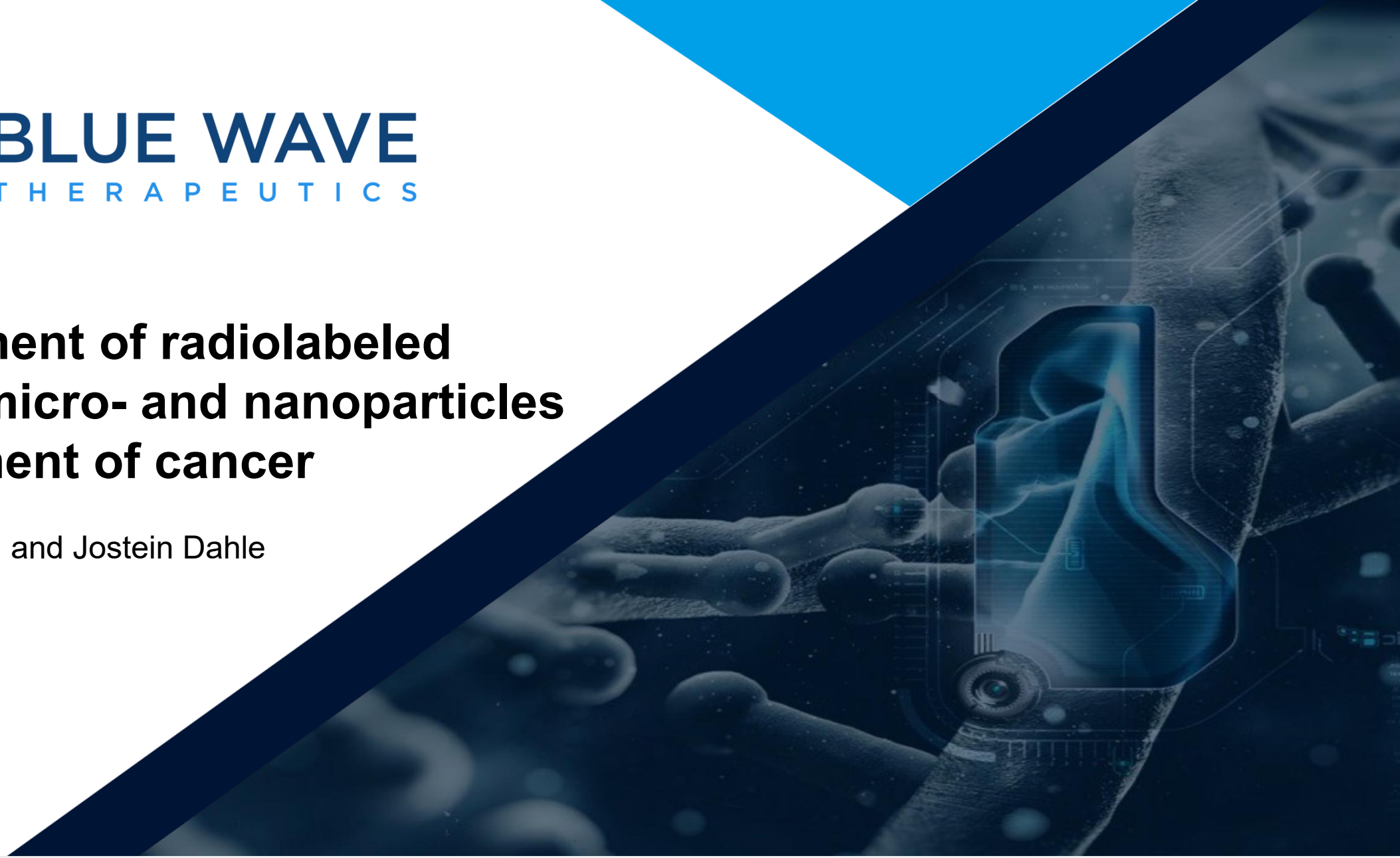
BLUE WAVE THERAPEUTICS

Development of radiolabeled alginate micro- and nanoparticles for treatment of cancer

Michael Dornish and Jostein Dahle

SNMMI 2025
Session SS22



Disclosure

- Michael Dornish and Jostein Dahle are co-founders and shareholders in Blue Wave Therapeutics

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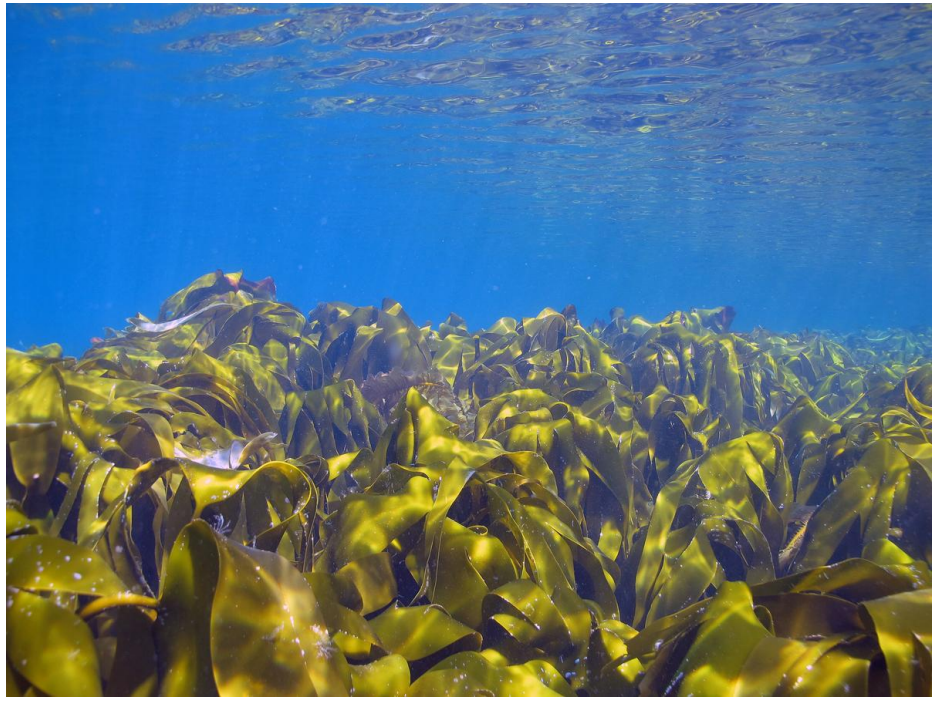
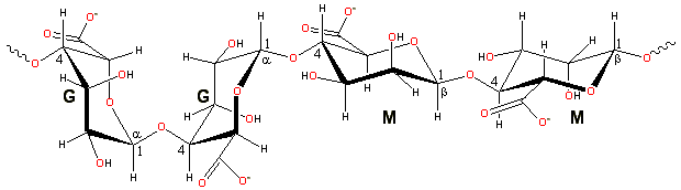
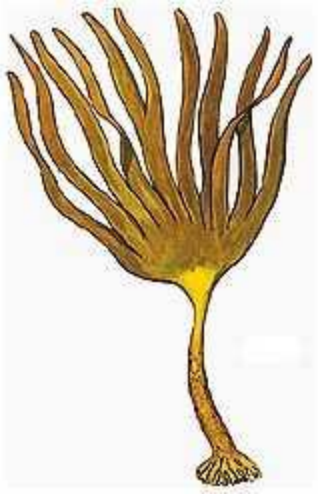
What is alginate?



Alginate is a structural polysaccharide extracted from seaweed and kelp





Mannuronate-rich

Guluronate-rich

Laminaria hyperborea

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Alginate in everyday life

Ingredients: WATER, SOYBEAN OIL, VINEGAR, WHEY PROTEIN CONCENTRATE (FROM MILK), SALT, CONTAINS LESS THAN 2% OF SPICE, PROPYLENE GLYCOL ALGINATE, SORBIC ACID AND CALCIUM DISODIUM EDTA AS PRESERVATIVES, POLYSORBATE 60, DRIED GARLIC, XANTHAN GUM, OLEORESIN PAPRIKA, ACESULFAME POTASSIUM AND SUCRALOSE (SWEETENERS), GUAR GUM, YELLOW 6, YELLOW 5, CARAMEL COLOR, NATURAL FLAVOR.

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Alginate in medical products

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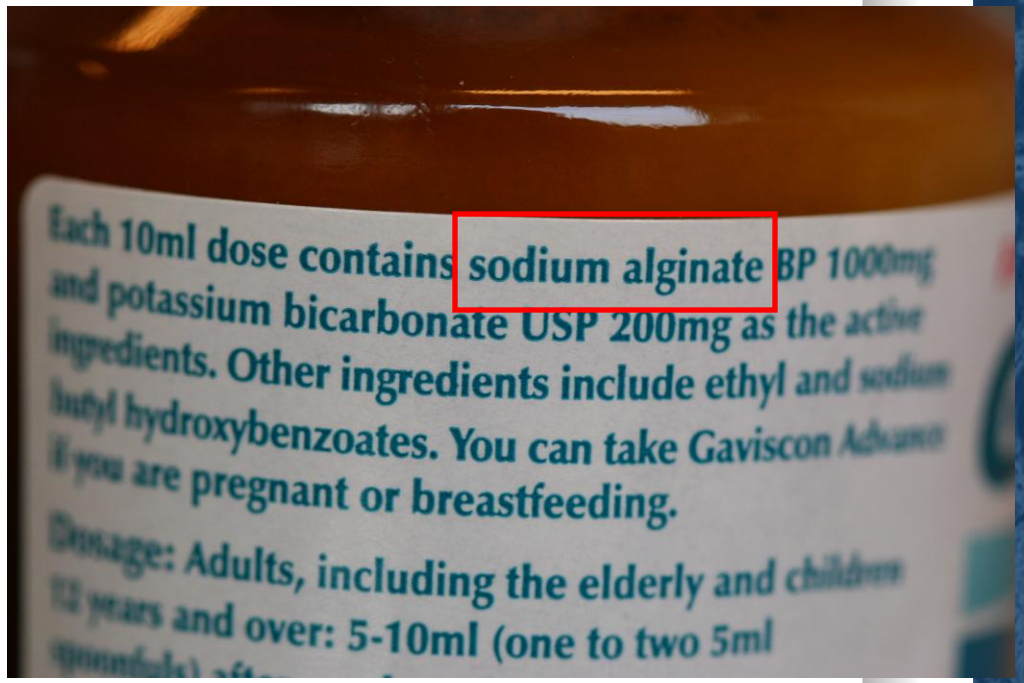
Alginate in medical products



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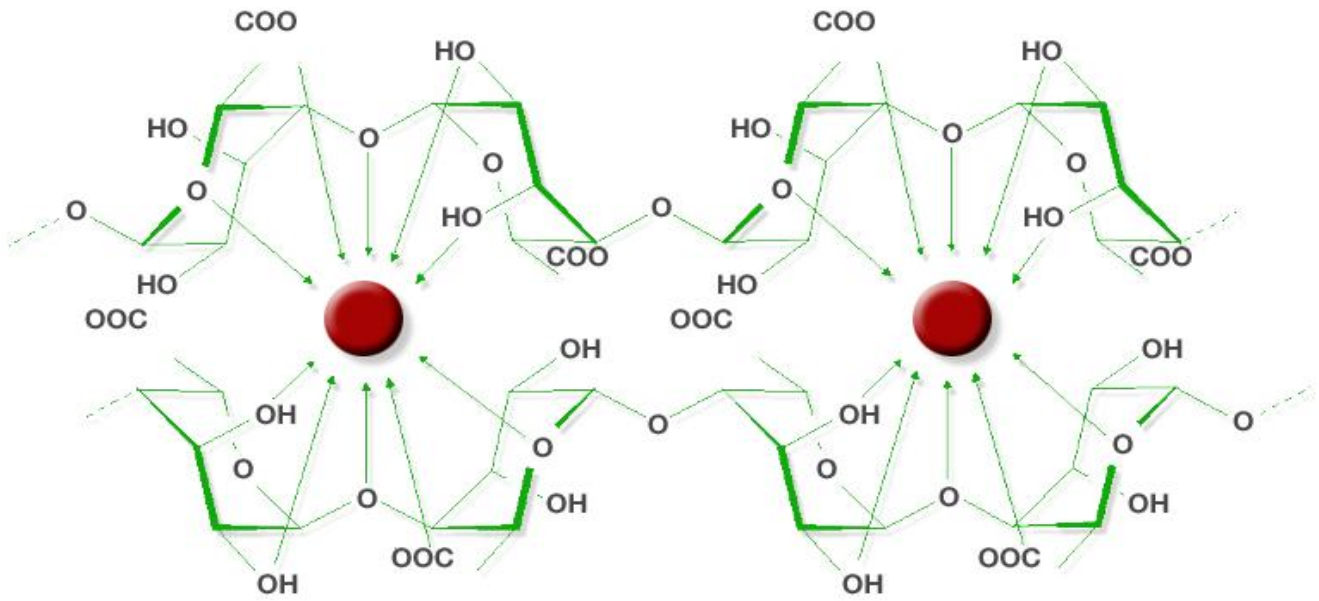
Alginate chelation of cations



Affinity :
Ca < ^{89}Sr < $^{223/224/225}$Ra

Other:
$^{64/67}$Cu,
^{90}Y,
$^{211/212}$Pb,
$^{211/212/213}$Bi,
^{111}In,
^{227}Th,
^{177}Lu,
$^{223/224}$Ra,
^{225}Ac,
^{221}Fr

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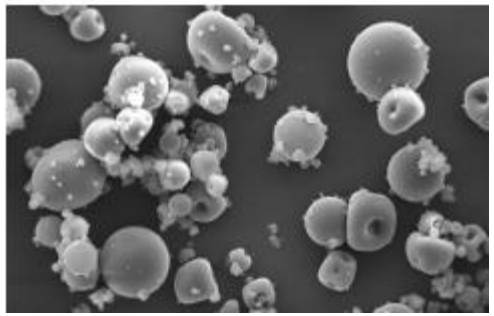
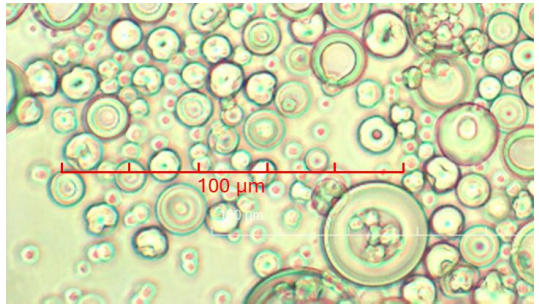
Producing alginate nanoparticles



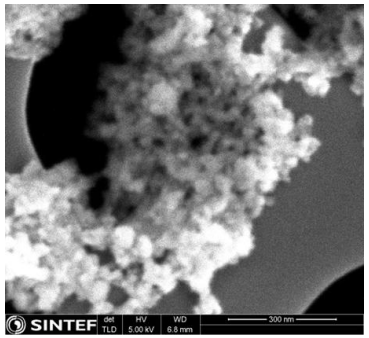
Ca^{2+}

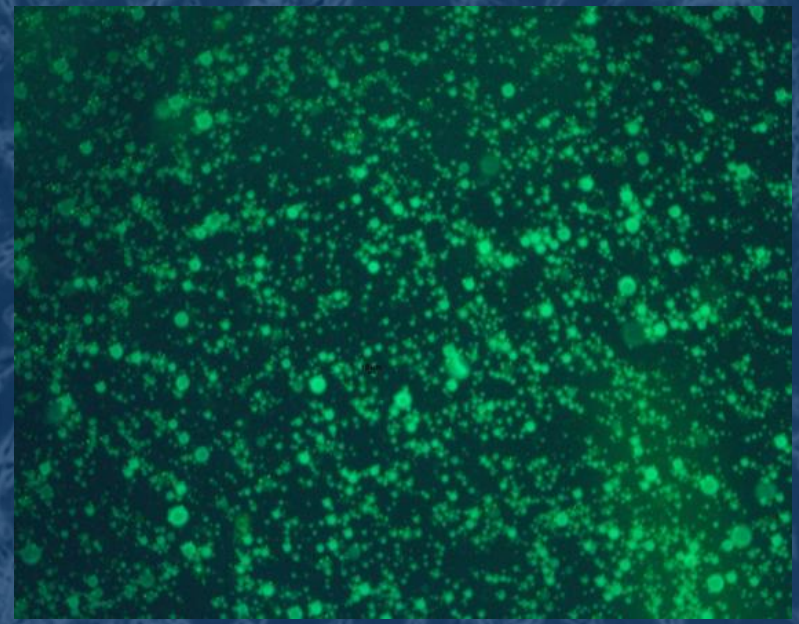


Sodium alginate (soluble) spray dried microparticles (10-12 µm)

Conversion to calcium alginate (insoluble) microparticles (10-12 µm)

Bead milling to nanoparticles (60-80 nm)





Fluorescence-labelled microparticles

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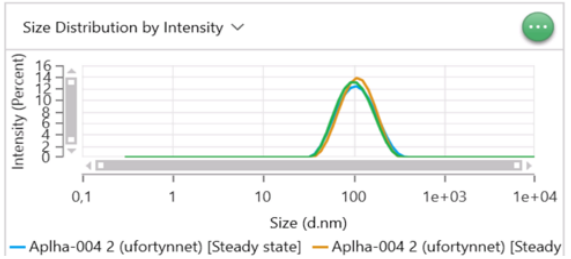
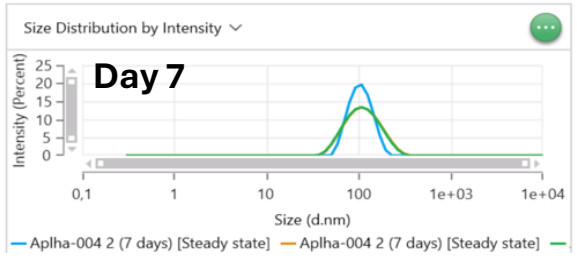
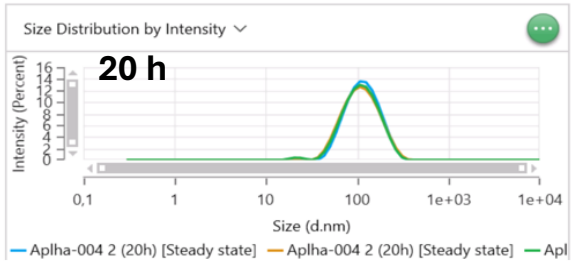
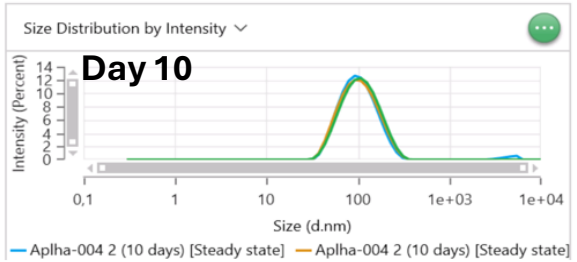
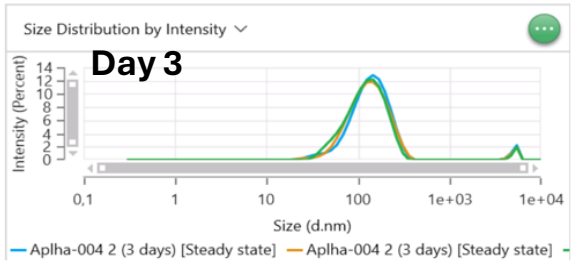
Alginate nanoparticles (≈ 60-80 nm)

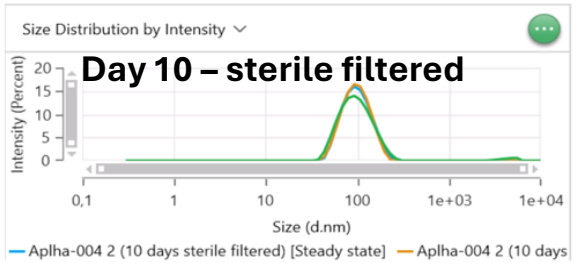


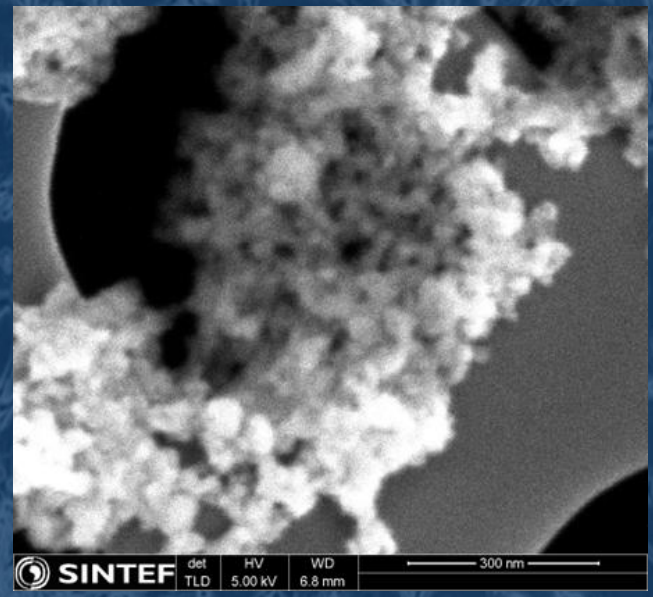












ARAspheres nanoparticles Batch C71, 14 Jan2025

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Peptide targeting

- **RGD-peptide** targets many different integrins and tumors
- **Other peptides** specific to different cancer cell receptors can be used, such as peptides that bind to **EGFR** (YHWYGYTPQNVI)

Tumor type	Integrins expressed	Associated phenotype	RGD binding
Breast	$\alpha_6\beta_4/\alpha_v\beta_3$	Increase tumor size and grade	✓
Cervical	$\alpha_v\beta_3/\alpha_v\beta_6$	Decreased patient survival	✓
Colon	$\alpha_v\beta_6$	Reduced patient survival	✓
Glioblastoma	**$\alpha_v\beta_3/\alpha_v\beta_5$**	**Expressed at tumor/normal tissue margin and possible role in invasion**	✓
Melanoma	$\alpha_v\beta_3/\alpha_5\beta_1$	Promotes lymph node metastasis	✓
Non-small cell lung carcinoma	$\alpha_5\beta_1$	Decreased survival in patients with lymph node/negative tumors	✓
Ovarian	$\alpha_4\beta_1/\alpha_v\beta_3$	Increased peritoneal metastasis and tumor proliferation	✓
Pancreatic	$\alpha_v\beta_3$	Lymph node metastasis	✓
Prostate	$\alpha_v\beta_3$	Increased bone metastasis	✓

Desgrosellier and Cheresh, *Nat. Rev. Cancer*, **10**, 9-22, 2010

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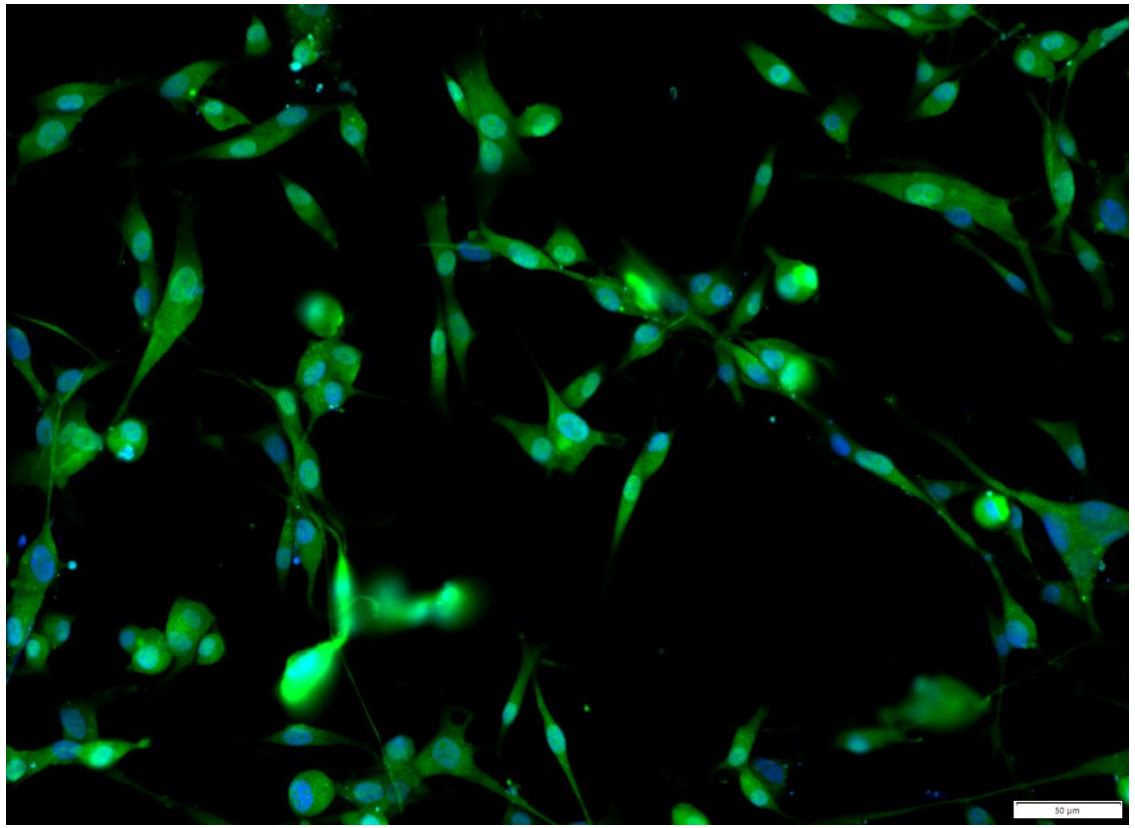
Proof of Concept
RGD-alginate binding to cellular integrins



Human glioblastoma cells (U87-MG) showing binding of fluorescent RGD-alginate (green) to cell surface integrins. Cell nuclei are stained blue

(Courtesy of Minerva Imaging)

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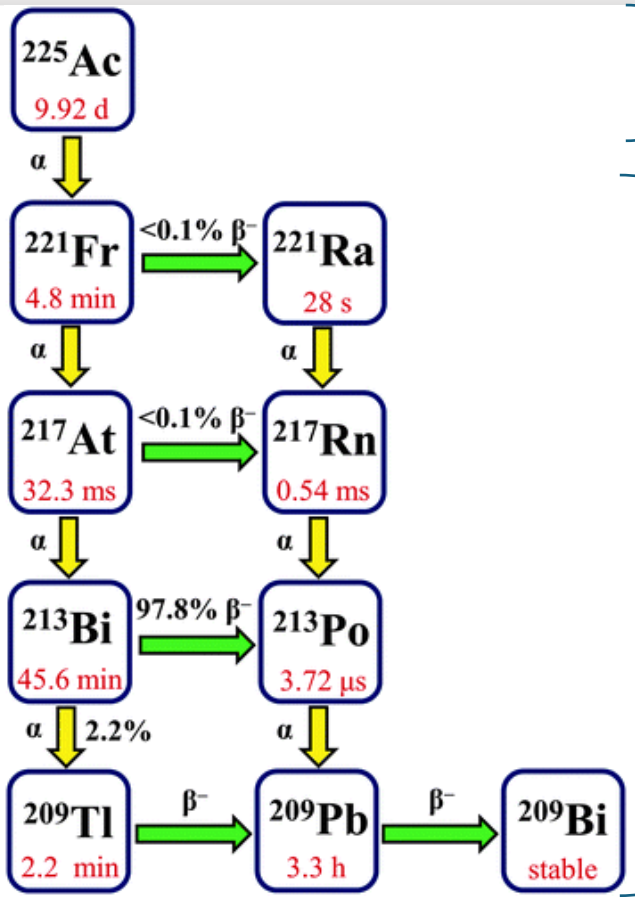
Actinium-225
Need for stable retention of daughter nuclides



Unstable chelator results in uptake in bone and liver

Will not be retained by chelators due to unsuitable chemistry for Fr, Ra and At and the recoil effect

- Actinium characteristics
  - Half life: 9.92 days
  - Alpha emitter
  - 8 short-lived radioactive daughters
  - Total of 4 alpha particles are emitted
  - 3+ oxidation state in aqueous solution
  - 1+ charge of francium-221
  - ^{221}Fr emits γ at 218 keV
    ^{213}Bi emits γ at 440 keV
  - ^{217}At, ^{213}Po and ^{209}Pb have no or below 0.1 % γ and cannot be detected
  - Toxicity: Unbound ^{225}Ac concentrates in bone and liver
- The recoil effect

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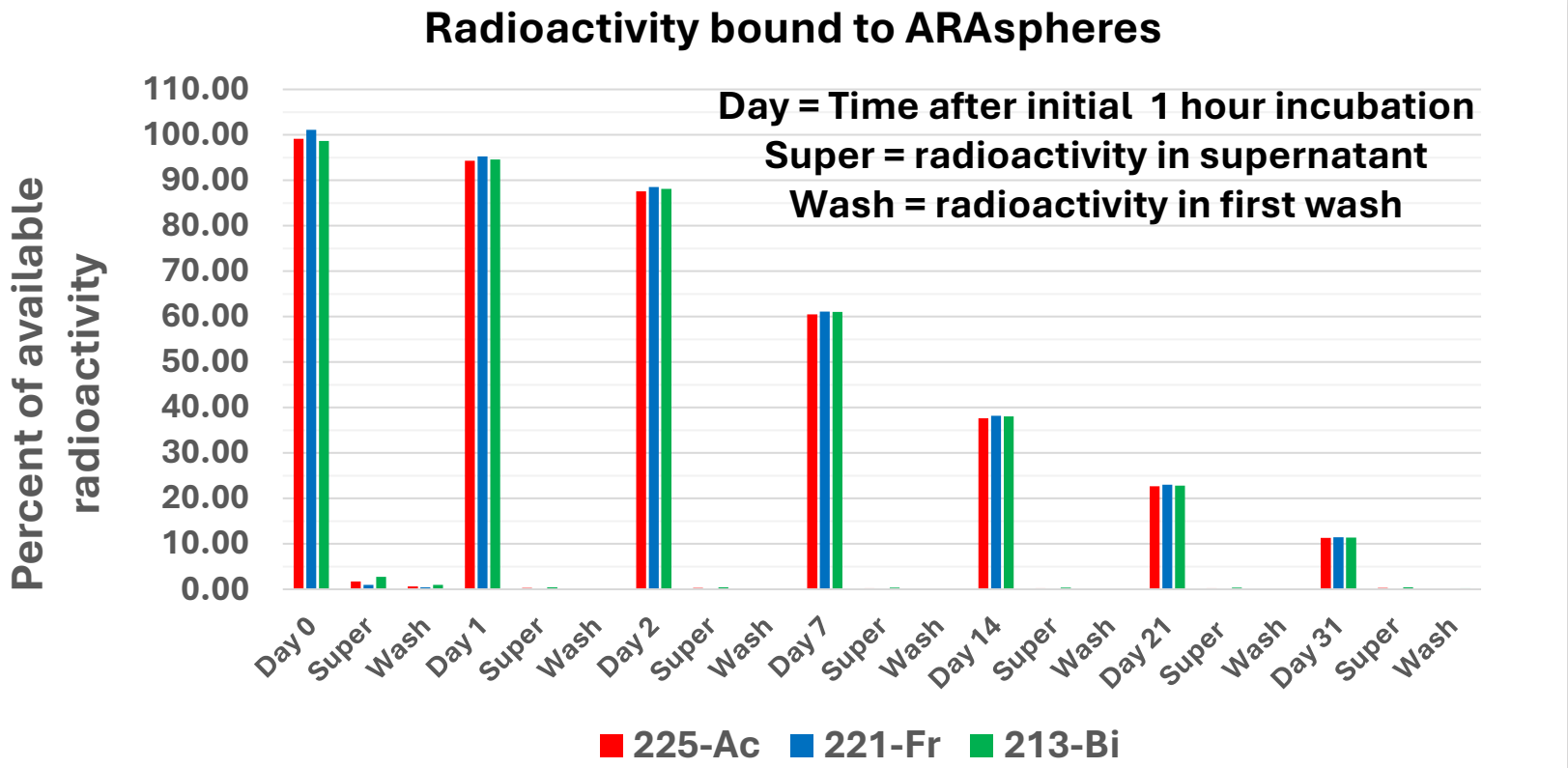
ARAspheres

Actinium-225 binding and retention of decay daughters



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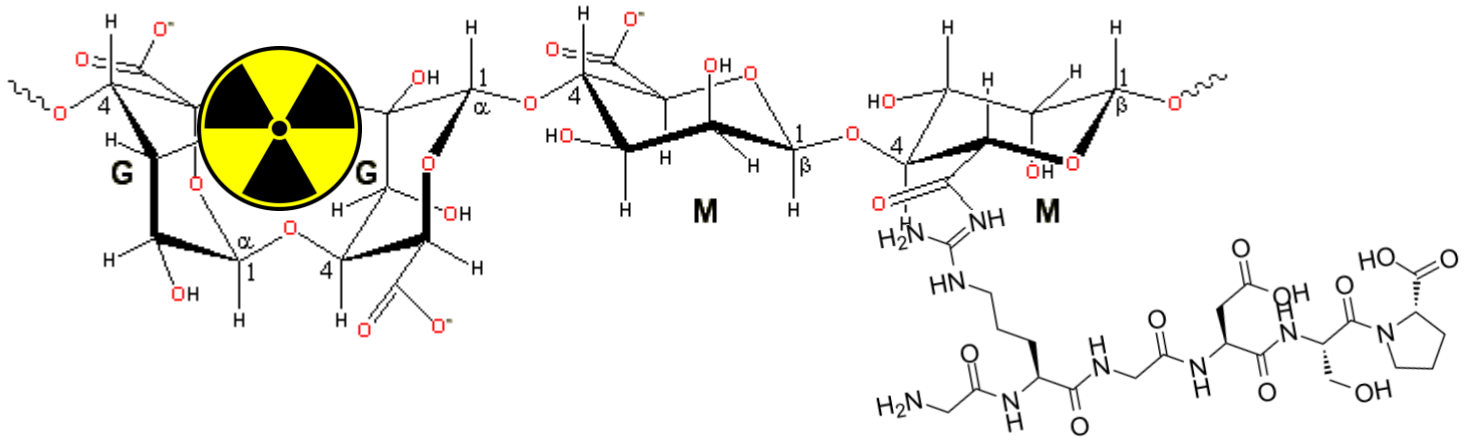
ARAspheres
(ARA = actinium-RGD-alginate)



Radionuclide Alginate RGD peptide

ARA = actinium-RGD-alginate

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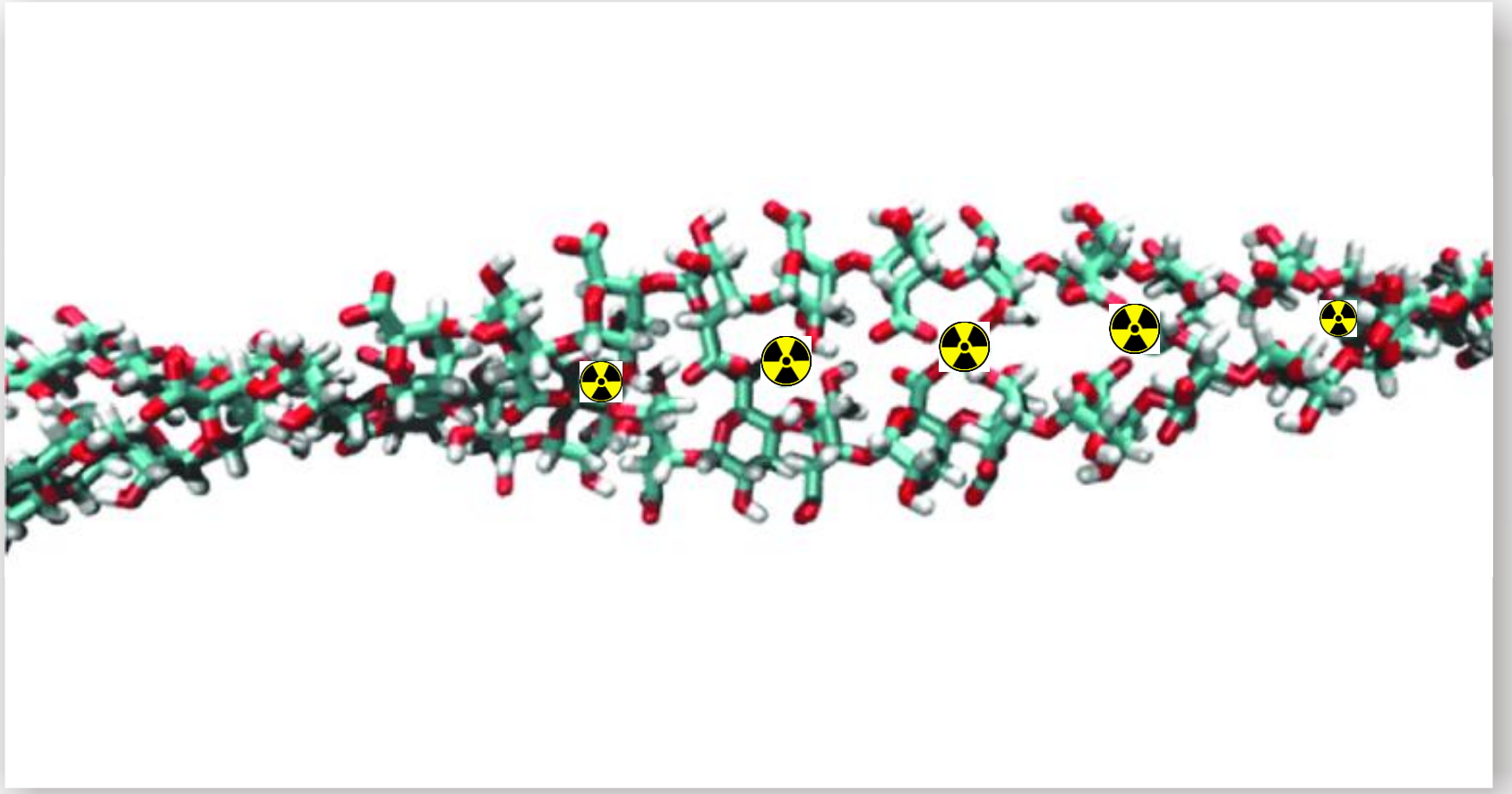
Chelation of radionuclides by alginate

- **Alpha emitters** (^{225}Ac, ^{223}Ra) highest energy + decay daughters add to total radiation dose
- **Beta emitters**: longer range but lower in energy - ^{177}Lu, ^{90}Y

Radionuclide	Emission	Chelation by alginate	Decay daughters bound
^{89}Sr	β	Yes	^{89}Y – stable, non-radioactive
^{177}Lu	β	Yes	^{177}Hf – stable, non-radioactive
^{223}Ra	α	Yes	^{219}Rn, ^{215}Po, ^{211}Pb, ^{211}Bi, ^{207}Tl, ^{207}Pb (stable)
^{224}Ra	α	Yes	^{220}Rn, ^{216}Po, ^{212}Pb, ^{212}Bi, ^{208}Tl, ^{208}Pb (stable)
^{227}Th	α	Yes	^{223}Ra and daughters
^{225}Ac	α	Yes	^{221}Fr, ^{217}At, ^{213}Bi, ^{213}Po, ^{209}Tl, ^{209}Pb, ^{209}Bi (stable)
Cu, Pb, Zn, Ba	stable	Yes	These non-radioactive divalent cations bind to alginate. Their radioactive isotopes will also bind, such as $^{64}Cu/^{67}Cu$

Alginate retains decay daughters



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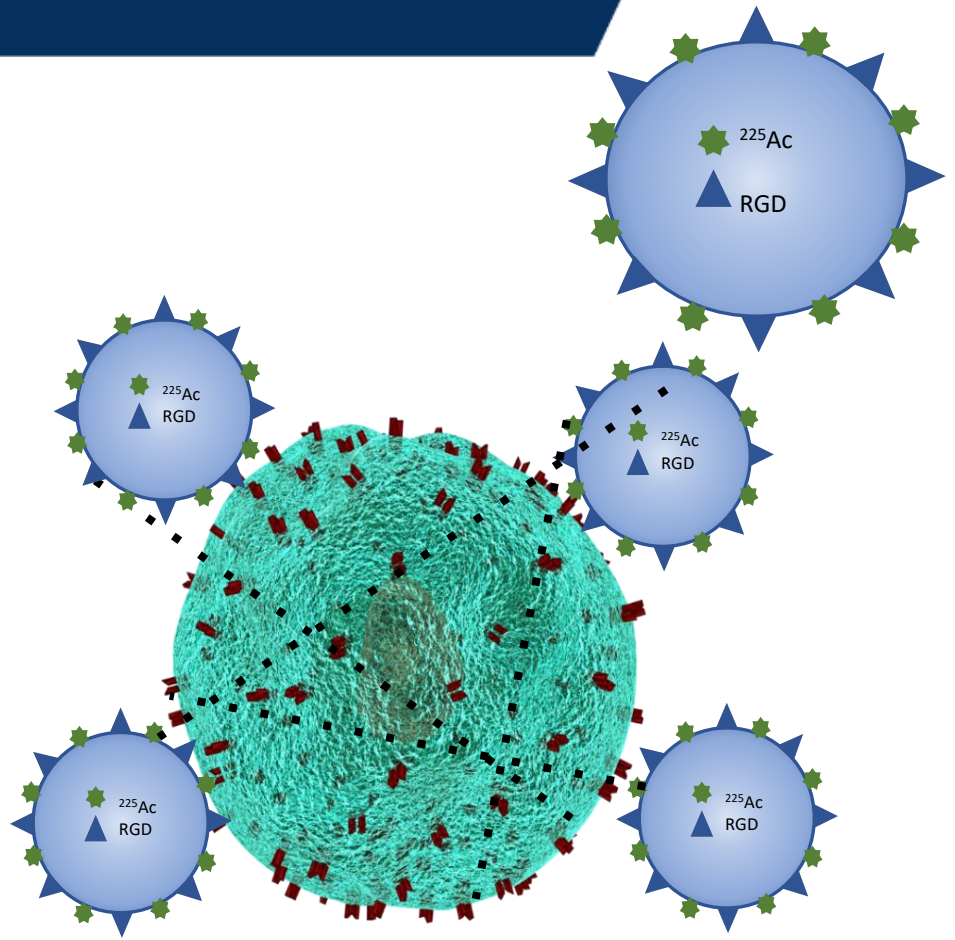
ARAspheres (^{225}Ac-RGD-Alginate Nanoparticles)

Carrier: **nanometer-sized** alginate nanoparticles which can diffuse in the brain

- The nanoparticles carry **RGD, a clinically validated targeting peptide,** which binds to specific tumor cell receptors (αvβ3 integrins), highly expressed on glioblastoma cells
- Alginate is an excellent **chelator**

Payload: alpha particle radiation emitting radionuclide (**actinium-225**), with a **$t_{1/2}$ of 10 days**

- **Range:** a few cell diameters
- **Mechanism of action:** cell death by **alpha** radiation-induced unrepairable **DNA damage** to tumor cells



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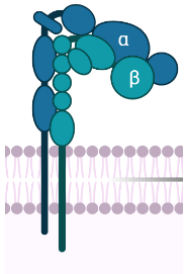
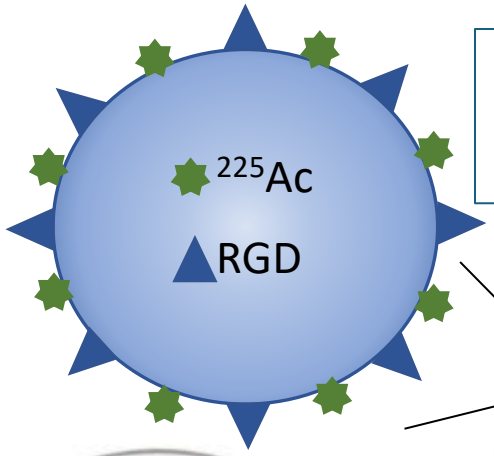
ARAspheres is Poised to Overcome Limitations of Current GBM Treatments

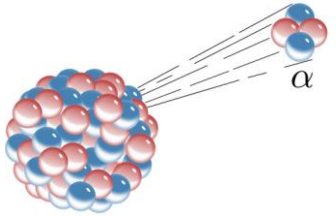
Clinically validated target, targeting αVβ3 integrin

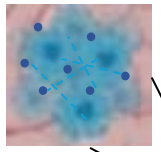




Direct injection of radioactive nanoparticles after surgery

Actinium-225 ($T_{1/2}$ = 10 days)





Alpha-radiation of remaining tumor cells

- Nanoparticles
- Diffuse into brain tissue
- Stable for 30-60 days
- Biodegradable
- Selective internal radiation from day 1
- Compatible with Standard of Care (EBRT/chemotherapy)

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