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DISSERTATION TITLE: *Development of Separation Technology for the Removal of Radium-223 from Targeted Thorium Conjugate Formulations*

Metoder for fremstilling og rensing av en ny type målrettede kreftlegemidler basert på det radioaktive elementet thorium-227 har blitt utviklet og studert i dette arbeidet. Thorium henfaller ved stråling til et annet radioaktivt element uten de samme målrettede egenskapene. Hensikten med arbeidet har vært å finne nye og forbedrede metoder som både fjerner det uønskede radioaktive elementet og bevarer thorium i kreftlegemidlene før administrasjon til pasienten.

New methods for radiochemical purification and preparation of a group of novel targeted radioactive cancer therapeutics have been developed and tested. Focus has been given to user-friendliness and minimization of the number of operational steps. Studies of the influence of product composition and process variables reveal the potential for development of easy to operate methods which give both a pure and potent product.

Conventional cancer drug treatments such as chemotherapy are often ineffective. The targeted cancer radiotherapy under development in Bayer AS which utilizes the radioactive element thorium-227, may give hope to cancer patients through a localized and efficient therapy within a number of cancer types. The first clinical candidate reached a phase I clinical trial in 2015.

Thorium emits a very high energy radiation over a short distance. This means that the cell killing of the tumor can be localized, leaving healthy tissue unharmed. By attaching thorium to immune system derived proteins called antibodies, the radiation may be carried to the tumor cells in the patient's body. The antibodies are highly specific and capable of recognizing and binding to structures on the surface of various cancer cells.

The radioactive drugs are prepared directly in a radiopharmacy by simple complexation of thorium to an antibody conjugated with a chelator. When thorium emits radiation another radioactive element is formed; radium-223. Radium will not be attached to the antibodies and will thus have different tumor targeting abilities. It is therefore desirable to have a controlled amount of radium in the drug at the time of patient dose administration. Methods for purification of thorium at the radiopharmacy which remove radium with a high selectivity and efficiency while giving a high throughput of thorium have been the subject of this thesis.

The work has been carried out as a collaboration between the School of Pharmacy and Bayer AS through an industrial Ph.D. grant from the Research Council of Norway. The research has resulted in three patent applications.