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Review Article

A GESTALT OF ABZYMES

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ABSTRACT

Catalytic antibodies, developed by combining enzymes with the use of antibodies complimentary to the haptenic group, resembling the reaction transition state are the newer vista in biologics. Catalytic antibodies offer new possibilities for their potential therapeutic applications because of a high degree of reaction specificity, stereo selectivity, regioselectivity and greater affinity towards transition state analog and their latent ability to block unwanted protein-protein interactions. This review aims at basic synthetic aspects, the updated information on mechanical, biochemical and therapeutic aspects to figure out the potential of this novel biocatalyst as a powerful therapeutic.

Keywords: Abzymes, Antibody, Catalytic, Monoclonal.

INTRODUCTION

Abzymes[1] are catalytic antibodies [2] generated against a proposed substrate transition state or an enzyme active site, also called catmab (from catalytic monoclonal antibody). So an abzyme is a monoclonal antibody with catalytic activity. Abzymes are potential tools in biotechnology, e.g. to perform specific actions on DNA. Antibodies or immunoglobins, are proteins produced by blood cells as part of the immune response to antigenic challenge by any foreign substance. Antibodies are commonly characterized as either monoclonal or polyclonal. Monoclonal antibodies are immunoglobins raised against a particular portion of the antigen called an epitope catalytically and can be used to investigate the immune response. Polyclonal antibodies, on the other hand, are the collection of antibodies elicited against all epitopes of an antigen elicited by an immune response. Enzymes are the most efficient, specific and selective biological protein catalysts, offering solutions to many synthetic problems[3]. Catalytic antibodies offer new possibilities for their potential therapeutic applications because of a high degree of reaction specificity, stereo selectivity [4], regioselectivity [5] and greater affinity towards transition state analog and their latent ability to block unwanted protein protein interactions. Biocatalysis has been successfully used not only in small-scale synthesis but also in the pharmaceutical industry for the preparation of enantiomerically pure intermediates and products[6].

History

In 1946, Pauling[7] noted similar features between mechanisms of antibody-antigen recognition and the interaction of a transition state with an enzyme. In 1969, Jencks proposed a theory that amalgamated the specific properties of antibodies and the catalytic properties of enzymes into one molecule, the abzyme. The term itself is an amalgamation of the words antibody and enzyme. Jencks believed that antibodies generated during anti-antigen immune responses against chemically stable transition state analogues of a reaction of interest. In 1966, Slobin[8] reported the first antibody with enzymatic capabilities when antibodies specific towards p-nitrophenyl esters were elicited in rabbits by immunization with a p-nitrocarbobenzoxy conjugate of bovine serum albumin. A year later, Tramontano[9] et al (1986) and Pollack[10] et al (1986) produced the first Monoclonal antibodies with catalytic properties.

Natural Abzymes

Naturally occurring abzymes have been detected in the serum of patients with several autoimmune disorders such as Systemic lupus erythematosus[24] (SLE), Autoimmune hepatitis, Grave's disease, Polymyositis, Polyarthritis, Sjogren's syndrome, Scleroderma, Rheumatoid arthritis and Viral disorders such as viral hepatitis, AIDS and milk of healthy women. Milk of healthy women contains sIgA-antibodies with protein kinase activity. ATP-hydrolyzing IgG at present is the only example of natural abzymes catalyzing a bi-substrate reaction. All the natural abzymes (small sub-fractions of polyclonal IgG and sIgA) isolated from human milk are having higher catalytic activity than that of abzymes isolated from patients with autoimmune diseases because of their higher amylolytic activity). In 1989, Paul et al discovered the first natural catalytic antibody in the serum of bronchial asthma[25] patients that is nothing but immunoglobin G (IgG), which is hydrolyzing vasoactive intestinal peptide. In 1992, Shuster et al detected both DNA and RNA hydrolyzing antibodies in above auto immune disorders. The antibodies IgM and IgG displaying amylolytic activity from serum of patients with multiple sclerosis (a chronic degenerative demyelinating disease of the central nervous system), monoclonal antibody light chains, or Bence Jones proteins from urine of patients with multiple myeloma are other naturally occurring abzymes.

Table 1: Some of the abzymes and the reactions catalyzed

S. No	Abzyme	Reaction catalyzed
1	McPC603	Ester hydrolysis
2	39A11	Diels Alder
3	13G5	Exo Diels Alder
4	7C8	Hydrolysis of Chloramphenicol
5	Jel103	Nuclease
6	Jei42	Peptidase
7	43C9	Amide hydrolysis
8	1F7	Chorismate mutase
9	5C8	Cyclase
10	17E8	Ester cleavage
11	7G12	Chelation
12	28B4	Oxygenation
13	38C2 & 6D9	Activation of prodrugs of insulin and Chloramphenicol
14	YX1-40H10	Detoxification of Methamphetamine
15	20G9	Hydrolysis of phenyl acetate
16	sIgA of human milk	Protein kinase

Catalytic Antibodies over Enzymes

One of the most important advantages of catalytic antibodies over enzymes is that the desired reaction can be selectively programmed into the antibodies by using an appropriately designed hapten, which is not possible with enzymes. Catalytic antibodies almost always demonstrate a high degree of substrate selectivity. In addition, such catalytic antibodies produced have sufficient regioselectivity to give a single product for a reaction. They can be produced by immunization with a single handed version (only left- or only right-handed) of a hapten, and only substrates with the same handedness can act as substrates for the resulting catalytic

antibodies. The net result is that a high degree of stereo selectivity is observed in the antibody- catalyzed reaction [26].

Advantages

- They are biocompatible and have long serum half-lives.
- Can be useful in lower doses as compared to other drugs.
- High affinity binding for a preselected substrate.
- They have the ability to carry out a pre-determined chemical reaction with efficiencies useful for medical applications.
- They have latent ability to block unwanted protein interactions.

Synthetic Aspects

Abzymes are created by immunizing an animal against a transition state analog[27] (TSA) of the desired reaction. Any non-lethal TSA antigen that can be coupled to a carrier protein can potentially create a useful abzyme. Reactive immunization is a novel method to select and create the most catalytically active abzymes. Use an immunogen that will react at physiological pH or will bind covalently to a B-cell receptor.

Ligand-based Abzymes Production

Monoclonal abzymes were first generated against transition state analogues by Pollock and Tramontano. These antibodies were generated against antigen analogues of the transition state for the ester hydrolysis of the p-nitophenylphosphorylcholine and monoaryl phosphate esters respectively. In both experiments, a phosphorus atom was used to model the unstable tetrahedral carbon atom of the proposed transition state generating a chemically stable transition state analogue (Fig 1). When immunized with an accurate transition state analogue, antibodies will be produced against the molecule which will confer the ability to catalyze the desired reaction.

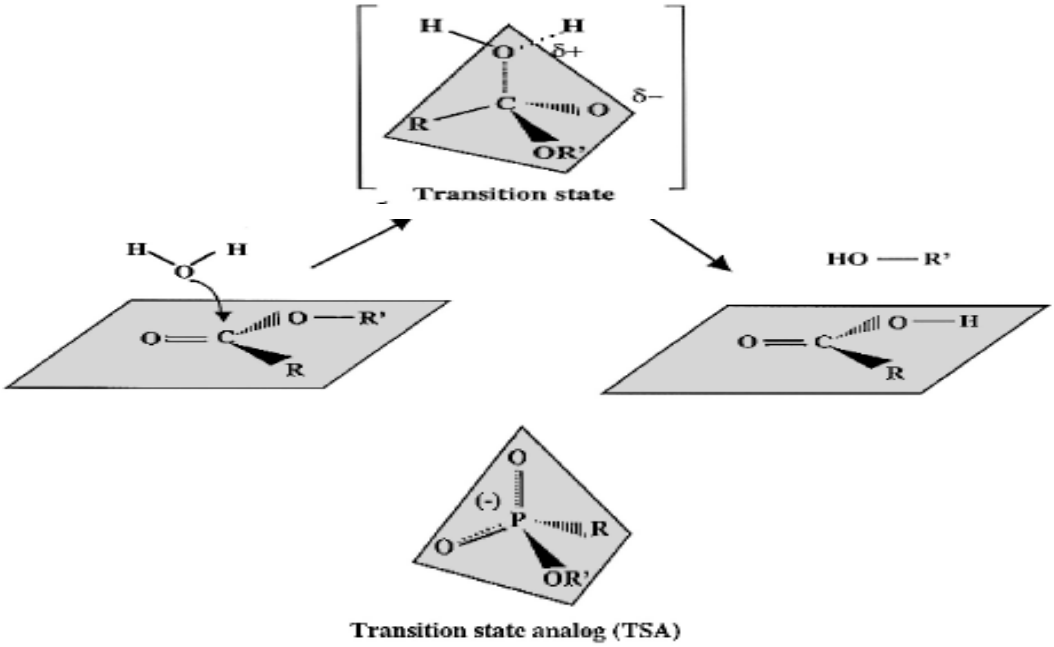

Fig. 1: Ligand-based approach of abzymes synthesis

Anti-idiotypic abzyme production

Anti-idiotypic abzyme production [28] was pioneered by the work of Izadyar et al in 1993 and this group was successful in the production of monoclonal anti-idiotypic antibodies with cholinesterase activity. This method is similar to the mysterious immune system production of naturally occurring abzymes observed in patients with several autoimmune and viral diseases. This approach was developed in an effort to conserve some part of the enzyme active site catalytic machinery in the antigen-binding portion of an antibody.

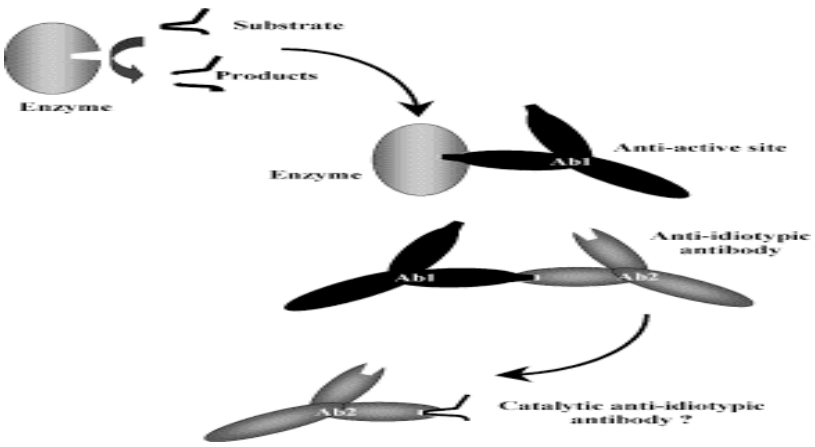

Fig. 2: Anti-idiotypic approach for the generation of abzymes

Applications of Abzymes

Abzymes in organic synthesis

To date there are more than 100 artificially generated monoclonal abzymes to catalyze more than 100 separate chemical reactions. They have been found to catalyze the hydrolysis of amides, esters, reactions like cyclization, decaboxylation, lactonization, photochemical thymine dimer cleavage, bi molecular amide bond formation, beta elimination, photo induced cleavage, photo induced dimerization, Claisen rearrangement of chorismic acid to prephenic acid, 6-membered ring lactonization, proton transfer redox reaction, enantioselective reactions, disfavored ring closures, hydride transfer, acyl transfer, Aldol/Michaels and Oxy-cope rearrangements and other reactions that are not known to be catalyzed by any known enzymes. Reymond and co-workers have reported a number of catalytic antibodies (10F11and 9D9) which catalyze the Retro-Diels-Alder reaction[29-31] of the Diels-Alder adducts of nitroso compounds.

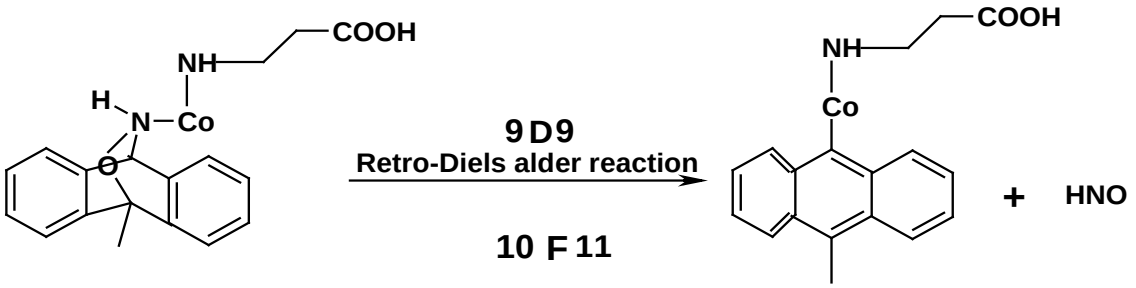

Fig. 3: Retro-Diels-Alder reaction[32] by 10F11and 9D9

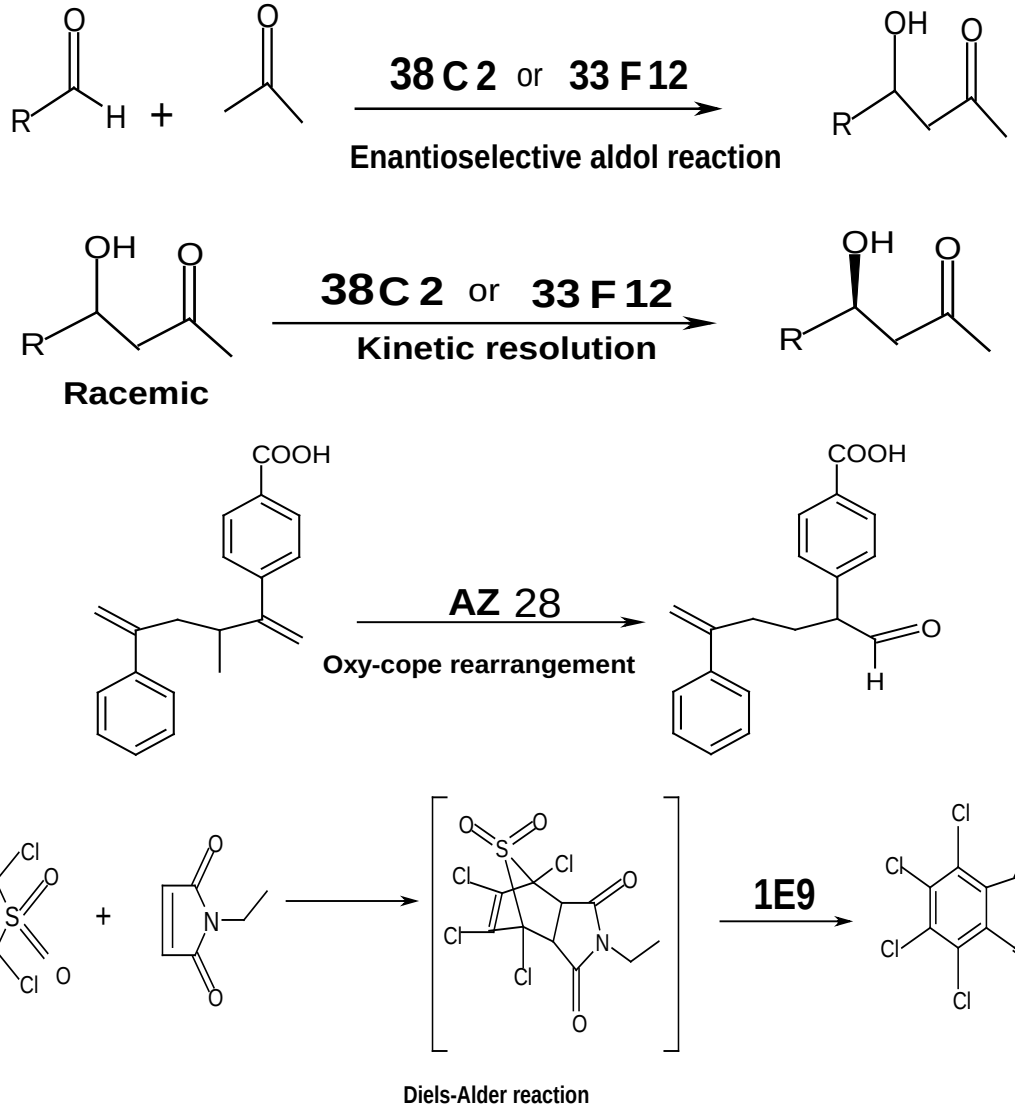

Fig. 4: Some of the Abzymatic applications like Aldol condensation, Enantiomers preparation, Oxy-cope rearrangement and Diel's alder reactions

Synthesis of Naproxen via Antibody-Catalyzed Ester Hydrolysis

Considerable efforts have been devoted to improving the preparation of the enantiomerically pure *S*-(+)-naproxen[33], a widely prescribed non-steroidal *anti* -inflammatory drug (NSAID), which has been made industrially through, diastereomeric crystallization. Antibodies 5A9, 6C7, and 15G12 shown better yield of *S*-(+)-naproxen, from its ester salt.

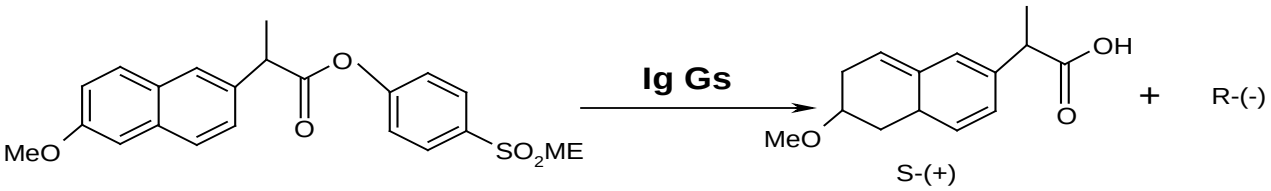

Fig. 5: Synthesis of *S*-(+) - Naproxen

Abzymes in natural product synthesis

Natural product synthesis is the center piece of synthetic chemistry, mainly because of their high selectivity, specificity and phenomenal rate acceleration enzymes thereby offering solutions to many synthetic problems that are difficult or even impossible to solve efficiently by other chemical means. Biocatalysts, not only in small-scale synthesis but also used in the pharmaceutical industry for the preparation of enantiomerically pure intermediates and products.

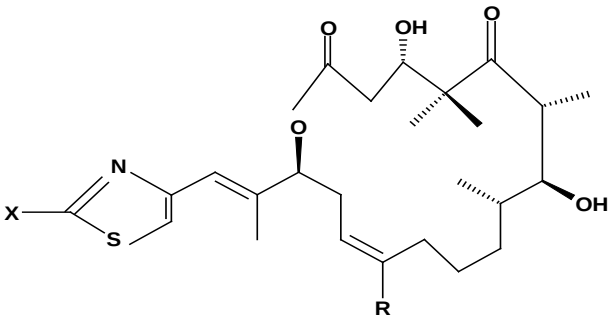

Fig. 6: Basic skeleton of Epothilones

Epothilones are molecules of current interest because of their medical promise and synthetic challenges. Epothilone A and epothilone B are powerful cytotoxic agents isolated from myxobacteria (*Sorangium cellulosum* strain). They possess a taxol-like mode of action, functioning through stabilization of cellular microtubules, and exhibit cytotoxicity even in taxol-resistant cell lines. Epothilone B has been reported to be about 3400 times more active than taxol against the resistant human leukemic cell line CCRF-CEM/VBL in cell-culture cytotoxicity studies. Desoxy precursors of epothilone A, B, C and D also possess comparable biological properties, particularly the tubulin polymerization activity. Besides epothilones A–E, many analogs of these compounds have been synthesized and studied for their effects on tubulin polymerization in vitro and in vivo.

Epothilone A; R=H; X=Me	Epothilone C; R=H; X=Me
Epothilone B; R=H; X=Me	Epothilone D; R=H; X=Me
Epothilone E; R=H; X=CH2OH;	Deoxyepothilone E; R=H; X=CH2OH
Epothilone F; R=Me, X=CH2OH;	Deoxyepothilone F; R=Me; X=CH2OH

Retrosynthetic analysis[34] of the epothilone skeleton suggested that epothilones A-F could be obtained from antibody 38C2-catalyzed aldol and retro-aldol reactions. However, the antibody 38C2-catalyzed aldol reaction afforded compound (-)- **22** in modest enantiomeric purity (75%) at 10% conversion, and these yields decreased even further as the reaction progressed as a result of retro-aldol reaction. This problem was satisfactorily solved by using the more recently discovered antibodies, 84G3, 85H6, and 93F3.

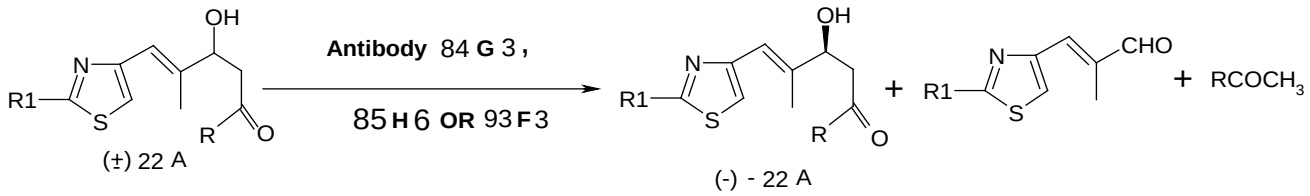

Fig. 7: Use of 84G3, 85H6, and 93F3 antibodies

Synthesis of 1-Deoxy- L -Xylose using 38C2 Antibody

1-Deoxy-l–xylose which was isolated from *Streptomyces hygroscopicuus,* is a key intermediate in the biosynthesis of thiamin (vitamin B) and of pyridoxal (vitamin B6), as well as an alternative non-mevalonate biosynthetic precursor of terpenoid building blocks. Using 38C2, the total synthesis of this natural product by Shabat [35] et al. was achieved via a two-step synthesis, which is considered to be the shortest synthesis known to date for this molecule.

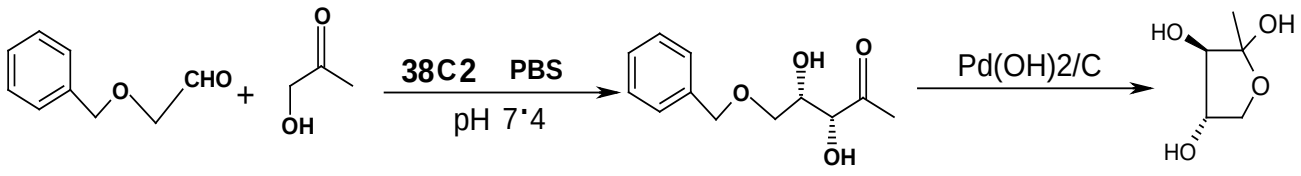

Fig. 8: Synthetic scheme of 1-Deoxy-l–Xylose

While all the natural aldolases use hydroxyacetone in its phosphate-protected form, aldolase 38C2 antibody is known to use unprotected hydroxyacetone in the aldol addition reaction.

Formation of Steroid A and B Rings via Cationic Cyclization

In efforts to mimic the natural enzyme oxidosqualene cyclase, several catalytic antibodies were elicited against charged transition state analogs. For example, antibody HA5-19A4, was catalyzing the cationic cyclization of the dienol sulfonate to produce the closely related decalin systems, with an average enantiomeric excess of 53 % which represent rings A and B of the steroid nucleus[36].

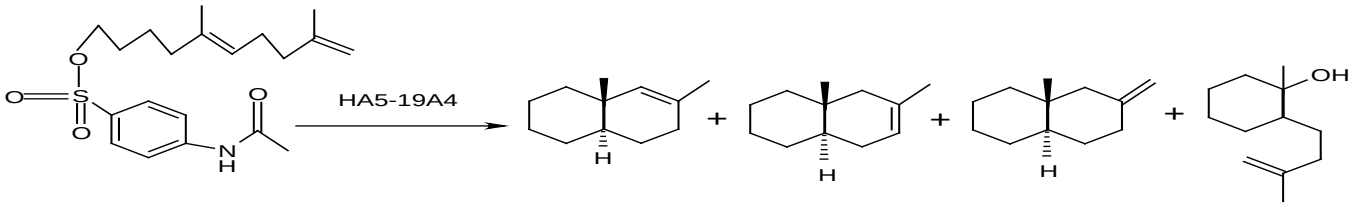

Fig. 9: Synthesis of steroid rings using HA5-19A4

Three antibodies, 15D6, 20C7, and 25A10, which have been elicited against a 4-aza-steroid aminoxide initiated the cationic cyclization of an oxidosqualene derivative and catalyzed the formation of below compound from polyene at neutral pH. The latter represents ring A of the lanosterol nucleus[37].

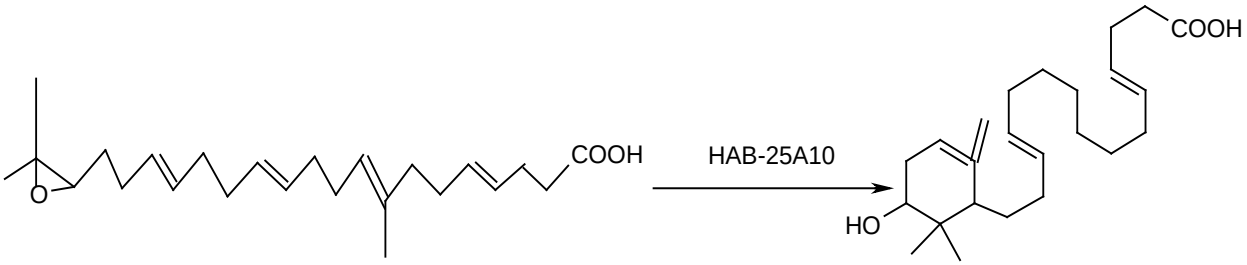

Fig. 10: Synthesis of Lanosterol nucleus using HAB-25A10

Abzymes in different therapies

- For treating genetic deficiency of an extracellular enzyme [38].
- To prevent cocaine addiction and overdose. Murine Mab15A10 degrades cocaine into non toxic ecgonine and benzoic acid and is also used for drug abuse of methemohetamine and toxic effects of certain drugs [39, 40].
- To destroy specific viral and bacterial pathogen coat [41] by carrying out sequence specific cleavage of peptides or carbohydrates.
- To scavenge bodies from autoimmune metabolites[42].
- To protect normal cells from cytotoxicity in drug therapy [43].
- To design catalysts suitable for passive immunotherapy of major disease or to elicit catalytic immunity via vaccination[44].
- To cleave hazardous compounds, including drugs and toxins rapidly.

In chemotherapy of cancer to lessoning drug damage to normal tissues antibody-directed enzyme prodrug therapy (ADEPT) has been developed. ADEPT is a currently practiced tumor drug therapy in which a prodrug is activated by enzymes conjugated with antibodies specific to tumor antigens. The antibody enzyme conjugate is administered first to allow for tumor localization and circulation. The prodrug is significantly less active and is selectively cleaved by the enzyme-antibody conjugate at the tumor site converting it to the parent cytotoxic drug. The use of prodrugs allows for the effective tumor cell damage without causing peripheral cytoxicity of normal cells.

The enzyme component of the antibody enzyme conjugate is normally bacterial in origin and is designed as such to avoid activation by any circulating endogenous enzymes and to be specific for prodrugs. However, the bacterial origin of the enzyme creates a problem when injected into the patient because non-human antibodies elicit host immune responses. Unfortunately, this limits the repetition of ADEPT treatments. The concomitant administration of immunosuppressant will allow for slightly more repetitions of the therapy, but still only allowing two to three cycles of treatments. However, when compared to free drug administration, ADEPT can achieve higher concentrations of drug at the tumor site where the amount of active drug generated depends on the residence time of the conjugate and the amount of prodrug reaching the tumor.

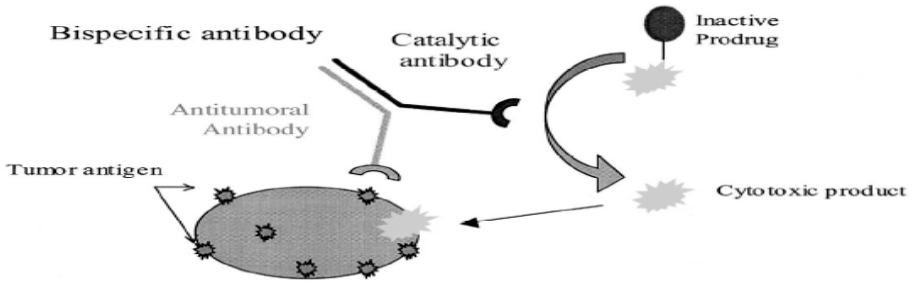

Fig. 11: Selective activation of prodrugs at tumor site by the Antibody Directed Abzyme Prodrug Therapy (ADAPT)

In 1999 Shabat[45] et al applied the commercially available abzyme 38C2 to the anticancer drugs oloxrubicin and camptothecin. They demonstrated that weakly toxic or nontoxic concentrations of the corresponding prodrugs can be activated by therapeutically relevant concentrations of the 38C2 abzymes to kill colon cancer cell lines. This group also demonstrated that in vivo antitumor activity could be elicited by antibody 38C2 injection into a neuroblastoma mouse model and the resulting localized activation of the etoposide prodrug.

- **For protecting the cardiac mitochondria from free radicals**

The selenium-containing peroxidases[46] catalyze the reduction of a variety of hydroperoxides (ROOH or H_2O_2) by using GSH, thereby protecting mammalian cells against oxidative damage. Cytosolic glutathione peroxidase (cGPX) is one of the selenium-containing peroxidases, which specifically uses GSH as the reducing substrate. cGPX was first detected in bovine erythrocytes by Mills. It contains one selenocysteine (Sec) residue in each of the four identical subunits, which is essential for enzyme activity.

- **Treatment of HIV**

At University of Texas Medical School, Houston researchers S Planque et al developed an abzyme which degrades the super antigenic region of the gp120 CD4 binding site. Gap 120 protein was present in the outer coat of the HIV virus and it is involved in the attachment of virus to the CD4 receptors of the T-lymphocytes. In immune compromised patients though T-lymphocytes produce antibodies to the more changeable parts of the viral coat but not to the unchanged part Gap120, the antibodies become inactive. Due to this virus changes the coat rapidly. The abzyme after its binding to super antigenic region of the gp120, it renders the HIV virus inert by destroying the site. A single abzyme can destroy thousands of HIV viruses. Treatment of HIV infections[47] by abzymes is under Human clinical trials and in near future preventative vaccines and microbicides can be prepared by abzymes.

CONCUSION

Abzymes due to their biocompatibility and long serum half-lives are applied to treat number of dreadful diseases like AIDS and cancer. By transition state analog approach, bait and switch approach, reactive immunization approach and anti-idiotypic antibody approach these antibodies are synthesized presently. Abzymes till yet even though showed some applications, they are in the starting of their research. In the near future, due to scientific advances a number of new abzymes can be synthesized and these catalytic antibodies will surely emerge as potential therapeutics.

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