Clinical Application of New Nanoparticle "Cholesterol Pullulan (CHP)" for Cancer Vaccination

Expanded application for vaccine therapy of cancer by encapsulating cancer-specific antigens

Phase I clinical study led by physicians of Mie University in progress

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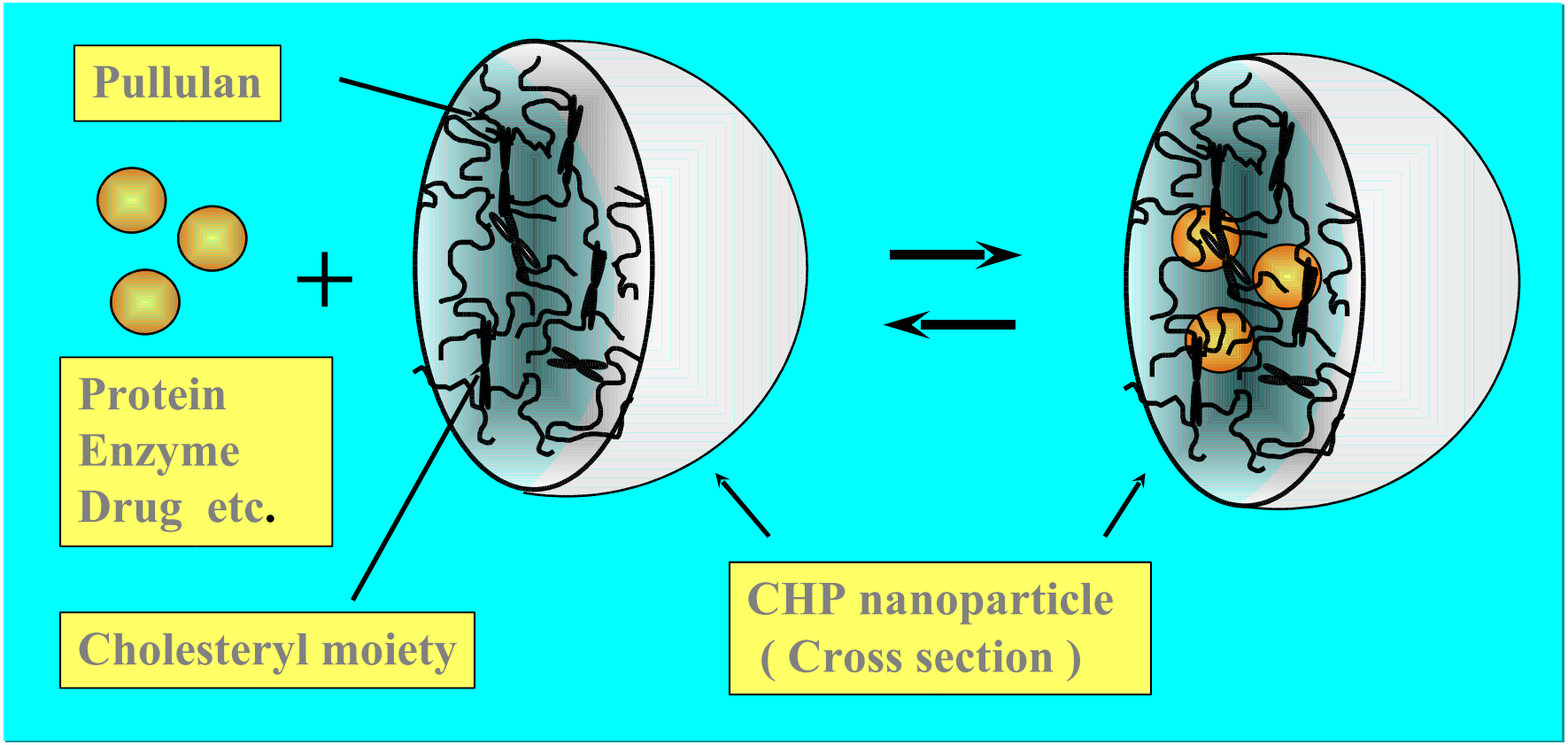
Cholesterol Pullulan（CHP） Nanoparticle

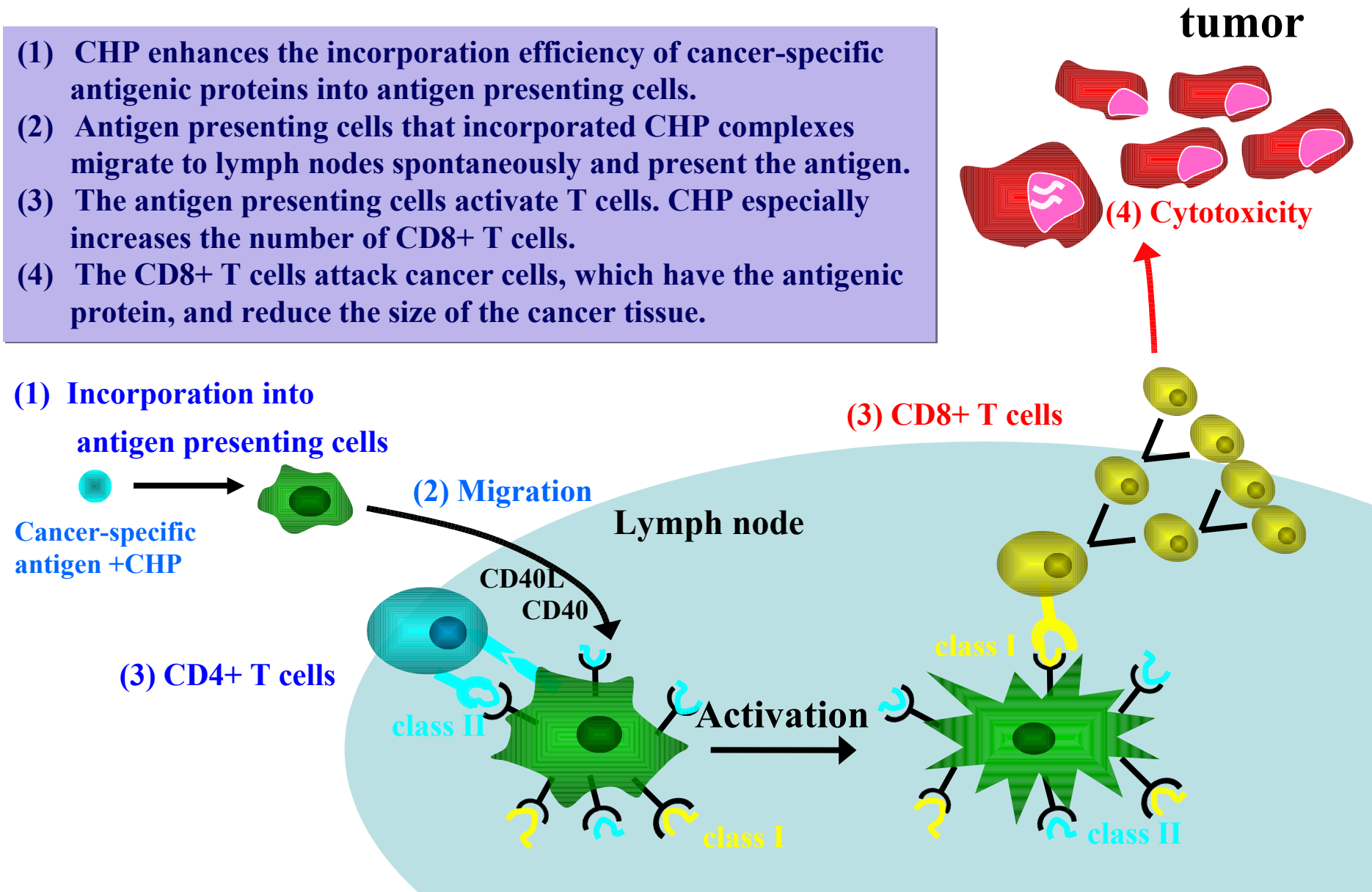
Macromolecular Complexation between Protein and the Self-Assembled Nanoparticle of CHP



K. Akiyoshi and J. Sunamoto, *Supramolecular Science*. **3**:157-163(1996)

Effects of CHP on Immunocytes

(1) CHP enhances the incorporation efficiency of cancer-specific antigenic proteins into antigen presenting cells.
(2) Antigen presenting cells that incorporated CHP complexes migrate to lymph nodes spontaneously and present the antigen.
(3) The antigen presenting cells activate T cells. CHP especially increases the number of CD8+ T cells.
(4) The CD8+ T cells attack cancer cells, which have the antigenic protein, and reduce the size of the cancer tissue.



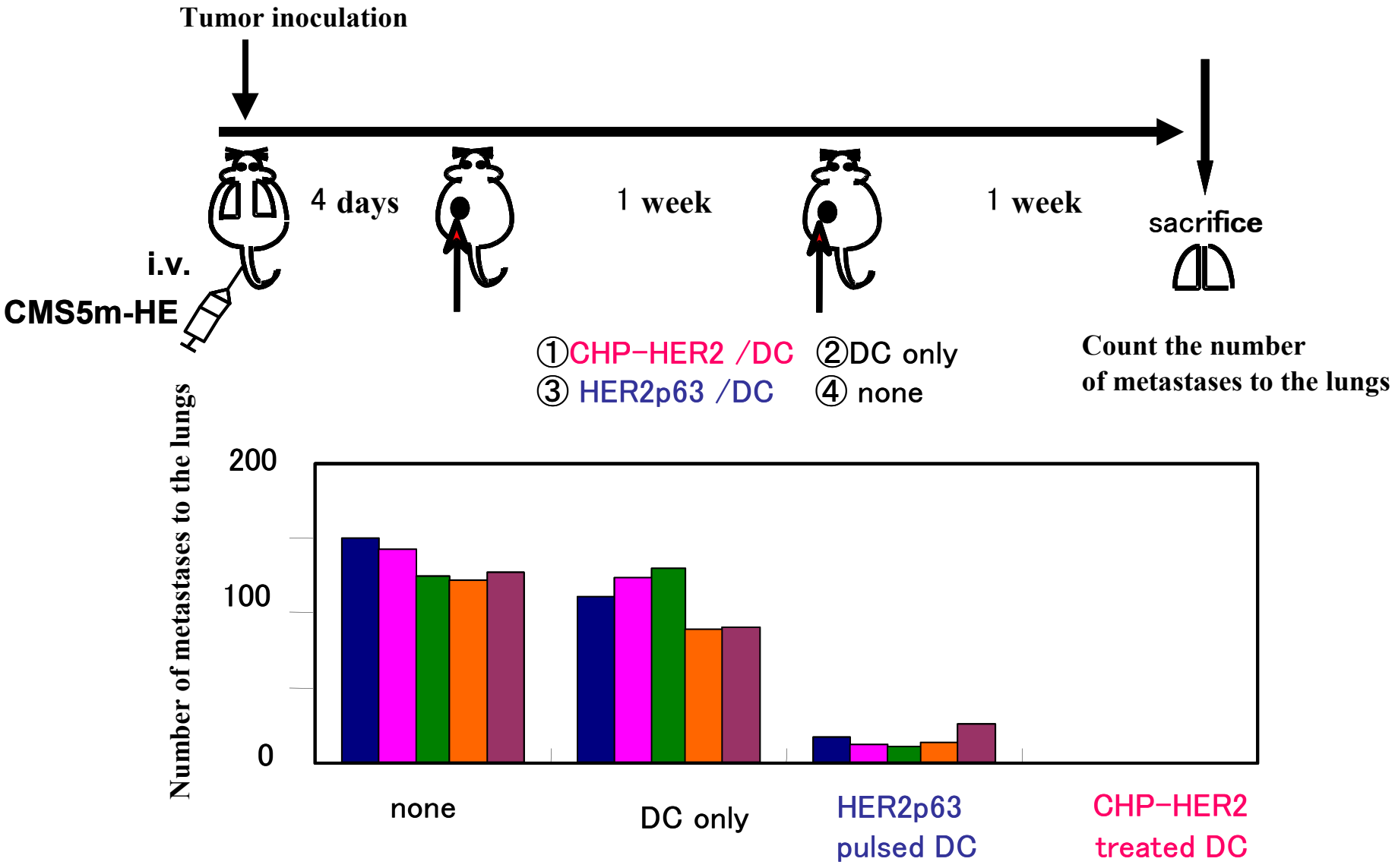
Clinical Study using CHP-HER2 by the Group of Prof. Shiku of the Department of Medicine, Mie University

＊ Pre-clinical studies

- **CHP-(146Her2) complexes were used.**
- **Curing of tumor was studied using CHP-(146Her2) immunized mice.**
  CHP-HER2 complexes perfectly suppressed the metastasis of cancer cells to the lungs（Fig.1)

Fig.1

Tumor Curing Experiment of mice using CHP-HER2 Immunization in comparison with others



Clinical Study using CHP-HER2 by the Group of Prof. Shiku of the Department of Medicine, Mie University

* Phase I clinical Study led by physicians

- **CHP-(146Her2) complexes were used.**
- **Safety:**

  Test conditions: 300 μg of CHP-Her2 complexes was hypodermically injected at intervals of two weeks.

  Results: The safety of CHP-Her2 complexes was confirmed.
- **Antibody Titer:**

  The antibody titers against 146Her2 in the blood of the subjects were measured using the ELISA method, and rises in antibody titers was confirmed (Fig. 2).
- **Antibody expression:**

  The presence of the antibody against 146Her2 in the blood was confirmed using the Western blotting method (Fig. 3).
- **Activation of CD8+ T cells:**

  The number of CD8+ T cells was confirmed to have increased as well as CD4+ T cells in the vaccinated subjects by flow cytometry (Fig. 4).

Fig. 2 Appearance of antibodies reactive with 146Her2 recombinant protein after vaccination with CHP-Her2 (ELISA)

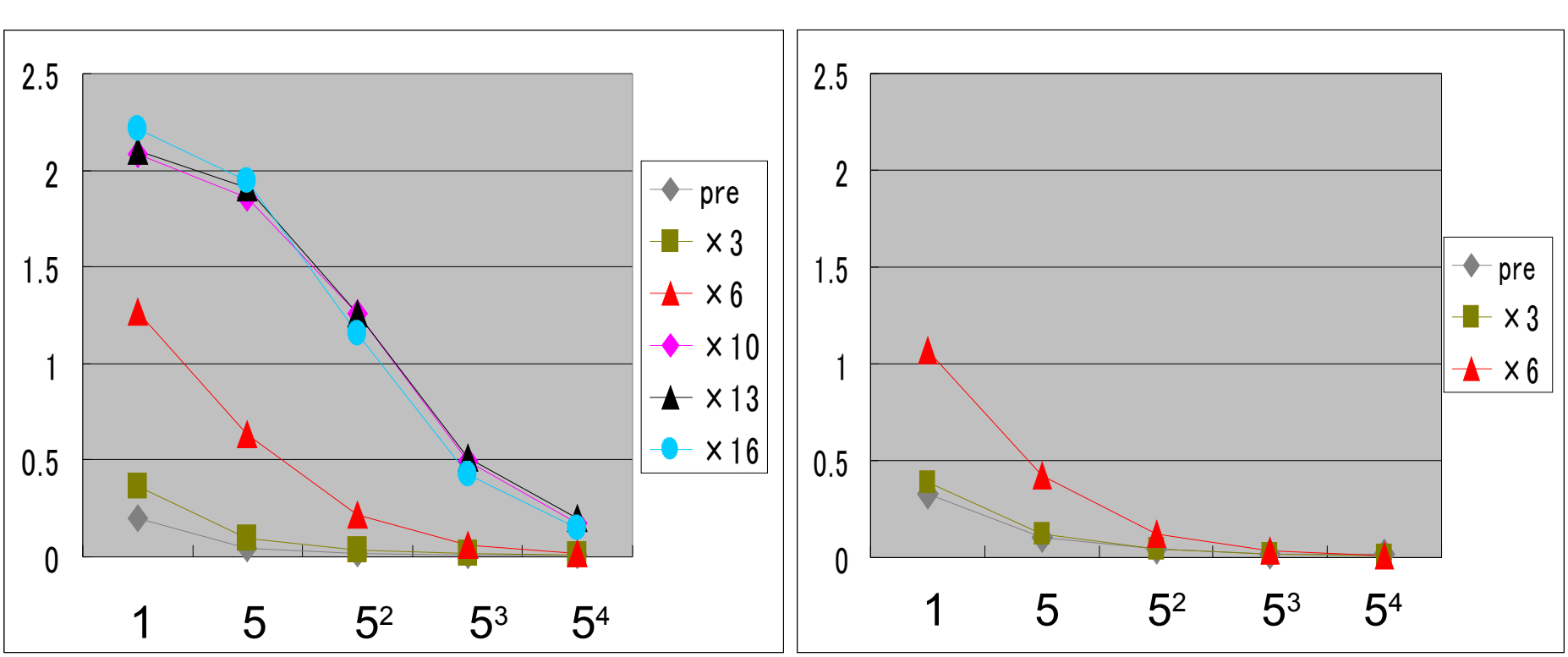
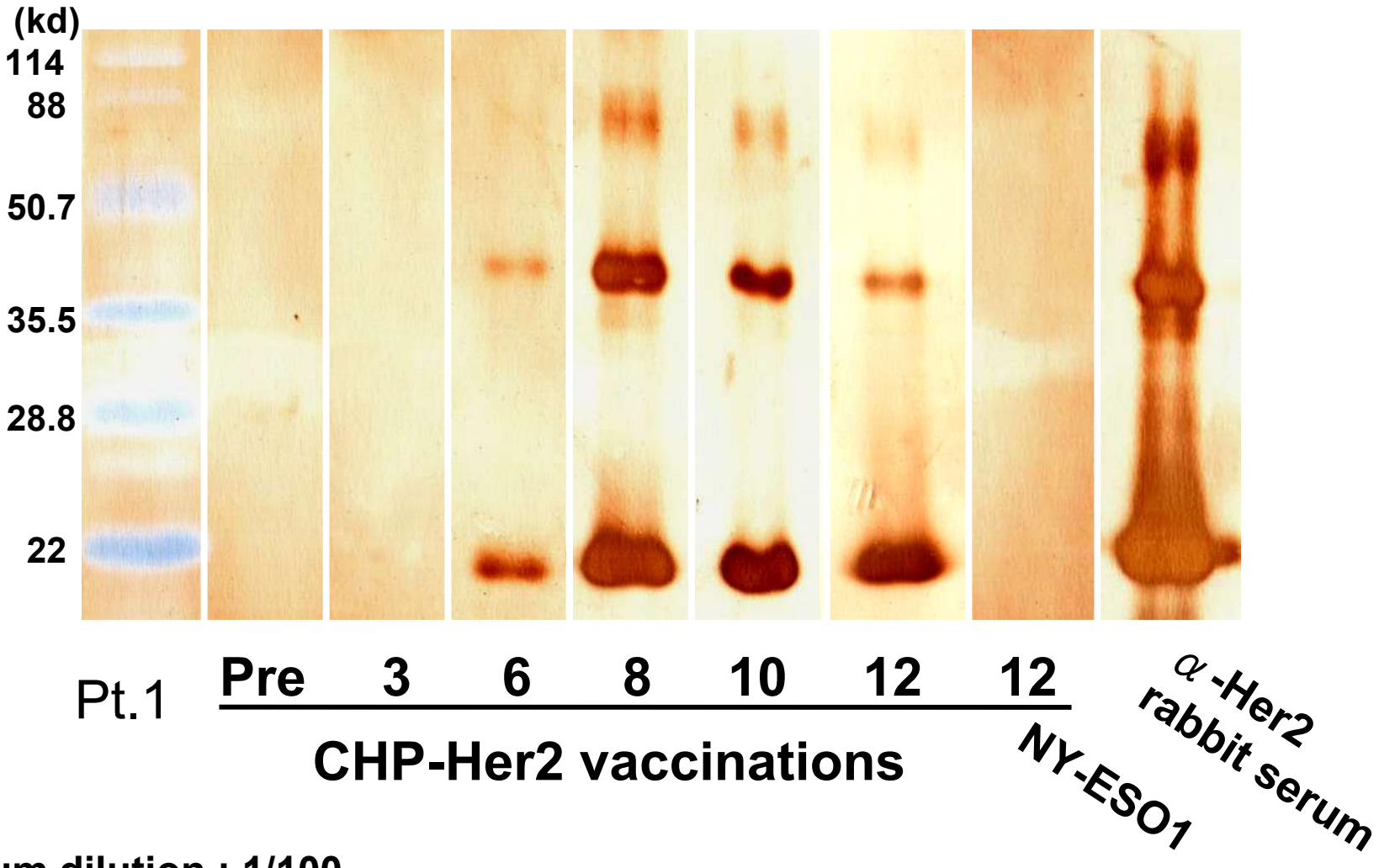
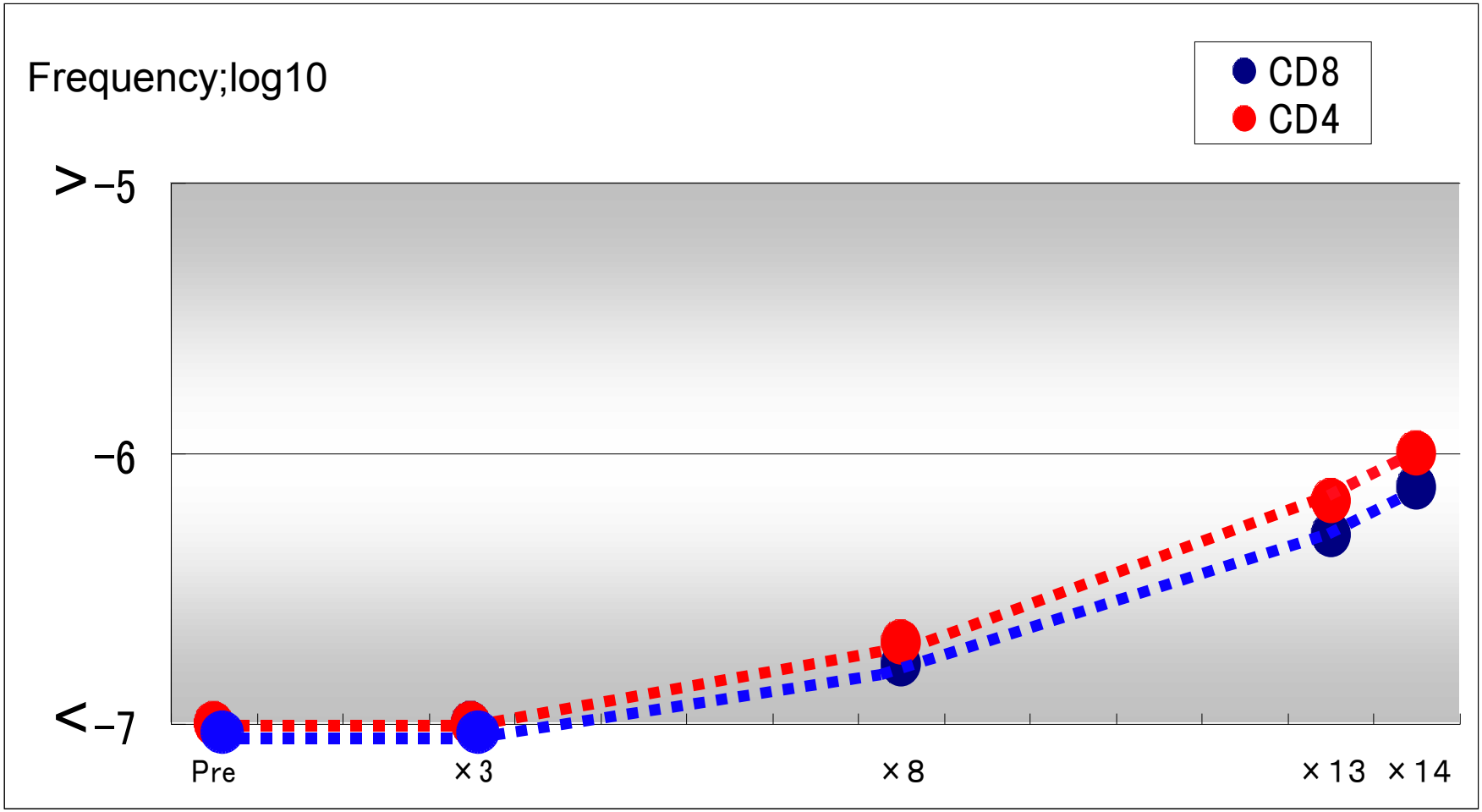


Fig. 3 Appearance of antibodies reactive with 146Her2 recombinant protein after vaccination with CHP-Her2 (Western blotting)



Serum dilution : 1/100

Fig.4 Elevation of 146Her2 specific CD8+ / CD4+ T cell frequency following CHP-Her2 vaccination



Major Papers Published

Nagata, Y., Furugen, R., Hiasa, A., Ikeda, H., Ohta, N., Furukawa, K., Nakamura, H., Furukawa, K., Kanematsu, T. and Shiku, H.: Peptides derived from a wild type murine proto-oncogene c-erB-2/HER2/neu can induce CTL and tumor suppression in syngeneic hosts. J. Immunol. 159: 1336-1343, 1997.

Ikeda, H., Ohta, N., Furukawa, K., Miyazaki, H., Wang, L., Kuribayashi, K., Old, L.J. and Shiku, H.: Muated mitogen-activated protein kinase: a tumor rejection antigen of mouse sarcoma. Proc. Natl. Acad. Sci. USA 94: 6375-6379, 1997

Okugawa, T., Ikuta, Y., Takahashi, Y., Obata, H., Tanida, K., Watanabe, M., Imai, S., Furugen, R., Nagata, Y., Toyoda, N. and Shiku, H.: A novel human HER2-derived peptide homologous to the mouse K(d)-restricted tumor rejection antigen can induce HLA-A24 restricted cytotoxic T lymphocytes in ovarian cancer patients and healthy individuals. Eur. J. Immunol. 30 : 3338-3346, 2000.

Nishikawa, H., Tanida, K., Ikeda, H., Sakakura, M., Miyahara, Y., Aota, T., Mukai, K., Watanabe, M., Kuribayashi, K., Old, LJ. and Shiku, H.: Role of SEREX-defined immunogenic wild-type cellular molecules in the development of tumor specific immunity. Proc. Natl. Acad. Sci. USA. 98:14571-14576, 2001.

Ikuta,Y.,Katayama,N.,Wang,L.,Okugawa,T.,Takahashi,Y.,Schmitt,M.,Gu,X.,Watanabe,M.,Akiyoshi,K.,Nakamura,H.,Kuribayashi,K.,Sunamoto,J. and Shiku,H..:Presentation of a major histocompatibility complex class 1-binding peptide by monocyte-derived dendritic cells incorporating hydrophobized polysaccharide-truncated HER2 protein complex: implications for a polyvalent immuno-cell therapy. Blood 99:3717-3724, 2002.