

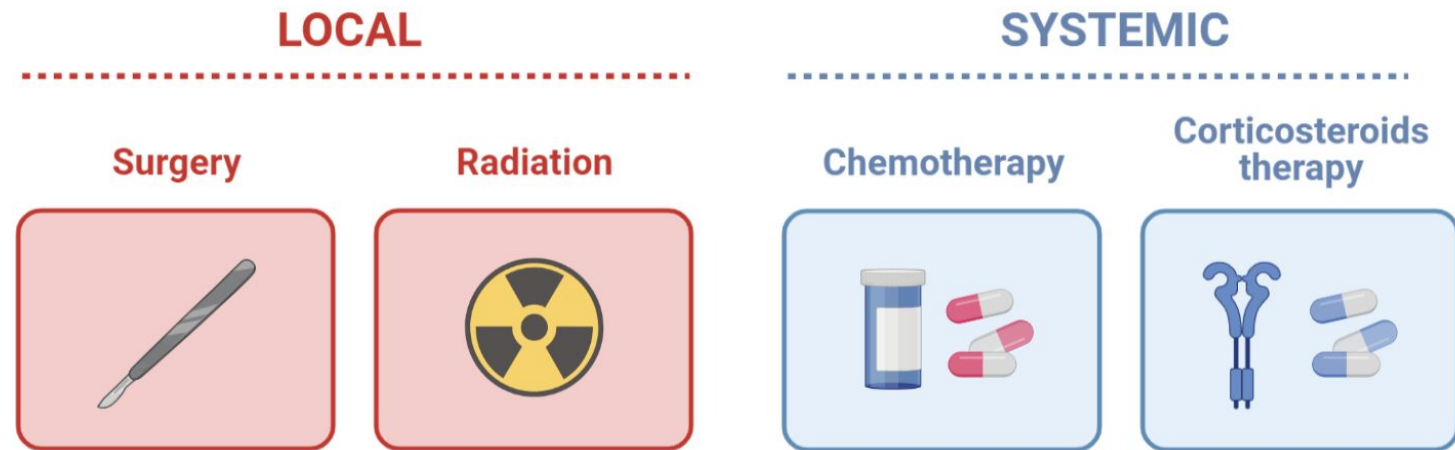
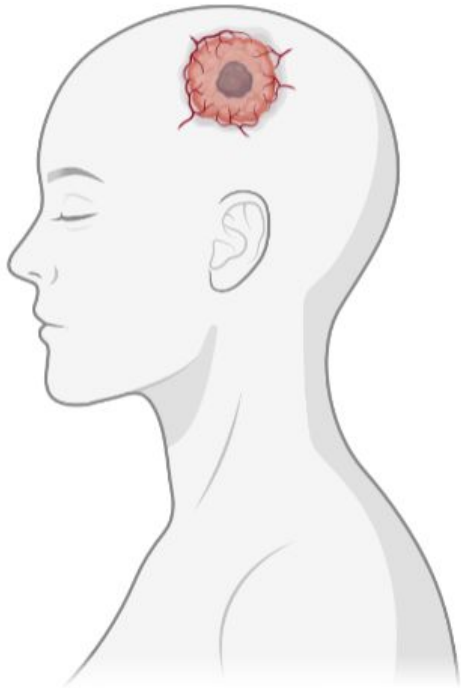
Hyaluronic Acid-Conjugates for Improved Glioblastoma Local Immunotherapy

Alessio Malfanti, PhD
University of Louvain, Belgium

alessio.malfanti@uclouvain.be

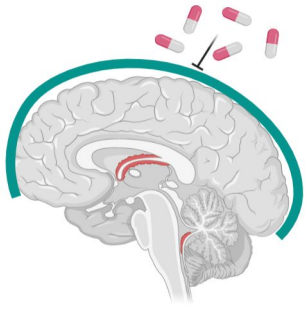
Glioblastoma (GBM) is an Unmet Clinical Need

- Most Common and Aggressive Brain Cancer
- Fast and Infiltrative Tumor Supported by the Local Environment
- Incidence: 10 per 100,000 population every year

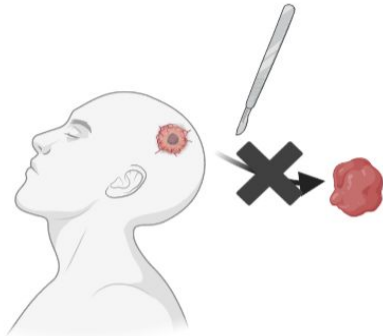


Median survival <16 months

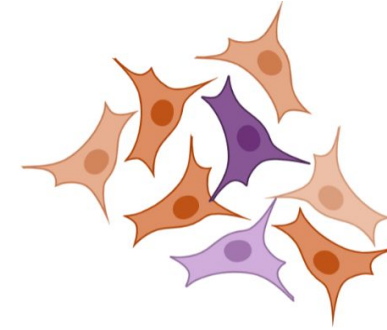
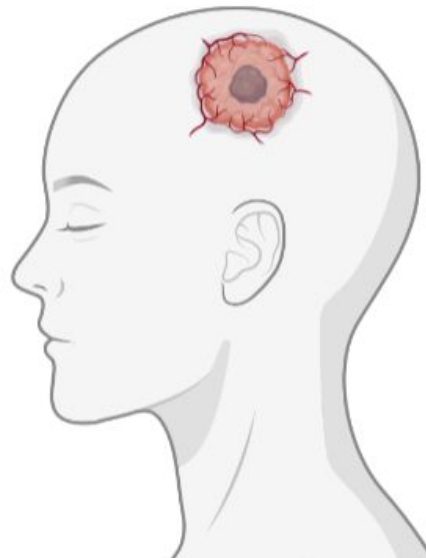
Glioblastoma (GBM) is an Unmet Clinical Need



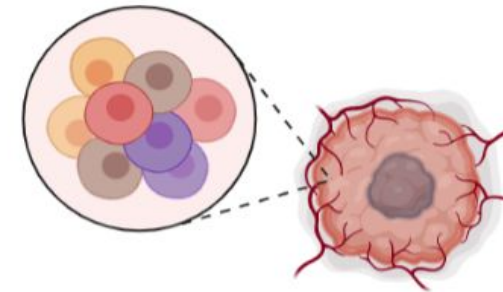
Blood Brain
Barrier



Unresectable
GBM



Drug
Resistance



Intra and inter patient
heterogeneity

Bastiancich* C, Malfanti* A, et al. (2021) Advanced Drug Delivery Reviews, 177, 113951
Bausart M., Pr  at V & Malfanti A. (2022) Journal of Experimental & Clinical Cancer Research 41(1)

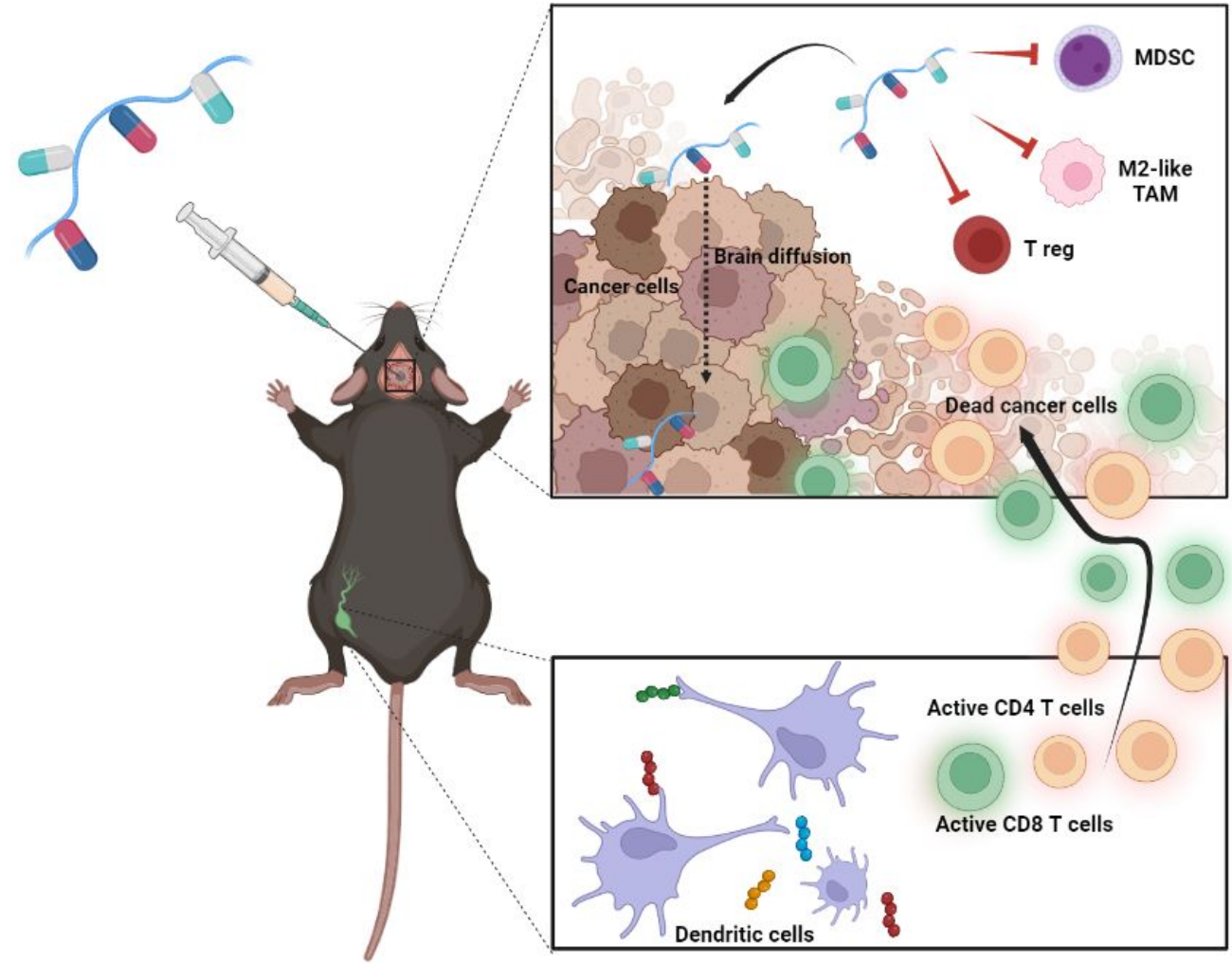
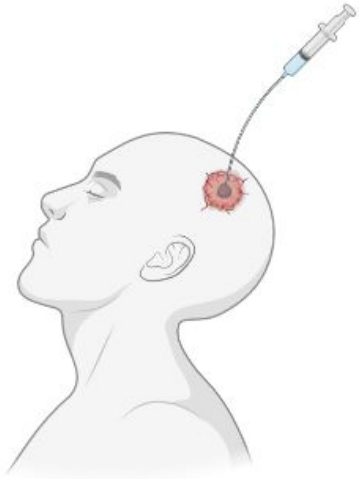
GBM DOES NOT Respond to Immunotherapy



- Absence of T Cell Priming/Activation
- Deficit of T Cell Homing to the Tumor Bed
- Modified Production of Chemokines and Cytokines Affecting T Cell Trafficking
- Low Mutational Burden
- Suppressive Tumor Immuno Microenvironment

Bastiancich* C, **Malfanti* A**, et al. (2021) Advanced Drug Delivery Reviews, 177, 113951
Bausart M., Pr  at V & **Malfanti A**. (2022) Journal of Experimental & Clinical Cancer Research 41(1)

Local Treatment of GRM



- Bypass the BBB
- High doses/low systemic side effects
- Implementing the SOC

Bastiancich C, **Malfanti A.**, Advanced Drug Delivery Reviews (2021)

Malfanti A.* et al. (2022) Pharmaceutics

Catania G., Rodella G, ... & **Malfanti A.*** (2023) Biomaterials

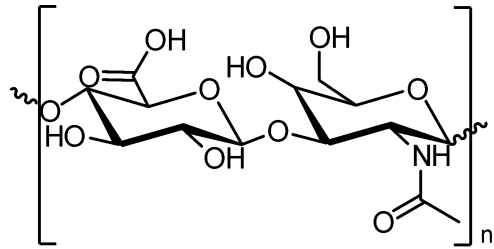
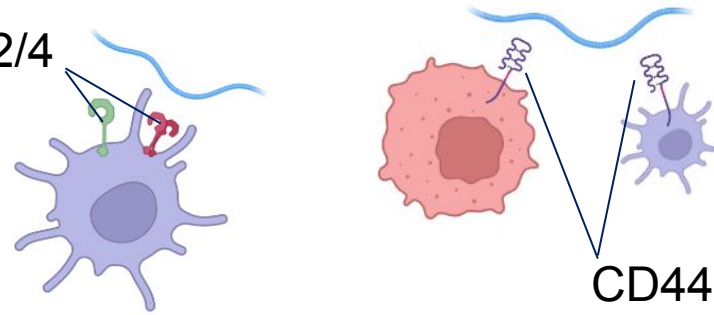
Chellen T.,... & **Malfanti A.*** (2023) submitted

Bausart M., ... **Malfanti A.** & Pr  at V. (2023), Nanomedicine: Nanotechnology, Biology and Medicine

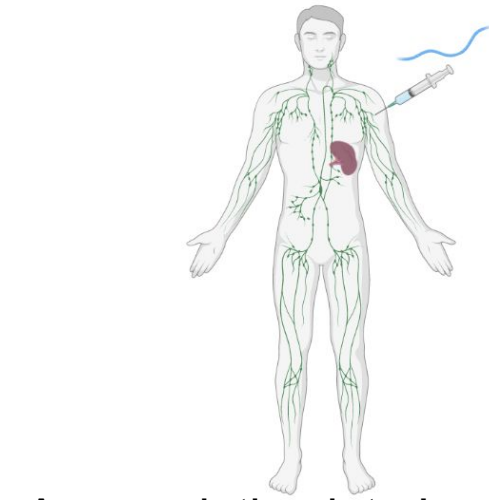
Bausart M., Pr  at V & **Malfanti A.** (2022) Journal of Experimental & Clinical Cancer Research 41(1)

Hyaluronic Acid for Local Combination Immunotherapy

Toll Like Receptors 2/4

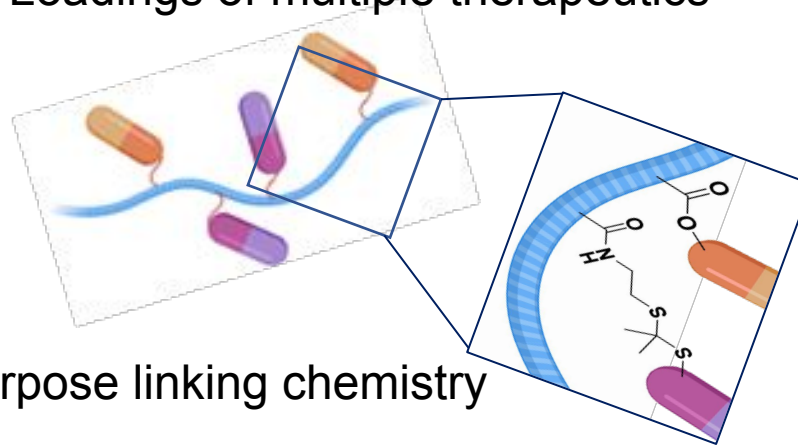


Hyaluronic Acid (HA)
100 kDa



Accumulation into Lymph nodes

Loadings of multiple therapeutics



Fit-for-purpose linking chemistry

- Immunogenic cell death inducers
- Adjuvants
- Immunomodulators
- Antigens for vaccines

Bastiancich C, **Malfanti A.**, Advanced Drug Delivery Reviews (2021)

Malfanti A.* et al. (2022) Pharmaceutics

Catania G., Rodella G, ... & **Malfanti A.*** (2023) Biomaterials

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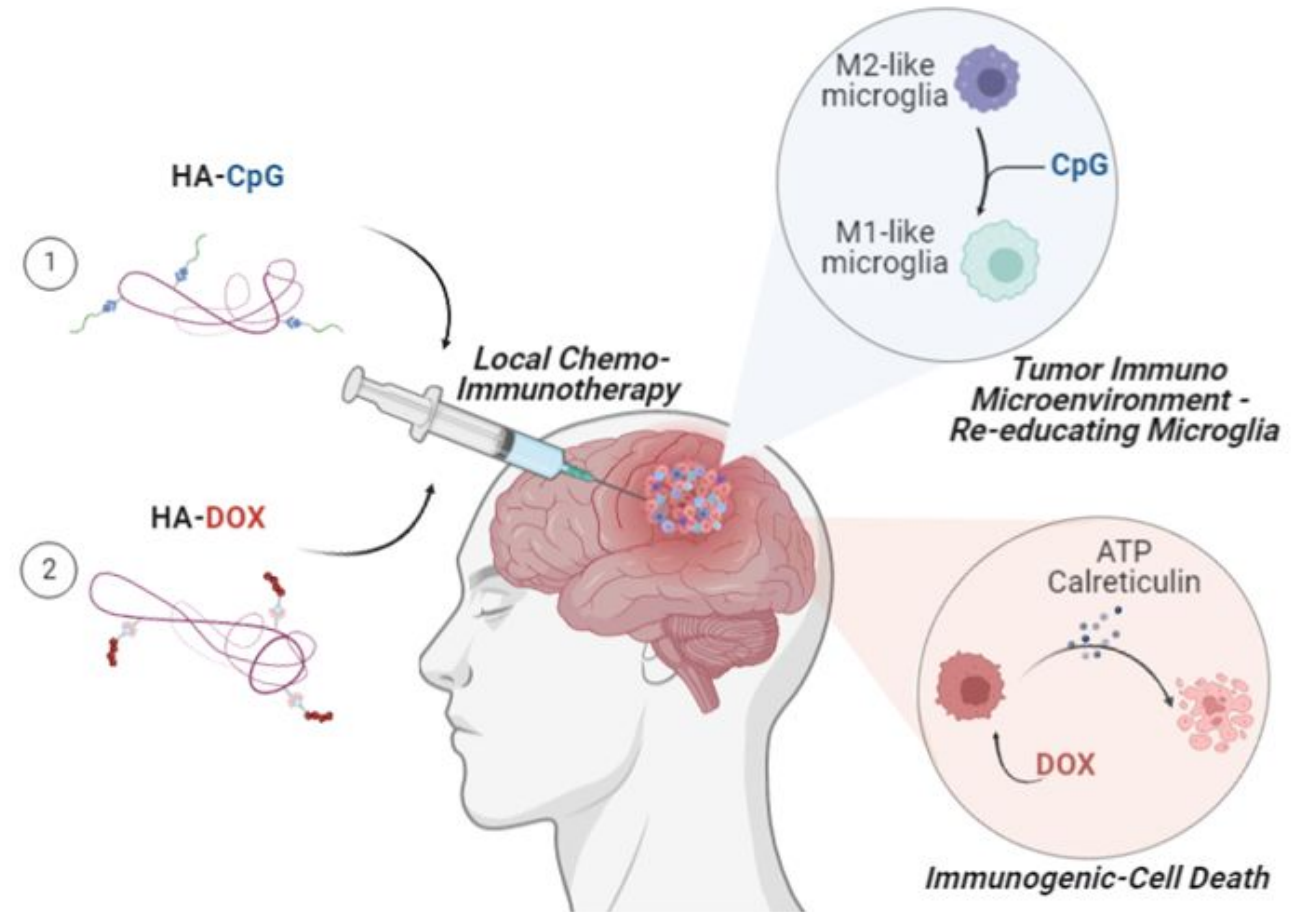
Combination of HA-DOX+ HA-CpG Induces Long-Term Survival in Unresected GBM



Giuseppina
Catania

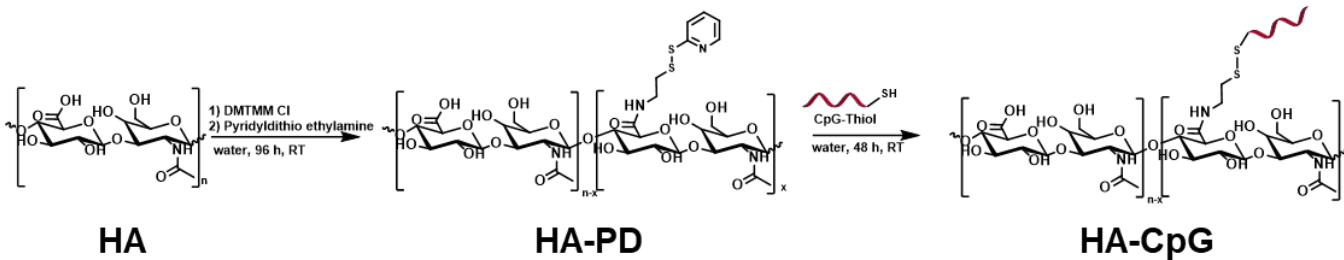


Giulia
Rodella



Malfanti A.* et al. (2022) *Pharmaceutics*
Catania G., Rodella G., ... & Malfanti A.* (2023) *Biomaterials*
Bausart M., Pr  at V & Malfanti A. (2022) *Journal of Experimental & Clinical Cancer Research* 41(1)

Hyaluronic Acid-CpG Reprograms ProTumor-Like Macrophages

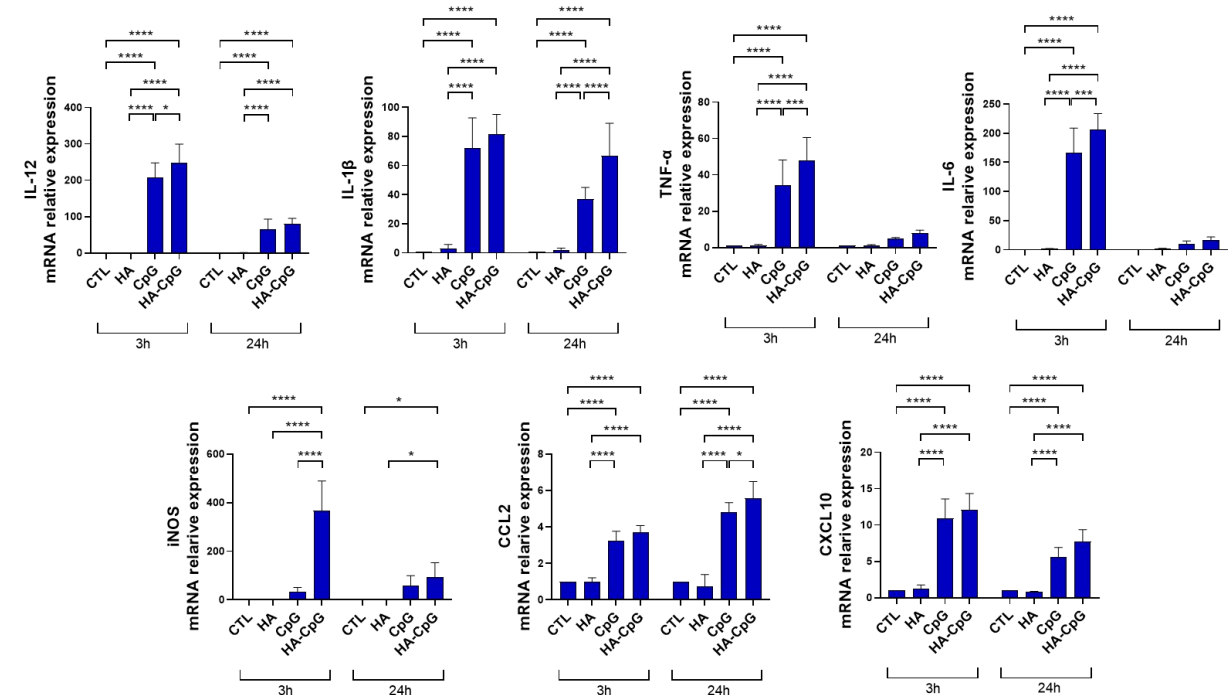
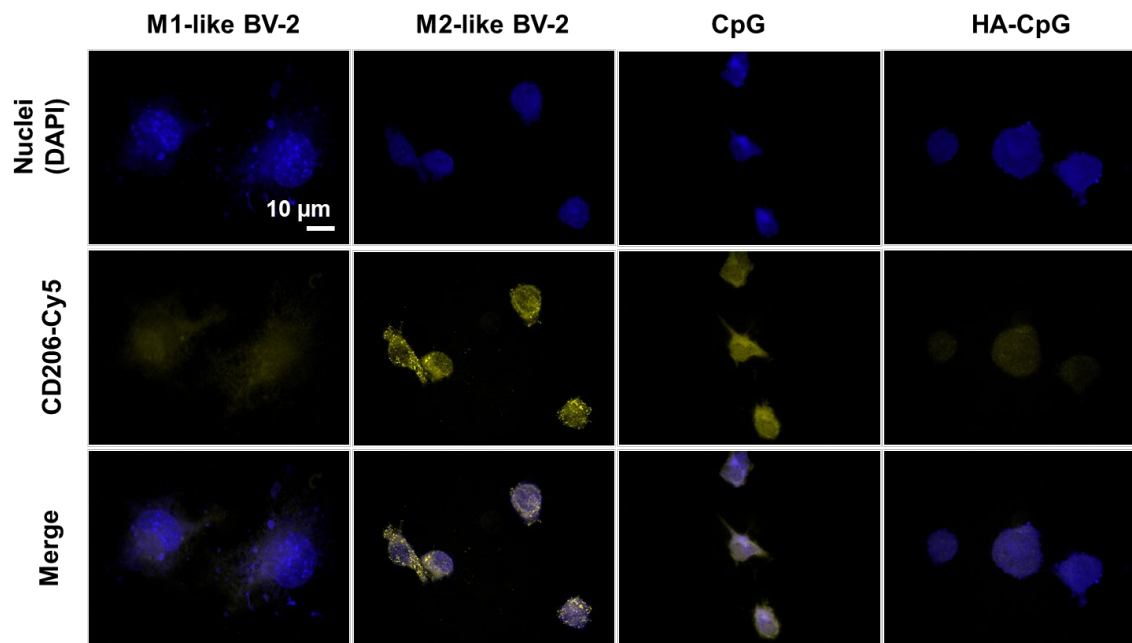


Conjugate
HA-CpG

Drug Loading
(%w/w)
30.71

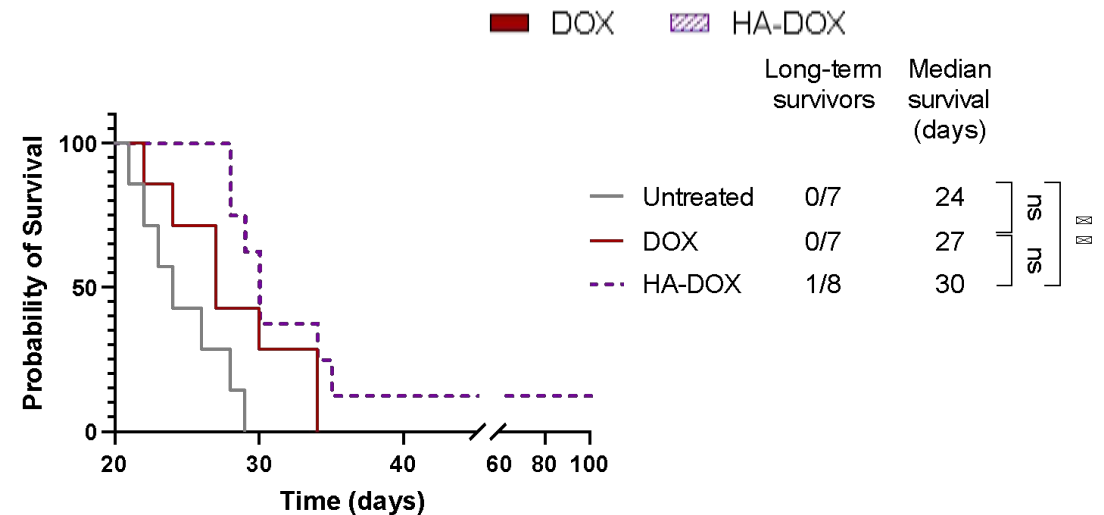
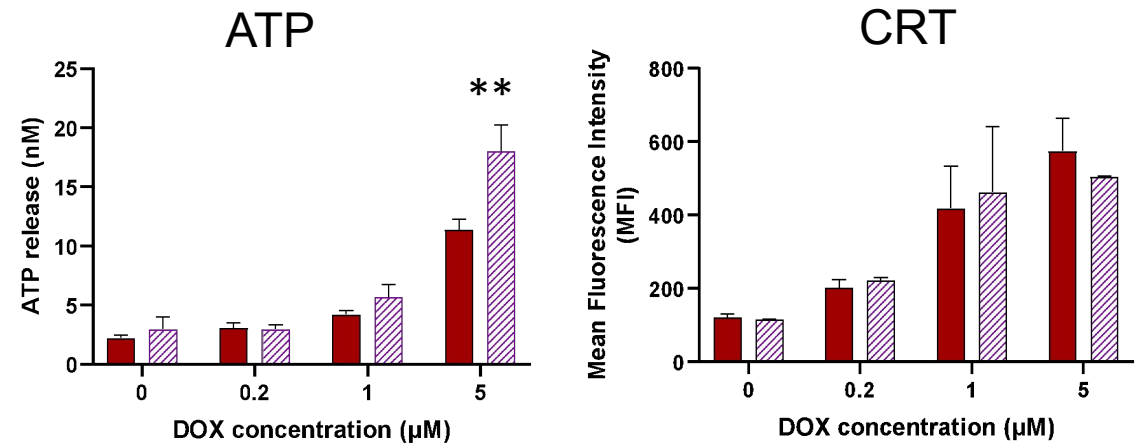
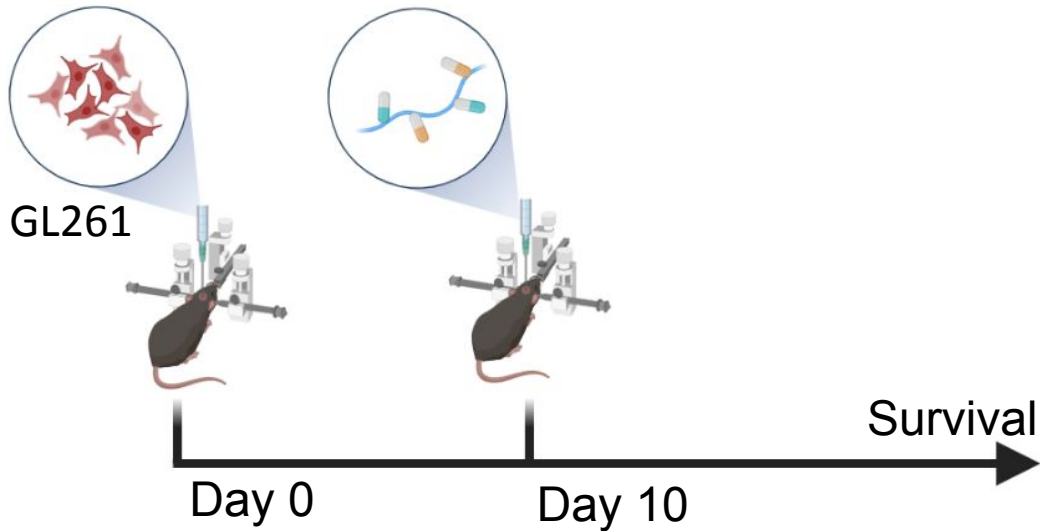
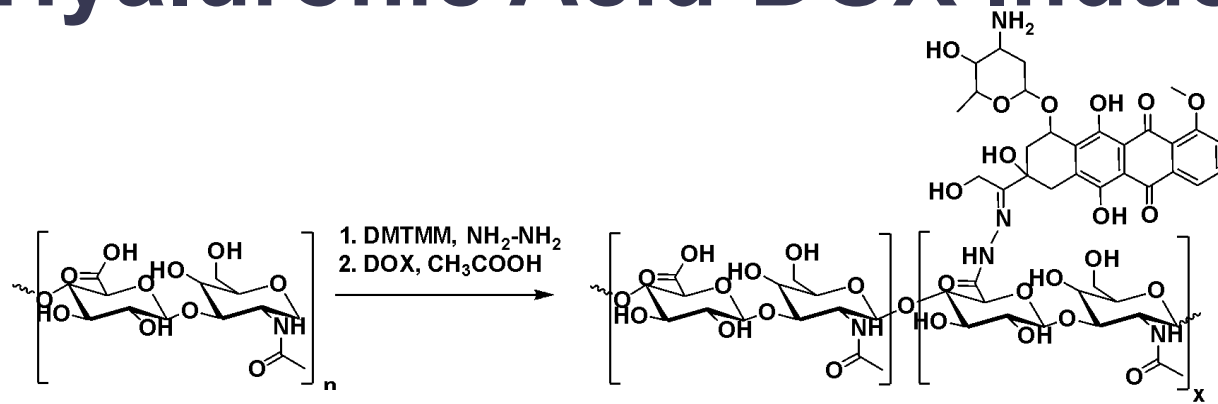
Size
(nm)
17.2 nm

Zeta Potential
(mV)
-24.5



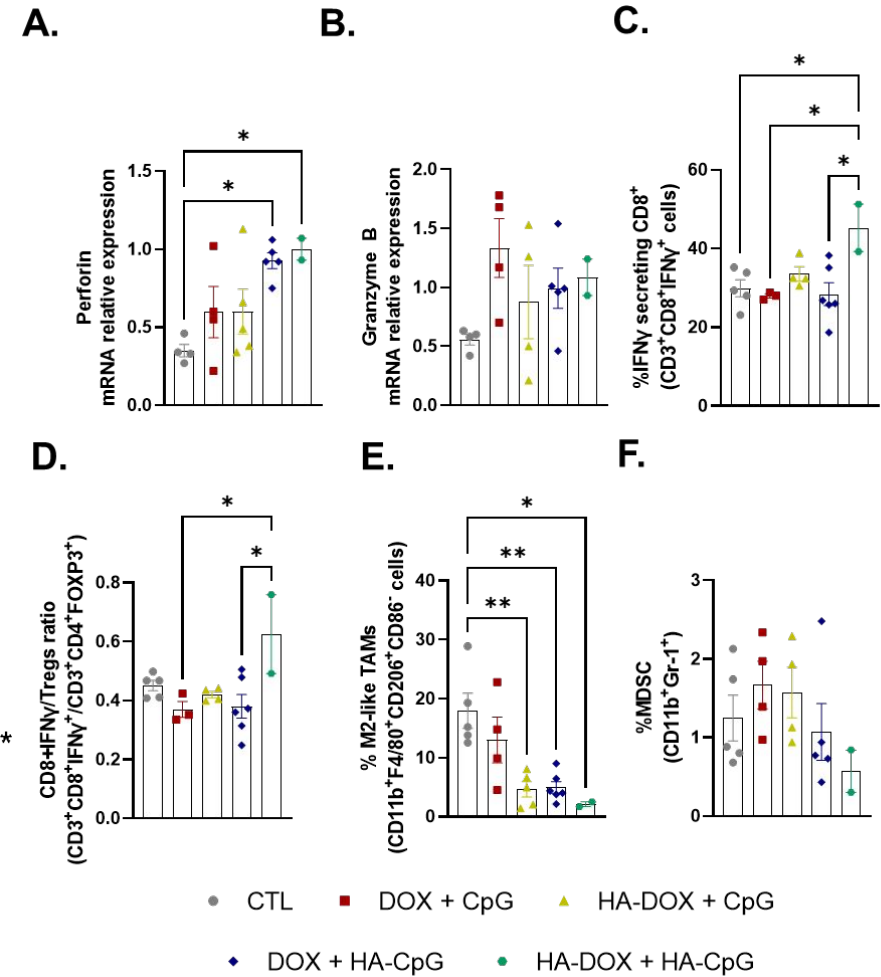
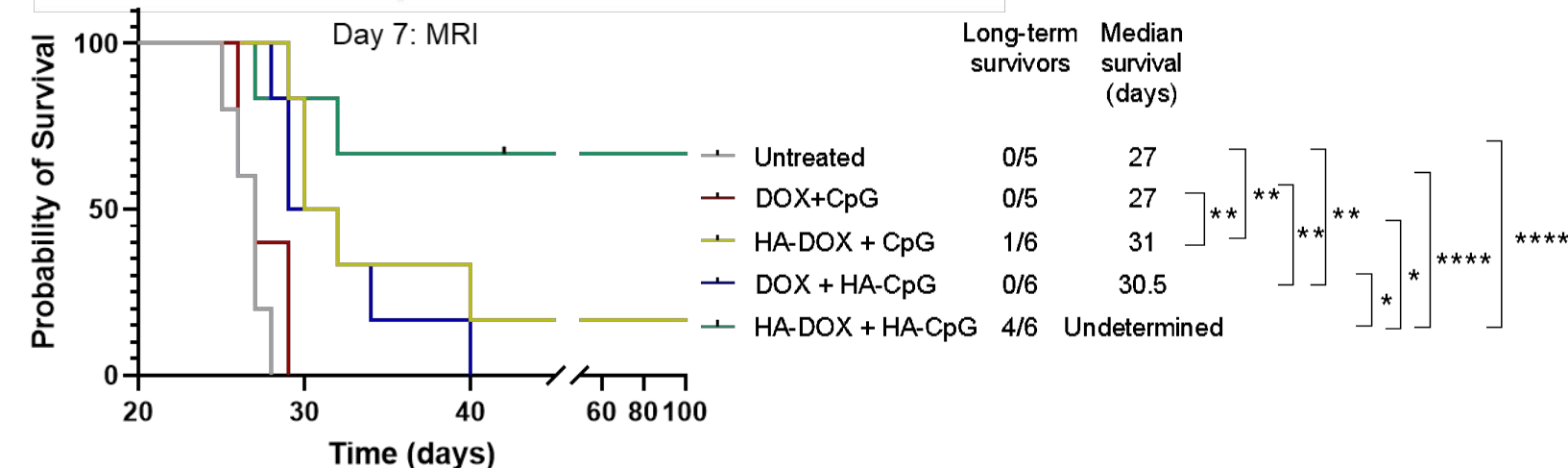
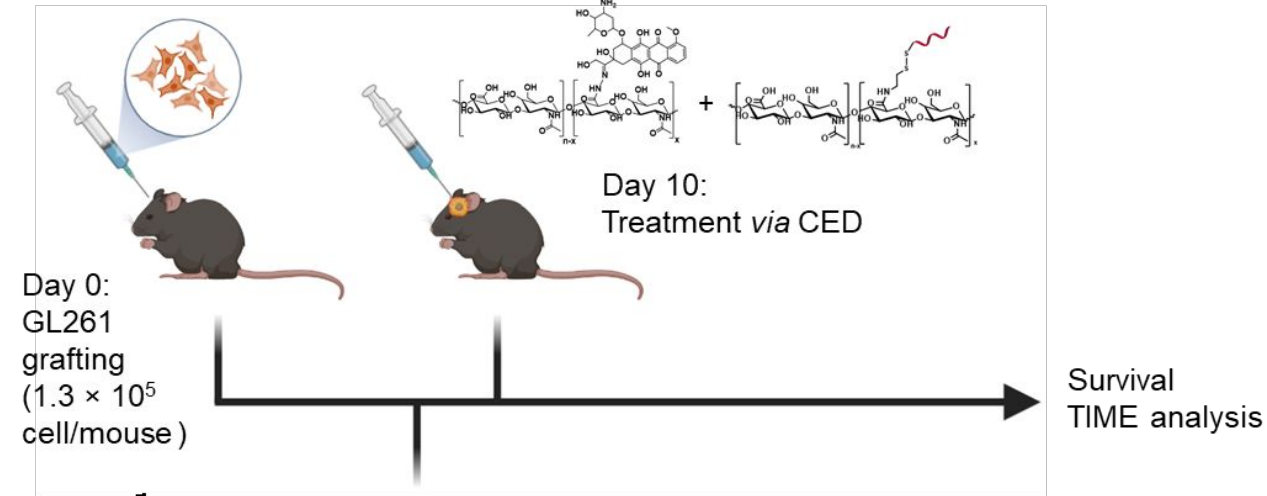
Catania G., Rodella G, ... & Malfanti A.* (2023) Biomaterials

Hyaluronic Acid-DOX Induces Immunogenic Cell Death



Malfanti A.* et al. (2022) *Pharmaceutics*
 Catania G., Rodella G., ... & Malfanti A.* (2023) *Biomaterials*
 Bausart M., Pr  at V & Malfanti A. (2022) *Journal of Experimental & Clinical Cancer Research* 41(1)

HA-DOX+ HA-CpG Elicits an Immune Response and Induces Long-Term Survival

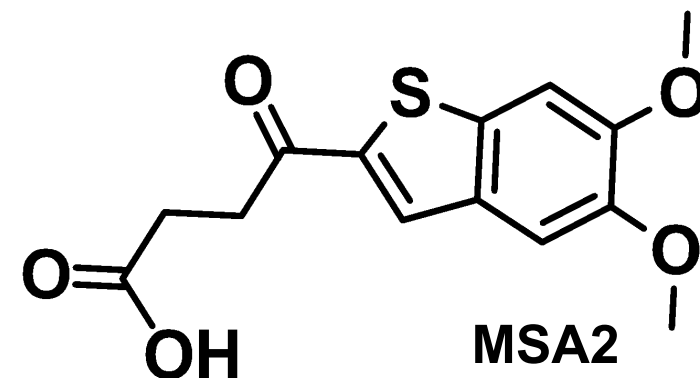
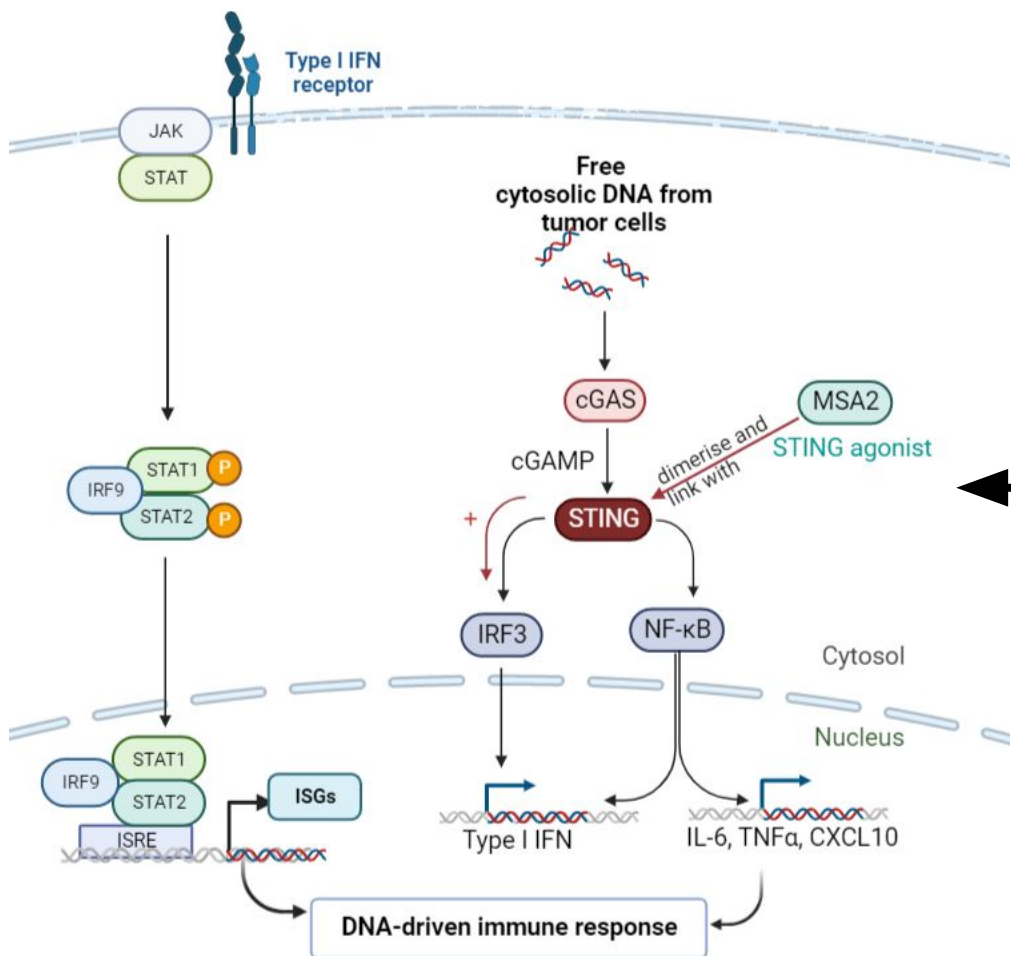


Catania G., Rodella G., ... & Malfanti A.* (2023) Biomaterials

STING Pathway Can Switch GBM from “Cold” to “Hot”

STING : STimulator of INTERferones GENes

Present on Both Cancer and Immune Cells

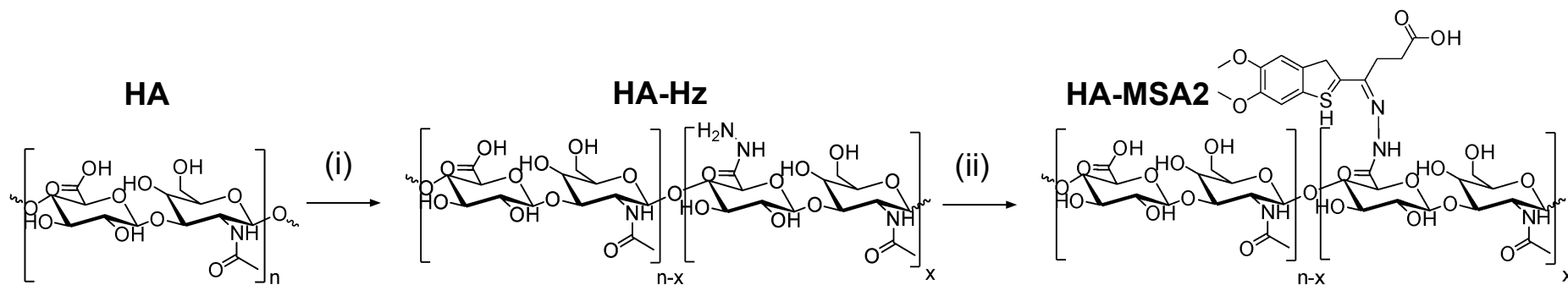


- Induces inflammation in mostly tumor tissues
- Activates in acidic microenvironment
- Low water solubility
- Poor cell permeation

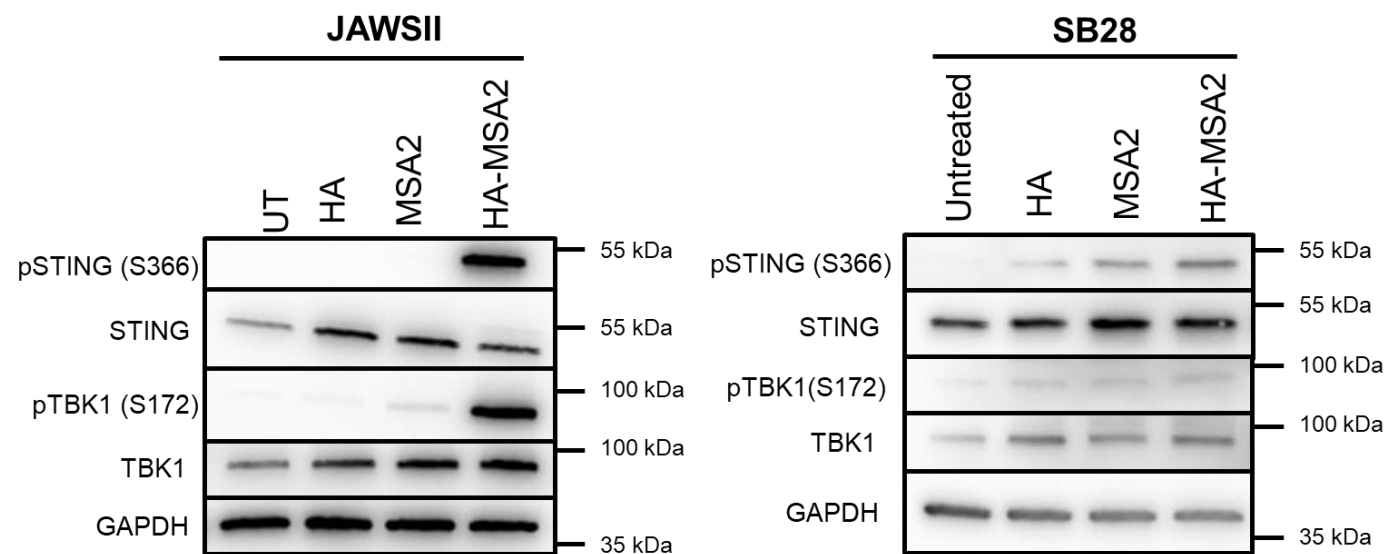
HA-STING Triggers the STING Pathway



Teenasha Chellen

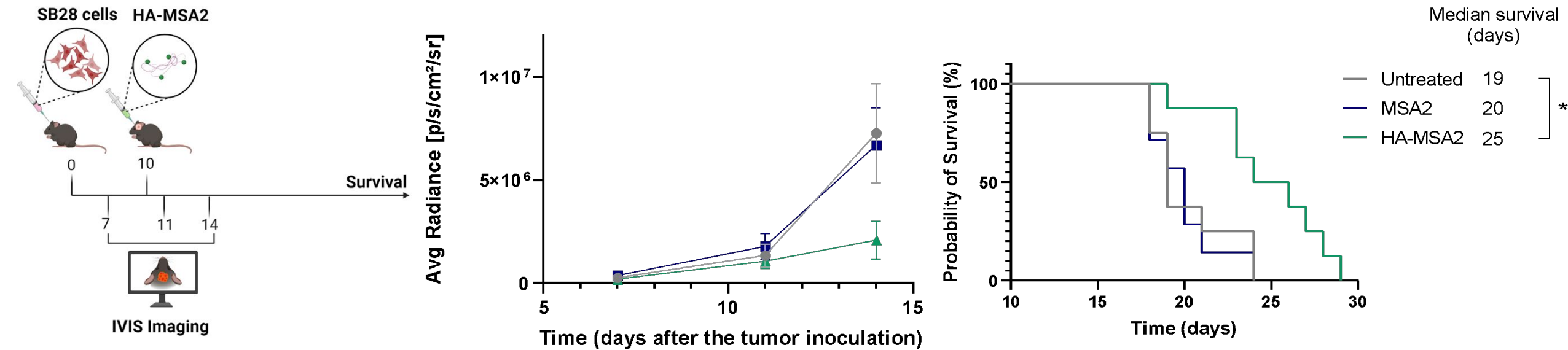


Conjugate	HA-MSA2
Drug loading (%w/w)	1.37
Size	12.96 ± 3.834
Zeta-potential	-25.78 ± 2.326



Chellen T.,...& Malfanti A.* (2023) submitted

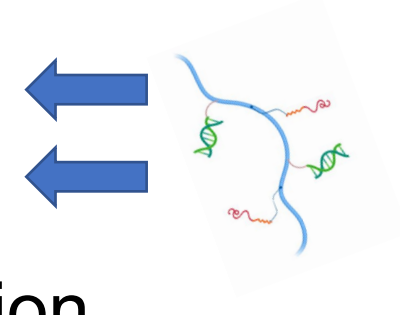
HA-STING Control GBM Growth and Extend the Survival



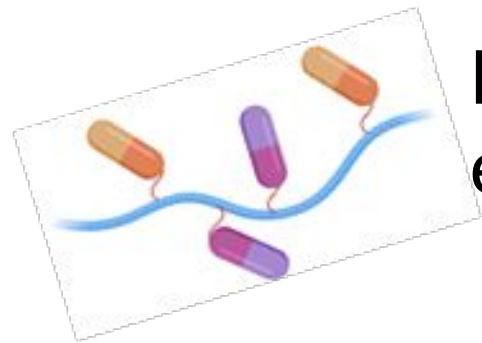
Chellen T.,...& Malfanti A.* (2023) submitted

Summary

Immunotherapy of GBM is still a challenge



Local Targeting Multiple Arms of GBM can be the solution



HA-based conjugates have the potential to be effective nanocarriers for local GBM immunotherapy

Our strategy can be used in combination with current standard of care allowing the use of other immunotherapies



Prof. Veronique Pr  at
 Prof. Ana Beloqui
 Prof. Bernard Gallez
 Prof. Anne Des Rieux

Giulia Rodella
 Giuseppina Catania
 Teenesha Chellen
 Leo Guilbaud
 Mingchao Wang
 Dr Mathilde Bausart
 Valentina Marotti
 Jingjing Yang
 Giuditta Leone
 Jerome Conq

email : alessio.malfanti@uclouvain.be



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