A brief note on the current state of gene therapy activities in Japan / [British Embassy, Tokyo].

A BRIEF NOTE ON THE CURRENT STATE OF GENE THERAPY ACTIVITIES IN JAPAN

Clinical trials

1. Compared to the US and Europe, the number of clinical trials conducted in Japan is very small. Only one trial has been completed; that undertaken by Hokkaido University Hospital to treat an ADA deficient four year old boy which was finished after 11 treatments in March 1997. Its protocols depended on the data from the US National Institute of Health.

2. As attachment 1 shows, there are three proposals which are under study by the Central Council for Gene Therapy Clinical Research of the Japanese Ministry of Health and Welfare (MHW). The trial by Kumamoto University Hospital is to treat four HIV patients by using a vector developed jointly by a Japanese firm called Green Cross Co and the US firm Bioagen. Although their plan was approved by the Council and was expected to start in July 1997, the proposal has currently been shelved while a small problem is addressed. MHW has asked both the university group and Green Cross to provide further information on the vector's data.

3. The trial proposals by the Tokyo University's Institute of Medical Science (IMS) and the Medical School of Okayama University target cancer treatment. The Okayama University group aims to treat lung cancer by using a vector comprising P53, which infects cancerous cells to cause their apoptosis. The Tokyo University IMS group aims to treat kidney cancer by using a vector comprising GM-CSF gene (granulocyte macrophase colony stimulating factor) in order to enhance anticancer immunity (See Attachment 1-2).

Development of vectors

4. As shown in the clinical trial proposals, vectors to be used are predominantly those developed by US venture firms. However,the following are some current activities in Japan.

- To catch up with development of vectors, DNAVEC Research Inc was set up in March 1995 to develop novel vectors. During the seven years of operation, MHW will invest 70% of the total capital, which amounts

to about 4.5 billion yen, and the rest has been invested by seven private pharmaceutical companies, including Yamanouchi, Sankyo, Shionogi, Hisamitsu, Tanabe, Kyowa Hakko Kogyo and Sumitomo Pharmaceuticals. Recently DNAVEC announced a success in the development of a new RNA vector using the Sendai virus. A corporate brief is at Attachment 2.

- Also major pharmaceutical firms appear to be steadly undertaking basic R&D to develop gene therapy drugs, but their activities are not publicly available. The Japanese firms which succeeded in product commercialization are the above mentioned Green Cross Co and Takara Shuzo Co Ltd which recently commercialized a reagent called "RetroNectin". Using adhesive characteristics of fibronectin, Takara Shuzo succeeded in introducing genes into the blood stem cells with almost 100% effectiveness. The technology was developed jointly with the US Indiana University, School of Medicine.

- Many Japanese university research groups are actively undertaking R&D of various vectors, both virus and non-virus types, but their R&D status is still basic. A Society for Gene Therapy was set up recently, headed by Professor Shigetaka Asano, Tokyo University's IMS with about 700 members who are mostly university researchers.

- US RPR Gencell Co (a division of gene therapy of Rhone Poulenc Rora) has completed a fairly large-scale gene therapy facility in Funabashi City in Chiba Prefecture in 1995, according to an article by Nikkei Newspaper. Collaborating with Japanese universities, it aims to provide supporting services for gene therapy. The Okayama University group will use the vectors developed by RPR Gencell. It has also been reported that Sandoz' Japan office is interested in gene therapy trials.

MHW's Health Science Council(HSC)

5. The promotion of human genome and gene therapy R&D is the next important area to brain science according to the "R&D Planning" panel of the Health Science Council(HSC), which was set up in May 1997 by MHW. MHW has been funding several research groups, mostly of universities to promote gene therapy R&D. Succeeding to the Central Council for Gene

Therapy Clinical Research, HSC has established another panel called the "Advanced Medical Technology Evaluation" to oversee the safety of gene therapy clinical trials according to the guidelines set up in February 1994. HSC consists of 16 members with Dr Kumao Toshima as its president.

Yasuko Otsuka (Ms)
Science and Technology Section

15 July 1997

CURRENT GENE THERAPY TRIALS IN JAPAN (Attachement 1-1)

Trials	Target disease and vector used	Approval by university ethical committee	Approval by MHW & Monbusho and implementation
1. Hokkaido University Hospital , a group led by Prof Yukio Sakiyama	• ADA deficiency for a 4 year boy • vectors imported from the US NIH	July 1994	-Feb 1995 approved -1st treatment started on 1 Aug 95 - Trial was completed with the 11 treatment in march 97. The boy started school.
2. Kumamoto University Hospital (led by Prof Kiyoshi Takatsuki)	• four HIV patients to enhance immunity to prevent on-set AIDs • a vector developed jointly between Green Cross and US Bioagen. • Green Cross owns vector's worldwide marketing rights.		-Applications submitted to panels of MHW & Monbusho was approved on Dec 96. -Green Cross applied for its drug approval to MHW on 28 Nov 95. Although its safety was approved on May 97 by MHW CPAC and it was likely to be started in July 97, the trial is currenly being suspended due to further information concerning ICR. So CPAC has asked to clear the point.
3. Tokyo University, Medical Res Institute, (led by Prof Shigetaka Asano)	• kidney cancer to synthesize GM-CSF to enhance immunity • vector made by Somatix Therapy Ltd venture firm	approved 6 August 96	MHW panel is currenly studying the application.

4. Okayama University Hospital, (led by Prof Noriaki Tanaka)	• lung cancer by inserting p53 gene (cancer suppression gene). • vector developed by US RPR Gencell Co	approved 11 Sept 96	MHW panel is currently studying the application
5) Nagoya University (Two groups)	• malignant brain tumor with better interferon • vector (liposome) developed by Nagoya Univ and firms	University's IRB is studying the application	
6) Japanese Foundation for Cancer Research	• breast cancer	University's IRB is studying the application	

IRB: Institutional Review Board
CPAC: Central Pharmaceutical Affaris Council

Yasuko Otsuka (Ms), S&T Section
15/7/97

Attachment 1-2

Fighting cancer on the strength of genes

Tokyo U., Okayama U. to join gene therapy battle against deadly illness

y Yoshiaki Sato
omiuri Shimbun Science Writer

In their quest to discover new ways to fight cancer, two medical institutions recently applied to the government for ermission to carry out cancer treatment als using gene therapy. If the request is anted, it will be the first time that such erapy has been used to treat cancer in is country.

The applications have been made by the ospitals run by Tokyo University's stitute of Medical Science (IMS) and the edical school of Okayama University.

What does cancer treatment involving e use of gene therapy entail, and what ance does it have of conquering malig- nt tumors?

The human body is composed of about 0,000 types of genes. The genes must nction properly if they are to produce zymes and other proteins essential to man health.

Studies conducted over the past 12 years so have revealed that cancer formations e due to a malfunctioning of, or defect , the genes specifically responsible for e reproduction of cells and other cellular ocesses.

Many experts hope that gene therapy ill eventually lead to a long-awaited cure r cancer in the 21st century. However, at ultimate goal may remain elusive if ne therapy techniques remain at their rrent levels.

Gene therapy techniques worldwide main at the experimental stage and are able to perform the scientists' desired nction of selectively targeting and nor- alizing defective genes.

Instead of concentrating directly on fective genes, current gene therapy orks by incorporating normal genes into ncerous cells in the hope of synthesizing bstances that contain cancer-killing operties. This method administers genes weak, cancerous cells in a way similar the administration of drugs to a patient.

This does not mean the therapeutic nes are administered orally. Instead, nes are conveyed into the body using a ctor, which is a series of modified cells to which cancer-busting genes have been corporated.

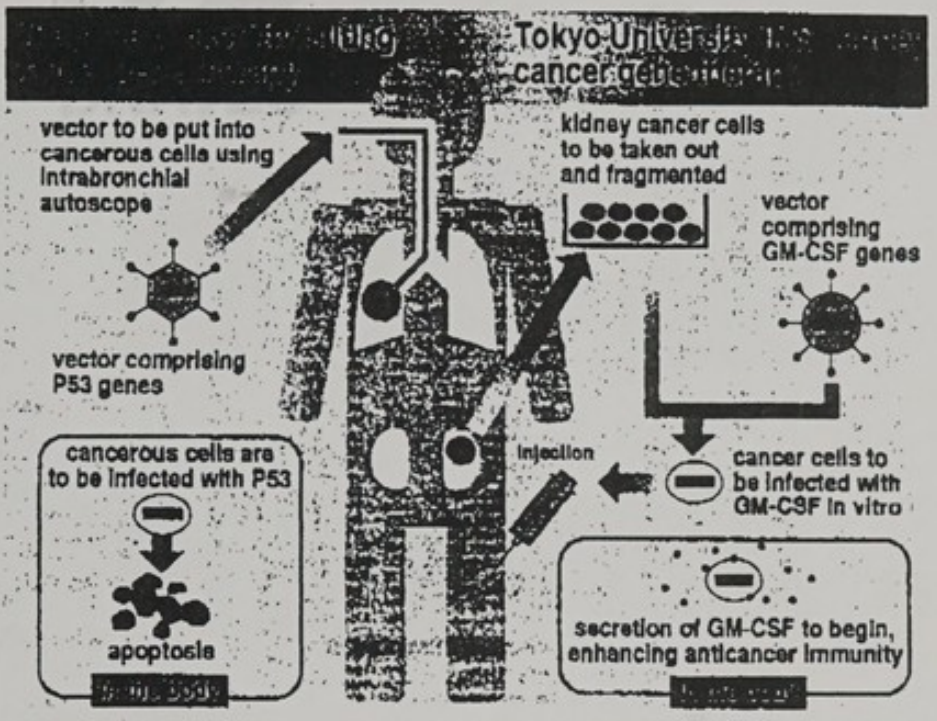
Pieces of cancerous cells such as lym- hocytes and marrow stem cells are then ken from the patient and "infected" with e viruses containing the genes. The rus-infected cells are then reinserted into e patient's body to allow the cancer- rbing genes to work.

In the tests planned by the Okayama niversity team, similar cancer-curbing nes, known as P53, will be used in the experimental treatment of lung cancer.

It is widely acknowledged that such genes are capable of suppressing the proliferation of cancerous cells. Many cancer patients are known to be deficient in these cancer-curbing genes.

P53 has attracted the attention of experts because of its ability to drive cancerous and other anomalous cells into "committing suicide," a phenomenon called apoptosis (referred to on this page on Dec. 7).

In the forthcoming tests, adenoviruses, which cause cold-like symptoms, will be used as the vector through which P53 will be inserted into the patient's cells.



The Okayama University team plans to directly insert the P53-modified adenoviruses into lung cancer cells by means of an intrabronchial autoscope—a device that records and magnifies movements in the bronchus. The team will also combine anticancer drugs with the adenovirus-made vector containing P53.

No precedent exists for this method of cancer treatment anywhere in the world, although similar tests have been conducted by the University of Texas in the United States. There, a combination of P53 and retroviruses, a viral species different from adenoviruses, was used. Six out of a total of nine patients who underwent the tests reportedly responded well to the treatment. In those cases, the growth of cancerous formations was either reduced or halted altogether.

The most common form of gene therapy for the treatment of cancer involves the removal of a piece of cancerous tissue and cancer-affected lymphatic corpuscles from the patient's body. They are then mixed with genes capable of producing substances that strengthen the body's ability to fend off cancerous cells, and are finally reinserted into the body.

With this procedure, it is hoped that the reintroduced cells will work as a form of vaccine. Before being returned to the patient's body, the cancerous cells are exposed to a large amount of radioactivity to deprive them of their reproductive power.

The IMS team will employ this method on a kidney cancer patient, using the gene that produces granulocytic macrophage-conducting system factor (GM-CSF), a substance that protects the body against infection and activates the human metabolism.

GM-CSF has the property of increasing the number of cells capable of producing antibodies to fight antigens. This in turn stimulates an immune response in the body, aided by granulocytes and macrophages. It can also augment an organism's ability to attack cancerous cells.

In the IMS tests, the GM-CSF genes will be put into a commonly used virus vector, which will then be incorporated into kidney cancer cells taken out of the patient.

After processing the cells with radioactivity to strip them of their ability to reproduce, they will be returned to the patient's body through an injection in the arm or leg.

It is expected that GM-CSF will then be produced in the patient's body to strengthen its immunity against cancer.

A similar method has already been employed in the United States (for kidney cancer) and the Netherlands (for skin cancer), and has led to a shrinkage of cancerous cells in some of the patients involved.

Prof. Shigetaka Asano of IMS says: "Although we cannot hope for a complete cure for cancer through this method, it can prove effective in reducing cancer cells that have spread from an original base to other parts of the body."

In the United States and Europe, the gene therapy has been conducted on more than 1,000 patients since 1990, including those with hereditary diseases and AIDS.

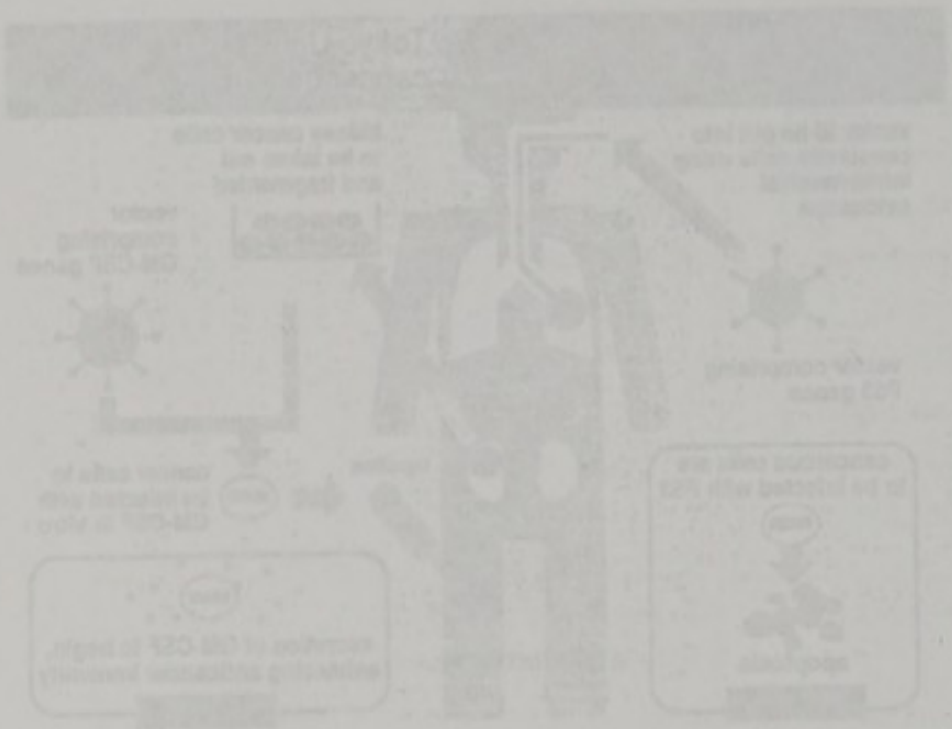
In the field of cancer treatment, this therapy was first used to treat a case of melanoma (a form of skin cancer) in the United States in 1991. It was subsequently used in six European countries for various cancers, including cancer of the colon, breast, brain and prostate as well as leukemia.

Nevertheless, gene therapy is still at the experimental stage.

In Japan, gene therapy has only been used once in the case of a boy treated for immune deficiency symptoms at Hokkaido University. Much remains to be done before the method can be comprehensively employed, experts say.

However, Prof. Keiya Ozawa of Jichi Medical School points out: "Gene therapy has the potential to provide an unconventional, yet promising perspective on cancer treatment."

Gene therapy, when combined with progress in uncovering the nature of cancer, has the potential to become one of the most effective developments ever in the treatment of the disease.



Attachment 2

DNAVEC

株式会社ディナベック研究所
DNAVEC Research Inc.
〒305 茨城県つくば市観音台一丁目25番11号
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Tsukuba-shi,ibaraki 305,Japan
Tel +81-298-38-0540
Fax +81-298-39-1123
Homepage:http://www.dnavec.co.jp

DNAVEC, where Creative Intelligen
are Integrated, is Provided with Ide

創造的な頭脳と最先端技術を結集。ここに理想の研究・開発システム

■研究の基本方針

遺伝子治療の基盤技術であるベクターの開発をその主要な任務とし、また、独立した特許で保護された技術の提供をめざすため、新しい骨格のベクターを検討します。

プロジェクトの前期においては特許で守られた新規なコア技術を確立し、後期においては実用的なベクターを仕上げ、治療への応用研究とベクターの生産技術の開発を手がけます。

●

■研究テーマ

●新規ベクターの構築：安全性を考慮した高性能の新しいウイルスベクターと非ウイルスベクターを開発する。

●治療用遺伝子の細胞内存在状態の制御技術の開発：安全性を充分に確保しつつ、遺伝子発現の安定化と時間制御を可能とする技術を開発し、ベクターに搭載する。

●開発したベクターの標的細胞への導入法の検討や、癌の治療系を検討する。

●

Basic Research Principles

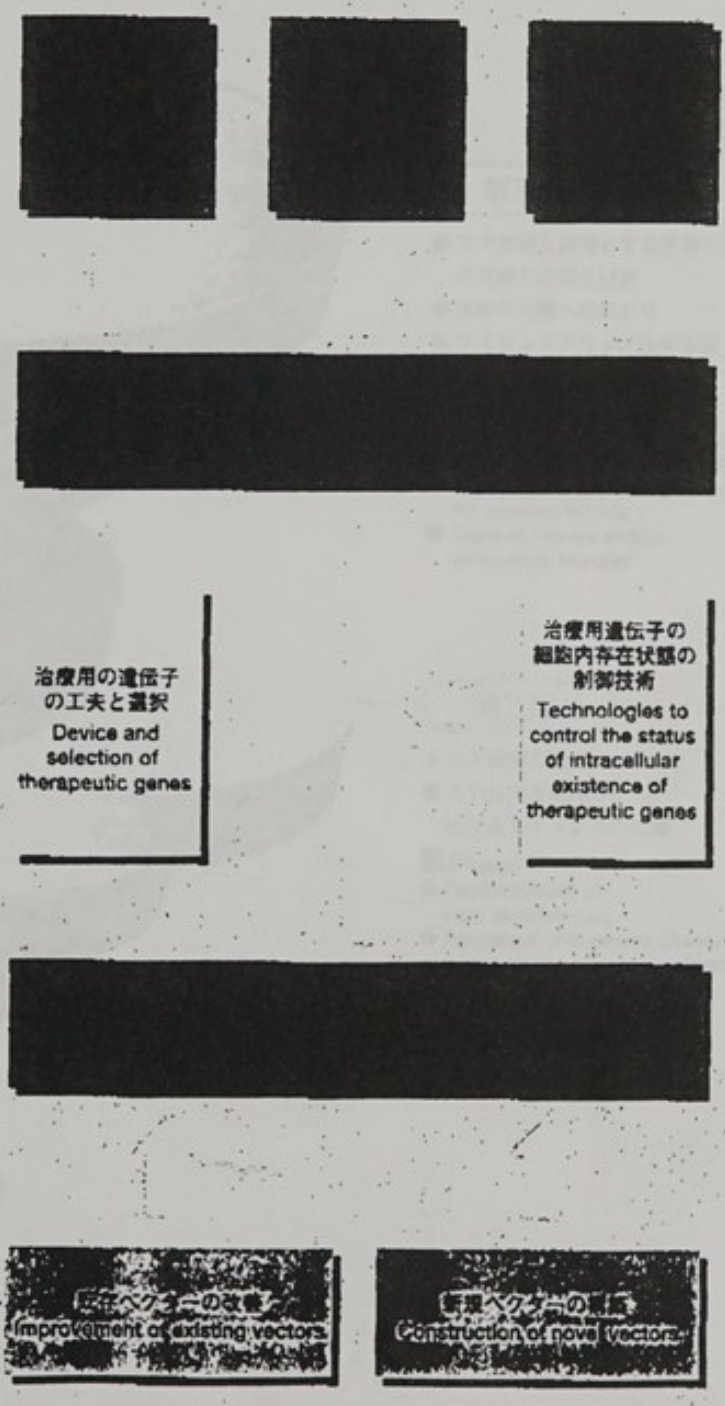
The primary mission of DNAVEC is to develop the vectors of new types and skeletons protected by potent and independent patents.

DNAVEC will establish the original core technologies in its early phase and will complete the practical vectors and proceed to the researches on clinical application and the development of vector manufacturing technologies in its late phase.

●

Research themes

- Construction of novel vectors: DNAVEC will develop novel viral and non-viral vectors while considering the safety to a satisfactory level.
- Development of technologies which control the intracellular localization of therapeutic genes: DNAVEC will develop technologies which enable stabilization and chronological control of gene expression while ensuring the safety to a satisfactory level.
- DNAVEC will also examine the methods to transfer the developed vectors into the target cells and investigate the new therapeutic systems for cancer.

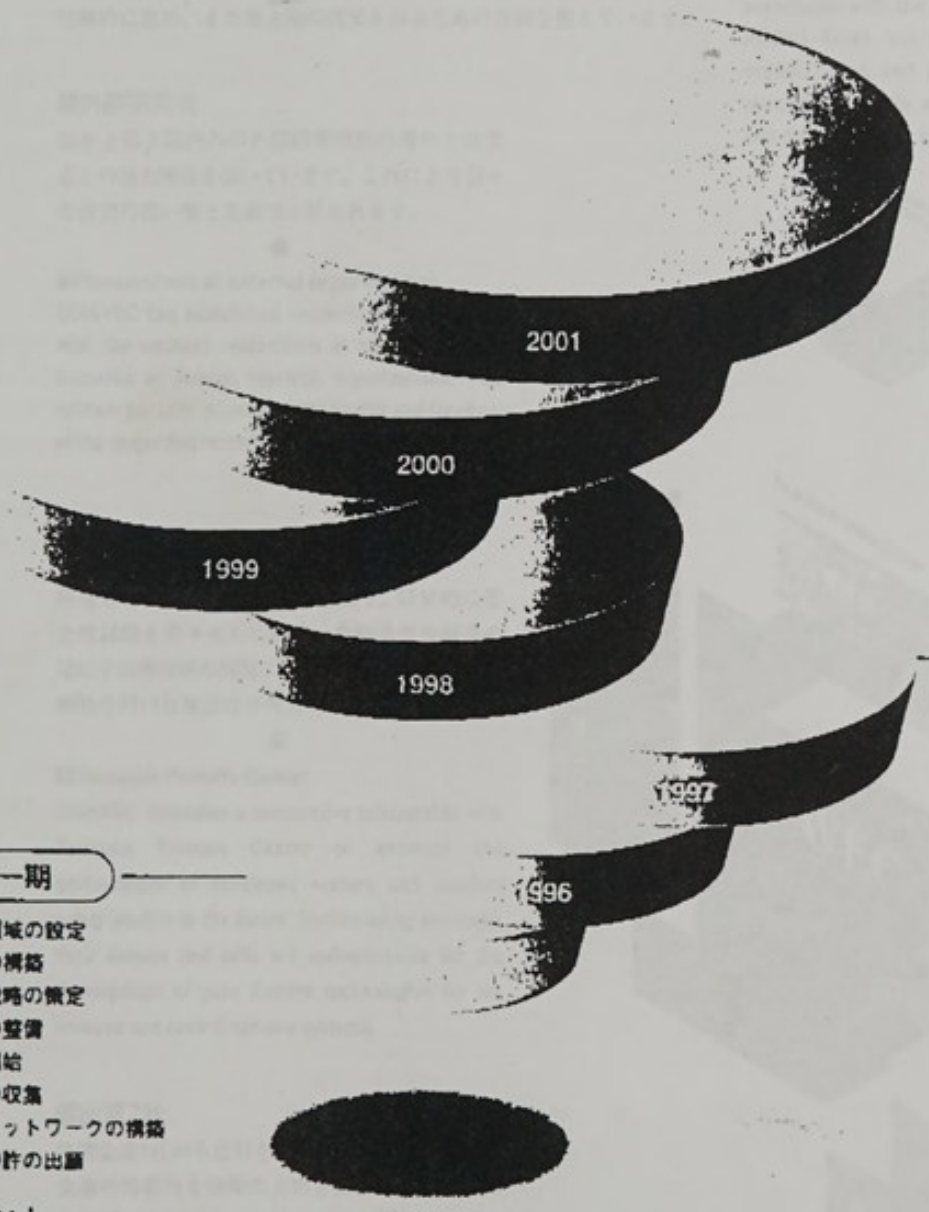


e and State-of-the-Art Technologies
l Researches and Development Systems

である。

■経営方針に基づく7年間の全体計画

■Entire schedule for a 7-year period based on the business policies of DNAVEC



第三期

- コア技術を基礎とする実用ベクターの構築と応用化研究
- 技術の外部への広がり
- ライセンスアウト／技術移転

■Phase III

- Construction of the practical vectors based on the core technologies and research for application thereof
- Expansion of technologies towards the external worlds
- Grant of license and/or technology transfer

第二期

- コア技術の確立
- コア技術を活用したビジネスチャンスの形成

■Phase II

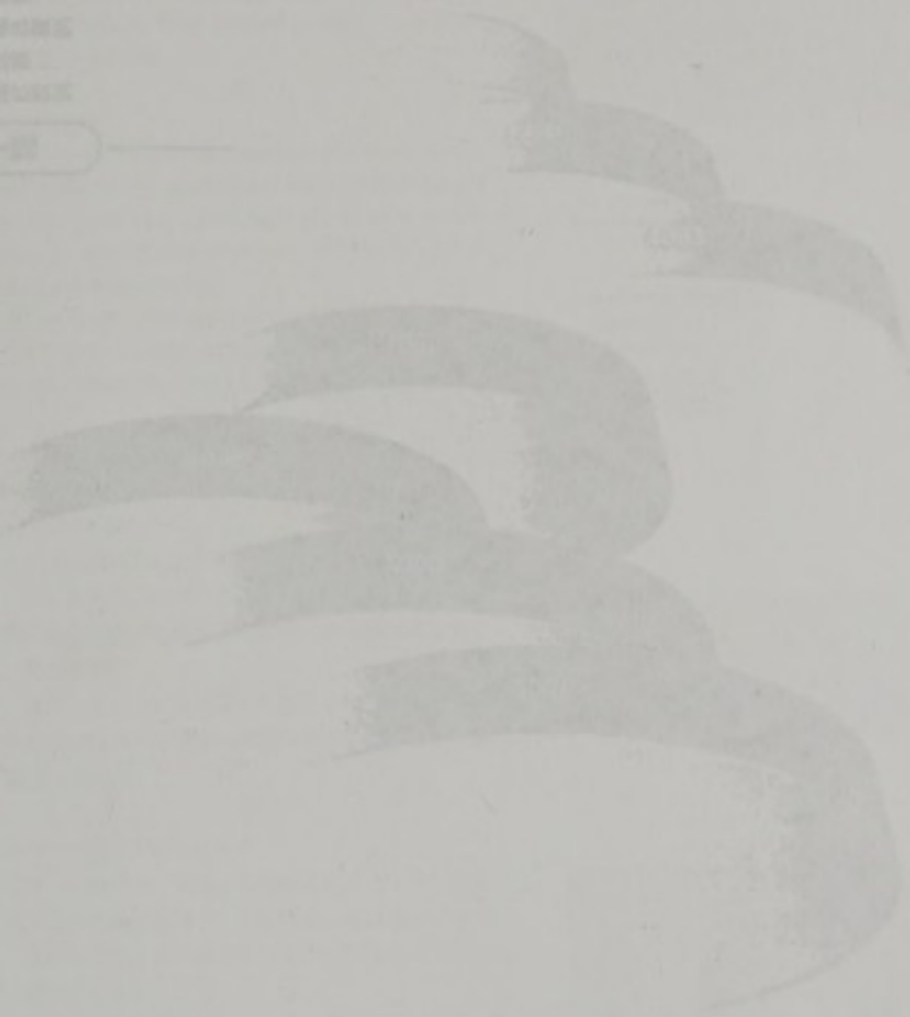
- Establishment of core technologies
- Formation of business chance based on the core technologies

第一期

- 研究領域の設定
- 概念の構築
- 研究戦略の策定
- 施設の整備
- 研究開始
- 材料の収集
- 研究ネットワークの構築
- 基本特許の出願

■Phase I

- Determination of research fields
- Construction of concepts
- Establishment of research strategies
- Arrangement of facilities
- Onset of research activities
- Collection of materials
- Construction of research network
- Filing of basic patent applications



DNAVEC's Most Advanced Research Activities are Sustained by a Solid Network

充実のネットワーク、最新の設備群が、先端的な研究活動を支える。

当研究所は、医学・薬学界および関連領域との連係はもちろん、先鋭の研究機関・研究者との連携など、全世界に広がる緊密なネットワークを構築。また研究設備・施設の充実を図り、先端的な研究をより効率的に進め、また最大限の成果を得るための体制を整えています。

To more efficiently encourage the forefront researches and maximally utilize the achievements therefrom, DNAVEC has established a worldwide network by means of which it not only maintains an efficient association with the medical and pharmaceutical worlds as well as their related fields but also keeps in close contact with the research organizations and researchers at the forefront of their respective speciality, collects and comprehends up-to-date scientific information, and develops other activities.

■外部研究者

20を上回る国内外の外部研究機関の優れた研究者との協力関係を築いています。これにより個々の研究の高い質と先端性が保たれます。

●

■Researchers at external organizations

DNAVEC has established cooperative relationships with the eminent researchers at not less than 20 domestic or foreign research organizations. This relation partially maintains high quality and forefront of the respective research at DNAVEC.

■筑波霊長類センター

開発したベクターの性能の検討や、将来的に安全性試験を行うために提携。免疫系や中枢系の遺伝子治療技術の開発には、サルの個体や組織、細胞を用いた検討は不可欠です。

●

■Tsukuba Primate Center

DNAVEC maintains a cooperative relationship with Tsukuba Primate Center to examine the performance of developed vectors and conduct safety studies in the future. Studies using monkeys, their tissues and cells are indispensable for the development of gene therapy technologies for the immune and central nervous systems.

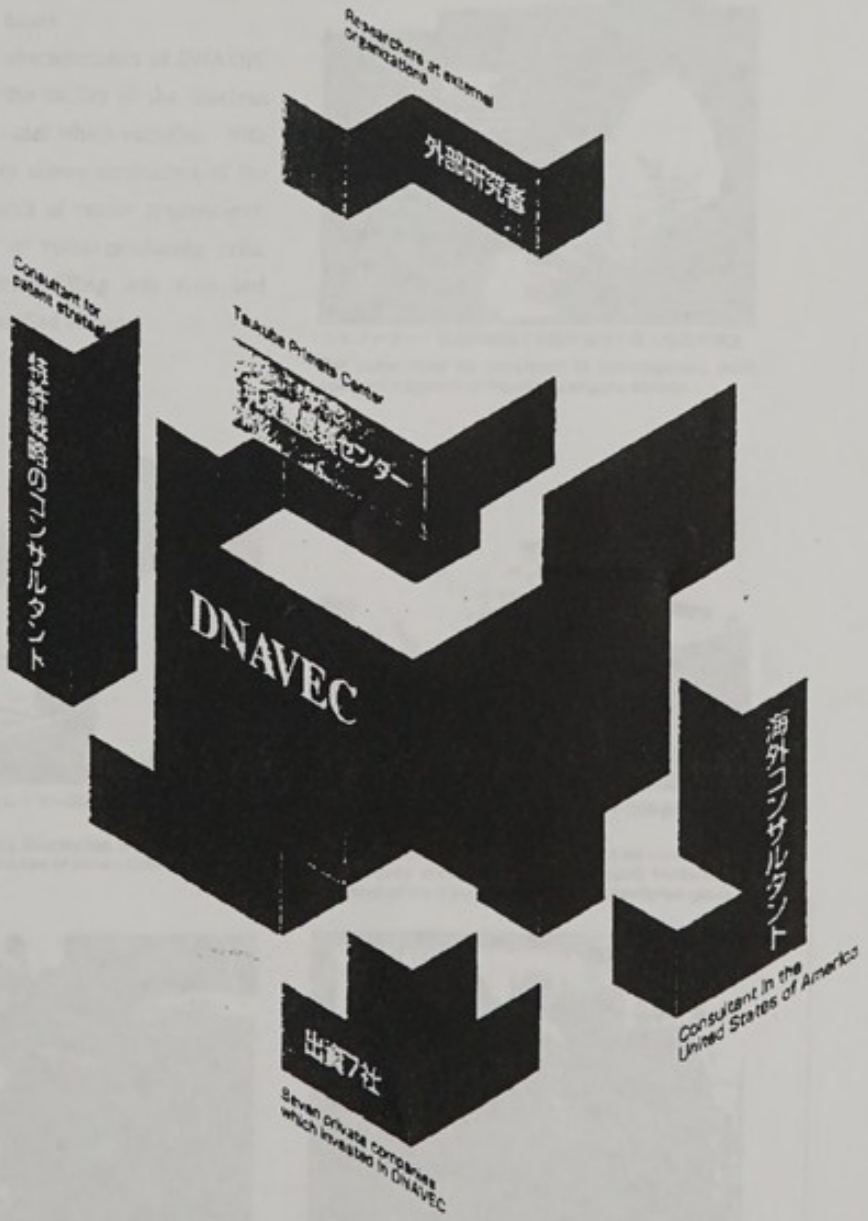
■出資7社

民間企業7社から出資を受けているほか、各々の企業の特徴的な技術の支援を受け、創造的な研究活動に役立てています。

●

■Seven private companies investing in DNAVEC

DNAVEC has received investment from seven private companies and utilizes, for its creative research activities, the technical supports which are characteristic of and provided by the respective company



ch Activities
and State-of-the-Art Facilities

■研究設備

当研究所の最新鋭設備の数々。将来、オリジナルのベクター骨格を臨床投与可能な製剤に仕上げるための、応用技術に関する基礎的な検討ができるようになっています。

また、大きな特徴の一つは、注射用医薬品生産の実施基準（cGMP）に対応した「研究用バイオクリーンルーム施設」を利用できること。この施設を利用して、ベクター生産細胞の培養、精製、バイアル分注充填および凍結乾燥までのベクター製剤の基礎的研究を一貫して実施することが可能です。

●

The most up-to-date facilities at DNAVEC are shown in the photographs on this page. DNAVEC is capable of examining preclinical studies on applied technologies in order to finish an original vector skeleton in a clinically administrable preparation in the future.

One of the major characteristics of DNAVEC is availability of "the facility of the bioclean room for research use" which complies with cGMP. This facility allows conduction of the entire basic research of vector preparations, including culture of vector-producing cells, purification, separate filling into vials and lyophylization of purified vectors.

■特許戦略のコンサルタント

強力な知的財産権で守られた技術を確立することが、当研究所の使命です。その実現のため優秀な特許弁理士と契約しており、効果的な特許の作成の指導のほか、研究戦略にもアドバイスを受けています。

●

■Consultant for patent strategies

One of the missions of DNAVEC is to establish the technologies which are protected by potent intellectual property rights. DNAVEC has executed an agreement with an eminent patent attorney to achieve its mission and receives advice on research strategy in addition to the guidance for the effective preparation of a patent dossier.

■海外コンサルタント

米国における遺伝子治療の推移を正確に把握し、また技術的アドバイスを受け、かつ米国での調査活動を行うため、米国内のコンサルタント会社と契約しています。

●

■Consultant in the United States of America

DNAVEC has executed an agreement with a consultant company in the U.S. to accurately comprehend the research course of gene therapy in the U.S., to be advised for technical issues, and to conduct survey activities in the U.S.

セルソーター：造血幹細胞の分離や遺伝子導入効果の判定

Cell sorter:Used for separation of hematopoietic stem cells and judgment of the effects of gene transfer

細胞内注入装置付共焦点レーザー顕微鏡：導入遺伝子の細胞内動態の観察

Confocal Laser Scanning Microscope with a intracellular injector: Used for observation of intracellular kinetics of a transferred genes

凍結組織切片作製装置：開発したベクターの動物体内分布や遺伝子治療効果の判定

Frozen tissue microtome:Used for observation of the animal body distribution of a developed vectors and judgment of the therapeutic effects of transferred genes

自動塩基配列解析装置：ベクターの構造の確認やクローン化した遺伝子の構造の解析

Automatic DNA sequencer :Used for identification of the structures of a vectors and analysis of the structures of cloned genes

GMP対応施設：臨床試験用のベクターの生産が可能な施設

cGMP-complying facility:Capable of producing the vectors for clinical trials

DNAVEC was Established as Part of National Projects.

ディナベック研究所は、国家プロジェクトとして創立された企業である。

厚生省所管の特殊法人である医薬品副作用被害救済・研究振興調査機構[略称:医薬品機構]が積極的に推進する、先端的医療技術の研究開発振興プログラム。1988年に始まり、10以上のプロジェクトを発足しています。

当研究所は、12番目に誕生した7年間のプロジェクトとして1995年3月に発足。過半数出資の医薬品機構を中心に、民間からは、協和発酵工業、三共、塩野義製薬、住友製薬、田辺製薬、久光製薬、山之内製薬の7社が参画、資本総額は45億円前後になる見通しです。また、民間企業は資本投下のほか、研究員を当研究所に派遣するなど、意欲的な取り組みを見せています。

●

当研究所社長には久光製薬社長の中富博隆、取締役には民間7社の代表が就任。また取締役研究所長には協和発酵工業の東京研究所の長谷川潤が就任し、研究テーマ別に複数の研究室を設定するなど、創造的な研究体制を整えています。

●

社外組織としては、研究遂行上のアドバイザーとして10名前後からなる研究顧問を迎えています。また出資8法人の連絡組織として、各法人の代表からなる運営委員会が組織されています。

DNAVEC was established in March, 1995 as the twelfth project of 7-year duration, in the research and development promoting programs, initiated in 1988 and encouraged by The Organization for Drug ADR Relief, R&D Promotion and Product Review (The Drug Organization), under the control of the Ministry of Health and Welfare of Japan. The Drug Organization has invested in DNAVEC to cover more than half of its capital, while seven private companies listed in the DATA PROFILE below have invested in DNAVEC to cover the rest of the capital; DNAVEC prospects to have the total capital of approximately 4.5 billion yen. These private companies have shown active involvement in DNAVEC through dispatch of their researchers.

●

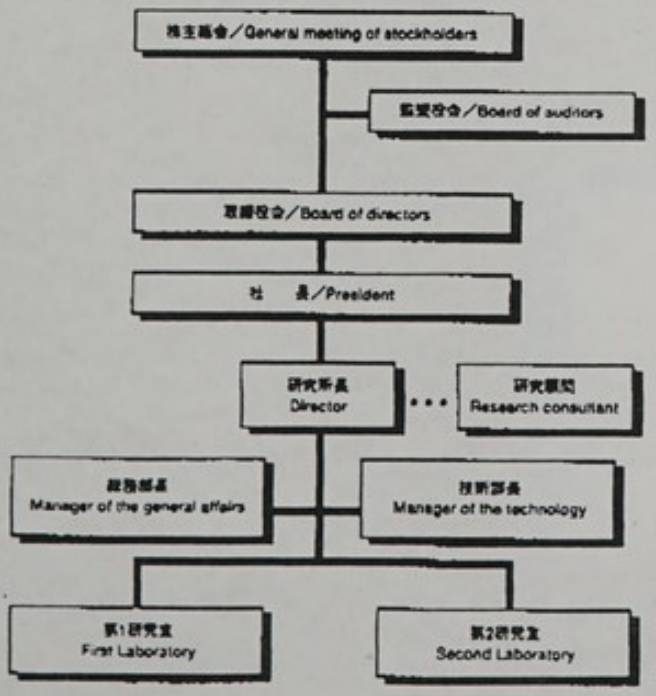
Mr. Hirotaka Nakatomi, President of Hisamitsu Pharmaceutical Co., Inc., and Dr. Mamoru Hasegawa at Tokyo Research Laboratories of Kyowa Hakko Kogyo Co., Ltd. have assumed the posts of president of DNAVEC, and Directer of research institute, respectively.

●

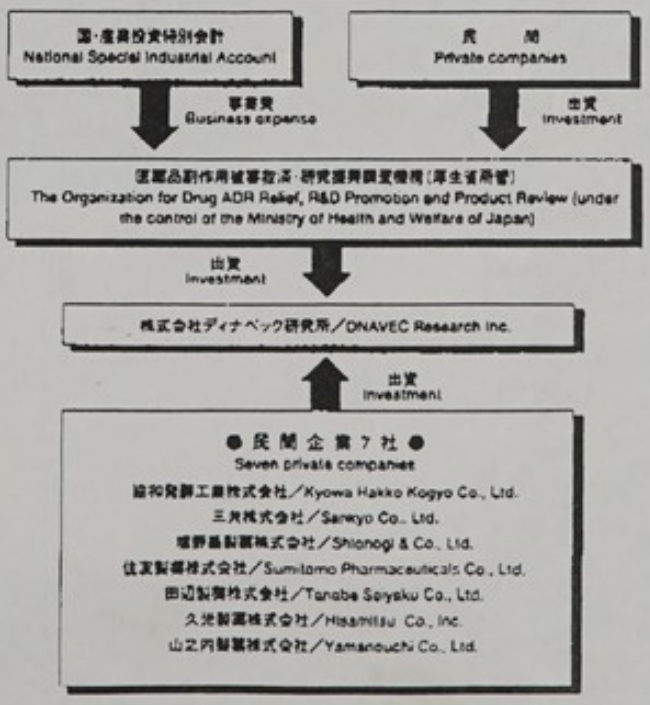
DNAVEC has welcomed about 10 research advisors and has organized a steering committee which is comprised of the representatives from each of 8 investing entities; the committee functions as a liaison committee among the entities involved.

DATA PROFILE

組織図
Diagram of organization



仕組み図
Diagram of Investment



DNAVEC was Established as Part of National Projects.