ABZYMES - A CHALLENGE FOR THE MEDICAL BIOTECHNOLOGY AND PUBLIC HEALTH

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Summary

A new branch of the Medical biotechnology – abzyme biotechnology is emerging. Abzymes are antibodies with catalytic activity. They combine the specificity and substrate turnover efficiency of the enzymes with the selective targeting of the antibodies. The catalytic antibodies have been developed for catalysis of almost all reactions occurring in the living systems and even for catalysis of kinetically and thermodynamically unfavorable reactions.

The catalytic antibodies are part of the antibody’s repertoire in vivo. Natural antibodies have been found in healthy people, in patients with clinical autoimmune syndrome as well as in individuals resistant to AIDS. The strategies for obtaining abzymes are discussed.

The unique characteristics of abzymes provide their great practical relevance. The abzymes which recognize, bind and transform target cell or molecule selectively would be therapeutically valuable.

Synthesis of specific catalytic Abs, able to neutralize drugs and toxins would destroy them into circulation, before initiating toxic effects on nervous system and other tissues.
The first potential anti-drug vaccine was developed by immunization with a stable transition state analog of cocaine. In 2008, Abzymes neutralizing HIV by destroying its T-cell attachment site have been designed. The potency of this abzym revives the hopes for its clinical application as immunotherapeutic and topical microbicide reagent.

The identification of IgMs and recombinant Ig fragments that hydrolyze amyloid β-peptide provides a foundation for the development of catalytic antibodies for treatment of Alzheimer’s disease.

Engineered bispecific Abs are suitable for antibody directed enzyme prodrug therapy – activation of the prodrug at the moment of its delivery to the target cells, tissues or organs. Catalytic antibodies are a great challenge for the medical biotechnology.

Engineered Abzymes with prescribed catalytic and cytotoxic activity belong to a new generation of diagnostic and therapeutic tools that will enrich the list of biopharmaceuticals.

1. Introduction

The biological drugs – medicines isolated from living organisms have been used in therapy for a long time. The advances made in medical biotechnology enrich the list of diagnostic tools and medicines for prophylactics, prevention and therapy. Many enzymes, proteins, hormones, antibodies, vaccines are produced by biotechnological methods.

The discovery of the catalytic antibodies called abzymes [or catmab – catalytic monoclonal antibody] in 1886, which combine the properties of the enzymes and antibodies, drives the research for the design of a new generation of effective and highly specific therapeutical agents in prevention and treatment of cancer, drugs dependence and drug abuse, virus infections, for manipulating AIDS pandemic.

In June 2008 the scientific group of Sudhir Paul UT Huston laboratory announced that a new strategy for attacking HIV has been developed – to destroy by abzymes the Achilles heel of HIV – the cellular attachment site of the envelope protein gp120, which is constant in all known HIV strains. In that way the virus could not infect target cells T helper cells of the immune system.

2. Structure and Function of Enzymes

Biochemical transformations in the living cells are catalyzed by biological catalysts. Most biological catalysts are proteins. Nucleic acids also can catalyze some reactions. Catalytic proteins are referred to as enzymes and catalytic ribonucleic acids as ribosymes.

Catalysts are substances that increase the rate of chemical reactions. The reactions proceed when the products have less chemical energy than the reactants. Reactions tend to proceed until equilibrium is reached. The catalyst enzymes do not affect the position of equilibrium of a reversible reaction. Many substances, although capable of reacting,
do not actually do so. The reason for that is that reactants do not have enough energy to react at normal temperature. There is an energy barrier – activation energy.

![Energy Barrier](image)

**Figure 1.** Enzymes accelerate the chemical reactions by reducing the activation energy

The reacting molecules pass through a transition state – the state with higher energy than the energy of the reactants. The enzymes speed up the reaction, like other catalysts, providing alternative pathway for the reaction through another transition state with lower activation energy.

The enzymes are proteins – polypeptides made by linking together hundred or even several thousand amino acid monomer units by peptide bonds. The polypeptide chain folds in a unique three-dimensional structure. The folding depends on the number and the sequence of the amino acids of the polypeptide chain that is genetically determined. The specific folding in a three dimensional structure referred to as tertiary structure creates surfaces with precise shapes. The so formed pocket, cleft or crevice on their enzyme surface is called the active site (center) where catalysis takes place. Several amino acids in the active site take part in the positioning, binding of the substrate and in the catalytic act. The mode of action of an enzyme can be represented as follows:

\[
E + S \leftrightarrow ES \rightarrow E + P
\]

The substrate (S) binds into the enzyme (E) active site forming an enzyme substrate complex (ES). The substrate is transformed into the product (P) that dissociates from the enzyme. The enzymes are very efficient catalysts. A single enzyme molecule can transform many substrate molecules. The chemical reaction that involves breaking and forming of chemical bonds takes place in the active site.

Over 100 years ago, Emil Fisher suggested that the substrate binds to the active center in a manner similar as a key fits into a lock. Only substrates that are complementary in
shape and chemical groups (and charge) to the active site can fit to it. Actually, the enzymes are highly specific – an enzyme can bind and transform one or several similar substrates. The “lock and key” concept was changed and developed. It becomes clear that both enzyme and substrate are flexible. When an ES is formed the substrate induces the enzyme protein molecule to fit around it. The “induced fit” model is now generally accepted.

![Figure 2. Schematic representation of an enzyme reaction](image)

In 1940s Linus Pauling suggested that the active center of an enzyme is complementary not to the substrate itself but to its transition state (see figure 2). The enzyme stabilizes the transition state of the substrate and pushes the reaction to proceed. He proposed also that an antibody raised to the transition state of a substrate should have catalytic activity.

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**Biographical Sketches**

**Ilko Getov** was born in Sofia, Bulgaria and graduate master of pharmacy at the Faculty of Pharmacy in 1988. He obtained PhD in Pharmacoepidemiology and pharmacovigilance at Medical University Sofia. He has appointed to the staff of the department of Social pharmacy in 1996 and received Associate professorship in 2005. He specialized in post marketing surveillance and drug regulation in Germany, Italy, etc. Ilko Getov gives lectures on Social pharmacy, Pharmacoepidemiology and Clinical pharmacy. He published original scientific papers in international and local journals and has several textbooks for pre- and postgraduate students. He is a member of Global Development Committee at International Society of Pharmacoepidemiology, European Society of Clinical Pharmacy and EURODURG, joint the WHO Drug policy monitoring project – level II in 2003-2004, acting as evaluator of the projects for EU LLL Program. At national level he is a Chair of Expert commission on medicines advertising at Bulgarian drug agency, member of a Supreme Pharmacy Council at the Minister of health, etc. Mr. Getov participates as a lecturer in Pharmacoepidemiology in post-graduated courses at the Faculty of Pharmacy, University of Belgrade, Serbia. He is married and has one daughter.

**Trenka Argirova** was born in the city of Panagurishte, Bulgaria. Graduated in biology at the University of Sofia she received a PhD degree in biochemistry. She was appointed to the staff of the Department of Biochemistry of Sofia University in 1966 and specialized at Courtauld Institute of Biochemistry in London and in Moscow University. Her early investigations and original papers published are in the field
of protein synthesizing apparatus of the cells and later on in the biochemistry of autoantibodies in autoimmunity. As an Associated Professor in biochemistry she has been giving lectures in Biochemistry and in Metabolic regulations for students in Bachelor and Master Degree programs at University of Sofia. She has published text books and manuals in biochemistry and immunochemistry. Member is of the Bulgarian Society of Biochemistry, Biophysics and Molecular Biology and joint member of the Federation of the European Biochemical Societies. Argirova participated in the organization of the training courses on biochemical education and TEMPUS projects.