Rabies vaccine development

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Outlines

1. **Rabies**
2. **Rabies virus**
3. **Rabies epidemiology**
4. **Rabies vaccine development**
5. **Perspective**

Rabies-one of the oldest infectious diseases

- **Rabies is a dangerous disease known for more than 5000 years and is still prevalent in our world today.**
- **It is present in the animal populations of almost every country in the world; about 69, 000 human deaths from rabies occur each year.**
- **More than 7 million people worldwide received post-exposure treatment each year.**

Old disease

- Ancient Babylon(1930 BC)
- Baghdad school(1224年)

The human cost of rabies

Having not received post-exposure prophylaxis after a dog bite, a 16-year-old boy suffers the terrifying symptoms of rabies.

Lankester et al. Science 345(6204):1562-1564.

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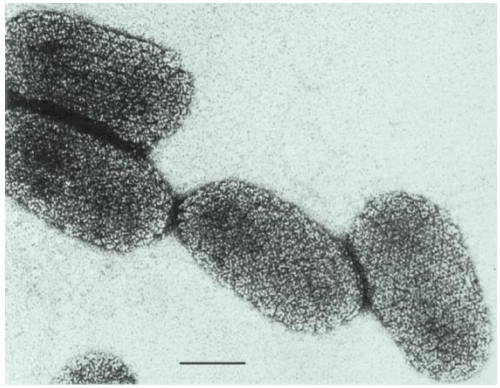
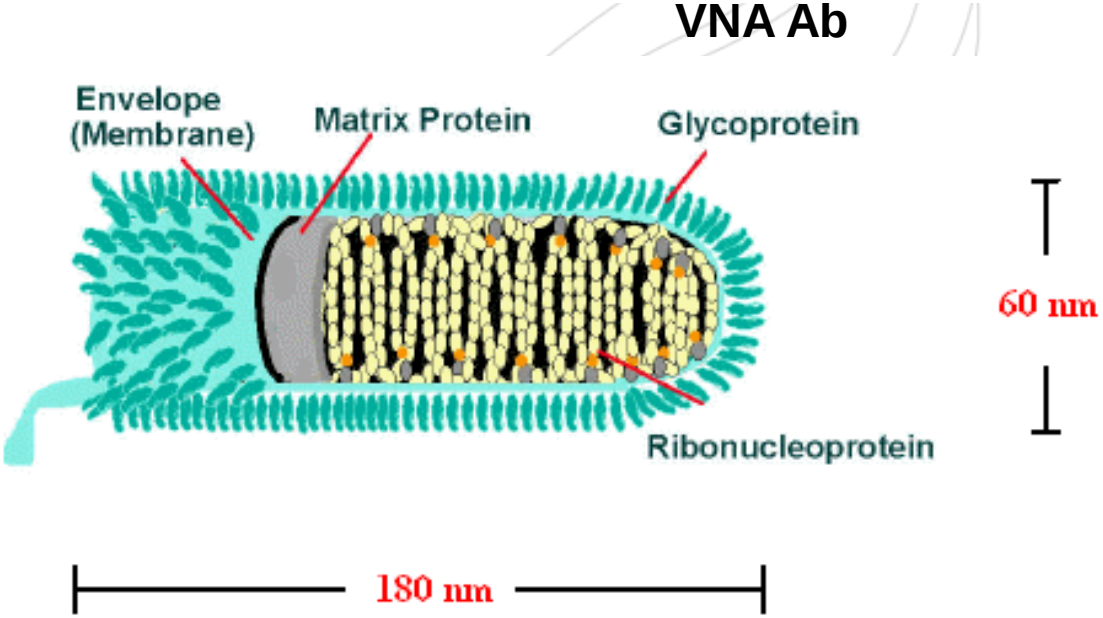
Rabies virus





Adapted from *CDC web site*

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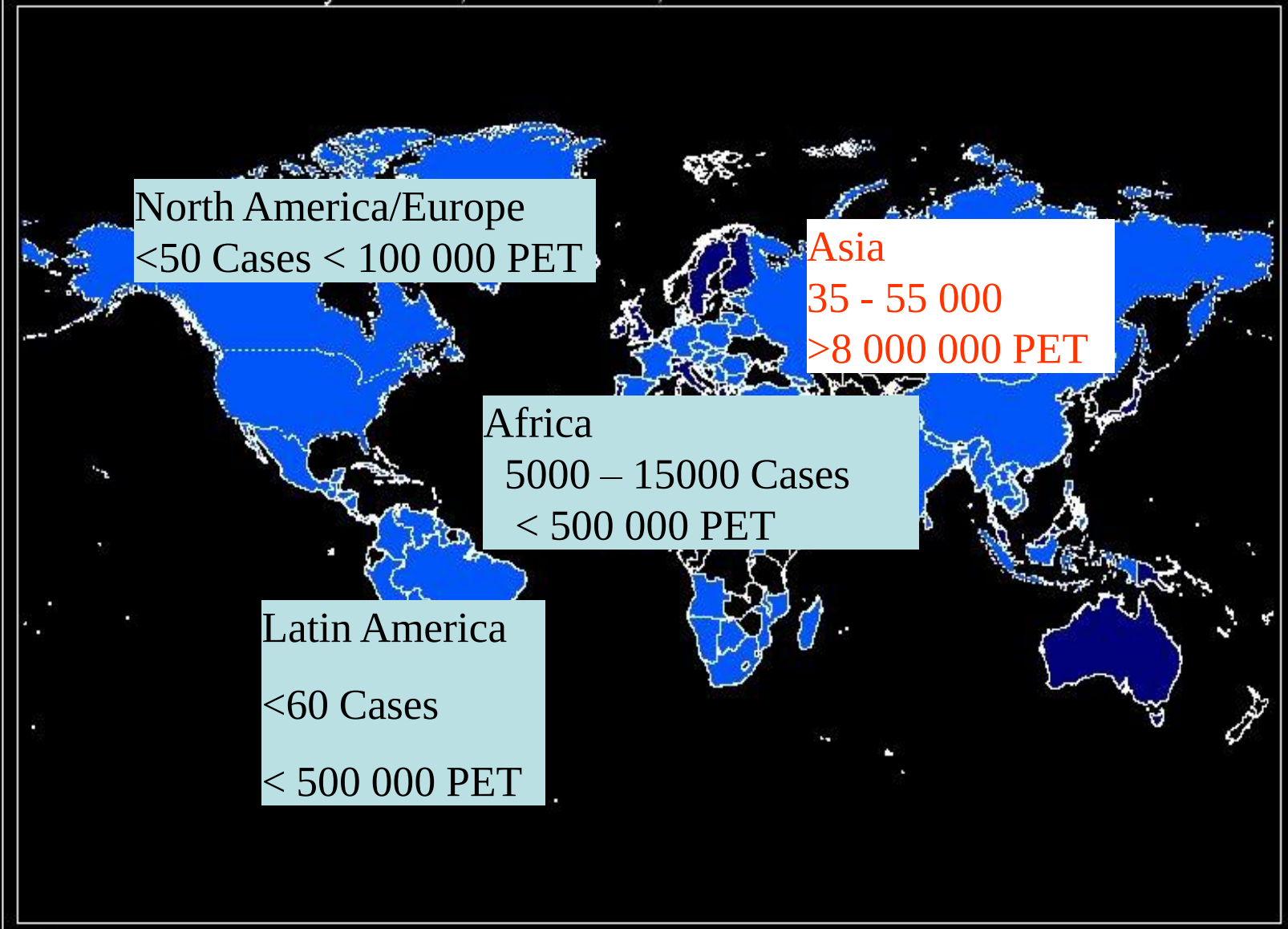
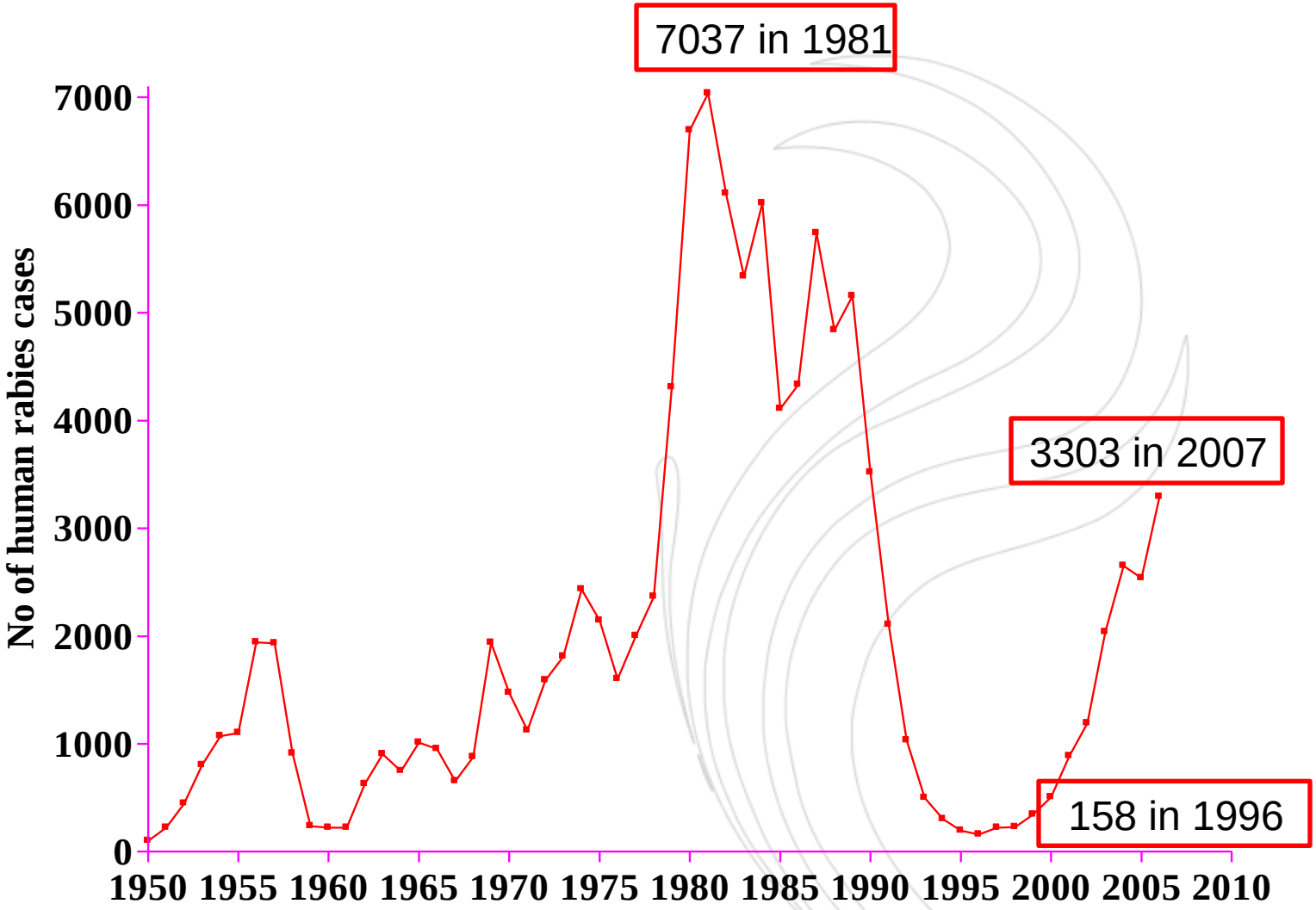
Occurence of Rabies in Countries

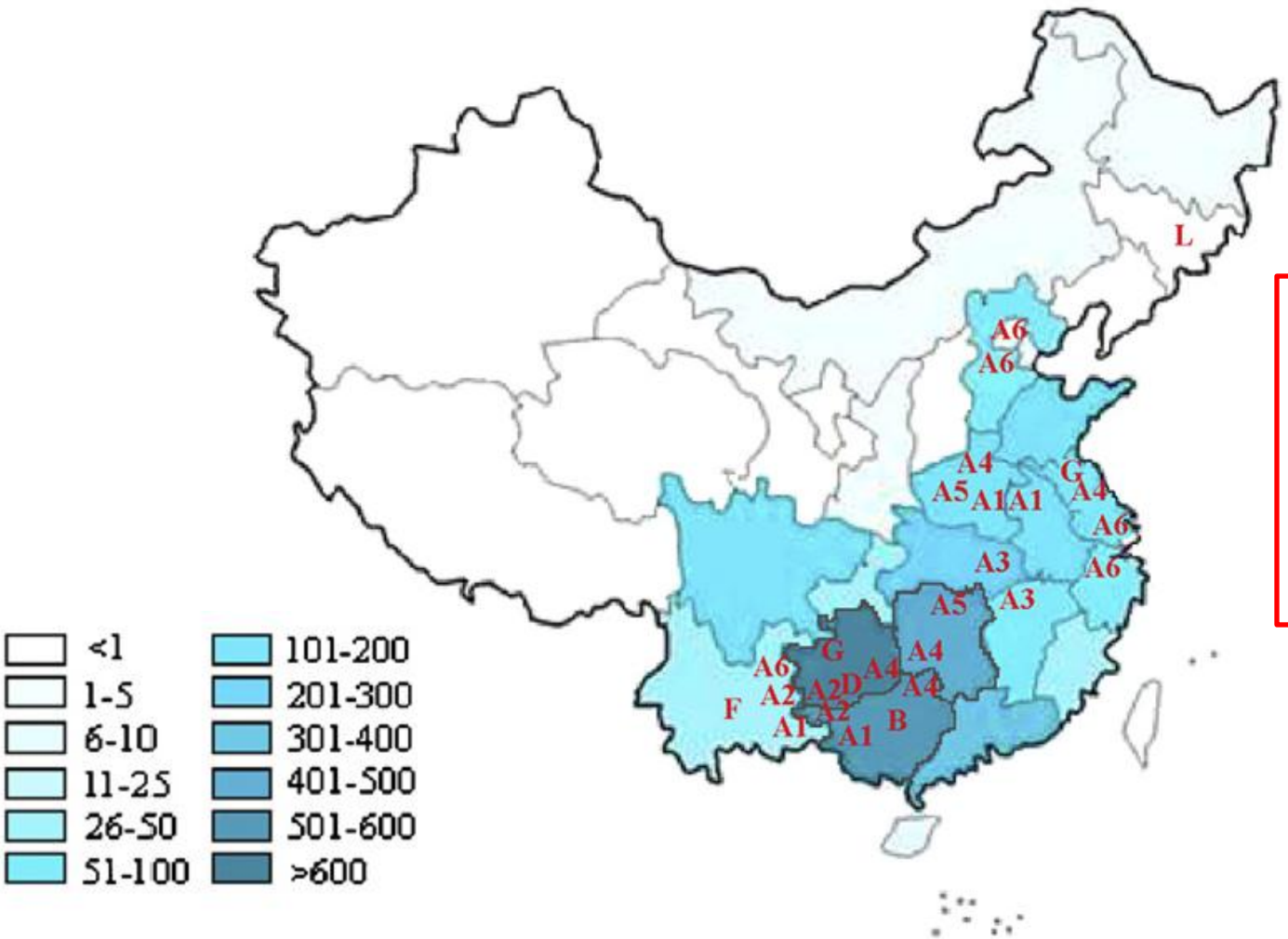
Rabies endemicity status, worldwide, 2000



The human rabies cases in China from 1950-2007



Geographical distribution of RABV in China



Jiangsu
Hunan
Guangxi
Guangdong
Jiangxi

Y.-Z. Zhang et al. / Infection, Genetics and Evolution 9 (2009) 87–96

Outlines

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Rabies control in China

1. Epidemiological surveillance

Surveillance system

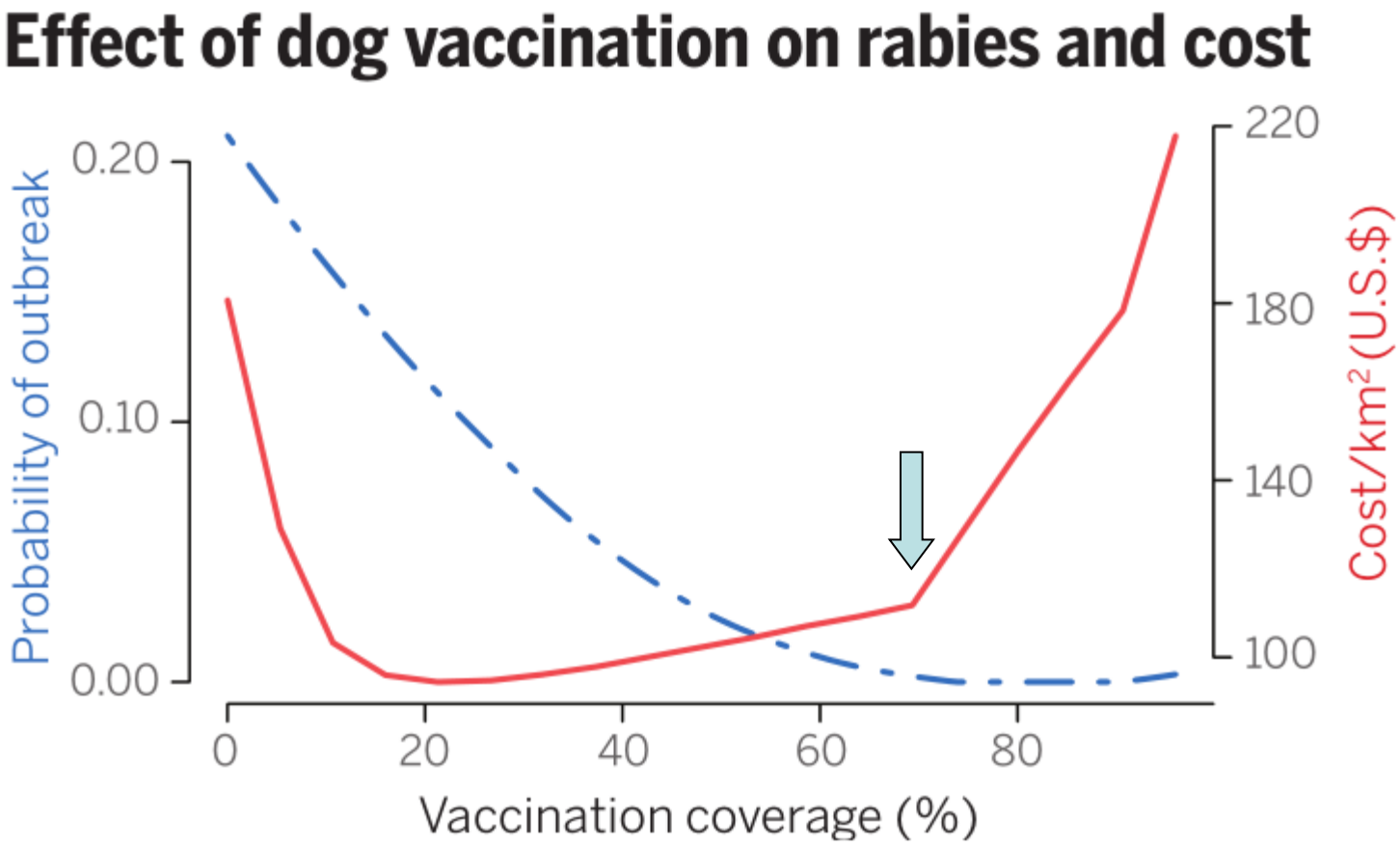
2. Mass vaccination

vaccines used in human and animals

3. Dog population control

vaccinated, licensed

Mass vaccination



Lankester et al. Science. 2014. 345(6204):1562-1564.

Vaccination of dogs in China

- **Low <u>vaccination</u> coverage: in city areas, dog rabies vaccination coverage is less than <u>70%</u>; in rural areas, this coverage is even less than <u>3%</u>.**

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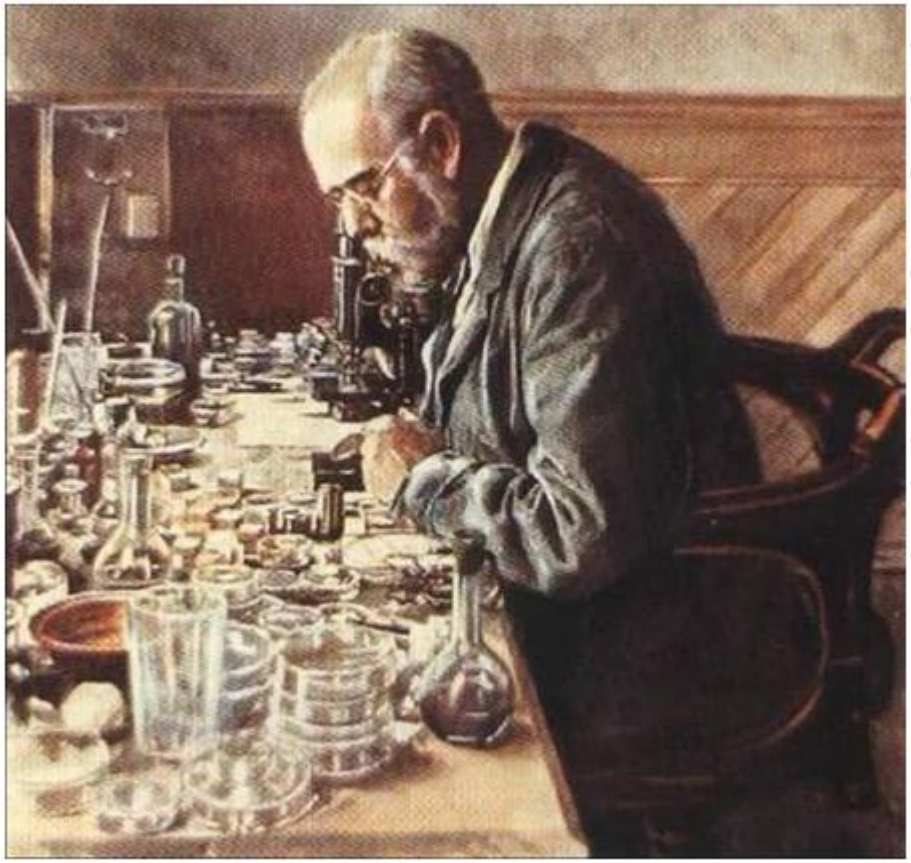
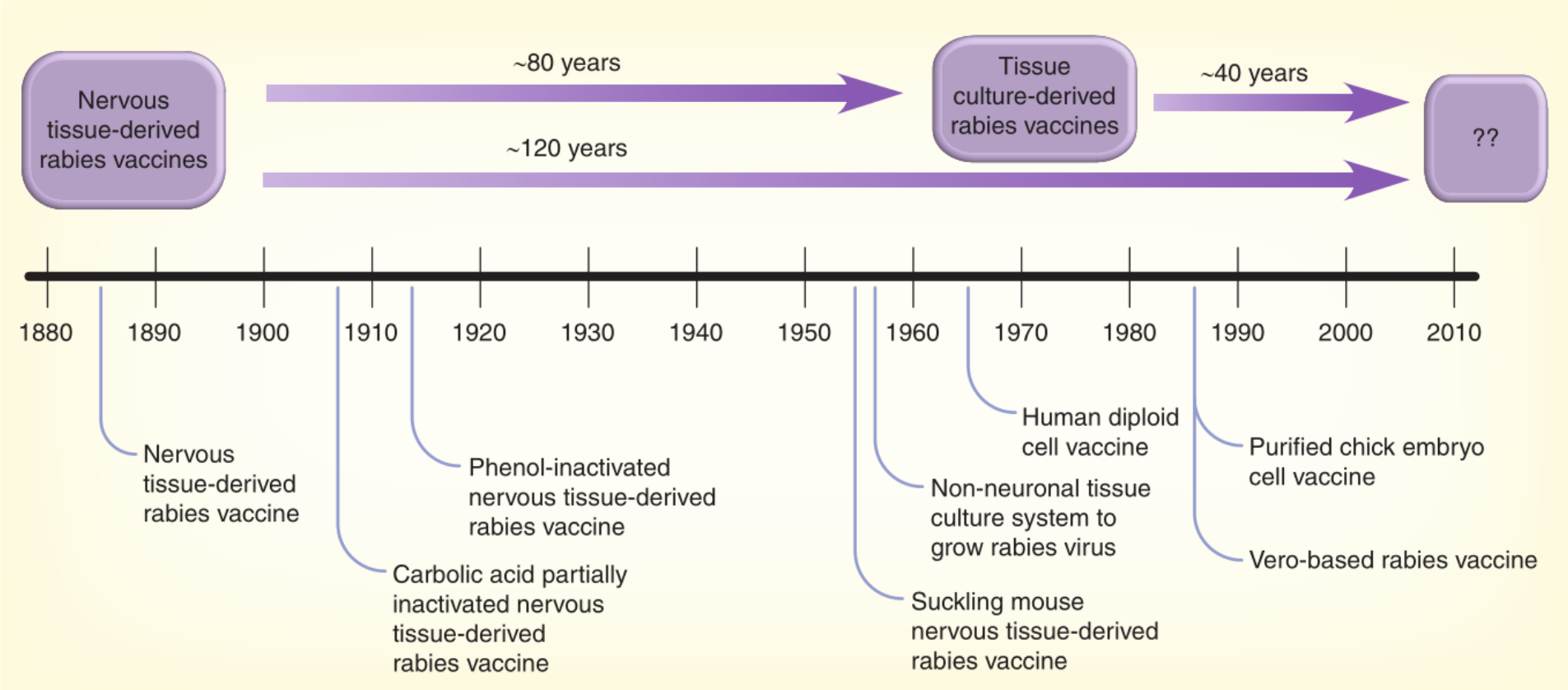
First vaccine



•Louis Pasteur (1885)

Timeline of human rabies vaccine development



McGettigan et al. Expert Rev. Vaccines. 2010

Rabies vaccine in China

Human	Domestic animals	Wildlife animals
Inactivated vaccines: aG, CTN-1, PM, PV strain primary hamster kidney cell culture vaccine (PHKCV), 1980; CTN-1 in Vero cells, 2000; purified Vero cell rabies vaccine (PVRV), 2006; the human diploid cell culture vaccine (HDCV)	Inactivated vaccines: LEP-Flury CVS-11 SAD	Recombinant vaccines: under development

Pros and Cons

	Inactivated vaccine	Attenuated live vaccines	Recombinant vaccines
Advantages	High safety	High efficiency ***And*** Low cost	High efficiency ***And*** Oral immunization
Disadvantages	Expensive ***And*** Multiple doses (≥ 4)	Cause diseases for young ***or*** immunocompromised individuals	Induce local reactions

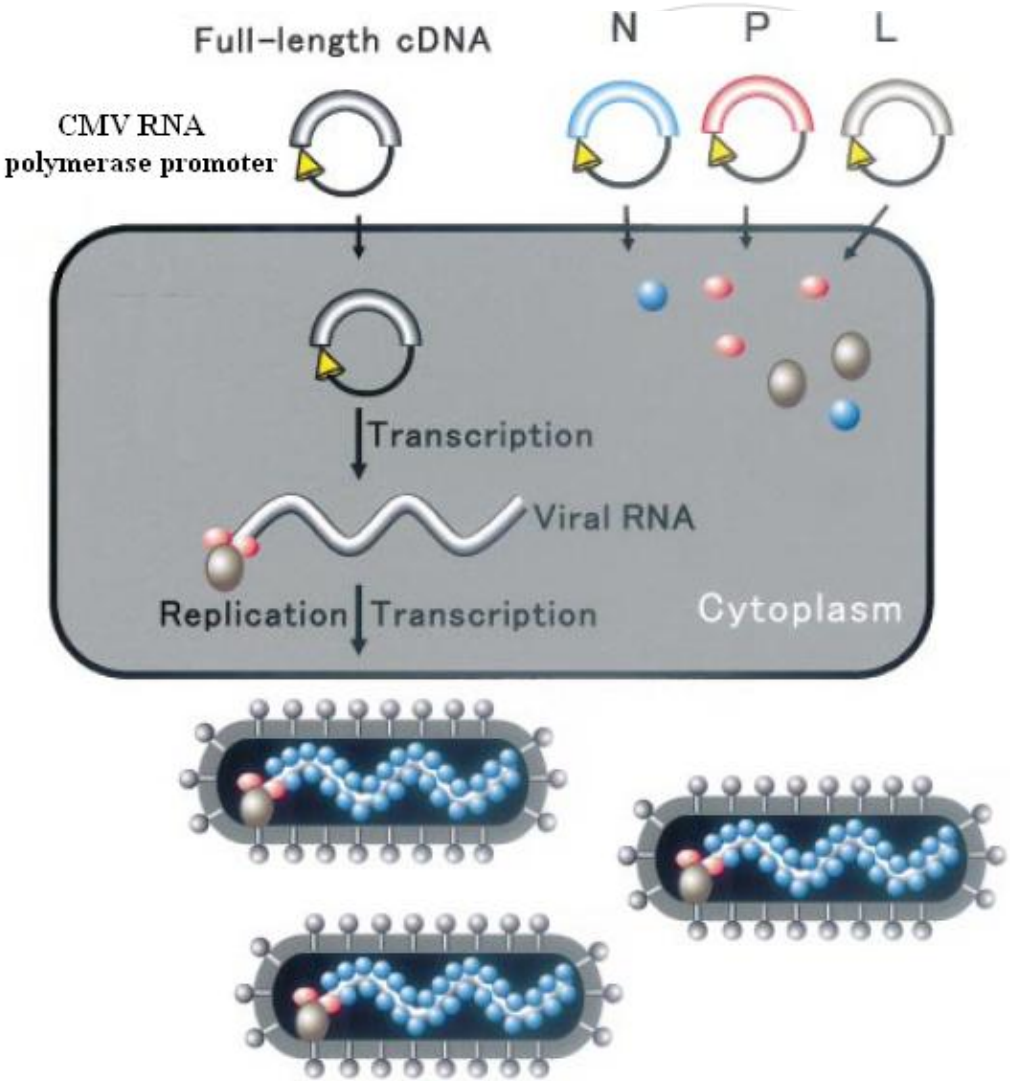
Subunit rabies vaccine

1. **Newcastle disease virus expressing RABV G protein (Journal of virology, 2011)**

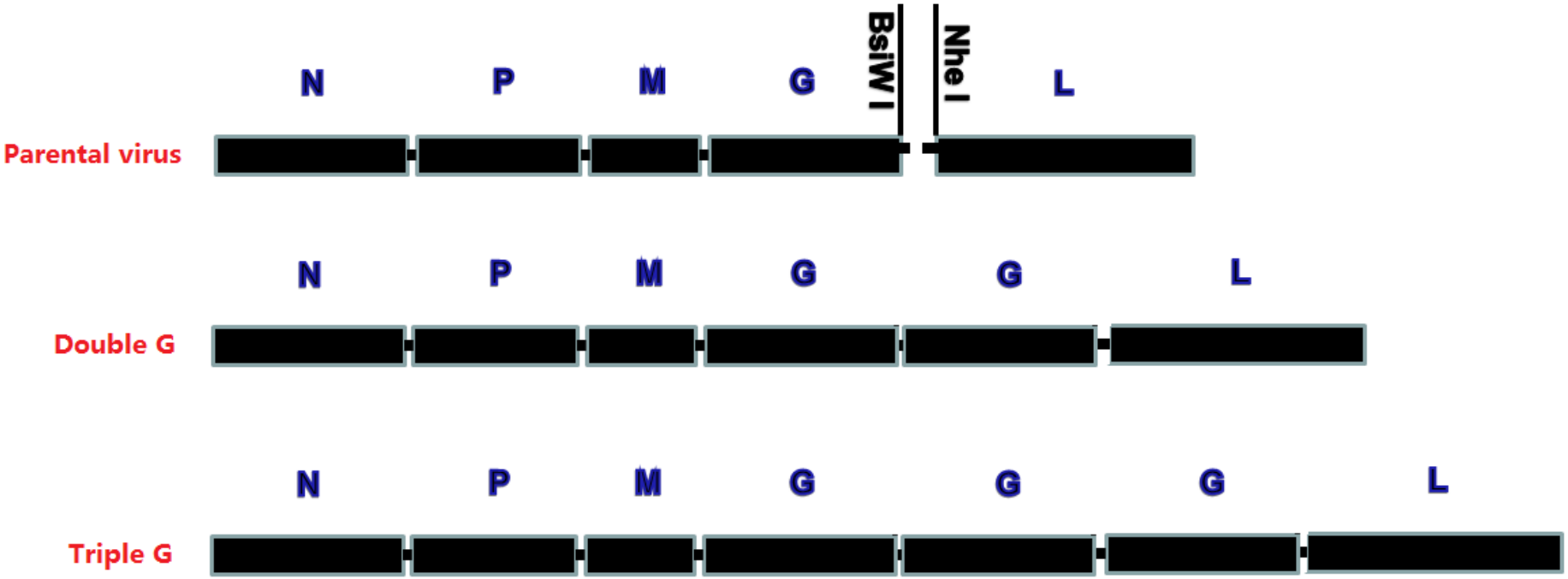
2. **Parapoxvirus expressing RABV G protein (Journal of virology, 2012)**

3. **Canine parainfluenza virus expressing RABV G protein (Journal of virology, 2012)**

Recombinant RABV with reverse genetics

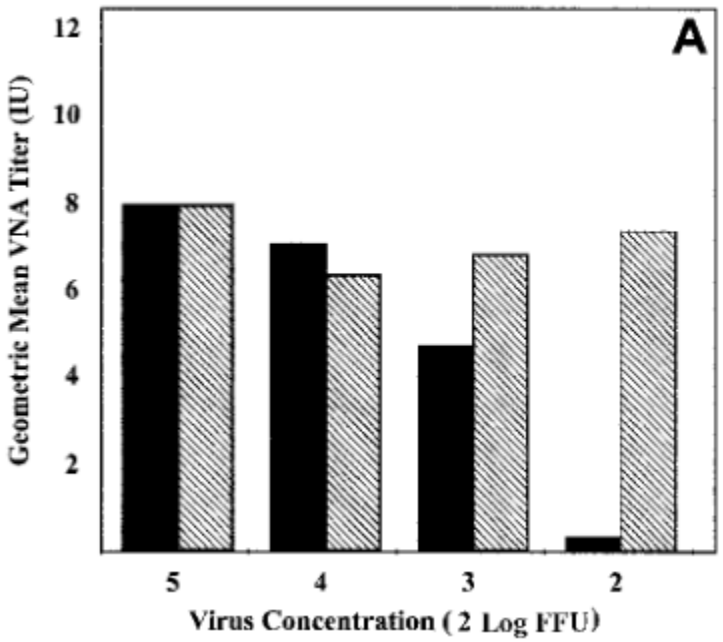


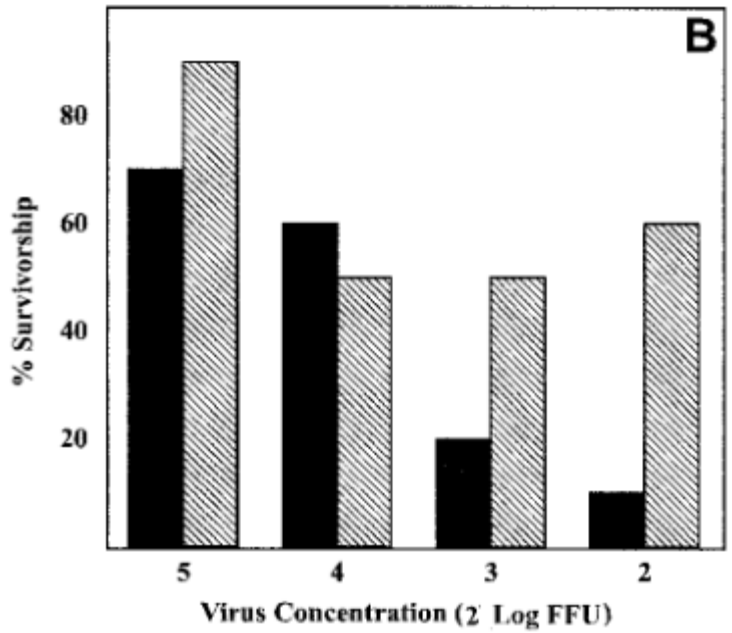
The construction of the recombinant vaccines enhancing glycoprotein expression



More glycoprotein, higher VNA titers!

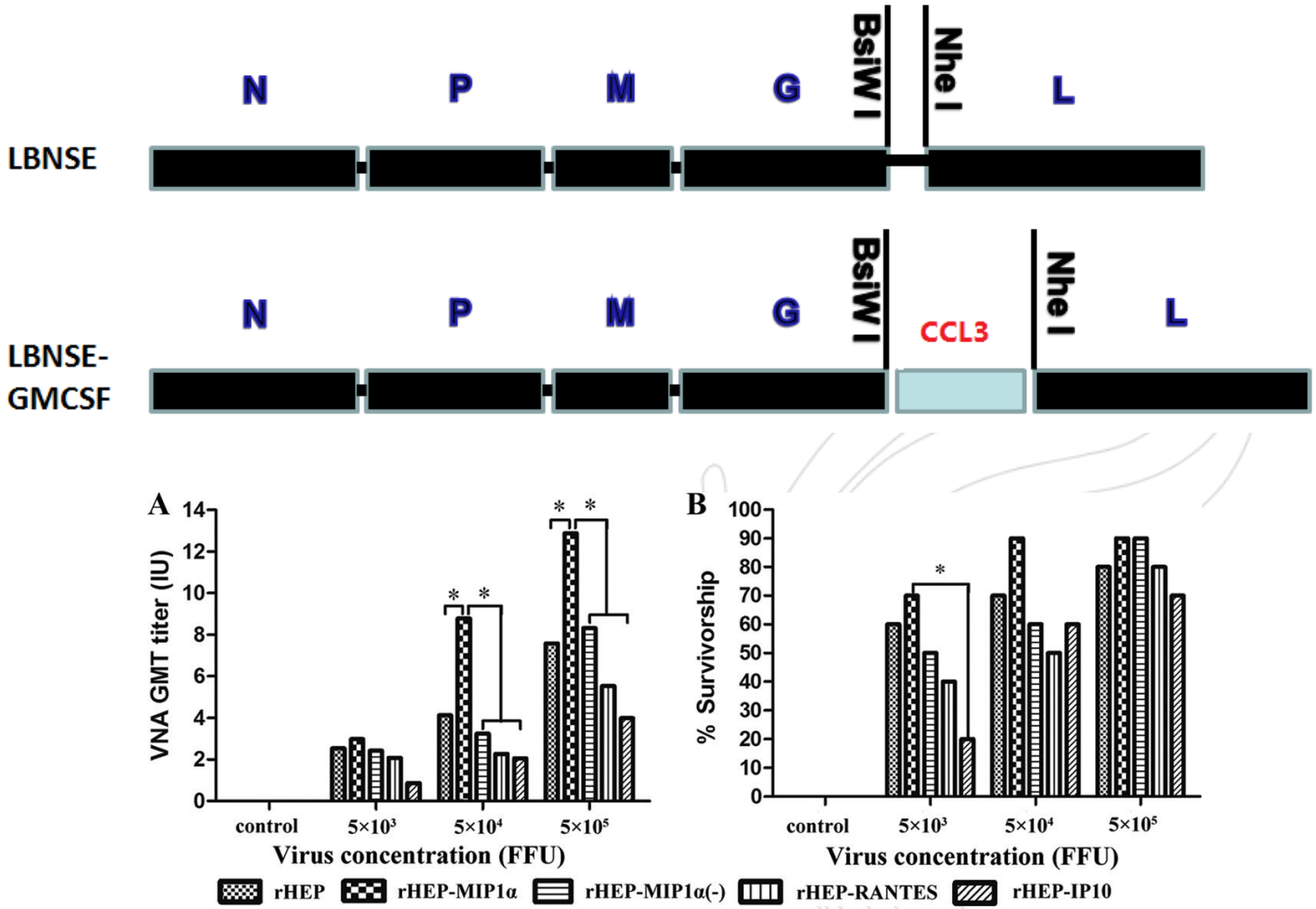
Overexpression of the rabies virus glycoprotein results in antiviral immune response





Faber et al. Journal of Virology. 2002

The construction of the recombinant vaccines stimulating innate immunity

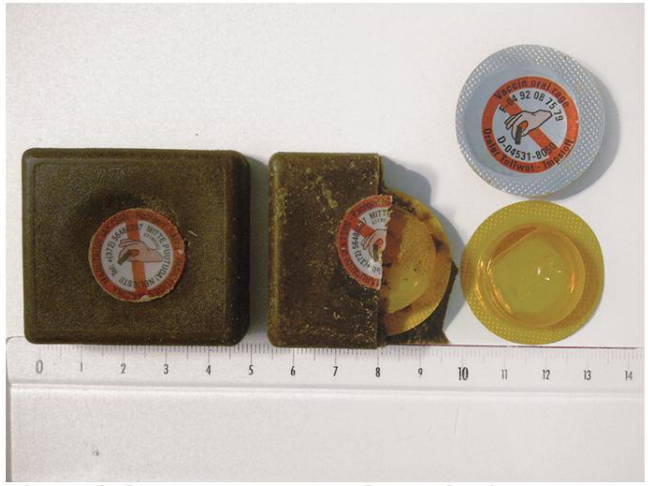


Stray dogs and wild animals




Oral rabies vaccine

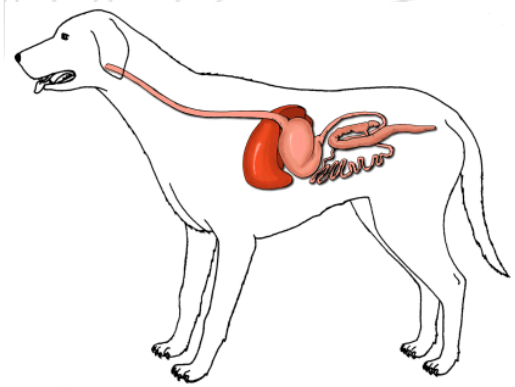
1. **SAD or SAD modified live-attenuated rabies vaccine-SAG2 (Europe)**



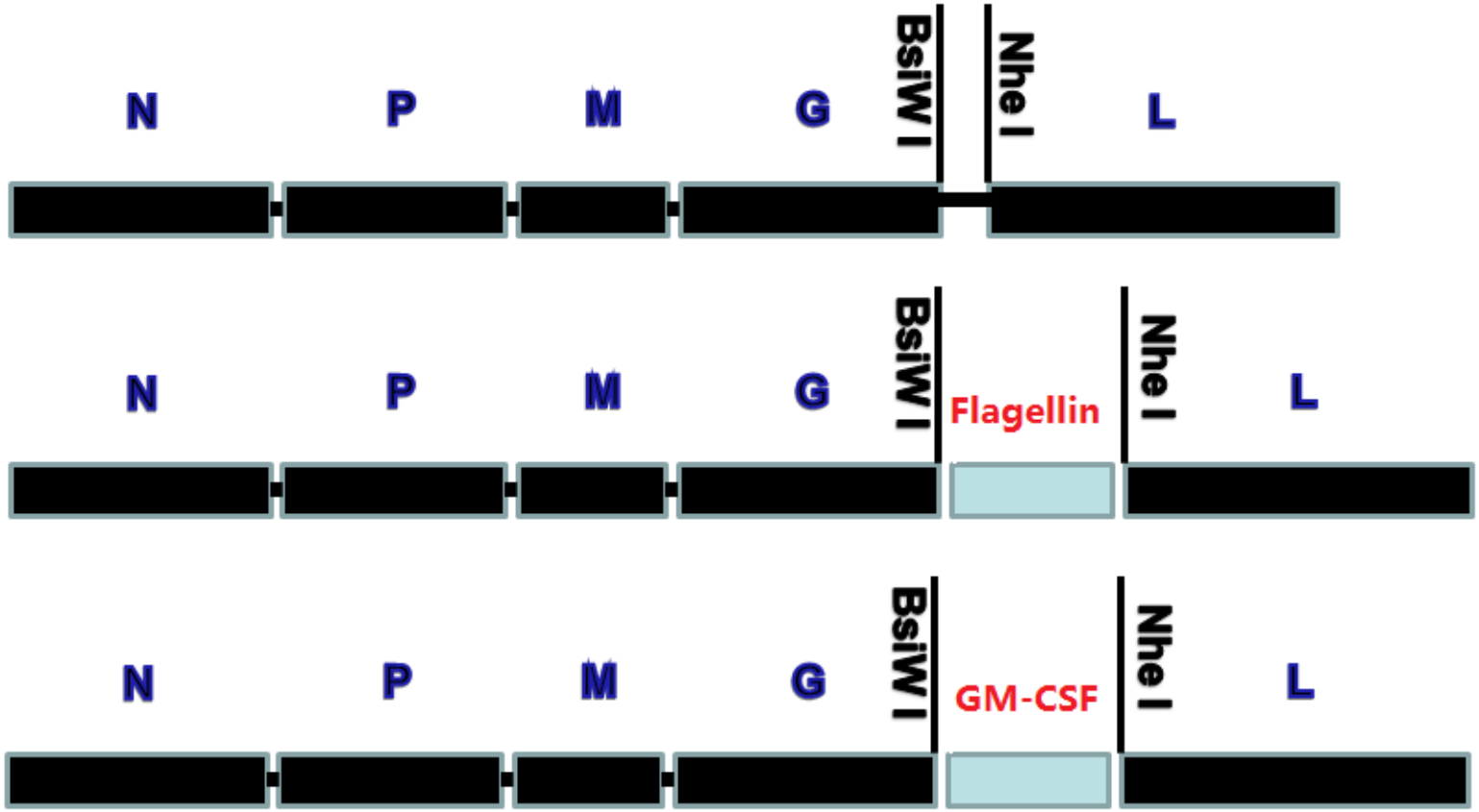
2. **Vaccinia virus expressing rabies virus glycoprotein (US)**

Obstacles for oral vaccination

- Short windows
- Hard to induce mucosal immunity
- Low VNA titers



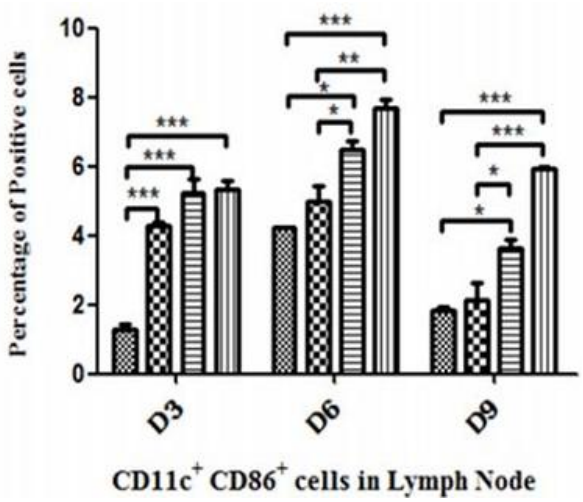
The construction of the recombinant oral vaccines



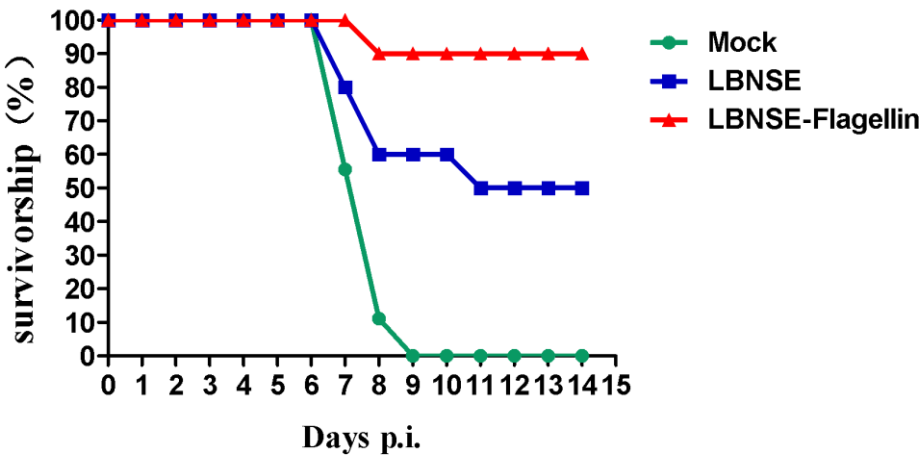
GM-CSF: granulocyte-macrophage colony stimulating factor

Oral vaccine

- 控制发展中国家狂犬病的关键是众多流浪犬的免疫，而流浪犬的有效免疫方式是口服免疫,而犬的口服免疫效果通常比较差。
- 表达沙门氏菌鞭毛蛋白（Flagellin）的重组疫苗能够有效刺激TLR5信号通路，激活树突状细胞和B细胞，促进体液免疫的发生，最终提高口服性疫苗免疫效果。



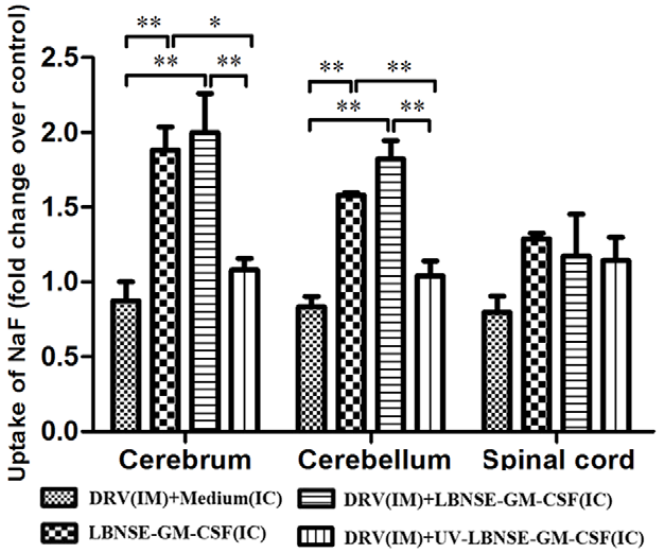
激活树突状细胞



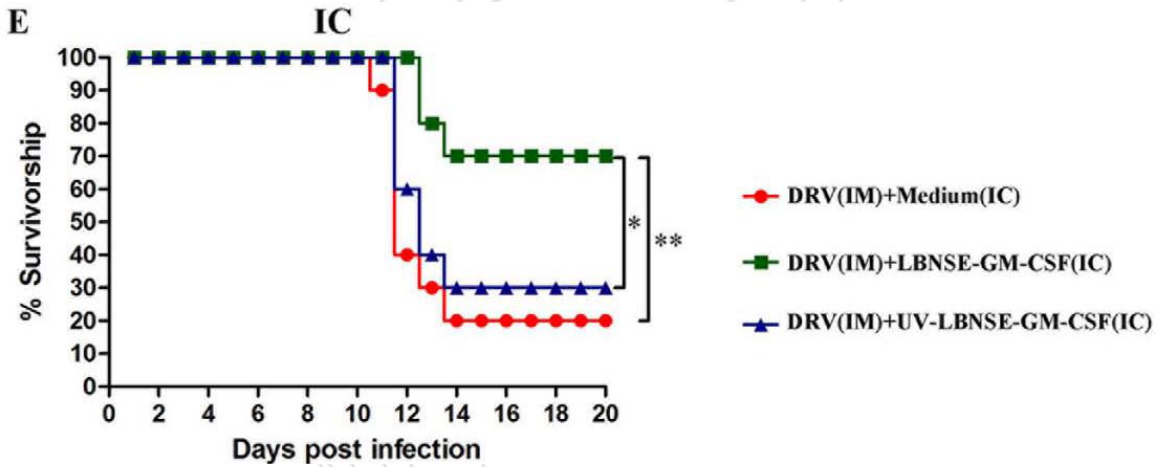
提高小鼠保护率

Therapeutic vaccine

- 在小鼠感染狂犬病野毒5天后，大脑直接注射表达粒细胞集落因子（GM-CSF）的重组病毒仍然能够清除野毒而保护动物不发病，可作为治疗性疫苗。



促进血脑屏障打开



小鼠存活率增加

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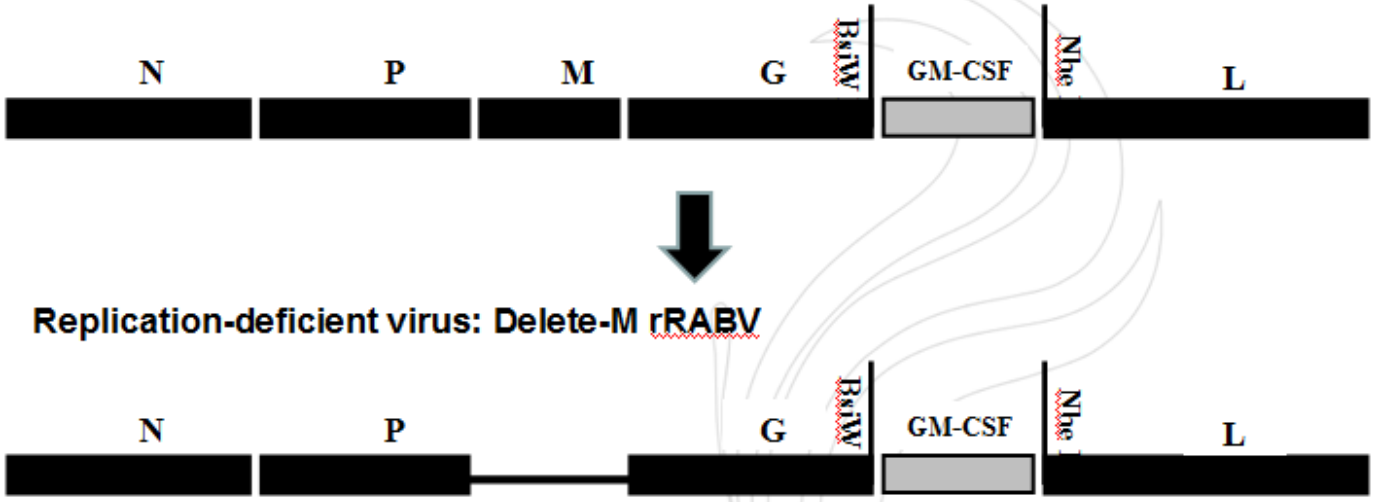
Perspective for future RABV vaccines

1. Live attenuated vaccine for animals

- high safety, low cost, high efficiency
- replication-defective vaccines
- reduce to one shot



Perspective for future RABV vaccines

2. Oral vaccine for animals

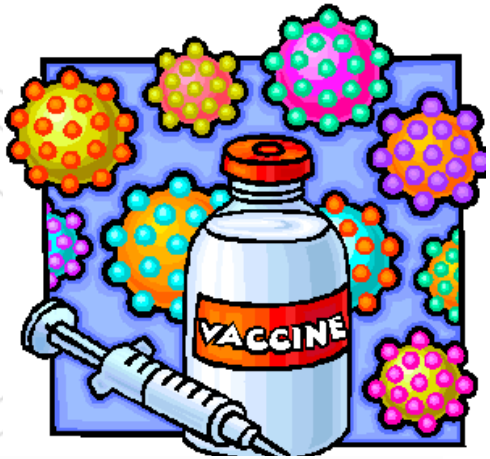
- Used for stray dogs and wild animals
- Live-attenuated rabies vaccine expressing GM-CSF
- Themo-stability
- Bait design?

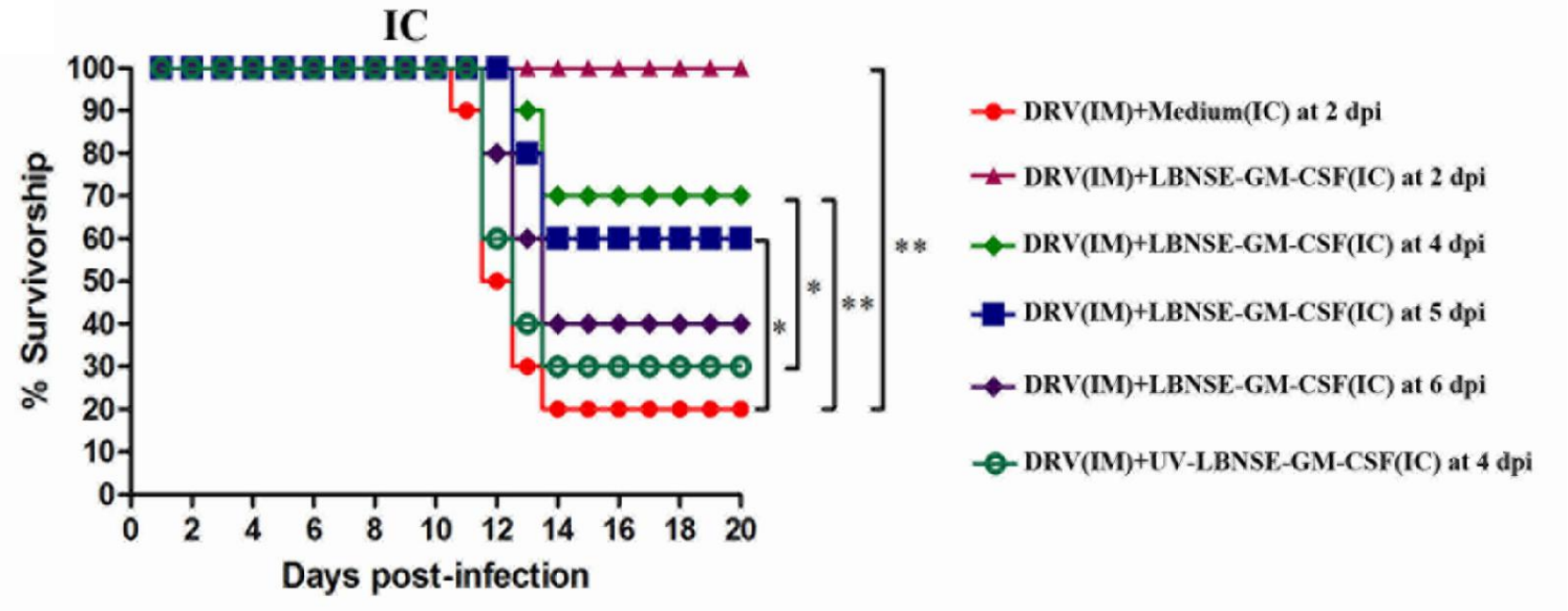
Bait containing oral rabies vaccine
(dimensions 1 1/4" X 1 1/4" X 3/4")

Perspective for future RABV vaccines

3. Therapeutic vaccines for human

- Induce production antibody and enhance the permeability of BBB
- Live-attenuated rabies vaccines SAD-TriG and SAD-GM/CSF were tested in a mouse model



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