

# Current initiatives in Japan for nanomedicines

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# Regulated products by MHLW/PMDA

- Drugs
  - Cellular and tissue-derived products
  - Blood products
  - Vaccines
- Quasi-drugs
- Cosmetics
- Medical devices

# Regulation by MHLW/PMDA

- ✓ Review and confirmation of the quality, efficacy and safety for each product, GMP/GLP/GCP/GPSP inspections and conformity audits by PMDA
- ✓ Manufacturing/distribution business license and approval of manufacture and distribution by MHLW
- ✓ Report of any adverse effects generated after marketing of product.
- ✓ Reexamination and reevaluation

# Current regulation for nanomedicines

- ✓ Nanomedicines have been regulated within a general framework of the **Pharmaceutical Affairs Law** on a product-by-product basis.
- ✓ At present, we have no specially designed regulations for nanomedicines.
- ✓ Regulators and reviewers are gathering and analyzing information about the state-of-the-art technology on nanomedicines.

e.g. *In vivo* gene delivery by cationic tetraamino fullerene.

Nakamura E. et al. *Proc. Natl. Acad. Sci. USA*, **107** 5339-5344 (2010)

# The MHLW-supporting research activities with respect to nanomedicines (1)

## Background

### Science and Technology Basic Law

Objectives : To achieve a higher standard of science and technology, to contribute to the development of the economy and society of Japan and so on.

*The First Science and Technology Basic Plan (FY1996-2000)*

*The Second Science and Technology Basic Plan (FY2001-2005)*

*The Third Science and Technology Basic Plan (FY2006-2010)*

#### ➤ 4 priority promotion areas

(in the 2nd and 3rd S&T Basic Plans):

- Life science
- IT
- Environment science
- **Nanotechnology and Materials**

# The MHLW-supporting research activities with respect to nanomedicines (2)

The second science and technology basic plan (2001-2005)

Statement ; promotion of nanotechnology application to medicine

## 1. Health and Labour Sciences Research Grants (2002-)

For therapeutics and diagnostic application of nanomedicines

Research on Advanced Medical Technology (**nanomedicines**) (2002 - 2006)

Research on Nanotechnical Medical (2007 - 2009)

Research on Medical Devices for Improving Impaired QOL (2010-)

## 2. Collaboration with other ministry concerning to nanomedicines

Nanotech-DDS Working Group (2003)

Council for Science and Technology Policy, Cabinet Office

*Inter-ministry Projects (2004)*

Nano-DDS, Nanomedical devices

# The MHLW-supporting research activities with respect to nanomedicines (3)

The third science and technology basic plan (2006-2010)

## **3. 5-year Strategy for the Creation of Innovative Pharmaceuticals and Medical Devices (2007-2011)**

- regenerative medicine

## **4. Establishment of a new section at National Institute of Health Sciences (NIHS) (2008)**

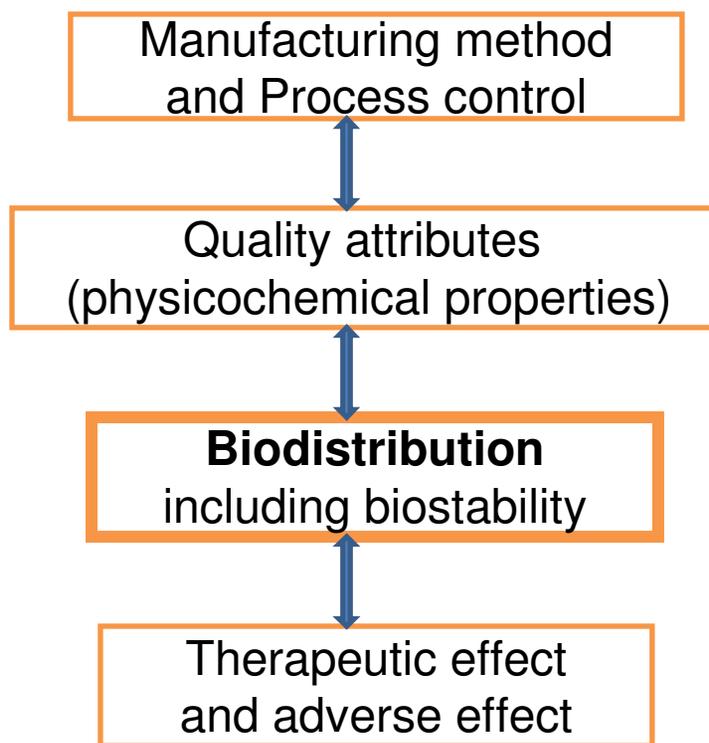
- for research on ensuring and evaluating quality of nanomedicines and other highly-functionalized pharmaceuticals.

# Research activities of nanomedicines and nanomaterials at MHLW/NIHS

## 1. Study of evaluating and ensuring the quality of nanomedicines

Objectives: Development of evaluation strategy of nanomedicines from the standpoint of quality, efficacy and safety

Nanomedicines are mainly developed for control of biodistribution of APIs



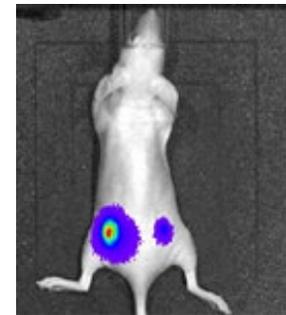
The knowledge about the relationship between each element is important for ensuring efficacy and safety as medicines.

Especially, the knowledge about biodistribution is considered to be the key.

# Research activities of nanomedicines and nanomaterials at MHLW/NIHS

## 1. Study of evaluating and ensuring the quality of nanomedicines

- Characterization of physicochemical property.
- Analysis of biodistribution from the level of whole body to that of intracellular organelle. (bioimaging)
- Linkage between the physicochemical properties including structure and the altered biodistribution.
- Linkage between the biodistribution and pharmacological & toxicological effects.
- Understanding the impact of the altered biodistribution.

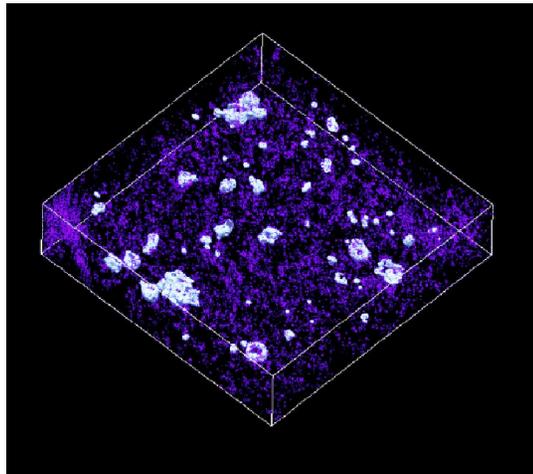


### Output

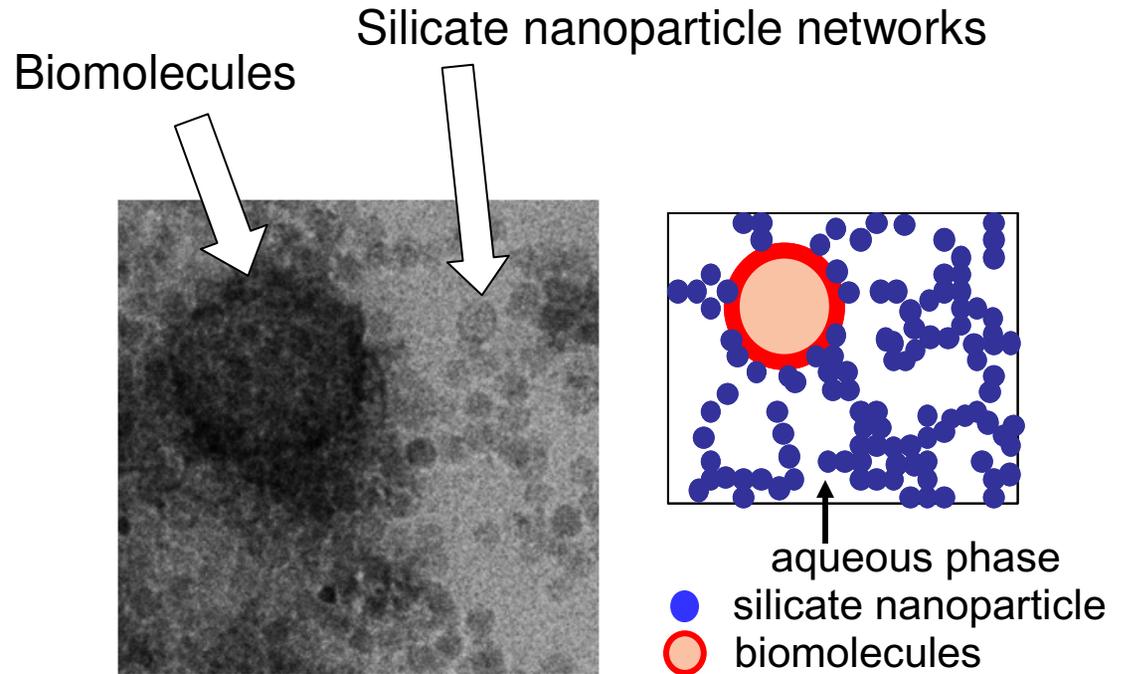
- Identification of critical quality attributes of nanomedicines.

# Research activities of nanomedicines and nanomaterials at MHLW/NIHS (2)

## 2. Study about biocompatible materials using nanoparticles



3D image constructed from TEM images of biomolecules-encapsulating gel using silicate nanoparticles.



High resolution TEM image of nanoparticle networks encapsulating biomolecules (left) and its schematic illustration (right).

# Research activity of nanomedicines and nanomaterials at MHLW/NIHS (3)

## 3. Study about evaluation of health effects by manufactured nanomaterials

Fiscal year

2004

Survey research of public information about health implication of nanomaterials

2005

The initial research on methodology of health risk assessment of manufactured nanomaterials started, (using  $C_{60}$  and  $TiO_2$  as reference materials)

2006

(to 2008)

Restarting the project of “Research on the hazard characterization and toxico-kinetic analysis of manufactured nanomaterials for the establishment of health risk assessment methodology”, as the expanded project, (add focus on **long-term effects**, ex. **MWCNT**)

*Courtesy: Dr. Hirose (NIHS)*

# Research activity of nanomedicines and nanomaterials at MHLW/NIHS (3)

## 3. Study about evaluation of health effects by manufactured nanomaterials

Fiscal year

2007  
(to 2009)

“Research on the dermal toxicity evaluation methodology of the manufactured nanomaterials“ (separated from the above project due to focusing on **dermal exposure**)

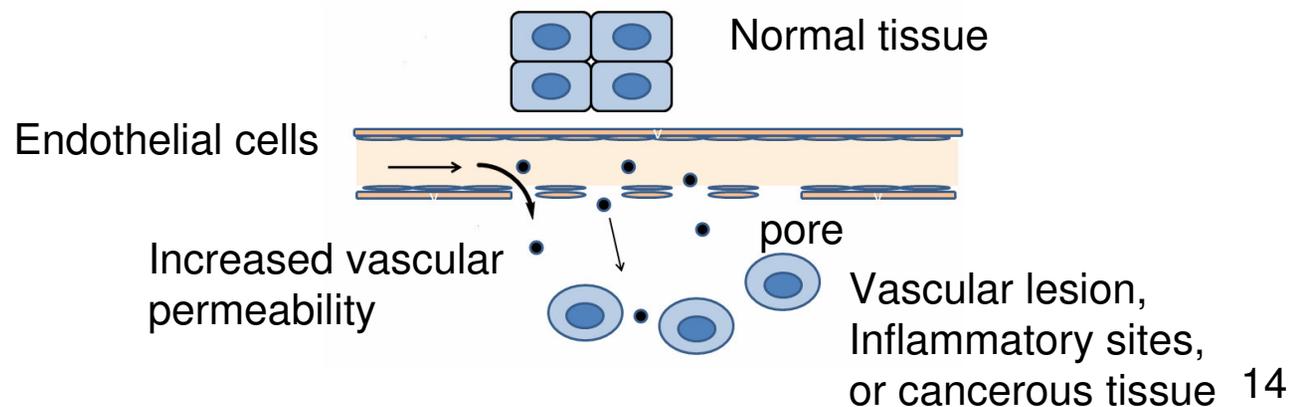
2008  
(to 2010)

“Research on the inhalation toxicity evaluation methodology of the manufactured nanomaterials“ (separated from the above project due to focusing on **inhaled exposure**)

*Courtesy: Dr. Hirose (NIHS)*

# Development of nanomedicines in Japan

1. Nanoparticulates with a particle size of around 100 nm effectively accumulate in vascular lesion or inflammatory sites including cancerous tissue.
2. The **EPR (Enhanced Permeation and Retention) effect** was discovered by Japanese researchers.  
( Matsumura, Y., and Maeda, H. *Cancer Res.* **46**, 6387-6392 (1986))
3. Since then, many nanometer-sized DDS drugs such as block copolymer micelles using the EPR effect have been developed.



# Approved nanomedicines# in Japan

- Lipid microspheres  
(Palux, Liple, Limethason, Diprivan, POPION)
- Liposomes  
(AmBisome, Doxil, Visudyne)
- Polymer-conjugated proteins  
(SMANCS, PEGASYS, PegIntron, SOMAVERT)
- Antibody-conjugated drugs  
(MYLOTARG, Zevalin)
- Nanocrystal drug (EMEND)
- Imaging agent (Resovist)

**# These pharmaceuticals are classified as "nanomedicines" by their sizes in this slide.**

# Future Issues

- ✓ Kick-off discussion would be started among MHLW regulators, PMDA reviewers, and NIHS researchers about the regulation of nanomedicines.
- ✓ Researches should be promoted especially in the area of analytical method of nanoparticles and the evaluation method of biodistribution of nanomedicines in the human body. In these researches, discussion would be done about the regulation of nanomedicines.
- ✓ Open discussion would be followed between industry, academia, and regulatory authority about the appropriate regulation of nanomedicines, enhancing the medical application of nanotechnology.
- ✓ International cooperation with other organizations.