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Targeted Alpha Therapy Research - a Radiochemistry Perspective

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One of the greatest challenges in the treatment of different types of cancers is an efficient therapy of occult metastasis. Today chemotherapy is generally employed as an adjuvant treatment to eradicate the minimal residual disease. However, despite that chemotherapy often is a very aggressive method the cancer cells can transform and become resistant towards the chemicals used. This means that the quality of life of the patient is affected in a negative way without resulting in a therapeutic effect. Therefore, new types of treatment for disseminated cancer are of vital importance. One such method is targeted alpha therapy.

Targeted alpha therapy utilizes the high energy and short tissue range (50-100 μm) of the alpha particles. This range is orders of magnitude shorter than the beta particle range from other radionuclides widely used within nuclear medicine, such as iodine-131 or yttrium-90, resulting in a significantly higher LET for the alpha particles. This means that if administered to the cancer cells by a tumor specific carrier agent, e.g. an antibody, the alpha emitting nuclide efficiently kills the tumor cell by causing irreparable double strand breaks of the DNA, while sparing the surrounding healthy tissue. This makes the method suitable for treatment of disseminated occult cancers in the form of micro tumors and even single cancer cells. A radioactive nuclide with suitable properties is, however, needed to conduct this type of treatment. The half-life should be relatively short to be able to achieve a high dose and avoid prolonged irradiation in the body but still long enough to be able to perform the radio synthesis and allow for distribution to the target cells. In the same way the daughter nuclides must have a suitable decay pattern. The production route should also be fairly straight forward to ensure availability of the nuclide. One nuclide that fulfils these demands is astatine-211.

Astatine-211 is produced using a cyclotron by circa 30MeV alpha particle activation of bismuth-209 through the reaction 209Bi(α, 2n)211At. The half-life is 7.2 hours and the mode of decay is 100% alpha emission along two different routes. Astatine-211 is therefore a promising nuclide for targeted alpha therapy. At Sahlgrenska Academy in Gothenburg, Sweden, radiolabelling research of monoclonal antibodies and polypeptides using astatine-211 has been on-going for almost 20 years. The research is performed within the targeted alpha therapy (TAT)-group that are moving towards phase II/III clinical trials using astatine labelled monoclonal antibodies for patients with disseminated ovarian cancer. This after a successful phase I trial conducted in 2009. The TAT-group is an interdisciplinary group consisting of chemists, physicists, biologists and clinicians from different research centers.

Today efforts concerning radiochemistry within the group are directed towards increasing the specific activity of the immunoconjugates, investigating the shelf-life of the prefabricated conjugates before labelling and designing new linker-molecules. There is also a focus on simplifying the chemical production route by automating the radio synthesis.

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