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ASEAN Bio-preparedness Meeting and Exercise, 2015

Bio-preparedness in Japan

Department of Immunology and Microbiology, National Defense Medical College

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CBRN terror in Japan

- August 30, 1974. Bombing attack to Mitsubishi Heavy Industry headquarter building in Tokyo
  - Anti-Japan Armed Front for East Asia — 8 people were killed, 376 injured.

- April, 1990. Air spraying of botulinum toxin in Tokyo
- June 28, July 2, 1993. Kameido anthrax incident in Tokyo
  - Aum Shinrikyo cult
  - Bio-terror attacks were not successful. (no victims)

8 years before U.S. anthrax attack

- June 27, 1994. Matsumoto sarin attack in Nagano
  - Aum Shinrikyo cult — 8 peoples were killed, 660 injured

- March 20, 1995. Tokyo subway sarin attack.
  - Aum Shinrikyo cult — 13 peoples were killed, 6,300 injured
- September 30, 1999, Tokai-mura criticality accident in Japan
  2 peoples were killed, 1 severe injury
- March 11, 2011, Fukushima Dai-ichi nuclear accident

Today's Topics

- Bioterrorism in Japan and our preparedness

  Public health, Police, and Self Defense Force

- Pandemic diseases in Japan and our preparedness

  Swine Flu, Avian Flu (H5N1), Ebola virus disease

- Catastrophe (disaster) in Japan and our preparedness

  Blood substitutes (red blood cell substitute, platelet substitute)

Bioterrorism

Backgrounds

- Attempt at biological attacks by Aum Shinrikyo

  April, 1990. Air spraying of botulinum toxin in Tokyo

  June 28, July 2, 1993. Kameido anthracis incident in Tokyo

  These bio-terror attacks were not successful. (no victims)

- 9.11. attacks and Anthrax attack in U.S. (2001)

  Increasing threat of terrorism

Air spraying of anthrax bacteria in Tokyo

Actions/response against bioterrorism

Ministry of Health, Labour and Welfare (Public health)

Headquarter of Ministry of Health, Labour and Welfare

- Stockpiling smallpox vaccine (2002~)

  LC16m8 (Kaketsuken, Kumamoto, Japan)
  cell-cultured attenuated Smallpox vaccine

- Amendment of Infectious Disease Control Act (2003-7)

  Terrorist Attack Preparedness Action Plan (2004)

  Security sectors demanded to establish a pathogen control system,
  because there was no such a regulation to ban terrorists to possess highly dangerous pathogens.

  The pathogen control scheme was added to the Infectious Disease Control Act (2006)

- Establishment of Civil Protection Act (2004) Cabinet

  Legislation of a crisis management

  NBC attacks were included in the scenarios of Civil Protection Plan

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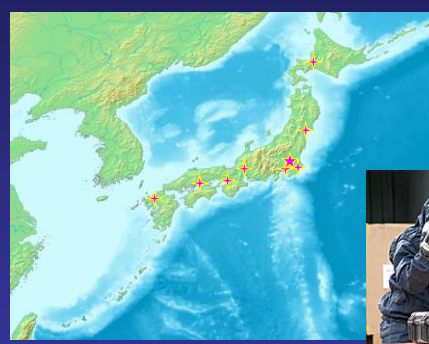
Actions

Headquarter of National Police Agency

National Police Agency

- Counter-NBC terrorism squad in Police (2000~)

  Tokyo Metropolitan Police, police of other metropolitan areas (8 cities)



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Actions

Ministry of Defense

- Central Readiness Force (CRF) (2007)

Central Readiness Force (CRF) was established in 2007 in order to quickly response to new defense issues such as international peace cooperation activities and CBRN terror. CRF is a new unit in the Japan Self Defense Force under the direct control of the Minister of Defense.

Headquarter of Ministry of Defense

1st Helicopter Brigade at Fukushima

Crew members back to the front-line base

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- Central NBC Weapon Defense Unit (CNBC) (2007)

Special force for a quick response to CBRN threats

NBC reconnaissance vehicle

Dispersion of radiological substance

They joined the mission for Fukushima nuclear accident to cool down nuclear reactor in cooperation with Fukushima 50

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- NBC Countermeasure Medical Unit (NBCCMed) (2008)

Medical unit of countermeasure for CBRN threats

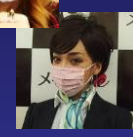
Field operation systems

Training for CBRN terrors

Pandemic Flu

Backgrounds

- Swine Flu /H1N1 (2009)



Strengthening of quarantine activity at the airports

- Avian Flu /H5N1

Highly pathogenic Avian flu

Area where H5N1 has occurred

- Birds
- Human, Birds

Actions Ministry of Health, Labour and Welfare (Public health)

Medical countermeasures preparedness for pandemic flu in Japan

- Anti-viral drugs
  - Stockpiling Tamiflu® and Relenza® for 45% of Japanese population
    Discussion on reducing stockpile is going.
  - Conditional licensure for Avigan®
    in case of novel flu resistant to current anti-virus

- Vaccines
  - Stockpiling pre-pandemic vaccine for H5N1 (for 3 strains, 10 million dose/each)
  - Prototype cell-cultured vaccine has been licensed for early development of pandemic vaccine

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Ebola outbreak in West Africa

Preparedness for Viral Hemorrhagic Fevers in Japan

- Viral Hemorrhagic Fever is classified in the Category 1 infectious diseases under the Infectious Disease Control Act.
- Patients of Category 1 infectious diseases are to be hospitalized in specified or class 1 infectious disease hospitals, with negative pressured private wards.
  (specified infectious hospitals: 3, class 1 infectious hospitals: 45)
- Viral Hemorrhagic Fever is a quarantine diseases under the Quarantine Act and the patients are to be isolated and high risk contacts are to be quarantined strictly.

National Center for Global Health and Medicine
(Specified Infectious Disease Hospital)

National Institute of Infectious Diseases

- We are not operating BSL4 laboratories but diagnosis capacity for Viral Hemorrhagic Fever is available in the National Institute of Infectious Diseases at BSL3 laboratory.
  Government recently reached an agreement with local community in operating a BSL4 facility

Ebola outbreak in West Africa

Japan's response to outbreak of Ebola virus disease in West Africa

Japan supported activities related to Ebola outbreak financially, in-kind and in personnel.

- Total funding: USD 184 million
- Development and in-kind contribution

ν Medical equipment, vehicles (ambulances), thermography cameras

ν Portable Ebola virus test kit

Portable RT-LAMP assay device (Genie III) and specific primers developed in Nagasaki Univ.
High specificity and sensitivity was shown by testing clinical samples in Guinea.
Provided to Guinea on request in April 2015 for use intensive campaign.

ν Anti-viral drug for Ebola virus

Avigan® provided for an emergency use and
Toyama Chemical Co. has performed a clinical trial in Guinea.

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Catastrophe in Japan and our preparedness

March 11, 2011. 2: 43 pm. Great East Japan Earthquake (M=9.0)

Twenty to thirty minutes later, huge tsunamis (max: 40 m; 131 ft high) attacked the Pacific coast of East Japan.

Tsunamis completely destroyed the coastal cities.

Approximately 20,000 people were killed or remain missing.

Almost all structures were destroyed and many ships were loft up in the midtown.

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Japan Self Defense Force quickly responded and immediately sent 100, 000 soldiers into the disaster area.

Many foreign rescue teams helped us. Appreciated!



However, rescue teams could not reach the most devastated area by a land route due to huge rubble.


Air evacuation was only effective.


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Infrastructures and transportation systems were severely shredded.


Serious shortage of medical resources including the blood for transfusion may occur in the center of devastated area in such a catastrophe.

The center of devastated area

Medical resources

Blood for transfusion (RBC, Platelets)

supply ↓↓ **demand** ↑↑

National stockpile is needed

Development of the blood substitutes is crucial for the prevention of mass casualties.

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Project 1

Liposome-encapsulated Hb (LEH)

Hemoglobin-based oxygen carrier (HBOC)

Artificial red blood cells

Packed liposome-encapsulated Hb
(artificial RBC)

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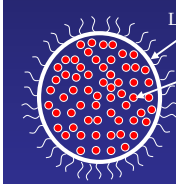
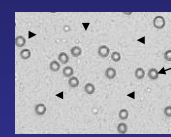
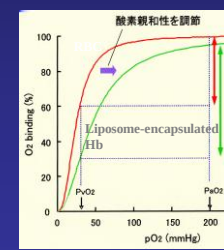
	Liposome-encapsulated hemoglobin	Stored RBC for transfusion
Blood typing	No need	Blood typing needed (A, B, O, AB)
Storage	at 4 °C, stable for 6-12 months	at 4 °C, stable for 21 days
Contamination risk	No risk (inactivation of virus)	Can not be denied

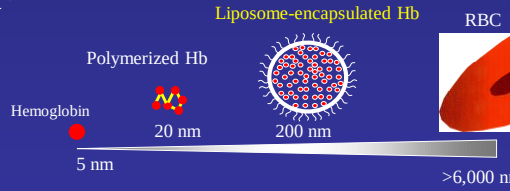
Structure; encapsulated hemoglobin by a lipid bilayer membrane

Hemoglobin prepared from outdated human RBC provided by Japan Red Cross at present









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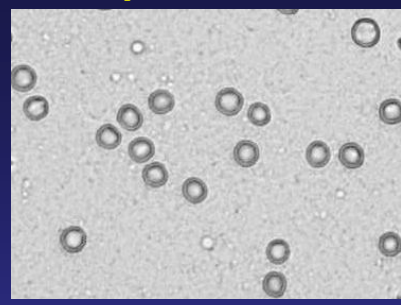
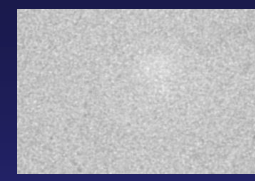
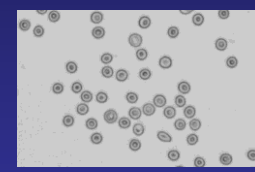
Liposome-encapsulated Hb-transfused mouse



Liposome-encapsulated Hb



Red blood cells



Liposome-encapsulated Hb can be used for intraosseous resuscitation because of its small size.

Red blood cells are too big to effectively flow into the systemic circulation through the tortuous vascular architecture in the bone marrow.

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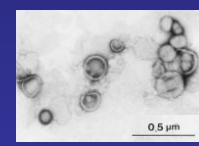
Project 2

H12-ADP-liposome

Fibrinogen γ-chain peptide (H12)-coated, ADP-encapsulated liposomes

Artificial Platelets

Packed Platelets



Bioconjugate Chem. **16**, 1589-6, 2005.

Artificial Platelets

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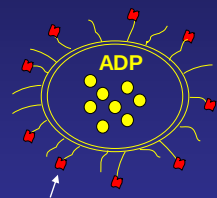
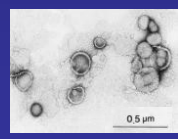
	H12-ADP-liposome	Stored platelet for transfusion
Condition for storage	No need to agitate at room temperature.	Need to continuously agitate at 20-24°C
Platelet viability	6 months available	2-3 days
Contamination risk	No risk (full synthetic product)	Still present

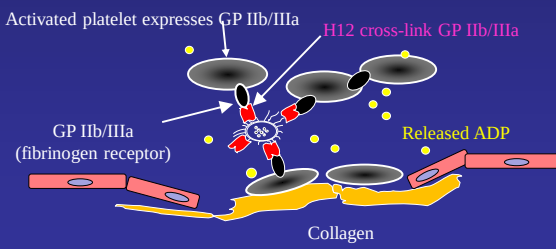
Structure; fibrinogen-γ chain-coated liposomes that encapsulate adenosine diphosphate (ADP) with a lipid bilayer membrane



H12:HHLCGAKQAGDV



H12 (ADP) liposomes augment platelet aggregation by cross-linking platelet upon binding and releasing ADP. No aggregation by themselves but support platelet aggregation.



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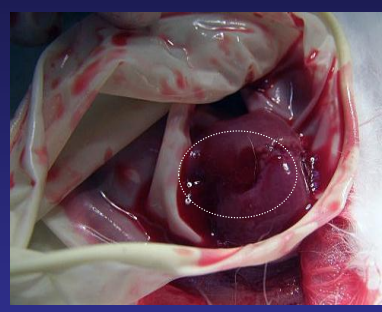
Hemostasis by administration of H12(ADP)liposome after bleeding from the penetrating liver injury in thrombocytopenic rabbits



PPP (at 10 min)

H12-(ADP)-liposomes/PPP (at 10 min)

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Multiple injury

Emergency evacuation

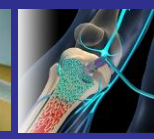
Intensive care

Transfusion of Liposome-encapsulated Hb
H12(ADP)liposome

Lethal hemorrhagic shock

Insertion of a catheter into peripheral vessels is difficult in the pre-hospital resuscitation, because these vessels are usually collapsed in the hemorrhagic shock.

Intraosseous transfusion with liposome-encapsulated Hb and H12-(ADP)-liposomes



Hemostatic resuscitative transfusion (RBC: Platelet: Plasma = 1:1:1)

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