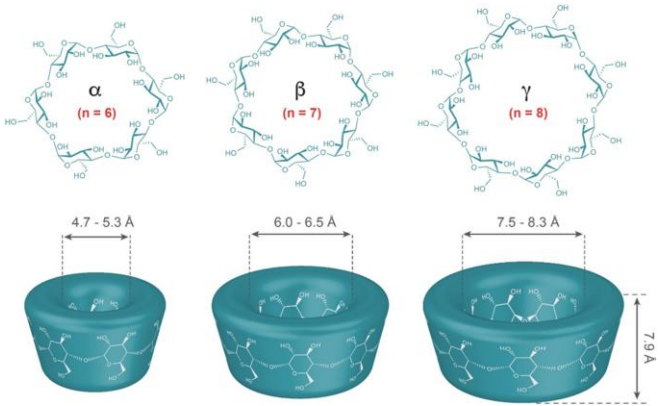
β-cyclodextrin-based nanomedicines for cancer therapy

Anna Scomparin
University of Turin
anna.scomparin@unito.it

CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025
NEXT-GENERATION DELIVERY INNOVATIONS

β-Cyclodextrin as drug carrier



Crini, G., *et al*. *Environ Sci Pollut Res* **29**, 167–170 (2022).

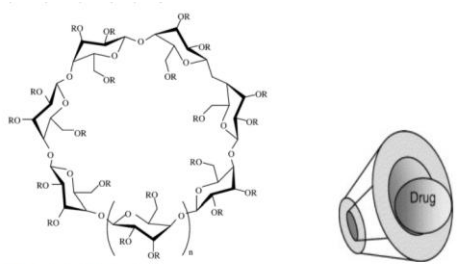
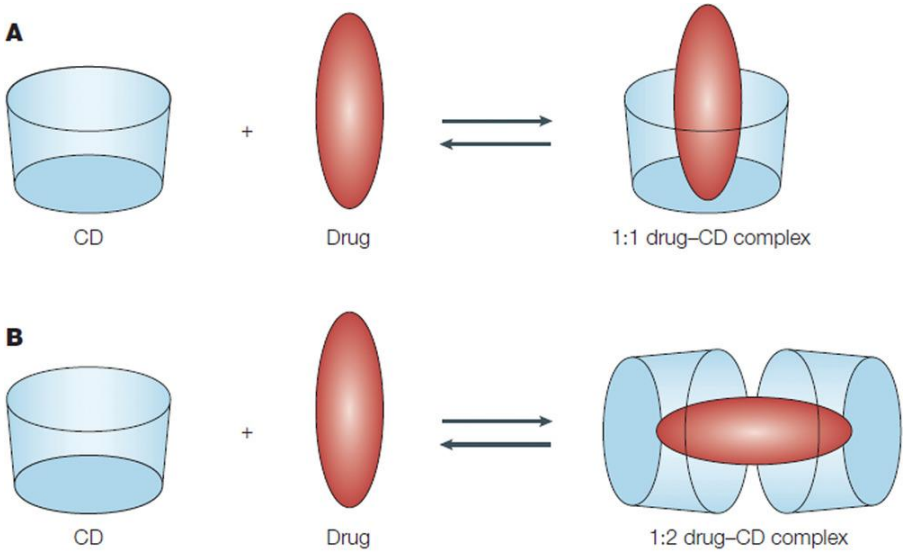


Figure 1: β-Cyclodextrin structure

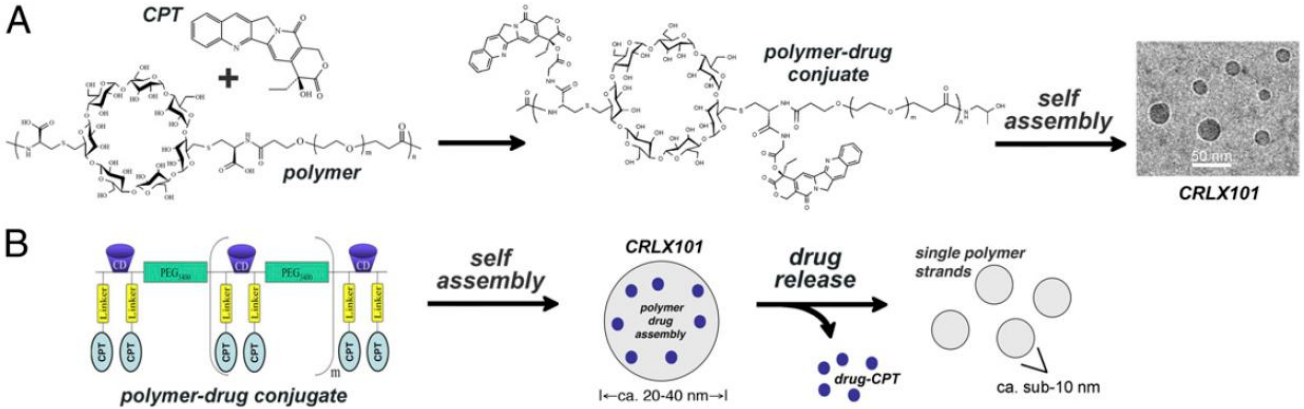
SBE-β-CD:	R = $-(CH_2)_4-SO_3^-Na^+$
HP-β-CD:	R = $-CH_2-CHOH-CH_3$
RM-β-CD:	R = $-CH_3$

Wankar, J., *et al., Adv. Funct. Mater.* 2020, 30, 1909049



Questions and answers on cyclodextrins used as excipients in medicinal products for human use
9 October 2017 EMA/CHMP/495747/2013 Committee for Human Medicinal Products (CHMP)

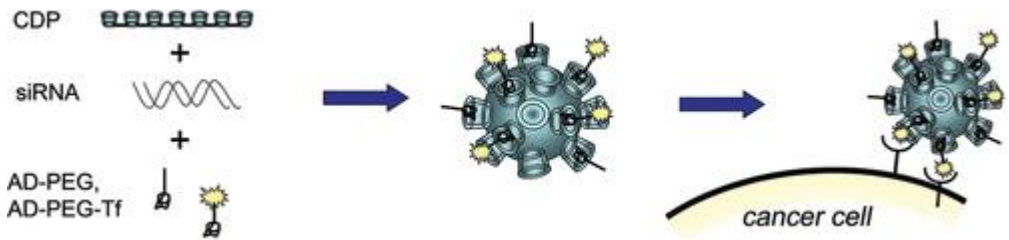
Cyclodextrin-containing NPs in clinical trials



CPT conjugated polymer CRLX101

Eliasof *et al.,* PNAS, 2013, 110:15127–15132

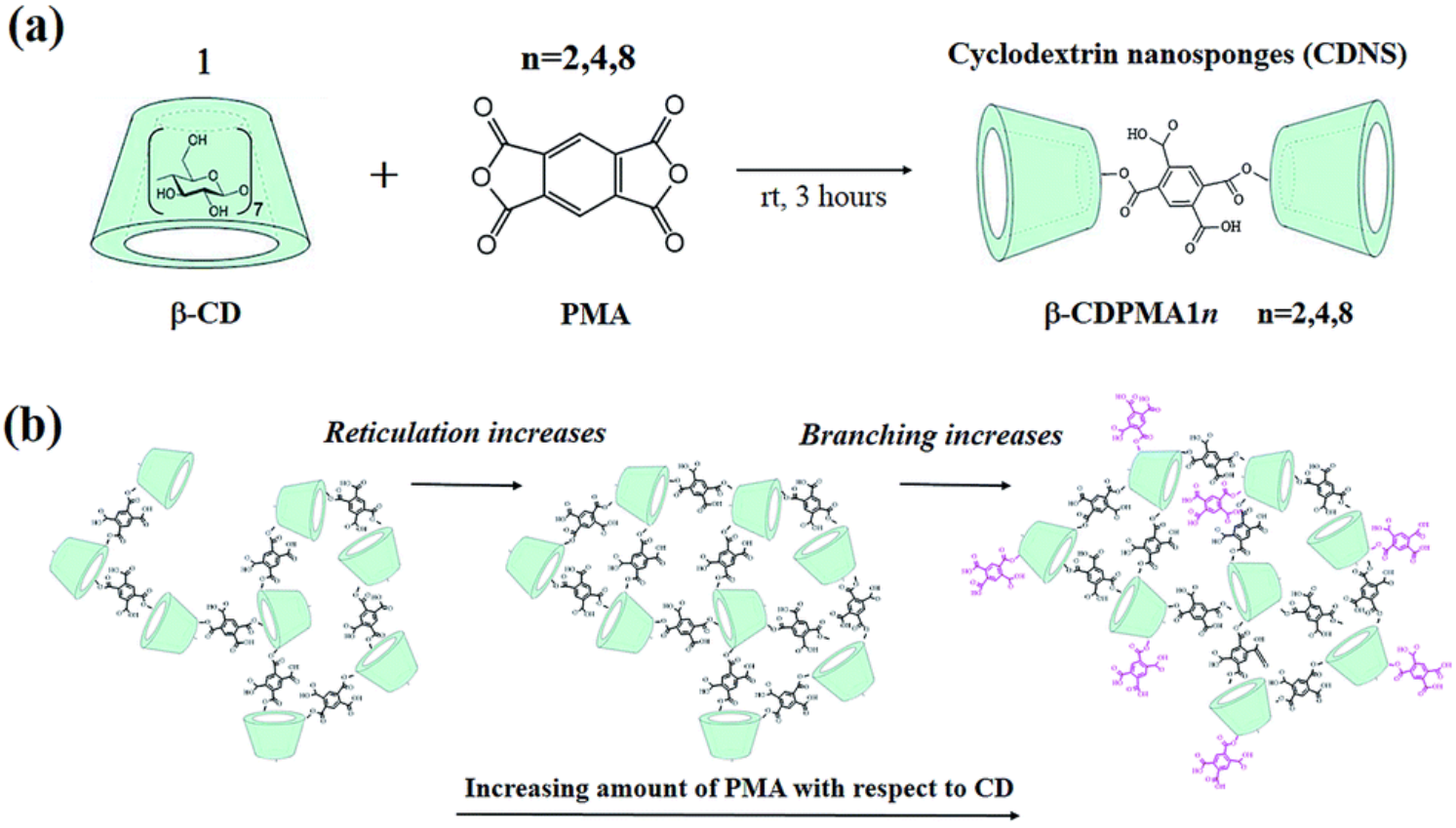
Transferrin Targeted siRNA loaded polymer – CALAA-01



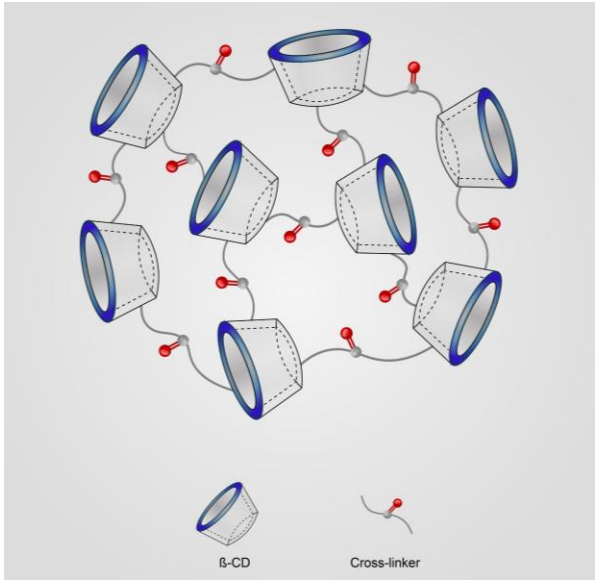
Davies, Mol. Pharmaceutics 2009, 6, 3, 659–668

β-Cyclodextrin crosslinking strategy

Prof. Trotta
UniTO

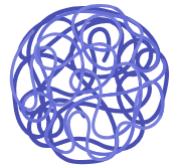


β-Cyclodextrin-based polymers



I. Branched cationic polymers

II. Crosslinked, hyperbranched cationic polymers: NS-Q^+



III. Crosslinked, hyperbranched polymers: Nanosponges (NS)

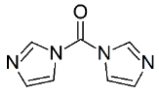
”Insoluble materials with distinctive nanometric porosity and superior absorption/complexation properties.”

Molinar, C. *et al.* (2023). Cyclodextrins and Cyclodextrin-Based Nanosponges for Anti-Cancer Drug and Nutraceutical Delivery. In: Malviya, R., Sundram, S. (eds) Targeted Cancer Therapy in Biomedical Engineering. Biological and Medical Physics, Biomedical Engineering. Springer, Singapore.

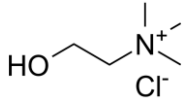
I. Branched β-Cyclodextrin cationic polymers for siRNA delivery

Monomer: β-Cyclodextrin

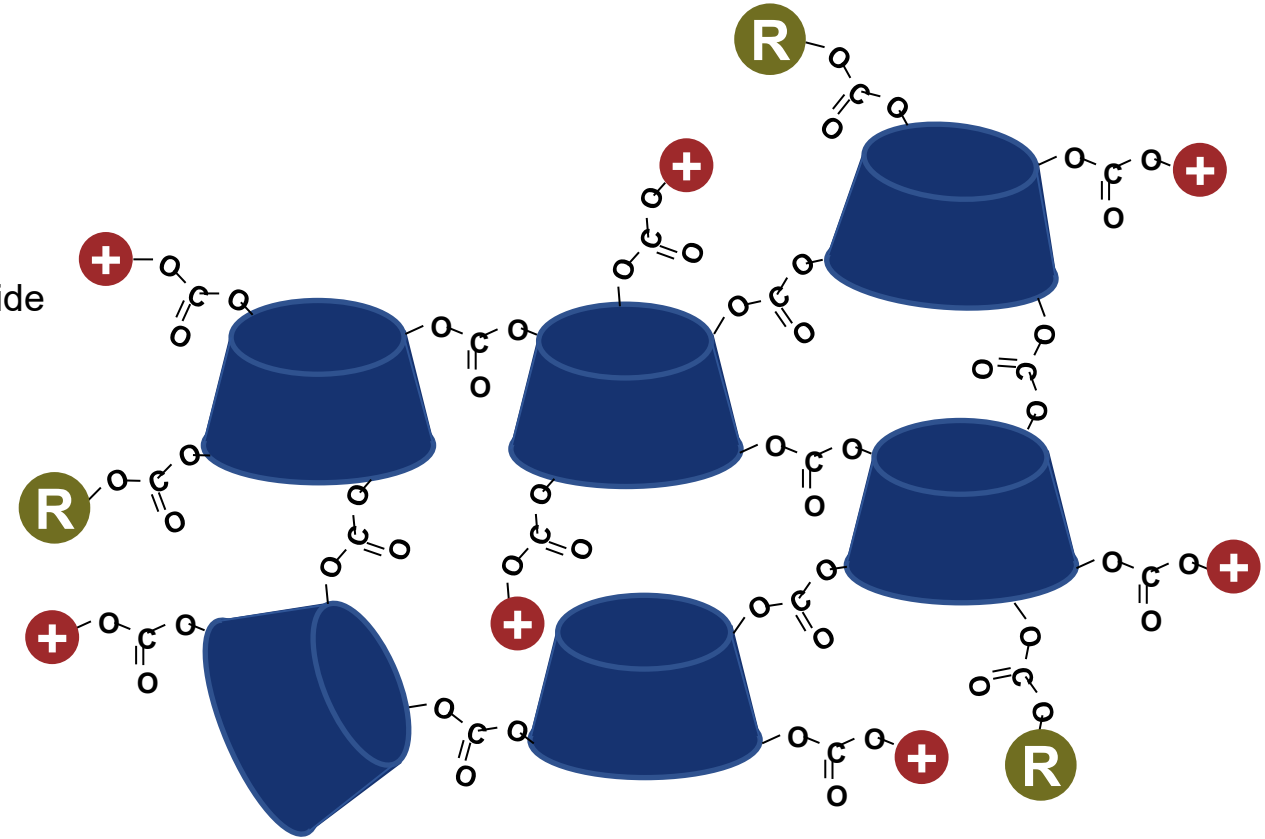
Linker: Carbonyldiimidazole



Positive charge: Choline chloride



Alkyl chain:
C0 - H
C1-methyl
C5-pentyl
C10-decyl
C14-tetradecyl
C16-hexadecyl
C18-octadecyl



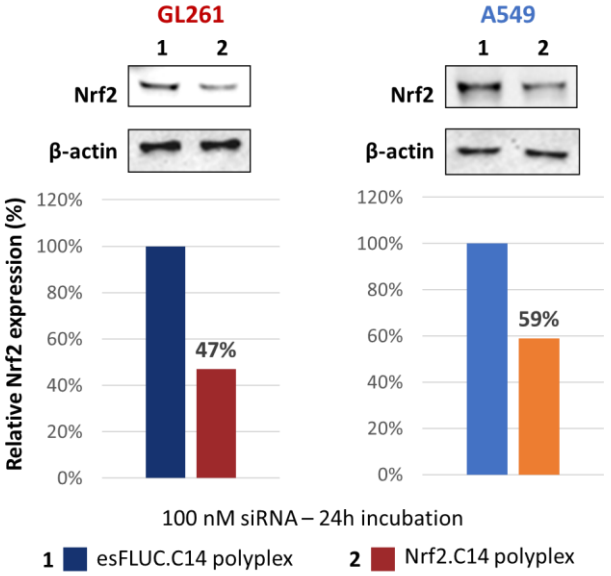
Branched β-Cyclodextrin cationic polymers are able to form polyplexes for siRNA delivery

Elementary analysis

Polymer	N%	C%	H%	S%
βCD-C14	3.78	38.05	6.64	-

Polyplexes Physico-chemical characterization

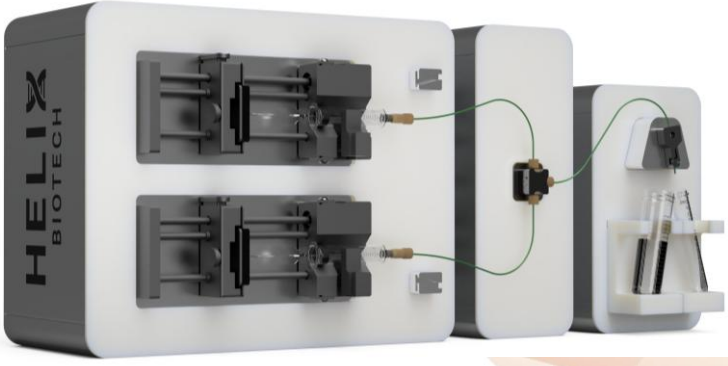
Polyplex (N/P=10)	Hydrodynamic diameter (nm)	PDI	ζ Potential (mV)
βCD-C14: Nrf2 siRNA	189,00±2,86	0,22±0,01	27,35±1,01



C14 polyplex showed ~ 50% knockdown of Nrf2 gene in two tested cell lines

Reproducible formulations of polyplexes

Polyplex (N/P=10)	Hydrodynamic diameter ± SD (nm)	PDI ± SD	ζ Potential ± SD (mV)
βCD-C12: siRNA	147,8 ± 2,47	0,11 ± 0,03	47,14 ± 1,37
βCD-C14: siRNA	150,7 ± 2,28	0,16 ± 0,02	35,48 ± 2,72
βCD-C16: siRNA	197,8 ± 4,11	0,25 ± 0,05	36,94 ± 1,65
βCD-C18: siRNA	179,6 ± 8,28	0,27 ± 0,07	29,44 ± 1,38

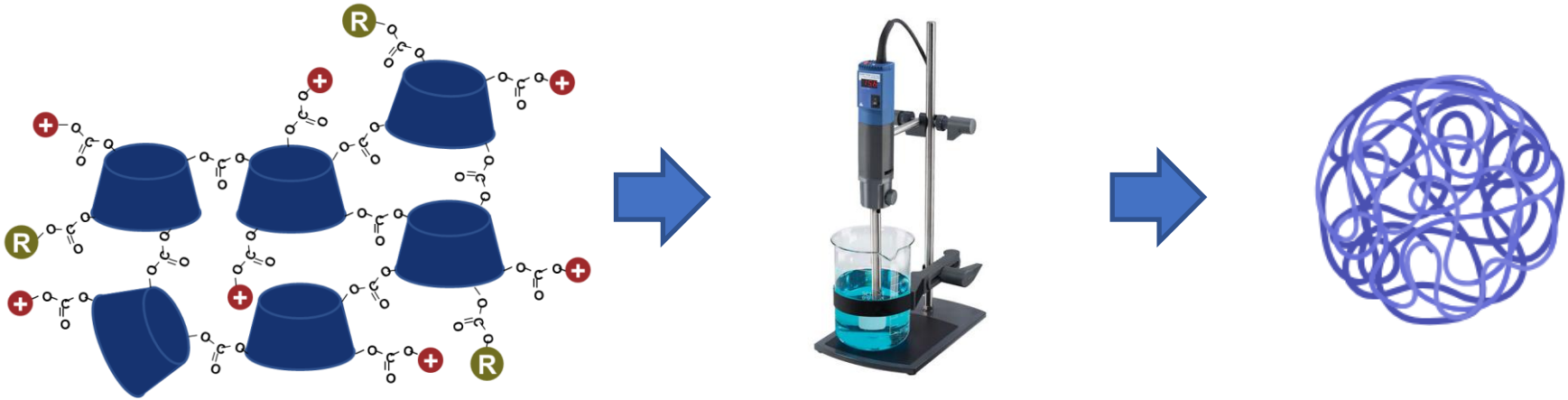


Poster #276

Nova™ Impinged Jet Mixing

HELIX BIOTECH

II. Crosslinked, hyperbranched cationic polymers: NS-Q⁺



	Hydrodynamic diameter ± SD (nm)	PDI ± SD	ζ Potential ± SD (mV)
NS-Q⁺	143.4 ± 1.98	0.24 ± 0.01	+13.46 ± 0,76

Olaparib loaded NS-Q⁺ are cytotoxic on mesothelioma cells

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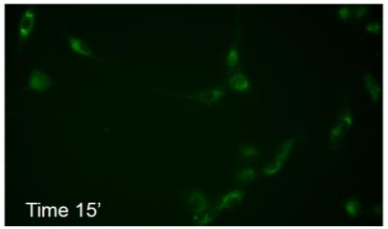
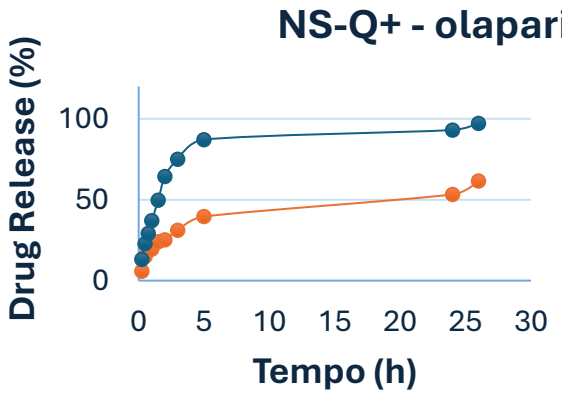
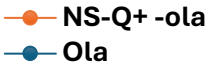
DEPARTMENT OF ONCOLOGY
UNIVERSITY OF TURIN

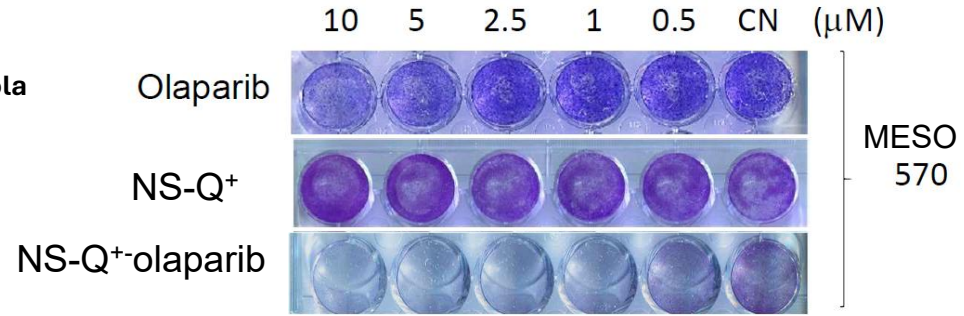
	Hydrodynamic diameter ± SD (nm)	PDI ± SD	ζ Potential ± SD (mV)	E.E (%)	D.L (%)
NS-Q⁺	143.4 ± 1.98	0.24 ± 0.01	+13.46 ± 0.76	-	-
NS-Q⁺-olaparib	433.8 ± 31.7	0.3 ± 0.02	+13.94 ± 1.23	55.6	5.2



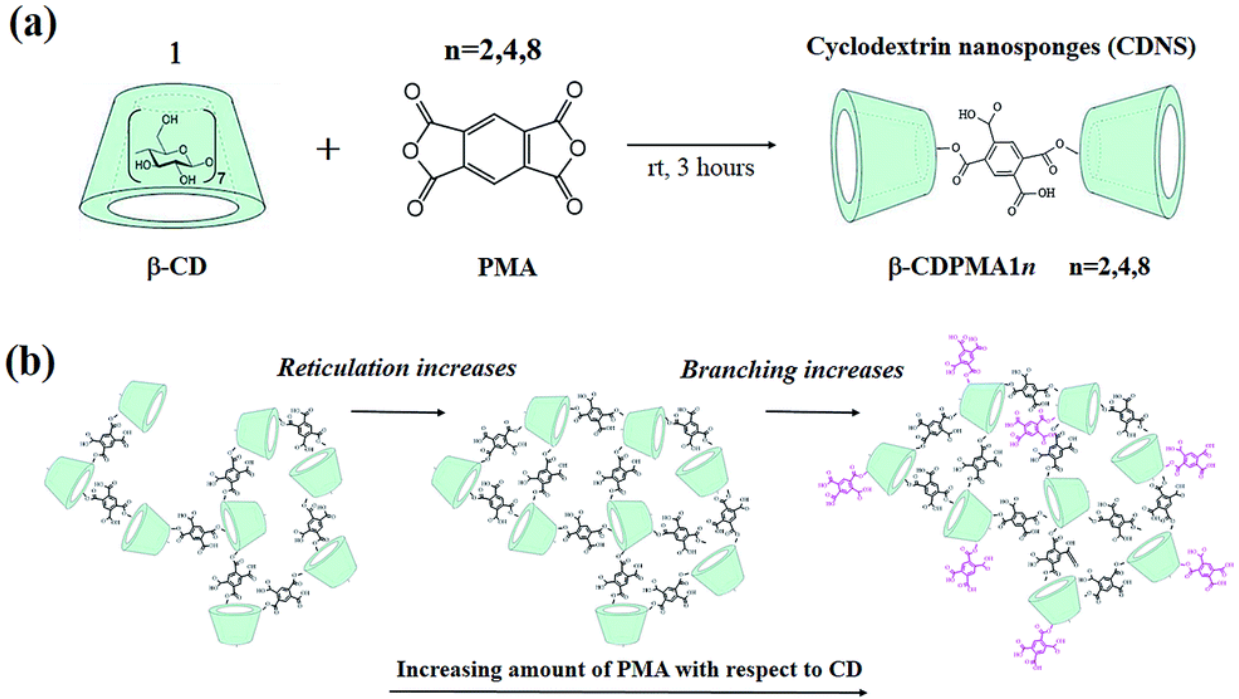
6-coumarin loaded NS-Q⁺





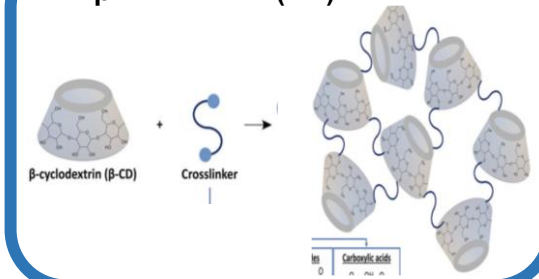


III. β-Cyclodextrin nanosponges (NS)



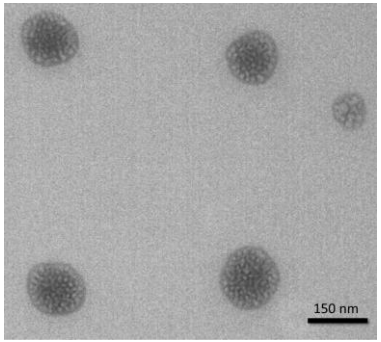
Post-synthetic NS formulation

β-CD : PMDA (1:4)



Ultraturrax homogenizer

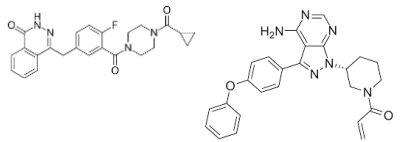
High Pressure Homogenizer (HPH)



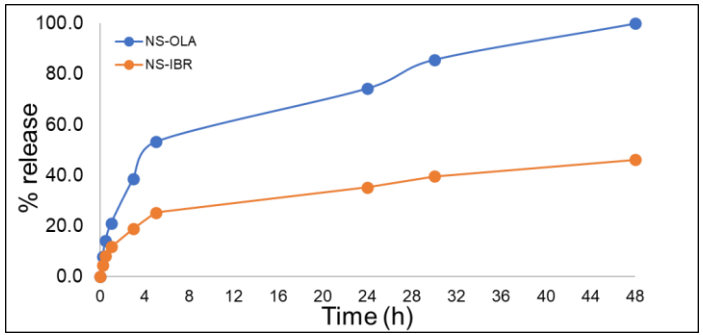
	Size (nm)	PI	Zeta (mV)	E.E (%)	D.L (%)
NS blank	177± 18.05	0.2 ± 0.01	-31.6 ± 3.02	/	/

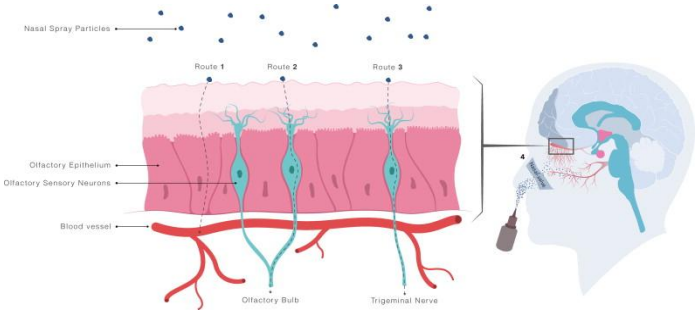
β-Cyclodextrin NS loaded with anticancer drugs for Glioblastoma treatment

Anticancer agents



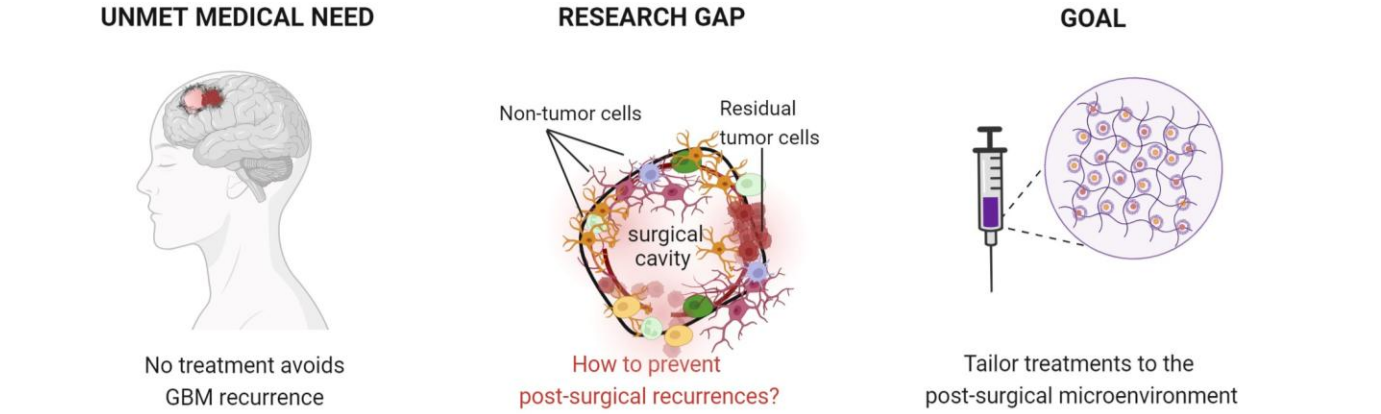
	Size (nm)	PI	Zeta (mV)	E.E (%)	D.L (%)
NS blank	177± 18.05	0.2 ± 0.01	-31.6 ± 3.02	/	/
Olaparib (OLA_NS)	344.8 ± 31.7	0.3 ± 0.02	-13.4 ± 2.8	43.1	3.9
Ibrutinib (IBR_ NS)	406 ± 67.1	0.3 ± 0.01	-16.7 ± 0.07	38.1	3.7

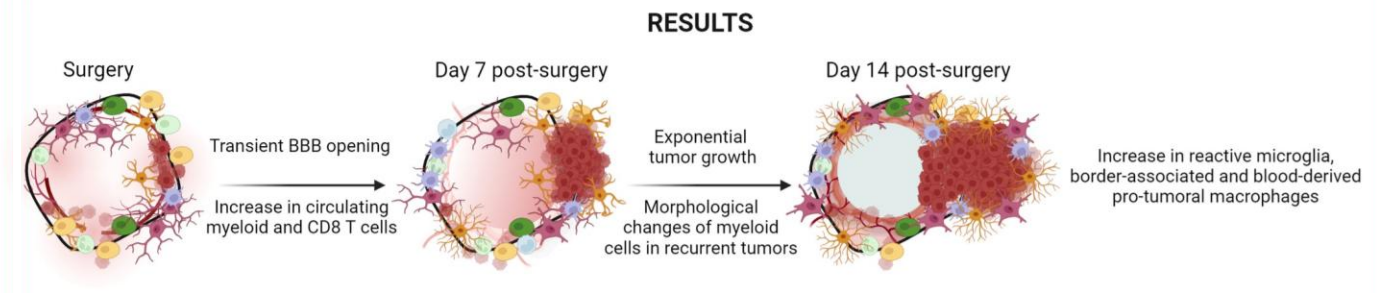




Understanding GBM TME plasticity

Dr. Chiara Bastiancich





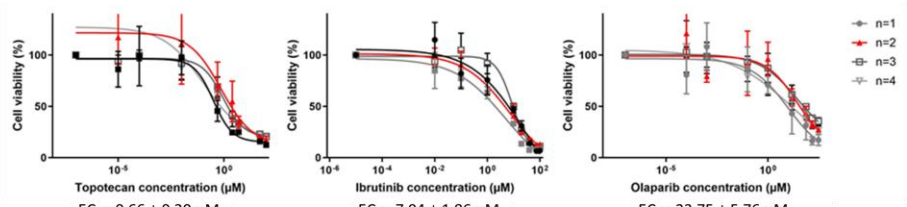
Bastiancich *et al.* In preparation

Novel synergistic drug combinations

Chiara Molinar

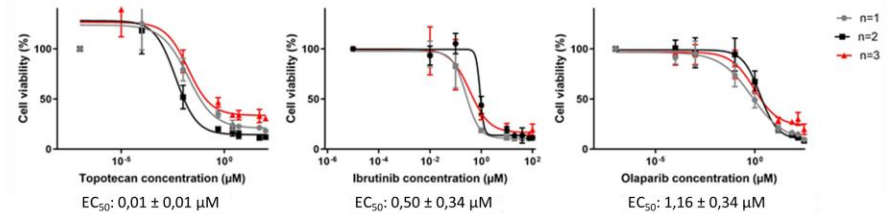
Dr. Chiara Bastiancich

GL261-DsRed cells 2D; 72h treatment (n=4)

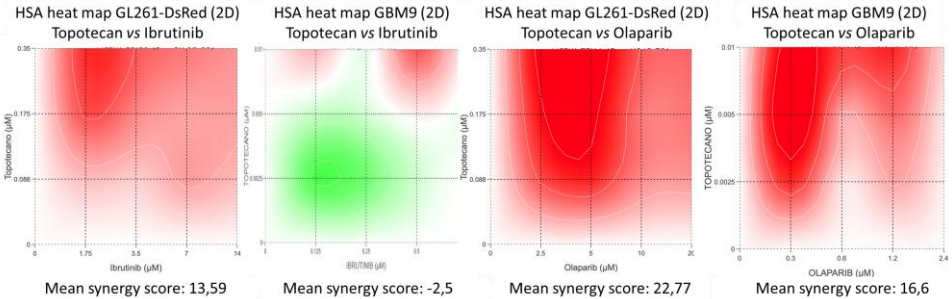


EC_{50}: 0,66 ± 0,30 μM | EC_{50}: 7,04 ± 1,86 μM | EC_{50}: 23,75 ± 5,76 μM

GBM9 cells 2D; 72h treatment (n=3)

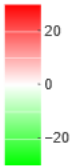


EC_{50}: 0,01 ± 0,01 μM | EC_{50}: 0,50 ± 0,34 μM | EC_{50}: 1,16 ± 0,34 μM



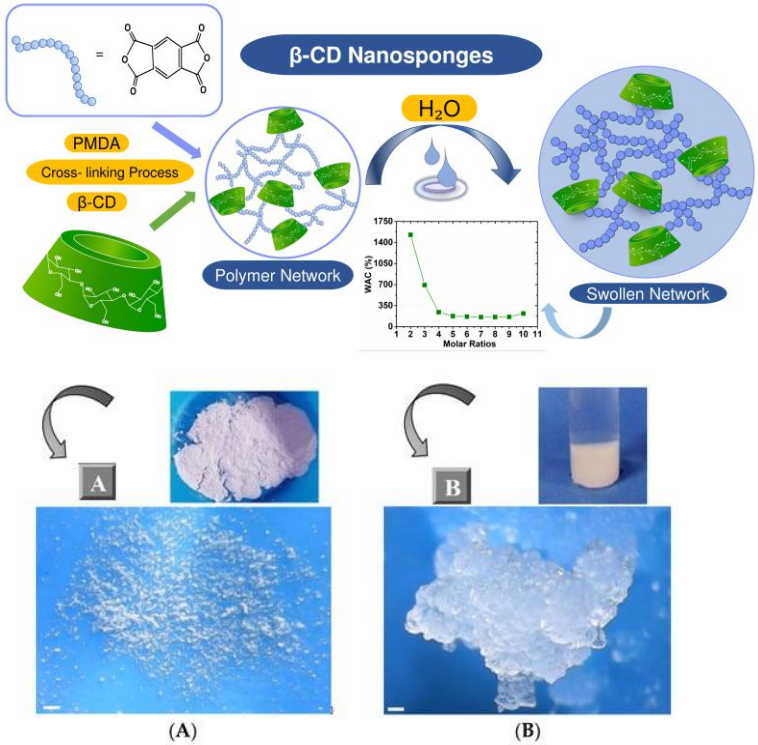
Mean synergy score: 13,59 | Mean synergy score: -2,5 | Mean synergy score: 22,77 | Mean synergy score: 16,6

The synergistic score obtained with SynergyFinder is the excess of observed effect over expected effect calculated by a reference model.

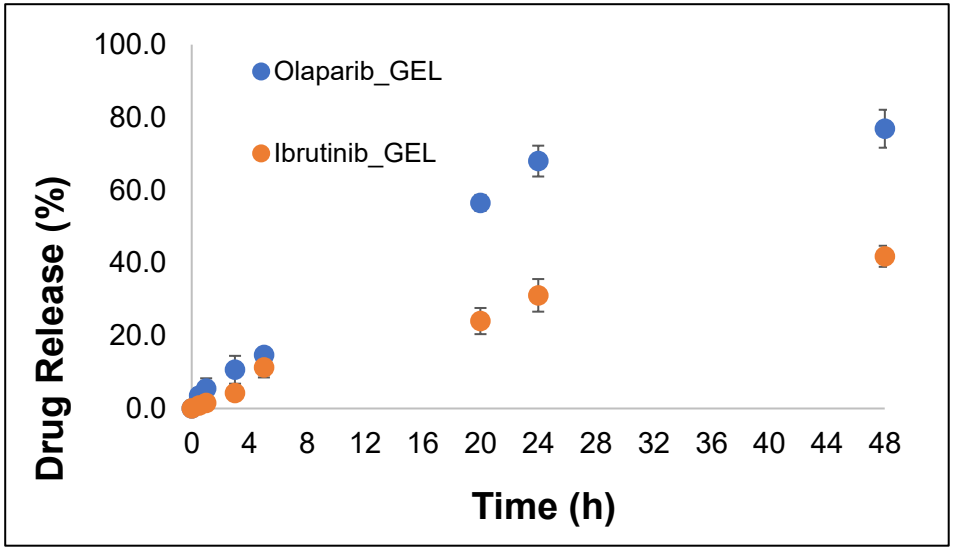


- Synergistic interaction: score > + 10
- Additive interaction: score between – 10 to + 10
- Antagonistic interaction: score < – 10

β-Cyclodextrin NS form amorphous gel



Hoti G. et al, Materials **2021**, *14*(3), 478;

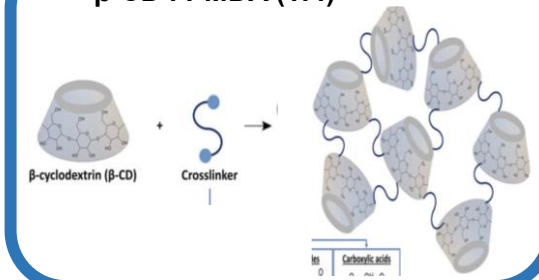


- **41%** release of IBR in NS gel formulation in 48 hours
- **80 %** release of OLA in NS gel formulation in 48 hours

Formulation	Viscosity at 37° C (mPa·s)
β-CD NS gel	3191

β-Cyclodextrin NS as a platform for chemo-immuno therapy for pancreatic cancer

β-CD : PMDA (1:4)



Ultraturrax homogenizer

High Pressure Homogenizer (HPH)

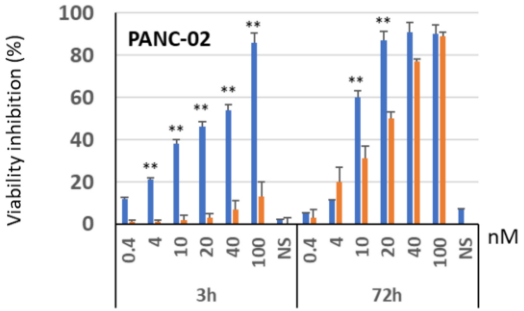
Gemcitabine/Oleic Acid ion couple

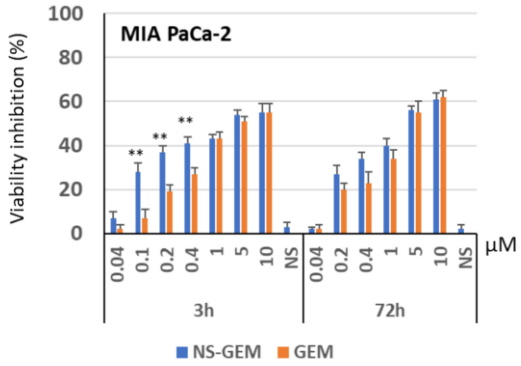
	Average diameter ± SD (nm)	PDI	Zeta potential ± SD (mV)	Encapsulation Efficiency (%)	Drug loading (%)
Blank NS	238.8 ± 2.4	0.20 ± 0.01	-30.20 ± 4.55	-	-
NS-GEM	245.5 ± 5.6	0.19 ± 0.02	- 28.40 ± 3.92	98	5.5

M. Argenziano et al. InternationalJournalofPharmaceutics682(2025)125869

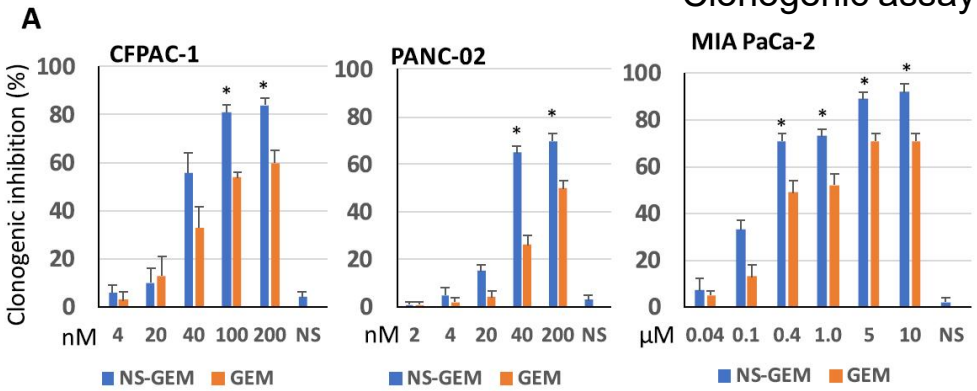
NS-GEM overcome gemcitabine resistance on PDAC cells

Proliferation

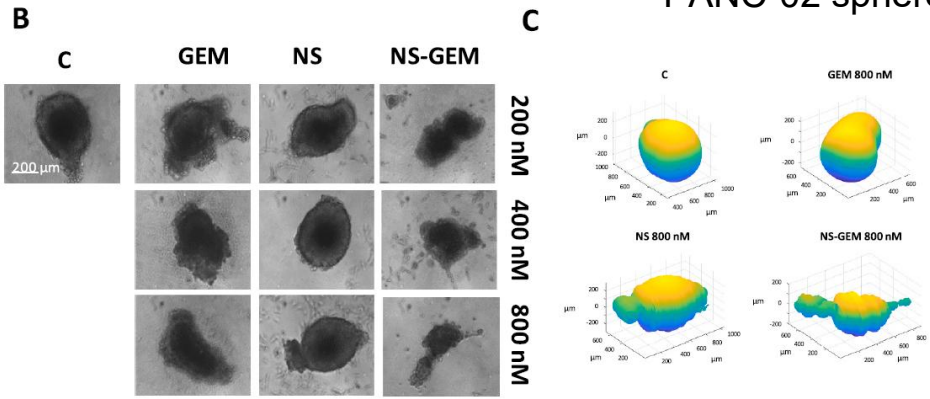




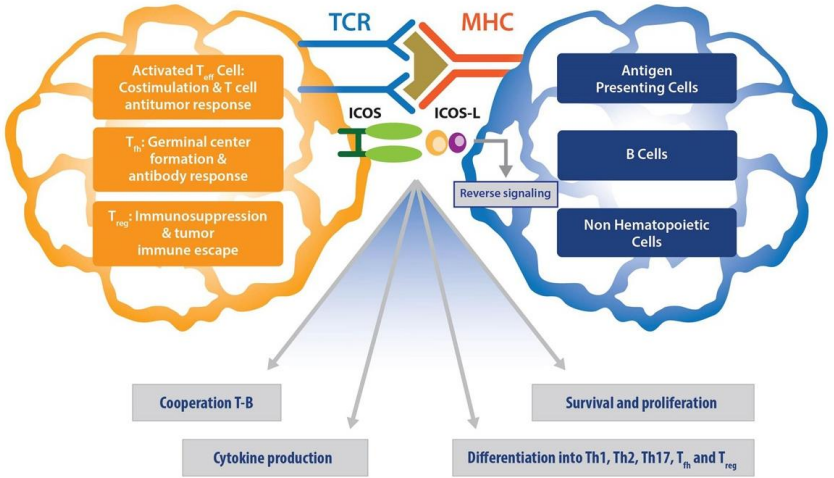
Clonogenic assay



PANC-02 spheroids



ICOS as immunocheck point in cancer therapy



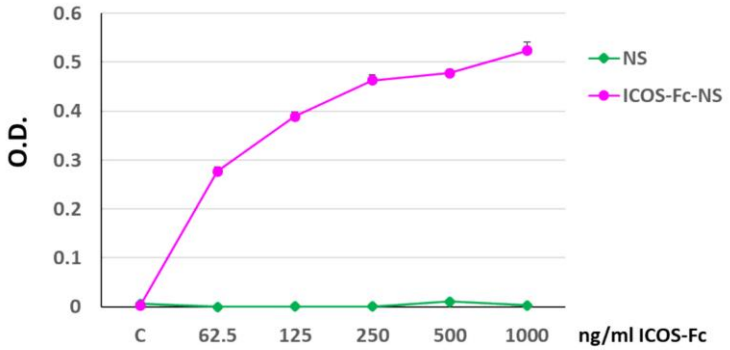
- Inducible T cell costimulatory factor
- ICOS Ligand (CD28 or B7-H) is expressed in:

DC, B cells, MΦ, epithelial cells, fibroblasts

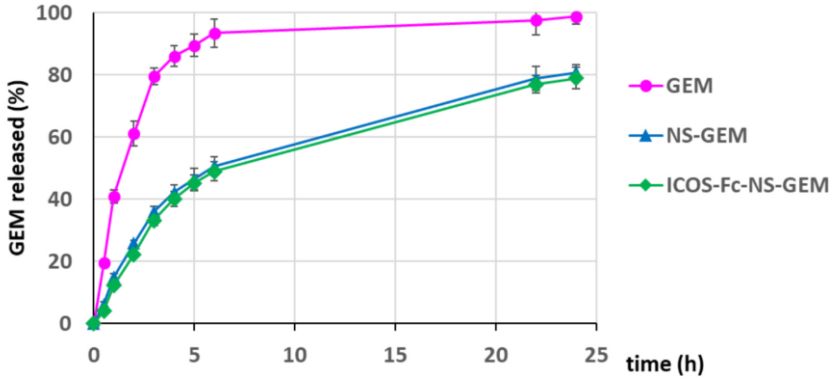
NS-GEM were decorated with ICOS-Fc

	Average diameter ± SD (nm)	PDI	Zeta potential ± SD (mV)	Encapsulation Efficiency (%)	Drug loading (%)
Blank NS	238.8 ± 2.4	0.20 ± 0.01	-30.20 ± 4.55	-	-
NS-GEM	245.5 ± 5.6	0.19 ± 0.02	-28.40 ± 3.92	98	5.5
ICOS-Fc-NS	240.2 ± 3.5	0.20 ± 0.02	-29.23 ± 5.29		
ICOS-Fc-NS-GEM	250.5 ± 4.5	0.22 ± 0.01	28.02 ± 4.03	98	5.5

ICOS-Fc-NS effectively bind to ICOS-HIS coated plate (ELISA test)

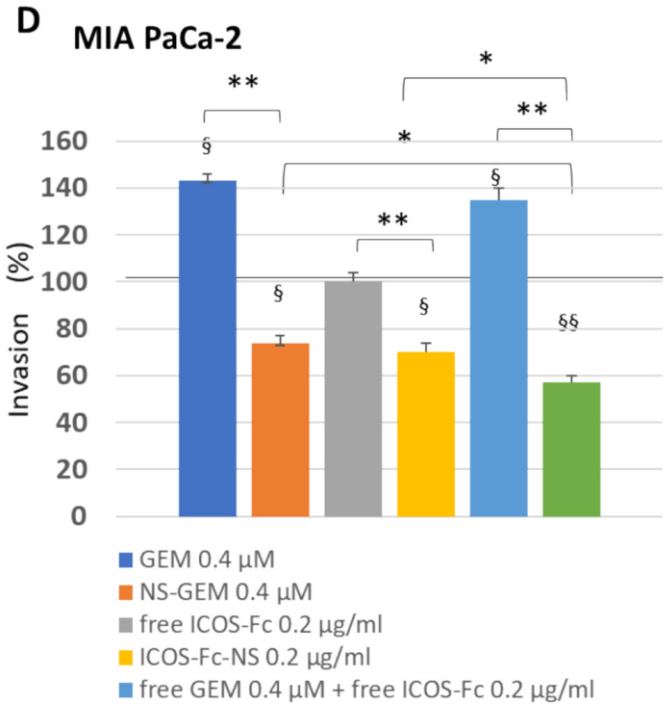


The decoration of NS with ICOS-Fc does not alter GEM release profile

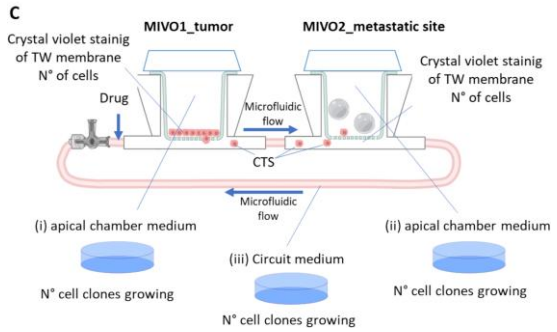


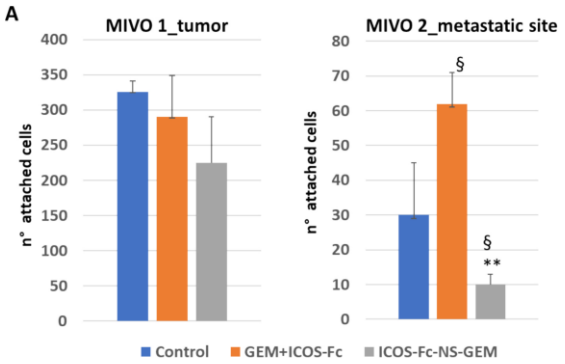
ICOS-Fc-NS-GEM are able to inhibit invasion and migration of MIA-Paca-2 cells

Invasion

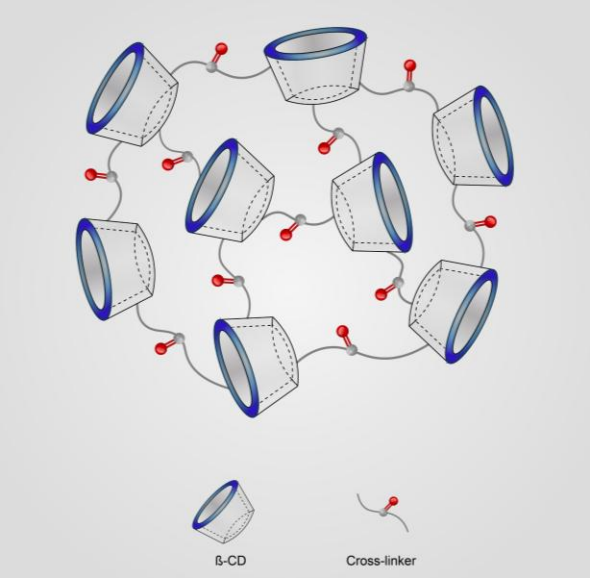


3D fluid-dynamic model to study cancer migration and metastasis.





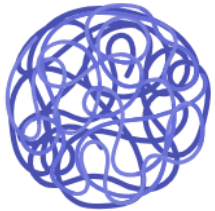
β-Cyclodextrin-based polymers for anticancer nanomedicine



I. Branched cationic polymers

II. Crosslinked, hyperbranched cationic polymers: NS-Q^+

III. Crosslinked, hyperbranched polymers: NS



Molinar, C. *et al.* (2023). Cyclodextrins and Cyclodextrin-Based Nanosponges for Anti-Cancer Drug and Nutraceutical Delivery. In: Malviya, R., Sundram, S. (eds) Targeted Cancer Therapy in Biomedical Engineering. Biological and Medical Physics, Biomedical Engineering. Springer, Singapore.

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