Development of diagnostic and therapeutic antibodies against tropical infectious diseases

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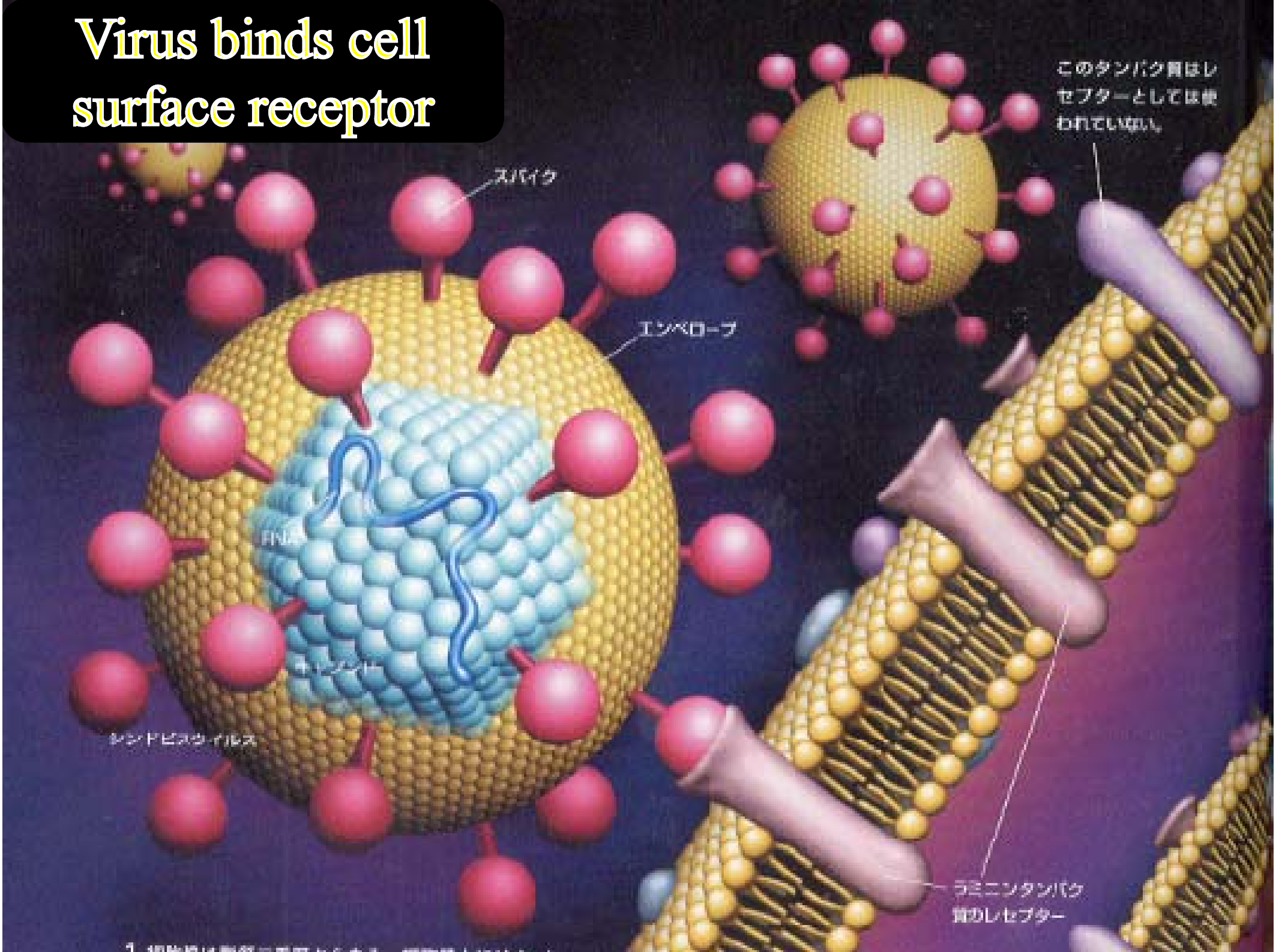
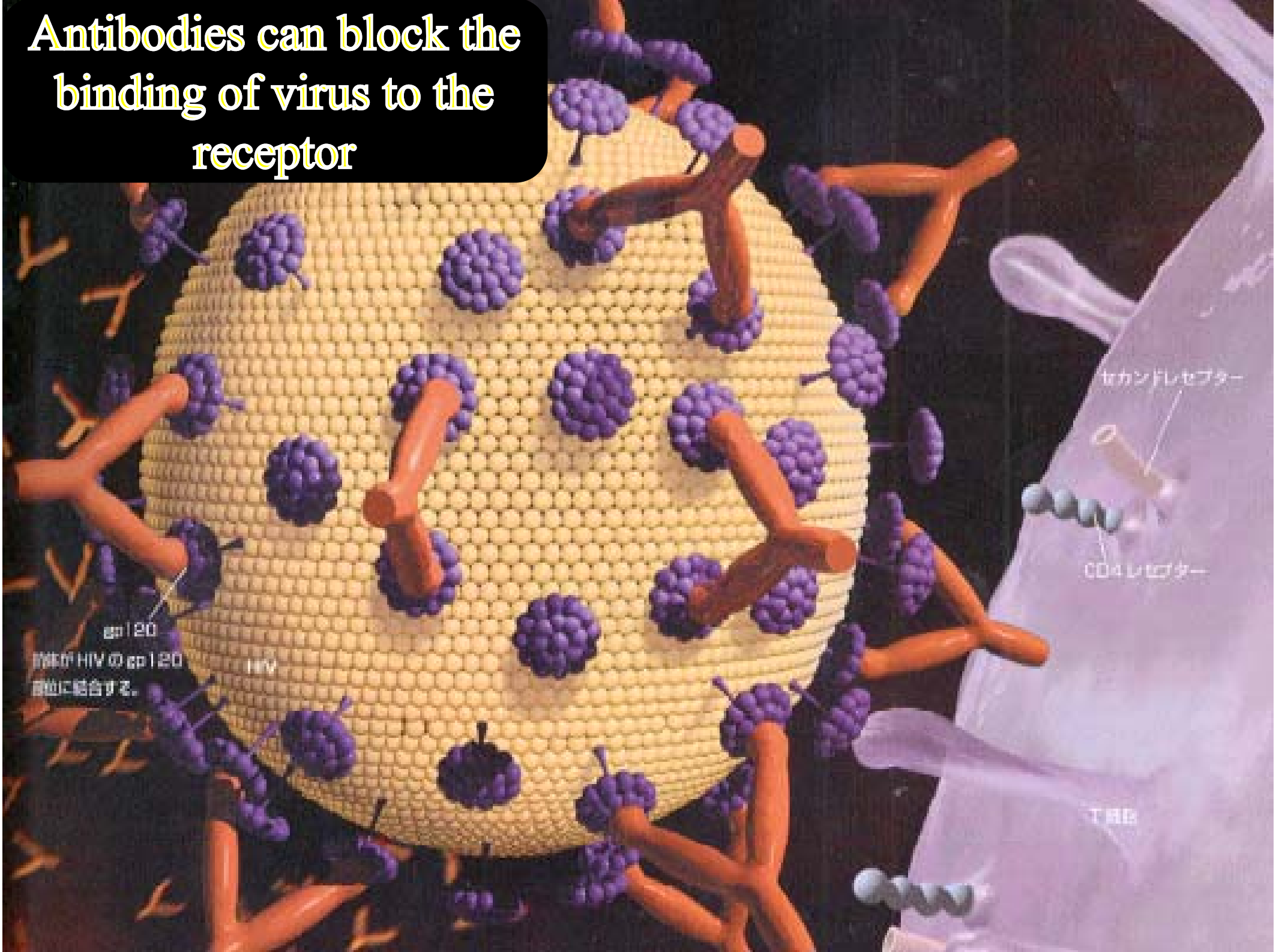
http://virology.biken.osaka-u.ac.jp/index_english.html


Virus binds cell surface receptor
このタンパク質はレセプターとしては使われていない
スパイク
エンベロープ
RNA
ラミニンタンパク質のレセプター


Antibodies can block the binding of virus to the receptor
gp120
抗体がHIVのgp120
領域に結合する。
HIV
セカンドレセプター
CD4レセプター
T細胞

Possible immunotherapy with convalescent human serum

Year of study	Disease	Prophylaxis or treatment	Number of study subjects	Trend in benefit
1907	Measles (Rubeola)	Prophylaxis	Unknown	Prevention.
1918	Measles[a]	Prophylaxis	1	One child in a family of four children was given serum from the first infected child and was protected; the other two contracted measles.
1918	Measles	Prophylaxis	4	Prophylaxis was effective.
1918	1918 Pandemic flu	Treatment	56	Early administration generally resulted in distinct improvement in clinical symptoms.
1923	Varicella-Zoster virus	Prophylaxis	42	Seven contracted a mild form of the disease, 35 escaped without symptoms.
1963[b]	Bolivian hemorrhagic fever	Treatment	4	Individuals recovered after 6–8 weeks.
1959–1983	Argentine hemorrhagic fever	Treatment	4,433	Mortality rate of 3.29% (versus 42.85% in individuals treated before convalescent plasma was used).
1974–1978	Argentine hemorrhagic fever	Treatment	217	1.1% mortality rate of those treated with immune plasma.
1969	Lassa fever	Treatment	1	The individual recovered.
1984	Lassa fever	Prophylaxis and treatment	27	All study subjects given plasma on or before the 10th day survived with a rapid response to therapy.
1995	Ebola hemorrhagic fever	Treatment	8	12.5% fatality rate (versus overall case fatality rate of 80%); inconclusive regarding neutralizing antibodies in convalescent blood.
1993	HIV-1	Treatment of stage IV AIDS individuals	63	Randomized double-blind controlled trial. Study subjects were given 250 ml of HIV-immune plasma every 4 weeks. No significant toxicity and effect were found.
1995	HIV-1	Treatment of symptomatic HIV infection	86	Randomized double-blind controlled trial. Study subjects were given 300 ml of plasma rich in anti-HIV-1 antibody every 14 days for 1 year. Clinical benefit was observed.
2002[c]	HIV-1	Prevention of vertical transmission in Uganda	60	Phase 1/2 trial showed it is safe, well tolerated and similar pharmacokinetic property as other immunoglobulin products.
2003	SARS	Treatment	1	Fever decreased after administration of convalescent plasma.
2007	Influenza A (H5N1)	Treatment	1	Viral load was reduced after infusion of plasma; the individual recovered.

[a]Other studies refer to ref. 1. [b]Immune BHF gamma globulin was used. [c]HIV hyperimmune globulin was used.

Marasco & Sui, Nature Biotech. 25:1421-1434, 2007

Commercial development of antiviral MAbs

	Virus	Stage of development	mAb	Isoform	Target	Development technology	Company (location)	Indication	Reference
Acute cytopathic	RSV	Approved	Synagis (Palivizumab; MEDI-493)	IgG1	Glycoprotein F	Humanized	MedImmune	Prophylaxis in high risk infants[b]	111
	RSV	Phase 3	Numax (Motavizumab; MEDI-524)	IgG1	Glycoprotein F	Humanized and affinity matured from palivizumab	MedImmune	Prophylaxis in high risk infants	53,54,112
	Rabies	Phase 1	CR4098	IgG1	Glycoprotein antigenic site III	Immune Ab phage display library	Crucell (Leiden, The Netherlands)	Post-exposure prophylaxis; use in combination	57[c]
			CR 57		Glycoprotein antigenic site I	EBV immortalization			
	Rabies	Preclinical (clinical trials to start in India in 2008)	17C7	IgG1	Glycoprotein, either antigenic site III or minor site A	Transgenic HuMab-Mouse (Medarex)	Massachusetts Biologic Laboratories	Post-exposure prophylaxis	10
	WNV[d]	Phase I	hE16 (MGAWN1)	IgG1	Envelope (E) protein, domain III	Humanized	Macrogenics (Rockville, MD, USA)	A potential therapy for diseases associated with severe West Nile Virus infection	113
	WNV	Pre-clinical	CR4374	IgG1	E protein, domain III	Immune human Ab phage display library	Crucell	Protected mice from infection	114
	SARS	Pre-clinical	CR3014	IgG1	S1-RBD	Immune phage display Ab library	Crucell	CR3014 protected ferrets	116
			CR3022					CR3022 neutralized CR3014 escape viruses; mixture of CR3014/3022 showed synergistic effect	116
Acute cytopathic/latent reactivation	CMV	Phase 2	TI-23	IgG1	Envelope glycoprotein gb	Human hybridoma	Teijin Pharma (Tokyo, Japan)	Treatment of CMV Retinitis in HIV individuals / CMV pneumonia in bone marrow transplantation—individuals	117
	CMV	Information not available	HCMV37	IgG1	Envelope glycoprotein gb	Humanized	Scotgen Biopharmaceuticals (Aberdeen, UK; closed doors in 1997)	HCMV infections in immunocompromised individuals	118
	EBV	Phase 2	Rituxan (Rituximab)	IgG1	CD20	Chimeric	Genentech (S. San Francisco, CA, USA)	Treatment, EBV-associated post-transplant lymphoproliferative disorders (interstitial pneumonia)	119
	VZV	Preclinical	TI-57	IgG1	Envelope glycoprotein III	Human hybridoma	Teijin Pharma	Treatment of Varicella Zoster	120

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RSV

FDA-approved

Preventive use in babies born prematurely

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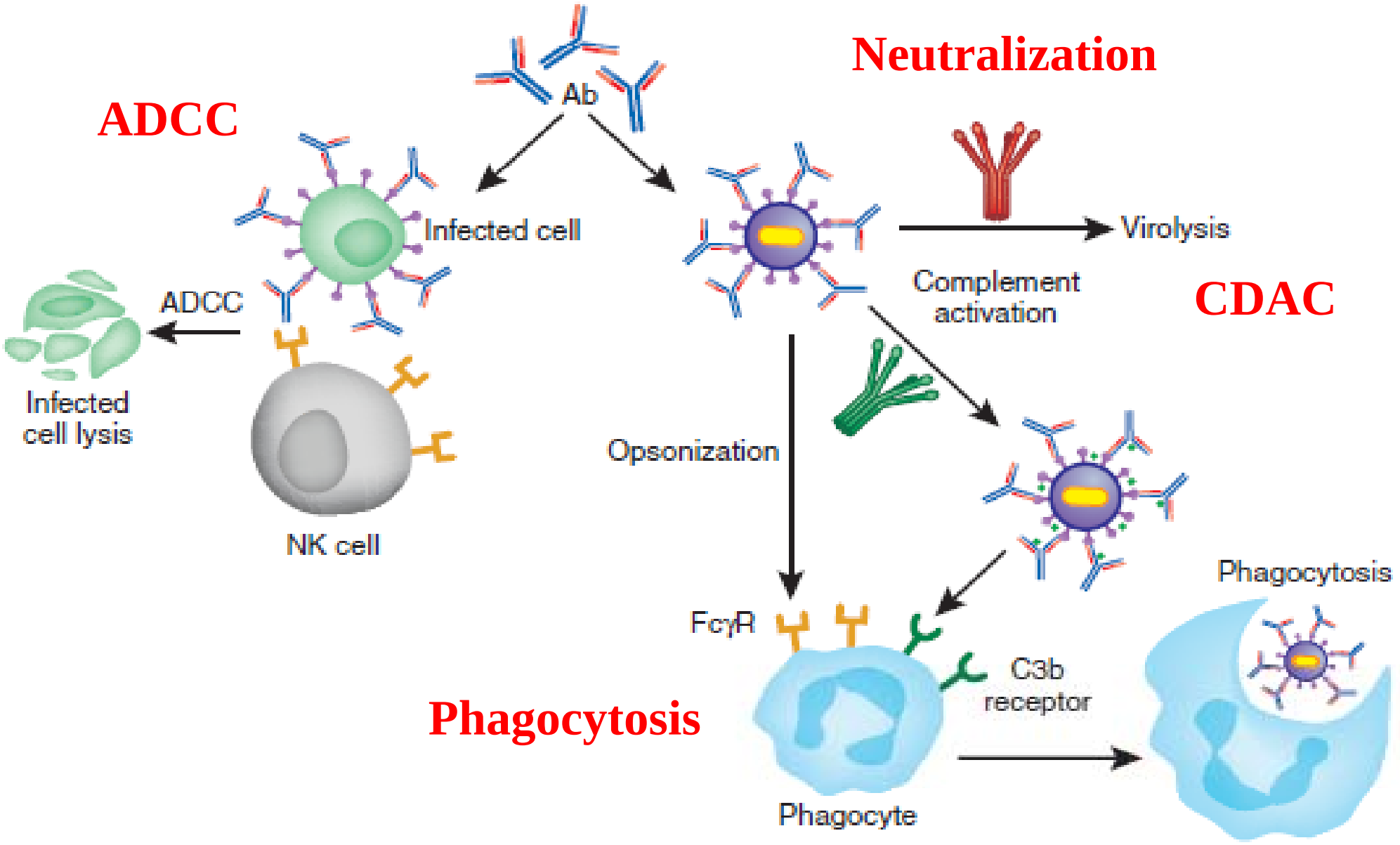
Anti-viral Abs could be effective for virus neutralization as well as killing infected cells



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Science and Technology Research Partnership for Sustainable Development (SATREPS)

- against Global Issues in Infectious Diseases -

2009~2012

Development of therapeutic human antibodies and pursuing novel therapeutic candidates against infectious diseases, especially dengue hemorrhagic fever

Japan side: JST (Japan Science and Technology Agency)
Thai side: JICA (Japan International Cooperation Agency)

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Development of therapeutic human antibodies and pursuing novel therapeutic candidates against infectious diseases, especially dengue hemorrhagic fever

Dengue virus, Influenza virus, and botulinum toxin

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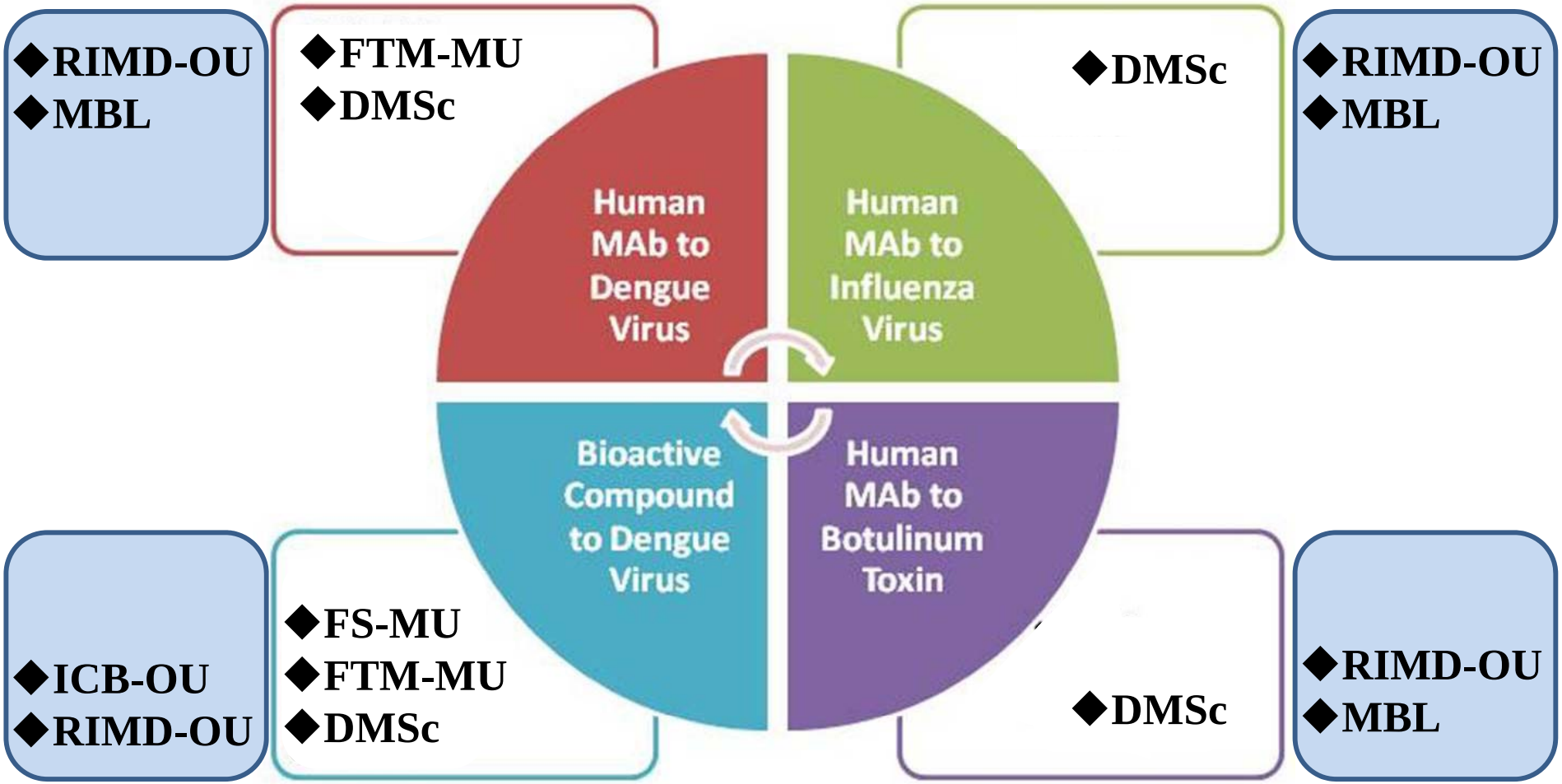
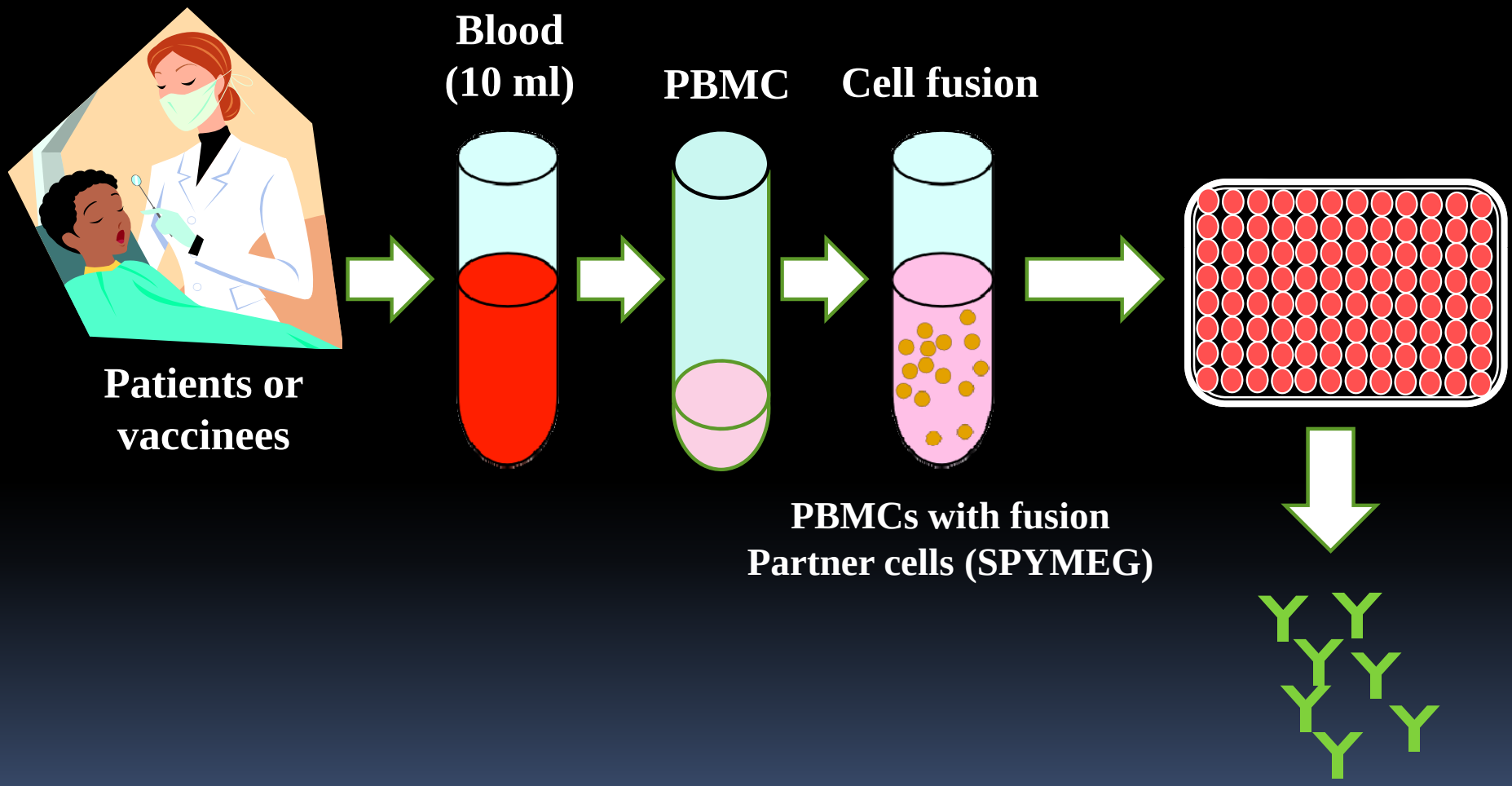
Ministry of Education and Science

Ministry of Foreign Affair

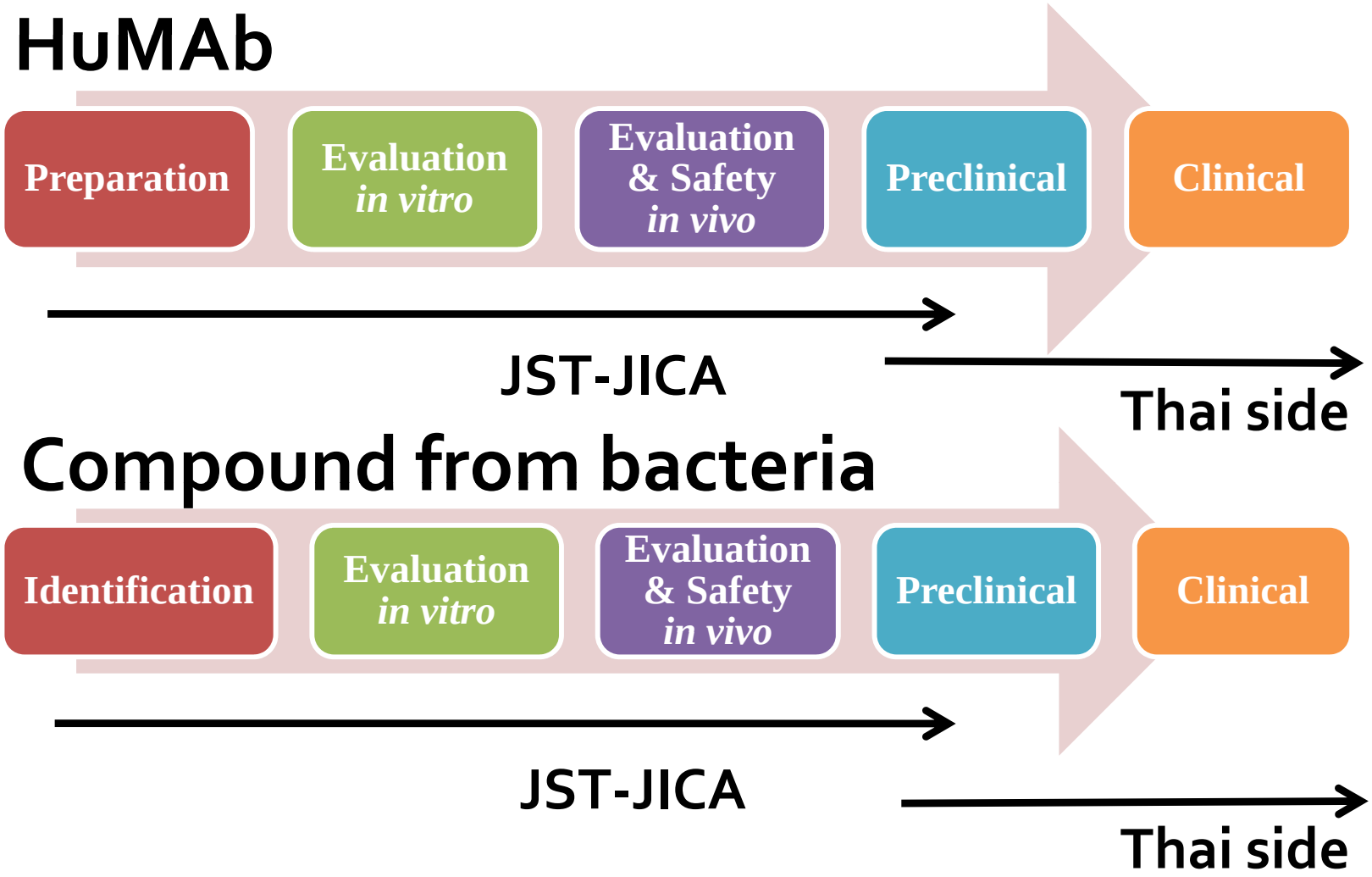
Four projects on JST-JICA



HuMAb preparation with human PBMCs

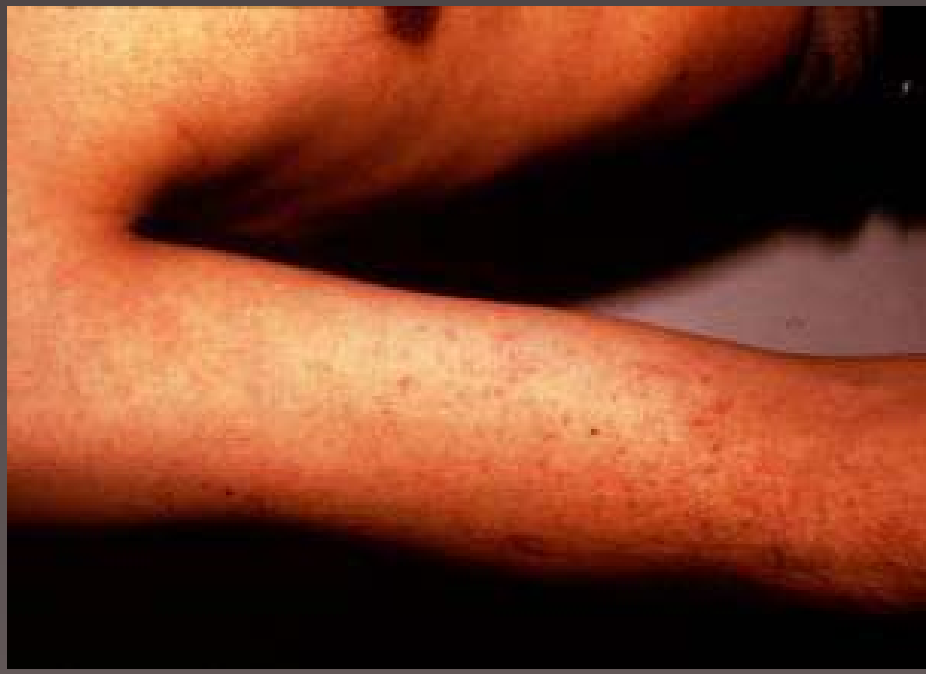


Process Flow on JST-JICA projects



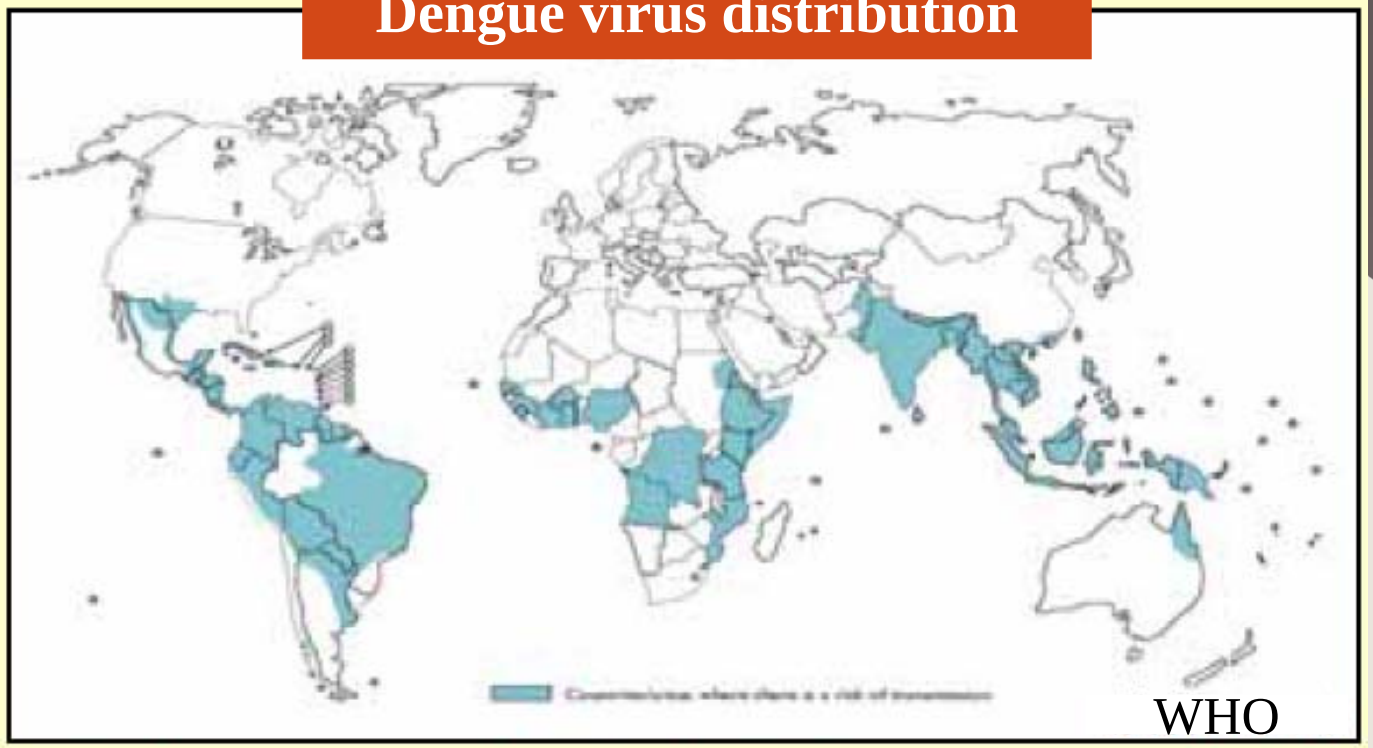
Dengue Fever, Hemorrhagic fever

- Typical arthropod-borne disease
- Mostly subclinical cases
- 4 serotypes of virus



Dengue patient

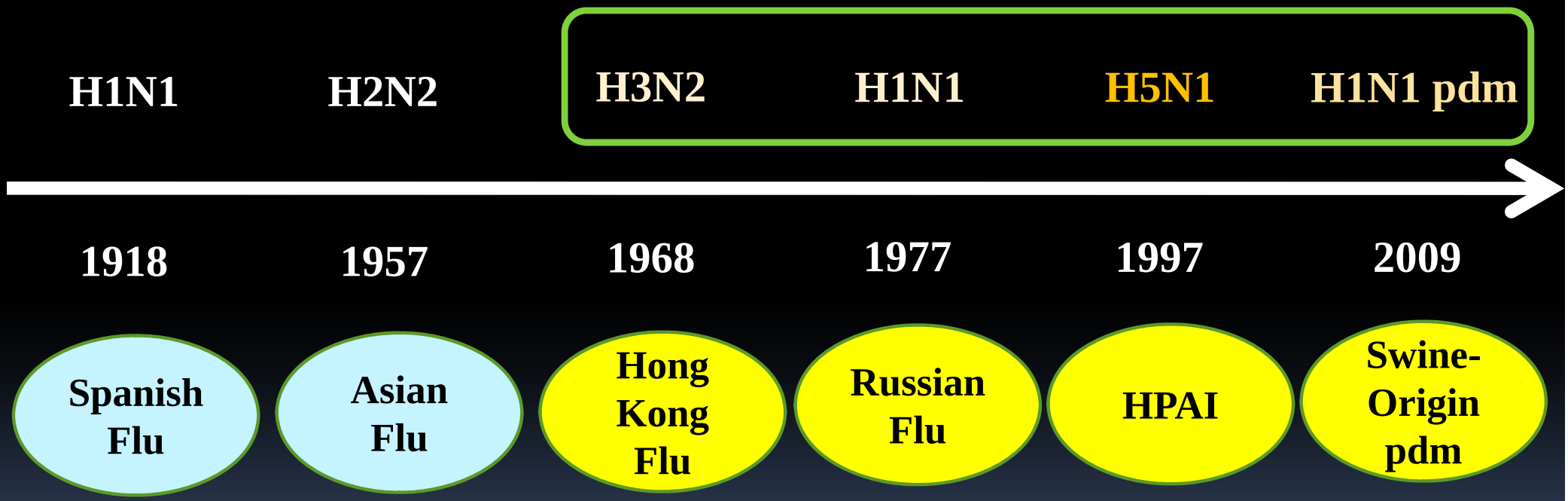
Dengue virus distribution



WHO

Mosquito

Influenza A virus in human



At early May 2009 in Japan

WHO

		Phase
Pandemic Interfase （no human case of subtypes that are prevalent in animals）	Lower risk of human infection	1
	Higher risk of human infection	2
Pandemic Alert （detection of human case of new subtypes）	No or only limited number of human-to-human transmission	3
	Increased number of human-to-human transmission	4
	Considerable number of human-to-human transmission	5
Pandemic	Efficient human-to-human transmission	6

Feb 2009: Outbreak of respiratory illness in Mexico
April 2009: CDC identified Swine-origin influenza virus
June 2009: WHO declared pandemic alert to phase 6

Strategies against influenza

- **Prevention → Vaccine**
  - **HA split vaccine**
  - **Pandemic-------time-consuming**

- **Therapy → Drugs**
  - **Anti-viral--------escape mutants**
  - **Human Abs**

High risk

- ✓ **Premature infants**
- ✓ **Elderly people**
- ✓ **Patients with underlying diseases**
- ✓ **(Diabetes, Dialysis-treating patients)**
- ✓ **Pregnant women**
- ✓ **HIV-infected individuals**