Biotechnology in the Czech Republic and directions of their development

Libor Grubhoffer

BIOTECHNOLOGY

opportunity for intersectoral cooperation and technology transfer

19th September, 2018, Vodňany

Biotechnology

- They are crucial for the development of human society in the 21st century.
- They should guarantee a man's gentle approach to natural resources, energy demands and the protection of the natural environment.
- They also have high added value in intellectual property.
- They represent a key segment for a knowledge-based economy.

The main areas of life in which biotechnology benefits

- Food, nutrition of humans and livestock.
- Animal and livestock health (systemic, civilization, infectious diseases, epidemiology of diseases, research of new drugs, new generations of drugs and therapeutic procedures).
- Energy, energy sources, fuels - artificial photosynthesis.

Brief history of biotechnology

- Humanity has been using biotechnology for several thousand years - food preparation (eg, dairy products, beer, wine) or medicines (use of wound healing fungi)

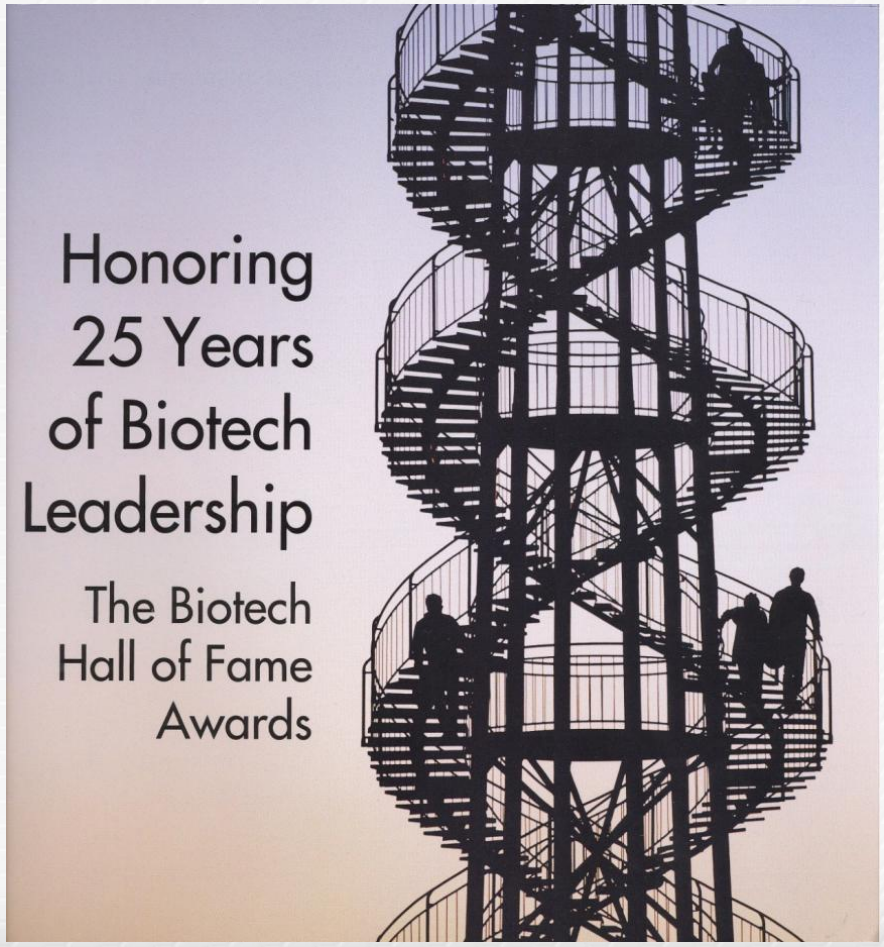
(Up to 1865)	▪ alcoholic beverages (beer, wine), fermented foods (dairy products including cheeses, vinegar)
Éra Pasteura	▪ alcohols and ketones (ethanol, butanol, glycerol, acetone), organic acids (lactic, citric), aerobic wastewater treatment
Modern industrial biotechnology (1940-1960)	▪ penicillin (aseptic submersion cultivation technology), other antibiotics, microbial transformation of steroids
1960-1975	▪ amino acids, single cell protein proteins (SCP), animal cell culture (antiviral vaccines), technical enzymes (biodetergents), immobilized enzymes and cells (fructose syrup), anaerobic waste treatment (biogas), microbial polysaccharides , ethanol into propellants
New biotechnology I (after 1975)	▪ monoclonal antibodies (hybridoma technology), gene engineering (1982 cattle diuretic, human insulin 1982), bioinformatics (bioprocessors, biochips), synthetic protein constructs
New Biotechnology II (after 1990)	▪ Complete Human Genome Analysis, Human Organ Replacement, Gene Therapy, Nano-Biotechnology

Source: Folta J., Vývoj biotechnologie a průmyslové chemie, Společnost pro dějiny věd a techniky, Národní technické muzeum, Praha 2006.

BIOTECHNOLOGY

opportunity for intersectoral cooperation and technology transfer

Milestones of Modern Biotechnology Development (I)



Produced by
Life Sciences Foundation
San Francisco, CA

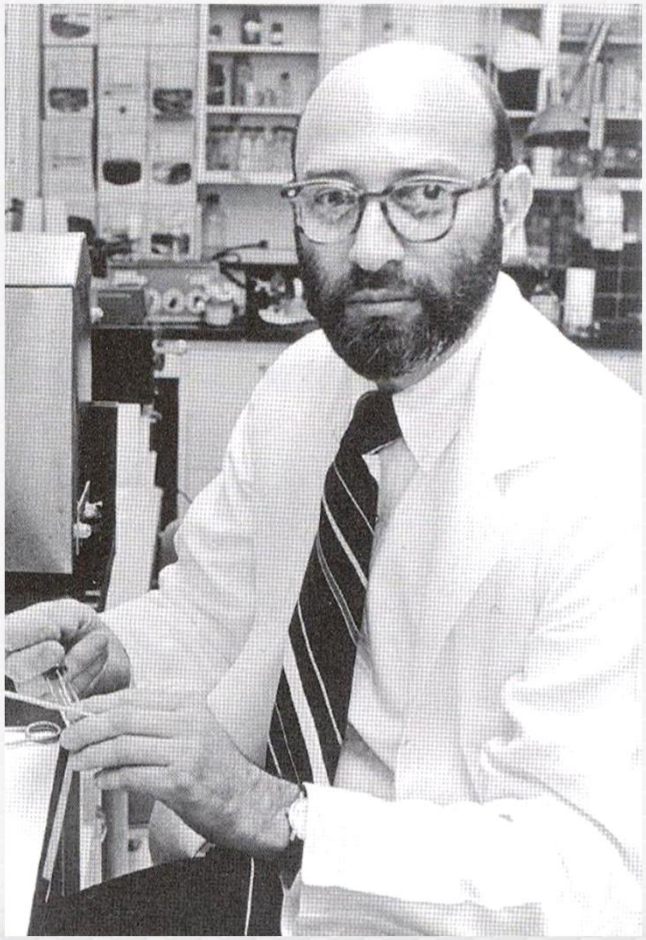
Production Manager:
Donna Lock

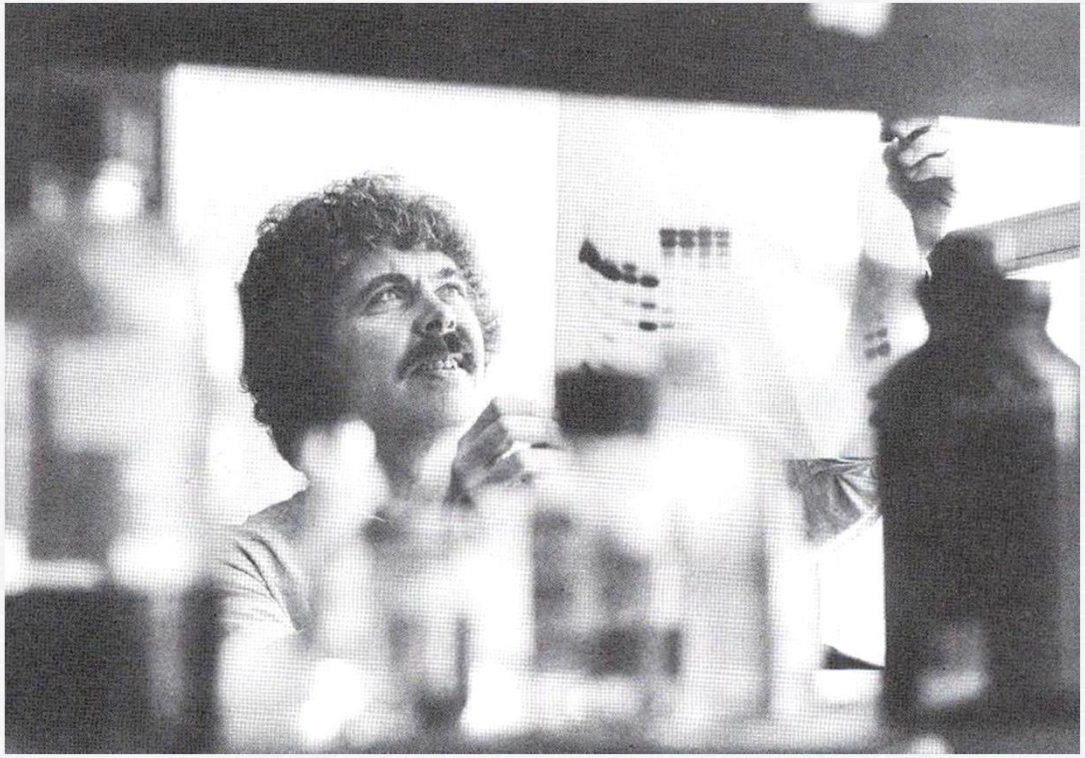
Writers:
Mark Jones
Brian Dick
Heather Nelson

Design/Layout:
Zach Rais-Norman

Published by Life Sciences Foundation
One Embarcadero Center, Suite 2700
San Francisco, CA 94111
www.biotechhistory.org

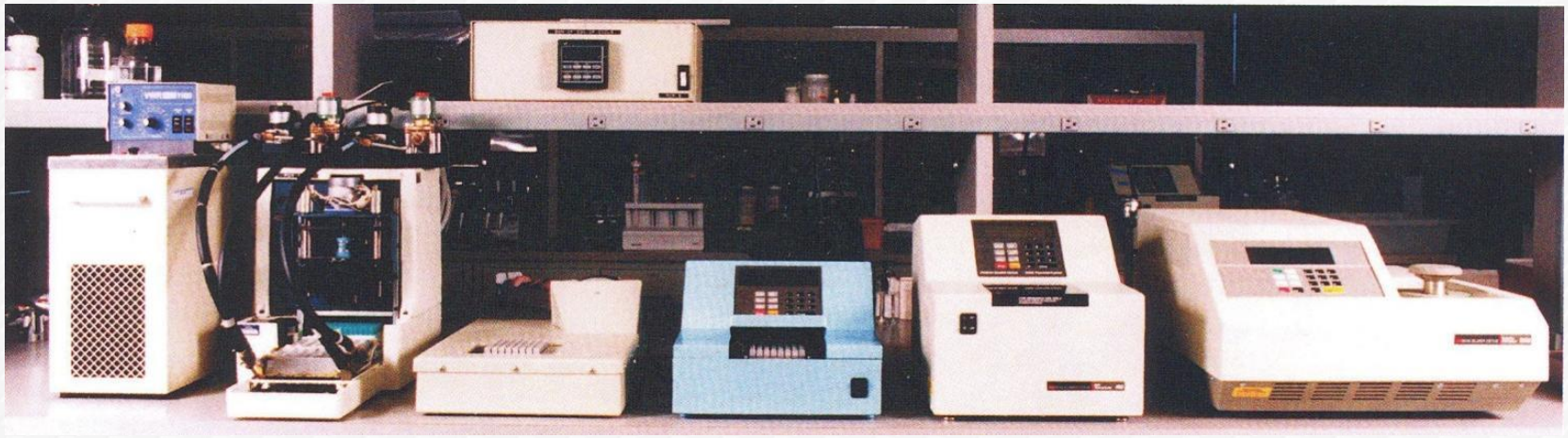
Milestones of Modern Biotechnology Development (II)

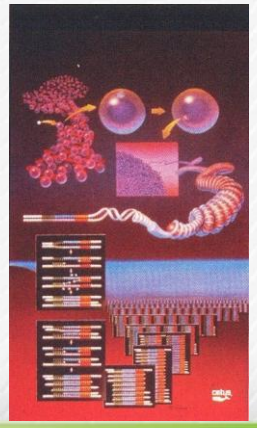


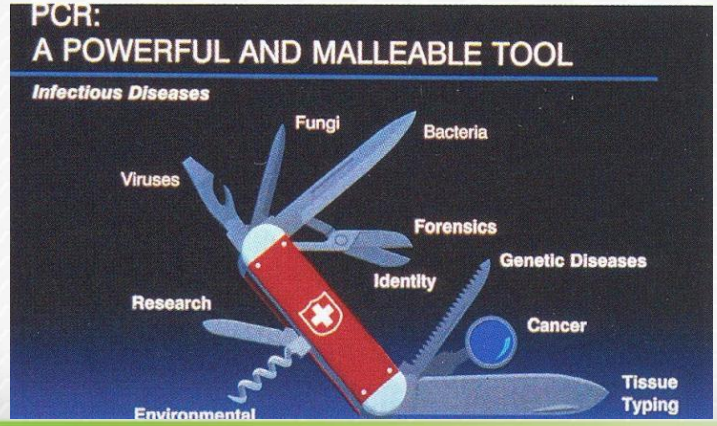


Recombinant DNA Technology (Stan Cohen, Herb Boyer)

Milestones of Modern Biotechnology Development (III)

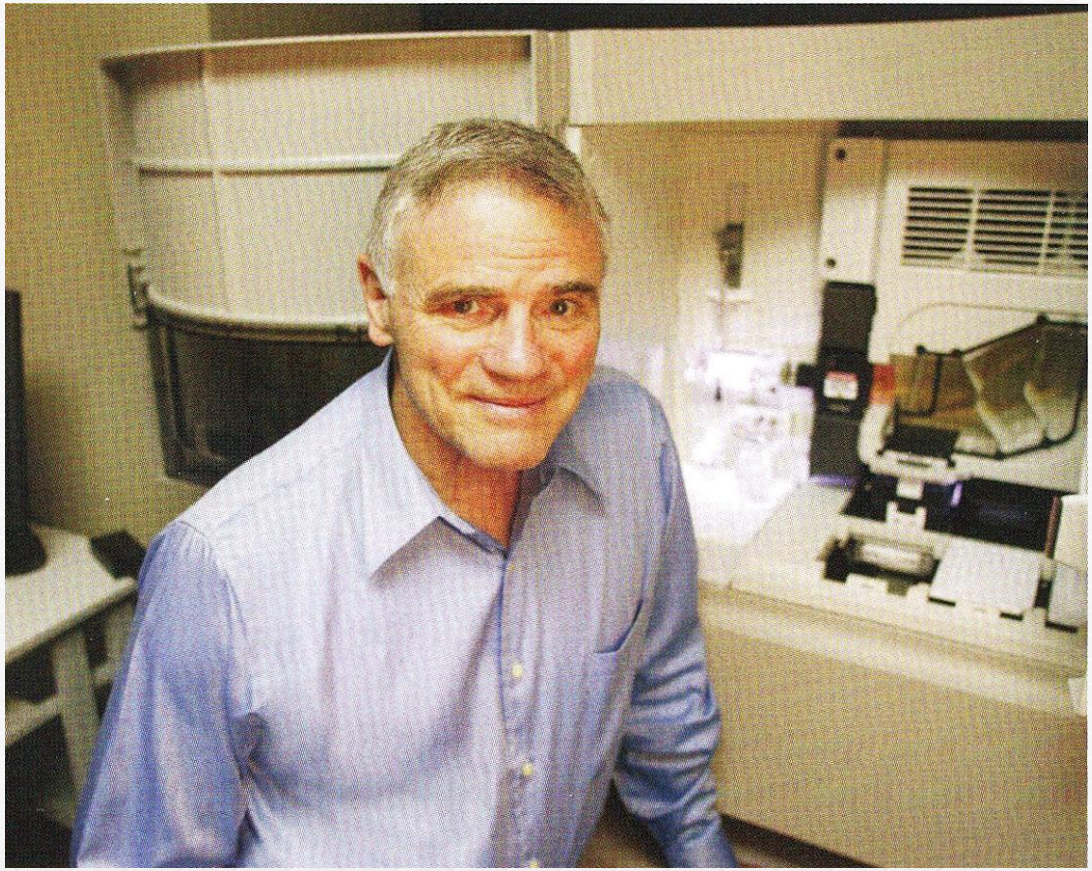






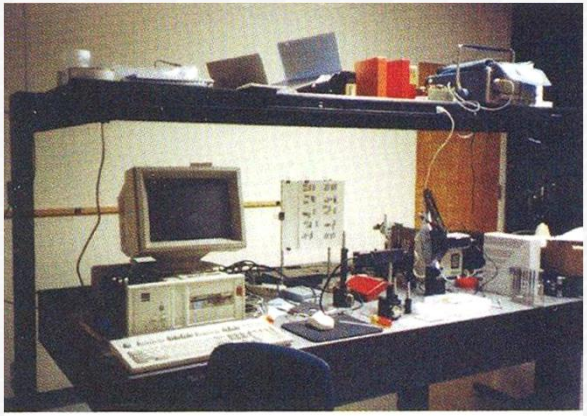
Molecular Cloning Technology by PCR (Kary Mullis)

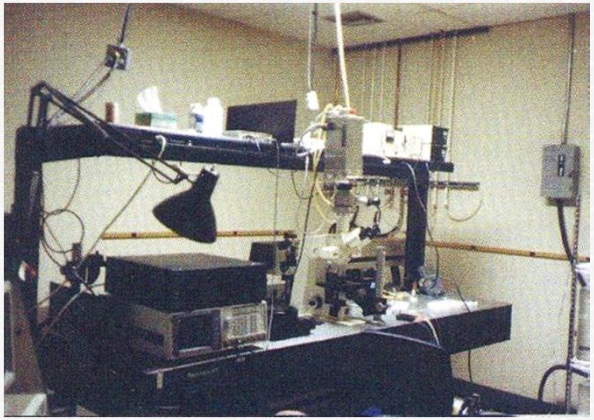
Milestones of Modern Biotechnology Development (IV)

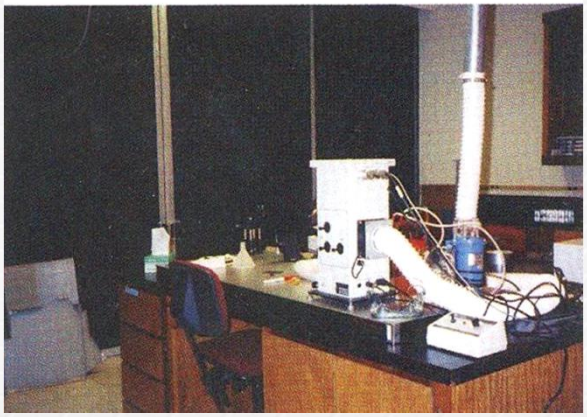


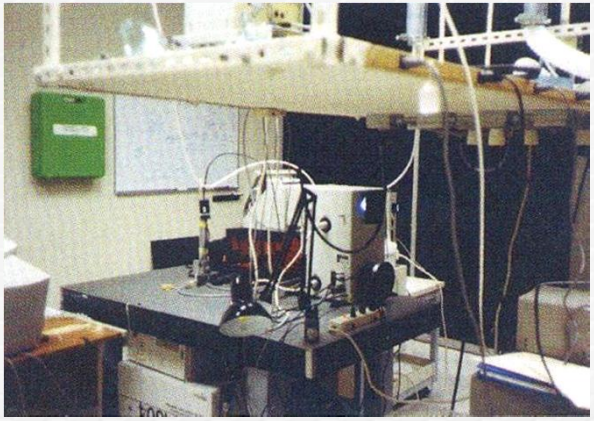
Atomated DNA sequencing
(Leroy Hood)

Milestones of Modern Biotechnology Development (V)









DNA "chipping" - DNA microarrays (Stephen Fordor)

Milestones of Modern Biotechnology Development (VI)

Hybridoma technology (César Milstein, Georges Köhler)

Important milestones of Czech biotechnology development (I)

Year	Note
1088	first mention of hops in the founding charter of the Vyšehrad chapter and the first brewery in Bohemia
13th century	the first distillery production report, the first big distillery was founded in Kutna Hora for Wenceslas IV.
14th century	the first report on wine production under the reign of Charles IV.
1456	Establishment of the Brewery Guild in Prague
1585	Tadeáš Hájek of Hájek wrote the book *De cerevisia* on the process of making beer
1680	Patents were granted to make the production of spirits the privilege of the authority
1816	Teaching of brewing, production of ethanol, yeast, lemon acids, lectures in the field of chemistry of natural substances at *the Royal Czech Technical School*
1837	J. E. Purkyne encouraged the study of chemical processes in the cell
1838	first molasses distillery at the Prague brewery "U Gürtlerů"
1845	Karl Napoleon Balling published a textbook of yeast chemistry (*Die Gärungschemie*)
1865	G. Mendel formulated basic laws of genetics (Brno)
1869	established the first malting school in the world in Prague ("*Fachschule*")
1887	founded the Research Institute of Brewing and Malting
1890	established the first collection of microorganisms in the world F. Kral in Prague ("*Kral's Bakteriologisches Laboratorium in Prag*")
1892	K. Kruis draws attention to the suitability of microorganisms as models for biological subjects
1899	prof. I. Honl and prof. J. Bukovsky used for the treatment of leg ulcers the filtrate of *Pseudomonas aeruginosa* (antibiotic pyocyanase)
1914	first yeasthouse using molasses (Kolín)

Important milestones of Czech biotechnology development (II)

Year	Note
1918	Karel Kruis and Jan Šatava publish works on the development and germination of spore and sexuality of yeasts
1923	began the production of insulin (*Pancreas - Hormon*) in the *Norgine* pharmaceutical factory in Ústí nad Labem
1928	production of citric acid in Kaznějov (the first in the world based on molasses)
1933	in Prague carried out the first biotransformation of steroids (Pasternak, Magasanick, Chergaff)
1933	prof. He publishes the work of "*Penicillium themophylum polyformum*", which describes the testing of antibiotics in laboratory animals
1934	first experiments on continuous cultivation of microorganisms (Málek)
1944	penicillin isolation in *Frágner's factory* in Dolní Měcholupy; obtained a biologically active preparation called *Mykoin BF 510*
1949	production of penicillin started in Roztoky u Prahy (*Penicilin, n.p.*)
1952	Founded by the *Research Institute of Antibiotics and Biotransformation in Roztoky u Prahy* (VÚAB)
1961	First Patent on Immobilization and Co-Immobilization of Enzymes and Cells in Genes (Czechoslovak Patent 113908)
1962	Development of lysine production technology and its introduction into production in n.p. *Biotics*
1964	introduction of 6-aminopenicillanic acid production for the production of semisynthetic penicillins in *n.p. Penicillin* in Roztoky u Prahy
1970	construction of a "platform" for outdoor algae cultivation and introduction of algae production at the *Biotechnology Laboratory of the Ministry of Health of the Czechoslovak Academy of Sciences in Trebon*
1984	start of production yeast production in *SMC Paskov* with annual production of 25 ths. pool
1985	production of the "*Bathurin*" preparation against caterpillars in *JZD AK Slušovice*

Source: Folta J., Vývoj biotechnologie a průmyslové chemie, Společnost pro dějiny věd a techniky, Národní technické muzeum, Praha 2006.

Small Biotechnology Enterprises in Czechoslovakia in 1970-1990 (I)

Small biotechnology enterprises were mostly based on the *Unified Agricultural Cooperative (JZD).* The bulk of applications were therefore directed to the agricultural sector. The application concerned the following fields:

- **Disposal of agricultural waste** (especially slurry) and their conversion to biogas (in 1984 about 80 biogas stations were in operation).
- **The production of bacterial fertilizers** (*Rhizobin* - used to bacteria the seed of legumes and legumes).
- **Production of cultures of lactic bacteria and probiotics** (1972 *JZD Hustopeče*, stabilized culture of lactic bacteria called Lactisil containing *Streptococcus faecium M 74*).
- **Protection of plants against insect pests by preparation of pheromones** (*JZD Práche*).
- **Use of plant explants for the recovery of ornamental plants** (*JZD Tuřany*).

Small Biotechnology Enterprises in Czechoslovakia in 1970-1990 (II)

- **Production of microbial insecticides and enzyme hyaluronidase** (*JZD Slušovice* - production of insect pests preparation under the name *Bathurin 82* and mosquito larvae called *Mosquée*; insecticides from fungi - *JZD Blatnička*, mykoinsekticid *Baverol* and mycofungicide *Supresivit*).

- **Production of preparations against mites harmful to grain and insect pests in silos** (*JZD Dražice* - production of predatory mite *Chayletus eruditus*, which destroys mites of the family *Acaridae*, procedure developed by the Research Institute of Food Industry).

Molecular Fundamentals of Biotechnology (I)

- Modern molecular biotechnology has established in our countries a historical tradition of biotechnology, especially in the applications of food and medical research:
  - traditional use of biomass to produce various food supplements, vitamins, growth factors;
  - advanced technologies for the cultivation of micro-organisms, bacteria, yeasts and algae;
  - the cultivation of animal cells in vivo for the development of vaccines against serious infectious diseases of viral or bacterial origin;
  - production of culture media, sera, specific antibodies;
  - research and development of antiparasitic vaccines.

- The history of Czechoslovak biotechnology began immediately after the establishment of a separate Czechoslovakia by the construction of a modern state health institute in Prague in the 1920s.

- The further development of biotechnology has taken place with the ideological background of exemplary care about human health and the background of the ongoing "East versus West" duel during the Cold War.

Molecular Fundamentals of Biotechnology (II)

- The quality of Biological and Chemical Sciences in Czechoslovakia has achieved excellent results in global competition, for example in the field of research, development and production of vaccines against infectious diseases:
  - childhood epidemic poliomyelitis (Salkova and Sabin's vaccine and their unique area application in the pediatric population);
  - a vaccine against varicella, which has been significantly involved in the history of eradication of chicken pox;
  - and other significant vaccines to prevent serious infectious diseases in children.
- These successes have always been Dimitrij Slonim, a legend of Czechoslovak virology and and WHO expert in vaccine production and technology.

Molecular Fundamentals of Biotechnology (III)

- Successful years of Czechoslovak biotechnology with regard to immunological production and vaccine production are associated with non-existent institutions:
  - the national biogene company;
  - Immunological Research Institute;
  - Institute of Serum and Vaccines (SEVAC).
- Representatives of those who have continued their success after 1989 are:
  - Bioveta, a.s .;
  - Biopharm - Research Institute of Biopharmacy and Veterinary Medicines, a.s.
- It was the original Institute of Serum and Vaccines, np., As well as the Institute of Molecular Genetics and the Microbiological Institute of the Czechoslovak Academy of Sciences, where the foundations of molecular biotechnologies in the former Czechoslovakia were born.

Molecular Fundamentals of Biotechnology (IV)

- **80s of the last century:**

- first steps in gene cloning technology in the *E. coli* bacterial system;
- development of suitable vectors, plasmids and phages;
- cloning into eukaryotic systems using vaccinia virus as a vector;
- production of essential enzymes, endonucleases, restriction endonucleases in the era before the revolutionary molecular cloning technology by PCR (polymerase chain reaction);
- successful completion of the genome sequence analysis of a small bacterial virus phage PZQ - we included it among the European countries where it was first sequenced a complete genome (Vaclav Paces laboratory at the Institute of Molecular Genetics of the Czechoslovak Academy of Sciences);
- successful cloning of the artificial gene for human peptide neurohormon in *E. coli* and preparation of its recombinant form (Vaclav Pacez's laboratory at the Institute of Molecular Genetics of the CSAV).

Molecular Fundamentals of Biotechnology (V)

- Historical tradition in Czechoslovakia also includes hybridoma technology for the development and production of monoclonal antibodies for diagnostic purposes (research, clinical laboratory diagnostics) and therapeutic procedures ("humanized antibodies") in the so-called biological therapy, especially tumor diseases.
  - The Institute of Serum and Vaccines and the Institute of Molecular Genetics AV, shortly after the discovery and publication of hybrid technology for the preparation of monoclonal antibodies to Nobel Prize winners G. Kohler and C. Milstein, managed to introduce the production of selected monoclonal antibodies as diagnostic tools for rapid laboratory diagnosis of antigenic markers of some serious diseases humans and animals.

Molecular Fundamentals of Biotechnology (VI)

- By combining the possibilities of molecular tools of genomic analysis and gene expression (enzyme tools - endonucleases, polymerases, ligases, transcription factors) and mapping of antigenic determinants (epitopes), using monoclonal antibodies and systematic work on methodological issues of molecular biotechnology, unique Czechoslovakia created dynamic assumptions for dynamic development of molecular biotechnologies. In our modern era called "OMICS", which utilizes, for the integration and interpretation of large database files of sequential data, highly efficient bioinformatics and structural and system biology.

Vaccination history - some important discoveries (I)

Year	Note
1796	first experiments with variole vaccination (Jenner)
1885	post-exposure application of rabies vaccine (Pasteur)
1892	cholera vaccine (Haffkine)
1898	Typhus Vaccine (Wright)
1913	immunization against diphtheria - toroid (Behring)
1921	TB vaccine (Calmatte and Guérin - BCG)
1923	terický anatoxin – toxioid (Ramon a Glenny)
1923	pertussis vaccine (Madsen)
1927	tetanus anatoxin - toxoid (Ramon and Zoller)
1932	yellow fever vaccine (Sellard and Laigret)
1937	first inactivated influenza vaccine (Salk)
1949	mumps vaccine - live attenuated (Smorodinstev)
1954	inactivated poliomyelitis vaccine (Salk)
1957	live attenuated vaccine against poliomyelitis (Sabin)
1960	measles vaccine (Schwarz)
1962	rubella vaccine (Weller, Neva, Parkmann)
1966	mumps vaccine (Weibel, Buynach, Hillemann)

Vaccination history - some important discoveries (II)

Year	Note
1967	rabies vaccine cultured on diploid cells (Wiktor)
1968	polysaccharide vaccine against meningococci. C (Gotschlich)
1971	polysaccharide vaccine against mengococcus. A (Gotschlich)
1973	varicella vaccine (Takahashi)
1976	vaccine against pneumococcal infections
1980	vaccine against Hemophilus influenzae b
1992	viral hepatitis A vaccine
2007	human papilloma virus vaccine (zur Hausen)

Source: Helmanová P., Nepovinné očkování z pohledu veřejnosti, Masarykova univerzita, Brno 2010.

History of Vaccination in Czechoslovakia

Disease	Year of Initiation of Vaccination	Note
Smallpox	1821	imperial document, ended in 1980
Rabies	1918	prophylactic use - before bitting
Tuberculosis	1923	first use of the vaccine
	1953	compulsory vaccination, Czech vaccine
Diphtheria	1947	began vaccination of children
Tetanus	1952	vaccinated children in collectives
Coughing cough	1958	all children vaccinated with DTP
Polio	1960	all children vaccinated
Measles	1969	all children vaccinated
Rubella	1982	all girls vaccinated at the age of 12
	1986	all children were vaccinated at 2 years
Viral hepatitis B	1982	vaccination at risk groups
	2001	newborns and children at 12y vaccinated
Mumps	1987	all children vaccinated with *Mopavac*
Meningococal meningitis	1995	extraordinary vaccination on request
Measles, rubella and mumps	1996	all children vaccinated with the *Trivivac*
H. influenzae type b	2001	part of tetravachin together with DTP

Source: Beran J., Očkování – otázky a odpovědi, Galén, Praha 2006.

Thank you very much for your attention ☺

Czech Academy of Sciences

BIOLOGY CENTRE CAS