Rejoice with Rhenium: The Chemistry of Obtaining and Using Rhenium to Treat Cancer

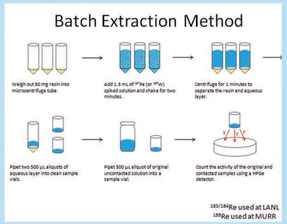
Sam Groveman[a], Matthew Gott[b], Kimberly Reinig[b], Silvia Jurisson[b], Lynn Francesconi[a]

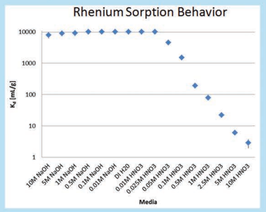
[a]Department of Chemistry, Hunter College of the City University of New York, 695 Park Avenue, New York, NY 10065, USA. [b]Department of Chemistry, University of Missouri 125 Chemistry Bldg 601 S. College Ave. Columbia, MO 65211

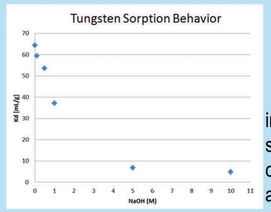
^{186}Re Production and Separation

Several accelerator-based production pathways by bombarding tungsten and osmium targets with protons and deuterons are being assessed for producing high specific activity ^{186}Re. The reaction pathways being evaluated are: ^{186}W(p ,n)^{186}Re, ^{186}W(d, 2n)^{186}Re, ^{189}Os(p, α)^{186}Re, and ^{192}Os(p, α3n)^{186}Re. Studies are focused on target design to determine the optimal production rate with the highest radionuclidic purity and yield.

Once the ^{186}Re is produced, several methods are being evaluated for isolating the rhenium from the different target materials. Studies have been performed chemically separating tracer rhenium from macro-scale tungsten using ion exchange chromatography. Additional ion exchange resins will be evaluated to determine the most efficient means of isolating rhenium and allowing for recovering the expensive target materials.





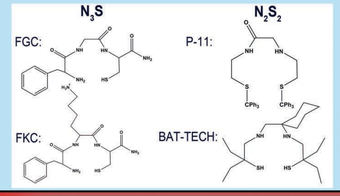


Re show good sorption to the resin in base (far-left) while the W shows poor sorption at high pH (left). Thus, the Re can be retained in base and W eluted, allowing for separation.

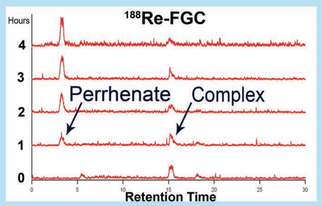
N_xS_{4-x} Ligands for Re

Our overall objective is to develop bifunctional chelates for conjugation of ^{188}Re to 6D2, an IgM, and other antibodies. In Phase 1 clinical trials where ^{188}Re is introduced into 6D2 by direct labeling, ^{188}Re-6D2 has shown no adverse effects and in fact, target tumors were observed to stabilize or decrease in size in nearly all patients.[3]

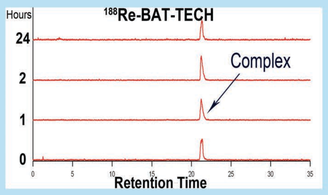
Two families of ligands are being investigated called N_2S_2 and N_3S, where N and S represent the number of nitrogen and sulfur bonds to the central Re. While the N_3S ligands have been found to be unsuitable and quickly decompose to perrhenate, the N_2S_2 ligands, currently under investigation, are showing tremendous promise. Stability is evaluated by reinjecting HPLC purified complexes that have been dried by rotovap and reconstituted in phosphate buffer at pH 7.4 back into the HPLC over time at regular intervals.



N_3S ligand FGC forms a ^{188}Re complex that is unstable after only 1 hour.



N_2S_2 ligand BAT-TECH forms a ^{188}Re complex that is still stable after 24 hours.

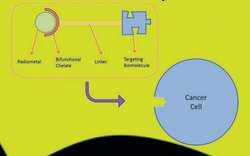


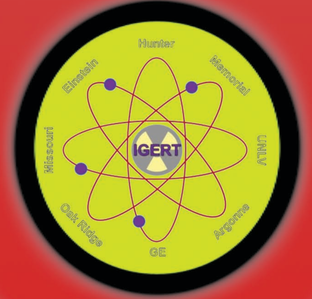
Introduction

Radiochemistry has numerous applications in nuclear medicine, primarily in helping to develop radiopharmaceuticals. Isotopes or Re, specifically, can beused to treat cancers with high energy beta emissions. The difficulty lies in delivering the radiation to the desired site in the body.

Antibodies are nature's targeting vectors and the ability to use antibodies as the targeting agents for radiotracers is of great importance for both imaging and therapy. Antibodies are extremely specific targeting moieties. Various diseases, specifically different types of cancers, are known to overexpress different antigens compared to normal, healthy tissue.

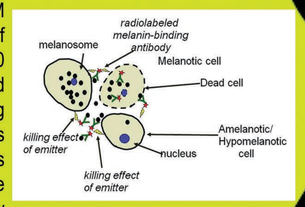
In order to use antibodies as the targeting mechanism for a Re, one has to utilize a bifunctional chelator which can both bind the metal and conjugate an antibody. Designing an appropriate ligand for each Re is very important as the ligand used can have a great effect on the behavior and stability of the metal-antibody complex.





Radioimmunotherapy

Radioimmunotherapy is the use of radiolabeled antibodies to target cancer sites and kill tumors with high energy radiation. ^{188}Re has a β_{max} energy of 2.12 MeV which is ideal for killing tumors, and its half-life of 16.9 hours is optimal to match the biological residence time of peptides and fast circulating IgM antibodies.[1] ^{186}Re has a β_{max} of 1.07 MeV and a half-life of 90 hours, and thus is better suited to longer circulating antibodies. This provides localized dose to tumors while minimizing exposure to the rest of the healthy tissue. Since ^{188}Re and ^{186}Re both also have a ~15% gamma emission at ~150 keV, they can be easily tracked in the body using SPECT imaging. A fast circualting IgM antibody, 6D2, targets melanin from lysed melanoma cells and, if paired with an appropriate radioactive payload, could prove to be a very effective treatment for melanoma.



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References

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[4] Benny, P. B.; Green, J. L.; Engelbrecht, H. P.; Barnes, C. L.; Jurisson, S. S., Inorg. Chem. 2005, 44, 2381-2390.

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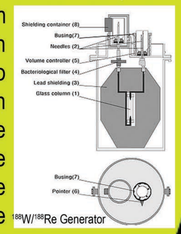
Obtaining Rhenium

Rhenium-188 can be easily and conveniently obtained from a ^{188}W/^{188}Re generator in high specific activity. Tungsten-188, with a half-life of 69 days, is absorbed onto an ion-exchange column. The tungsten decays into ^{188}Re via β$^-$ decay, and the ^{188}Re is eluted with a saline charge. Generators like these can provide relatively inexpensive on-site access to ^{188}Re for facilities like laboratories and hospitals.



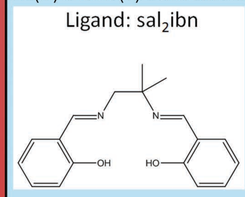
Rhenium-186 is obtained from using a cyclotron to bombard a tungsten or osmium target with protons or deuterons. The ^{186}Re is then chemically separated from the target and purified for use in a lab or hospital. See "^{186}Re Production and Separation" (upper left) for details.

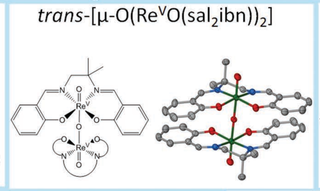
Kinetics and Redox Stabilities of Re Complexes

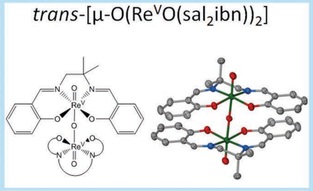
A major challenge for the development of potential Re radiopharmaceuticals is the kinetic and redox stability of the radiotracer complexes under the high dilution experienced *in vivo*. Instability leads to release of rhenium and oxidation to perrhenate.

Various rhenium Schiff base complexes have been explored for potential applications to diagnostic and therapeutic nuclear medicine. The tetradentate N_2O_2 Schiff base ligands have shown very interesting chemistry with technetium, particularly in the field of nuclear medicine.

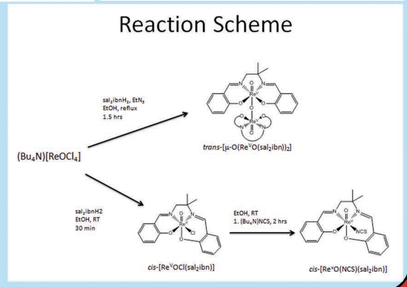
Translation of the "Tc-Q" chemistry to Re has highlighted some of the differences in chemistry between these two congeners, including redox chemistry and substitution kinetics. Efforts have led to a variety of potential Re(III) and Re(V) Schiff base theranostic agents with and without coordinated phosphines.







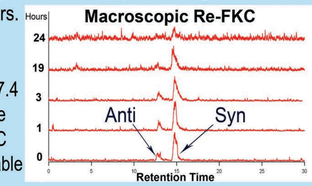
Mononuclear rhenium Schiff base complexes convert to dinuclear species when water or base is present. The isolated mononuclear complex cis-[ReOCl(sal_2ibn)], readily dimerizes to form trans-[μ-O(ReO(sal_2ibn))$_2$], when exposed to the atmosphere. However, the mononuclear complex can be trapped and stabilized with thiocyanate to form.



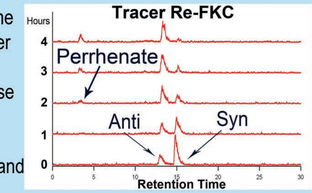
Tracer vs. Macroscopic Levels

The stability of the ^{188}Re N_3S complexes was evaluated both at the pure tracer level and when a macroscopic amount (1.34 µmol) of cold rhenium is added to the ^{188}Re reaction. The Re-FKC complex is known to have syn and anti diastereomers which can be observed by HPLC. Later measurements have significantly less signal due to decay according to the half-life of ^{188}Re of 16.9 hours.

After HPLC purification and reconstitution in pH 7.4 phosphate buffer, the macroscopic Re-FKC complex remains stable past 24 hours.



Under the same conditions, the tracer Re-FKC complex begins to decompose to perrhenate after only 2 hours. This reveals the FKC ligand to be unsuitable.



The fact that the behavior seems to be very different at the macroscopic versus tracer levels is highly significant for the evaluation and future of these ligands. It is an issue that should be considered when developing all such radiometal chelators.