Catalytic Antibodies

Edited by Ehud Keinan

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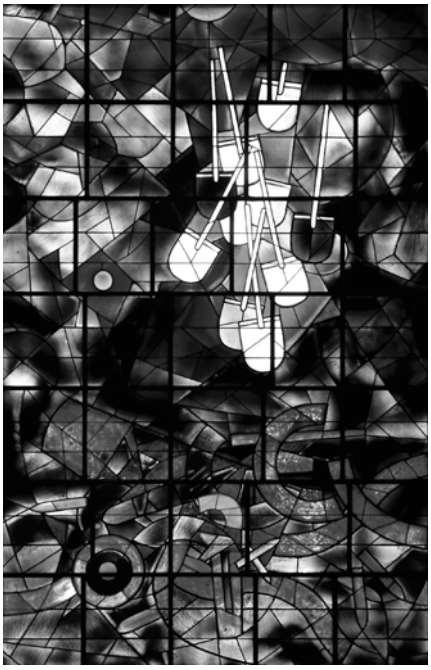

"וְכִתְּתוּ חַרְבוֹתָם לְאִתִּים,
וַחֲנִיתוֹתֵיהֶם לְמַזְמֵרוֹת ..."
(ישעיהו ב,ד)

"And they shall beat their swords
into plowshares, and their spears
into pruning-hooks ..."

Isaiah (2:4)

Antibodies represent the major weapon our body utilizes to attack foreign invaders. The idea of chemists using antibodies to catalyze their non-biological reactions is reminiscent of the biblical metaphor of a military weapon being converted to a working tool. This phrase from Isaiah inspired Mordecai Ardon (1896–1992), whose monumental stained glass windows adorn the Jewish National and University Library on the campus of the Hebrew University of Jerusalem. Photo courtesy of the Hebrew University.

Foreword

It is not our intent here to review the many accomplishments of the field of antibody catalysis. The chapters contained in this volume amply attest to the vigor and accomplishments of the field. Rather we will attempt to extract some of the general principles that have and continue to guide the field.

The first issues concern why one would attempt to make enzymes since there are already some 4000 enzymes known that cover many chemical transformations that one might desire to accomplish. The simple answer is that there are many transformations that existing enzymes do not cover and one might wish to have enzymes for these transformations. However, there is a much deeper answer to this question that goes to the heart of the field and, indeed, is the centerpiece of chemistry. Chemists make things in order to understand the rules of chemistry. For instance, the object of natural product chemistry is not to obtain carloads of material, but rather to understand the general principles that govern how atoms and molecules interact. One learns from both the successes and failures of attempts to accomplish a given transformation. Likewise, if we are to understand the complex chemical engines that are protein enzymes we must ultimately make them. As with natural products, we can learn from both successes and failures. In every case when the binding energy of antigen-antibody union is converted to catalysis, we can state that we know a route by which the transformation under consideration can occur. The initial problem – that one didn't know in detail exactly how the transition state is bound – has largely been obviated by the many crystal structures of catalytic antibodies bound to their transition state analogues. Of course, a catalytic antibody tells one *a* way that a given transformation can proceed, but not necessarily *the* way that a natural enzyme might accomplish the same transformation. The fact that proteins can accomplish the same transformation by a variety of routes is in of itself very interesting and one can only wonder why certain roads were not taken by evolution especially if they are isoenergetic.

So what have we learned? The first very large lesson is that it is not very difficult to generate protein catalysts so long as one correctly understands some of the general chemical principles of the reaction. In stating that it is easy to obtain catalysis we are not making a statement about overall efficiency, but for now are only concerned about starting with binding energy and winding up with catalysis. The lessons that

one derives from the experimental conversion of binding energy to catalysis in real time speaks most generally to the large subject of enzyme evolution. This is because evolution can improve things so long as the function is useful and, thus, the fact that it is rather easy to get catalysis started in the confines of a generic protein-binding pocket gives a selectable function. One of the main insights upon which the field of antibody catalysis was founded is that even a combinatorial library as large as the antibody repertoire was, when used randomly, not large enough to achieve catalysis in real time. Thus, relative to the evolutionary time scale, the process was shortened by millions to billions of years by programming the binding with detailed chemical instructions. These instructions were given, of course, by use of transition state analogues as antigens. The process by which the early antibody catalysts were generated is not precisely identical to evolution for two reasons. First, there is presumably no process in evolution in which a concert of chemical instructions is given at once. Second, screening rather than selection was used to find the early catalysts. Thus, unlike the real time induction of antibody catalysts, evolution does not need instruction because it has time and selection on its side. However, one can assume that immunization with a transition state analogue is simply a device that shortens the time to reach a point that evolution would come to anyway. From this vantage point, antibody catalysis can teach us much about the evolution of enzymes. In the simplest of terms, immunization with a transition state analogue does select for a concert of binding parameters such as the size of the binding pocket, the geometrical arrangement, of protein functionalities around the transition state, and the distribution of charges. Presumably evolution would have to do the same and, in this sense, these parameters are like state functions in that their overall energetics are independent of the pathway by which they were formed. Because we understand that proteins are complex and dynamic entities, we would not expect one-step perfection even though a proper concert of favorable binding interactions has been achieved. In this sense it is paradoxical that we can learn the most about enzyme evolution from the imperfection of antibody catalysts. This is because we can isolate binding parameters and learn what they worth in terms of rate acceleration. Further, because of the fact that antibodies are easy to engineer we can make stepwise improvements and study how they affect catalysis. Finally, the focus here on imperfect enzymes is not to say that, as we will see later, enzymes that rival natural catalysts have not been achieved.

The extraction of information that relates binding to catalysis depends on how many different binding motifs can be generated because this becomes the database from which the general principles are extracted. Fortunately, the antibody repertoire is sufficiently large that a sizeable database of binding interactions is achieved. Another feature that needs to be recognized derives from the fact that the induction of an immune is, itself, an evolutionary process that selects for binding energy. Thus, in making a database on the best way to bind to organic functionalities, we are also learning about the permitted and most successful ways that substrates and transition states might be bound. One of the early difficulties of the field was that the fine details of how binding occurred were not totally controlled by the experimenter. While this is still somewhat the case, this has largely been obviated by the bait and switch strategy and covalent immunization.

One of the most startling lessons from the field concerns how precisely a complex enzyme mechanism can be copied into another protein with a completely different fold and presumably dynamic repertoire. This was seen in the ease by which aldolase antibody catalysts that proceed by an enamine mechanism were generated by immunization with a simple 1,3-diketone antigen to select for a reactive lysine in the antibody active site. The mechanism and rate acceleration of these antibody aldolases are nearly identical to nature's own enzymes. One interesting side point that came out of these studies concerns the vigor with which immunological evolution drives toward binding energy even to the point of taking covalent options when they are available. Thus, even though a diketone antigen ''offered'' the opportunity for covalent binding if a lysine with a perturbed pK_a appeared by mutation, there were many other ways that binding energy could be achieved without resorting to the covalent option (for instance by simple binding to the benzene ring that was also present in the hapten). The fact that most antibodies mutated to express a rare lysine that is not present in the germ line speaks to the fact that antibody evolution is, as expected, a chemistry driven process but also one whose chemistry is only limited by opportunity so long as the reaction in question increases binding energy beyond that which can be achieved by a concert of non-covalent interactions. In other words, any chemical reaction that can happen will.

One of the largest lessons about proteins and catalysis came from an antibody that is not a catalyst and, thus, is not covered in this volume. Several of us reasoned that the time had come to use the binding energy of antibodies to perturb electronically excited states in the same way that thermal transition states have been studied in the field so far. To attempt this, antibodies were made to stilbene. Remarkably, even though these antibodies were not ''taught'' about the excited state, when irradiated with U.V light they adapted to and perturbed the excited state of stilbene and emitted intense blue light. These antibodies were called ''blue fluorescent antibodies''. This effect means that proteins that bind to ground states can adapt to high-energy states of the ligand with sufficient energy to perturb the excited state surface. This is probably a general property of proteins and may explain how enzymes bind to ground state substrates while also maintaining the property of adapting to transition states. Again we see a lesson from antibodies that goes to the centerpiece of protein catalysis.

In terms of breaking news, recent events have demonstrated that all antibodies have the catalytic potential to generate highly reactive oxygen species including ozone and a masked form of the hydroxyl radical. This may be the most potent effector function of antibodies ever discovered. Thus, this preface ends with a remarkable irony. The able workers whose beautiful experiments are detailed in this volume turned antibodies into enzymes to learn more about natural enzymes only to ultimately find out that antibodies were natural enzymes all along!

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"What I cannot create I do not understand."
Richard P. Feynman

Preface

It is now 18 years since the first antibody catalysts elicited against transition-state analogs were induced. At this age of maturation we found it appropriate to comprehensively cover the field of antibody catalysis in one volume. The catalytic antibody technology merges the combinatorial diversity of the immune system with a programmable design by the experimenter. In fact, no other area of bioorganic chemistry has taught us so much about the use of large libraries of molecules in the service of chemistry. We have learned from the immune system that natural evolution does not necessarily require billions of years; it may be completed on a laboratory timescale. This lesson of applying the three major components of evolution – diversity, selection and amplification – has inspired biologists and chemists alike on their quest to discover new functional biopolymers, new catalysts, new drugs, and even new solid-state materials with desired physical properties.

There are many conceptual steps on the way towards the realization of a new antibody catalyst, including mechanistic understanding of the specific reaction to be catalyzed, scholarly prediction of the transition state of highest energy, creative design of a chemically stable transition state analog (TSA), and the planning of synthetic schemes for haptens and substrates. Yet, as is appropriately expressed by the above-cited dictum of Feynman, antibody catalysis is primarily an experimental science where the keys to success reside in the details of the experimental procedures, including organic synthesis, immunization protocols, screening procedures, production of monoclonal antibodies, kinetic experiments, and crystallographic studies.

Many facets of biocatalysis are not yet fully understood, particularly those related to the dynamics of the protein catalyst along the reaction coordinate. Even when some of that can be envisaged, we do not yet know how to design the antibody active site in order to achieve the desired dynamic properties. Therefore, the use of a TSA, even an optimal one, which is often impossible to make, represents only a "snapshot" of a continuous, dynamic process and only a general guideline for the immune system to produce the appropriate catalyst. The resultant, broadly diverse population of relevant antibodies reflects the variety of ways by which the immune system can respond to the given TSA. The beauty of this approach is the element of serendipity, allowing us to find valuable items that were not looked for. Consequently, the importance of efficient screening strategies can never be overestimated.

One of the most significant trends in modern science is the collapse of traditional barriers between well-defined scientific disciplines. Antibody catalysis has illustrated, probably more than any other field, the rewards of working at the interface of biology and chemistry. The diverse chapters of this book reflect the broad spectrum of activities in this highly interdisciplinary field.

Chapter 1 describes structural and functional studies of the immunological evolution of catalytic antibodies, which have provided important insights into the evolution of binding energy and catalysis in biological systems, including antibodies and enzymes. These studies suggest that there is an intrinsic conformational flexibility within the germline antibody combining site. The binding of ligands to the germline antibody induces conformational rearrangements that result in enhanced complementarity between the antibody and the ligand. Consequently, structural plasticity in the combining site allows a limited number of protein scaffolds to bind a broad array of substrates with moderate affinity. Then, somatic mutations and selection processes optimize the complementarity of the combining site with its hapten by fixing the conformation of the CDR loops. Interestingly, these mutations are introduced not only at the hapten combining site but also at the peripheries of that site.

Chapter 2 analyzes the main achievements in the field and defines the key challenges ahead of us. The chapter examines the structure and mechanism of representative catalytic antibodies that were generated by various strategies for different reaction types. It concludes that the field has progressed rapidly from simple model reactions to complex multistep processes, thus defining the scope and limitations of this technology. Now that the approach is well established, attention must be paid to strategies for optimizing catalytic efficiency and for promoting more demanding transformations. Development of improved transition-state analogues, refinements in immunization and screening protocols, and elaboration of general strategies for enhancing the efficiency of first-generation catalytic antibodies are identified as evident, but difficult, challenges for this field. In addition, learning how to create, manipulate and evolve large combinatorial libraries of proteins outside the immune system should help to automate the processes of catalyst discovery and optimization.

Chapter 3 reviews the theoretical studies that have been performed on antibody catalysis to date. Various tools have been applied to the computational investigations of different types of reactions that have been catalyzed by antibodies. Many insights about both quantitative and qualitative aspects of antibody catalysis have been obtained. It may be concluded that quantum mechanical computations on model systems can now be carried out with high accuracy, affording good qualitative determinations of the mode of binding of haptens, substrates, and transition states into antibody binding sites. Yet, the major challenges to be met on the way to a full understanding of antibody catalysis in particular, and biocatalysis, in general, include the development of practical quantitative computation methods for solvation energies and protein-ligand interaction energies.

Chapter 4, which is written by a science historian, brings in to this book a unique historical perspective of the field, drawing special attention to the initial endeavors

to establish antibody catalysis as a scientific discipline at the crossroads of chemistry and immunology. The chapter is neither a comprehensive coverage of the history of the field and the chronological development nor a presentation of the key individuals who contributed to the field. It treats the emergence of this field as a case study and a model for what does it take for a new scientific discipline to be born. Dr. Ben Chaim's thesis is based on many hours of recorded interviews with almost all the active scientists in the field. I believe that this rather unusual, thought-provoking contribution blends well with the scientific chapters of this book.

Chapter 5 covers the use of catalytic antibodies in the synthesis of natural products. One of the main goals of the field of antibody catalysis has been to learn how to design catalysts to improve the overall yield of existing synthetic routs, thus allowing practical construction of more totally synthetic drugs and other important natural products. The examples covered by this chapter, including (–)-α-multistriatin, epothilones, brevicomis, 1-deoxy-l-xylose, (+)-frontalin, the formal synthesis of (–)- and (+)-mevalonolactone, partial synthesis of the steroid skeleton, and naproxen, testify for the important role catalytic antibodies may play in asymmetric synthesis. The remarkable ability of these biocatalysts to control the rate, stereo-, regio-, chemo-, and enantioselectivity of many reactions, including highly disfavored chemical processes, and sometimes even with high substrates promiscuity, render these agents valuable tools for the total synthesis of pharmaceuticals, fine chemicals, and complex natural products.

Chapter 6 presents an impressive number of X-ray crystallographic studies of catalytic antibodies, which have provided valuable descriptions of the specific interactions with substrates and TSAs within the antibody combining sites. The antibodies studied catalyze a variety of chemical transformations, including ester hydrolysis, Diels-Alder reaction, cationic cyclization, elimination, decarboxylation, aldol reactions, sulfide oxidation, rearrangements, and metal chelation. This chapter catalogues and critically assesses the contributions that structural studies have made to the understanding of the catalytic mechanism. Comparisons are made to natural enzymes that catalyze similar reactions.

Chapter 7 reviews several remarkable cases of antibody-catalyzed disfavored chemical transformations. Catalysis of such reactions is a most compelling aspect in both enzymes and catalytic antibodies not only because the reactions are synthetically useful but also because these biocatalysts reveal how nature solves particularly difficult problems. Biochemical and structural studies of the enzymes and antibodies that catalyze disfavored reactions provide chemists with insights into important mechanistic considerations as well as a starting point in the development of *de novo* catalysts for these and other disfavored processes. The examples covered in this chapter include formal violation of the Baldwin's rules for ring closure, exo-Diels-Alder reactions, formation of a ketal in water, *syn*-elimination to produce a cis olefin, and selective formation of C-C bonds via cationic cyclization reactions.

Chapter 8 underscores the importance of screening methods for catalytic antibodies. Selective transition state binding is just one of many elements of catalysis, one that

can be well designed by immunization with an appropriate TSA. Therefore, a good TSA-binder may not necessarily be a good catalyst. Although screening for binding is easily performed by the well-established immunological methods, one should keep in mind that this approach is reminiscent of searching for a lost coin under the street lamp. Certainly, the optimal approach would be the screening for actual catalysis rather than for binding.

Chapter 9 highlights the strengths of directed evolution for the design of novel enzymes with emphasis on catalytic antibodies. The representative techniques of displayed combinatorial protein libraries that are described in this chapter do not cover the entire field of directed evolution. They demonstrate, however, the great opportunities in the employment of such techniques for the development of functional proteins, and of catalytic antibodies in particular. The various strategies harness a number of important technologies, including the methods of cloning and expression of Fab and scFv in different organisms, the ways of physically linking the phenotype to its genotype, the means of creating large libraries in very small volumes, methods of clone selection, and techniques of amplification of clones having the desired properties.

Chapter 10 reviews the medicinal applications of catalytic antibodies, particularly for prodrug activation. The addition of a targeting device to the relevant catalytic antibody renders this treatment highly selective for tumor cells, thus allowing the conversion of a nontoxic prodrug into a toxic drug in high local doses at the tumor site. The concept of using catalytic antibodies as therapeutic agents has become even more appealing when it was shown that most of the amino acids in a mouse antibody molecule could be replaced with human sequences, thereby making it compatible for *in vivo* treatment in humans. Furthermore, since antibodies can catalyze specific reactions that are not catalyzed by natural enzymes they can be used *in vivo*, avoiding specific catalytic competition with natural proteins.

Chapter 11 discusses the development of the concept of reactive immunization and its application to the creation of aldolase antibodies *in vivo*. The *in vitro* application of this strategy can be achieved using phage display selections with reactive compounds. Reactive immunization *in vivo* and reactive selection *in vitro* utilize designed reactive compounds that covalently react with antibodies during their induction and selection in such a way as to effectively program a reaction mechanism into the selected protein. The direct consequence of this strategy is the development of efficient catalysts that operate via experimenter-defined mechanisms. This approach has provided highly proficient aldolase antibodies that had not been accessible by traditional immunization with transition state analogs. Broad scope, enhanced catalytic activity, and defined chemical mechanism are three features that distinguish antibodies derived from reactive immunization from those obtained by immunization with transition state analogs.

Chapter 12 is devoted to the newly discovered antibody-catalyzed water oxidation pathway. A central concept within immunology is that antibodies are the key molecular link between recognition and destruction of antigens/pathogens. The antibody catalysis field has demonstrated that the antibody molecule is capable of performing

sophisticated chemistry, but there was no compelling evidence that antibodies use this catalytic potential in their normal immune function. It was found recently that all antibodies, regardless of source or antigenic specificity, can catalyze the oxidation of water by singlet oxygen via a pathway, which is postulated to include trioxygen species such as dihydrogen trioxide and ozone, to the ultimate product, hydrogen peroxide. It has been shown that oxidants generated by antibodies and by activated human neutrophils, which are present in inflammatory tissues, can kill bacteria.

Chapter 13 describes the known enzymes and antibodies that catalyze photochemical reactions. Biocatalysis is an attractive and useful strategy by which mechanistic manifolds can be restrained and a reactive intermediate such as excited species in photochemical reactions can be channeled into a single product. The lesson we learn from the very few known natural photoenzymes shows that catalysis originates mainly from entropic stabilization of a productive conformer and from the involvement of a photoactive group. Such groups may be available in the form of either a cofactor or an amino acid residue. The few reported examples of photocatalytic antibodies have demonstrated that this approach can be utilized successfully for the design of novel photocatalysts and this opportunity should be considered seriously, particularly because natural evolution has voted against the development of photocatalytic enzymes.

Chapter 14 highlights the high selectivity of catalytic antibodies, including chemo-, regio-, stereoselectivity, and, in particular, enantioselectivity. The ability of antibodies to discriminate between closely related isomeric transition states have been utilized in asymmetric synthesis and other selective transformations, some of which have no enzymatic equivalent.

Chapter 15 analyzes various examples of catalytic antibodies as mechanistic and structural models of hydrolytic enzymes, emphasizing the ability of antibodies to mimic multiple aspects of enzyme catalysis. Undoubtedly, these research efforts have created unique opportunities to learn about enzyme structure and function, about antibody diversity, and about evolution. Although hydrolytic catalytic antibodies have shown high selectivity, they are still inferior to natural enzymes in terms of catalytic efficiency. It is relatively easy to install in antibodies individual parameters of a catalytic machinery but it is still very difficult to design an optimal catalyst having all catalytic elements operating in concert, including the relative positioning of catalytic residues and the appropriate protein dynamics. The obvious consequence is that the keys for obtaining better catalysts are screening methods for catalysis and techniques of directed evolution.

Chapter 16 focuses on the use of transition state analogs as archetype antigens. Many catalytic antibodies elicited against TSAs have rarely approached the catalytic efficiency of enzymes. Yet, from a pragmatic perspective, the achievement of enzyme-like efficiency is not the ultimate condition for a satisfactory catalytic activity either *in vitro* or *in vivo*. From a chemist's point of view, the ability to program an antibody to catalyze reactions for which there is no enzymatic counterpart, such as the Diels-Alder cycloaddition, the 1,3-dipolar cycloaddition, or the Bergman cycloaromatization

reaction, with reasonable rate enhancement and with high regio-, chemo-, stereo-, and enantioselectivity, is a good reason to continue exploring the scope of these remarkable bioctalysts.

Chapter 17 highlights the advantages of using polyclonal catalytic antibodies, which, in contrast with antibodies produced by the hybridoma technology, represent the entirety of the immune response. The study of polyclonal catalytic antibodies has already contributed significantly to the understanding of how the immune system works and of the requirements for successful hapten design. Recently this has led to interesting developments in therapeutic applications, both by active or passive immunization.

Chapter 18 is devoted to the experimental work that is needed for the general production and purification of catalytic monoclonal antibodies via the hybridoma technology. Since antibody catalysis is primarily an experimental science, the keys to success reside in the details of the experimental procedures. Although hybridoma technology is a mature and well-established method, it involves a variety of independent variables and steps. Each step can be carried out in many different ways, and the diversity of the published approaches reflects specific biological problems and experimental tradition that characterize any given laboratory. The literature offers a broad variety of methods, which differ from one another in speed, convenience, reproducibility, and cost. The immunization protocols and the methods of producing monoclonal antibodies described in this chapter have been used continuously over the past two decades in our Scripps laboratories, without claiming that these methods are superior to others.

Finally, **Chapter 19** focuses on naturally occurring catalytic antibodies, which have been surprisingly discovered in the immune system. Such catalysts could function as important mediators of the immunological defense, regulation, and autoimmune dysfunction.

Due to the page limit of this volume, these nineteen chapters describe only some of the most important aspects but certainly do not cover fully the entire science of catalytic antibodies. Likewise, not all the active researchers in the field could be represented in this book. I thank the authors who agreed to participate in this endeavor for their contribution and insight and apologize to the many other scientists who could not be included in the project. It is my hope that this volume will stimulate further research and attract young scientists to join the intriguing field of catalytic antibodies.

Haifa, August 2004 *Ehud Keinan*

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