When treating cancer, a frequently used approach for destroying tumour cells is via external beam radiotherapy. A major drawback of this technique, however, is that it requires the radiation dose to pass through healthy tissues to reach the intended tumour cells. Targeted radionuclide therapy avoids such normal tissue exposure by irradiating tumours from within the body. Application of such a targeted approach has mainly employed beta particle emitting radionuclides of several millimetres effective range (path length). More recent developments have shown the potential of high energy, short path-length alpha particle emitters in delivering lethal DNA-damaging doses of radiation to individual cells. Not only does this approach avoid the development of radioresistance, it also targets and destroys tumour cells selectively while reducing damage to neighbouring normal tissue. Tumour-selective delivery of radiation may be enhanced still further by delivering the alpha emitter attached to specific tumour cell binding proteins, such as monoclonal antibodies (mAbs). This concept has been reduced to practice at industrial scale, with high quality compounds produced for clinical evaluation in primary tumours of the blood and brain, as well as secondary skeletal metastases. Judging by their promising clinical performance to date, alpha emitter-based drugs are anticipated to have significant development potential for the future treatment of cancer.

RADIONUCLIDE THERAPY

The use of radionuclides – that is, radioactive isotopes – to target and irradiate cancers from within has existed for more than 50 years, being applied in chemical forms with a natural biochemical affinity for target tissue or cells. Earliest examples have been the use of radiiodine (as dissolved iodide salt) to target thyroid disease through its innate affinity for thyroid cells, and radiostrontium (as dissolved strontium dichloride salt) to target painful skeletal metastases as heavy alkaline earth metal analogues of calcium are incorporated during the tumour calcification process (see Box 1).

Where cytotoxic radionuclides have no intrinsic affinity for target tissues, next-generation products are likely to engage tissue or tumour-selective binding proteins to achieve targeted delivery. This group of compounds includes radionuclides chelated with bone-seeking phosphonates (to target skeletal metastases) or linked via a chelator to a cell target-specific peptide or mAb (for example, radioimmunotherapy to target neuroendocrine tumours or non-Hodgkin’s lymphoma). Until now, these approaches have largely been exemplified using beta-emitting radionuclides with radiation ranges of typically several millimetres (see Box 2).

ALPHA VERSUS BETA PARTICLES

While radioimmunotherapy strategies have been pursued in treating cancer for decades, their limitations often result from incompatible properties of cell targeting and radionuclide components. Efforts are increasing to combine targeting proteins with radionuclides to form products with greater therapeutic benefit and more attractive safety profiles and half-lives (see Box 3).

Alpha particle-based radionuclides are showing increasing promise in this respect. At the cellular level, their toxic potency is over 100 times greater than that of beta emitters and, on an atom-by-atom or molecule-by-molecule basis, they are among the most cytotoxic compounds in existence with fewer than five DNA hits required to kill a cell. The range of alpha particle radiation is ideally suited to cellular dimensions (typically 0.05mm, approximately three cell diameters), enabling selective tumour cell targeting with
Properties

AlpharadinTM is based upon a ready-to-use formulation of radium-223 chloride, which can be administered by intravenous injection on an outpatient basis. Radium-223, which can be administered by intravenous injection on an outpatient basis. Radium-223 chloride, which can be administered by intravenous injection on an outpatient basis. Radium-223 decays via radon-219 (t1/2 3.9 s), polonium-215 (t1/2 1.8 ms), lead-211 (t1/2 36.1 min), bismuth-211 (t1/2 2.1 min) and thallium-207 (t1/2 4.8 min) to lead-207 (stable) – a decay sequence that releases a total of four distinct alpha particles accounting for more than 95% of the energy released.

Preclinical Results

The therapeutic efficacy of AlpharadinTM has been demonstrated in a MT-1 nude rat skeletal metastasis model, in collaboration with the Tumour Biology Group at the Norwegian Radium Hospital. In this model, animals usually show signs of paralysis 20-30 days after tumour cell inoculation, owing to tumour growth in the spine. Forty per cent of nude rats treated with AlpharadinTM demonstrated unprecedented survival in this aggressive tumour model, with no visible sign of treatment-associated toxicity.

Clinical Evaluation

AlpharadinTM entered Phase I clinical trials in Scandinavia in late 2001, and demonstrated a broad dose range of acceptable safety and tolerability with no prohibitive side effects. Preliminary indications of efficacy were demonstrated based on the measurement of markers of bone metabolism, as well as pain palliation. AlpharadinTM is currently being tested in several Phase II trials in patients with skeletal metastasis of hormone refractory prostate cancer. The double-blind placebo-controlled trial involves 64 patients with painful skeletal metastasis and is currently in its follow-up phase at 11 centres in Norway, Sweden and the UK.

Algera has recently announced promising preliminary results from these studies, based on four-month follow-up evaluation of biomarker data. AlpharadinTM treatment met the primary endpoint of the trial by demonstrating a highly statistically significant decrease of bone alkaline phosphatase (bone-ALP) compared with placebo (ITT: p<0.001). A marked effect of AlpharadinTM on other recognised markers of bone turnover – such as S-PINP (bone formation) and S-CTX-I and S-ICTP (bone resorption) – was also observed.

Patients treated with AlpharadinTM also showed a significantly improved PSA (prostate specific antigen) response compared with placebo. Together, these data show that AlpharadinTM treatment results in a clear, measurable effect on the microenvironment of bone metastasis, which may be indicative of a positive therapeutic effect.

Clinical endpoints, such as delay of disease progression, long-term safety and survival, as well as further biomarker data, will be analysed at 12 months. Results of this analysis are anticipated during the second half of 2006.

CLINICAL EXPERIENCE WITH OTHER ALPHA EMITTERS

In the US, researchers at Duke University (Durham, NC) have taken one alpha emitter-based product, astatine-211-labeled chimeric 81C6 mAb, into Phase I clinical trials for brain cancer. Preliminary data indicate the potential of this therapy. However, astatine-211 can only be produced at a few sites around the world (in a cyclotron), and even then only in single patient doses. These problems are further compounded by the short t1/2 (7.2 h) of the radionuclide, limiting long distance shipment of compounds (see Table 1). The development of astatine-211

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**Box 1:** Key considerations when selecting an alpha emitter for therapeutic applications, includes:

- **Suitability for Shipment**
- **Radiochemistry and Dosimetry**
- **Production of Radionuclide**
- **Sustainability by Shipment**

**Box 2:** The decay of radionuclides results in the emission of different types of radiation depending on the isotopes used:

- Alpha particle emitters include radium-223, thorium-227, actinium-225, astatine-211 and bismuth-212
- Beta particle emitters include phosphorus-32, strontium-90, iodine-131, samarium-153 and strontium-89
- Gamma emitters include technetium-99m and iodine-123
- X-ray emitters include iodine-125

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**Box 3:** Key properties of alpha-emitting radionuclides:

- High energy and patient cytotoxicity
- Short path length (2-10 cell diameters) = less damage to surrounding normal tissues
- Anti-tumour and pain palliation effects
- Simple, cost-effective and scalable manufacturing
- Easy to strip, handle, administer and dispose

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Reduced normal tissue exposure. While external beam radiation and beta-particle radiation are classified as having low linear energy transfer (LET), the high LET of alpha particle radiation gives it significant advantages: the damage inflicted upon a cell from high-LET radiation is irreparable and cytotoxicity per radiation absorbed dose unit is greater. Further, its effectiveness is independent of either tumour oxygenation or the dose rate – that is, the time span over which the dose is delivered.
for large-scale commercial use would therefore require new cyclotrons in the future.

Researchers at the Memorial Sloan Kettering Cancer Center (New York) have clinically evaluated the alpha emitter bismuth-213, generated from actinium-225. The t_{1/2} of this radionuclide is only 46 minutes, limiting its use to institutes where labelling and administration of the compound can be carried out in close succession. In addition, generator source material is difficult to obtain in amounts required for clinical trials, meaning that although encouraging results have been obtained, bismuth-213 is currently considered unsuitable for commercial exploitation.

### Table 1: Alpha-emitting radionuclides currently evaluated against cancer

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Production scalability</th>
<th>Development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>^{213}Bi</td>
<td>46 minutes</td>
<td>Difficult</td>
<td>Clinical phase I</td>
</tr>
<tr>
<td>^{212}Bi</td>
<td>1.0 hour</td>
<td>Good</td>
<td>Preclinical phase</td>
</tr>
<tr>
<td>^{211}At</td>
<td>7.2 hours</td>
<td>Difficult</td>
<td>Clinical phase I</td>
</tr>
<tr>
<td>^{225}Ac</td>
<td>10.0 days</td>
<td>Difficult</td>
<td>Clinical phase I</td>
</tr>
<tr>
<td>^{223}Ra</td>
<td>11.4 days</td>
<td>Good</td>
<td>Clinical phase II</td>
</tr>
<tr>
<td>^{227}Th</td>
<td>18.7 days</td>
<td>Good</td>
<td>Preclinical phase</td>
</tr>
</tbody>
</table>

### ALPHA EMITTER-BASED CANDIDATES IN PRECLINICAL DEVELOPMENT

Actinium-225 has a t_{1/2} of 10 days and has potential for development as a therapeutic. Decay occurs via francium-221 (t_{1/2} 4.9 min), astatine-217 (t_{1/2} 32.3 ms), bismuth-213 (t_{1/2} 45.6 min), polonium-213 (t_{1/2} 4.2 µs), lead-209 (t_{1/2} 3.3 h) to bismuth-209 (stable), a pathway that releases a total of four distinct alpha particles. Presently, the generation of actinium-225 from surplus uranium-233 is very inefficient, making this radionuclide commercially less viable. Preclinical studies have been carried out, and an initial Phase I clinical trial is due to start shortly at the Memorial Sloan Kettering Cancer Center.

Algeta's recent preclinical studies have demonstrated that thorium-227, the parent isotope of radium-223, may be utilised in targeted therapy when conjugated to a tumour-selective mAbs. Thorium-227 has a t_{1/2} of 18.7 days, making it very suitable for application in cancer.

In a research collaboration commencing in August 2006, Algeta will combine its TH-1 technology with Affibody molecules that specifically target tumor cells over-expressing HER2, such as those present in breast and other cancers. Affibody molecules are small robust protein molecules (about 25 times smaller than mAbs) that can be designed to bind to any target protein with high specificity and affinity.

### RADIATION PROTECTION, HANDLING AND LOGISTICS

With all radiotherapies and their production, there are concerns over safety. Radiation protection management of alpha particle emitters will vary according to the specific isotope. For example, the fraction of energy emitted from radium-223 and daughters as alpha particles is approximately 95%, beta particles account for <4% and gamma radiation and X-rays <2%. The penetration range of alpha particles in human tissue is <0.1mm. Once injected, both alpha and beta particles are stopped by the patient's tissue. Due to attenuation in the patient's body mass, gamma radiation outside the body is minimal. This is in contrast to many other radionuclides that require extensive shielding from high-energy gamma emission. Because of the limited t_{1/2} of alpha emitters currently considered suitable for medical use, waste disposal is not a significant obstacle. In addition, shielding requirements for alpha emitters are highly manageable compared with those required for beta and gamma emitters.

### INDUSTRIAL-SCALE MANUFACTURE AND APPLICATION OF ALPHA EMITTERS

Radioisotopes utilised for radiopharmaceuticals are produced commercially by three methods: in a nuclear reactor, in a cyclotron or linear accelerator, or using a radionuclide generator. The latter, used for radium-223 production, uses longer-lived parent nuclides that produce short-lived daughter isotopes upon decay. Daughter isotopes can be derived as needed by elution of the generator system. Actinium-227, the generator nuclide for radium-223 production, has a t_{1/2} of 21.8 years and is produced in a nuclear reactor by neutron irradiation of radium-226. The production process is fully scalable to meet future commercial demand.

Other isotopes produced from generator systems include bismuth-213 and actinium-225, both of which are in very limited supply (and may remain so) owing to the scarcity of uranium-233 source material.

### MARKET POTENTIAL FOR ALPHA EMITTERS

The development of alpha particle emitters as therapeutics is currently focused mainly in the field of cancer. Cancer remains one of the world's largest unmet medical needs, despite increasing understanding of the disease and the availability of novel therapies.

The principle of customised, targeted therapies for the future treatment of cancer is potentially well served by recent developments in alpha particle emitter technology. Given the wide range of targeting modalities through which alpha particle emitters may be combined into products, the potential of this class of drug for broad therapeutic application in cancer is very high. Alpha emitter-based products therefore stand to have a significant impact on the oncology therapeutics market of the future.

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