Abstract. – The innovative crisis is a consequence of scientific stagnation in pharmaceutical research. As a result of innovative crisis the number of innovative drugs put on the market has decreased. Biopharmaceutical research methods combined with findings in molecular mechanism of diseases will allow the discovery of new innovative diagnostics and drugs.

Key Words: Innovative crisis, Biopharmaceuticals, Biodiagnostics, Infectious diseases, Cancers, Simple genetic diseases, Polygenic diseases.

Causes of Innovative Crisis

The lack of therapeutic innovation due to the introduction of an insignificant improvement for existing drugs and/or the absence of discovery of new drugs with an original mechanism of action is called innovative crisis.

The innovative crisis is a consequence of scientific stagnation in pharmaceutical research in both industry and academia. Scientific stagnation in industry has occurred due to improper development of research methods and improper research planning. Scientific stagnation in academia has occurred due to improper correlation between basic and applied research.

Improper development of research methods refers to the use of chemical research methods (i.e. lead screening and lead design) for a long period of time as unique drug research methods and the delayed development of biopharmaceutical research methods (i.e. recombinant DNA technology and monoclonal antibody development).

Lead screening is based on searching natural and synthetic compounds libraries for identifying a lead compound (i.e. new chemical entity – NCE), which is actually the active ingredient of a new drug. The first modern drug discovered by lead screening was ibuprofen in 1966. Lead design is based on designing a lead compound that mimics or blocks effects of a natural mediator. The first modern drug discovered by lead design was salbutamol in 1966.

In recombinant DNA technology the human gene that codes a protein is identified and cut from the rest of the human DNA using restriction enzymes. The human gene is combined with DNA of a bacteria or yeast using ligase enzymes. The bacteria or yeast is cultivated in fermentation containers, where it synthesizes large quantities of human and bacterial proteins. After purification the human protein is used as biopharmaceutical. Human insulin synthesized by bacteria (i.e. Escherichia coli) was put on the market in 1982 and anti-hepatitis vaccine A and B synthesized by yeast (i.e. Saccharomyces cerevisiae) was put on the market in 1986.

In monoclonal antibody development the DNA sequence that codes an antibody is inserted into phage DNA. The phage DNA is added to bacteria (i.e. Escherichia coli) where it synthesizes the monoclonal antibody. After purification the monoclonal antibody is used as biopharmaceutical. A platelet antiaggregant, abciximab was put on the market in 1994.

Improper research planning refers to pharmaceutical research focused on safety or based exclusively on animal pathophysiology.

Improper research planning focused on safety relies on the assumption that drugs safety can be increased without affecting drug efficacy. Several viruses have the ability to kill cancer cells in vivo (e.g. Adenovirus, Reovirus, and Poliovirus). In an attempt to decrease virulence, wild-type viruses have been genetically engineered by gene deletion to obtain mutant viruses (e.g. mu-Aden-
Proper correlation between basic and applied research was done by teaming basic scientists with clinician scientist, and recruiting medical doctors in basic and applied research. As a result, the entire process of drug discovery, from research to preclinical and clinical development can be done in medical faculties.

Biosensors are devices made of a biological recognition system and a transducer. The biological recognition system produces an effect by interaction with the analyte. The transducer converts the effect produced by the recognition system into information and then into a measurable signal. Depending on the biological material they use for recognition, there are enzyme, antibody, nucleic acid, microorganism and cell biosensors. The first medical diagnostic device based on enzyme biosensor for glucose measurement was put on the market in 1975.

Biochips are a type of biosensors. The biological recognition system (i.e. DNA, RNA, protein) covers the surface of a chip (i.e. glass, plastic, silicon). The transducer is an integrated circuit microchip. Depending on the biological material they identify, there are nucleic acid biochips and protein biochips.

Nucleic acid biochips are used to identify an unknown nucleic acid sequence by hybridization. Double-stranded DNA must be heated to create single-stranded DNA. The single-strand nucleic acid (i.e. DNA or RNA) is put on the biochip's surface. If the investigated nucleic acid is complementary with the nucleic acid sequence on the biochip surface they bind to each other and generate fluorescence, which is analyzed by a computer.

Protein biochips are used to identify an unknown protein by mass spectrometry. The protein is washed and put on the surface of the biochip, then crystallized using a chemical solution. The ionized protein is transformed in gaseous state using a laser beam and put into motion using electric current. The protein mass is determined according to the energy generated by the electric current and the motion speed of the protein.

A diagnosis system developed in 2007 can detect infectious agents’ proteins in less than 15 minutes and nucleic acids in less than 2 hours. Although this system was developed for military use in the fight against bio-terrorism, it can also be employed for civil use.

A protein biochip that can simultaneously detect six tumor markers in blood serum was developed in 2009. A project funded by the European...
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The European Commission for developing a nucleic acid biochip for the diagnosis of breast, cervical and colorectal cancer is expected to be implemented in hospitals by 2015.

Biochips for diagnosis of single gene and polygenic disorders are under development. Biomarkers for Fabry disease have been detected in urine using a protein biochip, thus opening the way for the development of a diagnosis biochip. A nucleic acid biochip that can detect multiple genes affected in hypertrophic cardiomyopathy was developed in 2008.

**Solutions to Innovative Crisis**

New biopharmaceutical research methods combined with new findings in molecular mechanism of diseases will allow the discovery of new molecular therapies “tailored” for infectious diseases, cancers, simple and complex genetic diseases.

An infectious disease is caused by multiplication of an infectious agent in human cells. In order to produce a disease an infectious agent must enter into the human body, attach to a target cell, enter into the cell, multiply, generate and release progenies that will attach to other target cells. Upon release of progenies, the target cell usually dies.

There are several antiviral drugs on the market that block the infectious agent’s attaching and multiplication mechanisms. New molecular therapies for infectious diseases will most likely act on the human immune system and/or target cells. A DNA vaccine of avian influenza virus has been developed and successfully tested in chicken, thus paving the way for testing in humans. Although the prevention of influenza infection by blocking the receptor binding region of the viral hemagglutinin was proven a few years ago, by the time of writing this paper no target cells receptor blocking drugs have been put on the market.

Cancers are caused by a series of mutations in genes involved in cell growth. A normal cell becomes a cancer cell if it comes in contact with carcinogens, DNA destruction occur, cellular repair mechanisms do not work, but transcription and translation are intact. The cancer cell is immortal; it divides and generates a tumor. Cancer cells can spread in the organism and generate metastasis.

There are several oncostatic drugs on the market that treat cancers. The aim of new molecular therapies will be to cure cancers. Genetically modified lymphocytes that target tumor vasculature have been developed and successfully tested in mice, thus paving the way for testing in humans. New biopharmaceuticals that block transcription and translation (e.g. DNA antisense) in neoplastic cells are in clinical trials. MG98, an antisense oligonucleotide to DNA methyltransferase 1 (DNMT1), could reverse malignant phenotypes by down-regulating DNMT1. This new drug candidate was well tolerated and showed early evidence of clinical activity in patients with advanced solid tumors during phase I clinical trials. Neoplastic cells can be killed by oncolytic viruses. The first oncolytic virus was put on the market in 2005 in China. Several other oncolytic viruses designed for specific types of solid tumors are being tested with success in late stage clinical trials.

A simple genetic disease is caused by mutations in a single gene not involved in cell growth. A normal cell becomes a mutated cell if it comes in contact with mutagens, DNA destruction occur, cellular repair mechanisms do not work, but transcription and translation are intact. The mutated cell synthesizes a nonfunctional protein which generates a severe physiological dysfunction.

New molecular therapies for single gene diseases will be gene therapies. Research experiments on animals show so far promising results. In a mouse model of human hemophilia A, haematopoietic stem cells transfected with a lentiviral vector synthesized sufficiently factor VIII to be considered as a possible therapeutic option. In experiments on a mouse model of human beta-thalassemia, disease-free embryonic stem cells from oocytes of affected animals could be obtained, thus paving the way for obtaining disease-free embryos from affected parents. Although findings are promising, moving results from research to preclinical and clinical development will be most likely slow and difficult, due to ethical concerns.

A polygenic disease is caused by mutations in multiple genes not involved in cell growth. A normal cell becomes a mutated cell if it comes in contact with mutagens, DNA destruction occurs, cellular repair mechanisms do not work, but tran-
cription and translation are intact. The mutated cell synthesizes hypofunctional proteins which generate a moderate physiological dysfunction. In time, complications of polygenic disease cause cell death.

New molecular therapies for polygenic diseases will most likely target cell death and regeneration. New therapies that prevent cell death by blocking necrosis are in research. Inhibition of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) death pathway in human neurons could be used as a new therapeutic strategy in degenerative diseases. The blockade of the TRAIL death receptor DR5 by a specific antibody has prevented human and mice neuronal cell death in vitro. New therapies that replace dead cells by cellular regeneration using stem cells are in research. Before stem cells can enter clinical trials, strategies for standard characterization must be developed. The osteogenic differentiation of human mesenchymal stem cells in cultures is possible by electrochemical impedance spectroscopy. This is important for the development of future therapies based on human cell implants.

Conclusions

Scientific stagnation in pharmaceutical research can be overcome by discovery of new biopharmaceuticals and biodiagnostics. In the future we can expect that new biopharmaceuticals and biodiagnostics will be discovered, and used in the molecular diagnosis and therapy of diseases. This will improve survivability and health-related quality of life, and protect innovative pharmaceutical companies from profit decrease due to generic competition.

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