Hot Science Cool Talks

UT Environmental Science Institute

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Biological Weapons and Bioterrorism

Dr. Brent L. Iverson

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Biological Weapons and Bioterrorism

The History, the Danger, and What American Science is Doing About It

Dr. Brent L. Iverson

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Take Home Lessons:

1. Biological weapons are cheap to make and easy to conceal.

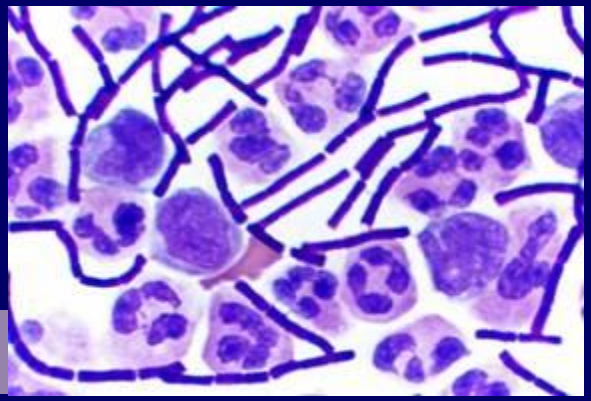
2. They have been of little military significance thus far, but of tremendous value from a propaganda perspective

3. Points 1 and 2 make biological weapons ideal for terrorism

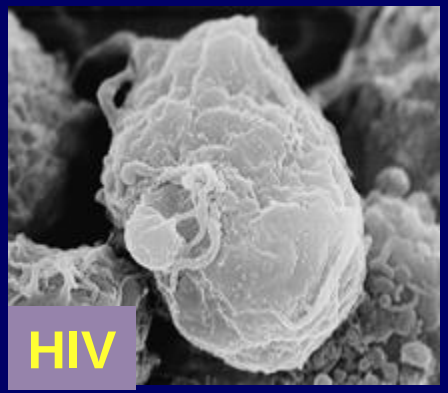
4. American scientists are still playing “catch-up”, but have created several promising approaches to reduce the threat of biological weapons

What are Biological Weapons?

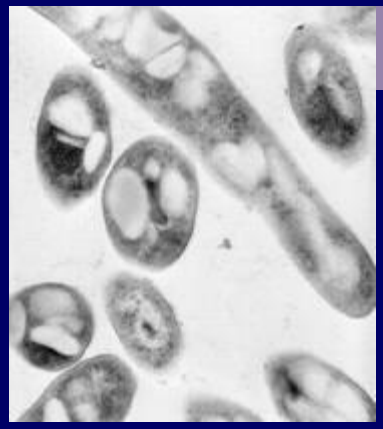
Biological weapons are any disease causing bacteria, virus, or natural toxin that can be used against an enemy



Anthrax



HIV



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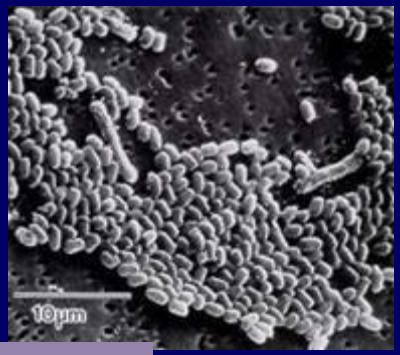
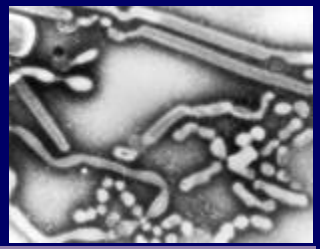
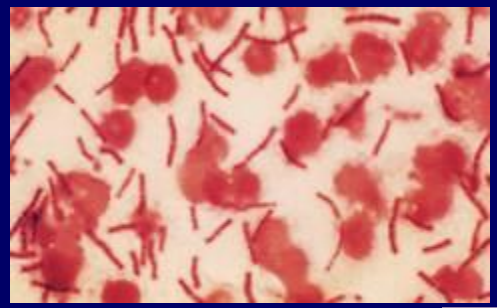


Anthrax



Influenza A

Ebola



Anthrax

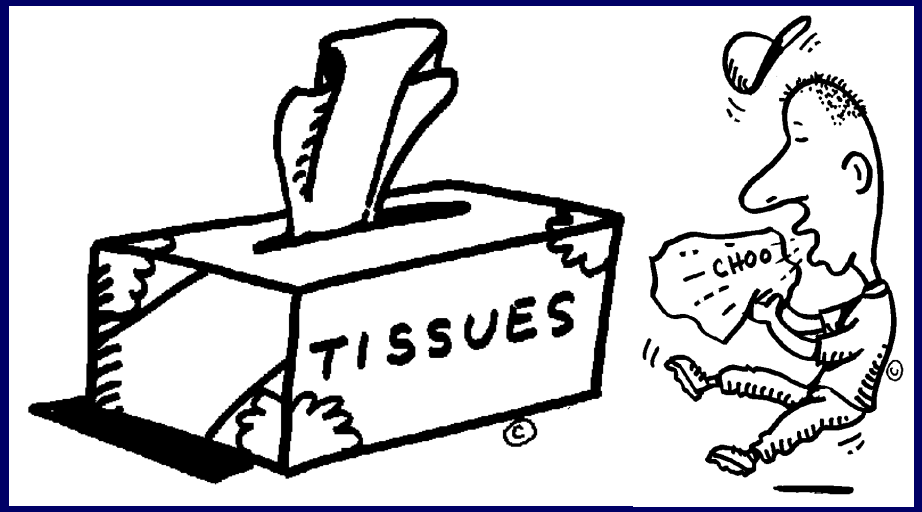
What are Biological Weapons?

There is a so-called “Australia Group list” of potential bioweapons for use against humans that has 20 viruses (ex. smallpox, Ebola), 13 bacteria (ex. anthrax, plague), and 19 toxins (ex. botulinum toxin, ricin)

http://projects.sipri.se/cbw/research/AG-bw-list-02.html

What are Biological Weapons?

Some are infectious, some are not, some kill you quickly, some only make you feel real bad. Almost all start out with mild symptoms…… "I thought it was the flu"

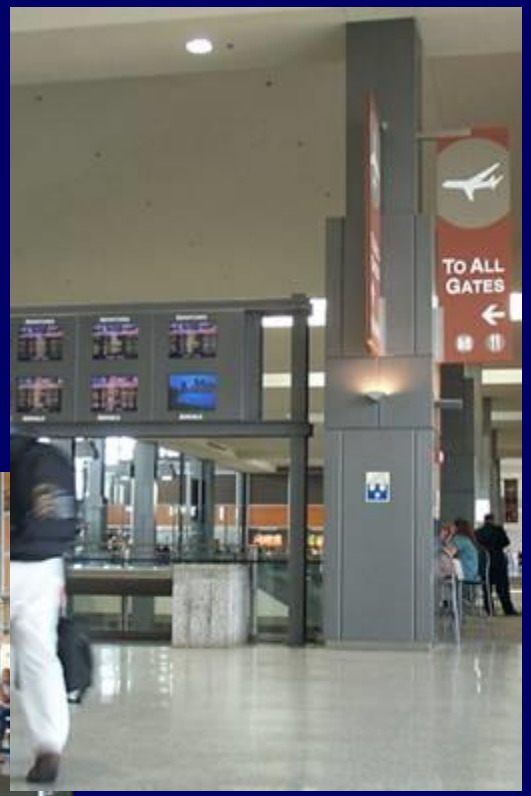


There is an analogous list for crop plants and livestock

http://projects.sipri.se/cbw/research/AG-bw-list-02.html

What are Biological Weapons?

Highly contagious agents are easy to spread on a small scale, just have an infected individual walk through an airport.



What are Biological Weapons?

Non-contagious agents (anthrax or botulinum toxin) or a large scale attack require “weaponization” - making the agents in a form that causes maximum infection and/or death.

“Weaponization” involves making particles of just the correct small size (a few microns) to 1) “float” in air instead of settling, 2) evade body’s “particle” defenses, and 3) penetrate deep into lungs.

The germs or toxins are adsorbed onto inert particles of the appropriate size. This process is the “secret” of germ warfare.

Miller, J. *et al*., “Germs”, Simon and Schuster, 2001

What are Biological Weapons?

Why is anthrax a popular bioweapon?

Anthrax is natural bacteria found in environment - easy to get

Has two states:

1) quickly growing bacteria that kill mammalian host
2) spore state that survives in environment for decades.

Spores can be mass produced using common equipment

Anthrax is infectious, but not contagious so killing can be more easily “controlled”

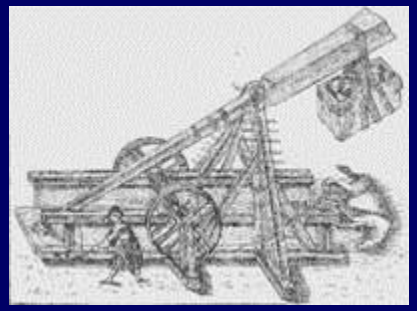
In weaponized form, as few as 8,000 - 10,000 inhaled spores will kill a healthy adult.

Meselson, M. *et al*., Science, **1994**, *266*, 1202-1208

Mock, M. and Fouet, A., Ann. Rev. Microb., **2001**, 55, 647-71

An Abbreviated History

Biological Weapons have been contemplated since antiquity



Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are two often cited examples:

14th Century - Tartars' siege of the city of Kaffa. The Tartars catapult cadavers infected with plague into city

see image of Kaffa at
http://nautarch.tamu.edu/PROJECTS/crimea/crimea.htg/shipf.gif

see image of trebuchet at
http://www.fogelvrei.de/img/Pest_karren.jpg

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

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14th Century - Tartars' siege of the city of Kaffa. The Tartars catapult cadavers infected with plague into city

Although plague did eventually lead to the surrender of Kaffa, most experts doubt the cadavers were effective

Plague epidemic and infected rodents were already in the area (hence the cadavers), the fleas that transmit the disease greatly prefer plague infected rodents to cadavers

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

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18th Century - British commander Sir Jeffrey Amherst orders blankets used in smallpox clinic given to Native Americans as gifts

Sir Jeffrey Amherst

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are two often cited examples:

18th Century - British commander Sir Jeffrey Amherst orders blankets used in smallpox clinic given to Native Americans as gifts

Smallpox is spread most effectively through direct inhalation of respiratory droplets (coughing), blankets were likely not that contagious

Although a devastating smallpox epidemic did occur among Native Americans at this time, previous contact with early settlers is likely the major cause

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed military examples:

Various native warriors dipped arrows and spears in biological poisons (ex. “arrow frogs” of South America).

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed military examples:

In WWI, Germans targeted livestock and cavalry horses in various European countries using animal specific diseases. This was apparently very successful.

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed military examples:

In WWII, Japanese admitted to launching at least 11 attacks on Chinese cities using pathogens including Anthrax, Cholera, Salmonella, and Plague.

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An Abbreviated History

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There are confirmed military examples:

In WWII, Japanese admitted to launching at least 11 attacks on Chinese cities using pathogens including Anthrax, Cholera, Salmonella, and Plague.

Unknown civilian casualty numbers, but believed to be in the tens of thousands, in addition to over 10,000 deaths of Chinese prisoners used for experiments!

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

The main impact of biological weapons has been propaganda:

China, the Soviet Union, and North Korea accused the US of using biological weapons in the Korean war.

Leitenberg, M. Crit. Rev. Microb., **1998**, *24*, 169-194

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

The main impact of biological weapons has been propaganda:

Allegations have now been shown to be fraudulent, but this proved to be extremely effective campaign that took the US years to overcome.

During the Cold War, superpowers traded accusations without substantiation …….until Soviet defections…….These were very successful and powerful propaganda campaigns since you do not need a “smoking gun” i.e. a missile or bomb to make accusation.

Leitenberg, M. Crit. Rev. Microb., **1998**, *24,* 169-194

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed recent terrorist/criminal examples:

1984 in rural Oregon a religious cult infected 751 residents with food poisoning through Salmonella contamination at 10 restaurants in an attempt to win local elections.

Christopher, *et al*., JAMA, **1997**, *278*, 412-417
Torok, *et al*., JAMA, **1997**, *278*, 389-395
Kolovic, *et al*., JAMA, **1997**, *278*, 396-398

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed recent terrorist/criminal examples:

Early 1990's the Japanese Aum Shrinrikyo cult released Anthrax in Tokyo, but no known victims. Apparently, this was not "weaponized" correctly.

Christopher, *et al*., JAMA, **1997**, *278*, 412-417

Torok, *et al*., JAMA, **1997**, *278*, 389-395

Kolovic, *et al*., JAMA, **1997**, *278*, 396-398

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed recent terrorist/criminal examples:

1996 the pathogen that causes dysentery was introduced into pastries in the break room of the St. Paul's Medical Center in Dallas, infecting 45.

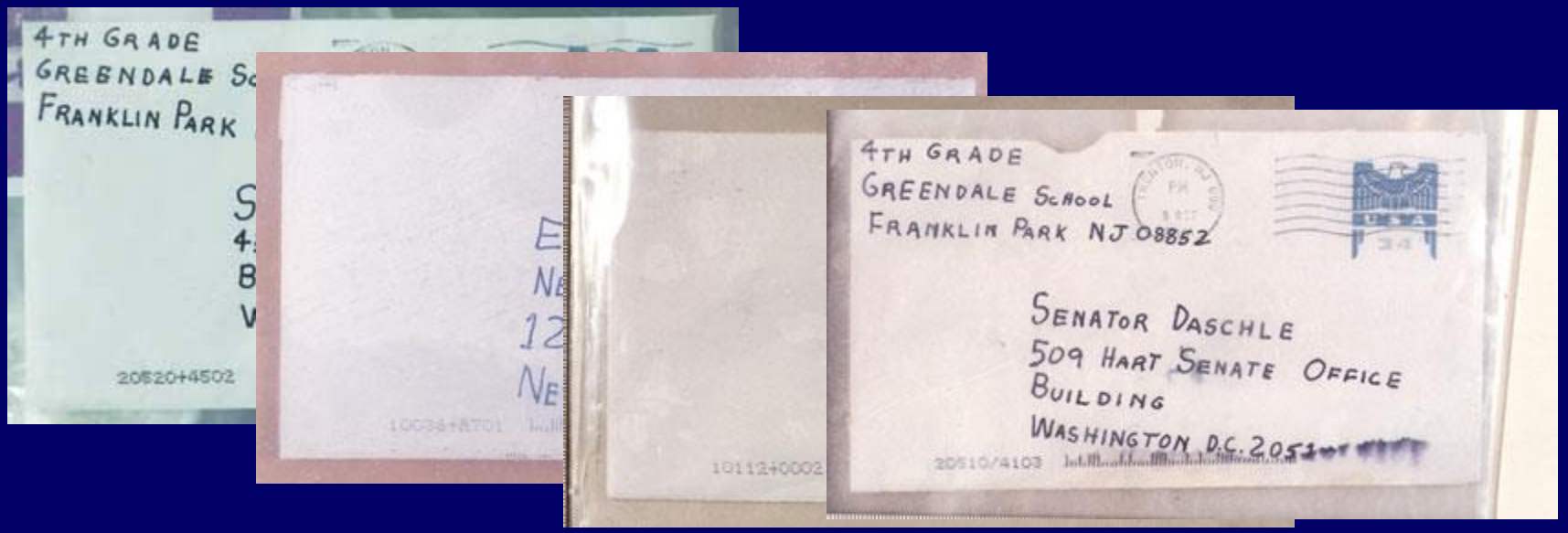
Christopher, *et al*., JAMA, **1997**, *278*, 412-417
Torok, *et al*., JAMA, **1997**, *278*, 389-395
Kolovic, *et al*., JAMA, **1997**, *278*, 396-398

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed recent terrorist/criminal examples:

September of 2001 Anthrax laden letters sent to several locations in US. 22 confirmed cases of anthrax were reported, 11 cases of inhalation anthrax, 5 deaths.



Inglesby, *et al*., JAMA, **2002**, *287*, 2236-2252

An Abbreviated History

Biological Weapons have been contemplated since antiquity

There are confirmed recent terrorist/criminal examples:

September of 2001 Anthrax laden letters sent to several locations in US. 22 confirmed cases of anthrax were reported, 11 cases of inhalation anthrax, 5 deaths.

A remarkable level of publicity surrounded the attack, leading to a widespread awareness and fear of bioterrorism that persists today.

With relatively little effort, a relatively small number of victims, and minimal risk of apprehension, perpetrator generated a great deal of terror.

Inglesby, *et al*., JAMA, **2002**, *287*, 2236-2252

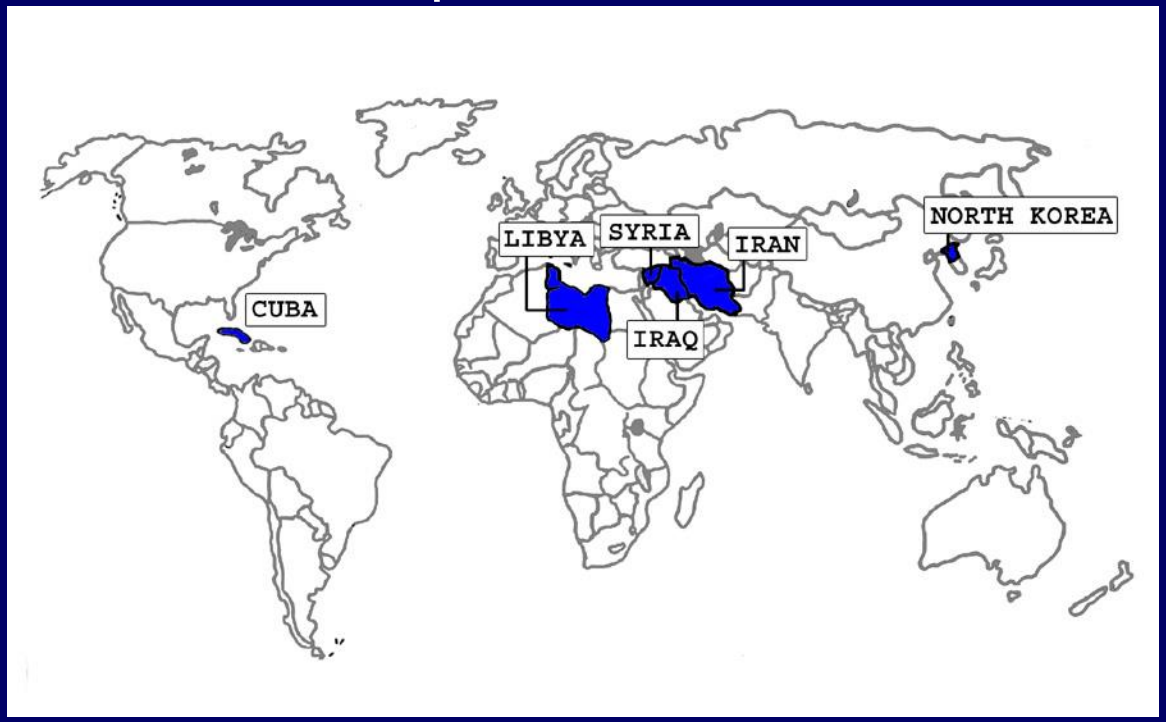
Military Production of Biological Weapons

During/After WWII, many nations carried out research and produced offensive biological weapons. (Belgium, Canada, France, Great Britain, Italy, Japan, the Netherlands, Poland, USSR, US)

Fidler, D. Microb. And Infect., **1999**, *1*, 1059-1066

Military Production of Biological Weapons

Currently 12 nations are thought to have offensive biological weapons (aka “poor man’s nuclear weapons”), including Cuba, North Korea, Libya, Syria, Iran, and Iraq.



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Military Production of Biological Weapons

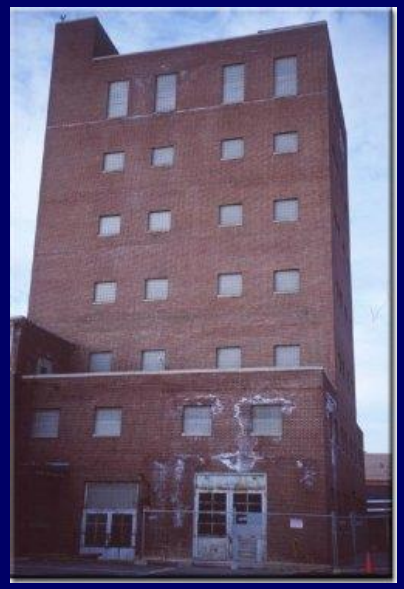
Currently 12 nations are thought to have offensive biological weapons (aka “poor man’s nuclear weapons”), including Cuba, North Korea, Libya, Syria, Iran, and Iraq.

There have been several international attempts to stop the proliferation of biological weapons with treaties, but none have proven effective.

Fidler, D. Microb. And Infect., **1999**, *1*, 1059-1066

Military Production of Biological Weapons

During the Cold War, the US had an active bioweapons program until Richard Nixon unilaterally dismantled it in 1969 and 1970 since it was not militarily significant and was a propaganda liability.



U.S. Bioweapons Research Through 1970 BC*

***"Before Cloning"**

Miller, J. *et al*., "Germs", Simon and Schuster, 2001

Military Production of Biological Weapons

"High Tech" Russian Bioweapons Research Through 2002 AC

Military Production of Biological Weapons

The Russians built an immense bioweapons production program, at one time employing ~60,000 scientists, engineers, and technicians.

Miller, J. *et al*., "Germs", Simon and Schuster, 2001

Military Production of Biological Weapons

The Russian bioweapon manufacturing and research capacity defied all reason, and was apparently underappreciated by US government until two key defections V. Pasechnik (1989) and K. Alibekov (1992).

Pasechnik

Miller, J. *et al*., "Germs", Simon and Schuster, 2001

Military Production of Biological Weapons

The Russian bioweapon manufacturing and research capacity defied all reason, and was apparently underappreciated by US government until two key defections V. Pasechnik (1989) and K. Alibekov (1992).

Pasechnik

Bioweapons facilities could be used for legitimate pharmaceuticals, so impossible to confirm via spy photos. US was fooled for decades!

Miller, J. *et al*., "Germs", Simon and Schuster, 2001

Military Production of Biological Weapons

Soviet Bioweapons Production listed as
TONS PER YEAR (Yes, this is in TONS)

E. tularensis **(Tularemia)**	**1,500**
variola virus (Smallpox)	**100**
Yersinia pestis **(Plague)**	**1,500**
Marburg virus (Hemorrhagic)	**150**
B. anthracis **(Anthrax)**	**4,500**

Pasechnik

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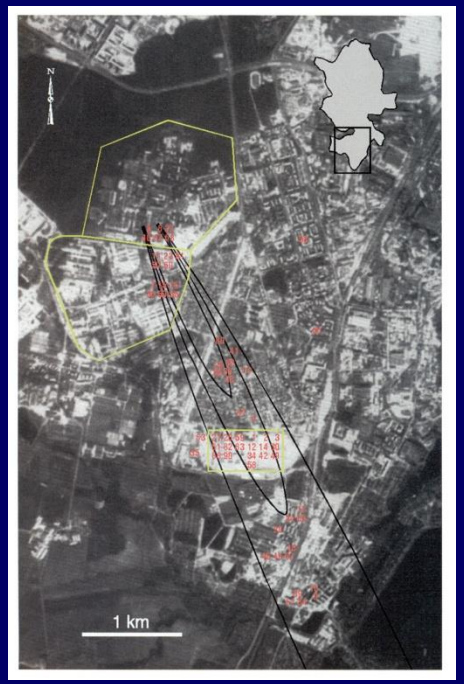
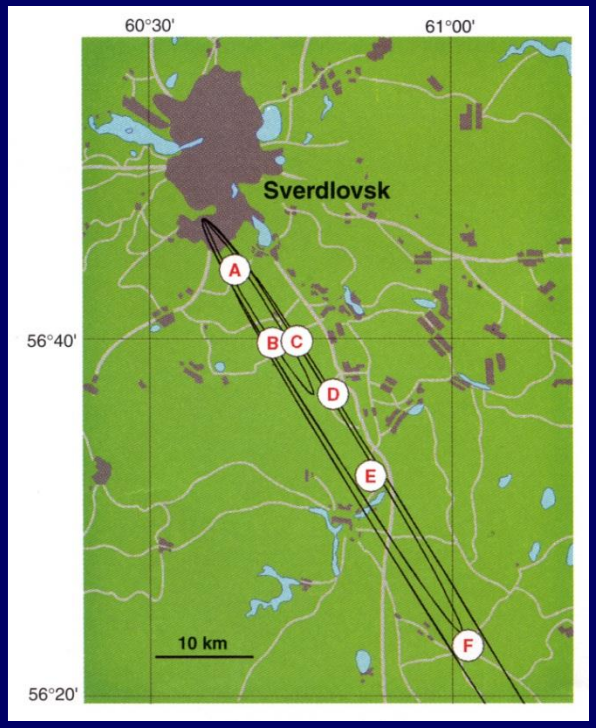
Pasechnik

Enough to kill 7.8 billion people per year!

Military Production of Biological Weapons

In 1979 a few milligrams to 1 gram of weaponized anthrax were released from manufacturing plant in Sverdlovsk, Russia.





Military Production of Biological Weapons

In 1979 a few milligrams to 1 gram of weaponized anthrax were released from manufacturing plant in Sverdlovsk, Russia.

Downwind of the accidental release, 66 people died of 77 known patients.

The U.S. was not able to confirm this until 1994.

Meselson, M., Science, **1994**, *266*, 1202-1208

Military Production of Biological Weapons

Iraq built a bioweapons program in about 5 years, and completely hid it from the outside world. It took UNSCOM's inspectors 4-5 years to find the Iraqi program after they were already inside Iraq!!!

At the start of the Gulf war, Iraq had enough anthrax and botulinum toxin to seriously hurt allied forces, but apparently no good way to disperse lethal aerosols.

Zilinskas, R., JAMA, **1997**, *278*, 418-424

Military Production of Biological Weapons

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Experts believe Iraq could rebuild its bioweapons manufacturing capabilities in around 6 months.

Zilinskas, R., JAMA, **1997**, *278*, 418-424

Military Production of Biological Weapons

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Iraq's current missile and aerosol dispersal capabilities are unknown.

Zilinskas, R., JAMA, **1997**, *278*, 418-424

Military Production of Biological Weapons

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UNSCOM left Iraq in 1998.

Zilinskas, R., JAMA, **1997**, *278*, 418-424

Take Home Lessons So Far:

1. Biological weapons are cheap to make and easy to conceal.

2. They have been of little military significance thus far, but of tremendous value from a propaganda perspective

3. Points 1 and 2 make biological weapons ideal for terrorism

What American Scientists Are Doing About It:

A lot!

Better detectors/surveillance systems and medical testing to quickly identify biological agent threats

Two different approaches to defend against a bioweapons attack:

Immunization and **Treatment**

What American Scientists Are Doing About It:

Immunizations work. HOWEVER…

The problem with immunizations (was the basis for Russian strategy): Takes around **1 year** to develop a new bioweapon,and takes US **10 years** to develop and get FDA approval of vaccine!

Vaccines must be approved on a case by case basis.

Stephan Johnston of UT Southwestern may have found the answer: a generalizable strategy for vaccine development

Tang and Johnston, Nature, **1992**, *356*, 152-4

What American Scientists Are Doing About It:

Johnston's Approach:
Immunize with genetic material from virus or bacteria, not the whole organism

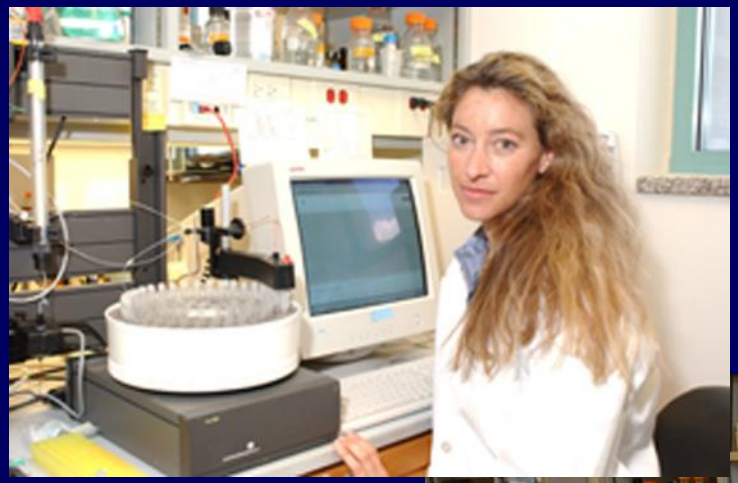
Revolutionary idea that works.

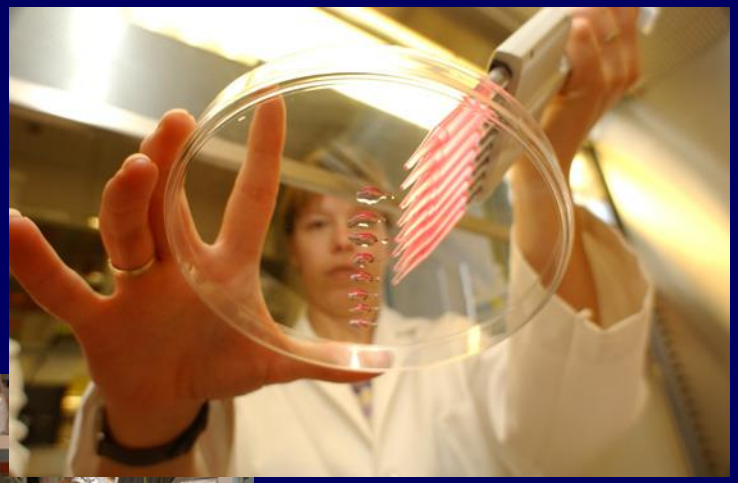
No risk of infection, since only part of genetic material used

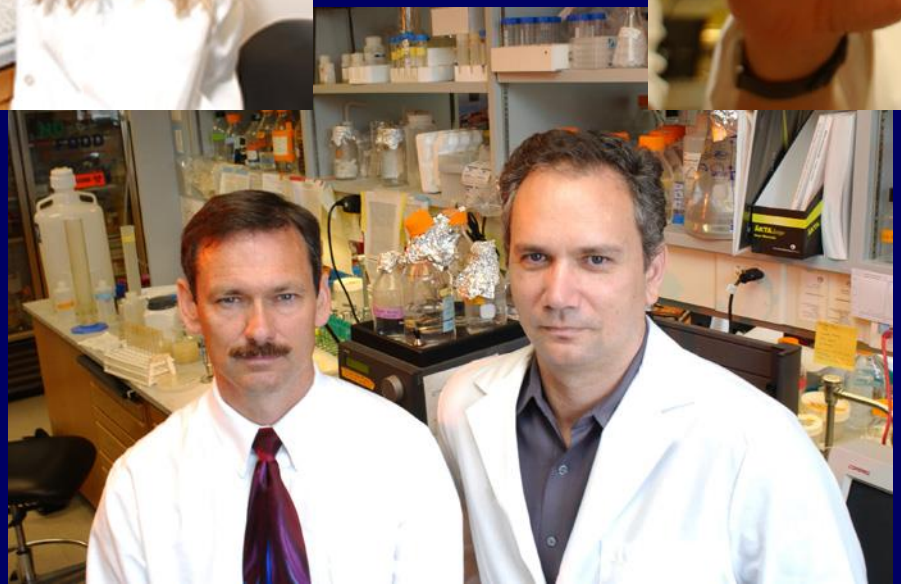
Simply change sequence of genetic material for new organism, so new vaccines are much, much faster to develop, produce, and FDA approve!

What American Scientists Are Doing About It:

We are using antibodies that have been modified with state-of-the-art genetic engineering to fight bacteria after a patient is infected.







What American Scientists Are Doing About It:

We are using antibodies that have been modified with state-of-the-art genetic engineering to fight bacteria after a patient is infected.

The approach is general and could be applied to other bacteria and toxins alike.

The idea is an old one, we have just improved upon it by incorporating engineered antibodies that can take on even infections as deadly as anthrax

Anthrax:
The Deadly Toxins Kill You, Not the Bacteria

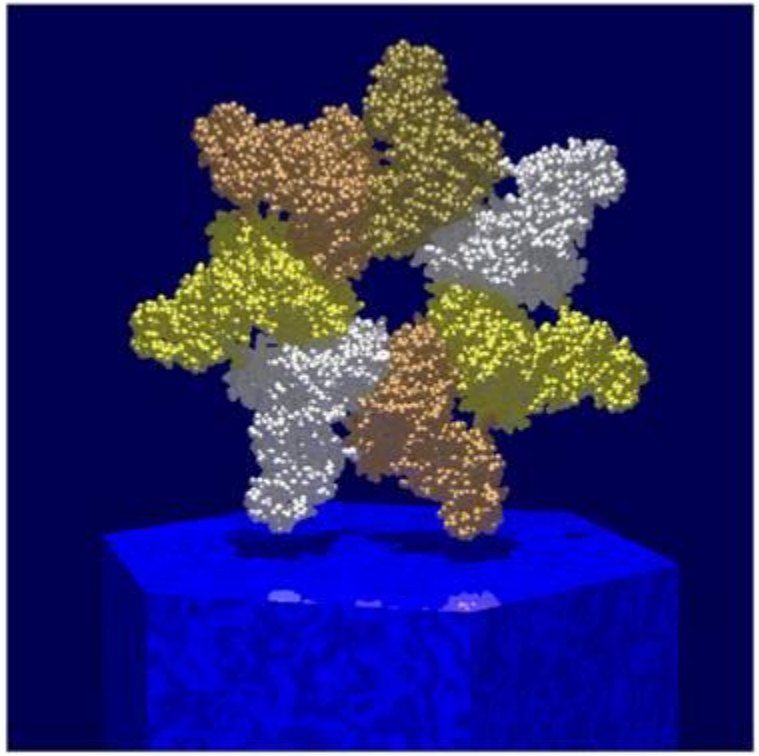
In a 1974 report, the World Health Organization panel concluded that 50 kgs of anthrax spores released from a small plane under proper atmospheric conditions would kill 95,000 out of a 500,000 population center.

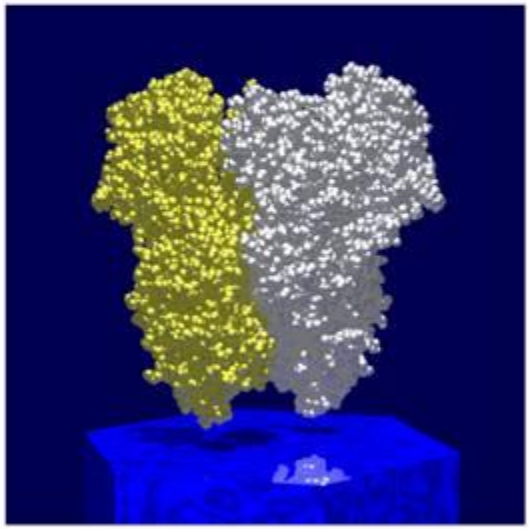
Spores are inhaled, then they germinate. (8,000 - 10,000 inhaled spores are fatal).

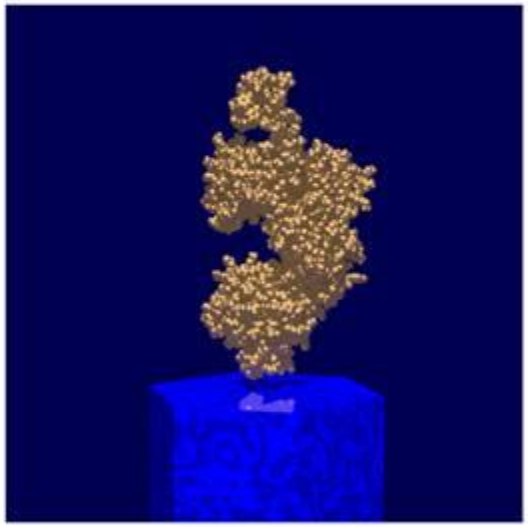
Vegetative bacteria multiply to very high levels- “I thought it was the flu”. Initial symptoms mild, so a fatal infection is present BEFORE unsuspecting patient seeks treatment

Bacteria release toxins - rapidly leads to septic shock-like symptoms and patient dies

The Three Anthrax Toxins







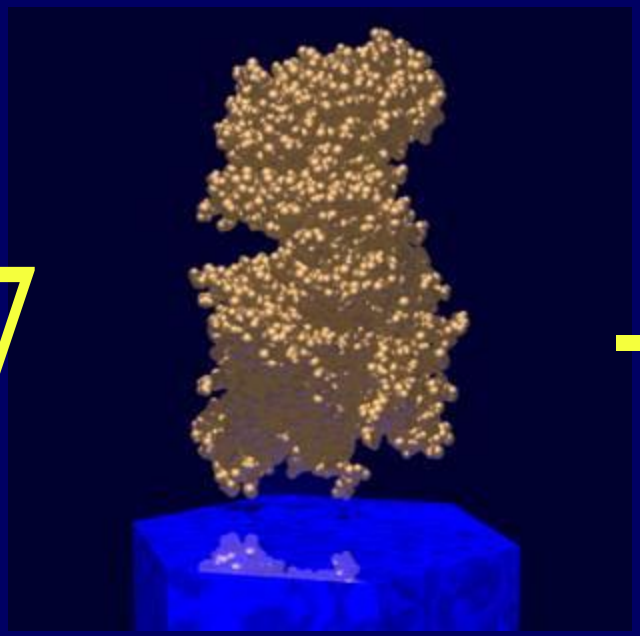
PA Toxin
Punches hole in target cell membrane - allows other toxins to enter cell

LF Toxin
Protease that cleaves important proteins inside cell - leads to septic shock-like symptoms, death

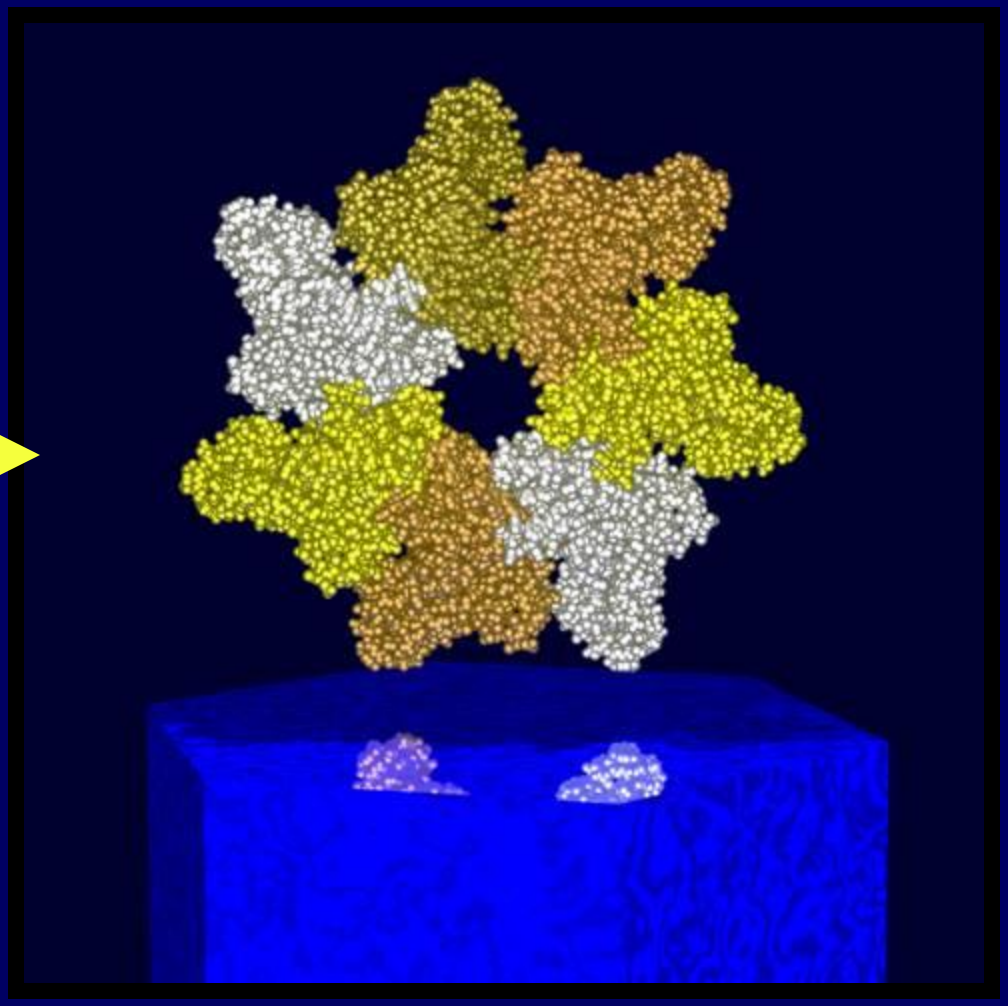
EF Toxin
Adenylate cyclase that leads to swelling in cutaneous anthrax

Anthrax PA Toxin - The Key Toxin

7

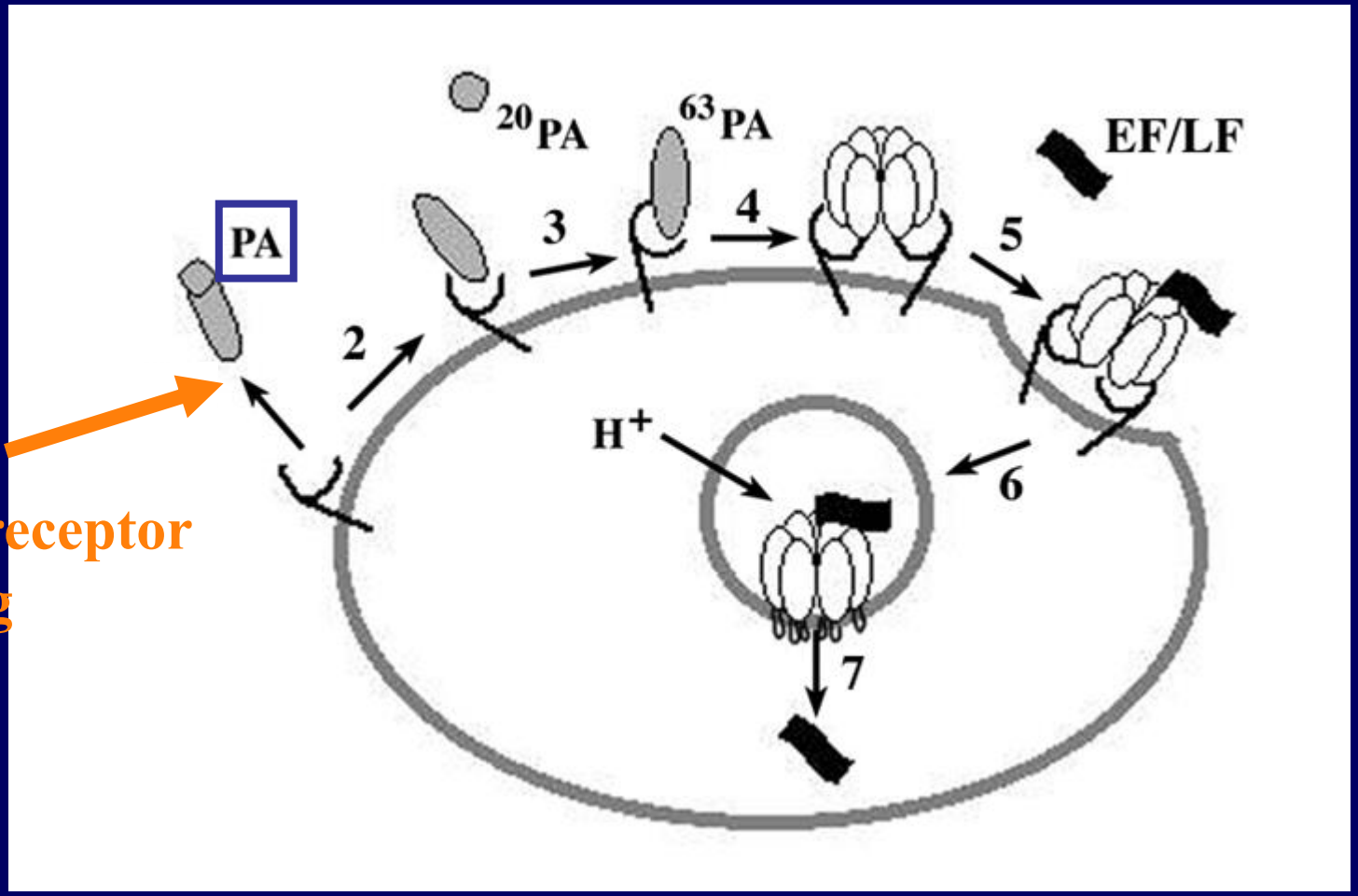


Structure of
anthrax PA toxin



Fully assembled, active
form of PA toxin

How The Anthrax Toxins Work (And How To Stop Them)



Block receptor binding

Figure adapted from Miller et al., *Biochem*, 38:10432 (1999)

*Little et al., *Infect Immun*, 56:1807 (1988)
Bradley et al., *Nature* 414:225 (2001)

How To Treat Late Stage Anthrax

Antibiotics kill the bacteria, but do nothing to neutralize the toxin already present - Explains why 5 people died *after* reaching the hospital last fall. They did not feel sick enough to enter hospital until they already had a fatal amount of toxin in them.

New approach: give specific agent that neutralizes the toxins along with antibiotics - an extremely powerful antibody, should save these late stage patients.

Antibodies

Carry out the “friend vs. foe” recognition mission of the immune system

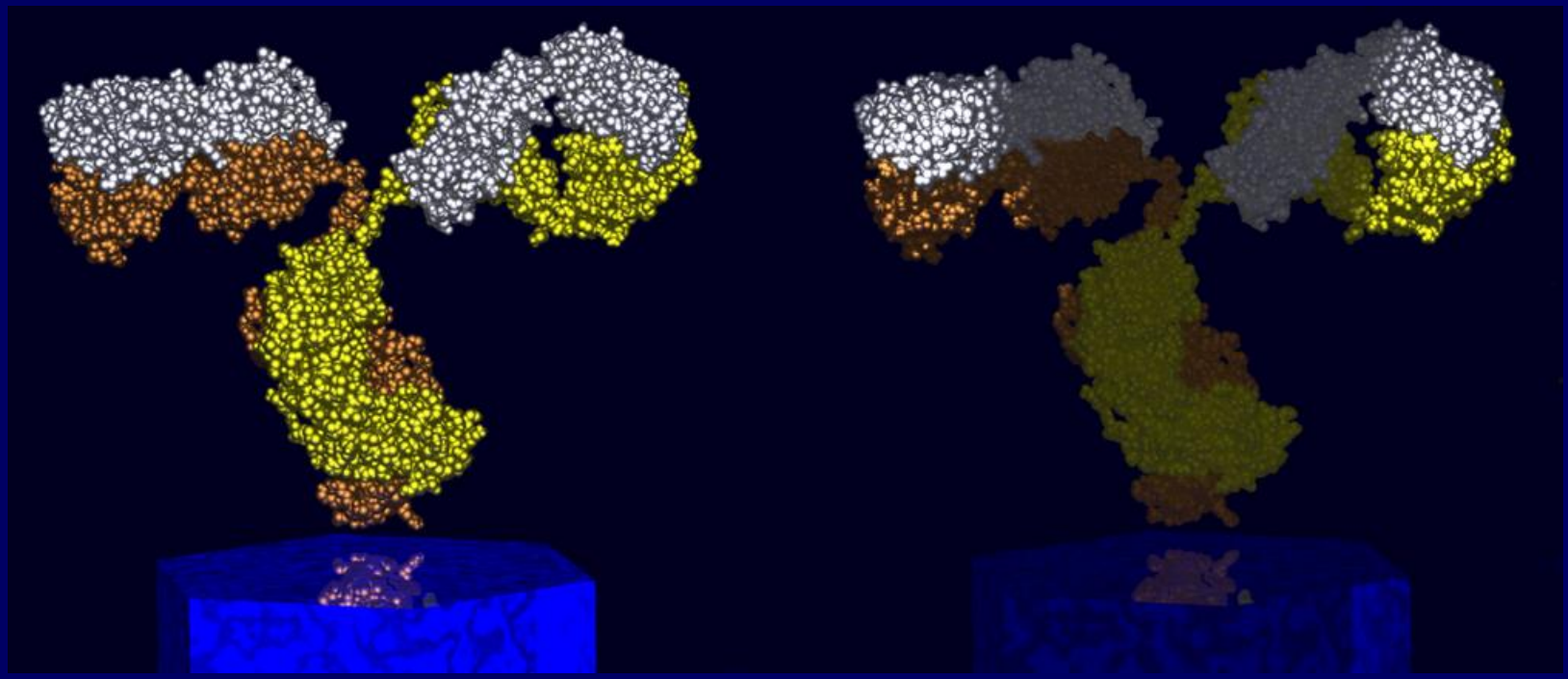
The most exquisite and versatile family of recognition molecules known

Extremely useful for detection purposes - form the basis of many medical diagnostics

Have two binding sites

Genetic engineering can be used to create molecules that only contain the binding sites. These have many advantages

Antibodies



The antibody molecule

The antibody molecule with the binding sites highlighted

Anti-toxin Antibodies

Old technology: Polyclonal anti-toxins and anti-venoms, “tried and true”

Developed 1890s, and widely used before antibiotics

Block toxin function

Anti-toxin Antibodies

Old technology: Polyclonal anti-toxins and anti-venoms, "tried and true"

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Block toxin function

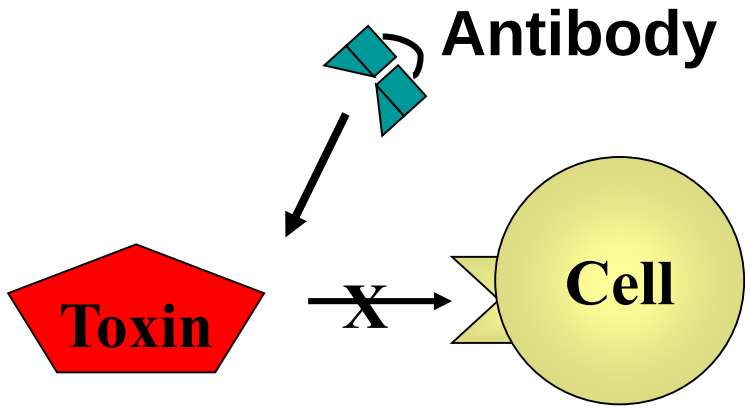
Drawbacks

Serum sickness, Lot-to-lot variability,Contamination, Low titre, Expensive, Limited targets,

Not powerful enough for some of the most deadly toxins

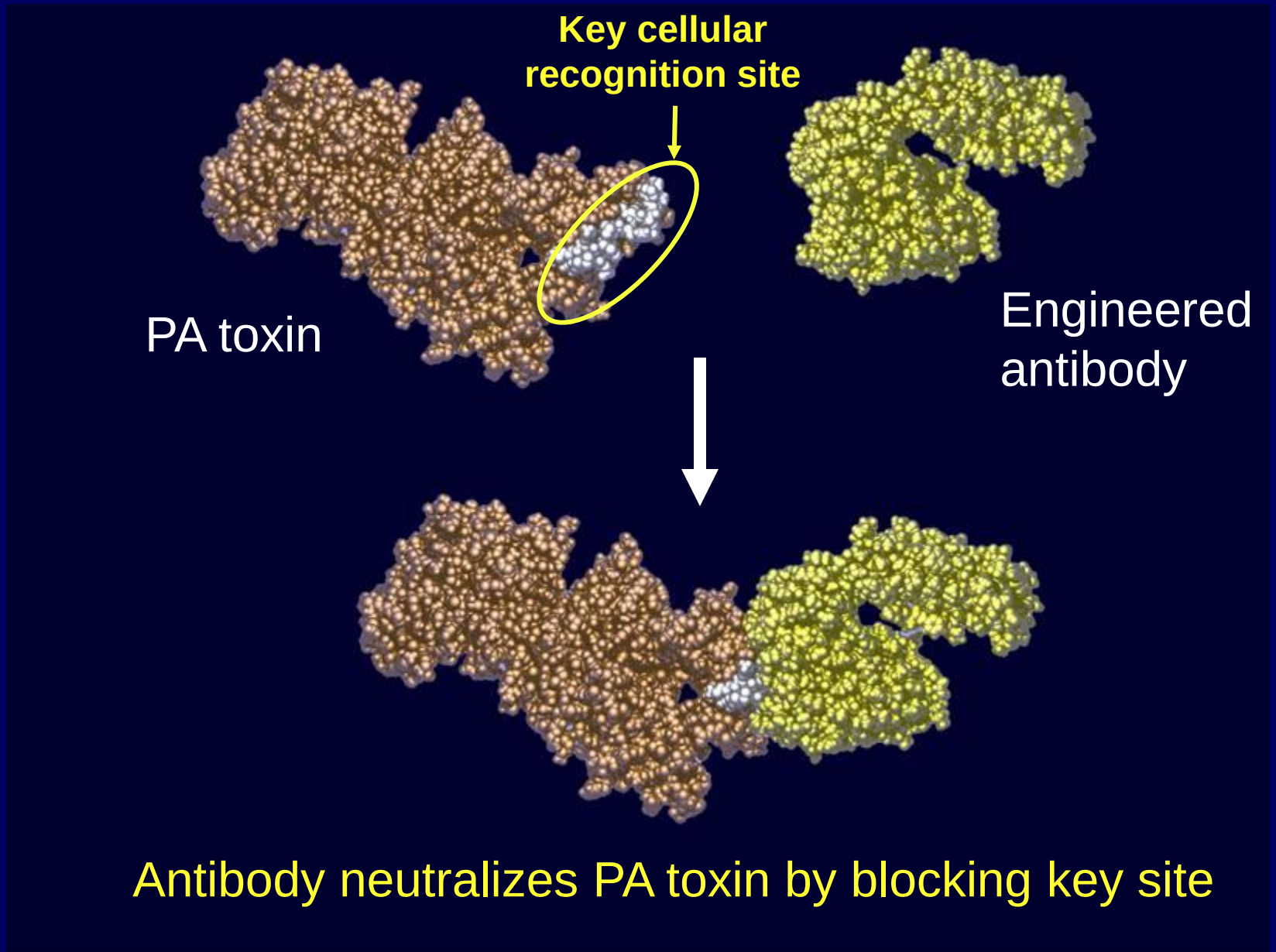
New technology: Use much more powerful "engineered" monoclonal antibodies

Anti-toxin Antibodies

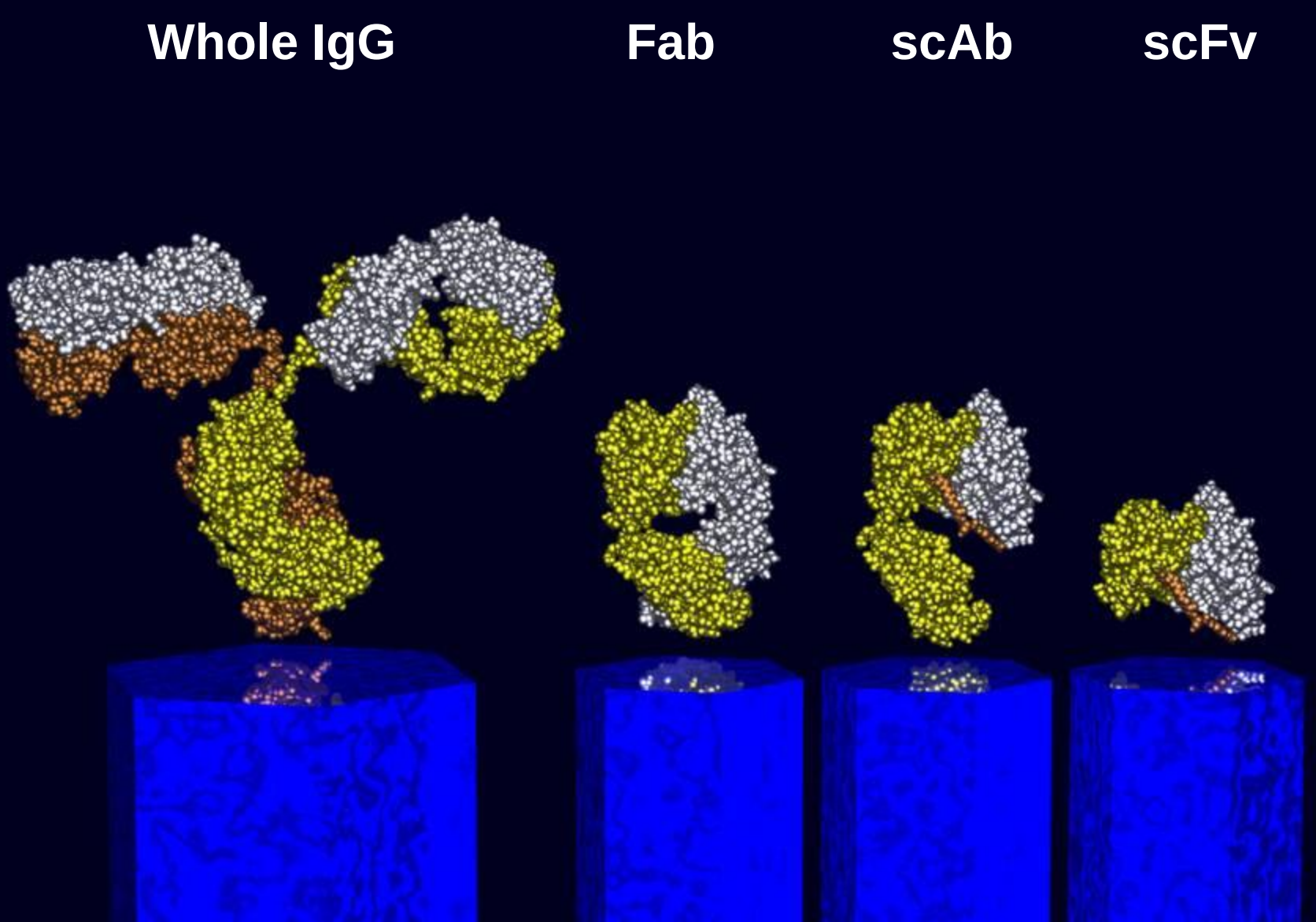


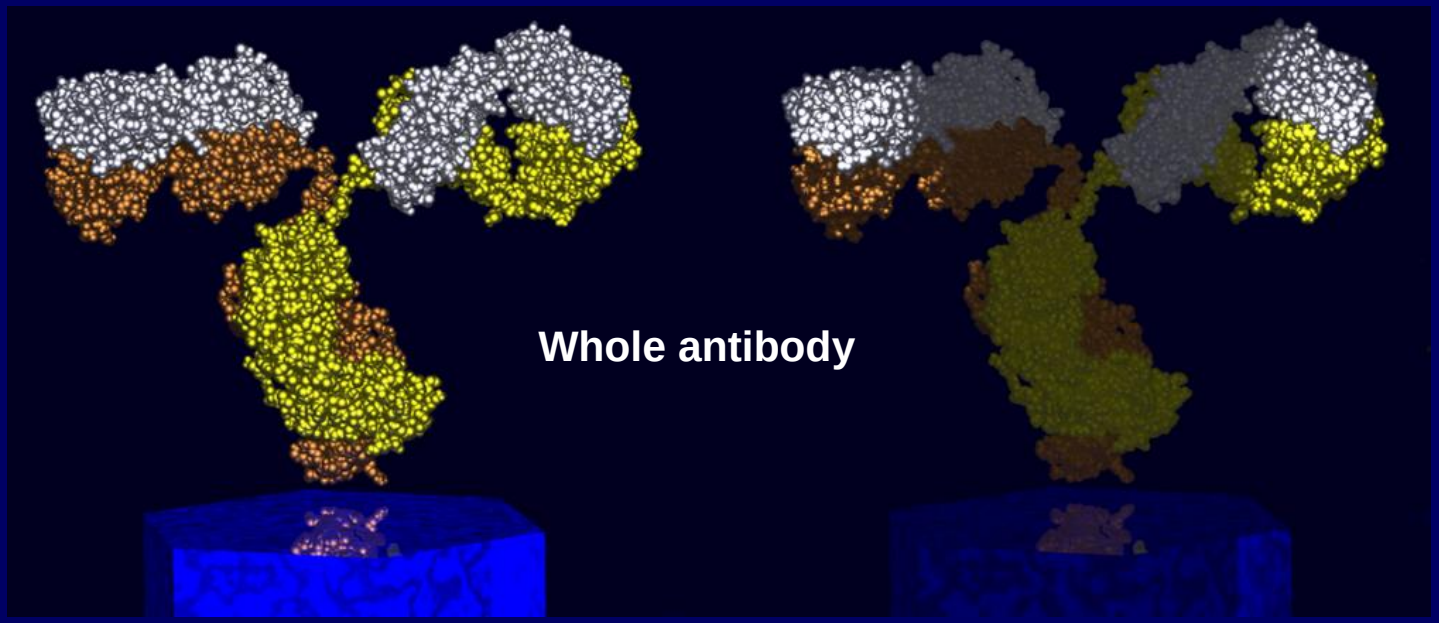
The general scheme

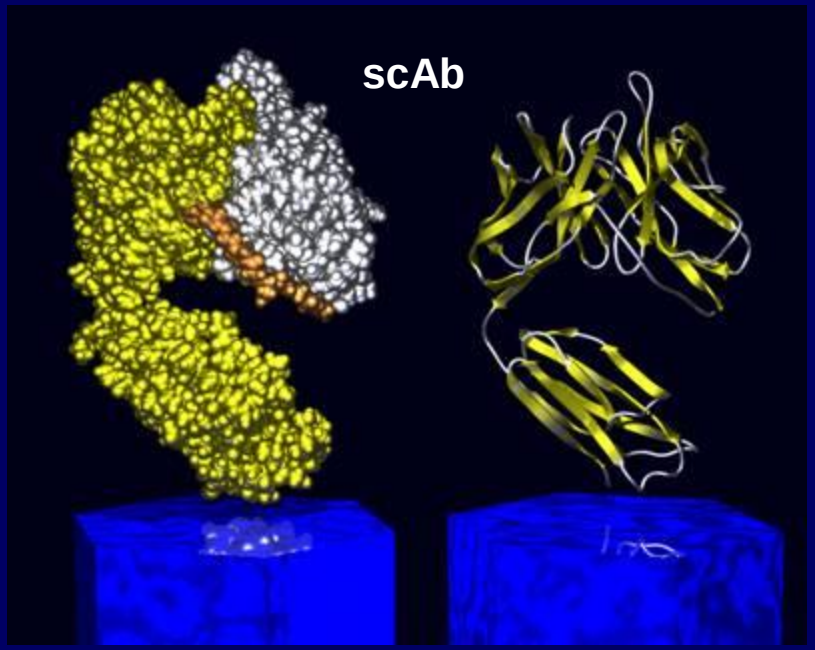
The Idea: Bind The PA Toxin And Don't Let Go

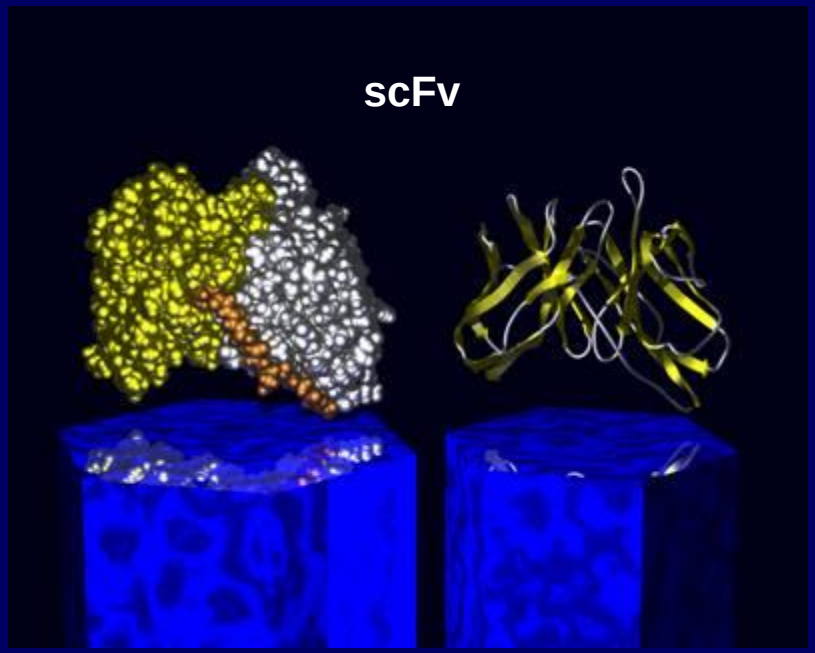


Engineered Antibody Fragments

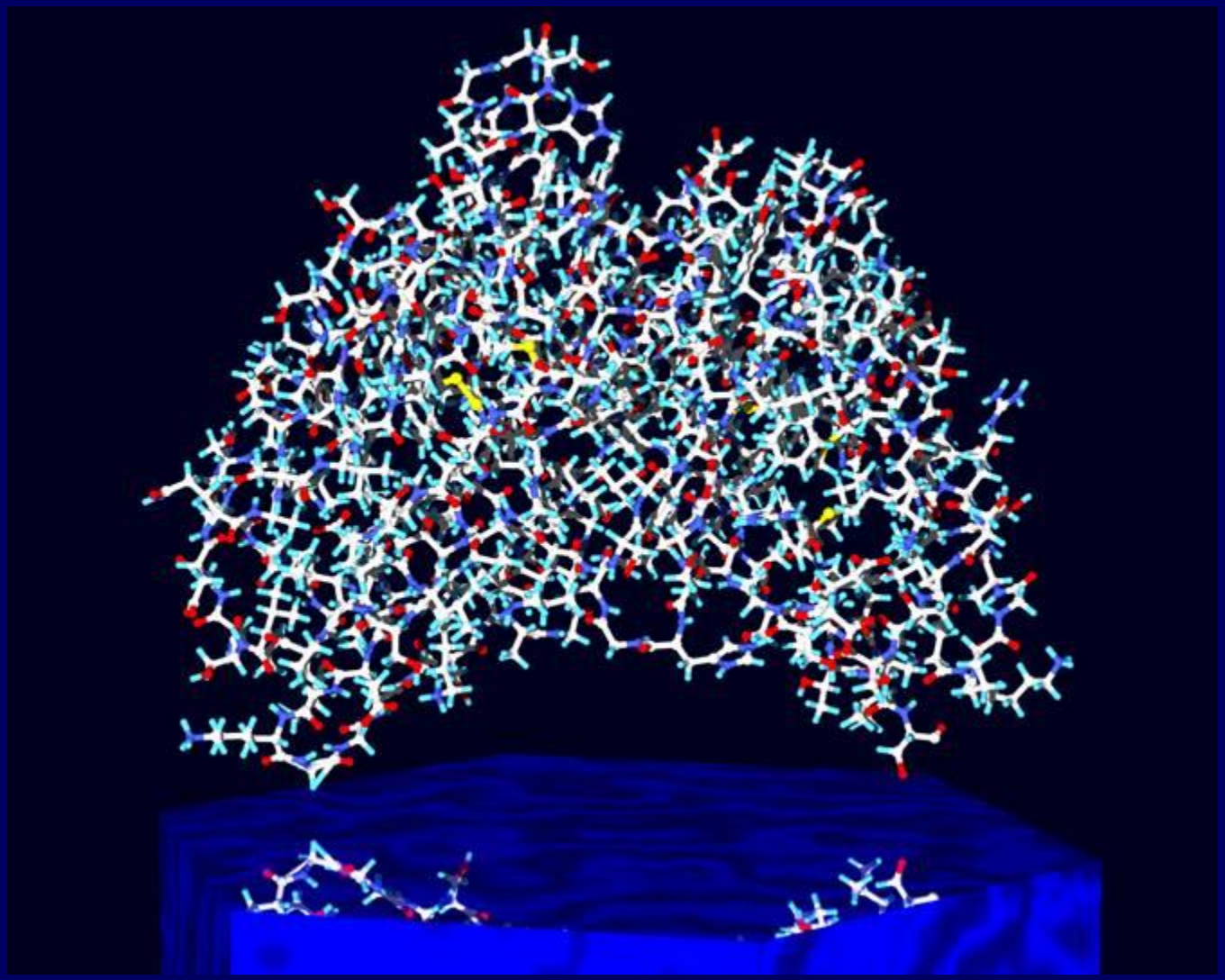



Whole antibody


scAb


scFv

Antibodies Are Very Complex. How Do We Improve Them?



How To Improve An Antibody: Evolution

Charles Darwin: Random DNA changes, then natural selection of organisms that happen to have beneficial changes

The process takes a very long time in Nature

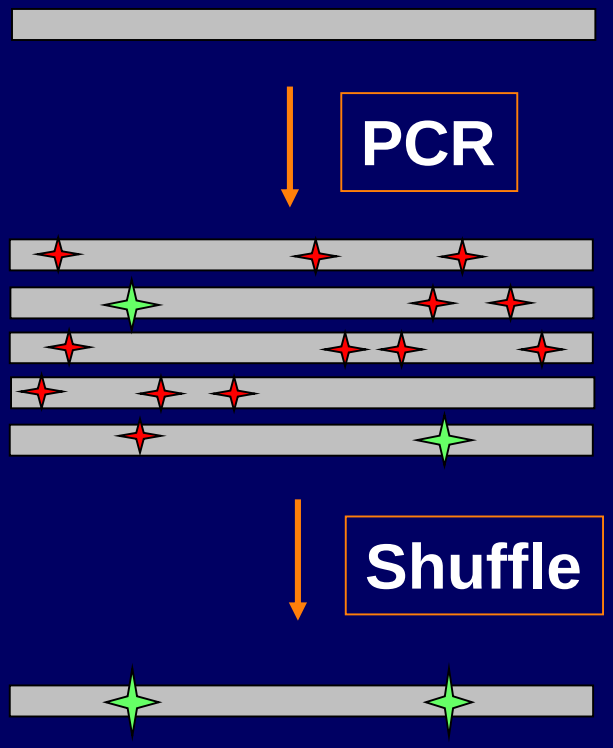
The idea will work with molecules like antibodies (as opposed to whole organisms) if we use molecular biology to speed up the process in the laboratory

The Wonders of Natural Evolution

How To Improve An Antibody: Evolution

We isolate millions of copies of the DNA that codes for our antibody that binds to the anthrax PA toxin

Error-prone PCR



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Randomized Gene pool

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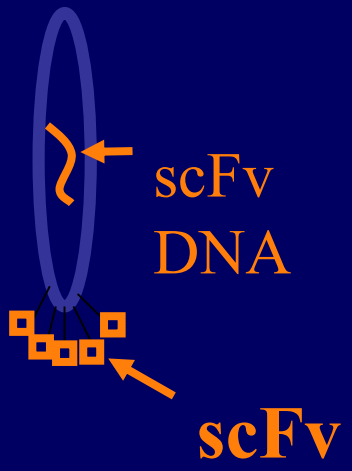
Phage Display



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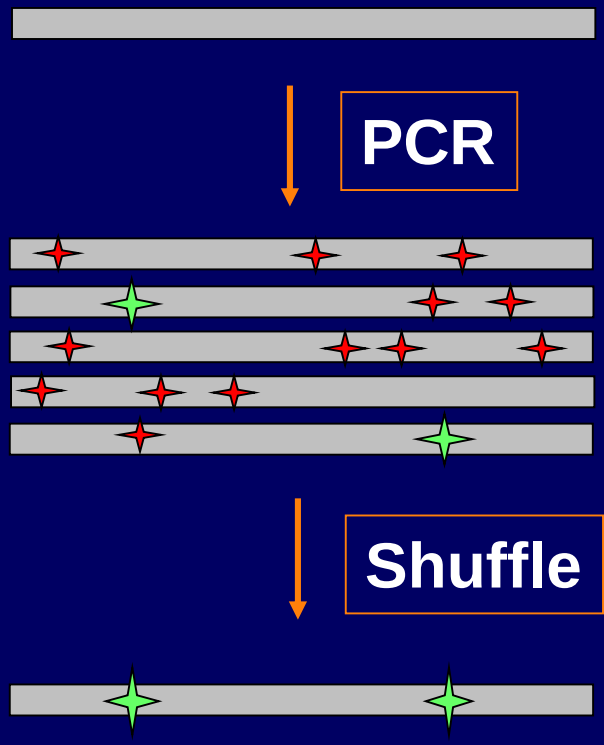
We can repeat the entire process if necessary

Directed Evolution (Technology)

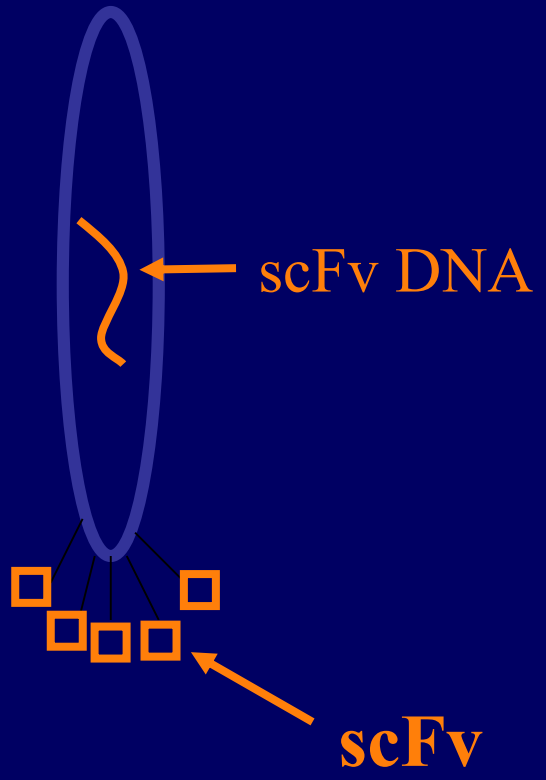
Error-prone PCR



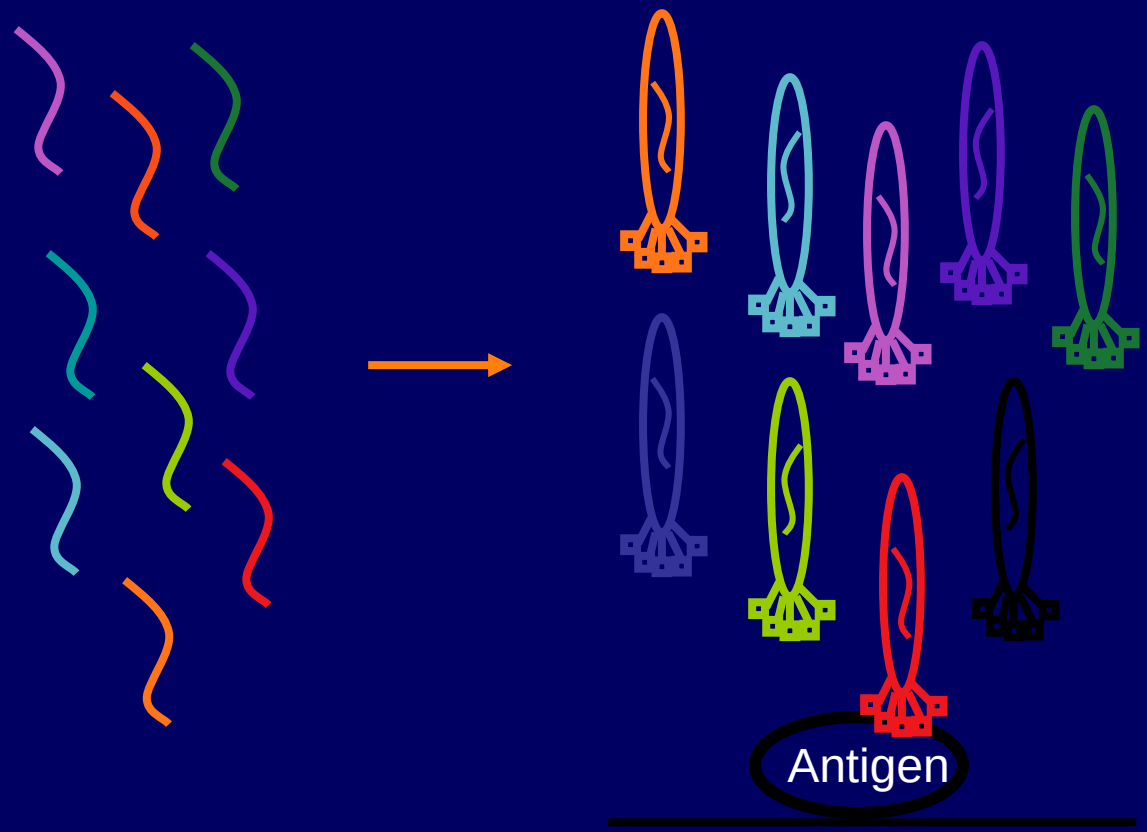
Stemmer

Phage Display

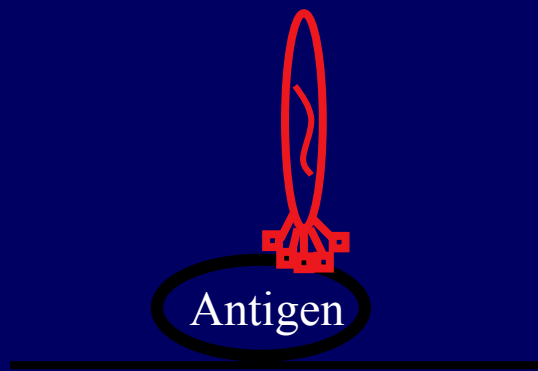
Smith, Lerner, Winter



Directed Evolution Technology: Phage Display "Panning"



The harsher the wash, the stronger (more fit) the antibody binding



Randomized Gene pool

Make phage "library"

Incubate with antigen

Wash

Repeat

How Powerful Did We Make Them?

Antibody Variant	k_{on} (*10^5 M^{-1} sec^{-1})	k_{off} (*10^{-4} sec^{-1})	K_d (nM)
L97 scFv	3.1 ± 0.7	190 ± 20	63
14B7 scFv	3.0 ± 0.4	32 ± 2	12
A2E scFv	3.2 ± 0.8	10 ± 1.5	4
1H scFv	6.4 ± 0.8	1.7 ± 0.4	0.25
14B7 scAb	2.8 ± 0.3	30 ± 0.8	12
1H scAb	6.1 ± 0.9	1.6 ± 0.4	0.26
14B7 Fab	2.9 ± 0.5	33 ± 2	12
14B7 mAb	5.7 ± 1.1	13.5 ± 1.2	2.3
PA-Receptor*			0.5

*Escuyer et al, *Infect & Immun* 59:3381 (1991)

Nat. Biotech., 2002, 20, 597-601

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$t_{1/2}$ ~100 minutes

Nat. Biotech., 2002, 20, 597-601

How Powerful Did We Make Them?

Our engineered antibody can stay bound to the PA toxin for 100 minutes on average

We found that the PA toxin is naturally flushed from an animal after 35 minutes

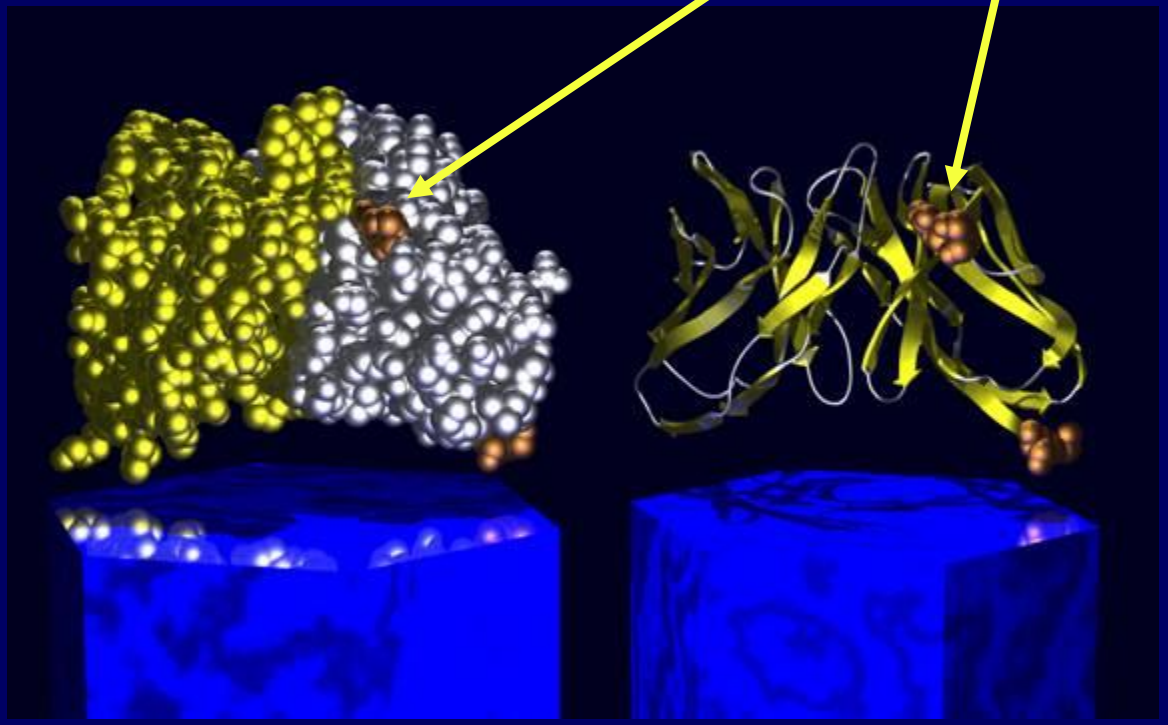
Our engineered antibody should be able to bind, and hold onto, the PA toxin long enough to block its activity until it is cleared from the animal.

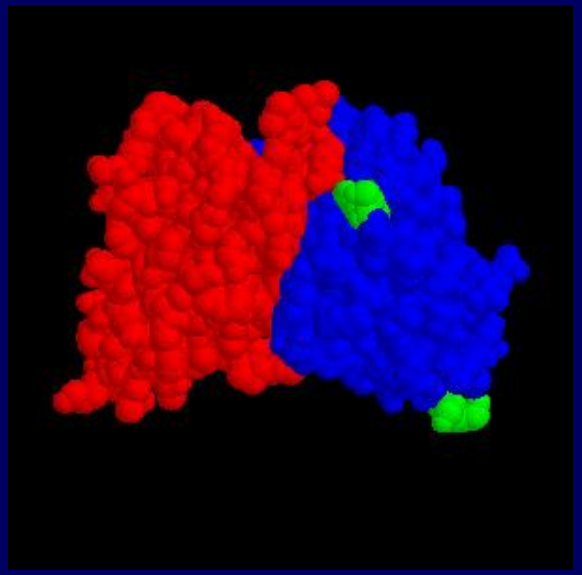
2 Adjacent Mutations Appear Important

Both Make the Surface
More Hydrophobic

L Q55:L
L S56:P

Maybe Helps
with Stability





Jennifer Maynard

Nat. Biotech., 2002, 20, 597-601

Does It Work?

Animal Model --> *Rat*

Challenge --> *Venous Injection of Toxin (10X Lethal Dose)*

Literature Protocol

--> *Pre-Incubate Neutralizing Agent + Toxin*

Our Protocol --> *Inject 4x and 1.5x Excess of Antibody 5 Minutes Prior to Toxin*

Nat. Biotech., 2002, 20, 597-601

Does It Work?

Treatment	k_{off} (*10^{-4} sec^{-1})	*TTD (min) **	*Survivors*
PBS	-	82,87,92,97,99	0/5
L97 scFv	190 ± 20	64,66,67,70,77	0/5
14B7 scFv	32 ± 2	85,103,112,123,130	0/5
A2E scFv	10 ± 1.5	171,242,271	2/5
1H scFv	1.7 ± 0.4	212,238	3/5
14B7 scAb	30 ± 0.8	102,115,140,172,292	0/5
1H scAb	1.6 ± 0.4	--	5/5
1H scAb, (1.5X concentration)	1.6 ± 0.4	152	4/5

***Total time of experiment 5 hrs**

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What Is Next?

More animal tests to optimize formulation of antibody

With optimized formulation, we need to test antibody with real anthrax spores

These animal studies will be carried out at the Southwest Foundation for Biomedical Research, in San Antonio

Take Home Lessons:

1. Biological weapons are cheap to make and easy to conceal.

2. They have been of little military significance thus far, but of tremendous value from a propaganda perspective

3. Points 1. and 2. make biological weapons ideal for terrorism

4. American scientists are still playing “catch-up”, but have created several promising approaches to reduce the threat of biological weapons

Collaborators at the University of Texas

Dr. George Georgiou

Dr. Steve Kornguth

Collaborators at the SFBR

Dr. Jean Patterson

Key students at the University of Texas

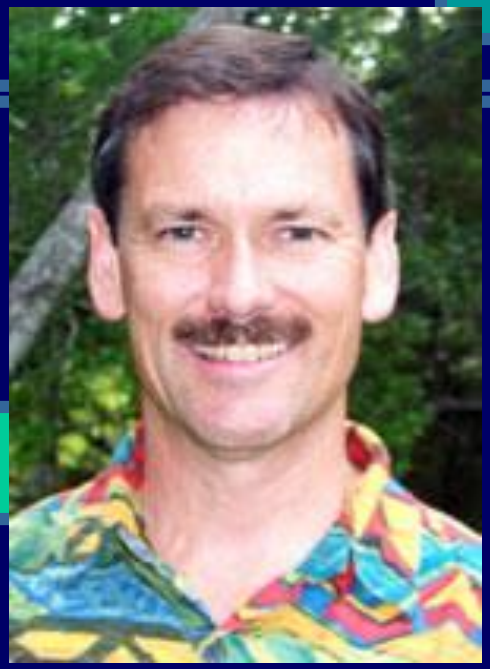
Dr. Jennifer Maynard

Dr. Andrew Hayhurst

Dr. Kitty Braat

Mr. Robert Mabry

DARPA, U.S. Army, ARO/MURI, SBCCOM



Dr. Brent Iverson

University Distinguished Teaching Professor

Dr. Brent Iverson is a professor at the University of Texas at Austin. His research area is the production, characterization, and manipulation of large, functional molecules from three different points of view: 1)Antibody and Enzyme Engineering, 2) Artificial macromolecules with defined higher order structure and function, and 3) The chemistry of nucleic acid binding, recognition, and modification.