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Radiopharmaceutical chemistry of trivalent metals (67,68Ga, 111In, 90Y, 177Lu)

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The use of trivalent metals as part of specific radioconjugates is well established in the radiodiagnosis and targeted radionuclide therapy. Their use has increased over the last 10 years, mainly because of the increasing interest in targeted radionuclide therapy. Only a few radiopharmaceuticals based on trivalent radiometals have achieved registration and major use in nuclear medicine, among them ^{67}Ga-citrate for the imaging of Hodgkin's disease and inflammation, ^{111}In-DTPA indicated for radionuclide cisternography, ^{111}In(oxine)$_3$ (oxine = 8-hydroxyquinoline) for the labeling of granulocytes, ^{111}In-DTPA-octreotide (Octreoscan) for the localization and follow-up of neuroendocrine tumors and ^{111}In labeled to several antibodies like capromab pendetide (ProstaScint) for prostate cancer metastases imaging and ibritumomab tiuxetan (^{111}In-Zevalin) for dosimetric calculations in conjunction with ^{90}Y-Zevalin used in the treatment of relapsed and/or chemotherapy refractive non-Hodgkin`s lymphoma.
This CME deals with the radiopharmaceutical chemistry of the radiometals Ga^{3+}, In^{3+}, Y^{3+} and Lu^{3+}.
The chemistry of all trivalent radiometals is somewhat similar as they behave within the HSAB (hard and soft acid base) concept and are termed hard acids. The concept indicates that hard acids prefer hard bases as ligands; in addition, as the metals are highly charged, the ligands should contain negatively charged donors to neutralize the metal ion charges. The negative ligand charges usually come from the carboxylate group, the phenolate group, the hydroxamic acid group and the phosphonic acid group. The difference as to the coordination chemistry comes from the difference in ionic radii of the 4 radiometals which are 62 pm for Ga^{3+}, 80 pm for In^{3+}, 90 pm for Y^{3+} and 100 pm for Lu^{3+}. The consequence of this is: Ga^{3+} prefers coordination number(CN) 6, In^{3+} CN 6,7 and 8, Y^{3+}, CN 8,9 and Lu^{3+} CN 8, 9.

As all trivalent radiometals are kinetically labile (with the exception of ^{105}Rh(III)), with other words they exchange their ligands very quickly (e.g. with serum proteins like transferrin) polydendate chelating agents are needed for efficient encapsulation and in vivo stabilization.
The radiopharmaceutical chemistry of Ga^{3+} gained new interest not only from the use of the carrier-free photon-emitter ^{67}Ga but also from the availability of a commercially available ^{68}Ge/^{68}Ga generator which produces the 68 min half-life positron emitter $^{68}Ga^{3+}$ in 1M HCl. A variety of small molecules like peptides may be developed which show adequate kinetics for the labeling with this short-lived positron emitter. This type of radiopharmaceutical chemistry may open a new generation of freeze-dried, GMP-produced PET radiopharmaceuticals. Indium-111 is often used and proposed as a surrogate of the pure α-emitter ^{90}Y despite some dissimilarities with regard to the pharmacokinetics of some radiopharmaceuticals.
Lutetium-177 has attractive properties as a short range β-emitter with an average β-energy of 133 keV; it is widely available and can be produced at low cost from high flux reactors. In addition, it has 2 γ-emissions at 113 keV (6%) and 208 keV (11%) which allow imaging during therapeutic applications.
One of the problems of the labeling with trivalent radiometals is their tendency to hydrolyse and potentially form colloids in solution if the pH is raised. pH-values above 4 is necessary in order to deprotonate the basic ligating groups of the chelators. This necessitates the use of carefully designed labeling protocols including weakly coordinating buffer anions to stabilize the radiometals.

The most important recent use of trivalent radiometals is by conjugating them to biomolecules via bifunctional chelating agents. The latter consist of a chelating moiety to complex the radiometal and a functional group for the covalent attachment to the biomolecule. The ideal chelator for the small Ga^{3+} is the hexadentate macrocyclic chelator NOTA (1,4,7-triazacyclononane-1,4,7-trisacetic acid). Bifunctional versions of NOTA are available, useful for antibody and peptide labeling. The most widely used chelator for biomolecule labeling is DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic

acid). Despite the fact that its cavety is too large to comfortably accommodate small radiometals like In^{3+} and Ga^{3+} it was successfully used with these radiometals because of the reasonable kinetic inertness of the radiometal complexes.
Yttrium-90 and ^{177}Lu have ideal ionic radii to bind very stably to DOTA.

Suggested reading:

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5) Anderson CJ, Welch MJ Radiometal labeled agents (non-Tc) for diagnostic imaging. Chem Rev 1999, 2219-34