



Protilátky

Od Nobelových cien k novodobým liekom

Host: prof. Dr. Ivan Lefkovits, PhD.,
Univerzitná klinika v Bazileji

Kedy: 21. novembra 2013 o 17.00 hod.

Kde: Centrum vedecko-technických informácií SR
Lamačská cesta 8/A, Bratislava, konferenčná sála
na 2. poschodí

Moderátor: PhDr. Zuzana Hajdu

prednáška bude

- o farmaceutickej firme dvadsiateho storočia
- o vzniku ústavu pre výzkum imunitného systému
- o ústavu s neobmedzenými možnosťami
- o horizontálnej strukture
- o úspechu, sláve a Nobelových cenách
- o farmaceutickej firme terajšieho storočia
- o nákladoch na vývoj liekov
- o nových formách podpory výskumu

What is science?

What is basic & applied research?

What is research & development?

Aim

- Knowledge
- Science
- Research & Development

Support

- State (society, tax payers)
- Private institutions (industry)

Hoffmann-La Roche, Basel zakládá Basel Institute for Immunology

Základný kameň April 1969

Otvorenie ústavu

- Prvá etapa: Oktober 1970

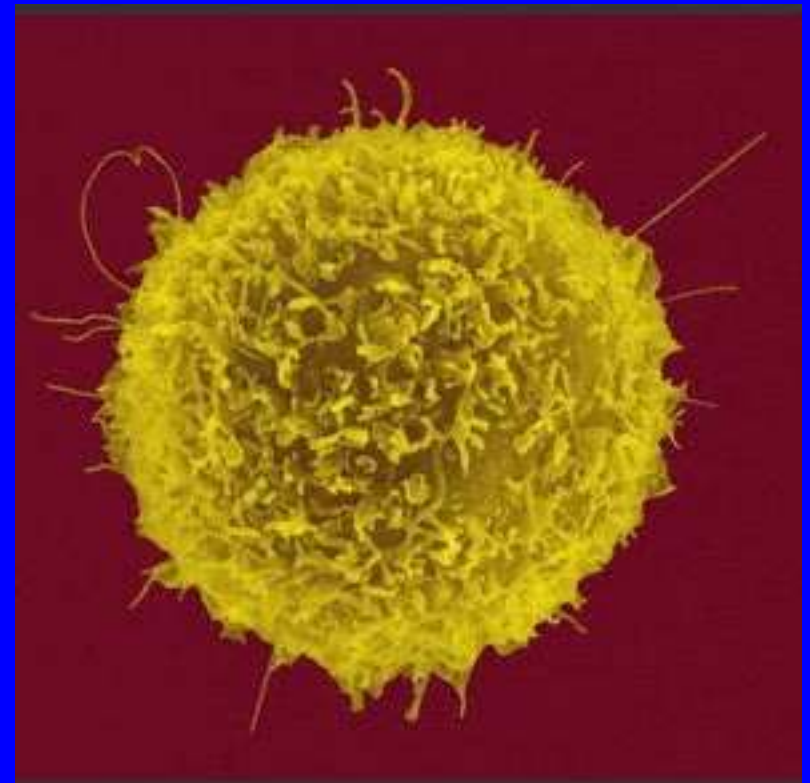
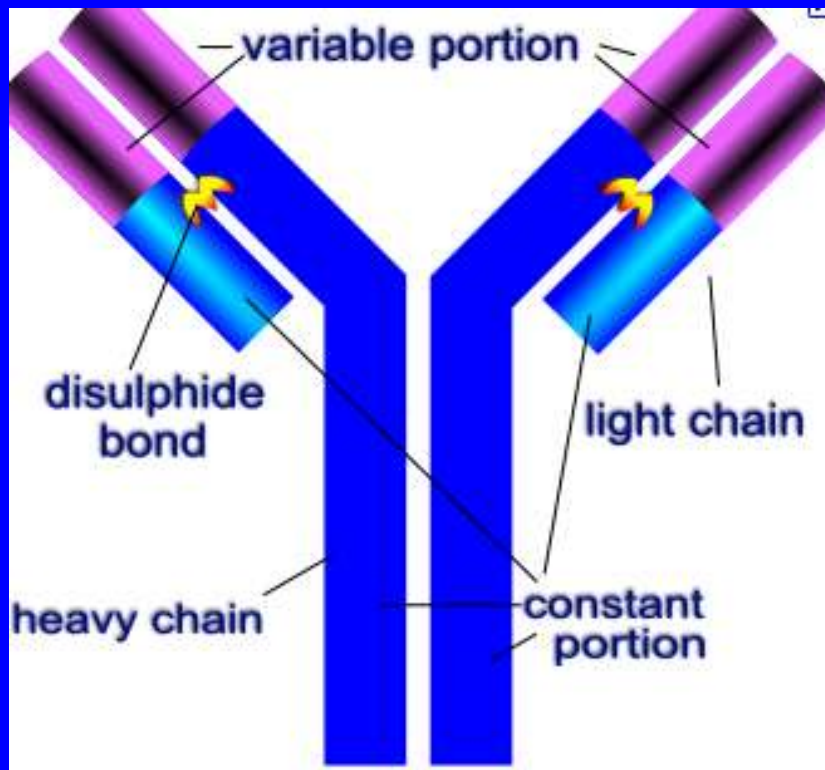
- Druhá etapa: April 1971

Imunitný systém

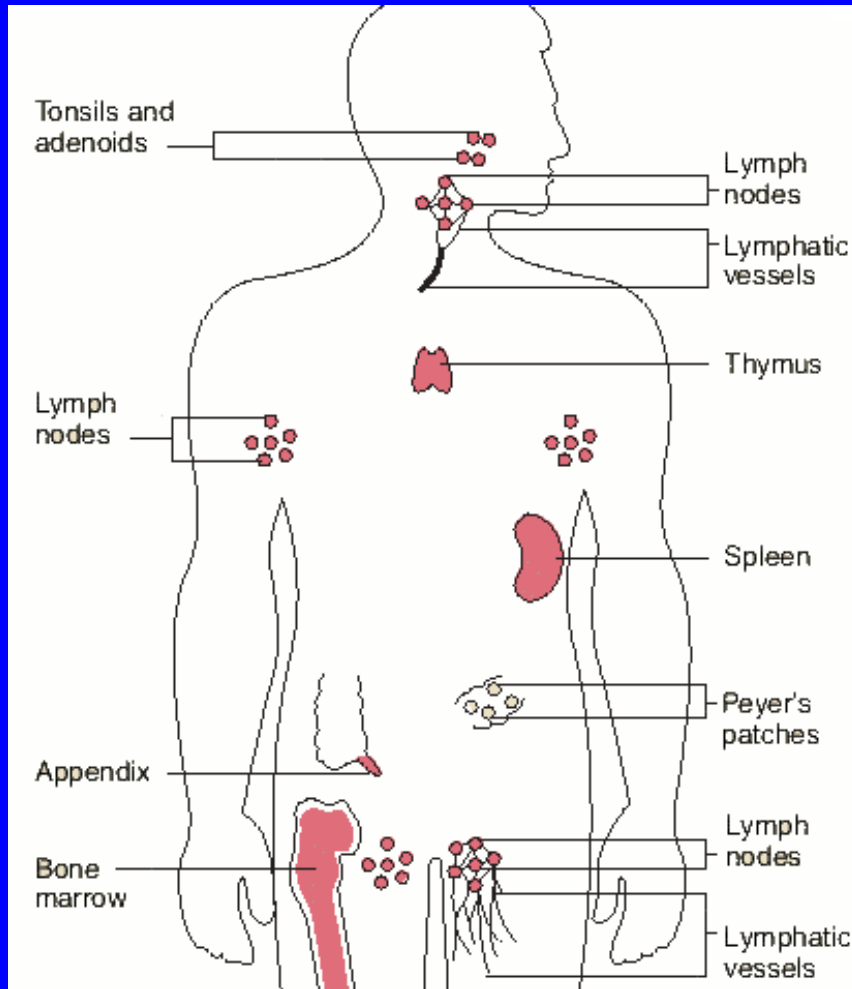
Protilátka Antigen

Antikörper, antibody, protilátka (Paul Ehrlich 1905)

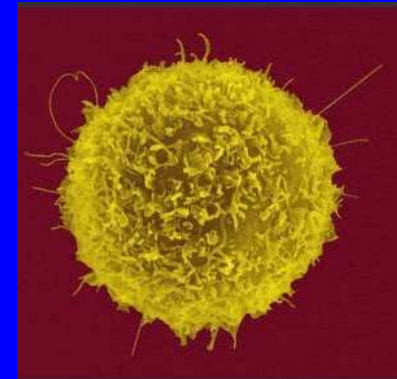
protilátka & lymfocyt



Ľudský organizmus

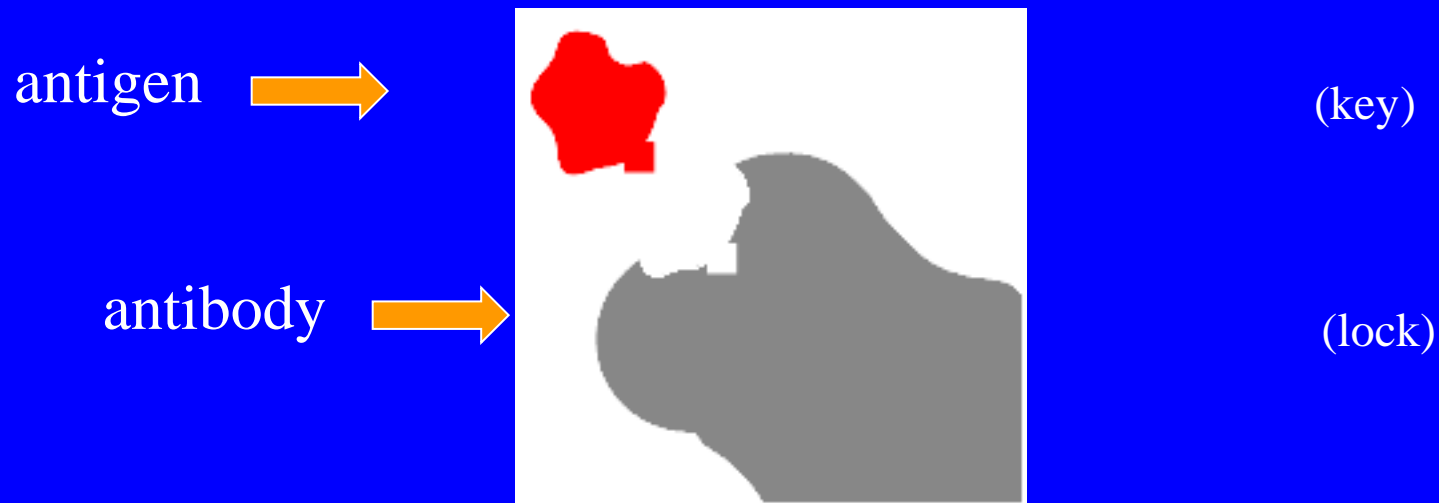


10^{12}



10^{12} cells = 1 kg
immune system

interakcia protilátky s antigénom



Protilátka

- Repertoár
- stovky milionov

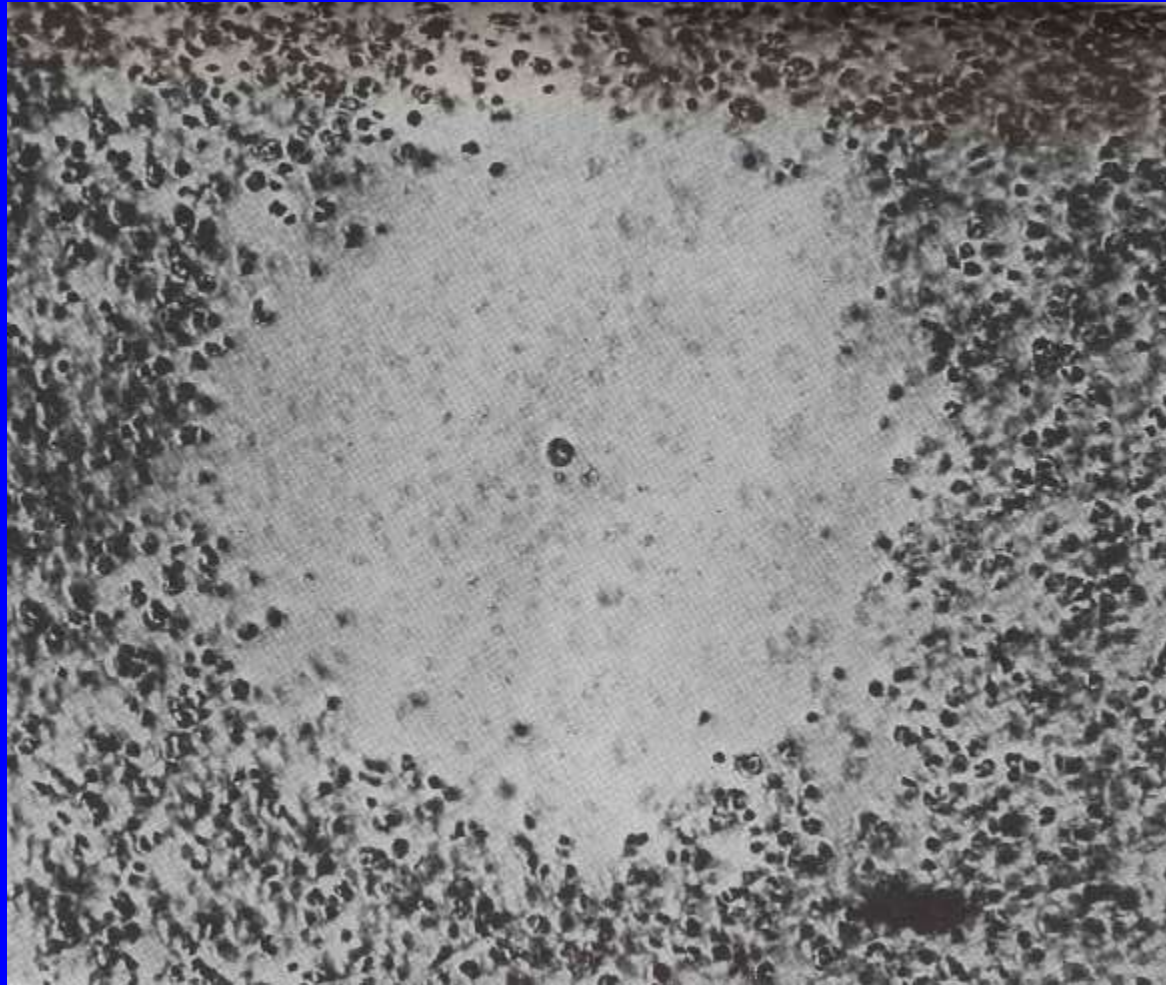
different
specificities

Antigen

- Spektrum
- stovky milionov

different bacteria,
viruses, allergens,
chemicals

Antibody-forming plaque



Self and non-self

during ontogeny the entire repertoire of specificities is created

- Specificities that are against own body constituents
- Specificities that are against pathogens, allergens and also against modified-self (cancer cells)

ANTI-SELF

ANTI-FOREIGN

Dva najkomplexnejšie biologické systémy

- Human brain 1kg
- Immune system 1 kg
 - 10^{12} cells

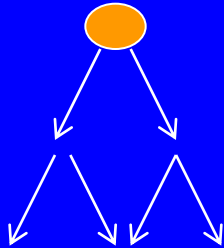
Common features: learning & memory

Two organs of learning and memory

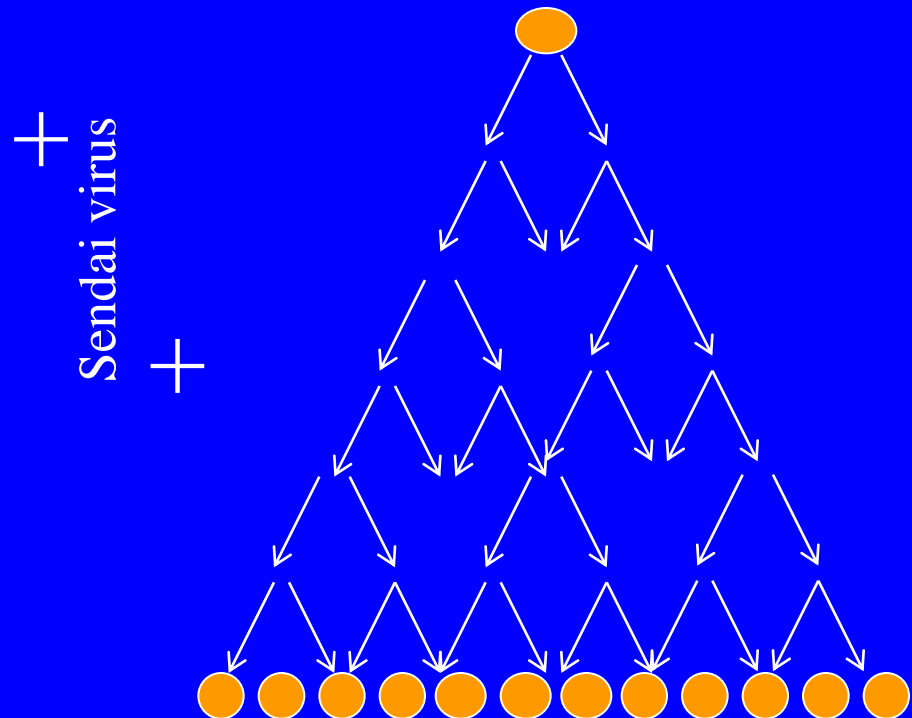
- Brain
- 1kg
- 10^{12} neurons and synapses
- Immune system
- 1kg
- 10^{12} lymphocytes and macrophages

cell fusion (immortalization)

- A cell producing specific antibody



- Tumor cell with the ability to duplicate indefinitely

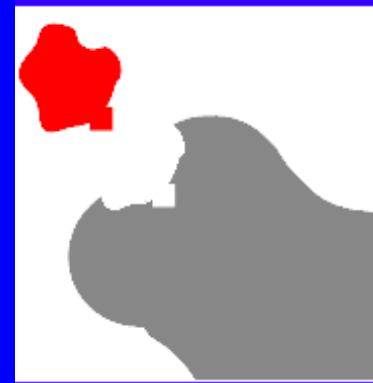
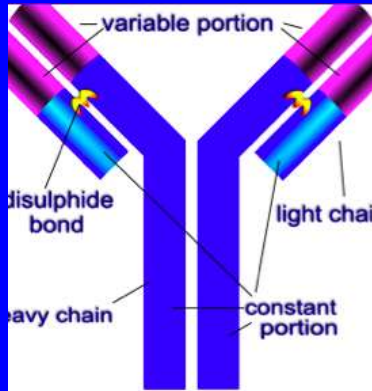


cell fusion (immortalization)

Result: hybridoma

hybridoma cell line produces monoclonal antibody

Prvá Nobelova cena: Georges Köhler (spolu s C. Milsteinom) Monoclonal antibody



Druhá Nobelova cena:

Niels K. Jerne

Mechanismus tvorby protilátok
klonálná selekcia

Tretia Nobelova cena:

Susumu Tonegawa

“Generation of diversity”

mechanismus somatickej tvorby

protilátok

Monoclonal antibody (mab)

- Fusion of antibody forming cell with an “immortal” cancer cell
- mouse mab
- chimeric mab
- “humanized” mab
- human mab

Fusion agent:
Sendai virus, later PEG

Do we remember Roche products of the seventies of the last century?

- Valium
- Librium
- Lexotanil
- Marcoumar
- Vitamin C
- 5-fluorouracil

These products are either not produced anymore, or were sold to other companies; whatever the case, they do not play any role in the main revenue of the company

Roche in 21st century

- is a leader in research-focused healthcare in pharmaceuticals and diagnostics.
- is the world's largest biotech company (oncology, infectious diseases, inflammation, metabolism and neuroscience).
- is involved in in vitro diagnostics and tissue-based cancer diagnostics, and in diabetes management.
- with personalised healthcare strategy aims at providing medicines and diagnostic tools for improvements in the health, quality of life and survival of patients.

Roche, Genentech, Chugai

- Roche has over 82,000 employees worldwide and invests over 8 billion CHF in R&D / year.
- Sales of 45.5 billion CHF / year

Roche

- Herceptin
- Kadcyła
- Avastin
- Perjeta
- MabThera

mab = monoclonal antibody

- Herceptin (trastuzumab)
- Kadcylla (trastuzumab emtansine)
- Avastin (bevacizumab)
- Perjeta (pertuzumab)
- MabThera (rituximab)
- GA101 (obinutuzumab) progression-free survival in patients with chronic lymphocytic leukemia (CLL)

ADC (antibody-drug conjugate)

- Herceptin (trastuzumab)

+

- DM1 chemotherapeutikum (emtansine)

= Kadcyła (trastuzumab emtansine)

bestselling mab for hematological cancers

- MabThera (rituximab)
príjem 3.4 miliard CHF / 2012

venujme pozornosť ďalším z nich

2018

Metmab (onartuzumab/RG3638) pre niekoľko rôznych typov rakovín.

2015

Ocrelizumab R1594 (Chronic lymphocytic leukemia)

Jan Vilček (not Roche) mentioned here because of mab

- Remicade:
- rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis
- Adalimumab
- Golimumab

The path from basics to a mab

If you know the biochemical pathway you might identify the biomarker

If you know the biomarker you might have a target

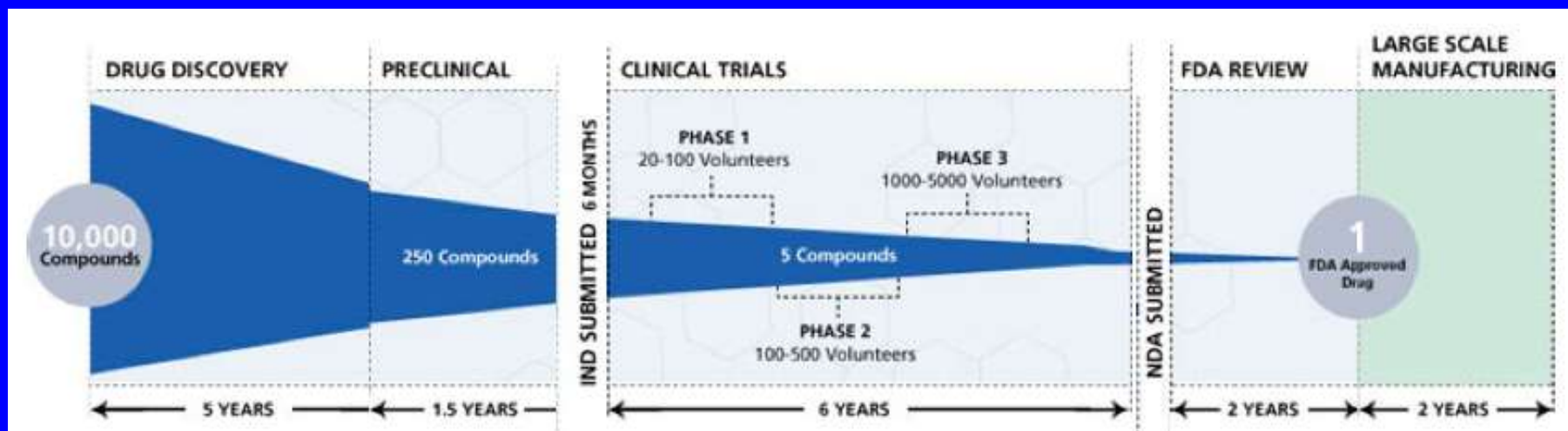
If you have a target you might be successful in making monoclonal antibody

Patent protection lasts 20 years

- Original drug
- Generic drug
- Biosimilar (monoclonal antibodies)
- Orphan drugs (7 years)

- 1 drug in 5000 reaches the consumer

10,000 : 1



Roche

HER2-positive metastatic breast cancer

- Breast cancer is the most common cancer among women worldwide. Each year about 1.4 million new cases are diagnosed, and over 450,000 women die of the disease annually.
- When increased quantities of the human epidermal growth factor receptor 2 (HER2) are present on the surface of the tumour cells, one speaks about “HER2 positivity”.
- HER2-positive cancer is a particularly aggressive form of breast cancer

1,000,000,000 *CHF investment*
7,000,874 *hours of work*
6,587 *experiments*
423 *researchers*
1 *drug*



costs of developing a modern drug

- 1,000.000.000 CHF
- Yearly profit of 100.000.000 CHF has to be generated over a period of 10 years to get even

1,000.000.000
CHF

costs

for running BII
for 30 years

1,000.000.000
CHF

fine

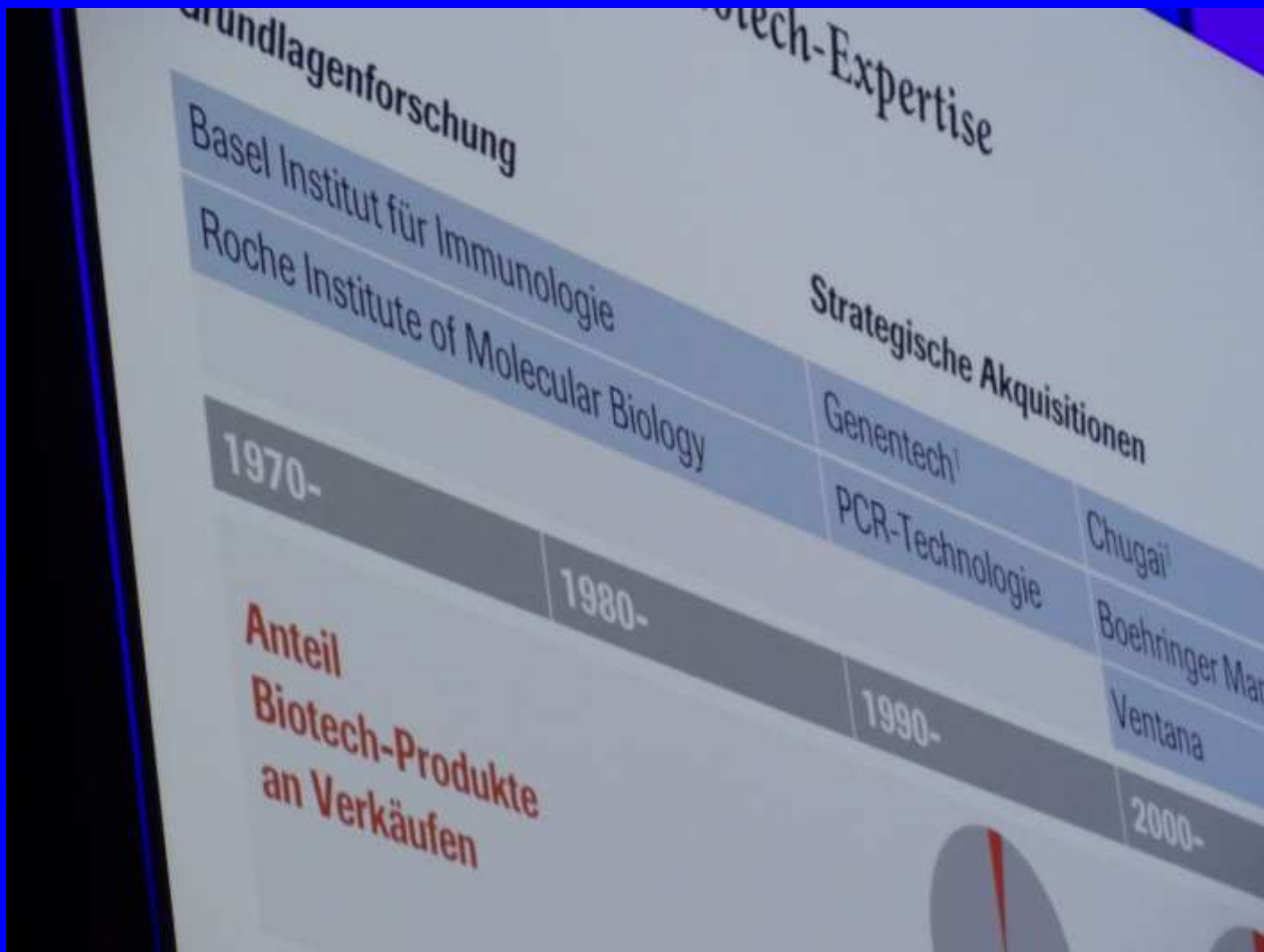
from a court
(e.g. punishment
for illegal price
agreements)
.....vitamins.....

1,000.000.000
CHF

costs

for developing a
modern drug
..... mab

Strategy of Roche



Acknowledgment

to Hoffmann-La Roche, Basel for 30 years of
unlimited support

to 500 former members of BII throughout the
existence of BII

First class scientists attract first
class scientists

Second class scientists attract
third class scientists