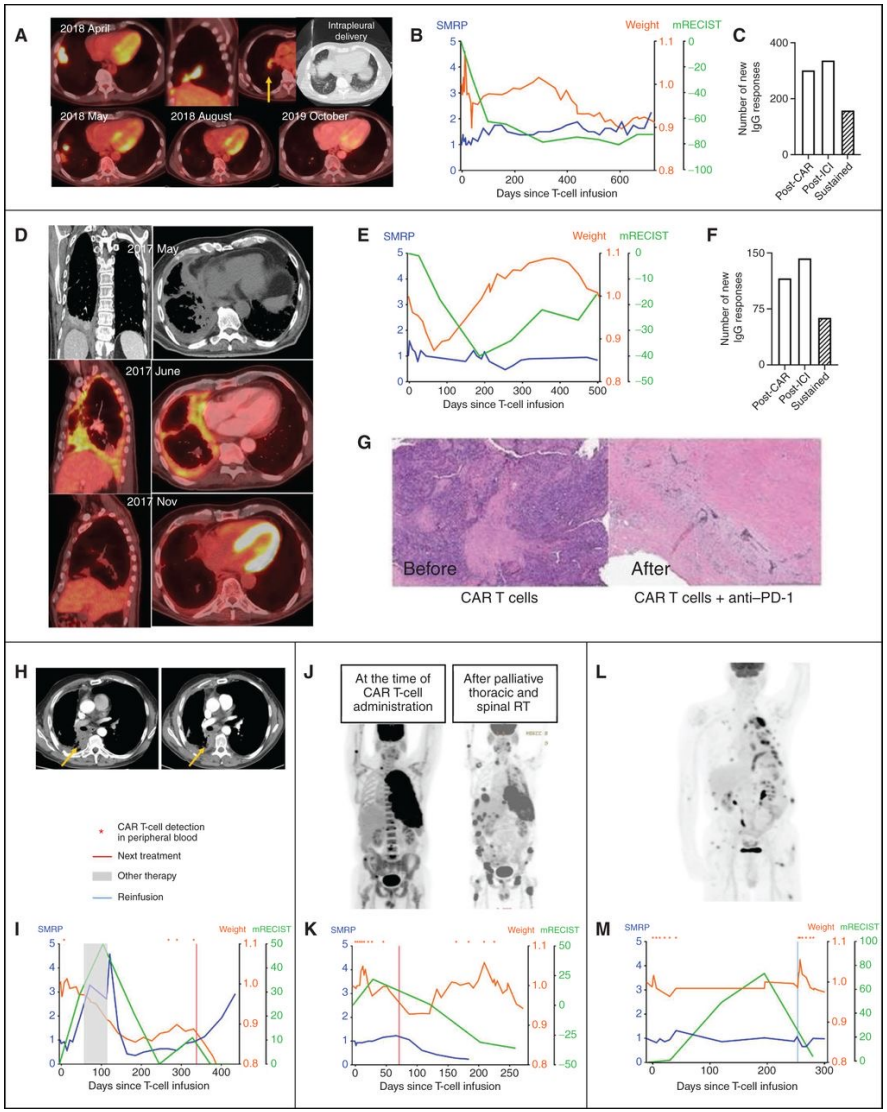
- **MSLN-targeted CAR T cells** followed by the administration of **pembrolizumab** were associated with unusual survival outcomes, reaching a median **OS of 23.9 months** in 18 pretreated patients with MPM.
- The **intrapleural** administration of CAR T cells was feasible and reached **long-lasting systemic circulation**. In 39% of patients, CAR T cells were detected in peripheral blood for more than 100 days.
- The treatment had **no grade 5 adverse events**, and all grade 4 events were reversible laboratory abnormalities associated with lymphodepleting chemotherapy.





Adusumilli PS et al. 2021 (*Cancer Discovery*)

CAR-T Towards Clinics

npj | Precision Oncology

www.nature.com/npjprecisiononcology

ARTICLE OPEN

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GD2 CAR T cells against human glioblastoma

Malvina Prapa[1,10], Chiara Chiavelli[1,10], Giulia Golinelli[1], Giulia Grisendi[1], Marco Bestagno[2], Rosanna Di Tinco[3], Massimiliano Dall'Ora[4], Giovanni Neri[1,5], Olivia Candini[4], Carlotta Spano[4], Tiziana Petrachi[6], Laura Bertoni[3], Gianluca Carnevale[3], Giuseppe Pugliese[1], Roberta Depenni[7], Alberto Feletti[8], Corrado Iaccarino[9], Giacomo Pavesi[9,11] and Massimo Dominici[1,11]✉

nature

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Accelerated Article Preview

GD2-CAR T cell therapy for H3K27M-mutated diffuse midline gliomas

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