

Advantages and limitations of immunoconjugates vs. other carrier compounds for alpha emitters

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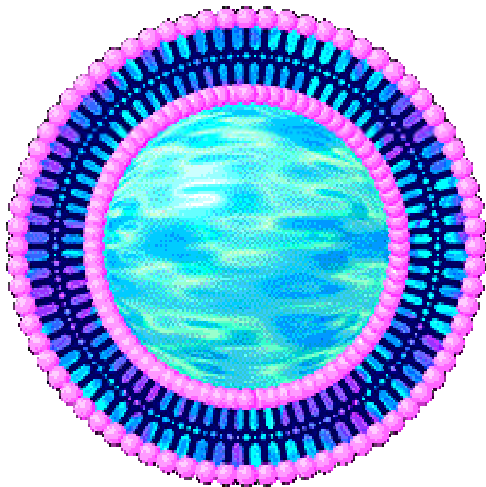
Monoclonal antibodies

- Advantages
 - Recognize cell specific receptors
 - Good labeling chemistry for several alpha-emitters
 - Radiolabel does not significantly alter the biodistribution of the antibody
 - Several well characterized antibody/antigen systems exist for cancer therapeutic applications

Monoclonal antibodies

- Disadvantages
 - Slow penetration into solid tumors
 - Slow blood clearance could affect significant hematological toxicity
 - Sensitive to radiolysis
 - Difficult to apply longer-lived ($t_{1/2} > 1$ day) alpha emitter candidates due to poor labeling yield and/or poor stability

Liposomes



- Liposomes are vesicles made of primarily phospholipid bilayer
- Surfaces may be coated with PEG to reduce RES interaction
- Diameters may vary from 50 nm to several μm
- Quite narrow size distribution can be obtained by extrusion
- Liposomes can be stored for several months
- Radionuclides can be loaded into the interior by ionophores

Liposomes

- Advantages
 - Relatively easy to prepare
 - Can be loaded in high yield with shorter-lived as well as longer-lived alpha emitters
 - Good resistance against radiolysis
 - Passive targeting of solid tumors
 - Can be conjugated with receptorbinding molecules including antibodies to target cellular receptors

Liposomes

- Disadvantages
 - Relatively slow penetration into tumors
 - Various degree of accumulation in the RES
 - Variable stability in vivo

Small compounds, general trends

- Advantages
 - Rapid diffusion and penetration into tumors
 - Rapid blood clearance
 - Often a more rapid elimination from the body

Small compounds, general trends

- Disadvantages
 - Rapid elimination could sometimes lead to less uptake into the target tissue
 - Could affect a larger exposure to tissues connected to elimination pathways (e.g. renal toxicity)
 - Chemical properties are often more affected when small molecular weight compounds are radiolabeled

^{212}Bi ($t_{1/2} = 60$ min) and ^{213}Bi ($t_{1/2} = 46$ min)

Compound	Advantage	Disadvantage	Potential usefulness
Liposome	<ul style="list-style-type: none"> -Can be rapidly loaded -No toxic daughters -low in vivo catabolism 	<ul style="list-style-type: none"> -Slow diffusion and localization vs. $t_{1/2}$ -High injection site exposure 	<ul style="list-style-type: none"> -Regional delivery -Cellular blood borne disease (leukemia)
Antibody	<ul style="list-style-type: none"> -Can be rapidly labeled -No toxic daughters -low in vivo catabolism 	<ul style="list-style-type: none"> -Slow diffusion and localization vs. $t_{1/2}$ -High injection site exposure 	<ul style="list-style-type: none"> - Regional delivery -Cellular blood borne disease (leukemia)
Small molecule	<ul style="list-style-type: none"> -Can be rapidly labeled -No toxic daughters -Rapid diffusion and targeting 	<ul style="list-style-type: none"> -Rapid elimination could cause renal and bladder toxicity 	<ul style="list-style-type: none"> -Tumors with high receptor expression and good blood flow

^{211}At ($t_{1/2} = 7.2 \text{ h}$)

Compound	Advantage	Disadvantage	Potential usefulness
Liposome (not tested)	-No toxic daughters (I.e. daughters too short lived to cause a problem)	-Slow diffusion and localization vs. $t_{1/2}$	-Regional delivery -Cellular blood borne disease (leukemia)
Antibody	-No toxic daughters -Well studied	-Labor intensive chemistry, modest yield -Slow diffusion and localization vs. $t_{1/2}$	- Regional delivery -Cellular blood borne disease (leukemia or lymphoma)
Small molecule	-No toxic daughters -Rapid diffusion and targeting	-Labor intensive chemistry, modest yield -Deastatination could be a problem	-Tumors with high receptor expression and good blood flow

The decay series from ^{225}Ac , ^{223}Ra

The actinium-225 series	The radium-223 series
^{225}Ac (α , 10.0 d)	^{223}Ra (α , 11.43 d)
^{221}Fr (α , 4.9 min)	^{219}Rn (α , 3.96 s)
^{217}At (α , 32 ms)	^{215}Po (α , 1.78 ms)
^{213}Bi (β , 45.6 min)	^{211}Pb (β , 36.1 min)
^{213}Po (α , 4.2 μs)	^{211}Bi (α , 2.17 min)
^{209}Pb (β , 3.25 h)	^{207}Tl (β , 4.77 min)
^{209}Bi (stable)	^{207}Pb (stable)

^{223}Ra ($t_{1/2} = 11.4$ days)

Compound	Advantage	Disadvantage	Potential usefulness
Liposome	<ul style="list-style-type: none"> -Can be rapidly loaded -Sufficient $t_{1/2}$ to obtain tumor accumulation -Mild tox. from released ^{223}Ra 	<ul style="list-style-type: none"> -Time for significant catabolism -Release of daughter product (^{211}Pb) 	<ul style="list-style-type: none"> -Systemic delivery -Solid tumors?
Antibody (not tested)	<ul style="list-style-type: none"> - $t_{1/2}$ compatible with antibody targeting- -Mild tox. from released ^{223}Ra 	<ul style="list-style-type: none"> - No validated chelator exist - Release of daughter product (^{211}Pb) 	<ul style="list-style-type: none"> Systemic delivery -Solid tumors?
Small molecules	<ul style="list-style-type: none"> -RaCl_2 an excellent bone-seeker -Daughter nuclides retained in bone -Less exposure during excretion with longer $t_{1/2}$ 	<ul style="list-style-type: none"> -Can not be stably bound to small molecular compounds at present 	<ul style="list-style-type: none"> -Skeletal metastases

^{225}Ac ($t_{1/2} = 10$ days)

Compound	Advantage	Disadvantage	Potential usefulness
Liposome	<ul style="list-style-type: none"> -Can be rapidly loaded -Sufficient half-life to obtain tumor accumul. 	<ul style="list-style-type: none"> -Time for significant catabolism -Release of toxic daughter product (^{221}Fr) 	<ul style="list-style-type: none"> -Systemic delivery -Solid tumors?
Antibody (not tested)	<ul style="list-style-type: none"> - $t_{1/2}$ compatible with antibody targeting- -Validated chelator exist 	<ul style="list-style-type: none"> - Validated chelator gives poor yield - Release of toxic daughter product (^{221}Fr) 	<ul style="list-style-type: none"> Systemic delivery -Solid tumors?
Small molecules	<ul style="list-style-type: none"> -Can be chelated to small molecules via DOTA -Less exposure during excretion with longer $t_{1/2}$ 	<ul style="list-style-type: none"> -Release of toxic daughter product (^{221}Fr) 	<ul style="list-style-type: none"> -Tumors with high receptor expression and good blood flow

Tissue distribution in mice (% of Injected dose per gram) 24 hours post injection

	^{223}Ra PEG-liposome	^{211}At -TP-3 IgG MoAb	$^{223}\text{RaCl}_2$
Blood	19.1 ± 2.1	15.1 ± 4.3	0.12 ± 0.07
Liver	3.5 ± 0.4	3.5 ± 0.1	0.27 ± 0.12
Muscle	0.51 ± 0.17	1.1 ± 0.2	0.24 ± 0.13
Femur	8.5 ± 0.8	2.6 ± 0.2	40.1 ± 7.7

Contributors

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