Letter of Intent to the INTC

Production of generator source of alpha-emitters for radiotherapy

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Response to concerns of the committee

First, I would like to apologize to the Committee for the apparent lack of clarity in my Letter of Intent. This was due to the fact that at the very time of its preparation and submission critical experiments were under way and basic Patent issues were being resolved.

Second, for the sake of clarity of the present Response, the basic terms should be precisely defined. The term Generator refers to an external device or setup, which is used for the preparation of a Source. The source is inserted into the tumor tissue. The generator is used for the preparation of a large number of sources throughout its effective lifetime.

Third, in the discussion and presentation that follows reference is routinely made to the isotopes of the decay chain that starts with Th-228. The chain originating with Th-227 is completely analogous, differing only in the relevant half-lives. This particular aspect will be discussed below.

The Response is organized in accordance with the itemization as presented to me by Dr. Luis Fraile.

Basic objective / type of tumors

The primary aim of our research project is the treatment of solid cancer tumors. Specifically included are breast cancer, prostate cancer as well as secondary tumors in the brain, liver and lungs. The only pre-requisite for eventual treatment is precise knowledge of the location of the tumor. Note, that in a large fraction of such tumors removal by surgery is impossible. This may be due to the location
of the tumor, to the general state of the patient, to attendant risks of surgery or simply because surgery does not represent the optimal first treatment option. Furthermore, many types of cancer respond poorly, or not at all, to chemotherapy, to conventional radiotherapy or to both.

The generator

The generator is basically a foil containing the 1.9-year-half-life isotope Th-228. The Th-228 atoms are embedded close to the outer surface of the foil, so that a sizable fraction of the daughters, the 3.7-day-half-life isotope Ra-224, can recoil out of the generator. These atoms are collected onto the source, either by direct implantation in vacuum or by electrostatic fields under partial pressure. In the latter case an appropriate thin layer of protective material is deposited onto the source.

The source

The source which is produced by the generator is subsequently inserted into the tumor. The source is typically a needle shaped metallic object, about 0.5 millimeters in diameter and 3 to 5 millimeters long. Its insertion into the tumor is therefore as easy and as simple as a routine biopsy. The essential property of the source is that the Ra-224 atoms are securely embedded under the surface or beneath the protective layer, while the daughters, the 56-second-half-life isotope Rn-220, have a sizable probability of recoiling into the surrounding tissue. These features are tested and ascertained as a matter of routine prior to the source insertion. Thus, one ends up with a source in the tumor which releases into it short-lived daughters of the Ra-224 atoms for the duration of the lifetime of the longer lived parent atom. In the ensuing decay chain - Rn-220 to the 0.15-second-half-life isotope Po-216 through the 10.6-hour-half-life isotope Pb-212 to stable Pb-208 - three alpha particles are emitted.

Transport in tissue

The Rn-220 atoms diffuse in the tumor tissue after their release until they decay, with the Po-216 decay following essentially instantaneously. If we assume that only diffusion occurs and that the diffusion coefficient is similar to that of radon in water ($2 \times 10^{-5}$ cm$^2$/s), then the average distance traveled by the radon atoms before they emit their alpha particle is about 0.4 millimeters. However, partial convection by the dense and chaotic system of blood vessels in the tumor will result in an increase of the average transport distance. This very complicated problem is studied by us both theoretically and experimentally. It is nevertheless safe to assume that both Rn-220 and Po-216 will completely decay in the tumor, while an unknown fraction of the Pb-212 may be evacuated from it and dispersed elsewhere.

Experience with Th-228

Work using a Th-228 generator and Ra-224 sources was conducted so far on mice with induced SCC (squamous cell carcinoma). The following picture shows an untreated mouse with a tumor of approximately 8 millimeters in diameter.
Two types of experiments are generally carried out: “physical” experiments, which are terminated after a brief period (1 or 2 days), designed to provide information about the transport of the radioactive species; “biological” experiments, which are allowed to run their course and in which clinical effects, if any, are observed. The latter are naturally more instructive and are reported here.

In the first pilot experiment 3 mice with tumors averaging 5.5 millimeters in diameter were treated with the special Ra-224 sources. The average nominal source strength (i.e. total Ra-224 activity in the source itself) was about 6 nanocuries, or about 60 nCi/g. Control groups of 7 untreated mice with the same tumor were monitored as well. A clear reduction of tumor mass was observed as a function of time, with eventual recurrence of the usual growth rate. The average tumor mass of the treated versus untreated mice (normalized to unity at zero time) as a function of days elapsed from treatment is shown in the next graph.
In the next pilot experiment a source of nominal strength of about 100 nanocuries was inserted into a tumor of 8 millimeter diameter, identical to the one whose picture is shown above, corresponding this time to about 400 nCi/g. Two control mice with untreated induced cancer were monitored as well. The treated tumor was observed to shrink monotonously until it disappeared completely at day 14 after the commencement of treatment. A picture of the mouse on that day is shown below. **So far (as of July 20, day 48 after treatment) the mouse displays no symptoms and appears healthy.**
The case for Th-227(Ac-227)  The Th-227 (in equilibrium with Ac-227) chain is identical in all respects to the Th-228 chain, except for the relevant half-lives. The source has a longer half-life (the 11.4-day-half-life Ra-223), while the species emitted into the tumor have shorter half-lives (4-second-half-life Rn-219; 1.8-millisecond-half-life Po-215; 36-minute-half-life Pb-211). The need for this alternative chain arises from this difference, since crucial operational aspects of the treatment depend on the interrelationship between the decay half-lives and characteristic times of the biological system. The escape time of the Lead atoms, for example, determines their relative contribution to the dose delivered far from the source. Also, there should be a proper matching of the overall irradiation time to the timescale of dead tissue removal from the tumor during treatment. The availability of the two decay chains permits a convenient means for studying the basic processes and may eventually prove to be essential for some specific clinical cases.

Safety and toxicity issues  The active species are always embedded in solids and are contained in insertion manipulators, so that very little, if any, activity is released into the environment in the form of short-lived radon. Toxicity (chemical and radiochemical) is essentially a non-issue in our case because of the total level of activity involved (microcurie or sub-microcurie of a few days half-life). The maximum total number of alpha-decays which may be dispersed over the entire body (as a result of Lead atoms
exiting the tumor) is in the $10^9$ range and is therefore negligible (a few millirads, body-averaged).

*The collaboration* The collaboration comprises at this stage the group of I. Kelson at the School of Physics and Astronomy and the group of Professor Y. Keisari at the School of Medicine (both at Tel Aviv University). Dr. U. Koester is the local contact at ISOLDE.