Terapie Cellulari per le Malattie Rare – per Tumori Rari

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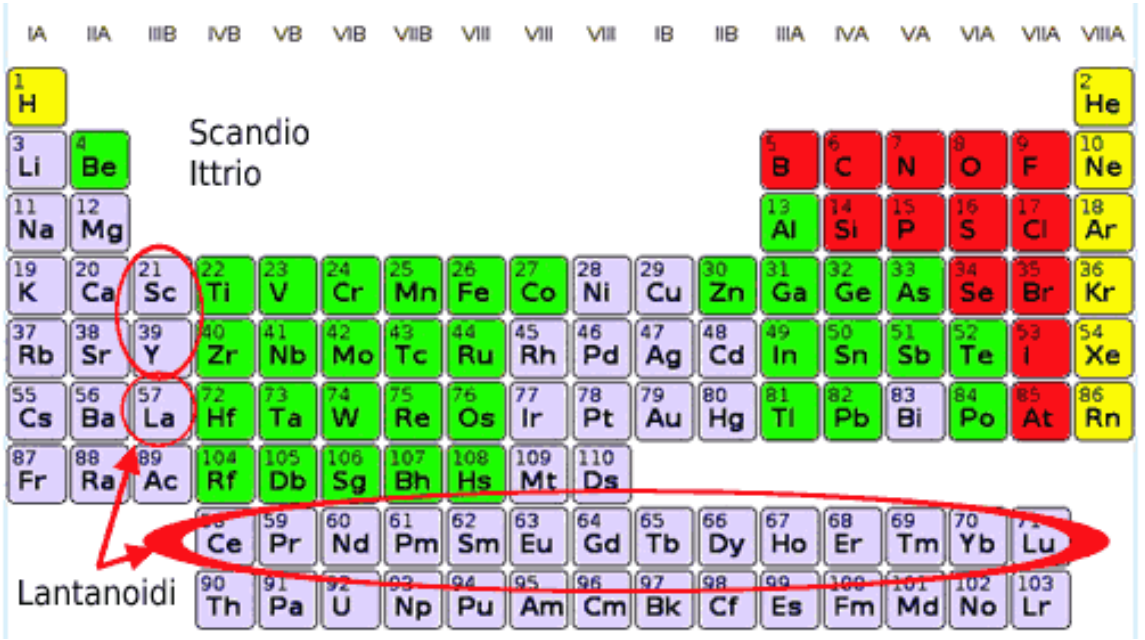
- ✓ Rare diseases are defined in the European Union as diseases with a prevalence of fewer than **5 cases out of a population of 10,000.**

- ✓ A **rare tumor** is generally defined as a type of cancer that occurs in a small percentage of the population.

- ✓ While definitions vary, a tumor is often considered rare if it has an incidence of fewer than **6 cases per 100,000 people per year**.

The Relevance of Talking About Rare Cancers: They are Precious!

«Terre Rare»



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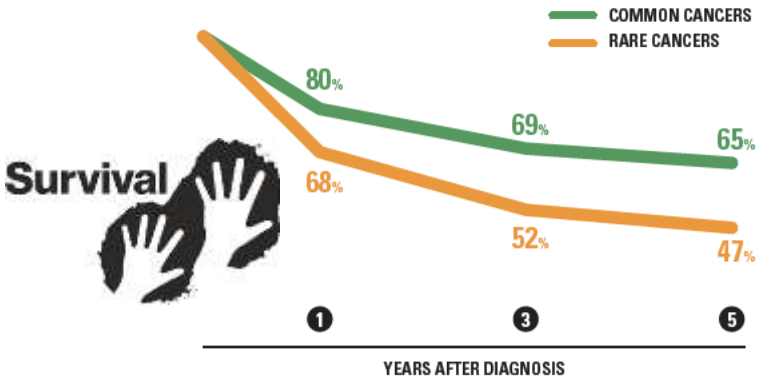
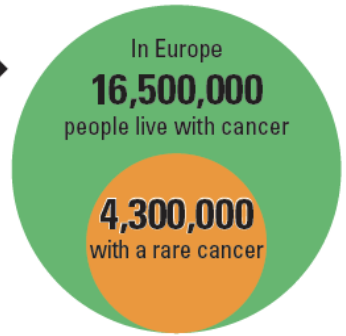
Major Issues with Rare Cancers

- ✓ Lack of information
- ✓ Misdiagnosis and delay in diagnosis
- ✓ Lack of scientific knowledge
- ✓ Lack of clinical experts
- ✓ Lack of appropriate treatment protocols



INCIDENCE
22% of all cancers diagnosed each year in Europe are rare.

PREVALENCE
24% of all people living with cancer in Europe have a rare cancer.



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Gastrointestinal & Abdominal

- **Gastrointestinal Stromal Tumor (GIST)** – A rare tumor of the digestive tract.
- **Pancreatic Acinar Cell Carcinoma** – A rare pancreatic cancer type.
- **Pseudomyxoma Peritonei (PMP)** – A rare tumor that produces mucin in the abdomen.

Genitourinary (Kidney, Bladder, Reproductive Organs)

- **Collecting Duct Carcinoma (CDC)** – A rare and aggressive kidney cancer.
- **Small Cell Carcinoma of the Bladder** – A highly rare and aggressive bladder cancer.
- **Ovarian Granulosa Cell Tumor** – A rare ovarian stromal tumor.

Skin & Soft Tissue

- **Merkel Cell Carcinoma** – A rare but aggressive skin cancer.
- **Dermatofibrosarcoma Protuberans (DFSP)** – A slow-growing soft tissue tumor in the skin.

Brain & Nervous System

- **Oligodendroglioma** – A rare brain tumor arising from oligodendrocytes.
- **Ependymoma** – A tumor that develops in the lining of the brain's ventricles or spinal cord.
- **Choroid Plexus Carcinoma** – A rare malignant tumor in the brain, often in children.

Head, Neck & Endocrine

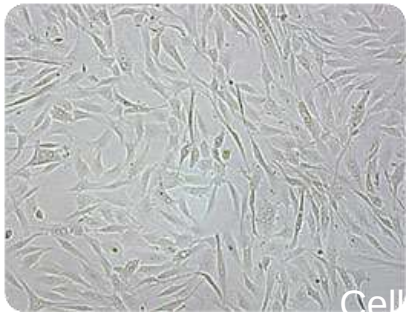
- **Paraganglioma** – A rare neuroendocrine tumor that develops in nerve tissues.
- **Nasopharyngeal Carcinoma** – A rare cancer of the upper part of the throat behind the nose.
- **Anaplastic Thyroid Cancer** – A highly aggressive and rare thyroid malignancy.

Bone & Soft Tissue (Sarcomas)

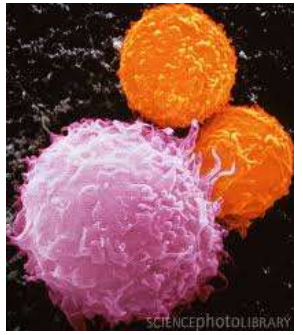
- **Ewing Sarcoma** – A rare bone or soft tissue cancer, mostly in children and young adults.
- **Chondrosarcoma** – A cartilage-forming bone cancer.
- **Alveolar Soft Part Sarcoma (ASPS)** – A slow-growing but highly metastatic soft tissue tumor.

Treating Patients By Cells

Gene delivery by non-immune cells: To deliver anti-cancer payloads by progenitor cells



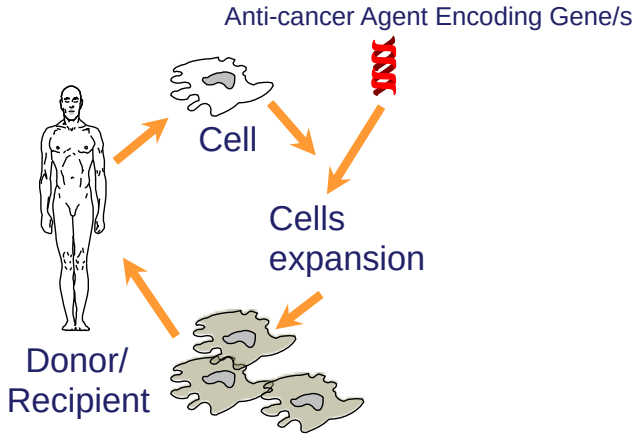
Mesenchymal Stromal Cells (MSC)



Lymphocytes (CAR-T)

Chimeric Antigen Recepto (CAR) T-Cell Therapy

Pancreatic Cancers



SCIENTIFIC REPORTS

OPEN

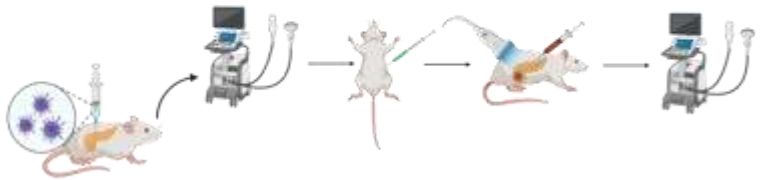
Soluble TRAIL Armed Human MSC As Gene Therapy For Pancreatic Cancer

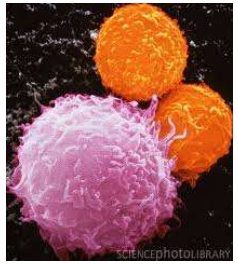
Cell Reports Medicine

CellPress

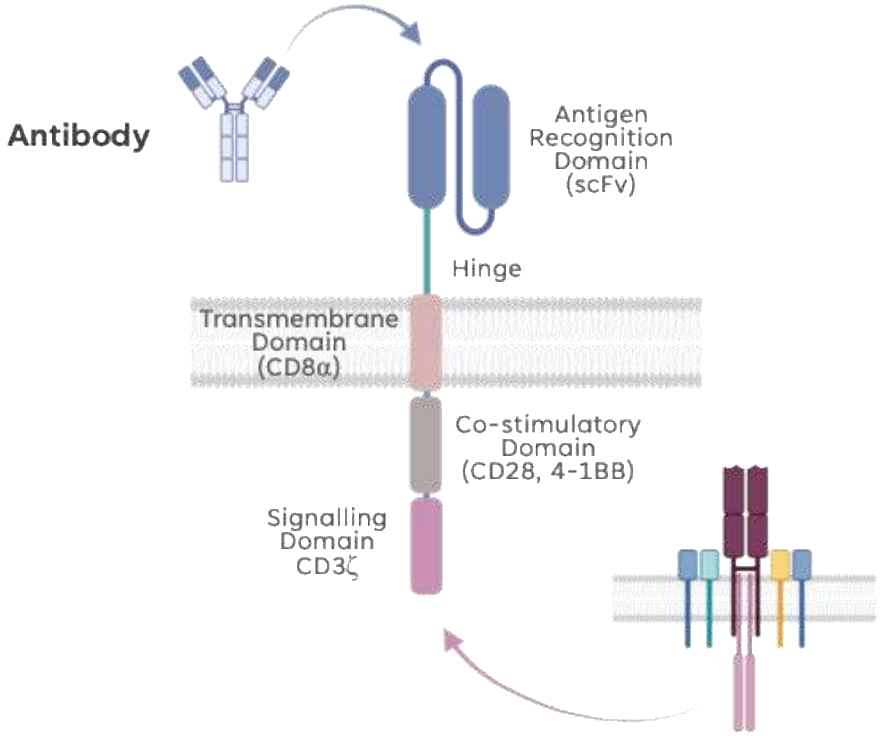
Article

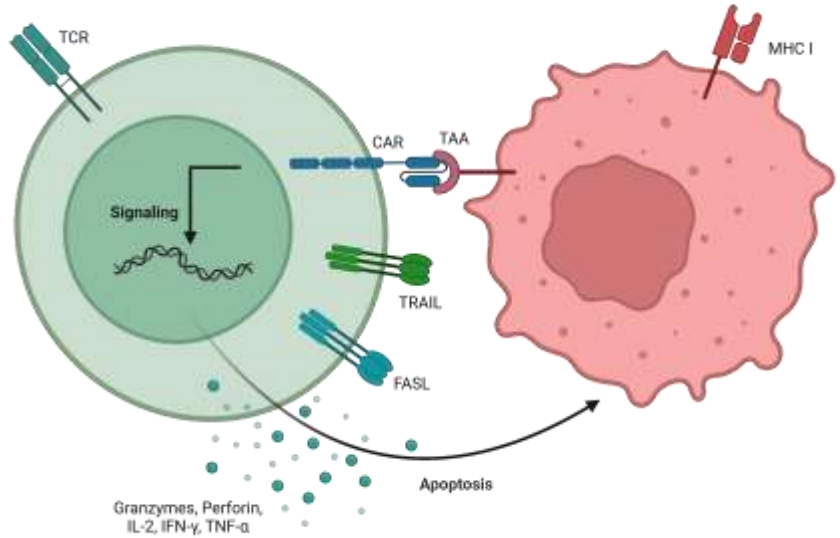
Combining gemcitabine and MSC delivering soluble TRAIL to target pancreatic adenocarcinoma and its stroma





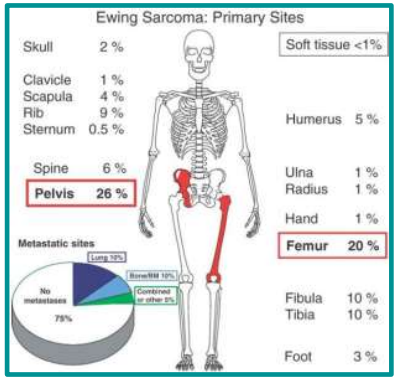
Lymphocytes (CAR-T)



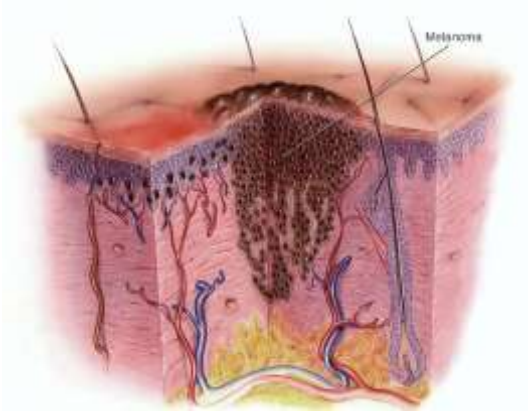


CAR-T TARGETS

Ewing Sarcoma

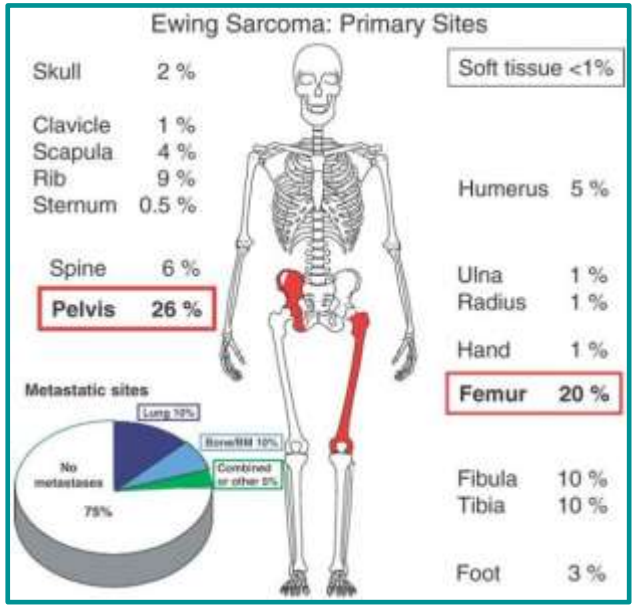


Skin & Soft Tissue

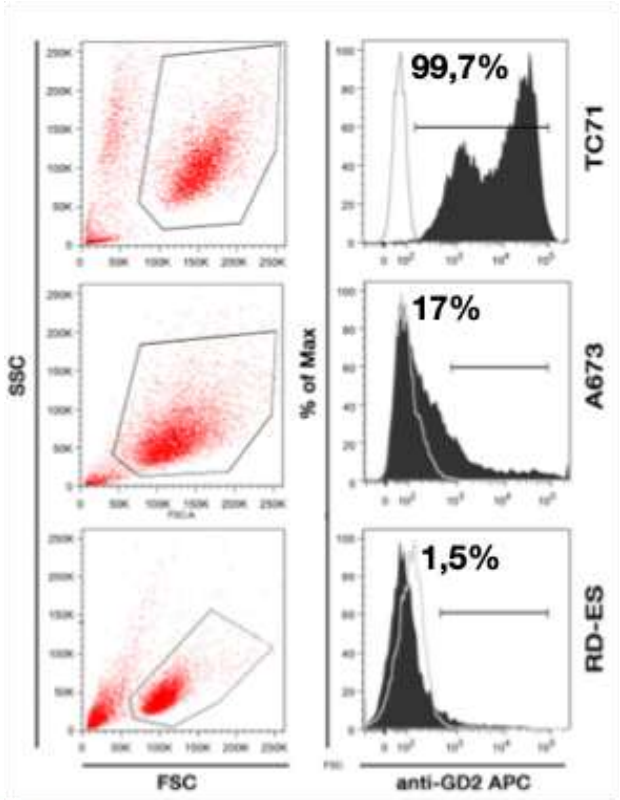


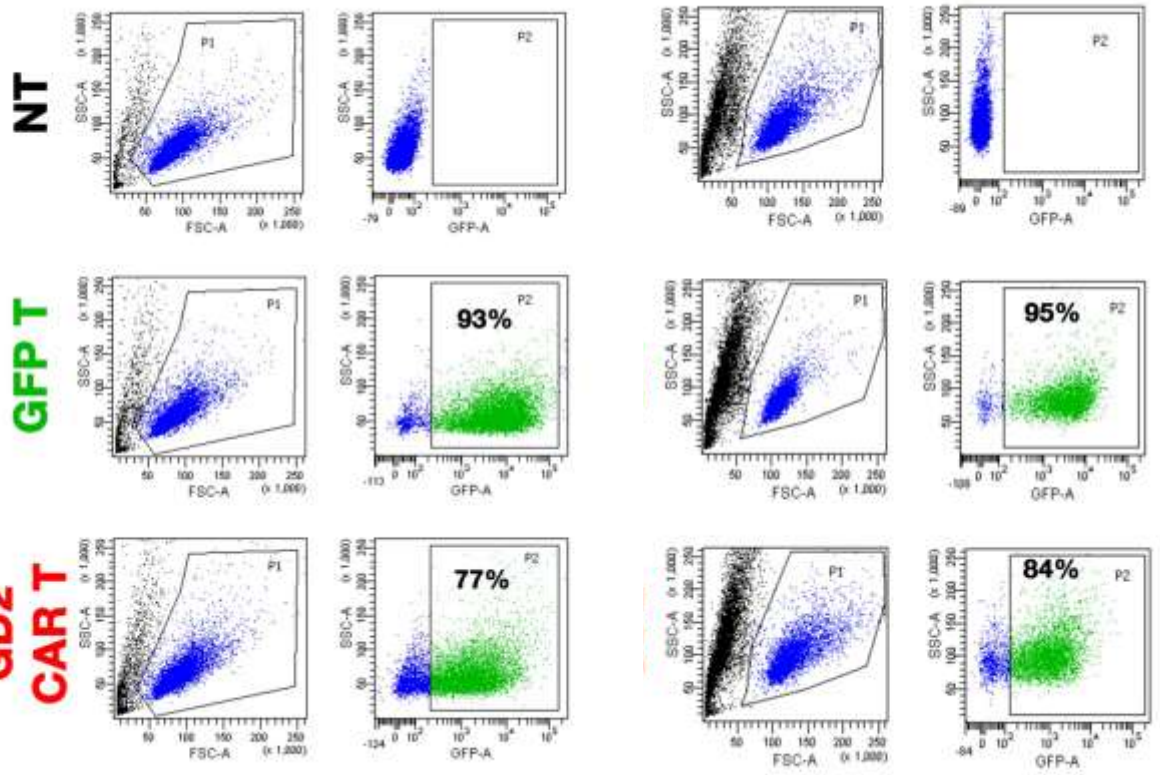
Anti-GD2 CAR-T for Ewing's sarcoma (ES)

- ✓ mesenchymal-derived tumor with strong metastatic potential
- ✓ 2nd most common malignant bone tumor in adolescents and young adults
- ✓ disease is higher in males (4.3 cases per million) compared to females (2.6 cases per million).
- ✓ The incidence increases with age, peaking between 10 and 14 years, with 8.2 cases per million in males and 6.6 cases per million in females.
- ✓ About 25% patients with clinical metastatic disease (OS<30%), while 80%-90% have subclinical microscopic widespread disease at baseline



ES express GD2 and T-cell effectors transduction

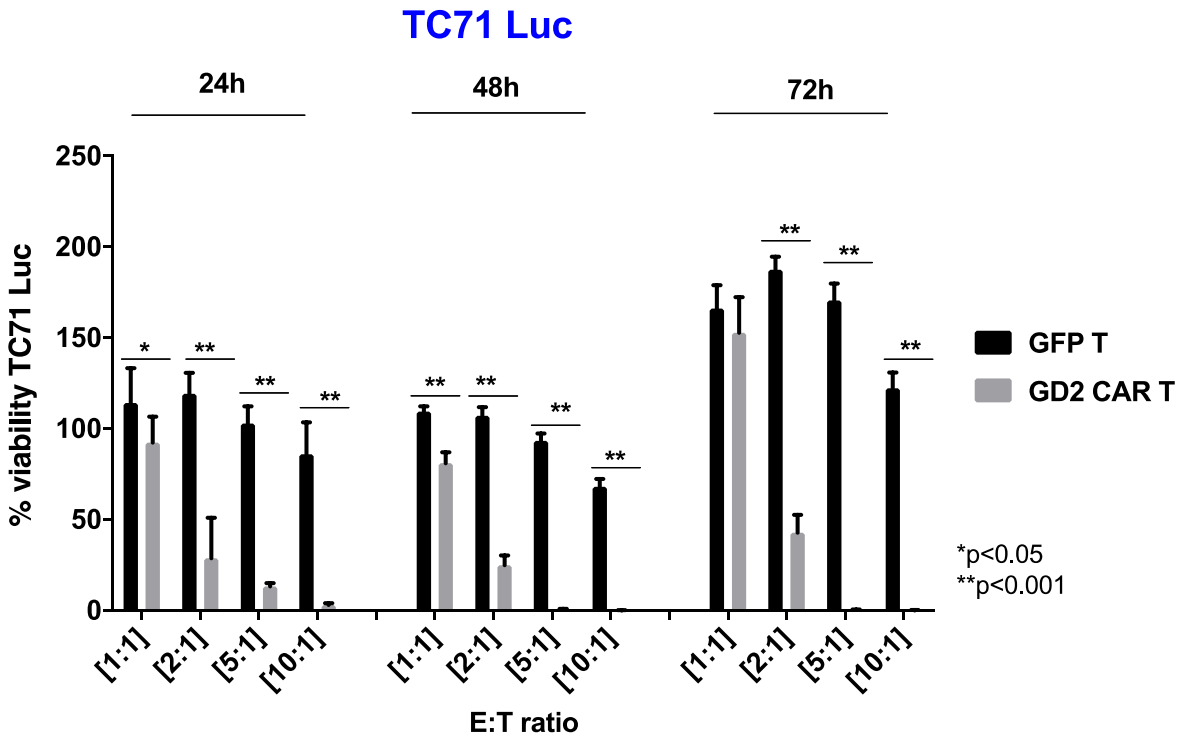


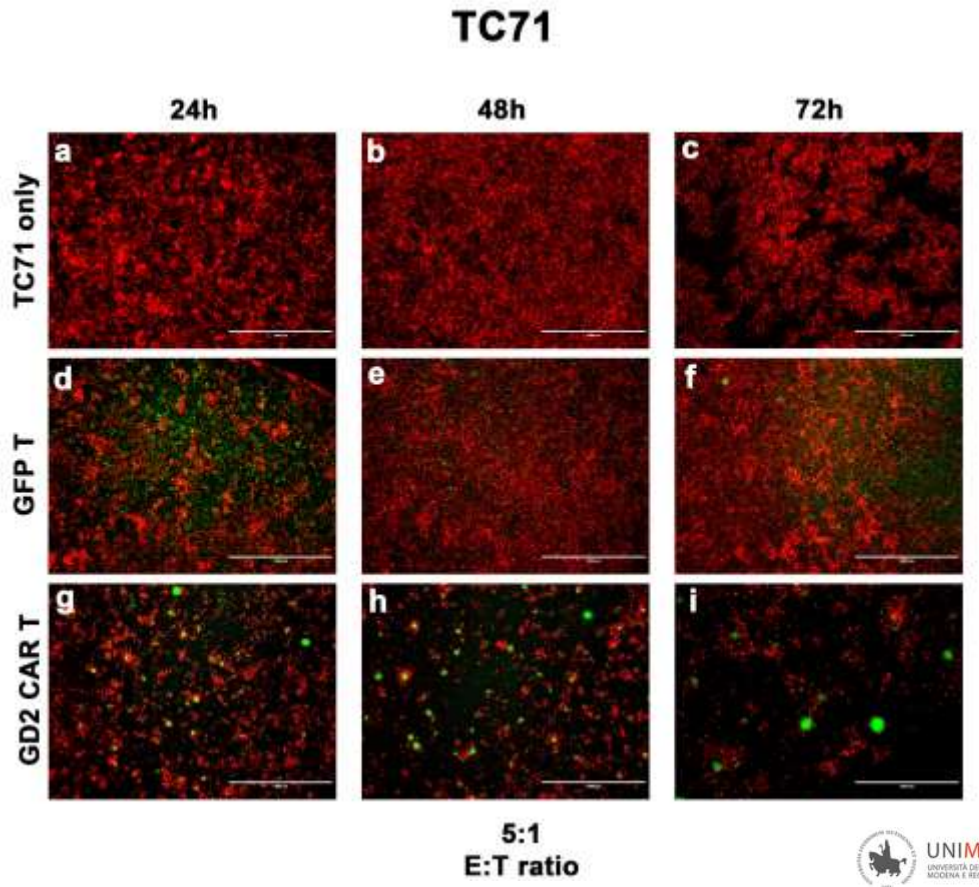


Donor 1 Donor 2

GD2 high

CAR-T anti ES in 2D Coculture: TC71





Golinelli G & Chiavelli C et al Submitted

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GD2 high

In Vivo Therapeutic Model for a Rare Cancer

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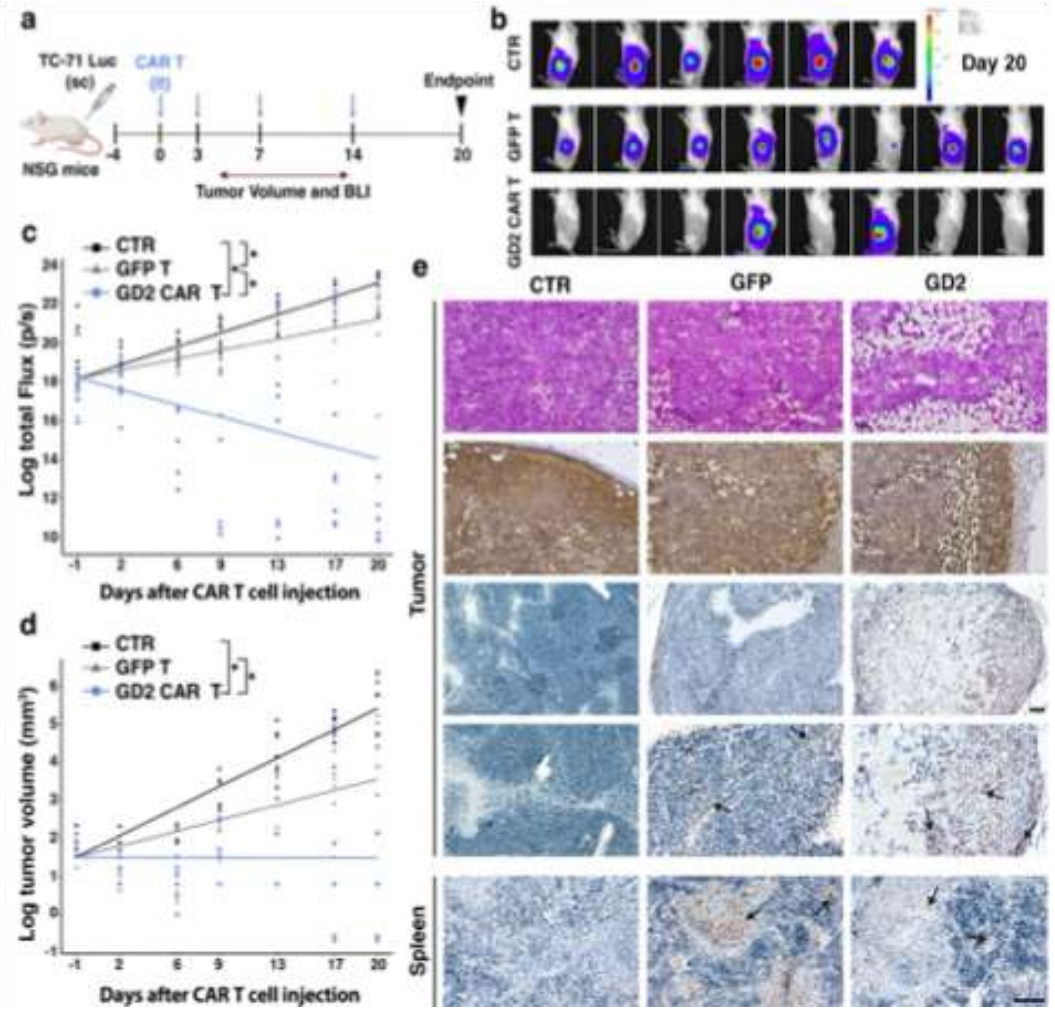


H&E

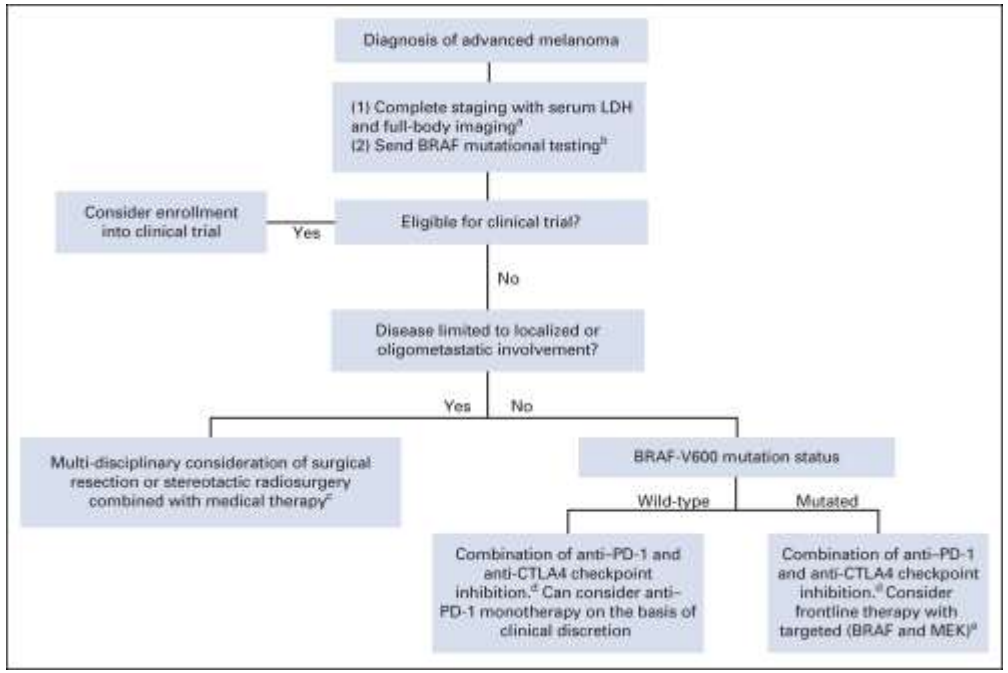
anti-GD2 antibody

anti-GFP antibody

Golinelli G & Chiavelli C et al Submitted

Skin Cancers: Malignant Melanoma

- ✓ As of 2018, the estimated 5-year survival rate is 29.8% in those with stage IV disease at the time of diagnosis (United States)
- ✓ Noncutaneous forms of melanoma, including mucosal and ocular subtypes, classically portend an even worse prognosis
- ✓ In 2022, it is estimated that there will be more than 106.000 new cases of invasive melanoma with 7.180 melanoma-related deaths in the United States
- ✓ According to GLOBOCAN for 2020, there were 324,635 cases of melanoma worldwide, representing 1.7% of all cancers and 57,043 melanoma deaths or 0.6% of cancer-related mortality
- ✓ 15000 new cases/yr in Italy



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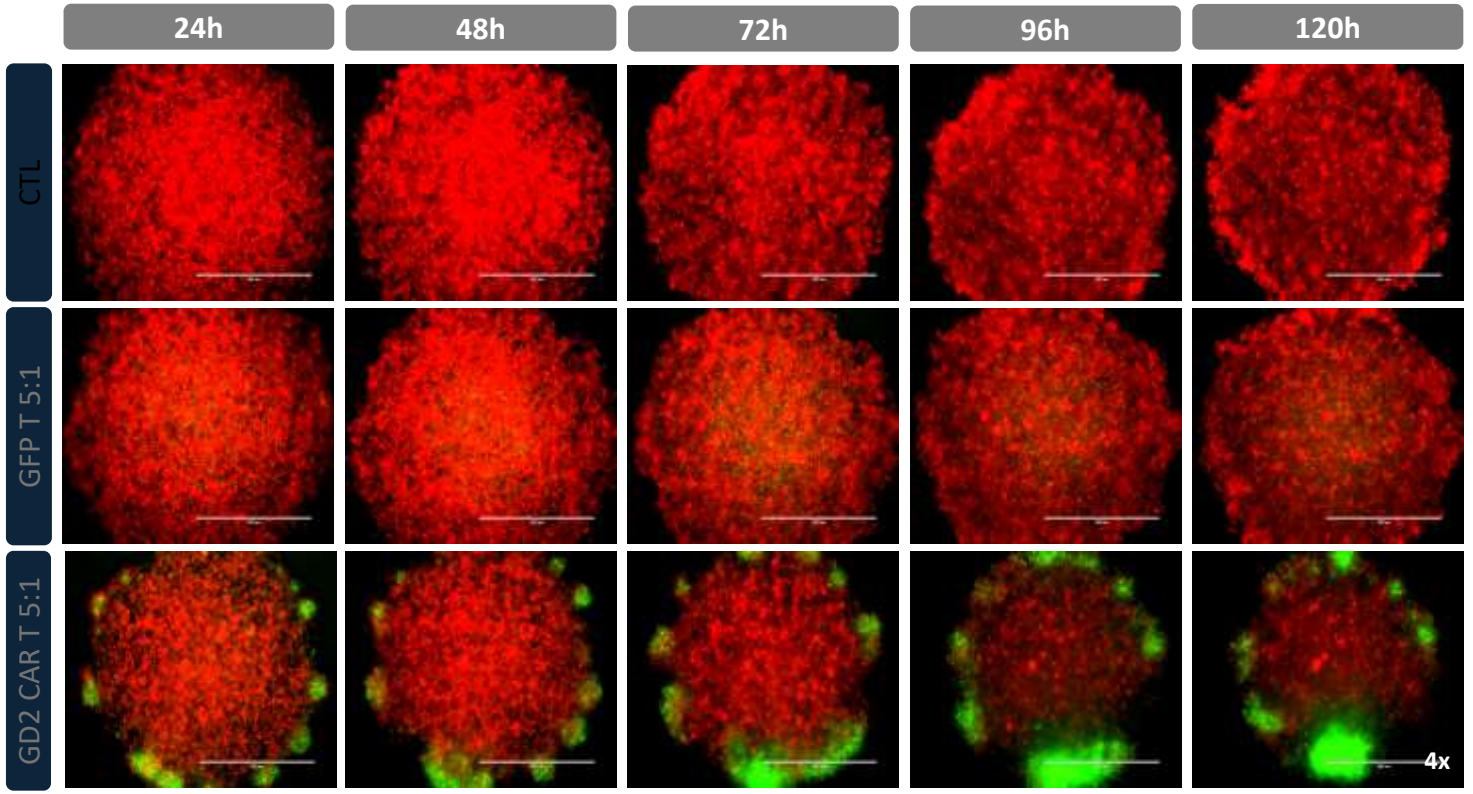
Allogeneic anti-GD2 CAR T against SK-MEL-5 Melanoma Cells in 3D



Chiavelli, Pugliese in preparation

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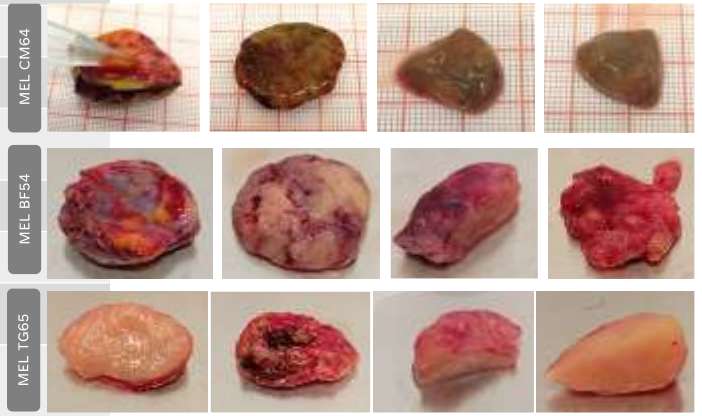
Melanoma Metastatic Lymph Node Samples: Primary Tumor Cell Isolation

PATIENT ID	MEL CM64	MEL BF54	MEL TG65
GENDER AGE	M 59	F 69	M 57
DIAGNOSIS	Melanoma	Melanoma	Melanoma
DISSOCIATION DATE	16.09.2022	23.11.2022	03.04.2023
STARTING MATERIAL	Metastatic axillary lymph node right	Metastatic obturator-iliac lymph node right	Metastatic axillary lymph node right
IHC MARKERS	MelanA, S100, PDL1	HMB45, S100mono, Melcocktail	S100mono
MOLECULAR MARKERS	BRAF p.V600K	BRAF p.V600K	BRAF p.V600E
DISSOCIATION PROTOCOL	Medium, Tough	Medium	Tough
CELL MEDIA	RPMI + 10% FBS, RPMI + HMGS2, DMEM-F12 + 10% FBS, DMEM-F12 + HMGS2	254 + HMGS2, RPMI + HMGS2, DMEM-F12 + 10% FBS	254 + HMGS2, DMEM-F12 + 10% FBS
CELL YIELD	High	High	Low



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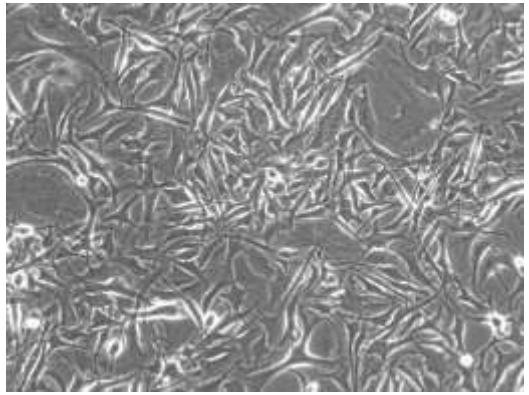
Patient-derived Melanoma Cells Characterization

PATIENT ID	MEL BF54
GENDER AGE	F 69
DIA<<<<<GNOSIS	Melanoma
DISSOCIATION DATE	23.11.2022
STARTING MATERIAL	Metastatic obturator-iliac lymph node right
IHC MARKERS	HMB45, S100mono, Melcocktail
MOLECULAR MARKERS	BRAF p.V600K



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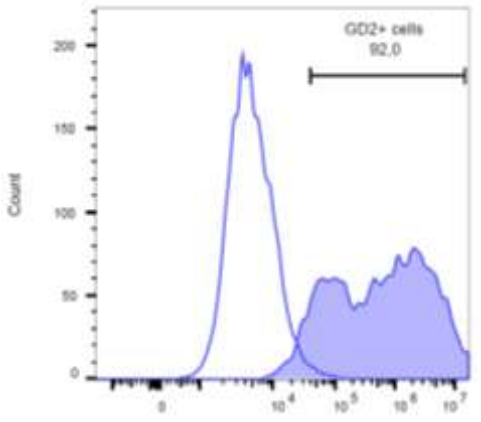
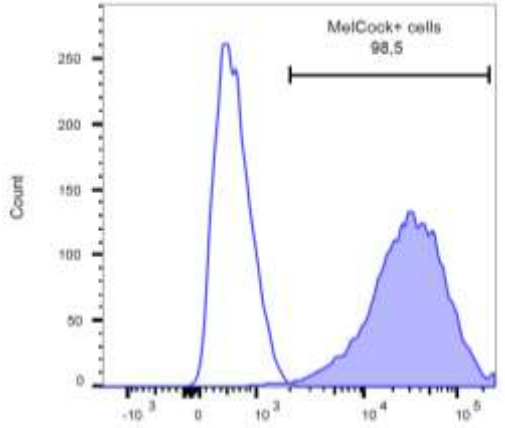
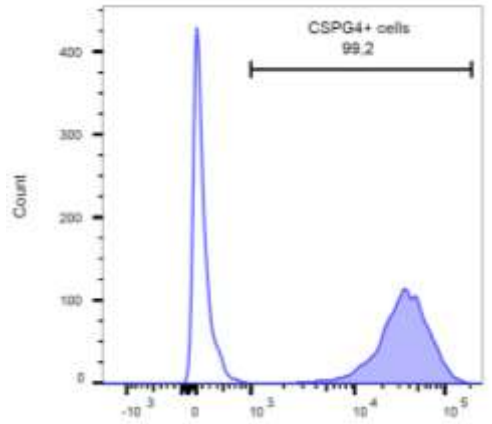


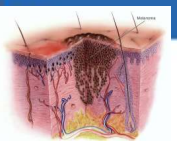
GD2⁺ cells	92.0%



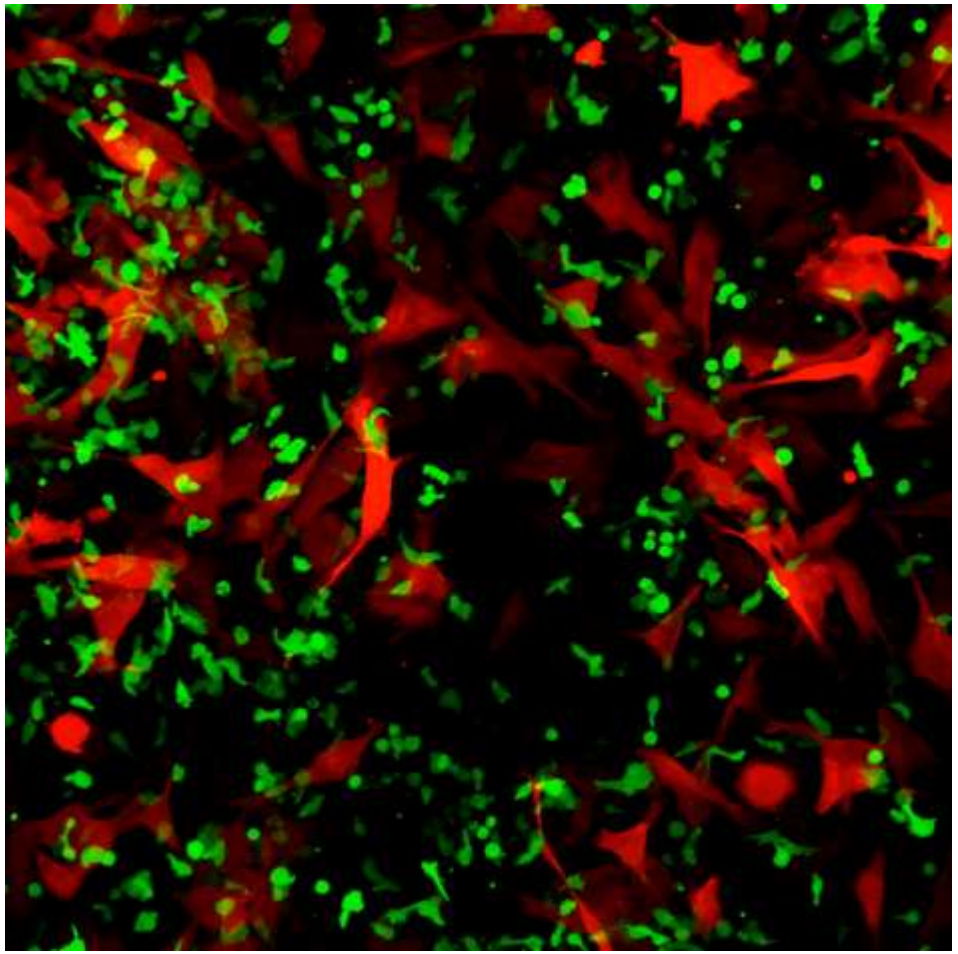
MelCock⁺ cells	98.5%



CSPG4⁺ cells	99.2%



Autologous **GFP Only T-cells** against Patient-derived Melanoma



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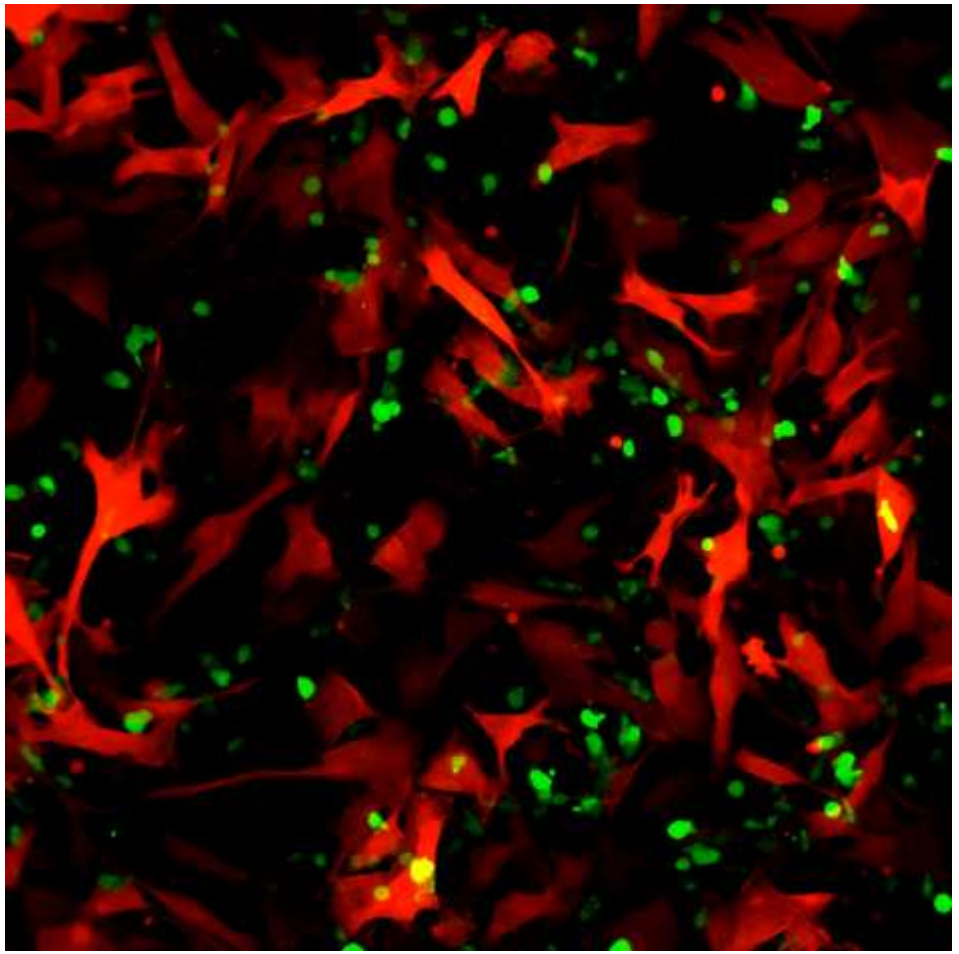
Autologous **anti-GD2 CAR T** against Patient-derived Melanoma



The Relevance of Investigating Rare Cancers

- ✓ **Unmet Medical Needs** – Rare cancers often have limited treatment options and lower survival rates due to less research and fewer clinical trials. Understanding them can lead to better therapies.
- ✓ **Scientific Discovery** – Studying rare cancers can reveal unique genetic mutations and biological mechanisms that may apply to more common cancers, leading to broader medical advancements.
- ✓ **Precision Medicine** – Research on rare cancers can contribute to personalized treatments, as many rare cancers are driven by specific genetic mutations that can be targeted with precision therapies.
- ✓ **Equity in Healthcare** – Patients with rare cancers deserve the same attention and advancements as those with more common cancers. Improving research ensures they have access to better diagnostics and treatments.
- ✓ **Potential Links to Other Diseases** – Rare cancers may share pathways with more common diseases, providing insights into broader medical conditions, including inflammation, immune system function, and genetic disorders.

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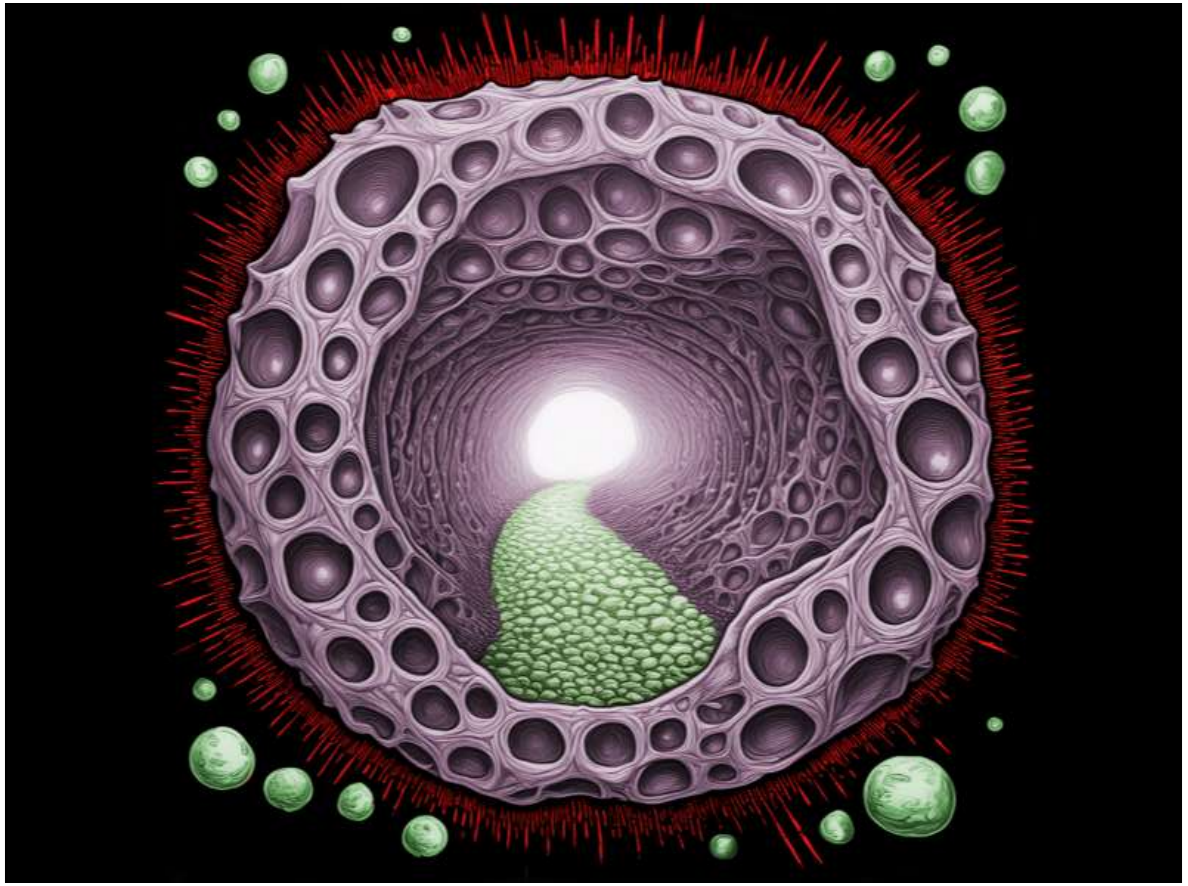
GRAZIE!



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