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Recent Trend of Cancer Research
— Molecular Target Therapy and Translational Research —

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1.1 Introduction

Cancer accounts for approximately 30 percent of the causes of death in Japan, and conquering cancer is an important problem in the attempt to maintain and increase Japanese people's health.

Recently, the mechanisms of the proliferation of cancer cells, invasion and metastasis have been clarified on the molecular level, and researches on new therapies to make such specific molecules a target (molecular target therapy) have progressed. Therapy with molecular target drugs is expected to lead to the reduction of side effects and the treatment of refractory cancer and advanced cancer, against which existing therapies are revealing their limitations. The development of molecular target drugs is being accelerated throughout the world, and it must be promoted in our country as well.

However, in Japan, it was pointed out that the part combining the results of exploratory basic researches and clinical practice was insufficient at the "Intellectual conference on future ideal ways of cancer research," etc., and the necessity of translational research (exploratory therapy or exploratory clinical research) to bridge the gap between basic researches and clinical practice has been regarded as important.

In this report, we will state the trend of research and development of molecular target drugs that are highly expected as new therapies, and consider measures to promote research and development in this area.

Figure 1: Target for the Millennium Project in cancer research

- Discovery of more than 50 genes including disease-related genes and drug reactivity-related genes.
- 50% reduction of anticancer drug-induced side effects, such as vomiting and headache, by optimal medications (tailor-made medicine), etc., for individual patients.
- Improvement of therapeutic results by optimal medications for individual patients.
- Start of the development of epoch-making new drugs, for example, a drug to improve the 5-year survival rate by 20%.

Source: "The Millennium Project" decided by the Prime Minister on Dec. 19, 1999

1.2 System to promote cancer researches

1.2.1 Measures taken in Japan

In our country, the promotion of cancer researches has been attempted in multiple ministry and agency, centering on the "Comprehensive 10-year Strategy for Cancer Control (1984-1993 (cumulative total of actual research expenses was ¥102.4 billion))" and the "Second Term Comprehensive 10-year Strategy for Cancer Control (1994-2003 (cumulative total of actual research expenses was (1994-2001) ¥147.1 billion))". In the Millennium Project, cancer researches were taken up as one of the themes, and the target shown in Figure 1 was set as the goal up to fiscal 2004.

Based on these policies, cancer researches in Japan have been promoted and subsidized from the Grant-in-Aid for Scientific Research by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), and from the Grant-in-Aid for Health Science Basic Research and Cancer Research Subsidy by the Ministry of Health, Labour and Welfare (MHLW).

In addition, future ideal ways of cancer research, etc., that follow the "Second Term Comprehensive

10-year Strategy for Cancer Control" are now being considered at the "Intellectual conference on future ideal ways of cancer research," collaboratively held by MEXT and MHLW.

1.2.2 Measures taken in the United States

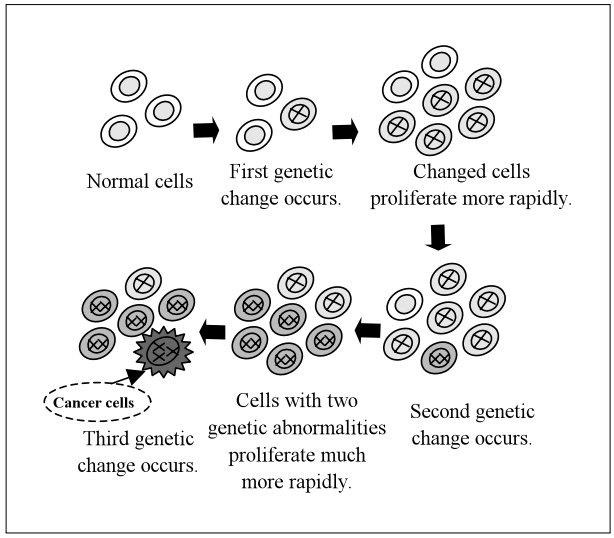
In the United States, since the National Cancer Act was established under the Nixon administration in 1971, the promotion of cancer researches has been taken up on a national basis centering on the National Cancer Institute (NCI). NCI is the largest institute that belongs to the National Institutes of Health (NIH). he budget of NCI tends to increase year by year, and for fiscal 2002, approximately $4,180 million (approx. ¥501 billion) has been appropriated.

1.3 Characteristics and therapies of cancer

1.3.1 Characteristics of cancer

Cancer is a disease attributable to genetic abnormality caused by any trigger such as chemical substances called carcinogenic substances, and radioactivity. Most cancer cells are formed by repeating multiple genetic changes and cell growth, as shown in Figure 2. A part of cancers such as some forms of breast cancer and colon cancer are gene related.

Figure 2: Conceptual flow chart of the multiple-stage process of carcinogenesis



Source: "Cancer -- Challenge of health science" (1998), the Second Term Comprehensive 10-year Strategy for Cancer Control, Cancer Research Subsidy

Cancer cells mainly have the following characteristics, and recently many molecules related to these characteristics have been clarified (Table 1).

i) Abnormal cell growth due to abnormality in the cell cycle, signal transmission system, cell

Table 1: Major biological characteristics of cancer cells and the related molecules

Characteristics	Related molecules
Abnormal cell proliferation	Proliferation-related molecule, signal transmission molecule, etc.
Invasion / Metastasis	Adhesion molecule, protease, bone metastasis-related molecule, etc.
Vascularization	Signal transmission molecule, protease, adhesion molecule
Drug resistance	Membrane transport protein, etc.

Source: Authors' own compilation

Table 2: Major cancer therapies and their outlines

Cancer therapy	Outline
Chemotherapy	Methods using anticancer drugs effective against cancer cells. Multiple anticancer drugs are often used concomitantly.
Surgical therapy	Methods to remove cancer cells by operation. Recently, enhancement of a patient's QOL is being attempted by low invasive endoscopic operation.
Radiotherapy	Methods to destroy cancer cells by radiation. Aiming to concentrate radiation on the area of focus as much as possible to reduce cytotoxicity in the surrounding normal cells; recently, methods using a gamma knife or ion beam have been developing rapidly.
Immunotherapy	Methods to utilize the immune system, which detects molecules or pathogens recognized as non-self, to attack them. A method using monoclonal antibody as a drug and a method using peptide vaccine are being developed.
Gene therapy	Methods to enhance a patient's immunity to cancer by introducing tumor suppressor genes to inhibit the development of cancer, or by introducing immune-related genes.

Source: Authors' own compilation

Table 3: Comparison between molecular target drugs and general anticancer drugs

Subject item	General anticancer drugs	Molecular target drugs
Hypothesis of efficacy	Empirical	Based on theory.
Main action	To destroy actively proliferating cells.	To inhibit, prevent and add the effects of molecules characteristic to cancer cells
Dosage setting	Higher dosage is desirable, although side effects are taken into account.	Optimal dose that may act on the target molecules.
Type of subject cancer	All cancers such as solid cancer.	Cancer with the target molecules.
Main efficacy	Regression of cancer.	To inhibit the progression of cancer.

Source: Authors' compilation based on the material prepared by Saburo Sone, professor at the School of Medicine, University of Tokushima

differentiation, or cell death (apoptosis).

ii) Formation of secondary tumors due to abnormality of cell adhesion, and, thereby, causing invasion or metastasis in the surrounding organs.

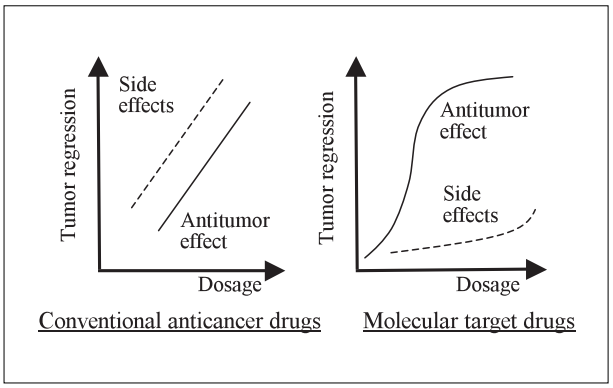
iii) Vascularization that forms new blood vessels to secure oxygen and nutrition.

iv) Drug resistance that makes drugs ineffective.

1.3.2 Cancer therapies

Major therapies for cancer are shown in Table 2. In an actual therapy, multiple therapies are combined occasionally.

Figure 3: Tumor regression of molecular target drugs and general anticancer drugs, and the relationship with occurrences of side effects



Source: Material prepared by Saburo Sone, M.D., Ph.D., professor at the University of Tokushima School of Medicine

1.3.3 Molecular target drugs

Anticancer drugs generally being used now inhibit and stop abnormal cell proliferation, as one of the characteristics of cancer cells, in order to destroy cancer cells.

When cells proliferate, there are 4 steps in the cell cycle including; i) gap phase of cell cycle and cell differentiation phase (G1 phase), ii) DNA synthesis phase (S phase), iii) cell division preparatory phase (G2 phase), and iv) cell division phase (M phase).

For cells frequently repeating the cell cycle, most anticancer drugs have an action to inhibit their DNA synthesis and cell division. For example, an anticancer drug called "Taxol" has an action to stop the progress of the M phase. However, cells frequently repeating the cell cycle are not limited to only cancer cells, but include normal cells such as hematopoietic cells and hair root cells. Therefore, most anticancer drugs also destroy normal cells, causing side effects.

On the other hand, the molecular target therapy is a therapy targeting molecules (Table 1) characteristic to cancer cells, and reductions in side effects may be expected from it. In addition, it is expected that molecular target drugs have possibilities to conquer intractable cancer such as advanced cancer and refractory cancer (e.g. lung cancer) for which there is the limit of the traditional treatment.

Also, molecular target drugs are being used based on individual patients' genetic abnormality and excessive protein expression, an aspect of tailor-made medicine (optimal therapy for individual patients), and are highly expected to represent what cancer therapy should be like after this.

In Table 3 and Figure 3, a comparison of the characteristics between general anticancer drugs and molecular target drugs are shown.

From the above, molecular target drugs are highly expected as new types of anticancer drugs, and various research and development are being accelerated throughout the world.

For example, STI571 (brand name: Glivec), developed as a drug for chronic myelogenous leukemia (CML) by Novartis Pharma , Switzerland,

was approved by the Food and Drug Administration (FDA) only 3 years after the start of clinical studies (May 2001). The drug is a molecular target drug that only acts on genetic products (protein with actions such as the abnormal proliferation of leukemia cells and the inhibition of apoptosis of blood cells) produced by the abnormality of the BCR-ABL gene as a cause of CML.

An anti-HER2 humanized monoclonal antibody, trastuzumab (brand name: Herceptin), developed as a breast cancer drug by Genentech, U.S.A., is a molecular target drug for metastatic breast cancer with excessive expression of a protein HER2. The excessive expression of HER2 is observed in approximately 20~25% of breast cancers. Herceptin selectively binds to the HER2, and has a cytotoxic effect on the cancer cells or an inhibitory effect on proliferation.

1.3.4 Problem in the development of molecular target drugs

As shown in Table 3, although efficacies of general anticancer drugs are evaluated from the regression of cancer, molecular target drugs are mainly aimed to inhibit the progression of cancer, and regression cannot be necessarily expected.

However, evaluations of anticancer drugs in clinical studies are mainly based on the regression of cancer. Therefore, the following criteria often shown as therapeutic effects of molecular target drugs have not been recognized as clinical evaluations in treatment; stable disease (state without exacerbation of cancer), time to progression (time to malignancy of cancer once again), and tumor dormancy (state of cancer growth settling down). In the future, it will be necessary to investigate the parameters for effective clinical evaluations.

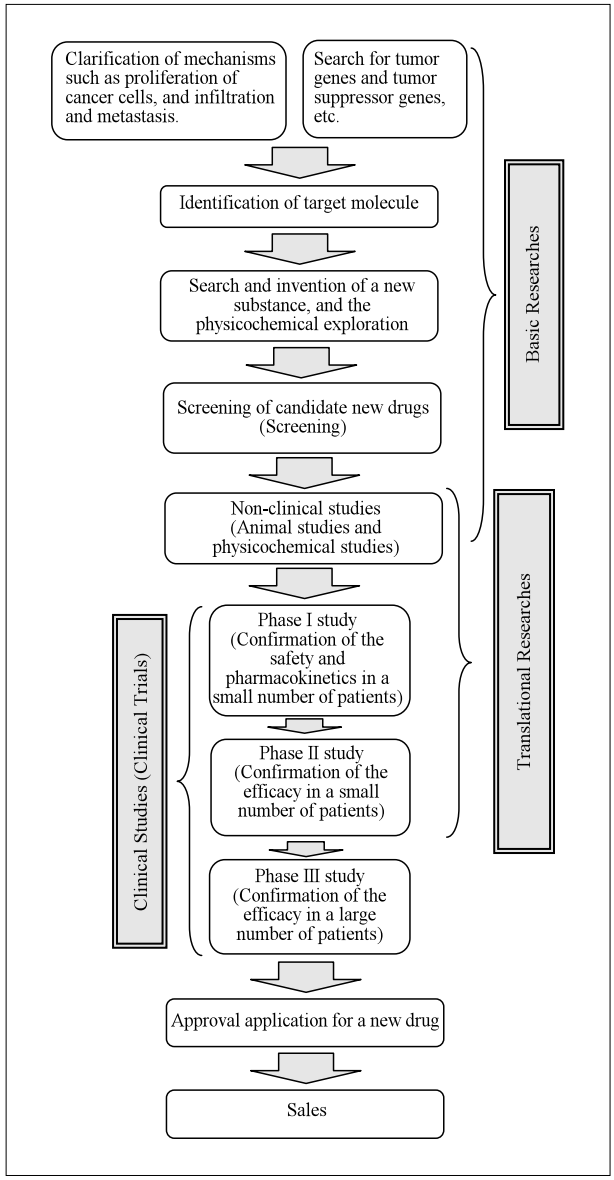
The development of a molecular target drug is based on exploratory basic researches, and high risk is associated with the stage to apply the drug as a therapy in clinical studies. Therefore, in order to promote the research and development of state-of-the-art therapies such as molecular target drugs, clinical trials conducted by the companies stated later are not sufficient, and clinical studies in a different form from the clinical trials are desired. Therefore, the necessity of translational researches is rapidly increasing.

1.4 System to promote the development of molecular target drugs — Promotion of translational researches —

1.4.1 What is Translational Research?

There is as yet no particular definition of translational researches that has obtained world consensus. In this report, we define this as researches to apply the results of exploratory basic researches for clinical studies to clinical studies in the development of state-of-the-art therapies such as molecular target drugs and

Figure 4. Process of research and development of molecular target drugs



Source: Authors' own compilation

regenerative therapy, and we distinguish them from clinical trials to obtain approval for drug, etc.

In Figure 4, the process of research and development of molecular target drugs is shown. Pharmaceutical development goes through basic researches, non-clinical studies, and clinical studies. Translational researches are likely to be in the range of the non-clinical studies to the phase II studies that can confirm the efficacy in humans.

In the current legal system, translational researches are outside of the regulations of the Pharmaceutical Affairs Law, as stated later. However, translational researches are aimed at establishing new therapies, and it is necessary to sufficiently secure ethical and scientific validity in clinical researches, and, therefore, it is also necessary to conduct researches according to the regulations of the Pharmaceutical Affairs Law and arrange for a system to conduct studies in translational researches.

1.4.2 Arrangement of legislation related to translational researches

In pharmaceutical research and development, a number of regulations have been made under ordinances based on the Pharmaceutical Affairs Law. Particularly, clinical studies (trials), which are conducted by medical institutions entrusted by a pharmaceutical company in order to obtain approval for drugs, etc., are being conducted according to Good Clinical Practice (GCP), strictly securing ethical and scientific validity.

On the other hand, GCP is not applied to clinical researches conducted mainly by researchers at universities and medical institutions, and the research data obtained there cannot be used for the approval application of drugs.

Thus, in clinical studies conducted mainly by universities and medical institutions, the research results are not smoothly integrated with pharmaceutical development and not required to comply with the provisions of GCP. As a problem, therefore, it was indicated that clinical studies were in a status that they could be conducted without sufficient consideration of the ethics and safety for patients and scientific validity.

In the background of such present status, the Ministry of Health, Labour and Welfare is proceeding with the amendment of the Pharmaceutical Affairs Law to extend its scope to utilize the results related to clinical researches. The proposed amendment was decided by Cabinet meeting, and submitted to the 154 times ordinary session of the Diet.

In the proposed amendment, the scope of clinical trials is to be extended to clinical researches conducted mainly by physicians and medical institutions intending to apply for clinical studies in the future (trial-type clinical researches). This will make it possible to use the results obtained from translational researches as part of the application data, and to provide new medical technologies to patients at an early stage while securing the ethical and safety aspects.

Thus, the results of translational researches will be easily combined to clinical trials, and the development of molecular target drugs is expected to accelerate.

1.4.3 Arrangement of the system to conduct translational researches

At medical institutions such as university hospitals, etc., efforts to arrange a system to conduct translational researches are getting under way.

As the first foothold of translational researches in Japan, Kyoto University Hospital established its Translational Research Center in April 2001. The Translational Research Center has implemented a public participation-type "Invited Research Project" with the functions such as preparing protocols, etc. and assessing the safety of the adopted project; actually conducting the clinical application, monitoring the safety and ethical aspects, and analyzing the biostatics.

Kobe City Government, which is proceeding with The Kobe Medical Industry Development Project, plans to establish a Translational Research Informatics Center in fiscal 2002, aiming to arrange a database of clinical researches, etc., in Japanese, in cooperation with the Ministry of Education, Culture, Sports, Science and Technology.

At the Council for Science and Technology Policy, Cabinet Office, in the promotion strategy of prioritized areas of life science (September 21, 2001) based on the Science and Technology Basic Plan 2001-2005 (decided by Cabinet meeting on

March 30, 2001), translational researches was taken up as one of the fields for which measures taken on a national basis should be strengthened, and measures to promote this were started.

1.4.4 Measures taken for translational researches in the United States

In the United States that has been extending the scope of the state-of-the-art therapy, measures taken for translational researches are being accelerated.

The National Cancer Institute (NCI) supports clinical researches being conducted by approximately 10,000 researchers at approximately 1,700 hospitals and cancer centers in the United States.

NCI is already proceeding with several programs for translational researches. For example, NCI started Specialized Programs of Research Excellence (SPOREs) to promote translational researches in cancer researches in 1992, and supports interdisciplinary research teams of translational researches for specific human cancers through public recruitment, etc. The budget of SPOREs for fiscal 2002 is approximately $107 million (approx. ¥12.8 billion), and is expected to further increase in the future.

1.5 Conclusion

To conquer cancer is an important problem in the attempt to maintain and increase Japanese people's health. Particularly, it is desired that therapies with less side effects, and therapies for refractory cancer and advanced cancer be established.

The research and development of molecular target drugs taken up in this article are important to our country as ways to explore new cancer therapies. In the development of molecular target drugs, translational researches are necessary to promote clinical studies, simultaneously with the promotion of basic researches.

To promote the development of molecular target therapy, the following measures are necessary.

(1) Promotion of exploratory basic researches targeted for clinical application

- Clarification of the mechanisms of the proliferation of various cancers, and invasion and metastasis, and identification of target molecules by searching for tumor genes and tumor suppressor genes.
- Search for drug reactivity-related genes, and search for and invention of new substances.

(2) Arrangement of a system to support researches

- Arrangement of an information management system such as a database specialized for cancer.
- Arrangement of a management system for research materials such as genes and cells (bio-resources).

(3) Arrangement of a system to conduct translational researches

- Following the current ongoing amendment to the Pharmaceutical Affairs Law, the legislation arrangement for the scope of clinical trials that is expected to extend in the future.
- Arrangement of a system to verify scientific validity, safety and ethics at institutions for translational researches such as university hospitals, and a system to deal with unexpected emergencies, as exploratory therapy is associated with high risk.
- Arrangement of participating teams (researchers of basic molecular biology, basic efficacy pharmacology, and clinical medicine, etc.) to effectively promote translational researches.
- To secure clinical research coordinators (CRC) to conduct duties dealing with subjects including informed consent, and human resources to conduct data management and analyses.
- To promote Japanese people's understanding about clinical studies, so as to recruit subjects more easily.

Through these measures, it is desired that new therapies such as those utilizing molecular target drugs be established to attain early realization of therapies with less side effects and improvement of the curing rate of cancer.

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