

Application of a 3D model of cancer cells in research on the effectiveness of neutron therapy (BNCT) in the treatment of melanoma

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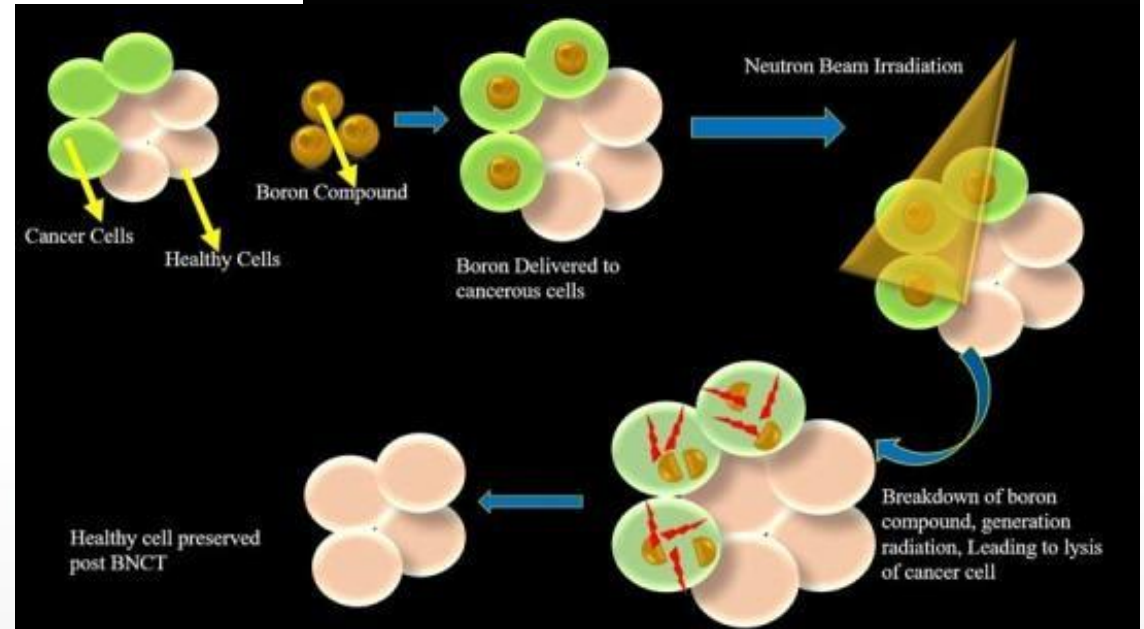
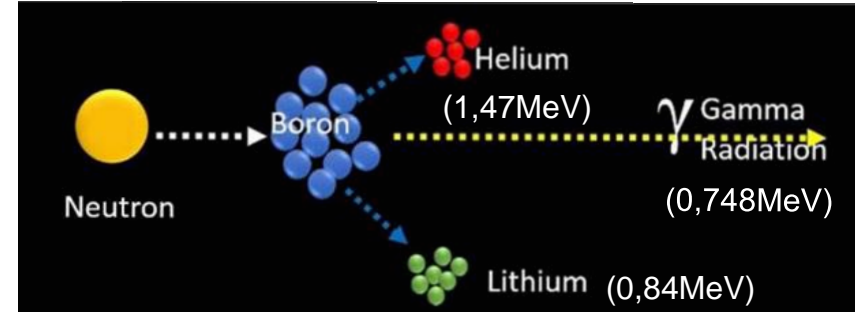
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Outline

- BNCT
- Project motivation
- Boron carrier
- A new strategy for boron delivery
- 3D model of cancer cells

BNCT

- Non-reactive isotope ^{10}B
- Selectivity by tumor cells
- Irradiated with neutron beam
- Nuclear reaction
- Ravaged tumor cells



Project motivation

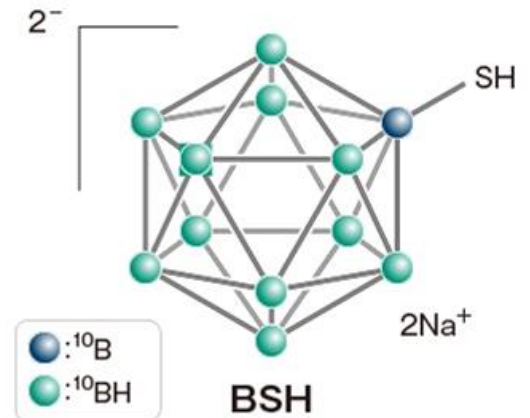
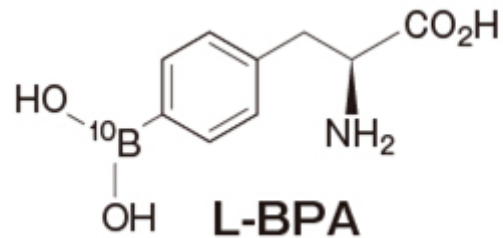
Increasing the effectiveness and selectivity of boron uptake into cancer cells by using new conveyors and boron carriers

- To increase boron concentration in the cancer cells:
 - greater therapy efficiency
 - less side effect for a patient
- To save laboratory animals

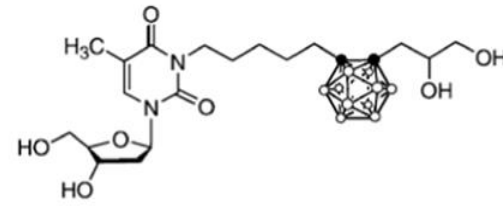
Boron carriers

Ideal properties of Boron compounds:

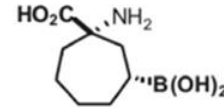
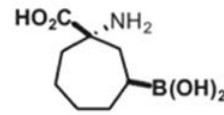
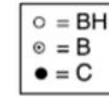
- Low systemic toxicity
- High tumor uptake ($\sim 20\text{-}50 \mu\text{g } ^{10}\text{B}$) and low normal tissue uptake ($>3:1$)
- Rapid clearance from blood and normal tissues
- Persistence in tumour during BNCT



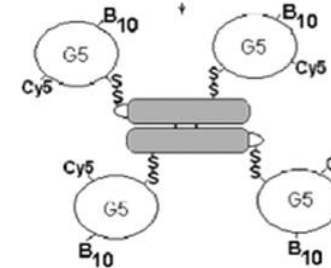
Boron carrier- a new strategy



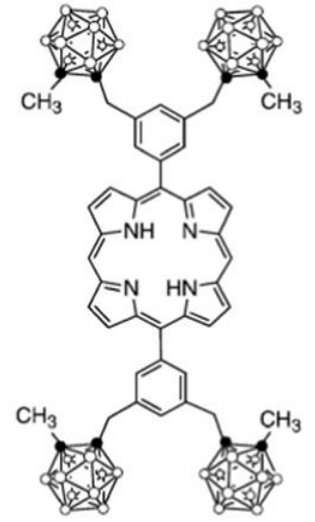
N5-2OH



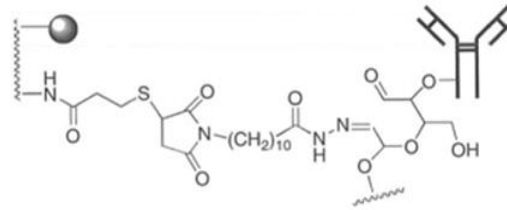
cis-ABCHC and *trans*-ABCHC



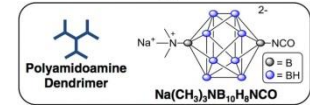
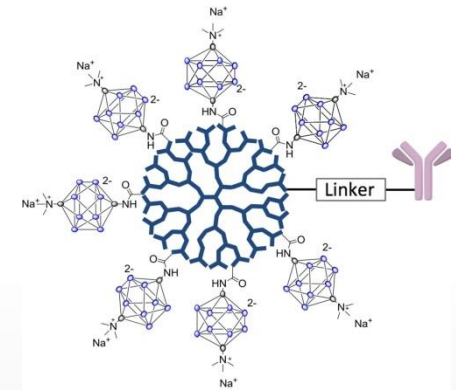
VEGF-BD-Cy5



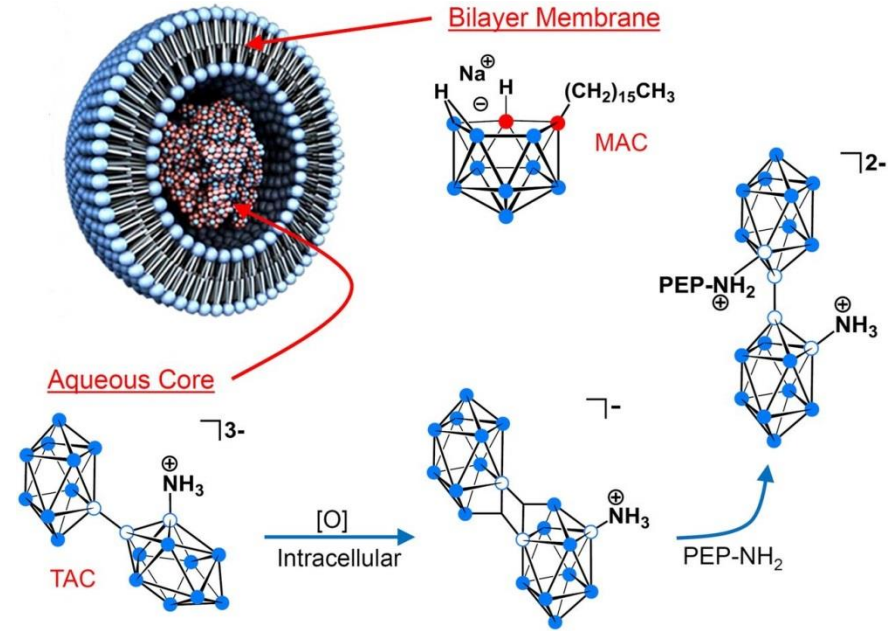
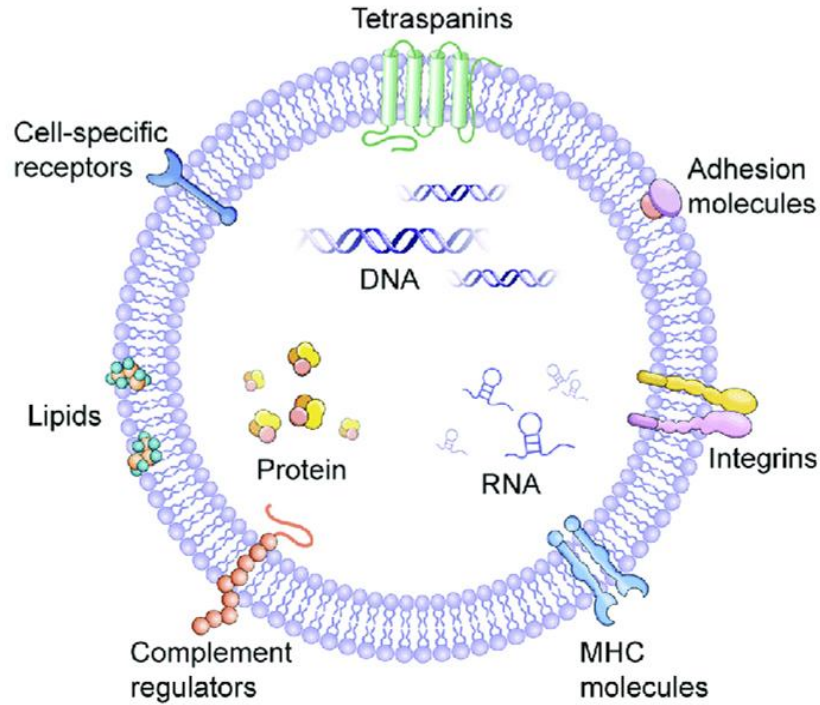
H₂DCP



EGFR-targeting MoAb, C225-G5-B₁₁₀₀



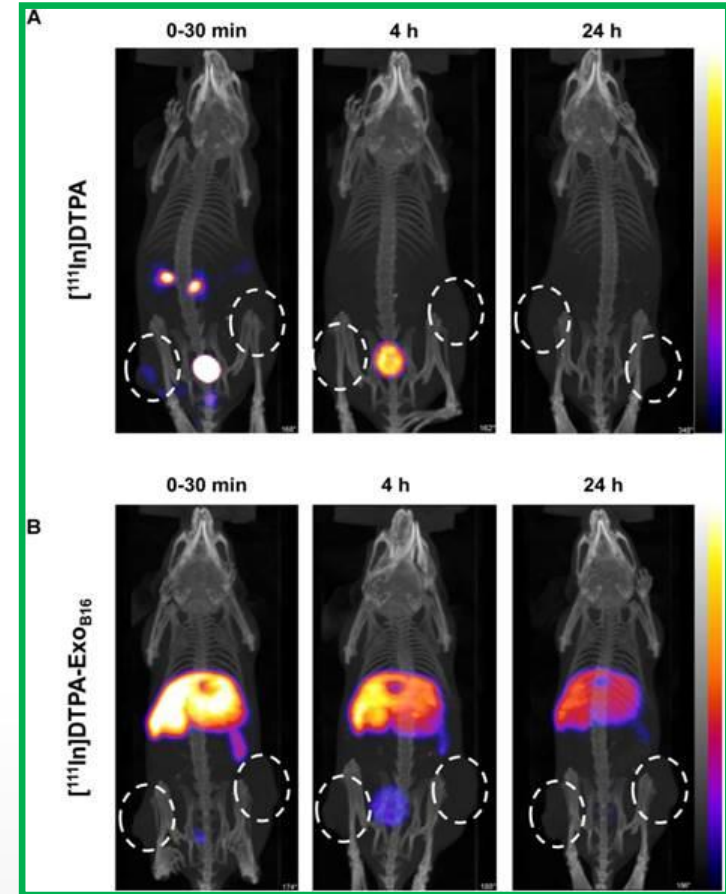
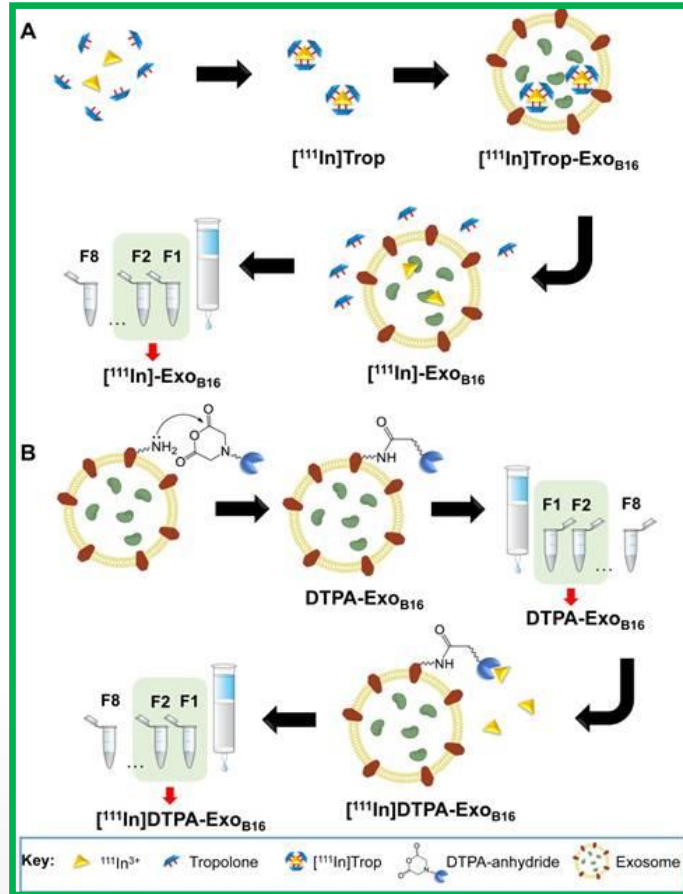
Boron conveyors – a new strategy



https://www.researchgate.net/publication/324726787_Extracellular_Vesicles_as_Carriers_of_Non-coding_RNAs_in_Liver_Diseases

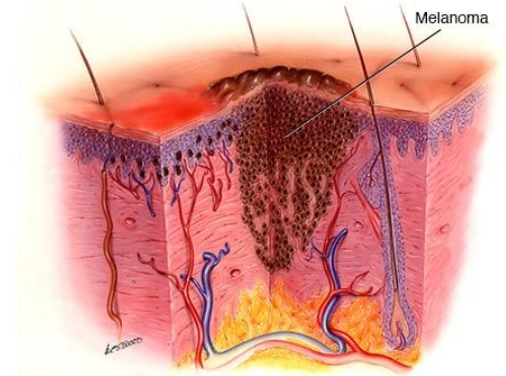
<https://link.springer.com/content/pdf/10.1186%2Fs40880-018-0299-7.pdf>

EV as delivery agents

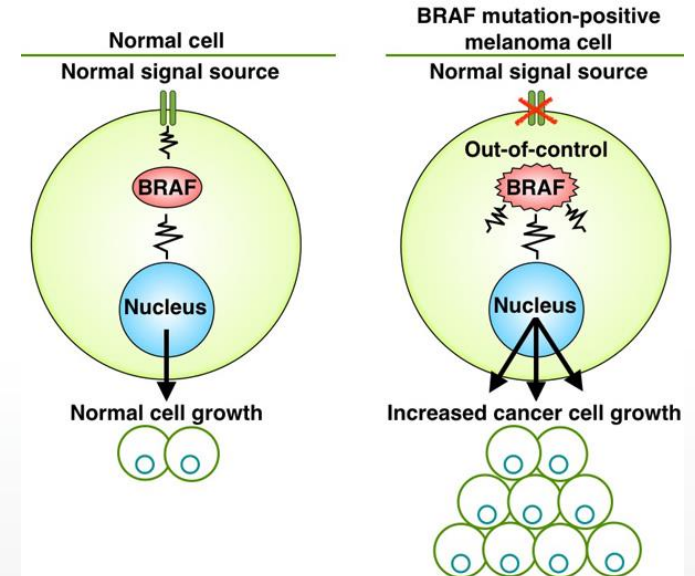


Melanoma- BRAF mutation

- Melanoma- the most serious type of skin cancer
- BRAF plays an important role in both normal and cancer cells
- About 50% of melanoma cancers harbors activating BRAF mutations
- BRAF mutation-uncontrolled growth and proliferation of cancer cells
- Formation of mass of cancerous cells



<https://www.drugs.com/mcd/melanoma>



<https://incytepathology.wordpress.com/2012/04/10/braf/>

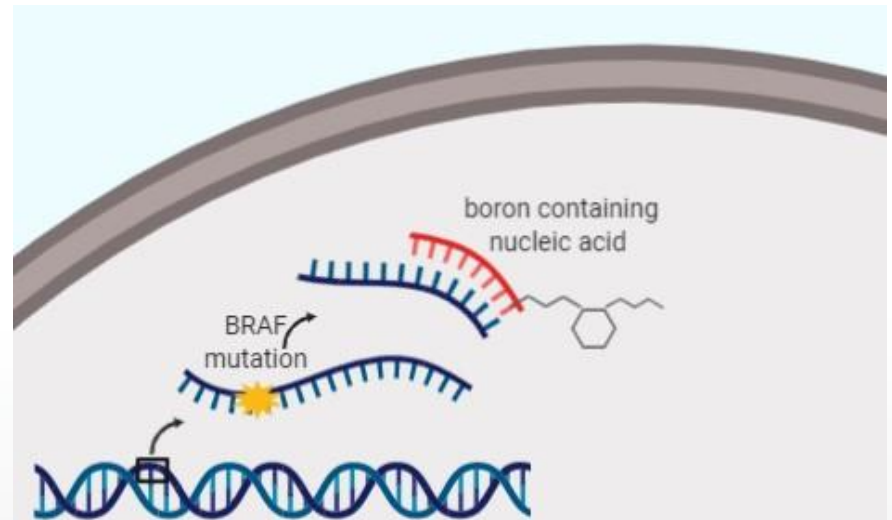
Boron-containing nucleic acid

- Boron carrier complementary to BRAF mutation in tumor cells

→ high specificity

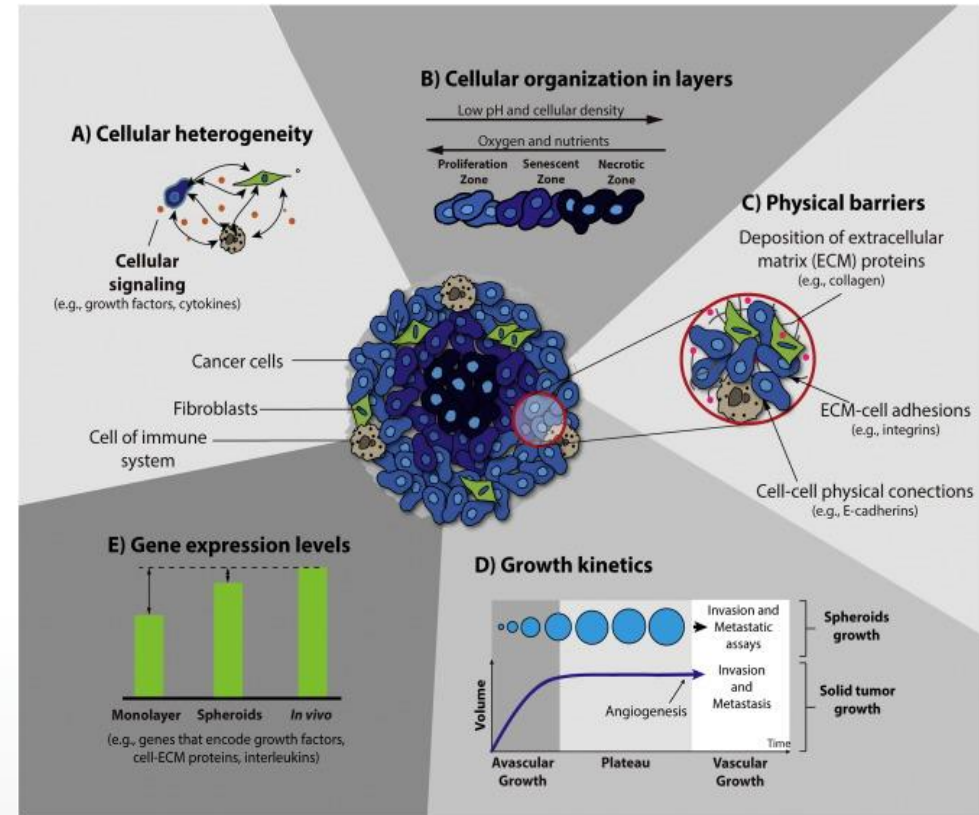
→ high effectiveness

BNCT



3D model of cancer cells

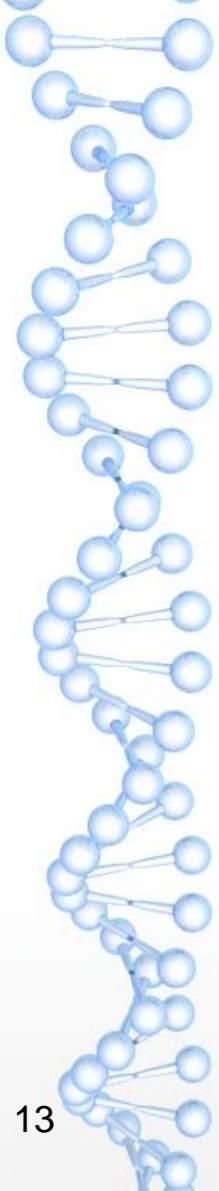
- Multicellular tumor spheroids
- 3D model- spheroids
- Similarity with the tumor
 - ✓ internal structure
 - ✓ cell-cell signaling
 - ✓ ECM deposition
 - ✓ growth kinetics
 - ✓ gene expression patterns
 - ✓ drug resistance





Limitations

- Low boron concentration in conveyors
- No or low boron conveyors/carriers uptake into tumor cells
- Sufficient concentration of boron in cancer cells to BNCT
- Maintaining high level of boron during neutron radiation
- Increasing the scale of experience
- Side effect of radiation in adjacent cells



Thank you for your attention



Backup

1. BPA (boronophenylalanine, $\text{Na}_2^{10}\text{B}_{10}\text{H}_{10}$)
2. BSH (sodium borocaptate, $\text{Na}_2^{10}\text{B}_{12}\text{H}_{11}\text{SH}$, undecahydro-mercapto-*closo*-dodecaborate)
3. N5-2OH (3-[5-{2-(2,3-dihydroxyprop-1-yl)-*o*-carboran-1-yl}pentan-1-yl] thymidine)
4. *cis*-ABCHC and *trans*-ABCHC (1-amino-3-borono-cycloheptanecarboxylic acid)
5. VEGF-BD-Cy5 is a heavily boronated vascular endothelial growth factor (VEGF) linked to Cy5 for near infrared imaging of the construct
6. H₂-DCP (di [3,5-(*nido*-carboranylphenyl) tetra-benzoporphyrin])
7. C225-G5-B₁₀₀₀ is a heavily boronated form of the monoclonal antibody cetuximab that specifically targets the human epidermal growth factor receptor (EGFR)
8. Conjugation scheme for the linkage of a boron-containing dendrimer to cetuximab

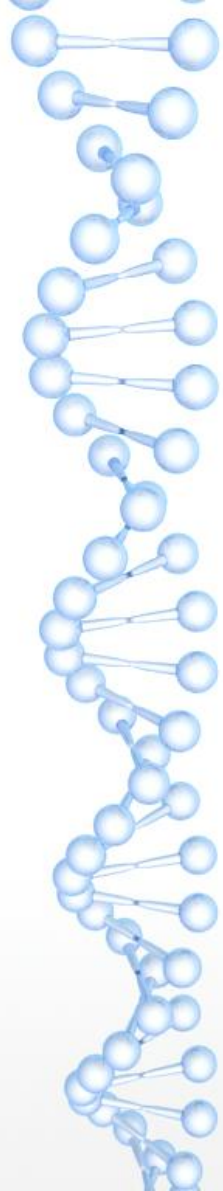


Table 1.1 Isotopes with high values of thermal neutron capture cross sections [4–7]

Nuclide	Interaction	Cross section σ_{th} (b)
^3He	(n,p)	5,333
^6Li	(n, α)	940
^{10}B	(n, α)	3,835
^{113}Cd	(n, γ)	20,600
$^{135}\text{Xe}^a$	(n, γ)	2,720,000
^{149}Sm	(n, γ)	42,080
^{151}Eu	(n, γ)	9,200
^{155}Gd	(n, γ)	61,100
^{157}Gd	(n, γ)	259,000
^{147}Hf	(n, γ)	561
^{199}Hg	(n, γ)	2,150
$^{235}\text{U}^a$	(n,f)	681
$^{241}\text{Pu}^a$	(n,f)	1,380
$^{242}\text{Am}^a$	(n,f)	8,000

(Wolfgang A.G. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa „Neutron capture therapy”, Springer

Pierwiastki emitujące kw. Gamma po wychwycie: efekt biologiczny mniejszy od boru, ale dawka rozłożona bardziej homogenicznie w większych obszarach

- Gadolin daje jeszcze możliwość obrazowania z MRI, ale nie wykazano skuteczności tego obrazowania
- Po pochłonięciu neutronu emituje kwanty gamma o łącznej energii ~8 MeV
- Być może reakcja z litem byłaby dobra, ale przekrój czynny jest sporo mniejszy...

^aRadioactive

