Boron-Rich Nanoscale Delivery Agents for the Boron Neutron Capture Therapy of Cancer

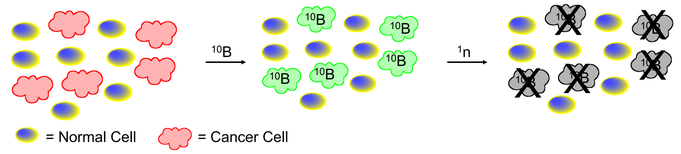
Peter Kueffer, Li Fang, Shuo Yang, Michael Lewis, Varyanna Ruthengael, Satish S. Jalisatgi, Mark W. Lee, M. Frederick Hawthorne

International Institute of Nano & Molecular Medicine

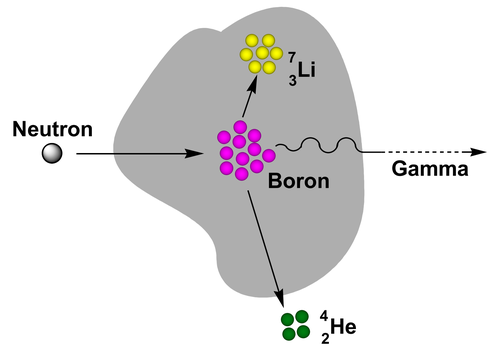
- BNCT is a targeted, tumor cell-selective and binary radiation therapy based upon the very facile capture of a neutron by the ^{10}B nucleus.

$$^{10}B + {}^{1}n \longrightarrow {}^{7}Li^{3+} + {}^{4}He^{2+} + \gamma + 2.4\ MeV$$

- The ^{10}B nucleus captures slow neutrons much more easily than elements found in the human body.
- The $^{7}Li^{3+}$ and $^{4}He^{2+}$ ions have short trajectories in tissue (one cell diameter) and create ionization damage in cancer cells, notably DNA double-strand breaking.
- ^{10}B is selectively delivered to cancer cells by various means (targeting tumor cell receptors with liposomes and related nanoparticles) prior to neutron irradiation.



Cancer cells with ^{10}B are killed by the Li^{3+} and He^{2+} produced In the binary sequence.

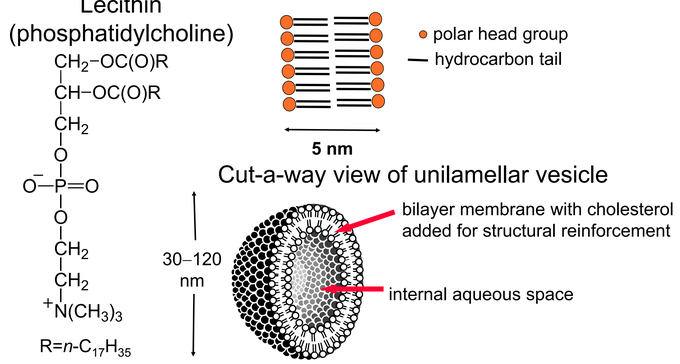


- Target compounds containing ^{10}B must be delivered selectively to cancer cells to provide one billion (10^9) ^{10}B-atoms per cancer cell (30 μg ^{10}B/g tumor).

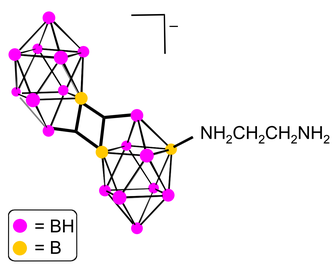
Liposomes as Nanoparticle Delivery Vehicles

Liposomes have demonstrated the ability to accumulate in tumors in high concentration relative to normal tissues, including blood if they are sufficiently small (30–120 nm diameter).

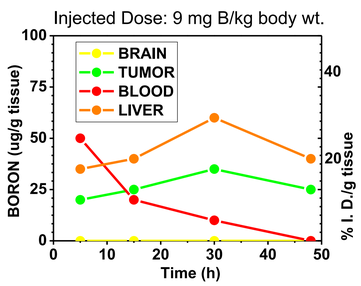
Typical Liposome Constituents and Structure



Biodistribution of Liposomes Containing Aqueous $Na_3[a^2\text{-}B_{20}H_{17}(en)]$ in BALB/c Mice Bearing Breast Cancer (EMT6) Tumors



$[B_{20}H_{17}(en)]^{3-}$

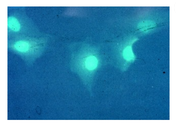


Oligomeric Phosphate Diester (OPD) Nanoparticles

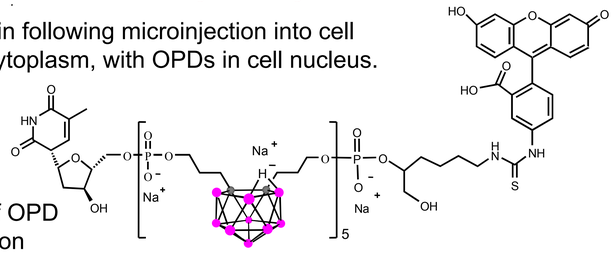
- OPDs derived from carborane diols may be prepared using solid phase synthesis or in solution (bench top).
- The structural variety of available diols coupled to the ease of linking OPDs to other functional structures ensures a wide range of properties (size, charge, lipophilicity, conjugation with reactive species and biomolecules such as DNA, peptides, folic acid, *etc.*).

Fluorescence Labeled OPD Microinjected in TC7 African Monkey Kidney Cells

Photo taken 20 min following microinjection into cell cytoplasm, with OPDs in cell nucleus.

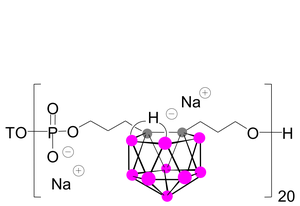


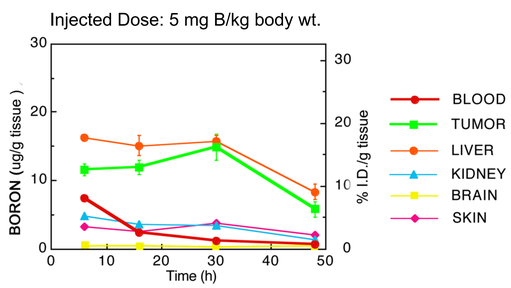
100 μM Solution of OPD
3×10^{-10} ml injection
1×10^{9} B-atom/cell



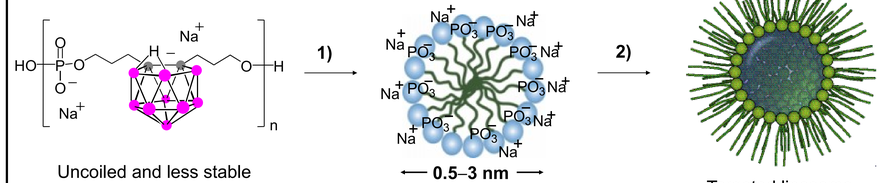
Biodistribution of a Typical OPD in Mice Bearing Breast Cancer (EMT6) Tumors

Delocalization of B in cellular nucleus greatly enhances BNCT efficacy





OPD Nanoparticles (Micelles)



1) Coiling of OPD in water or blood plasma
2) Encapsulation of OPD micelles in liposome with attachment of bioligands

- When dissolved in water (or blood plasma) OPD's are coiled into small nanoparticles (micelles).
- The plasma membrane of cells may be penetrated by liposomes (30–120 nm diameter nanoparticles) which encapsulate a large number of OPD micelles (0.5–3 nm diameter) in their aqueous core.
- The liposome carriers selectively target cancer cells by attached cancer cell-selective bioligands such as cancer associated antibodies.
- Once inside the cancer cell liposomes rupture and release OPD in the cell interior (cytoplasm) followed by OPD migration to the cell nucleus, association with genetic DNA and certain cell death from BNCT.