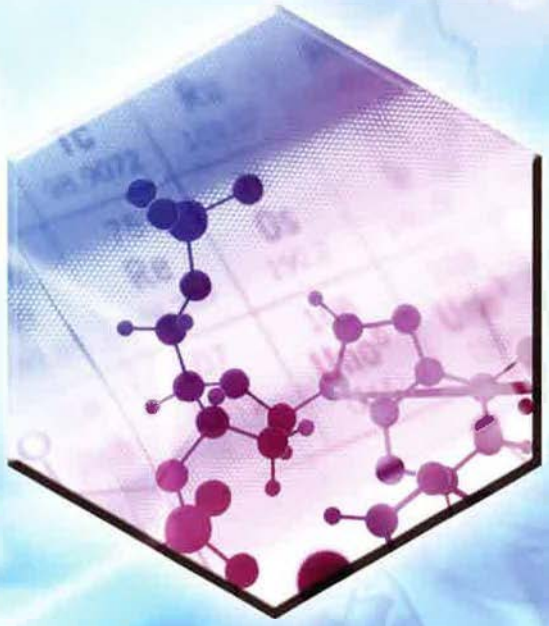
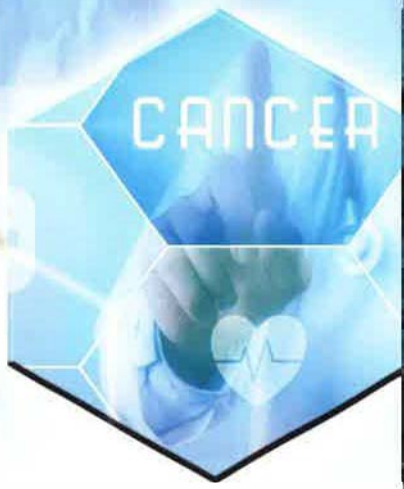
3rd generation cancer immunotherapy
based on new concept

iNKT Cancer Therapy





Supervised by Dr. Masaru Taniguchi

iNKT Cancer Therapy

Aiming to overcome the major problems in cancer therapy up to now of progression, recurrence and metastasis, iNKT Cancer Therapy, a 3rd generation cancer immunotherapy based on a new concept has been developed.

iNKT Cancer Therapy activates patient's own iNKT cells and prevents cancer progression, recurrence and metastasis by injecting a customized cancer vaccine which was made from patient's peripheral blood cells. There are five features characterized from current cancer immunotherapies.

iNKT cells

iNKT cells (invariant natural killer T cells) are a unique type of immune cell with a single invariant antigen receptor which were discovered by Masaru Taniguchi (Currently Senior Advisor, Riken Center for Integrative Medical Sciences) et al. in 1986. They are known as the 4th type of lymphocyte after T cells, B cells and NK cells.

iNKT cells are a unique type of immune cell because through an adjuvant effect mediated by their-interferon gamma production, they can activate NK cells in the innate immune system as well as helper, killer and gamma delta T cells in the acquired immune system.

Masaru Taniguchi M.D., Ph.D.

Senior Advisor, Riken Center for Integrative Medical Sciences
Group Director, Laboratory for Immune Regulation, Riken Center for Integrative Medical Sciences

【Short profile】
1974 Graduated from Graduate School of Medicine Chiba University
1980 Professor, School of Medicine, Chiba University
1996 - 2000 Dean, School of Medicine, Chiba University
1997 - 1998 President, Japanese Society for Immunology
2001 Founding Director, Riken Research Center for Allergy and Immunology
2005 - 2008 Member, Science Council of Japan
2013 - Current positions

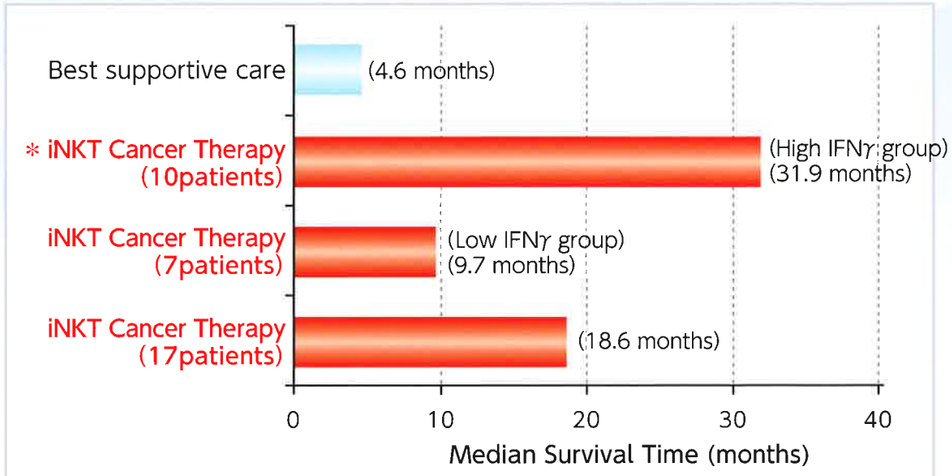
Dr. Taniguchi discovered an invariant Vα14 antigen receptor of iNKT cells in 1986 and iNKT cells that expanded clonally under physiological conditions in 1990. The latter was selected for publication as a Pillars of Immunology by the American Association of Immunologists, in recognition of its contribution to the advancement of immunology. In 1997, he discovered that an iNKT cell ligand was a glycolipid, and also developed an iNKT cell-deficient mouse. He has published over 400 papers in Nature, Science and other journals.

Clinical data in iNKT Cancer Therapy

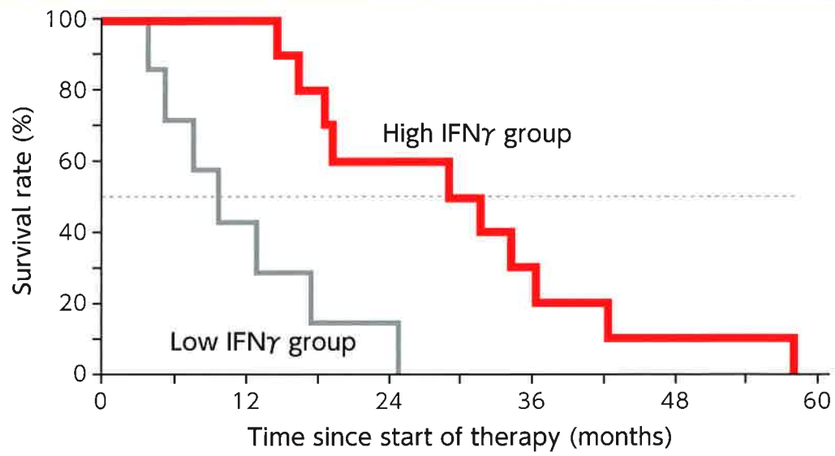
Japan's Ministry of Health Labour and Welfare has approved the clinical research of Chiba University and the National Hospital Organization using cultured patient peripheral blood cells(dendritic cells) pulsed with α-galactosylceramide, an iNKT ligand, as Advanced Medical Care B.

iNKT Cancer Therapy

- Phase I-II clinical studies in advanced non-small lung cancer patients (Stage IIIB, IV, recurrent).
- iNKT Cancer Therapy using cultured patient peripheral blood cells (dendritic cells) pulsed with α-galactosylceramide.
- Median survival time for all patients in treated group was 18.6 months, **around 4 times** longer than that for best supportive care.
- Among 17 patients in the treatment group, in 10 with high IFNγ production, median survival time was 31.9 months, **around 6.9 times** longer than that for best supportive care, even when they received the initial treatment only.



Prepared from Motohashi S, et al. J Immunol, 182:2492, 2009



Prepared from Motohashi S, et al. J Immunol, 182:2492, 2009

Approved as Advanced Medical Care B
2011: Advanced non-small lung cancer, 2014 Stage IIA – IIIA postoperative lung cancer

Features of iNKT Cancer Therapy

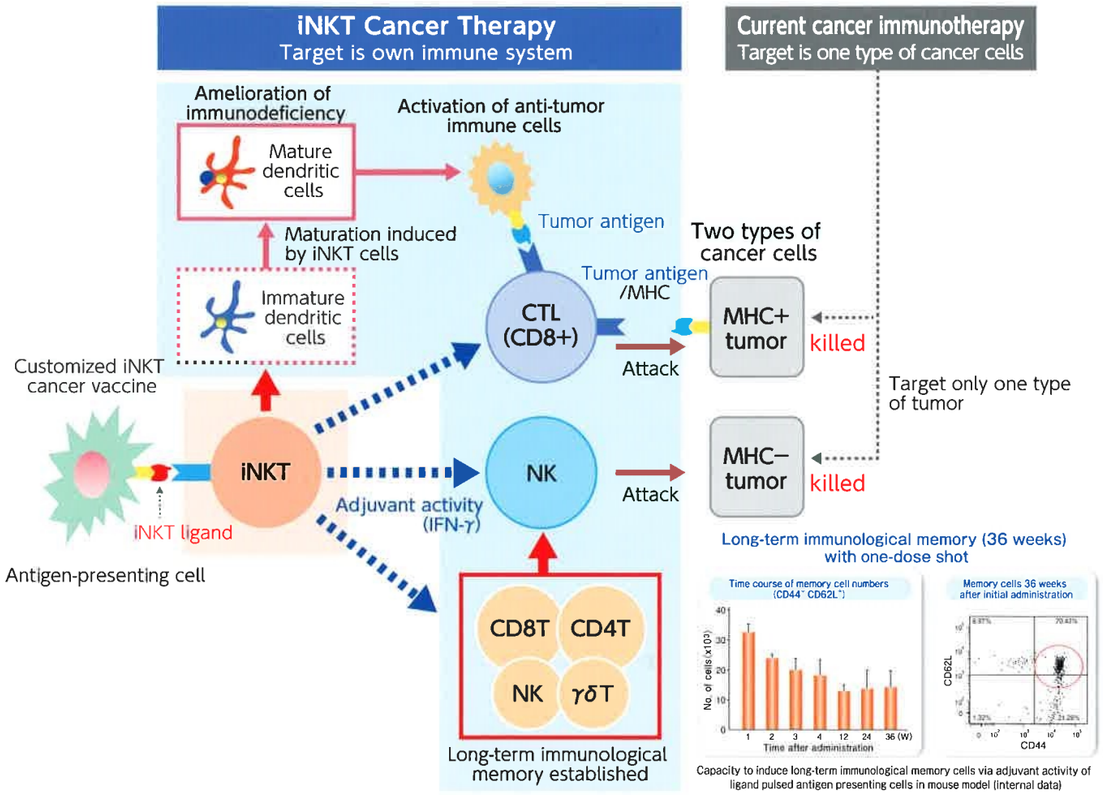
Feature 1

iNKT Cancer Therapy does not target the cancer cells themselves.
It activates own immune system through an adjuvant activity in the patient's body that has been weakened by cancer. It can thus be expected to be effective against any type of cancer.

Feature 2

A strong antitumor effect is achieved by iNKT cells via their adjuvant activity that activates other anti-tumor effector cells. Some of the activated immune cells (central memory, effector memory and other memory cells) remain in the body to provide long-term immunological memory responses.

Mechanism of iNKT Cancer Therapy : Anti-tumor mechanism via adjuvant activity



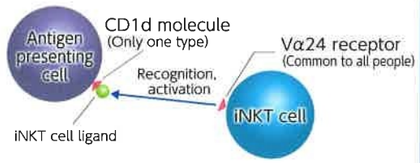
Capacity to induce long-term immunological memory cells via adjuvant activity of ligand pulsed antigen presenting cells in mouse model (internal data)

Feature 3

There are two types of cancer cells, one that constantly expresses tumor antigens and one that does not express tumor antigens, and they are present together in any type of cancers. If both cannot be eliminated at the same time there will be recurrence or metastasis. While current cancer immunotherapies target one of these types of cancer cells, iNKT cancer therapy eliminates both through an adjuvant activity. We can thus expect it to be effective in suppressing progression, recurrence and metastasis of tumor. However, as its tumor regression effect is not very strong, the tumor will stay the same size.

Feature 4

The iNKT cell antigen receptor is common to all people. As iNKT cells are activated by the iNKT ligand presented by a monomorphic CD1d molecule, efficacy can be expected in any patient regardless of HLA type.

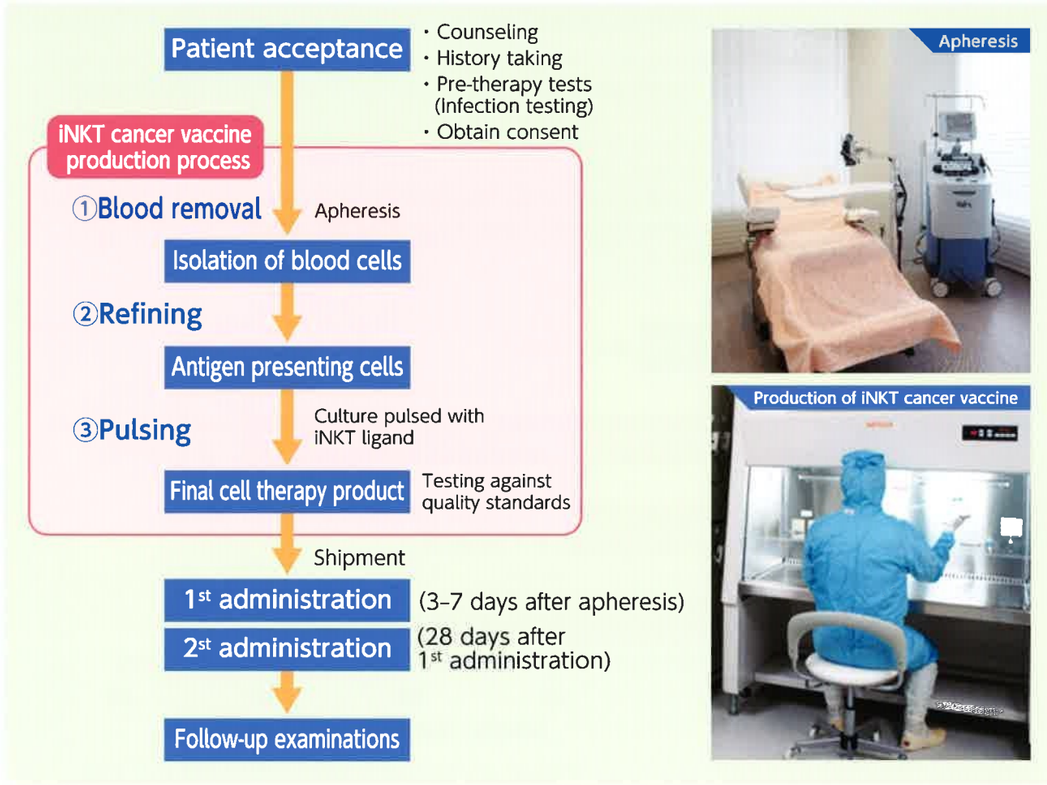


Feature 5

Only iNKT cells can interact with immature dendritic cells to induce their maturation, resulting in overcoming immune-deficiencies in tumor patents.

Flow of iNKT Cancer Therapy

The patient's peripheral blood mononuclear cells (PBMCs) are collected by apheresis. The isolated and refined antigen presenting cells are then pulsed with an iNKT ligand that specifically activates iNKT cells, and administered to the patient by infusion. This activates the iNKT cells in the body to mediate adjuvant activity. (Patent for manufacture of specific cell processed product jointly applied for with RIKEN)



Cautions in iNKT Cancer Therapy

(iNKT Cancer Therapy is not applied to the persons who have the following disease status)

- Serious complication or disease other than cancer
- Diagnosed with autoimmune disease
- Infected previously with hepatitis B virus (HBs antigen positive or HBs antibody positive)
- Infected previously with hepatitis C virus (HCV antibody positive) Note 1
- Infected with human immunodeficiency virus (HIV antibody positive) Note 2
- Infected with human T cell leukemia virus (HTLV-1 antibody positive) Note 2
- History of albumin hypersensitivity
- Woman who is pregnant or possibly pregnant or who is breastfeeding
- Previous allo-transplantation of organ and hematopoietic stem cells
- Apheresis not possible due to body condition

Note 1 : Therapy possible in case of newly testing virus-negative in genetic testing
Note 2 : Therapy possible if production of cell product determined possible at cell processing facility