



PUBLICATIONS



PATENTS



PRESENTATIONS



JULY 2001



Albany Molecular Research, Inc.



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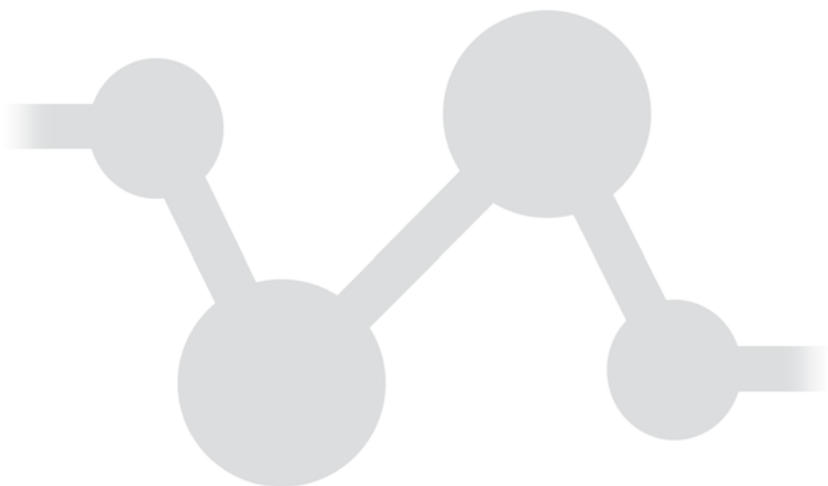
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Albany Molecular Research, Inc.

PRESENTATIONS





MICHELS, P. C.; KHMELNITSKY, Y. L.; BUDDE, C. L.;
ARNOLD, J. M.; NEWMAN, J. A.; CHEN, S. S.;
WANGIKAR, P.; UYSATINSKY, A. Y.; DORDICK, J. S.;
CLARK, D. S.

Combinatorial Biocatalysis for Rapid Synthesis of Libraries of Individual Small Molecules. Presented at the 4th Biocatalysis and Bioprocessing Conference, Iowa City, IA, May 15-16, 1995.

EnzyMed, Inc., has developed a biocatalysis-based technology for synthesizing libraries of organic compounds in solution. Advantages of biocatalysis for generating organic libraries include the natural diversity of enzymatic reactions, single step conversions under mild conditions easily amenable to iteration and automation, solution phase synthesis of libraries in a form readily available for immediate screening, and the ability to retrace the synthetic pathway leading to an active product. Furthermore, in contrast to traditional chemical techniques, the new technology employs *biotransformations* and therefore may have increased likelihood of generating biologically relevant structures that elicit a biological response. The potential of the biocatalytic synthetic methodology has been demonstrated by synthesizing diverse combinatorial libraries based on several small organic lead molecules.

KHMELNITSKY, Y. L.; MICHELS, P. C.; BUDDE, C. L.;
ARNOLD, J. M.; NEWMAN, J. A.; UYSATINSKY, A. Y.;
CLARK, D. S.; DORDICK, J. S.

Molecular Diversity through High-Speed Biocatalysis. Presented at the 4th Biocatalysis and Bioprocessing Conference, Iowa City, IA, May 15-16, 1995, presented at Enzyme Engineering XIII, San Diego, CA, October 15-20, 1995.

EnzyMed, Inc., has developed a biocatalysis-based technology for synthesizing libraries of organic compounds in solution. These libraries are subsequently screened for bioactivity to identify potential new pharmaceuticals. Advantages of biocatalysis for generating organic libraries include the natural diversity of enzymatic reactions, the compatibility of reaction conditions and high-throughput screening techniques, and the ability to retrace the synthetic pathway leading to an active product. The integration of enzymatic synthesis with high-speed robotics represents a new avenue of biotechnology for the discovery of new molecules and biotransformation schemes.

KHMELNITSKY, Y. L.

Biotransformations in Combinatorial Chemistry. Presented at Recent Advances in Fermentation Technology, San Diego, CA, November 4-7, 1995.

EnzyMed, Inc., has developed a biocatalysis-based technology for synthesizing libraries of organic compounds in solution. Advantages of biocatalysis for generating organic libraries include the natural diversity of enzymatic reactions, single step conversions under mild conditions easily amenable to iteration and automation, solution phase synthesis of libraries in a form readily available for immediate screening, and the ability to retrace the synthetic pathway leading to an active product. Furthermore, in contrast to traditional chemical techniques, the new technology employs *biotransformations* and therefore may have increased likelihood of generating biologically relevant structures that elicit a biological response. The potential of the biocatalytic synthetic methodology has been demonstrated by synthesizing diverse combinatorial libraries based on several small organic lead molecules as well as on large natural products such as taxol.

MICHELS, P. C.; KHMELNITSKY, Y. L.; BUDDE, C. L.; WANGIKAR, P.; UYSATINSKY, A. Y.; DORDICK, J. S.; CLARK, D. S.

The BIOACTIV™ Technology: Advantages of Biocatalysis for Combinatorial Library Generation. Presented at the Oxford Biotechnology National Conference on Biotechnology Ventures, San Francisco, CA, November 7, 1995.

EnzyMed, Inc., has developed a biocatalysis-based technology for synthesizing libraries of organic compounds in solution. These libraries are subsequently screened for bioactivity to identify potential new pharmaceuticals. Advantages of biocatalysis for generating organic libraries include the natural diversity of enzymatic reactions, the compatibility of reaction conditions and high-throughput screening techniques, and the ability to retrace the synthetic pathway leading to an active product. The integration of enzymatic synthesis with high speed robotics represents a new avenue of biotechnology for the discovery of new molecules and biotransformation schemes.



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ARNOLD, J. M.; NEWMAN, J. A.; UYSATINSKY, A. Y.;
CLARK, D. S.; DORDICK, J. S.**

Molecular Diversity through High Speed Biocatalysis. Presented at the International Conference on Combinatorial Library Methods for Basic Research and Drug Discovery, Tucson, AZ, December 2-4, 1995.

EnzyMed, Inc., has developed a biocatalysis-based technology for synthesizing libraries of organic compounds in solution. Advantages of biocatalysis for generating organic libraries include the natural diversity of enzymatic reactions, single step conversions under mild conditions easily amenable to iteration and automation, solution phase synthesis of libraries in a form readily available for immediate screening, and the ability to retrace the synthetic pathway leading to an active product. Furthermore, in contrast to traditional chemical techniques, the new technology employs *biotransformations* and therefore may have increased likelihood of generating biologically relevant structures that elicit a biological response. The potential of the biocatalytic synthetic methodology has been demonstrated by synthesizing diverse combinatorial libraries based on several small organic lead molecules as well as on large natural products such as taxol.

**MICHELS, P. C.; KHMELNITSKY, Y. L.; BUDDE, C. L.;
WANGIKAR, P.; UYSATINSKY, A. Y.; DORDICK, J. S.;
CLARK, D. S.**

Applying the Biological Evolution Paradigm to Drug Discovery. Presented at the IBC 1st Applied Molecular Evolution Conference, La Jolla, CA, December 6, 1995.

At the heart of Darwin's description of evolution are two basic concepts: (1) random (per)mutation of the "characteristics" of an organism, and (2) natural selection of the favorable new characteristics (adaptations) by selective survival pressures. This philosophy has been adopted as the paradigm for combinatorial synthesis programs for drug discovery. First, random permutative chemical synthesis, and then high-speed screening for selection of the surviving molecules possessing some favorable adaptation, such as the ability to bind strongly to a receptor or inhibit an enzyme.

Interpretations of Darwin's theory, and most of the initial development of combinatorial chemistry have focused on the mutation of DNA, and the resultant changes to the polypeptide sequence encoded by the DNA ("genotypic"). In the case of

natural evolution, DNA is the source of mutation and is the physical material that “survives” to be passed on to the next generation. In the case of combinatorial drug discovery, polypeptides (or the oligonucleotides encoding them) have been the most straightforward to synthesize, since they required only one chemistry, and a well defined, available set of building blocks.

On another level, evolution can be modeled from a “phenotypic” perspective. In nature, selective pressures discern not between DNA, and only sometimes for an expressed protein. More typically, it is the new product biomolecules that result from a functional mutation in an organism that determine survival and significant adaptive changes from a mutation. This phenotypic evolution requires that the new function of the mutated protein is recognized to offer a significant survival benefit. To accomplish this, the protein may accept new substrates, or perform new transformations to yield the new biomolecules that serve a new or improved survival function. Thus, the vast collection of natural product biomolecules, which enable all life, can be viewed as the product of the evolution of new enzymatic reactions.

EnzyMed is the first company to mimic—and try to improve—this process nature has used to generate the enormous diversity of life and natural materials/compounds. By using the diversity of enzyme catalysts in new combinations and on non-natural substrates, EnzyMed can generate libraries of synthetic “natural products” that may not only contain unique compounds not synthesized by nature, but also in a single compound or small library format that makes screening and identification of active compounds much easier than with typical natural products.

MICHELS, P. C.; KHMELNITSKY, Y. L., DORDICK, J. S.; CLARK, D. S.

Facile Generation of Combinatorial Libraries as Individual Compounds in Solution. Presented at the IBC Molecular Diversity and Combinatorial Chemistry Conference, San Diego, CA, January 24, 1996.

EnzyMed's biocatalytic combinatorial synthesis technology, BIOACTIV™, is uniquely suited for optimization of natural product leads. BIOACTIV™ consists primarily of automated enzyme-catalyzed reactions performed using a combinatorial strategy, as well as selected microbial transformations and chemical steps. The uniform, mild conditions and minimal side reactions characteristic of biocatalytic synthesis permit convenient automated linking of high throughput screening and synthesis.



For illustration, results from paclitaxel, erythromycin, and flavonoid libraries generated using BIOACTIV™ will be presented. Each library consists of up to several hundred derivatives and has yielded several derivatives of novel structure or with improved pharmacological properties. For instance, paclitaxel derivatives with dramatically increased water solubility were isolated from a library of over 200 paclitaxel derivatives.

MICHELS, P. C.; KHMELNITSKY, Y. L.; DORDICK, J. S.; CLARK, D. S.

Facile Generation of Combinatorial Libraries as Individual Compounds in Solution. Presented at the IBC Molecular Diversity and Combinatorial Chemistry Conference, San Diego, CA, January 24-26, 1996

The evolution of all life on earth has occurred through enzyme-catalyzed, combinatorial organic synthesis coupled with natural selection of the biomolecules with the best function. Mimicking this process, EnzyMed, Inc. has developed a biocatalysis-based, iterative technology for synthesizing large libraries of organic compounds in solution, coupled with screening for biological activity. The use of biocatalysis for generating organic libraries allows access to the natural diversity of enzymatic reactions, single step conversions under mild conditions easily amenable to iteration and automation, solution phase synthesis of libraries in a form readily available for immediate screening, and the ability to retrace the synthetic pathway leading to an active product. Furthermore, in contrast to traditional chemical techniques, the new technology employs *biotransformations* and therefore may have increased likelihood of generating biologically relevant structures that elicit a biological response. Indeed, “natural products” are the basis for a large proportion of the existing novel therapeutics.

The potential of the biocatalytic synthetic methodology has been demonstrated by synthesizing diverse combinatorial libraries based on several small organic lead molecules as well as on large natural products such as paclitaxel.

MICHELS, P. C.; KHMELNITSKY, Y. L.; DORDICK, J. S.; CLARK, D. S.

Generation of Natural Product Libraries with Combinatorial Biocatalysis. Presented at the IBC 5th Annual International Conference on High-Throughput Screening, Coronado, CA, April 25-26, 1996.

In the process of library generation using combinatorial biocatalysis, the lead compound is subjected to multiple rounds of iterative biocatalytic derivatizations. After the initial round of library synthesis, a population of first generation derivatives is produced from a single starting compound. Each of these derivatives is then used as a starting point for further diverse biocatalytic modifications, which may include both the reactions employed in the first round and additional new transformations made possible due to the introduction of new functionalities into the lead molecule as a result of initial derivatization. The process can be continued by applying further rounds of iterative modifications.

The large size and vast structural diversity of libraries produced using combinatorial biocatalysis stem from both wide selection of available biocatalytic transformations and large number of building blocks that can be added onto the lead molecule in the process of library generation. The diversity of biocatalytic libraries is further expanded due to the fact that enzymes can react at specific sites of a starting compound without affecting similar sites on the rest of the molecule, a feat that can be difficult to achieve using traditional chemical methods. This natural regioselectivity of enzymatic reactions opens an opportunity for creating focused libraries, where lead compounds are derivatized at specific sites in a controlled fashion. This feature of combinatorial biocatalysis will be illustrated through combinatorial biotransformations on several representative polyfunctional lead structures.

MICHELS, P. C.; KHMELNITSKY, Y. L., BUDDE, C. L.; ARNOLD, J. M.; NEWMAN, J. A.; CHEN, S. S.; WANGIKAR, P.; UYSATINSKY, A. Y.; DORDICK, J. S.; CLARK, D. S.

Generation of Natural Product Libraries with Combinatorial Biocatalysis. Presented at the 5th Biocatalysis and Bioprocessing Conference, Iowa City, IA, May 14, 1996.

EnzyMed's biocatalytic combinatorial synthesis technology, BIOACTIV™, is uniquely suited for optimization of natural product leads. BIOACTIV™ consists



primarily of automated enzyme-catalyzed reactions performed using a combinatorial strategy, as well as selected microbial transformations and chemical steps. The uniform, mild conditions and minimal side reactions characteristic of biocatalytic synthesis permit convenient automated linking of high-throughput screening and synthesis. For illustration, results from paclitaxel, erythromycin, and flavonoid libraries generated using BIOACTIV™ will be presented. Each library consists of up to several hundred derivatives and has yielded several derivatives of novel structure or with improved pharmacological properties. For instance, paclitaxel derivatives with dramatically increased water solubility were isolated from a library of over 200 paclitaxel derivatives.

**KHMELNITSKY, Y.L., MICHELS, P.C.; BUDDE, C.L.;
ARNOLD, J.M.; NEWMAN, J.A.; CHEN, S.S.;
UYSATINSKY, A.Y.; ASTAKHOVA, N.M.; WANGIKAR, P.;
CLARK, D.S.; DORDICK, J.S.;**

Biocatalytic Generation of Combinatorial Libraries. Presented at the 5th Biocatalysis and Bioprocessing Conference, Iowa City, IA, May 14, 1996.

EnzyMed, Inc., has developed a biocatalysis-based technology for synthesizing libraries of organic compounds in solution. Advantages of biocatalysis for generating organic libraries include the natural diversity of enzymatic reactions, single step conversions under mild conditions easily amenable to iteration and automation, solution phase synthesis of libraries in a form readily available for immediate screening, and the ability to retrace the synthetic pathway leading to an active product. Furthermore, in contrast to traditional chemical techniques, the new technology employs *biotransformations* and therefore may have increased likelihood of generating biologically relevant structures that elicit a biological response. The potential of the biocatalytic synthetic methodology has been demonstrated by synthesizing diverse combinatorial libraries based on several small organic lead molecules.

MOCEK, U.

Strategies for Accelerated Natural Products Discovery Programs. Invited speaker presentation at the 3rd Annual International IBC Conference on Natural Products Drug Discovery, Coronado, CA, March 1997.

Natural products discovery programs at Panlabs, Inc. exploit advances in technology and project management to cut months from the time to discover new drug

leads from natural products. These programs include newly designed premium extract libraries exhibiting maximum diversity and the application of new spectroscopic methods. Our streamlined approach quickly eliminates those samples of little value focusing on the structure elucidation of significant lead molecules.

MICHELS, P. C.; KHMELNITSKY, Y. L., DORDICK, J. S.; CLARK, D. S.

Combinatorial Biocatalysis for Drug Discovery and Optimization. Presented at the 213th ACS National Meeting, San Francisco, CA, April 14, 1997.

The search and identification of new compounds with useful or improved biological properties, e.g. drugs and agrochemicals, requires screening of large sets, or libraries, of novel compounds and derivatives. EnzyMed, Inc. has developed a unique technology for synthesizing such libraries of organic compounds in solution. The technology is based on the integrated approach that incorporates smoothly interfaced enzymatic processes, microbial transformations and chemical reactions. The technology platform can be viewed as a set of interconnected biocatalytic and chemical toolboxes, which are designed to complement and support each other. Specifically, chemical reactions are used to introduce reactive sites for subsequent biocatalytic steps, while certain enzymatic reactions create starting points for further chemical derivatizations. Highly efficient chemical synthetic methodologies, such as multicomponent reactions and microwave-assisted synthesis, have been successfully incorporated into our chemoenzymatic technology. The mild and uniform conditions typically employed for biocatalytic and selected chemical processes enable convenient integration of automated solution-phase synthesis and compound identification in a standard 96-well format. The versatility of this technology is demonstrated by the synthesis of diverse libraries from small organic precursors, as well as the iterative derivatization of complex natural products.

MICHELS, P. C.; KHMELNITSKY, Y. L.; DORDICK, J. S.; CLARK, D. S.

Combinatorial Biocatalysis for Drug Discovery and Optimization. Presented at the 38th Annual Meeting of the American Society of Pharmacognosy, Iowa City, IA, July 26-30, 1997.

Biocatalysis offers many attractive and frequently cited advantages for organic synthesis, especially for the modification of complex or labile intermediates. Most



important from a practical sense are its greater efficiency for certain chemistries, its regio- and stereo-selectivity, and its mild reaction conditions.

Yet, fairly few commercial and research processes routinely use biocatalysis. EnzyMed has developed its combinatorial biocatalysis approach for the rapid and broad application of biocatalysts as practical synthetic tools for medicinal chemistry and general organic synthesis.

**MICHELS, P. C.; KHMELNITSKY, Y. L., BUDDE, C. L.;
ARNOLD, J. M.; NEWMAN, J. A.; CHEN, S. S.;
WANGIKAR, P.; UYSATINSKY, A. Y.; DORDICK, J. S.;
CLARK, D. S.**

EnzyMed Express: Your Ticket to Accelerated Drug Discovery. Presented at the 38th Annual Meeting of the American Society of Pharmacognosy, Iowa City, IA, July 26-30, 1997; Theory and Practice of Combinatorial Biocatalysis. Presented at Enzyme Engineering XIV, Beijing, China, October 14, 1997.

EnzyMed's biocatalytic combinatorial synthesis technology, BIOACTIV™, is uniquely suited for optimization of natural product leads. BIOACTIV™ consists primarily of automated enzyme-catalyzed reactions performed using a combinatorial strategy, as well as selected microbial transformations and chemical steps. The uniform, mild conditions and minimal side reactions characteristic of biocatalytic synthesis permit convenient automated linking of high-throughput screening and synthesis.

For illustration, results from application of the BIOACTIV™ technology to mono-, di-, and sesquiterpenes, polyketides, alkaloids, and flavonoids will be presented. Each library consists of up to several hundred derivatives and has yielded several derivatives of novel structure or with improved pharmacological properties.

RICH, J. O.

Biocatalytic Synthesis of Solution-Phase Combinatorial Libraries. Presented at the 216th ACS National Meeting, Boston, MA, August 23, 1998.

The search for and identification of new compounds with useful biological properties, e.g. drugs and agrochemicals, requires screening of large sets, or libraries, of novel compounds. Combinatorial biocatalysis is a powerful methodology for producing such libraries of organic compounds in solution. The mild and uniform

conditions for biocatalysis enables convenient integration of automated, solution-phase synthesis, high-throughput screening, and compound identification in a standard 96-well format. The integration of biocatalysis with high-speed robotics represents a new avenue of biotechnology for the discovery of new molecules. The versatility of this approach is demonstrated by the synthesis of diverse libraries from small organic precursors, as well as the iterative derivatization of complex natural products.

PRESIG, C. L.; LAAKSO, J.; MOCEK, U.; WANG, P.; NG, J.; BAEZ, J.; BYNG, G. S.

Biotransformations of Canrenone and Mexrenone. Presented at the 216th Meeting of the American Chemical Society, Boston, MA, August 1998.

A collection of microorganisms known to hydroxylate exogenous steroids was screened for the ability to modify the antihypertensive drug, mexrenone. Thirty-nine biotransformations of mexrenone were analyzed; mexrenone metabolism was observed in the majority of them. Several monohydroxylated derivatives were detected by HPLC-MS-UV and identified. Data were searched for single eliminations; only the Δ 1,2 elimination of mexrenone by several bacteria was confirmed. Three previously unidentified compounds were isolated as major metabolites produced by *Bacterium cyclo-oxydans* and *Mortierella isabellina*. Δ 1,2-Mexrenone was produced by the former. 6β -hydroxymexrenone and 12β -hydroxymexrenone were produced by the latter.

**KHMELNITSKY, Y. L.; COTTERILL, I. C.;
USYANTINSKY, A. Y.; ARNOLD, J. M.; MICHELS, P. C.**

Microwave-Assisted Combinatorial Chemistry. Presented at the International Conference on Microwave Chemistry, Prague, Czech Republic, September 6-11, 1998.

A new, highly efficient MICROCOS technology (Microwave-assisted Combinatorial Synthesis) for generating combinatorial libraries will be described. The technology is applied to the high-throughput, automated, one-step, parallel synthesis of diverse compound libraries in 96-well plate format. The advantages of microwave-assisted chemistry for combinatorial synthesis include a broad range of available chemistries, simple reaction set-up and product recovery readily amenable to automation, extremely short reaction times, and high product yields. The advantages of the MICROCOS automated technology will be highlighted by the examples of generation of libraries of substituted pyridines and dihydropyrimidines using Hantzsch and Biginelli multicomponent condensations.



MICHELS, P. C.

Developing Combinatorial Biocatalysis as a Practical Synthetic Tool. Presented at the Rensselaer Polytechnic Institute Invited Alumni Lecture, Troy, NY, October 28, 1998.

Why is biocatalysis a relatively infrequently used tool for the synthetic chemist? Biocatalysis offers many attractive and frequently cited advantages for organic synthesis, especially for the modification of complex or labile intermediates. Most important from a practical sense are its greater efficiency for certain chemistries, regio- and stereo-selectivity, and mild reaction conditions. In addition, biocatalysis is often cleaner and more environmentally-benign than alternative synthetic approaches, which can be a key advantage in some regulatory environments or applications.

Yet, fairly few commercial and research processes use biocatalysis. What may be the primary reasons for this, and how are recent developments and new technologies promising to revolutionize the impact of biocatalysis? I will suggest significant issues that should be addressed for biocatalysis to be regarded as a more important synthetic tool.

GARR, C. D.

Drug Discovery: Working Smarter, Not Harder. Presented at DTP Molecular Diversity Workshop, National Cancer Institute, Arlington, VA, March 1999.

Combinatorial chemistry can be used as the link between process development, product development, and practice. It allows the synthetic organic chemist to use all the tools available wisely and proactively, making the most of chemistry.

COUTTS, L. D.; HERR, R. J.; EVANS, J.

Pharmaceutical Process Research and Development Symposium. Co-Founder and Co-Chair presentation at the ACS Northeast Regional Meeting, Potsdam, NY, June 22, 1999.

The First Annual Pharmaceutical Process Research & Development Symposium was held as a one-day seminar at the 1999 ACS Northeast Regional Meeting (NERM) in Potsdam, NY. It was co-founded and co-chaired by Jeff Evans (Bristol-Myers Squibb, Syracuse), R. Jason Herr (Albany Molecular Research, Inc.) and Lisa Coutts (Albany Molecular Research, Inc.). A list of ten speakers from the Northeast Region provided talks during the session held at Clarkson University.

The response was overwhelmingly positive, and consequently the Pharmaceutical Process Research & Development Symposium was expanded and will be held every year at the NERM.

D'AMBRA, T. E.

Examples of Process Research from Albany Molecular Research, Inc. Presented at the Pharmaceutical Process Research and Development Symposium, ACS Northeast Regional Meeting, Potsdam, NY, June 22, 1999.

Albany Molecular Research, Inc. is an integrated chemistry contract research organization that provides, as one of its offerings, chemical problem-solving process research. In this presentation, Dr. D'Ambra described several examples of projects completed at AMRI, including the development of syntheses for substantially pure intermediates for the patented synthesis of fexofenadine hydrochloride, the active ingredient in the non-sedating antihistamine AllegraTM. He also discussed some novel chemistry developed for the vitamin D analog (25*R*)-27-hydroxycholesterol as well as the description of a process route developed for the multi-kilogram preparation of a chiral amino epoxide for Vertex Pharmaceuticals, Inc.

MOCEK, U.; LAAKSO, J.; XUE, L.; GODDEN, J.; GARR, C.; CHEN, Z.; BAJORATH, J.

Strategies for an Integrated Natural Products Discovery Program. Presented at the 40th Annual Meeting of the American Society of Pharmacognosy, Joint Meeting, Amsterdam, Netherlands, July 1999.

Lead identification from natural products continues to play a significant role in drug discovery. We characterize natural product libraries, test them for binding to therapeutic targets, and elucidate the structures of active compounds. Computational comparison of these structures with synthetic chemical libraries aids in the development of novel leads from natural products. A primary goal of these investigations is the identification of analog structures that are synthetically accessible. Results of these studies will be presented.



BAKER, D.; MOCEK, U.; GARR, C.

Natural Products vs. Combinatorials: A Case Study. Presented at the Royal Society of Chemistry Conference on Biodiversity: New Leads for the Pharmaceutical and Agrochemical Industries, St. Andrews, Scotland, September 1999.

Historically, pharmaceuticals have largely been derived from natural product sources. With the development of combinatorial approaches to chemical synthesis in the last decade, drug discovery programs have adapted to large-scale screening programs of combinatorial chemical libraries of up to several hundred thousands of wells. Natural product screening programs are perceived by some in the pharmaceutical industry as antiquated, inefficient or even unproductive, despite a steady flow of natural product derived New Chemical Entities (NCE) into the market. Natural products hold great potential for novel drug discovery. Newer, automated and high-throughput technologies, which make high-throughput combinatorial chemical synthesis possible, can be adapted to improve the efficiency of natural product discovery programs.

Libraries of synthetic combinatorial chemicals complement libraries of natural product metabolites, but do not duplicate or replace them. Examples of side-by-side screening of synthetic combinatorial chemicals and microbial fermentation extracts indicate that both sets of chemical diversity can provide unique leads. The quantity of leads generated by each method is irrelevant, if the quality of the lead is not considered. Therefore, scientific research should be focused not on which type of library is better, but rather how to take advantage of both resources in a cost-effective manner.

To position natural products to meet the current drug discovery paradigm of high to ultra-high throughput random screening, certain well-known technologies should be used. Biological characterization as well as separation chemistries for semi-purification or full purification can be employed prior to screening to reduce the number of compounds in the screening mixture and to create links from the physical entities to databases containing chemical and biological characteristics. Lead candidate compounds from both synthetic and natural product sources can both be used to commence computational approaches to analogue generation for optimal lead drug development.

KHMELNITSKY, Y. L.

Chemoenzymatic Combinatorial Chemistry. Presented at Biotrans '99 - 4th International Symposium on Biocatalysis and Biotransformations, Giardini Naxos-Taormina, Italy, September 26 – October 1, 1999.

The search for and identification of new compounds with useful or improved biological properties, e.g. drugs and agrochemicals, requires screening of large sets, or libraries, of novel compounds and derivatives. EnzyMed Inc. has developed a unique technology for synthesizing such libraries of organic compounds in solution. The technology is based on the integrated approach that incorporates smoothly interfaced enzymatic processes, microbial transformations and chemical reactions. The technology platform can be viewed as a set of interconnected biocatalytic and chemical toolboxes, which are designed to complement and support each other. Specifically, chemical reactions are used to introduce reactive sites for subsequent biocatalytic steps, while certain enzymatic reactions create starting points for further chemical derivatizations. Highly efficient chemical synthetic methodologies, such as multicomponent reactions and microwave-assisted synthesis, have been successfully incorporated into our chemoenzymatic technology. The mild and uniform conditions typically employed for biocatalytic and selected chemical processes enable convenient integration of automated solution-phase synthesis and compound identification in a standard 96-well format. The versatility of this technology is demonstrated by the synthesis of diverse libraries from small organic precursors, as well as the iterative derivatization of complex natural products.

RICH, J. O.; KHMELNITSKY, Y. L.

Biocatalytic Synthesis of Combinatorial Libraries. Presented at Enzyme Engineering XIV, Kona, HI, October 14, 1999.

The search for and identification of new compounds with useful biological properties, e.g. drugs and agrochemicals, requires screening of large sets, or libraries, of novel compounds. Combinatorial biocatalysis is a powerful methodology for producing such libraries of organic compounds in solution. The mild and uniform condition for biocatalysis enables convenient integration of automated, solution-phase synthesis, high throughput screening, and compound identification in a standard 96-well format. The integration of biocatalysis with high-speed robotics represents a new avenue of biotechnology for the discovery of new molecules. The versatility of this approach is demonstrated by the synthesis of diverse libraries from small organic precursors, as well as the iterative derivatization of complex natural products.



KING, C. H. R.; HERR, R. J.; STEFFKE, S. H.

Synthesis of Optically Pure (+)- and (-)-18-Methoxycoronaridine Hydrochloride as Anti-Addictive Agents. Presented at the Eighth Asian Chemical Congress, Taipei, Taiwan, November 23, 1999.

Process improvement and scale-up of the racemic 18-methoxycoronaridine, and the development of a novel chemical resolution for the preparation of optically pure (+)- and (-)-18-MC hydrochlorides will be presented.

MOZHAEV, V. V.

Application of EnzyMed's Proprietary Technology Platform to Lead Derivatization and Syntheses of Compound Libraries. Presented at the Seminar at Biotechnology Research Institute, National Research Council of Canada, Montreal, Canada, December 3, 1999.

Application of biocatalysts (isolated enzymes and whole cells) gives multiple advantages over the use of traditional chemical methods for derivatization of lead compounds and library synthesis. The technology being developed at EnzyMed (now a division of Albany Molecular Research, Inc.) applies biotransformations provided by over 600 individual catalysts. The diversity of biotransformations performed at EnzyMed is constantly expanded by acquisition of new enzymes and cell catalysts, preferably with broad substrate. Successful combination of unique chemistry and specificity introduced by biocatalysts with versatility and robustness of traditional synthetic approaches of organic chemistry significantly expands the potential of our technology. Our technology platform utilizes an automated, miniaturized approach to combinatorial biocatalysis. The methods for catalyst screening and library synthesis have been developed in 96-well reaction plate format that can be applied in a high-throughput automated fashion. Any hit compound identified in the screen can be further derivatized in order to improve its biological activity or pharmacological properties and scaled-up to the amounts sufficient for biological screening. My presentation will show several examples of practical application of our technology to lead derivatization and optimization and combinatorial synthesis of small libraries of natural compounds.

**CHEN, Z.; PABBA, C.; MULLIGAN, S.; LATURNER, S.;
DOLAN, J.; GARR, C.**

New Strategies for Combinatorial Libraries from Natural Products. Presented at the 220th Meeting of the American Chemical Society, Washington, DC, August 23, 2000.

In the past decade, there has been tremendous impact made by the integration of combinatorial chemistry with drug discovery research, the effect being more rapid and efficient acceleration of the drug discovery process. At New Chemical Entities, Inc. (NCE), we apply several strategies to increase the success of library synthesis, the goal being the efficient synthesis of a collection of drug-like molecules from natural products scaffolds. Some parallel synthesis approaches we use to address both target-focused and lead expansion natural product libraries are solution phase, gel phase, resin-assisted and solid phase chemistry. Features of these processes are demonstrated, using well known natural product scaffolds as examples.

GARR, C. D.

Biologically Derived Chemical Diversity: A Rational Approach to Library Production for Drug Leads. Presented at CHI's High-Throughput Organic Synthesis Conference, San Diego, CA, February 2000.

Natural products have historically been the feedstock of drug discovery. With the advent of high-throughput organic synthesis, the emphasis has shifted to synthetic, usually at the sacrifice of overall chemical diversity inherent in natural products. New Chemical Entities, Inc. is focused on using automation, high-throughput technologies and chemo/bio-informatics, in part developed for combinatorial chemistry, to advance natural products. Lead finding, optimization and refinement can all be addressed competitively allowing for the capture of the quality in natural products, and the quantity of HTS. Examples of various techniques currently in use and under development will be provided.



MICHELS, P. C.; RICH, J. O.

Developing Combinatorial Biocatalysis as a Practical Approach for Synthetic Chemistry. Presented at IBC Enzyme Technologies 2000, Las Vegas, NV, February 28, 2000.

Biocatalysis offers many attractive and frequently cited advantages for organic synthesis, especially for the modification of complex or labile intermediates. Most important from a practical sense are its greater efficiency for certain chemistries, regio- and stereo-selectivity, and mild reaction conditions. Yet, fairly few commercial and research processes routinely use biocatalysis. EnzyMed, Inc. has developed its combinatorial biocatalysis approach for the rapid and broad application of biocatalysts as practical synthetic tools for medicinal chemistry and general organic synthesis.

The potential impact and applications of combinatorial biocatalysis can best be understood by examining the natural function of enzyme catalysts and the evolutionary processes that created them. Nature has long practiced solution phase divergent synthesis to create the unparalleled complexity of natural products. The broad array of chemistries required for the production of organic biomolecules all must occur under mild and uniform conditions within the living cell. Some of these reactions (such as aromatic or aliphatic hydroxylation, mild and selective oxidative reactions, decarboxylation, etc.) are difficult to reproduce using purely chemical means under any conditions. Since most natural products are polyfunctional and chiral, a high degree of catalytic selectivity is important. Thus, by necessity, enzymes have evolved to catalyze reactions with high catalytic efficiency, high selectivity, and with few byproducts on the full range of structures observed in nature.

These characteristics give biocatalysis the *potential* to complement the many strengths of traditional organic synthesis. To actually realize an efficient integration of biocatalysis and traditional organic synthesis, general approaches and specific protocols must be established to convert enzymes into ready-to-use, practical synthetic catalysts. Adapting the work of many researchers, we have established an array of methods useful for improving the synthetic versatility of a broad range of biocatalysts. The combined substrate tolerance of a collection of related enzymes in appropriate reaction media allow biocatalytic chemistries to be applied to virtually any molecule. Compound solubility; biocatalyst activity, stability, and specificity; process miniaturization, automation and scale-up all represent key issues. Appropriate catalysts can then be applied in an iterative fashion to produce libraries of derivatives from almost any starting compound. Examples of these approaches for catalyst preparation and utilization will be presented.

EnzyMed, Inc. has chosen to make this broad, synthetically-oriented biocatalysis platform, and the smooth integration of this platform with traditional organic synthesis, its core technology. We have focused the capabilities of this technology towards applications in drug discovery and development. Incorporating traditional medicinal chemistry principles and methods, the biocatalysis platform has been applied to lead discovery, lead optimization, metabolite modeling and synthesis, and the selective synthesis of intermediates.

In general, the evolution of combinatorial biocatalysis techniques with the maturation of genomics, molecular biology, and in vitro evolution approaches promise to provide highly efficient and tunable catalysts tailored for a broad range of synthetic goals.

JONES, L. D.

Frontiers in Drug Discovery. Presented at the Romeo Club – Albany Jewish Community Center, Albany, NY, March, 2000. Recent Advances in Drug Discovery. Presented at the Brandeis University Women's Club, Colonie, NY, November, 2000.

Classical drug discovery was carried out through laborious organic synthetic efforts, where prospective drugs were made one at a time. It typically took 12-14 years before a new drug entered the market. Modern drug discovery exploits three new core technologies: genomics, high-throughput biological screening and combinatorial chemistry. A description of how Albany Molecular Research, Inc. and similar companies are fueling growth in lead compounds was presented.

HU, X.; MUZZIO, M.

Role of Lyophilization in Purification of Combinatorial Libraries. Presented at PREP-2000, 13th International Symposium, Exhibit & Workshops on Preparative/Process Chromatography, Washington, DC, May 14-17, 2000.

Stabilizing synthetic products is a challenging issue in purification of combinatorial libraries. Solvent removal after prep HPLC is a process that often causes loss of some fragile compounds. Lyophilization was used in this study for preventing decomposition and conversion of target products during purification. Freeze lowered reactivity of compounds in solution. Conversion and decomposition of the target products was avoided in frozen states with reacting agents or without stabilizing agents. Lyophilization is a useful technique in stabilizing fragile organic compounds during solvent removal in purification.



GARR, C. D.

The Utilization of Biologically Derived Diversity through Combinatorial Technologies: Bringing Quantity to Quality. Presented at SRI's Combinatorial Technologies Conference, Princeton, NJ, July 24-26, 2000.

Natural products have historically been the feedstock of drug discovery. With the advent of combinatorial chemistry the emphasis has shifted to synthetics, usually at the sacrifice of overall chemical diversity inherent in natural products. New Chemical Entities, Inc. is focused on applying its integrated discovery know-how to balance the playing field. Paramount in the process are bio- and chemo-information capture, tracking and mining, high throughput technologies and a host of chemistry capabilities. As a demonstration of the approach, a test case will be provided.

ZIRBES, E. L.; REED, K.; MADJID-YUNUS, A.; MICHELS, P. C.

Using Iterative Biotransformations for the Generation of Novel Compound Libraries. Presented at the Society for Industrial Microbiology Annual Meeting, San Diego, CA, July 25, 2000.

The combinations of microbial and purified enzyme systems with classical medicinal chemistry provide powerful tools for the generation of novel compounds from current pharmaceutical and agrochemical compounds. Biocatalysis offers many attractive advantages for organic synthesis, especially for the modification of complex or labile intermediates. Biocatalytic reactions offer greater efficiency for certain chemistries, regio- and stereo-selectivity, and mild reaction conditions. Typical reactions include aromatic hydroxylation, O- and N- dealkylation, reductive and oxidative reactions. Microbial systems have the added advantage of being able to carry out multiple enzyme reactions on a compound. By using the BIOACTIV™ high-throughput screening system, the biocatalytic capability of over 600 different catalysts can be tested on a single compound. Once desired catalysts are identified, reactions can be scaled to allow for milligram to multi-gram scale production of biotransformation products. Examples of novel compounds generated using this system are presented.

JONES, L. D.

Trends in Pharmaceutical Contract Chemical Outsourcing. Presented at the American Chemical Society Meeting, New York City, NY, October 12, 2000.

The pharmaceutical industry has been outsourcing various functions for more than two decades. Historically, most outsourcing was piecemeal in nature, and was used to augment internal resources. Resource decisions, including outsourcing, were usually localized at the department level. In 1999, outsourcing accounted for approximately 25 percent of pharmaceutical spending, across the board. Outsourcing has grown more strategic as the industry has evolved and efforts have become more significant. Today, most drug companies have sophisticated procurement groups that drive this decision-making process.

KLEE, G. M.

Manufacture and Control of Active Pharmaceutical Ingredients used for Clinical Trials. Presented at the GMP Roundtable Meeting, Frazier, PA, October 20, 2000.

On July 19, 2000, the International Conference on Harmonization (ICH) released for consultation (at Step 2 of the ICH process) the Draft Consensus Guideline entitled, "Good Manufacturing Guide for Active Pharmaceutical Ingredients." Within the issued ICH Draft Consensus Guideline, Q7A, active pharmaceutical ingredients (APIs) used for clinical trials were given a separate section that outlines the special requirements needed for these APIs. Although brief [less than 100 lines of text covers the API clinical supply Good Manufacturing Practice (GMP) requirements], the section on APIs for use in clinical trials does offer companies a starting point for establishing their minimum manufacture and control procedures to meet GMP requirements. This presentation summarized the current challenges (to industry quality units and regulatory agencies) in the area of manufacture and control of APIs for clinical trials. Additionally, a set of procedures was outlined for meeting the ICH Draft Consensus Guideline requirements.



CHEN, Z.

Combinatorial Chemistry in Drug Discovery: Past, Present, and Future. Presented at East China University of Science & Technology, Shanghai, China, December 10-12, 2000; Presented at Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China, December 19, 2000; Presented at the National Laboratory for Microbial Resources at Yunnan University, Kunming, China, December 27, 2000.

This seminar was designed to teach the fundamentals of combinatorial chemistry and its application to drug discovery. The seminar focused on (a) what is combinatorial chemistry; (b) combinatorial chemistry in drug lead discovery and optimization – parallel synthesis; (c) combinatorial chemistry in drug lead discovery – natural products approach; (d) high-throughput purification processes; and (e) combinatorial chemistry in integrated drug discovery.

HERR, R. J.

The Synthetic and Medicinal Chemistry of Tetrazoles. Presented at the Eastern New York ACS section meeting, Schenectady, NY, January 17, 2001.

5-Substituted-1*H*-tetrazoles (RCN_4H) are often used as metabolism-resistant isosteric replacements for carboxylic acids (RCO_2H) in SAR-driven medicinal chemistry analog syntheses. This presentation provided a brief summary of the medicinal chemistry of tetrazolic acids and highlighted some examples of tetrazole-containing drug substances in the current literature. A survey of representative literature procedures for the preparation of 5-substituted-1*H*-tetrazoles, focusing on preparations from aryl and alkyl nitriles, was presented in sections by generalized synthetic methods.

RICH, J. O.

Developing Combinatorial Biocatalysis as a Practical Approach for Synthetic Pharmaceutical Chemistry. Presented at ACS Great Lakes Regional Meeting, Grand Rapids, MI, June 13, 2001.

Biocatalysis offers many attractive and frequently cited advantages for organic synthesis, especially for the modification of complex or labile molecules. Most important from a practical sense is its greater efficiency for certain chemistries, its regio- and stereo-selectivity, and its mild reaction conditions. Yet the use, or even active consideration of biocatalysis is routine for a relatively narrow range of

commercial and research processes. Albany Molecular Research, Inc. has developed its combinatorial biocatalysis approach for the rapid development and broad application of biocatalysts as practical synthetic tools for medicinal chemistry and general organic synthesis. Biocatalysis complements the many strengths of traditional organic synthesis. To actually realize an efficient integration of biocatalysis and traditional organic synthesis, general approaches and specific protocols must be established to convert enzymes into ready-to-use, practical synthetic catalysts. Adapting the work of many researchers, we have established an array of methods useful for improving the synthetic versatility of a broad range of biocatalysts. The combined substrate tolerance of a collection of related enzymes in appropriate reaction media allow biocatalytic chemistries to be applied to virtually any molecule. Compound solubility; biocatalyst activity, stability, and specificity; process miniaturization, automation and scale-up all represent key issues. Appropriate catalysts can then be applied in an iterative fashion to produce libraries of derivatives from almost any starting compound. Examples of these approaches for catalyst preparation and utilization will be presented. Albany Molecular Research, Inc.'s Biocatalysis Division has chosen to make this broad, synthetically-oriented biocatalysis platform, and the smooth integration of this platform with traditional organic synthesis, its core technology. We have focused the capabilities of this technology towards applications in drug discovery and development. Incorporating traditional medicinal chemistry principles and methods, the biocatalysis platform has been applied to lead discovery, lead optimization, metabolite modeling and synthesis, and the selective synthesis of intermediates.

MICHELS, P. C.

Practical Applications of Combinatorial Biocatalysis for Pharmaceutical Discovery and Development. Presented at Biochemical Engineering 2001, Sonoma CA, June 15, 2001.

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