We wish to herewith report safety evaluations, microdosimetry, and clinical requirements for first-in-human (FIH) study for handling of targeted alpha therapy (TAT) drug products labelled by 211At and 225Ac. 1) The safety evaluation method is proposed including delayed toxicity using the histopathological examination. The biodistribution study using PET or SPECT corresponding to alpha nuclides is also proposed. 2) Two scales of microdosimetry are proposed for the TAT design; one is the organ-microstructure scales and the other is the cellular and subcellular scales. Recently, the stochastic microdosimetric kinetic model was developed by the cellular-scale particle transport simulation using PHITS. 3) The dose of TAT drug for FIH study can be considered in the amount of radioactivity and mass, and radioactivity would often be a more important determining factor than mass. 4) In Japan, Medical Device system for regulatory approval of the synthesizer itself has been adopted as well as Medical Drug system for delivery of radiopharmaceuticals. We propose to start an automatic synthesis device at an early stage and to establish manufacturing process, quality control and GMP evaluations. The need for radiation shielding based on the calculation by effective dose rate coefficients for alpha particles is also introduced. The argument is concluded that the operation in hot cell used at many PET centers is sufficient.

Key Words: targeted alpha therapy (TAT), safety evaluation, microdosimetry, First-in-human clinical study, quality control and GMP

1. Introduction

Research and development for targeted alpha therapy (TAT) at Osaka University were adopted by JST's OPERA program in September 2017 and have been promoted under the domain name of Quantum Innovation for Safe and Small Society (QiSS). We decided to research to establish safety standards for the handling of TAT drug products labelled by astatine-211 and actinium-225 in the QiSS Research and Development Issue 6. We have already published the safety evaluations, the microdosimetry evalu-
330 Vol. 69, No. 10

RADIOISOTOPES

RADIOISOTOPES

ations,2) the quality control and GMP evaluations,3) and the clinical requirements for first-in-human study4) (See Fig. 1) on the Journal of Pharmaceutical and Medical Device Regulatory Science in Japanese. We wish to herewith summarize and present these four research results onto this report.

The surroundings for TAT in Japan have been changed during the decade. Because ALSYMPCA (ALpharadin in SYMPtomatic Prostate CAncer)5) reported that patients with metastatic CRPC (castration-resistant prostate cancer) treated with 223Ra had prolonged overall survival compared to placebo. In Japan, clinical trials for CRPC using 223Ra therapy was conducted since 2009 overcoming many problems such as legal issues6) and this therapy has been covered by public health insurance in Japan since 2016. Then, guideline for the introduction of alpha-emitting radiopharmaceuticals was developed.6)

In addition, the complete remission of metastatic prostate cancer in patients treated with 225Ac-PSMA-617 has sparked interest among physicians, scientists, and companies in the use of targeted alpha therapy.7) However, the most critical challenge has been the domestic availability of alpha emitters in Japan. Because the lack of a stock of parent nuclides with long half-lives, such as 233U, 229Th and 227Ac makes it impossible to produce 225Ac and 223Ra. Therefore, our demand for application has been focused on the accelerator-based alpha emitter, astatine-211(211At). Astatine-211 is a promising alpha emitter for targeted radionuclide therapy because it has a half-life of 7.21 h, which is sufficient for manufacturing 211At-labeled radiopharmaceuticals and accumulating them in targeted tissues after administration.8)

Non-clinical and clinical guidelines for diagnostic radiopharmaceuticals are known. Still, there is a need to establish non-clinical safety standards as well as standards suitable for beta- and alpha-emitting therapeutic radiopharmaceuticals such as the initial clinical dose. According to such high demand, based on the latest US and European guidelines,9, 10) we decided to consider regulatory science appropriate for TAT drug products.

Meanwhile, when fluorine-18 (18F) labelled fluoro-deoxyglucose (FDG) was approved in Japan, two application and approval systems have been adopted; "Medical Device" system for regulatory approval of the synthesizer itself, and "Medical Drug" system for delivery from radiopharmaceutical companies (See Table 1). However, the United States and Europe only adopt the application and approval of "Medical Drug" system for radiopharmaceuticals.

2. Consideration toward Safety Guidance for Targeted Alpha Therapy in Japan1)

Conventional beta-ray radiotherapy has been used

| Table 1 Characteristics and positioning of In-hospital Manufacturing and Delivery |
|-----------------------------------------------|
| **Quality/GMP** | **Synthesizer toward Medical Device application** |
| **First-in-Human Clinical Requirements** |
| **In-hospital Manufacturing** | **Medical Device Application** |
| Manufactured only for use in hospital | Compatible with medical device standards |
| Automatic synthesizers satisfy Quality and GMP | |
| ⇒ Ready for future production and sales |

Fig. 1 Rationale for Translational Research on Targeted Alpha Therapy in Japan.
I for thyroid cancer and 90Y-labeled antibodies for non-Hodgkin’s lymphoma. However, beta-ray radiation has the disadvantage that it destroys only DNA single strands, which can be repaired and tumor cells often survive.

On the other hand, in alpha particle radiotherapy, extremely intense linear energy is emitted, and the DNA double-strands of the tumor cells are cleaved, leading to the death of the tumor cells. The specific targeting allows it to attack only cancer cells with a significant therapeutic effect and few side effects (Fig. 2).

A German research group has reported that TAT has fewer side effects and is more effective than conventional anti-tumor therapies. Simultaneously, the TAT research project has also started in Japan to proceed with drug development. However, there is still no concrete international evaluation standard to conduct non-clinical studies for TAT drugs toward human clinical studies. Here, we discuss the requirements for an evaluation standard of non-clinical studies which is essentially necessary to proceed with clinical trial, while watching the current progress on the TAT drug development and the several subjects clarified by the previous TAT research. We focus on both 211At (astatine-211) and 225Ac (actinium-225) as the alpha-emitters. It also includes a discussion of monitoring endpoints that take into account initial human dose and dose escalation, identification of organs with suspected toxicity, physical half-life and stability of the drug, and accumulation in target cells. We also propose a method for evaluating TAT drug candidates that satisfy the safety profile, including delayed toxicity, using the histopathological examination.

Biological effects of radiation vary depending not only on the type of radiation itself, but also on the organs and tissues. And the revealing time of disorders depends on the characteristics of each organ or tissue. So, toxicological analysis that follows changes over time should be designed. Also, delayed toxicity and its recovery can be revealed by histopathological evaluation with some functional analyses, after a reasonable long-term course (see Table 2).

Stable isotope corresponding to an alpha particle can become a powerful tool to understand its distribution and toxicity. For example, 89Y-ibrutinomab tiuxetan would be used for toxicity test as an alternative to 90Y-ibrutinomab tiuxetan. However, stable isotopes corresponding to 211At and 225Ac are not present. Therefore, the strategy mentioned above cannot be applied. Alternatively, toxicity at the cellular level in mice can be assessed by histopathological evaluation after injection of alpha-emitting nuclide labeled compounds. Extended single-dose toxicity test Guidance for Exploratory IND studies 2006 was a useful reference.

In order to set an initial dose and escalation study, the biodistribution study with positron or single photon nuclides corresponding to alpha particles (PET or SPECT study) is adopted.

We expect that our new evaluation system can provide novel strategy for safety and dose escalation and verification issues for the development of new

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**Fig. 2 Characteristics of Alpha Particle.**

**Table 2 Preclinical Safety Evaluation**

|   |   |
|---|---|
| 1 | to identify an initial safe dose and subsequent dose escalation scheme in human |
| 2 | to identify potential target organs for toxicity and to examine whether such toxicity is reversible |
| 3 | to identify safety parameters for clinical monitoring |
TAT products in advance (See Fig. 3).

3. Microdosimetric models for TAT

Establishment of a reliable dosimetry protocol is a key issue in the design of TAT. The final goal of the dosimetry study is to evaluate the spatial and stochastic distributions of the absorbed doses that can predict likely toxicity and tumor response to treatment. The property of alpha particle is its short range and high linear energy transfer (LET). It has a range of 10–100 micrometers, which is only about 2–10 cells distance. Higher LET particles can effectively induce the DNA damages and lead to apoptosis of the cells.

$^{225}$Ac does not emit gamma rays. Thus, it is difficult to perform quantitative SPECT imaging for biodistribution study. Meanwhile, $^{211}$At can realize the rough pharmacokinetics required for dosimetry. Detailed preclinical dosimetry studies, so-called microdosimetry, must be combined with macroscopic whole-organ dosimetry.

Two scales of microdosimetry were proposed for the TAT design; one is the organ-microstructure scales and the other is the cellular and subcellular scales. Their features are summarized in Table 3. The physical quantities frequently evaluated in the former scale are the absorbed doses in organ microstructures such as nephron in kidney, which can be used in the estimate of the normal tissue complication effects. In the latter scale, the cellular S-value, which represents the absorbed dose in a target cell compartment arising from nuclear transformation of the radionuclide in a source cell compartment, is often evaluated because the absorbed doses are heterogeneously distributed in such microscopic scales due to the non-random distribution of radionuclides among each cell compartment. The probability densities of the absorbed doses in cell and cell nucleus are also calculated.

As an example of the microdosimetry in the organ-microstructure scale, Hobbs et al. developed a computational model for representing the microstructures of kidney and bone marrow cavity. It was applied on Ra-223 dichloride (Xofigo), which was the first alpha-emitter radiopharmaceutical that has received approval for the treatment of patients with castration-resistant prostate cancer metastasized to bone. It was implemented in a new clinical trial for treatment of patients with bone metastases in renal cell carcinoma. This approach was also illus-

![Fig. 3 New Evaluation System for TAT Drug Candidates.](image)

| Table 3 Features of microdosimetric models for two different scales |
|---------------------------------------------------------------|
| **Scale** | **Organ microstructure** | **Cellular and subcellular structure** |
| Physical quantities to be evaluated | Absorbed dose in organ microstructure | ✓ Cellular S-value |
| | | ✓ Probability density of absorbed dose in cell & cell nucleus |
| Main purpose | Estimation of normal tissue complication | ✓ Estimation of therapeutic effect |
| Related autoradiography technique | Alpha camera | ✓ Fluorescence imaging |
| | | ✓ Solid-state track detector |
trated for the immune checkpoint inhibitor, PD-L1 antibody to investigate as a means of alpha-particle emitter delivery in a combined immunological and TAT strategy.

As for the cellular scale microdosimetry, Goddu et al.\textsuperscript{15} evaluated the cellular S-values for various alpha emitters as well as beta and Auger emitters for the target→source combinations of cell→cell, cell→cell surface, nucleus→nucleus, nucleus→cytoplasm, nucleus→cell surface. Akabani et al.\textsuperscript{16} determined the probability densities of the normalized absorbed dose in tumor and normal tissue cells irradiated with alpha emitters (\textsuperscript{211}At and \textsuperscript{213}Bi) based on the autoradiography images, and estimated the cell survival fractions as a function of cumulated activity concentration. Recently, Sato et al.\textsuperscript{17} developed the stochastic microdosimetric kinetic model, which determines the cell survival fractions based on the probability densities of absorbed doses in cell and chromatin domain scales calculated by the cellular-scale particle transport simulation using PHITS.\textsuperscript{18} As an example, the cellular scale dose distributions for alpha and beta emitters calculated by PHITS are shown in Fig. 4.

These microdosimetric models require the experimental data of the radionuclide spatial distributions in the same scale as considered in the simulation. However, it is difficult to measure the radionuclide spatial distributions in such microscopic scales using the current autoradiography techniques. Thus, further improvements of the autoradiography techniques are desirable for the practical use of the microdosimetric models in the design of TAT.

4. First-in-Human Clinical Requirements\textsuperscript{4}

We summarize the requirements for first-in-human (FIH) clinical trials of targeted alpha therapy (TAT). Based on the development status of TAT drugs in Europe and the United States, we examined what requirements should be set for the FIH clinical trials of TAT drugs in Japan. In FIH, the determination of administration dose of the drug is important. The dose of radioactive drugs can be considered in the light of radioactivity and mass, and radioactivity would often be a more important determining factor than mass (see Table 4).

Specifically, we review the requirements for FIH clinical trials for conventional radiopharmaceuticals issued by the FDA and EMA. Considering very short range and extremely high LET which are different from conventional radiopharmaceutical drugs, we discussed how to set requirements such as the dosage of TAT drugs for FIH clinical trials. It is important to evaluate the toxicity at the cellular level by con-
ducting histopathological examination using animal experiments in which various conditions such as dose and elapsed time are changed in addition to analyzing the tissue distribution of TAT drugs using an appropriate animal model and incorporating molecular imaging technology.

Meanwhile, for conventional drugs, there are two approaches based on the NOAEL (no observable adverse effect level) and the MABEL (minimum anticipated biological effect level) for determining the initial dose in the FIH clinical trials. The former is obtained from toxicological data, and the latter is obtained from pharmacological data (see Table 4).

Furthermore, we reviewed the results of animal experiments conducted on TAT drugs at Osaka University, the results of research showing the usefulness of theranostics, and the results of clinical trials in Europe and the United States. The first TAT drug developed at Osaka University is $^{211}$At-NaAt, which turns into $^{211}$At ion in the body, for the treatment of differentiated thyroid cancer. Histological changes in normal organs were also evaluated to estimate the side effects. The importance of histopathological examination was demonstrated to estimate TAT drug potential (See Fig. 5) (Watabe T, et al. J Nucl Med. 2019. Quoted according to open access policy).

Recently, the labeling of alpha-particles on biomolecular drugs such as peptides and antibodies have been studied mainly in Europe and the United States. PET drugs, which already have a high diagnostic capability, is a good example of a theranostic agent that can be applied based on diagnostic results and has high potential as a therapeutic agent for

| Type of drugs                  | The most important determining factor of administration dose | Evaluation methods of toxicity | Evaluation methods               |
|--------------------------------|-------------------------------------------------------------|--------------------------------|----------------------------------|
| Conventional drugs             | Mass                                                        | NOAEL approach                 | MABEL approach                   |
| Conventional beta-ray radiotherapy | Radioactivity                                                | + Dosimetry                     | 1) Conventional calculation of exposure dose |
| TAT                            | Radioactivity                                                | + Micro-dosimetry               | 1) A unique mathematical model 2) Histopathological tests |

Fig. 5 HE staining images of normal ICR mice up to 15 days after NaAt (1 MBq) administration. (A) Thyroid gland: follicular structure is observed in control (CTL), but follicular structure is lost in the administration group. (B) Stomach: no significant change in the administration group as compared to the control (CTL).
TAT. In Japan, the development of TAT drugs at the preclinical (animal use) level has begun, and further development is expected to continue in the future. For the successful development, it will be important to establish interdisciplinary cooperation and pursue requirements for FIH clinical trials.

5. Quality Control and GMP production for Targeted Alpha Therapy products

We would like to focus on the issues of production, quality control and health regulation of alpha-labeled radiopharmaceuticals. The method of conjugation of radionuclides to drugs are similar to radio-diagnostics such as PET and SPECT. However, the regulation of radiation is significantly different between radionuclides that emit positron, gamma or beta rays and those that emit alpha rays. To ensure the safety of workers and the public, we must comply with Act on the Regulation of Radioisotopes which was revised on September 1, 2019. Radiation has different transmittance depending on the type. Alpha particles can be shielded with a sheet of paper, beta rays with an aluminum or plastic plate, and X-rays and gamma rays with a lead or thick iron plate. Neutrons can be shielded by water. That is, the transmissivity is in the order of gamma rays > beta rays > alpha particles (See Fig. 6).

In TAT product development, quality standard requires continuity and consistency, but shifting from manual synthesis to automatic synthesis may change the quality standards at radiolabeling step. When this shifts from preclinical trials to clinical trials, it may lead to re-examination. Since TAT products are administered intravenously, the sterility assurance is required for GMP. In general, when radiopharmaceuticals are manufactured, careful consideration is required for radiation protection because of the large amount of radioactivities used during the production and handling than when they are used on patients. Since it is difficult to meet these requirements by manual synthesis, it is necessary to start an automatic synthesis device at an early stage and to establish a manufacturing process considers occupational safety. It is necessary to conduct the quality control (QC) tests for synthesized products (see Table 5). In order to prevent labor, money and time loss due to re-examination, it is important to consider the final synthesis method in the early stages of development. In that case, it may be better to incorporate the concept of quality by design (QbD)#1.

The labeling process of TAT products is described. We introduce amino-acid derivatives targeting LAT1,19) borane-mediated labeling to antibody20) and pre-targeting method applying click reaction 21, 22) as

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#1 Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
labeling compounds. Automatic purification system of α-particle is required as a step before the abovementioned labeling synthesis. Next, the radiation exposure of workers and the public is also a big problem in performing radiosynthesis. X-rays and γ-rays are also emitted in TAT products. We introduce the need for radiation shielding based on the calculation by effective dose rate coefficients for alpha particles, 211At and 225Ac (see Table 6). Regarding radiation protection in TAT product manufacturing, it can be said that sufficient response, if it is operated inside the hot cell, which are already utilized by many PET centers (See Fig. 7). 225Ac does not emit gamma rays, but daughter nuclides emit gamma rays like 211Fr 218 keV (12%) and 213Bi 440 keV (27%). 211At emits γ-rays (687 keV) with a low emission rate of 0.26% and also emits X-ray (77–92 keV).

5.1 Radiation Shielding of 211At-TAT products

It was reported that at least 4 GBq of 211At was used in 1 drug synthesis under cGMP environment. When set to use 5 GBq of 211At in one synthesis, without effective shielding against X-rays, a relatively high effective dose rate of 29 μSv/h is simply achieved at 1 m distance. Therefore, depending on the operation method, shielding for X-rays (and γ-rays) may be necessary even in the case of 211At. In the case of 211At, since most of the radiation, except α-rays, is X-rays of 100 keV or less as described above, shielding with lead is easy. For example, when 5 GBq of 211At is shielded with 1 cm of lead, the effective dose rate when 50 GBq of 18F is shielded with 6 cm of lead is almost the same.

Table 6  Emission Gamma Rays and Effective Dose Rate Coefficients of Radionuclides 211At and 225Ac for Medical Use

| Nuclide | Radiation | Half Life | Emission Gamma Rays (Release rate 10% or more) | Effective Dose Rate Coefficients (μSv·h/MBq) |
|---------|-----------|-----------|-----------------------------------------------|--------------------------------------------|
| 211At   | α         | 7.21 h    | 687 keV (0.26%)                               | 5.8 × 10−1                                 |
| 225Ac   | α         | 10.6 d    | 211 keV (12%) 400 keV (27%) 551 keV (15%)     | 6.97 × 10−1                                 |
| 18F     | β−        | 110 m     | 511 keV (15%)                                 | 1.39 × 10−1                                 |
| 210Bi   | α         | 45.6 m    | 440 keV (27%)                                 | 2.36 × 10−1                                 |

Fig. 7  In-hospital Manufacturing System installed by Hot-Cells equipped with Automatic Synthesizers.
5.2 Radiation Shielding of $^{225}$Ac-TAT products

$^{225}$Ac itself does not emit gamma rays, but daughter nuclides emit gamma rays. Since the maximum single dose of $^{225}$Ac-TAT is reported about 40 MBq, the maximum amount of $^{225}$Ac used in the drug synthesizer is set to 100 MBq. Effective dose rate is of 0.7 $\mu$Sv/h at 1 m distance. Assuming that $^{225}$Ac/$^{213}$Bi is in equilibrium, the effect from $^{213}$Bi is an effective dose rate of 2.36 $\mu$Sv/h at a distance of 1 m. Estimated to be 3–4 times higher than the effective dose rate at 1 m distance when 50 GBq $^{18}$F is shielded with 6 cm of lead.

When a hot cell installed automatic synthesizer for TAT drug is used in combination with other nuclide TAT or PET drugs, 5 GBq of $^{213}$Bi from $^{225}$Ac/$^{213}$Bi generator is used, shielding is essential, because the effective dose rate at 1 m distance is 118 $\mu$Sv/h. If the $^{225}$Ac/$^{213}$Bi generator itself does not have sufficient shielding, it must be installed in a hot cell with lead shielding as well. Considering sharing the drug synthesizer with PET drugs such as $^{68}$Ga, from the viewpoint of the treatment of radioactive waste, when alpha and PET wastes are mixed, processing becomes complicated. It is therefore desirable to avoid sharing in a hot cell.

TAT product manufacturing inside the existing hot cell is possible without the risk of external exposure (See Fig. 7). These are simulation examples, and it is important to demonstrate that sufficient safety against radiation is ensured from the radionuclide and the maximum radiation dose used and measurement with actual equipment.

It is not necessary to introduce new hot cell designed for TAT products, and it is certain that conventional PET drug hot cells have sufficient shielding ability against external exposure by manufacturing TAT products. Based on the concept of ensuring safety, we hope that the understanding that TAT drug manufacturing is possible without the risk of external exposure inside the existing hot cell installed at the PET drug facility will be expected.

We introduce the points of QC based on the method of GMP validation including the calibration methods for QC equipments (see Table 7). We presented the technique to establish both quantitative evaluation method of radiation protection and safety-

| Measuring Equipment | OQ: Operational Qualification | PQ: Performance Qualification |
|---------------------|-------------------------------|------------------------------|
| **Radio HPLC**      | Radiation detector            | Linear check of voltage output |
|                     | UV-Vis detector               | Wavelength accuracy          |
|                     |                               | Noise and drift               |
|                     | HPLC pump                     | Accuracy and discharge volume |
|                     |                               | Temperature setting range     |
|                     |                               | and its temperature maintenance capability |
|                     | Auto-sampler                  | Accuracy, accuracy, linearity of injection volume |
|                     | Carry over test               | Presence of sample contamination |
|                     |                               | (Cleaning validation)         |
| **GC**              | FID                           | Sensitivity                   |
|                     |                                | Injectors test                |
|                     | Oven                          | Check even temperature in OQ |
|                     | Carrier gas flow meter        | Check the flow rate in OQ    |
|                     | Carry over test               | Presence of sample contamination |
|                     |                               | (Cleaning validation)         |
| **Radio TLC**       | Detection spot reproducibility and linearity | Detection spot reproducibility and linearity |
|                     | Reproducibility of dripping amount | Reproducibility of dripping amount |
| **$\gamma$-Spectrometer** | Energy calibration            | Repeatability, linearity, and sensitivity |
|                     | Confirmation of detection efficiency (Efficiency) | (\% Detection limit radioactivity (MDA)) |

Table 7 Points of QC based on the method of GMP validation including the calibration methods for QC equipments for $^{225}$Ac and $^{211}$At labeling TAT products
operating manufacturing system for $^{225}$Ac and $^{211}$At labeling TAT products.

6. Summary

Radionuclide imaging, including PET and SPECT, provides physiological and biochemical functions of human body with successful development of radiopharmaceuticals labeled with short lived radionuclides of positron or gamma emission. Recent introduction of TAT radiopharmaceuticals will further advance nuclear medicine by applying the innovative approach to use alpha particles for cancer treatment, which requires to establish practical procedures for the safe and efficient use of TAT radiopharmaceuticals.

Multidisciplinary approach creates the future by taking up the latest science and technology. Trying to bring about unprecedented technological innovation by fusing human resources and information from different fields, this is a trial of the “Alpha-Particles Design Lab.” It is a new attempt to develop the regulatory science of implementing alpha particles more widely into cancer treatments.

Making full use of theranostics concept based on PET drugs that are highly diagnostic, TAT radiopharmaceuticals are developed. The strength of the OPERA project, in which excellent chemists from the Department of Chemistry, the Graduate School of Science, Osaka University participate is utilized in the development power of TAT research based on the idea of the importance of target molecules and medicinal chemistry. And, several chemical candidates for tumor targets (amino acid derivatives, antibodies, virus-like particles, gold nanoparticles, etc.) have been labeled with $^{211}$At, and their biological evaluation is under investigation with the Institute of Radiation Sciences, Osaka University.

Administration of drugs into patients should not be a goal for research, but should be another starting point in the “bench to bedside” TAT scenario. With this strong conviction, Osaka University Hospital has been preparing radiopharmaceutical and imaging facilities as well as medical personnel to meet TAT standards in Japan. Preparation of investigator-initiated clinical trial using $^{211}$At-NaAt is ongoing in AMED project (principal investigator: Tadashi Watabe) in Osaka University Hospital (See Fig. 8).

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Comparison table of frequently used abbreviation words and their spelling out

| Acronym | Description |
|---------|-------------|
| AMED | Japan Agency for Medical Research and Development |
| DNA | Desaminohexonic acid |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| FHI | First-In-Human |
| GMP | Good Manufacturing Practice |
| IND | Investigational New Drug |
| JST | Japan Science and Technology Agency |
| LA71 | L-type Amino acid Transporter 1 |
| LRT | Linear Energy Transfer |
| MAEBL | Minimum Anticipated Biological Effect Level |
| NOAE | No Observable Adverse Effect Level |
| OPERA | Open innovation Platform with Enterprises, Research institute and Academia |
| PET | Positron Emission Tomography |
| PHITS | Particle and Heavy Ion Transport code System |
| PICS | Pharmaceutical Inspection Cooperation Scheme |
| PSMA | Prostate Specific Membrane Antigen |
| QBD | Quality by Design |
| QC | Quality Control |
| QSS | Quantum Innovation for Safe and Small Society |
| SPECT | Single Photon Emission Computed Tomography |
| TAT | Targeted Alpha Therapy |

**Appendix**

**Comparison table of frequently used abbreviation words and their spelling out**

| Acronym | Description |
|---------|-------------|
| AMED | Japan Agency for Medical Research and Development |
| DNA | Desaminohexonic acid |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| FHI | First-In-Human |
| GMP | Good Manufacturing Practice |
| IND | Investigational New Drug |
| JST | Japan Science and Technology Agency |
| LA71 | L-type Amino acid Transporter 1 |
| LRT | Linear Energy Transfer |
| MAEBL | Minimum Anticipated Biological Effect Level |
| NOAE | No Observable Adverse Effect Level |
| OPERA | Open innovation Platform with Enterprises, Research institute and Academia |
| PET | Positron Emission Tomography |
| PHITS | Particle and Heavy Ion Transport code System |
| PICS | Pharmaceutical Inspection Cooperation Scheme |
| PSMA | Prostate Specific Membrane Antigen |
| QBD | Quality by Design |
| QC | Quality Control |
| QSS | Quantum Innovation for Safe and Small Society |
| SPECT | Single Photon Emission Computed Tomography |
| TAT | Targeted Alpha Therapy |

**要旨**

日本におけるアルファ線核医学治療薬剤のトランスレーショナルリサーチの基盤
—アスタチン-211 とアクチニウム225 を活用した治療用放射性医薬品の萌芽—

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アスタチン-211 およびアクチニウム-225 で標識化
された TAT 薬剤のトランスレーショナルリサーチに
おける安全基準を確立したので、安全性評価、マイ
クロドメシトリ評価、ヒト初回投与試験の要件を
報告する。1) 病理組織学的検査を用いた遅延毒性を
含む安全性評価方法が提案されている。PET または
SPECT を用いた体内動態研究も提案されている。2) TAT
研究のために2つの微量線量測定が提案され、1
つは器官の微細構造のスケールで、もう1つは細胞
スケールと細胞内スケールである。最近、確率的微
小線量測定速度論モデルが、PHITS を使用した細胞
スケールの粒子輸送シミュレーションによって開発
された。3) ヒト初回投与（FIB）試験のための TAT
薬剤の用量は、放射能量と質量を考慮して検討するこ
と、放射能量は質量よりも重要な決定要因となるこ
ことが提案されている。4) 我が国では合成装置自体の
承認申請システムが、デリバリーサービスされる放射性医薬
品のシステムと共に採用されている。製造プロセス、
品質管理、GMP 評価を確立するため、自動合成装置
の検討に初期段階から着手することが推奨され、実
効線量率定数の計算に基づいた放射線防護の必要性
が提案されている。多くの PET センターで利用され
ているホットセル内の操作は十分な対応であると
提案されている。

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