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A Limiting Factor for the Progress of Radionuclide-based Cancer Diagnostics and Therapy

Availability of Suitable Radionuclides

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Advances in diagnostics and targeted radionuclide therapy of haematological and neuroendocrine tumours have raised hope for improved radionuclide therapy of other forms of disseminated tumours. New molecular target structures are characterized and this stimulates the efforts to develop new radiolabelled targeting agents. There is also improved understanding of factors of importance for choice of appropriate radionuclides. The choice is determined by physical, chemical, biological, and economic factors, such as a character of emitted radiation, physical half-life, labelling chemistry, chemical stability of the label, intracellular retention time, and fate of radiocatabolites and availability of the radionuclide. There is actually limited availability of suitable radionuclides and this is a limiting factor for further progress in the field and this is the focus in this article. The probably most promising therapeutic radionuclide, ^{211}At, requires regional production and distribution centres with dedicated cyclotrons. Such centres are, with a few exceptions in the world, lacking today. They can be designed to also produce beta- and Augeremitters of therapeutic interest. Furthermore, emerging satellite PET scanners will in the near future demand long-lived positron emitters for diagnostics with macromolecular radiopharmaceuticals, and these can also be produced at such centres. To secure continued development and to meet the foreseen requirements for radionuclide availability from the medical community it is necessary to establish specialized cyclotron centres for radionuclide production.

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During the past decade there has been an improvement in radionuclide-based methods for tumour diagnostics and imaging. PET (positron emission tomography) and SPECT (single photon emission computerized tomography) scanners are becoming more common, which allows for quantitative imaging and higher quality on pharmacokinetic oncology-related studies. Such scanners combined with CT (computerized tomography) have also been available for a few years.

Furthermore, the progress of radionuclide therapy, RNT, has been significant for haematological tumours, while the progress for solid tumours has, so far, been limited. A limiting factor is presently the lack of tumour-specific targeting agents for radionuclide-based treatment of the most common types of tumours (e.g. disseminated breast, prostate, and colorectal cancers). However, we foresee that successful characterization of new target structures will stimulate the efforts to develop new radiolabelled targeting agents (1, 2). There is also a need for better targeting agents in the related field of boron neutron capture therapy, BNCT (3). Compound development is, however, not the topic of this review. Instead we focus on the limited availability of the types of radionuclides that, according to preclinical studies, are the most promising for future clinical radionuclide therapy.

The use of radioactive nuclides for therapeutic targeting has at least three advantages:

1) Targeted radionuclides emitting alpha or beta particles are effective to induce double-strand DNA breaks and, consequently, cell inactivation. The biological action of these radionuclides is not counteracted by, as far as we know, resistance induction phenomena.
2) Radiation emitted by radionuclides delivered to a targeted tumour cell can also kill neighbouring tumour cells, even if the neighbour does not bind the agent (i.e. 'crossfire' irradiation).

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3) The biomolecules that deliver the radionuclides can be given in low concentrations if the nuclides are severely cytotoxic. This is especially the case for alpha emitters.

These three points give optimism for the therapeutic development of RNT and are often discussed in review articles (1, 2, 4, 5). The biological and medical aspects of these three points are not discussed in much detail below except when relevant for the choice of radionuclides.

The concept of crossfire irradiation means that the emitted radiation from nuclides targeted to one cell can reach surrounding cells. This helps to overcome the problem with genomic instability that might give heterogeneous expression of the antigens or receptors. High-energy beta emitters can give good crossfire irradiation, while low-energy beta and alpha emitters give only a limited such effect (in most cases only a few cell diameters). There is also a growing interest in therapeutic use of nuclides that emit Auger electron cascades since these give localized high-energy deposition. However, the application of Auger electron emitters is challenging since they have to be associated with the nuclear DNA to be efficient in cell killing. Principles for nuclear DNA uptake are emerging but so far are not in clinical use (1). The range of nearly all electrons from an Auger cascade is less than 1 μm and cells and tissues that do not take up the Auger emitters into their cellular nuclei are not, or are only marginally, irradiated. Combinations taking advantage of the efficient cell kill by alpha emitters, the subcellular local effects of Auger emitters, and crossfire effects from beta emitters might be a future possibility. A limiting factor for such a development is the limited availability of suitable types of radionuclides.

So far, clinical radionuclide therapy has been limited to the application of a few types of radionuclides and a few types of tumours. The radionuclides have so far mainly been beta emitters and applied in ionic form or coupled to low molecular weight substances. The radionuclide ^{131}I is in ionic form used mainly for treatment of hyperthyroidism and for eradication of differentiated thyroid carcinomas(1). The radionuclides ^{89}Sr and ^{153}Sm are as ions, or simple chelates, applied for bone pain palliation in osseous metastases. To a limited extent, ^{32}P is used for treatment of rheumatoid arthritis or haematological diseases (4).

Until recently, the use of targeting to tumour-specific cell surface antigens and receptors has been of limited clinical efficiency. Insufficient development of tumour-specific targeting vectors has so far been the main reason for the unimpressive results. It is now time to change this view and the reasons for this are given below. A remaining difficulty is the limited availability of suitable types of radionuclides and this is a major subject of this article.

NEW APPROACHES

During the last few years there has been increased interest in radionuclide tumour targeting for diagnostic purposes. An important event was the approval by regulatory agencies of labelled octreotide and several antibodies or antibody fragments for clinical diagnostics. Octreotide, an octapeptide synthetic analogue of the neuropeptide somatostatin, is a good example of the use of short peptides for tumour targeting. It was labelled with radioiodine in the late 1980s (6, 7). Further modification included an attachment of the chelator DTPA and a change of radionuclide to ^{111}In (8), which improved the pharmacokinetics of the peptide (9). The peptide is now commercially available and often used for detection of neuroendocrine tumours (10).

The ^{111}In-labelled antibodies ProstaScint and OncoScint and the ^{99m}Tc-labelled antibody fragments CEA-Scan and Nofetumomab are examples of antibodies and antibody-derived products now used clinically for diagnostic purposes. ProstaScint can be used for staging of prostate cancer (11, 12), detection of occult recurrences (13, 14), and detection of lymph node metastases (15). OncoScint, ^{111}In-labelled anti-TAG72 monoclonal antibody, is directed against colorectal and ovarian cancers (16). Its use in radionuclide-guided surgery has been claimed to be useful to detect recurrences and help the surgeon in the resection of small tumour deposits which otherwise are difficult to localize (17).

CEA-scan, an antibody Fab' fragment labelled with ^{99m}Tc, can possibly be used for staging of colorectal carcinoma (18) and imaging of breast cancer (19). Radioimmunoscintigraphy with CEA-scan has been reported to be more sensitive than conventional diagnostic modalities such as CT for detection of extrahepatic abdominal and pelvic colorectal carcinoma and seems to be complementary to conventional diagnostic modalities in imaging of liver metastases (20). Nofetumomab is a fragment of the NR-LU-10 antibody, initially designed for staging of non-small cell lung cancer. It has been shown, however, that due to the reactivity of this antibody (recognizing the Ep-CAM antigen), Nofetumomab may be used for diagnostics of gastrointestinal, breast, ovary, pancreas, kidney, cervix, and bladder carcinomas (21).

We conclude that the interest in radionuclide-based tumour targeting for diagnostics is increasing. It can now be expected that the development of tumour-specific substances, which supported the appearance of targeted diagnostics, will also facilitate the development of targeted radionuclide therapy. Positive results have already been obtained in treatment of non-Hodgkin's lymphoma. For the moment, an anti-CD20 antibody, ^{90}Y-labelled Zevalin, is approved for clinical use by the FDA (22) and another, ^{131}I-labelled Bexxar, is expected to be approved (23). A number of reviews report a high, up to 80%, response rate achieved with these radiolabelled antibodies in clinical trials

(5, 24–27). It is notable that therapy with radiolabelled antibodies is efficient even in patients who have not responded to therapy with the corresponding non-labelled antibodies (28).

For the moment, no radiolabelled antibody has shown sufficient antitumour action in the case of disseminated solid tumours (24). However, encouraging results were obtained by using radiolabelled somatostatin analogues to target neuroendocrine tumours. Initial attempts were performed using [^{111}In]OctreoScan (29–31). The therapy was well tolerated by patients with low, mainly haematological, toxicity (29, 32). Objective responses included biochemical and radiographic responses with prolonged survival. Nevettheless, the rate of objective radiological responses was modest, about 8% (31). Further progress was associated with the use of high-energy beta-emitter ^{90}Y and another somatostatin analogue, DOTATOC, and several centres reported higher rates (28–34%) of complete plus partial responses (33–36). A promising clinical study using [^{177}Lu-DOTA(0),Tyr(3)]octreotate for treatment of gastro-entero-pancreatic tumours has also been published (37). Quite high rates of objective responses (38%) were obtained, with the absence of serious side effects in this trial.

A critical question also concerns the future availability of radiopharmaceuticals. The pharmaceutical industry might be reluctant to produce radiopharmaceuticals because of limited shelf life due to the physical half-life of the radionuclides and also because of radiolysis during storage (1). These problems will probably be solved in the future when the pharmaceutical industry will mainly produce non-radioactive substances. These substances will be designed to make radioactive labelling effective and simple at local hospitals.

The substances can have a chelate coupled to them, as is presently the case for the somatostatin analogue Octreoscan (85) and certain antibody preparations (82). They can then be labelled with metal radionuclides such as ^{90}Y, different isotopes of indium or rhenium and possibly also with alpha emitters such as ^{213}Bi. The substances can also be designed to allow for halogen labelling with isotopes of iodine and the alpha emitter ^{211}At.

The radionuclides can be produced locally at the nuclear medicine department with applied generators or accelerators or they can be bought from companies specialized in radionuclide production. The radionuclides can then easily be coupled to the preformed substances at the local nuclear medicine department (1). Thus, we foresee that the availability of radiopharmaceuticals will not be a severe problem if radionuclide therapy proves to be effective.

A market assessment of therapeutic radiopharmaceuticals was published several years ago (38). According to this assessment, an exponential growth in revenues is expected in the US market for therapeutical radiopharmaceuticals (62 million US$ in 2000, 440 million US$ in 2001 and 6010 million US$ in 2020), and so far the prognosis seems to be fairly correct. Development of more effective targeting techniques has been called one of the major 'market drivers' in this area. It has been emphasized, however, that such expansion could not occur if there is not an adequate supply of radionuclides. The organization of relevant radionuclide production seems in fact to be a 'bottleneck' for the development of radionuclide therapy.

NUCLIDES FOR THERAPY

The choice of type of radionuclide is determined by a number of physical, chemical, biological, and economic factors. Examples of such factors are energy deposition of the emitted radiation, physical half-life, labelling chemistry, chemical stability of the label, intracellular retention time, and fate of radiocatabolites and availability of the radionuclide.

An important consideration is the aim of the treatment. In principle, there are, as for external radiation therapy, two approaches:

1) palliative treatment when complete remission is not expected but the goal is pain relief and improvement of the patient's life quality;
2) curative treatment with the goal to inactivate all tumour cells.

The last task might be difficult to achieve for a number of reasons. First, it is possible that, due to genomic instability, some of the tumour cells might not express the target antigens or receptors at a level high enough and thus escape the treatment. This might, to some degree, be solved by crossfire irradiation and also through the use of 'cocktails', i.e. simultaneous injection of several labelled molecules aimed at different targets (39). Another problem is caused by the possible existence of single disseminated tumour cells. Disseminated tumour cells are not exposed to crossfire irradiation and the number of emitted particles that crosses their cellular nucleus might therefore be limited.

The most widely used therapeutic radionuclide today is the beta emitter ^{131}I (40). Theoretical computations demonstrate that due to the approximately 1 mm mean range of the emitted beta energy, compounds labelled with ^{131}I are optimal for treatment of tumour cell clusters containing 10^5–10^6 cells (41), but not single cells and smaller cell clusters. However, ^{131}I is more efficient in eradication of small cell clusters than ^{90}Y (42). These two nuclides might be effective for palliative treatment, for example therapy of non-resectable tumours.

Prospects for curative treatment of disseminated tumours are associated more with alpha emitters and Auger-electron emitters. Both types of radiation have high LET (linear energy transfer) qualities, which can cause severe multiple DNA damages and DNA fragmentation and lead to cell

death after only a few decays. Thus, there is an urgent need for such suitable radionuclides in the marketplace.

The situation is complicated in the case of Auger electrons, because of their short range. Ideally, Auger emitters should be incorporated into the DNA or bound to it (43). Despite significant efforts and some progress in the development of labelled DNA-binding compounds (1, 44–46), there is not yet a reliable targeting procedure for Auger emitters. It can be expected that such targeting will appear in a few years (see below) but, until now, it seems that only alpha-emitters can be considered to be real candidates for curative treatment of disseminated tumours. The range of alpha particles is equal to some cells' diameters (most often 5–7 cells), which also make them efficient if the nuclide is located in the cytoplasm of the targeted cell or attached to its membrane. Moreover, a certain crossfire effect is present. High potency of alpha-emitting radiopharmaceuticals, in comparison with other types of radiation, has been demonstrated in several radiobiological and preclinical studies (47–51).

Emission of alpha particles is typical of the decay of nuclides with a high atomic number. However, it is likely that only a few types of such radionuclides may be considered for targeted tumour therapy when taking into account all required properties, such as physical half-life, decay scheme, chemical and biochemical properties, and availability. For the moment, only ^{211}At, ^{212}Bi and ^{213}Bi (see Table 1), are considered to be realistic candidates for therapeutic applications (51–53).

The alpha-emitting radionuclides with a short half-life are potential candidates for radioimmunotherapy directed at tumour targets easily accessible to radioimmunoconjugate molecules (54). For these reasons, bismuth-labelled conjugates were designed to treat haematological malignancies (55–58), or to damage tumour-associated vasculature (59–61). The results of preclinical evaluations were encouraging. However, therapy with bismuth-labelled conjugates of large established subcutaneous tumour models failed to cause regression (57). This and other circumstantial evidence indicates that the half-life of bismuth isotopes may be insufficient for targeting of tumour cells that are not well exposed to blood-born conjugates.

The alpha-emitting nuclide which, according to the view of the authors and others (62), has the highest potential in cases when the targeting molecule does not gain immediate access to the tumour cells is ^{211}At. This radionuclide has a longer half-life than the bismuth isotopes and there is therefore more time available for penetration over vessel walls and for interstitial penetration.

However, there is a problem associated with the clinical application of ^{211}At. The availability of ^{211}At is restricted, since an accelerator providing 28 MeV helium ions is necessary for the nuclear reaction ^{209}Bi(He^{2+}, 2n)^{211}At (63). This reaction is considered to be the best for routine production. Only a few accelerators with such properties are available for medical radionuclide production throughout the world. Moreover, such accelerators are in most cases multipurpose machines also used for physical and technical research, and the amount of time devoted for production of medical radionuclides is therefore most often limited. For this reason, the existing accelerators can be used mainly for research on astatine chemistry, radiobiology, and pharmacology, but not for production aimed at clinical treatments. Routine production for clinical treatments requires a dedicated cyclotron, operating full time for radionuclide production. Moreover, we believe that besides the capability to accelerate alpha particles, such an accelerator should also possess possibilities to accelerate protons and deuterons to allow for the production also of long-lived positron emitters (see below and Table 4).

The 7.2 h physical half-life of ^{211}At limits the possibilities for transport over large distances, e.g. between countries or long domestic distances. This is mainly a logistical problem, the solution of which depends mainly on the development of infrastructure and the national system of healthcare. There might be at least two solutions:

1) the organization of dedicated accelerator based therapy centres associated with large regional hospitals (similar to the organization of PET centres);
2) the organization of commercial accelerator centres that deliver astatine to a number of hospitals.

Apparently, the first arrangement is most appropriate for regions with a high population density. The second variant is suitable for countries with a large area and a low population density, which is true for the Scandinavian countries. We shall try to analyse the preconditions for the organization of an Accelerator-Based Centre for radionuclide production aiming at RadioNuclide Therapy, ABC-RNT, as suggested under point 2.

Table 1

Alpha-emitting nuclides considered for therapy, their physical half-life, and the production mode

Nuclide	Half-life	Production methods
^{211}At	7.2 h	Cyclotron
^{212}Bi	60 min	Generator
^{213}Bi	45.6 min	Generator

PRECONDITIONS FOR ABC-RNT

The preconditions for cost-efficient operation of an ABC-RNT are:

1) a sufficient number of patients who can benefit from radionuclide therapy;

2) availability of tumour-targeting agents with reasonably good tumour cell specific binding;
3) availability of labelling methods and qualified radiochemists to perform labelling and quality control;
4) availability of qualified and experienced clinicians to carry out the therapy;
5) prospects for further development of therapeutic agents;
6) full-time operation of a suitable accelerator.

As an example we consider these factors applied to Sweden. The mortality per year in Sweden of cancer is about 2 500 persons per one million inhabitants (64). Although significant differences exist between different countries, the numbers are in the same order of magnitude in many other Western countries. This mortality is to a large extent associated with dissemination and local spread of tumour cells and formation of local lymph node or distant metastases. Thus, in Sweden with 9 million inhabitants, at least around 20 000 patients might benefit from improved forms of tumour therapy. However, as regards radionuclide therapy based on tumour cell targeting, only tumours that express tumour-associated antigens or receptors on their outer cellular membrane can probably be successfully treated. In the authors' opinion it is reasonable to assume that in approximately half of all cancer cases cancerogenic mutations will lead to alterations of the cellular membrane that is suitable for targeting. In the other half, mutations will lead to mainly intracellular changes that it is not practically possible to target, at least not with macromolecular agents. Taking this crude assumption into account, there might at least be 1 000 patients per 1 million inhabitants who potentially will benefit from an effective targeted radionuclide therapy. Examples of possible tumour groups and the corresponding target structures, antigens, and receptors are given in Table 2. A crude estimate is also shown of the number of patients who could benefit from radionuclide therapy per million inhabitants (based on numbers from Sweden).

Summing up the patients in Table 2 gives a figure of about 500. If all other types of tumours also are considered this figure is reasonably close to the number estimated above, i.e. 1 000.

There are of course many more antigens and receptors of interest for other tumour groups than mentioned as examples in Table 2. For example, differentiation antigens (e.g. CD20 or CD22) in lymphomas and leukaemia are well-known and useful targets for radionuclide therapy (5, 82). Somatostatin receptors are highly expressed in neuroendocrine tumours and are also of therapeutic interest (83–85). Several other receptors, e.g. the receptors for vasoactive intestinal peptide (VIP) and gastrin (86, 87), can also be considered as targets. Furthermore, the receptors mentioned in Table 2 are also present in other tumours. Examples of this are that HER2 is also often over-expressed in ovarian cancers and EGFR is often over-expressed in gliomas and some squamous cell carcinomas (1). Few mutated receptors suitable for radionuclide therapy have been found so far. One example is the tumour-related unique mutation vIII of the EGF receptor often found in gliomas (88).

As seen in Table 2, antigens and receptors that might be used for targeting are identified for the most abundant cancer types. For many of those tumour types there are antibodies available, which are approved by regulatory agencies for tumour diagnostics and for imaging. However, these antibodies are in most cases approved for delivery of radiometals emitting photons and beta particles. To improve the possibilities for curative treatment there should preferably be a switch to an alpha emitter such as astatine-211. It is expected that a change of the label to astatine, to allow for efficient therapy, can change the pharmacokinetics, intracellular retention, and excretion of radiocatabolites. Thus, preclinical studies with astatine-labelled versions are necessary, even when approved antibodies are applied. Preclinical research is, of course, also needed when small peptides and receptor ligands are to be applied for astatine labelling. However, the chemistry of astatination of proteins and peptides is relatively well studied, which facilitates this type of research as described below.

Table 2

Examples of tumours and associated antigens and receptors of interest for radionuclide targeted diagnostics and therapy[1]

Tumour	Examples of antigens and receptors	Examples of references	Max no. patients for RNT
Prostate	PSMA, E4, EGFR	(65), (66), (67)	~200
Colon	A33, CEA, LewisY, MUC-1, Ep-CAM, HER2	(68), (69), (70), (71), (72), (73)	~100
Lung (NSCLC)	CEA, Ep-CAM, Lewis Y, EGFR, HER2	(69), (72), (74), (75), (76)	~85
Breast	HER-2, CEA, Ep-CAM, Lewis Y, EGFR	(69), (72), (77), (78), (79)	~75
Urinary (mainly bladder cancer)	MUC-1, Ep-CAM, EGFR HER2	(71), (72), (80), (81)	~40

[1]The estimated maximal number of patients per year and per million inhabitants who potentially might benefit from an effective targeted radionuclide therapy (RNT) is also given.

Astatine

From the chemical point of view, astatine is a heavier homologue of iodine and resembles this element in its general chemical nature but with some metallic character. However, the analogy between At and I is not as close as one might expect from their relative positions in the periodic table. Direct electrophilic astatination of targeting proteins gives a weak astatine–protein bond, which prohibits its application for targeted radionuclide therapy (89). The use of N-succinimidyl-astatobenzoate enables astatination of targeting proteins with a stable enough astatine–protein bond (90–93). Recently, N-succinimidyl 5-[^{211}At]astato-3-pyridinecarboxylate has been proposed as an agent for protein labelling with astatine (94). Its catabolites should be positively charged under lysosomal conditions, which may improve intracellular retention of astatine after internalization of the targeting molecule.

The technical capability of an accelerator required for ABC-RNT is not limited to production of astatine only. It can also produce other nuclides of interest for medical applications. Two groups of such nuclides are discussed below.

Beta-emitters

Though astatine is the most promising nuclide for curative treatment, there is also therapeutic interest in the use of other nuclides, such as beta emitters and nuclides giving Auger cascade electrons. An example is palliative therapy of bulky non-resectable tumours with high-energy beta emitters that have a rather long physical half-life (many days). The short physical half-life of astatine might be insufficient for appropriate penetration of targeting conjugates into very large tumour masses. When high-energy beta-emitting isotopes are used, a patient can also benefit from the 'crossfire irradiation' effect, which helps to overcome the possible heterogeneity of antigen expression. So far, the production of beta-emitting isotopes has been associated with the use of reactors. However, in a number of cases it is possible to produce therapeutically interesting beta-emitting radionuclides with a cyclotron. Some examples are given in Table 3.

The nuclide ^{64}Cu [$T_{1/2} = 12.8$ h; $\beta+ = 0.655$ MeV (19%); $\beta- = 0.573$ MeV (40%)] appear to be promising for targeted radiotherapy (95–97). This nuclide can be produced in large quantities using the ^{64}Ni (p, n)^{64}Cu nuclear reaction applying an enriched nickel target (98). The relatively short physical half-life of ^{64}Cu makes it difficult to transport this radionuclide over very long distances. Thus, this radionuclide should be produced quite near the site of use (mainly domestic use). However, it is possible to distribute ^{64}Cu using the same logistic network as used for delivery of ^{211}At.

The nuclide ^{114m}In is long-lived ($T_{1/2} = 49.5$ d) and metastable and emits photons of 190 keV, which are suitable for gamma camera based imaging. The nuclide also emits a substantial amount of conversion and Auger electrons, which makes it interesting for therapy. The main daughter radionuclide, ^{114}In ($T_{1/2} = 72$ s), decays by emitting high-energy beta particles (mean energy 777 keV), which is of interest for 'crossfire irradiation'.

Table 3

Therapeutic radionuclides, other than astatine, that can be produced with a 30 MeV cyclotron

Nuclide	Half-life	Emitted particles
^{64}Cu	12.7 h	β^+; β^-; Auger electrons
^{114m}In/^{114}In	49 d	β^-; Auger electrons
^{76}As	26.4 h	β^-;
^{80m}Br	4.42 h	Auger electrons
^{123}I	13.2 h	Auger electrons
^{111}In	2.81 d	Auger electrons, conversion electrons
^{203}Pb	2.16 d	Auger electrons
^{140}Nd/^{140}Pr	3.4 d/3.4 m	Auger electrons
^{143}Pm	265 d	Auger electrons
^{155}Tb	5.3 d	Auger electrons
^{167}Tm	9.25 d	Auger electrons

A number of radiopharmaceuticals have, for diagnostic purposes, been developed and labelled with ^{111}In, such as octreotide, bleomycin (99), and monoclonal antibodies (e.g. ProstaScint and OncoScint). By replacing ^{111}In with ^{114m}In, these substances might be of interest also for therapy. Theoretical radiobiological estimations have indicated that for a given effect in the tumour, a long-lived radionuclide (such as ^{114m}In) can result in less severe effects on bone marrow than a shorter-lived radionuclide such as the widely used ^{90}Y (100). Furthermore, a long-lived radionuclide might be more suitable for therapy of slowly growing tumours. The nuclide ^{114m}In can be produced using an accelerator aimed at ABC-RNT (101).

Arsenic isotopes, such as ^{76}As and ^{77}As, have been considered but not yet used for radionuclide therapy (52, 102). We assume that two factors have so far hampered the use of arsenic isotopes in nuclear medicine. The labelling chemistry is not well developed and it is necessary to use expensive enriched targets to ensure required isotopic purity of the product. However, cost-efficient methods for separation of arsenic from enriched targets using dry distillation and an increased interest in arsenic radiochemistry give hope that in the near future arsenic isotopes will be applied for both diagnostics and therapy (103, 104).

Auger electron-emitters

The use of Auger electron cascade emitters (see examples in Table 3) is not yet sufficiently developed. They are only efficient when the radioactive decay takes place near or inside DNA. However, there is still no conclusive answer as to how to achieve this. However, the use of Auger-electron emitters is attractive, and extensive research is devoted to solving the problems. There are at least three different

approaches for delivery of Auger electrons emitting radionuclides to the cell nucleus:

1) Treatment of steroid receptor-rich cancers using radiolabelled estrogen analogues. The oestrogen receptor–hormone complex can be used for delivery of Auger-emitting nuclides to nuclear targets since the complex binds to DNA. A number of cellular and animal studies have demonstrated the feasibility of radionuclide therapy using steroids carrying radiohalogens such as ^{123}I, ^{125}I or ^{80m}Br (44, 105, 106). A potential problem is that the retention time might be limited, i.e. the receptor–hormone complexes act as transcription factors and are then quickly released from the DNA after their function is fulfilled.
2) Translocation of internalized radiometals from the cytoplasm to the cell nucleus. It has been demonstrated that, after internalization and degradation of ^{111}In-labelled peptides, a fraction of the radioactive atoms is translocated to the cell nucleus and binds to the chromatin (107, 108). This creates a precondition for utilization of low-energy electrons and Auger electrons emitted from radiometals to be applied for therapy. The problem is that only a small fraction (about 10%) of the internalized radioactivity might be translocated into the nucleus.
3) Double targeting. This concept, which is under development in our laboratories, uses PEG-stabilized liposomes coupled to targeting peptides and the liposomes are loaded with DNA-intercalating cytotoxic molecules (109). Radioiodinated acridine derivatives, which were synthesized as DNA-binding compounds, demonstrated specific binding to DNA (110). Further research on other DNA binders is going on.

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) is a powerful diagnostic tool, and an ABC-RNT cyclotron can also be used for production of suitable positron emitters. PET provides the best spatial and temporal resolution among the available methods of nuclear diagnostics. An accurate attenuation correction enables PET to measure in vivo concentrations of the radioactivity with an accuracy of 5% (111). So far, PET has mainly been associated with the use of short-lived positron emitters such as ^{11}C ($T_{1/2} = 20.3$ min), ^{13}N ($T_{1/2} = 10$ min), ^{15}O ($T_{1/2} = 2.03$ min), and ^{18}F ($T_{1/2} = 109$ min). The use of these nuclides has, at several universities and hospitals, given rise to PET centres. These centres contain diagnostic installations with a cyclotron, a radiochemical laboratory, and at least one PET camera.

An important feature of ^{11}C, ^{13}N and ^{15}O as positron emitters is that they are biogenic and can replace stable isotopes of carbon, nitrogen, and oxygen in biologically active organic molecules with minor changes in their biochemical properties. However, the most often used PET tracer, [^{18}F]-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG), is labelled with the non-biogenic nuclide ^{18}F. The biodistribution of ^{18}F-FDG reflects local rates of transmembrane transport and 6-phosphorylation of glucose. Taking into account the important role that glucose plays in energy metabolism, it is easy to understand that ^{18}F-FDG is widely used in oncology, cardiology, and neurology. It has been demonstrated that ^{18}F-FDG-PET provides valuable information in diagnostics and staging of, for example, lung cancer (112, 113).

An important feature of ^{18}F-FDG is the relatively long physical half-life of ^{18}F, which enables at least short transport over some hundred kilometres. Both the utility of ^{18}F-FDG and the possibility to transport it have given rise to the setting up of satellite PET centres. In these cases the PET centre performs the PET investigations at the place of production of the positron-emitting isotopes. They also supply ^{18}F-FDG to distant scanners, which do not have their own accelerators for radionuclide production. Currently, about 50% of the PET centres in Germany work under this 'satellite scheme'. A further boost to the satellite concept was given by development of easy available and less expensive PET instrumentation. It has been shown that dual-head gamma cameras provide a satisfactory tool for ^{18}F-FDG-scans in the search for tumours and for imaging of those tumours. This provides an inexpensive alternative to PET cameras for satellite PET centres.

PET radionuclides from generators

Apparently, the organization of satellite PET centres is mainly associated with oncological investigations. However, PET-based applications in neurology and cardiology are also attractive but such investigations require simultaneous measurement of regional blood flow. The blood flow markers [^{15}O]water and [^{13}N]ammonia, which are suitable for clinical PET investigations, have a too short physical half-life to be delivered to satellite PET installations. An alternative is the use of generator produced blood flow markers of the metal type, ^{82}Rb or ^{62}Cu. There are, in principle, two generators suitable for this purpose: ^{82}Sr/^{82}Rb (25.3 d/ 1.27m) (114) and ^{62}Zn/^{62}Cu (9.1h/9.7 m) (115, 116). ^{82}Sr can be produced by the ^{85}Rb(p, 4n) nuclear reaction, which requires proton energy above 32 MeV (117). ^{62}Zn can be produced by the ^{63}Cu(p, 2n) reaction, at lower proton energy. The ^{62}Zn/^{62}Cu PET generator can be produced and distributed inexpensively from a single cyclotron production site operating under good manufacturing practice guidelines (118). Thus, by applying blood flow markers of metal type an ABC-RNT can provide local satellite PET centres with generators for production of suitable radionuclides.

Production of long-lived positron emitters

Another possible role of ABC-RNT in the field of PET is production of long-lived positron emitters. The short physical half-life of the radionuclides normally used restricts the time window in PET investigations to a few hours or less. However, there is increasing interest in the use of the good features of PET, high resolution and good quantification possibilities, in studies where longer investigation times are crucial, as in the examples below:

- Studies of antibodies for diagnostic purposes. Usually it takes half a day or more to decrease the background in blood, lymph, and normal organs and to achieve a good tumour to background signal in the images.
- Pharmacokinetic studies. Long-lived positron-emitting nuclides can be used to label various types of drugs with slow distribution patterns, especially those of high molecular weight. PET is then able to provide accurate kinetic data on the regional drug distribution in man. Different administration routes can be studied as well.
- Dosimetry for targeted radiotherapy. Biomolecules, which can specifically target tumour cells in vivo, can, for therapy, be labelled with beta- and alpha-emitting nuclides with a half-life of a few hours to several days. The same molecule can, in principle, also be labelled with a long-lived positron emitting nuclide, preferably of the same element as the therapeutic nuclide. PET can then quantitatively measure the uptake and the kinetics of the therapeutic nuclides, and the radiation dose to tumours and critical organs can be calculated.
- The physical half life is also critical from the commercial point of view when radionuclides, e.g. radiolabelled peptides (119), are transported from a cyclotron for diagnostic investigations at satellite PET centres.

The increasing interest in long-lived (sometimes called 'non-conventional') positron-emitting nuclides is showing up in an increasing number of publications (see reviews: 103, 120, 121).

The list of long-lived positron emitters that can be produced by an ABC-RNT machine is given in Table 4. Only nuclides with a half-life longer than 10 h are included. The versatility of radiophysical, chemical, and biochemical properties of long-lived positron emitters enables selection of a nuclide with optimal properties for a given study.

Table 4

Long-lived positron emitters that can be produced by an ABC-RNT cyclotron

Nuclide	Half-life	Nuclear reaction	Energy range (MeV)
^{55}Co	17.53 h	^{58}Ni(p,alpha)^{55}Co	17–0
^{57}Ni	36 h	^{59}Co(p,3n)^{57}Ni	30–23.4
^{64}Cu	12.7 h	^{64}Ni(p,n)^{64}Cu	20–2.5
^{71}As	65.28 h	^{70}Ge(d,n)^{71}As	9.5–0
^{72}As	26 h	^{72}Ge(p,n)^{72}As	13.7–5.3
^{66}Ga	9.49 h	^{66}Zn(p,n)^{66}Ga	6.05
^{76}Br	16.2 h	^{76}Se(p,n)^{76}Br	16–8
^{83}Sr	32.4 h	^{85}Rb(p,3n)^{83}Sr	30–22.6
^{86}Y	14.7 h	^{86}Sr(p,n)^{86}Y	15.7–6.1
^{89}Zr	78.4 h	^{89}Y(p,n)^{89}Zr	13.1–3.7
^{90}Nb	14.6 h	^{90}Zr(p,n)^{90}Nb	16.8–7.0
^{124}I	4.18 d	^{124}Te(p,n)^{124}I	12–8

CONCLUSION

There is progress in targeted tumour diagnostics using radionuclides and this gives promise for the progress also of targeted radionuclide therapy. The most promising tumour therapeutic nuclide, ^{211}At, requires regional production and a distribution centre with a dedicated cyclotron. Such a cyclotron centre can also produce β-emitters of tumour therapeutic interest and Auger emitters of potential therapeutic interest. Emerging satellite PET scanners may request long-lived positron emitters and the cyclotron centre can also produce these. In conclusion, it is necessary to establish specialized cyclotron centres for production of radionuclides of diagnostic and therapeutic interest to meet the requirements foreseen by the medical community.

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