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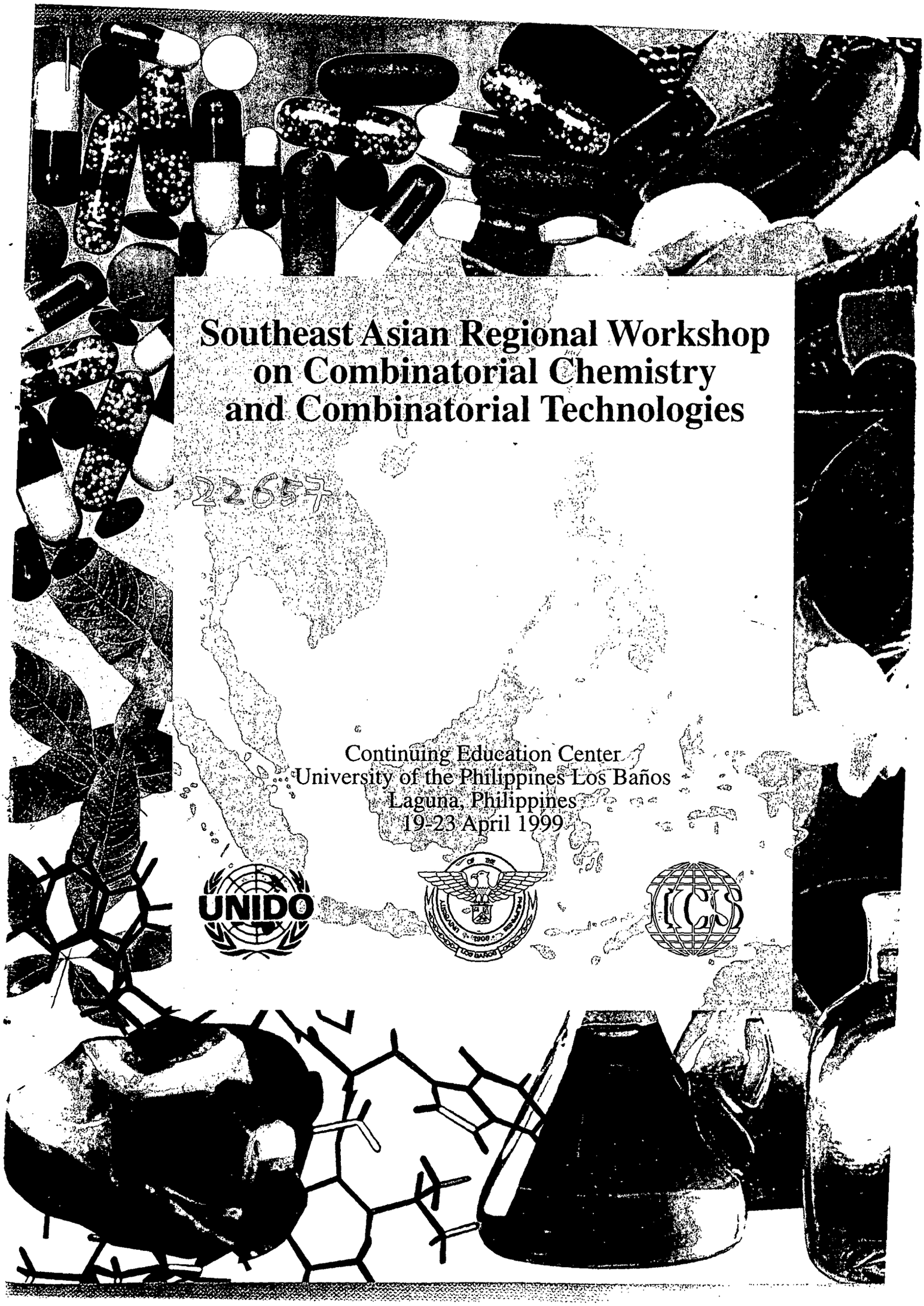


Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies

22657

Continuing Education Center
University of the Philippines Los Baños
Laguna, Philippines
19-23 April 1999

MESSAGE

Combinatorial Chemistry and Combinatorial Technology are new interdisciplinary fields joining combinatorial informatics and computer-assisted chemistry with automated synthesis of chemical "libraries" followed by automated screening. Their main output is in medicinal chemistry and drug discovery. It is generally accepted that the method has a great potential for the lead finding drug discovery process and the technology is expected to have a great impact also in agro-chemistry research, development of new materials and catalysts.

Developing and emerging economy countries have emphasized the urgent need to get acquainted with combinatorial technologies in order to enable local enterprises to remain competitive and economically viable in the coming decades. Moreover, many developing countries have abundant natural resources (especially naturally occurring compounds) that are presently well below their proper exploitation.

The International Centre for Science and High Technology (ICS), which is an autonomous institution within the legal framework of the United Nations Industrial Development Organization (UNIDO), with headquarters in Trieste, Italy, focuses on know-how transfer and technology transfer from developed countries to developing countries. Within the area of Pure and Applied Chemistry a subprogramme on Combinatorial Chemistry and Combinatorial technology is presently carried out and a Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies is organized as part of the ICS-UNIDO Work Programme 1999.

The main objectives of the workshop are to build awareness among researchers and technologists on CC/CT, to evaluate possible initiatives (as follow-up projects and feasibility studies) regarding CC/CT development and industrial implementation with the focus on natural product exploitation and to set-up a regional ICS-UNIDO network on Combinatorial Chemistry and Combinatorial technology.

I would like to express my thanks to the local organizer, the University of the Philippines, especially to Prof. Fajardo, Dr. Calanasan and Dr. Seneci, ICS Scientific Advisor, for the precious work during the organization of the workshop. I wish a fruitful event to all the lecturers, participants and institutions involved.

Prof. Stanislav Miertus
Area Coordinator
International Centre for Science
and High Technology

Republic of the Philippines
DEPARTMENT OF SCIENCE AND TECHNOLOGY

MESSAGE

I would like to extend my warmest greetings to all the delegates and participants to the Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies (CC/CT).

Combinatorial Chemistry and Combinatorial Technologies are relatively new fields that offer rich possibilities, especially for a region with developing economies.

Combinatorial chemistry, for instance by reducing the time and costs associated with producing effective, marketable and competitive new drugs, stands to revolutionize the chemical industry in the region. This early, it has already created excitement in the global pharmaceutical, agrochemical and biotechnology industries.

I thus join the entire science community in wishing for the success of this workshop. With the expected wealth of data that will be generated from this workshop, we could best appreciate and assess the potentials of combinatorial chemistry and policies to best harness these new methodologies.

Dr. Filemon A. Uriarte, Jr.
Secretary
Department of Science and Technology

UNIVERSITY OF THE PHILIPPINES LOS BAÑOS
College, Laguna, Philippines 4031

MESSAGE

In the quest for progress, the academe and the industries have an unwritten pact to be supportive of each other. The academe produces, verifies and tests the technology while the industry adopts such technology in commercial scale to reach as many sectors of the population. The academe depends on the industry for support in its research while the industry depends on the academe for innovations in its commercial pursuits.

It is in this light that the Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies will prove to be very beneficial to the Philippines. This will broaden the industrial base where we can be competitive as a nation in our efforts to be at par with the rest of the world in the new millenium. The trend in the world today is to maximize the benefits that can be derived from a combination of disciplines. The awareness that this five-day seminar will build among the researchers and technologists and the up-to-date knowledge it will provide can bee vital weapons in forging a greater alliance of academe and industries in fulfilling the common goal of national development.

We wish to thank the International Centre for Science and High Technology (ICS) and the United Nations Industrial Development Organization (UNIDO) for giving the University of the Philippines Los Baños (UPLB), through the Institute of Chemistry the chance to host this very important and significant activity.

Congratulations and God bless.

Ruben L. Villareal
Chancellor
University of the Philippines Los Baños

SPIK **CHEMICAL INDUSTRIES ASSOCIATION OF THE PHILIPPINES**
(Samahan sa Pilipinas ng mga Industriyang Kimika)

MESSAGE

This age of biotechnology, advanced sciences and high technology has spawned limitless potentials for the growth of industry in particular and the nation's economy in general. Unfortunately, however, reality is that only a few have optimized the benefits of said technological advances. By and large, most of us have remained passive gauging from the progress of our economic development vis-à-vis our Asian neighbors. It is apparent that a great number of our people have the desire to explore the vast opportunities presented and elevate their quality of life given proper environment. Yet, for some endless litany of excuses things could not get started, we choose to forego our big chance of becoming an economic pillar. We have to start rolling up our sleeves, get down to business, and immerse ourselves deep into science and technology.

The holding of the Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technology in the Philippines is therefore a much welcome event. If we are bent on uplifting our state of technology and in cascading the benefits thereof to our businesses, this is an event we should not let to pass.

As president of the Chemical Industries Association of the Philippines, also known as SPIK, with 11 sub-sectors under its mantle, I congratulate the participants of this workshop while urging industry players to actively partake the potentials of CC/CT. There is no better way to counterbalance the economic crunch we are experiencing now than to stock up our people with knowledge power.

To the organizers, the International Center for Science and High Technology, the United Nations Industrial development Organization and the Institute of Chemistry of the University of the Philippines Los Baños, I commend the leaders of these institutions for taking the cudgels in putting together this workshop. This type of activity breeds advancement, hence growth, which our country is in dire need of.

Edwin LL. Umali
President
SPIK (Samahan sa Pilipinas ng mga Industriyang Kimika)

MESSAGE

The UNIDO-sponsored Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies, which is held for the first time in the Philippines, is a timely and promising activity. This workshop shall be able to train combinatorial researchers and technologists from the Southeast Asian countries, who in turn could teach future trainors in this area. I predict that the workshop topic would be common currency among many scientists and technologists in Southeast Asia in a few years and would have long-term impact in many countries.

I wish to congratulate UNIDO and the Workshop Organizing Committee for making a good idea come true.

Ernesto J. Del Rosario
Director
Institute of Chemistry
UP Los Baños

MESSAGE

Welcome to the "Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies."

It is indeed a great privilege to bring together scientists and decision-makers from many parts of the country and the world for this activity. In addition to building awareness of the fast developing fields of Combinatorial Chemistry and Combinatorial Technologies (CC/CT), we hope this event promotes greater efforts in developing countries to implement CC/CT into programmes of industrial development.

On behalf of the Local Organizing Committee, I wish everyone a most rewarding and enjoyable time.

MABUHAY!

Norma N. Fajardo
Chair
Local Organizing Committee
Institute of Chemistry
UP Los Baños

WORKSHOP SPEAKERS

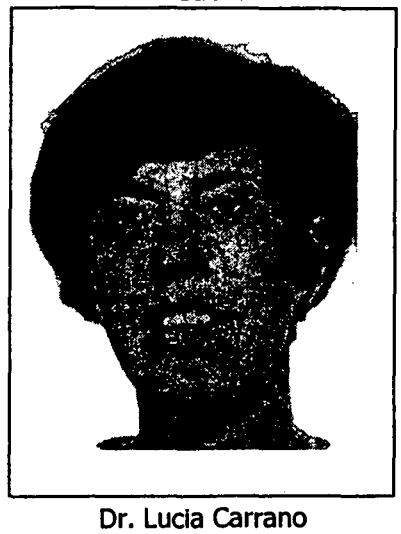
Prof. Stanislav Miertus
Area Coordinator, ICS

Dr. Pierfausto Seneci
Head, Lead Discovery Dept
GlaxoWellcome, Italy

Dr. Giorgio Fassina
Biopharmaceuticals
TECNOGEN, Italy

Dr. Anneliese Appleton
Molecular Simulations P/L
Australia

Dr. Franciscus T.M. van Amsterdam
Head, Scientific Computing & Lead
Generation, GlaxoWellcome, UK



Dr. Lucia Carrano
Microbial Technologies
Biosearch, Italy

Dr. Andrea Missio
Combinatorial Technologies
GlaxoWellcome, Italy

Local Organizing Committee

NORMA N. FAJARDO, Ph.D.
Chair

Technical

CLEOFE A. CALANASAN, Ph.D.
HEAD

EVELYN B. RODRIGUEZ, Ph.D.

JOSE H. SANTOS, Ph.D.

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EVAMARIE P. CAPAREDA, Ph.D.

RAYMOND B. MONTEREY

AUREA N. MIRANDA

Physical & Travel Arrangements

MA. CECILIA D. DE MESA
HEAD

GLADYS CHERISSE J. COMPLETO

ALVIN MAXIMO A. ALTAMIRANO III

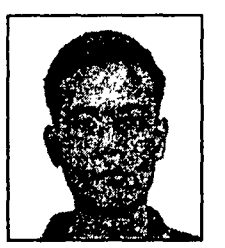
JOSE RENE L. MICOR

Ways & Means

MAXIMA E. FLAVIER, Ph.D.
HEAD

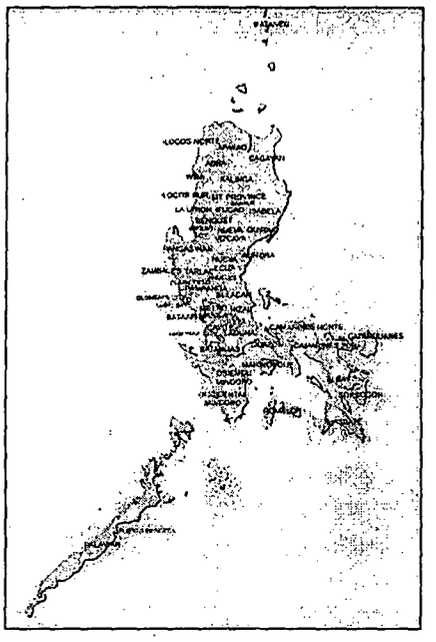
MA. FLORENCIA A. NAVERA

MA. ELENA C. VIERNES



NESTOR U. SORIANO, JR.

*THE PHILIPPINES



The Philippines is a rich tropical archipelago of 7,107 islands stretching gracefully over 1,800 kilometers between the twenty two degrees North of the equator. Strategically positioned east of the Asian mainland, and blessed with abundant natural resources, the country has attracted traders, explorers and adventurers for centuries.

The legacy of these early visitors remains today. Language, art, culture, ethnology, religion and architecture were influenced by settlers from powerful empires that rose and fell on the tides of history. Even the name is foreign. The Philippines was named for King Phillip II of Spain in 1543, twenty-two years before Spain established a permanent colonial presence here.

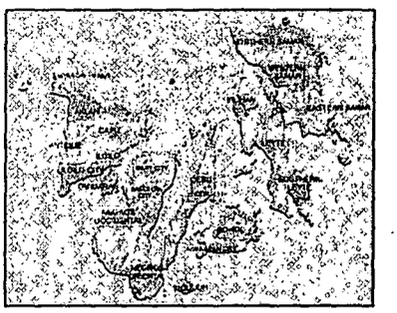
Manila is the premier international gateway and is the nation's political, social, cultural, commercial and transportation capital. Metropolitan Manila has grown from a small tribal village to a teeming energetic metropolis that sprawls across 626 square kilometers. Metro Manila embraces eight cities and 12 municipalities with a population of 10 million.

Four years of steady economic growth and an ardent commitment to building much needed infrastructure has enabled the Philippines to adopt a more prominent and respected role as the "Newest Tiger" economy of Asia.

The country is divided into three geographical areas: Luzon, Visayas, and Mindanao. It has 15 regions, 77 provinces, and 65 cities.

LUZON

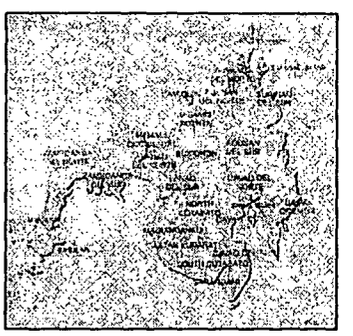
From Manila in Central Luzon, Vigan in the northwest is renowned for its Spanish architecture. Baguio at 1,500 meters above sea level is a cool mountain retreat known as the 'Summer Capital of the Philippines'. Northeast of Baguio you will see the majestic grandeur of the Banaue Rice Terraces, created more than 2,000 years ago by the Ifugao people using a few primitive tools and their hands. La Union, washed by the placid waters of the South China is a haven for water sports enthusiasts. The rugged south coast of Luzon, around Batangas and at Puerto Galera on Oriental Mindoro, contain some of the best dive sites. The island of Palawan, described as the last frontier, is dedicated to eco-tourism with stunning subterranean caves, unexplored dive sites, unspoiled beaches and verdant tropical jungles for trekkers.



MINDANAO

Mindanao, the second largest island in the Philippines, is a treasure trove of natural resources. Visitors seeking exotic flora and fauna who wish to discover authentic jungle forests and wildlife reserves will bask in the glow of Mindanao's flawless beauty. The slopes around Mt. Apo, the country's highest mountain, provide a sanctuary to the magnificent Philippine Eagle and are perfect for exploring ancient caves and trekking through lush tropical forests. Many Filipino Muslims live in central Mindanao, especially around Lanao Lake, where the Aga Khan Museum, Mindanao State university and King Feisal Center for Arabic Studies are based. Major cities, such as Surigao, Cagayan de Oro, Zamboanga, General Santos and Davao are easily reached by sea and air from Manila and Cebu and provide convenient starting points for nature trips inland.

*Adapted from The Best of the Islands Philippines, 1998.



VISAYAS

Cebu City, the Queen City of the South, with its International airport and thriving deep water harbor is the most important commercial and business center outside of Metro Manila. The Visayas are rich in history. Ferdinand Magellan first came ashore in the Philippines at Cebu in 1521 while attempting to circumnavigate the globe, but was killed by Lapu-Lapu on nearby Mactan Island only three weeks later. In 1565 Miguel Lopez de Legazpi arrived in Cebu to herald the beginning of Spain's colonial presence. Today, luxurious beach resorts on Mactan Island nestle beside palm fringed beaches and a rich kaleidoscopic of dive sites. Boracay Island, with its blindingly four kilometers of white beach and azure waters sheltering colorful coral reefs is a short ride from Caticlan on the north western tip of Panay. Boracay has perhaps the most photographed beach in the world and the island best resembles the tropical paradise travelers have always dreamed about.

The University of the Philippines Los Baños

On March 6, 1909, the Board of Regents of the University of the Philippines approved the establishment of the College of Agriculture as one of the first three units of UP. The first twelve students and four teachers of the college held their classes on June 14, 1909. The Department of Forestry was established on April 19, 1910 and was later elevated into a full college in 1949. The first batch of undergraduate students received their degrees during the graduation rites in 1911 and the MS and PhD degrees were first conferred in 1913 and 1963 respectively.

On November 20, 1972, the College of Sciences and Humanities was established by Presidential Decree No. 58 creating the UP System and granting autonomy to U.P. Los Baños. With the establishment of the college, UPLB assumed the task of transforming itself into a comprehensive university offering quality education in the natural sciences, social sciences and the humanities.

The UPLB Graduate School was created as a unit distinct from the College of Agriculture on December 21, 1972.

UPLB became a campus with seven colleges in 1983 when several institutes became full-fledged colleges and the College of Veterinary Medicine was transferred to Los Baños from Diliman.

At present the University offers the bachelor's, master's and PhD programs in 29, 53 and 19 fields respectively. Functions of the University have been pursued with academic zeal inspite limited financial resources. Total University income totalled to 707,391,223.59 for the year 1996 with government subsidy amounting to 592,525,000 and total university income of 114,866,223.59.

On the average Instruction accounted for 32%, Research, 17%, Extension, 4%, Personnel Benefits, 9%, General Administration, 8%, Foreign and Locally-Funded Services, 5%, of the total University Budget. The largest chunk has been used for Instruction to maintain its academic excellence.

The University has 966.84 ha. comprising the campus and experimental farms, 9,345 ha. land grants and 4,244 ha. forest reserve. In addition, the University has 405 buildings and structures, 67 of which are academics buildings, 36 administrative, 178 residential and the rest are cultural, sports and farm buildings.

The UPLB Main Library and the other units of the University has collected 281,888 volumes of publications. Of this figure 168,417 volumes are found at the Main Library. As a national center for International Information Systems for the Agricultural Sciences and Technology (AGRIS), the library has so far indeed 1,777 documents and 2,096 documents for the AGRIS and AGRIASIA databases.

PROGRAMME

Monday, 19 April

9:00	AM	Opening Ceremonies	
		Philippine National Anthem	*Raymond B. Monterey*
		Welcome Remarks	*Dr. Ruben L. Villareal* Chancellor, UPLB
		Overview of ICS-UNIDO Programmes and Activities	*Prof. Stanislav Miertus* Area Coordinator, ICS
		Introduction of Workshop Speakers	*Dr. Cleofe A. Calanasan* Head, Technical Comm
		Introduction of Participants	*Roy Roberto L. Gerona* Head, Secretariat
		Closing Remarks	*Dr. Ernesto J. del Rosario* Director, IC, UPLB
		Dr. Evamarie P. Capareda Master of Ceremonies	
10:00	AM	Combinatorial Chemistry and Combinatorial Technologies: An Overview *Dr. Pierfausto Seneci*	
11:00	AM	COFFEE BREAK	
11:30	AM	Solid-Phase Synthesis: An Overview	
12:30	AM	Case Study 1: Solid-Phase Synthesis	
1:00	PM	LUNCH	
2:30	PM	Round Table Discussion on the Morning Session	
3:00	PM	Combinatorial Synthetic Libraries: Design and Formats *Dr. Pierfausto Seneci*	
4:00	PM	COFFEE BREAK	
4:30	PM	Solid Phase Synthetic Libraries *Dr. Andrea Missio*	
5:30	PM	Case Study 2: Solid-Phase Synthetic Libraries *Dr. Andrea Missio*	
6:00	PM	Round Table Discussion on the Afternoon Session	

Tuesday, 20 April

9:00	AM	Structure Determination of Positives from Solid-Phase Libraries *Dr. Andrea Missio*	
10:00	AM	Case Study 3 : Structure Determination of Positives from Solid-Phase Libraries *Dr. Andrea Missio*	
10:30	AM	COFFEE BREAK	

11:00	AM	Solution-Phase Synthetic Libraries *Dr. Andrea Missio*
12:00	AM	Case Study 4: Solution-Phase Libraries *Dr. Pierfausto Seneci*
12:30	PM	Round Table Discussion on the Morning Session
1:00	PM	L U N C H
2:30	PM	Purification and Quality Control of Libraries *Dr. Pierfausto Seneci*
3:30	PM	Solid Phase Methodologies, Peptide Library Generation and Screening *Dr. Giorgio Fassina*
4:30	PM	C O F F E E B R E A K
5:00	PM	Case Study 6: Identification of a synthetic Ligand for the Affinity Purification of Antibodies *Dr. Giorgio Fassina*
5:30	PM	Biological Libraries *Dr. Giorgio Fassina*
6:30	PM	Round Table Discussion on the Afternoon Session

Wednesday, 21 April

9:00	AM	Computation Methods in Library Design *Dr. Anneliese Palmer*
10:00	AM	Software for Combinatorial Technologies *Dr. Anneliese Palmer*
11:00	AM	C O F F E E B R E A K
11:30	AM	Case Study 7: Computational Methods in Library Design *Dr. Anneliese Palmer*
12:00	NN	Round Table Discussion on the Morning Session
12:30	PM	L U N C H
2:00	PM	Bioassay Design *Dr. Franciscus van Amsterdam*
3:00	PM	LTS, MTS and HTS: Implications for Drug Discovery *Dr. Franciscus van Amsterdam*
4:00	PM	C O F F E E B R E A K
4:30	PM	Case Study 7: Low Throughput Screening *Dr. Franciscus van Amsterdam*
5:00	PM	Case Study 8: High Throughput Screening *Dr. Franciscus van Amsterdam*
5:30	PM	Round Table Discussion on the Afternoon Session
7:30	PM	B A N Q U E T — Sponsored by: Philab Industries, Inc. ANEST Tower

Thursday, 22 April

9:00	AM	Natural Products: An Overview *Dr. Lucia Carrano*
10:00	AM	Natural Products as Sources of Relevant Drugs *Dr. Lucia Carrano*
11:00	AM	C O F F E E B R E A K
11:30	AM	Case Study 9: Natural Products and Drug Discovery *Dr. Lucia Carrano*
12:00	NN	Natural Products and Combinatorial Technologies *Dr. Lucia Carrano*
1:00	PM	L U N C H
2:30	PM	Case Study 10: Combinatorialization of Natural Products *Dr. Pierfausto Seneci*
3:00	PM	Round Table Discussion on Natural Products and Combinatorial Technologies
3:30	PM	Patenting Issues in Combinatorial Technologies *Dr. Pierfausto Seneci*
4:30	PM	C O F F E E B R E A K
5:00	PM	Economics of Combinatorial Chemistry and Technology *Dr. Giorgio Fassina*
6:00	PM	Round Table Discussion on Patenting Issues and Economics of Combinatorial Technologies

Friday, 23 April

8:30	AM	Country and Institutional Reports
11:00	AM	C O F F E E B R E A K
11:30	AM	Round Table Discussion: Future Actions
12:00	NN	Closing Ceremonies

Workshop Assessment and Summary — *Dr. Pierfausto Seneci*

Response from Participants — *Dr. Cleofe A. Calanasan*, *Foreign Participant*, *Local Participant* (Industry), *Local Participant* (Academe)

Distribution of Certificates of Attendance — *Prof. Stanislav Miertus*

Closing Remarks — *Dr. Norma N. Fajardo*

Dr. Evamarie P. Capareda
Master of Ceremonies

1:00 PM E N D O F W O R K S H O P
L U N C H

ABSTRACTS

COMBINATORIAL CHEMISTRY AND COMBINATORIAL TECHNOLOGIES: AN OVERVIEW

Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

This lecture will provide the audience with a general overview of Combinatorial Technologies, describing the main fields in which this emerging discipline has found many applications. Pharmaceutical applications will be considered and extensively dealt with, but also other, more recent fields of interest will be covered: catalysis, both through synthetic organic and inorganic materials' libraries; supramolecular chemistry and dynamic combinatorial libraries; polymer imprinting and subsequent molecular recognition; biological libraries, including peptides (phage display) and oligonucleotides (SELEX, ribozymes); material sciences libraries, aimed to the discovery of new materials for various applications. A more specific description of Combinatorial Chemistry, intended as the synthesis of Organic Synthetic Combinatorial Libraries, will also be provided to the audience.

SOLID-PHASE SYNTHESIS: AN OVERVIEW

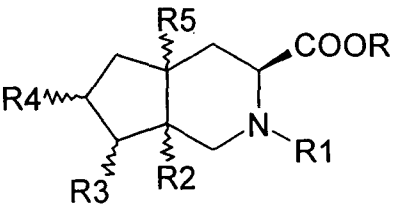
Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

This contribution will describe the so-called solid-phase synthesis (SPS), starting from the pioneering work of Merrifield in the early 60s. Heterogeneous reactions, such as in SPS. and homogeneous reactions, such as in classical organic chemistry, will be compared and their main differences will be highlighted: reaction kinetics (influence of the solid support, swelling properties, site accessibility), reaction monitoring and characterization of support-bound compounds (on-bead and off-bead analytical techniques), work-up/purification protocols will be thoroughly presented for both synthesis formats and their pros and cons will be critically discussed. Solid supports for SPS will be presented,. The main constituents of SPS will be finally presented: the support, with particular attention for resins but also mentioning other supports; the linker, whose influence on the synthetic flexibility of the solid-phase synthetic routes will be discussed; the protecting groups, with an introduction of the crucial concept of orthogonality.

CASE STUDY 1: SOLID-PHASE SYNTHESIS

Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

An excellent paper from Parke-Davis (Bolton, G.L. et al., Tetrahedron 53, 6611, 1997) presents the solid-phase synthesis of 1H-[2]pyrindinones (see Figure), based on a constrained α-amino acid scaffold.



Constrained α-aminoacid

All the major necessary steps to obtain a high quality, successful SPS will be described: the target selection and its related retrosynthetic study; the validation of the planned synthetic route and its transfer onto SP with concomitant selection of a suitable support and of a suitable linker; finally, the exploitation of a validated SP route for a single compound, to make it suitable for the production of a SP combinatorial library.

COMBINATORIAL SYNTHETIC LIBRARIES: DESIGN AND FORMATS

Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

The methodological aspect of combinatorial library design, especially applied to synthetic organic libraries, will be examined. The relevant aspects of chemical assessment (combinatorialization of a synthetic scheme), library design via computational methods (monomer selection, scaffold selection), monomer rehearsal and validation, and model library synthesis will be discussed. The selection of the most suitable format will be discussed, namely in terms of: solution-phase or solid-phase libraries; discrete libraries, made by individual compounds, or pool libraries where each sample contains several library components; structure determination methods, which allow to determine the structure of active library components (encoding methods, deconvolution, target-assisted structure determination, and so on).

SOLID-PHASE SYNTHETIC LIBRARIES

Andrea Missio
GlaxoWellcome, Italy

Combinatorial libraries have rapidly evolved from oligomer synthesis (peptides, peptoides, etc.) to the preparation of drug-like molecules. Many well-known reactions from traditional organic chemistry are now being adapted to solid-phase synthesis to allow the assembly of heterocycles or the decoration of core structures (scaffolds).

Successful examples of solid-phase organic reactions directed to the preparation of libraries will be presented.

CASE STUDY 2: SOLID-PHASE SYNTHETIC LIBRARIES

Andrea Missio
GlaxoWellcome, Italy

The famous 1,4-Benzodiazepine synthesis developed by J. Ellman will be illustrated in detail. Attention will be devoted to monomer selection, process research and equipment used throughout the synthesis.

STRUCTURE DETERMINATION OF POSITIVES FROM SOLID-PHASE LIBRARIES

Andrea Missio
GlaxoWellcome, Italy

Screening chemical libraries as mixtures of compounds is a time- and reagent-efficient process but structure determination of positives becomes an issue.

Different strategies have been elaborated to solve this problem: indexed libraries, iterative deconvolution, positional scanning, encoded libraries. All of them will be examined in detail.

CASE STUDY 3: STRUCTURE DETERMINATION OF POSITIVES FROM SOLID-PHASE LIBRARIES

Andrea Missio
GlaxoWellcome, Italy

An example from the literature will be discussed showing library synthesis, screening strategies, positive(s) selection and structure determination.

SOLUTION-PHASE SYNTHETIC LIBRARIES

Andrea Missio
GlaxoWellcome, Italy

A general overview of libraries prepared in solution will be given. Starting from simple synthetic procedures, this method has evolved to include multiple step sequences and elegant ways of purification. Examples of syntheses on soluble polymers and of dendrimer-supported combinatorial chemistry will also be presented.

CASE STUDY 4: SOLUTION-PHASE SYNTHETIC LIBRARIES

Andrea Missio
GlaxoWellcome, Italy

An example from our own laboratories will be presented. The lecture will detail the chemistry applied, the work-up procedure, the materials used for the synthesis and the quality control on final products.

PURIFICATION AND QUALITY CONTROL OF LIBRARIES

Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

This contribution will examine the crucial issue of purity and quality of any type and format of combinatorial libraries. the concept of "the right purity for each library format" will be introduced and critically discussed; the presentation of the most performing and available analytical techniques for library purification will follow. Specific aspects of solid-phase (automation of extractions and filtrations, HPLC/MS purification of cleaved samples, detection methods) and of solution-phase library purification (supported reagents for purification, multiphase extraction systems, soluble supports) will be presented and discussed. The concept of quality control of a library will be commented in terms of the expected and acceptable purities for each library format.

SOLID PHASE METHODOLOGIES, PEPTIDE LIBRARY GENERATION AND SCREENING

Giorgio Fassina
Biopharmaceuticals, TECNOGEN ScpA
Parco Scientifico, 81015 - Piana di Monte Verna, (CE) - Italy

The recently introduced technologies of combinatorial chemistry have revolutionized the classical methods of medicinal chemistry for drug discovery and lead optimization. These technologies involve the simultaneous synthesis of large arrays of compounds (molecular

libraries) in such a way that the resulting mixtures can be screened (in solution or while attached to a solid support) for their ability to bind a target molecule or inhibit a given biological activity.

The combinatorial synthesis of molecular libraries is carried out assembling building blocks in such a way that an exponentially increasing number of products, possibly in equimolar ratio, is produced after each synthetic step. This can be achieved using the solid phase methodology, applying the Portioning-Mixing (PM) method, also known as Divide-Couple-Recombine (DCR) method [1], or the pre-mix method [2]. This latter method involves the couplings of mixtures of activated monomers to one (or more) solid support at each cycle of the synthesis. The product distribution, in this case, is strictly influenced by the relative kinetics of the competing reaction, and unless corrections in the relative concentrations of monomers are introduced, the required equal representation of components in the mixture is not easily achieved. Since activated amino acids have a close reactivity toward amines, the pre-mix method is particularly amenable for the synthesis of peptide libraries but less useful in combinatorial organic synthesis where the building blocks can be quite different. Very complex peptide mixtures have been generated using this method (with and without concentration corrections), and successfully screened for biological activity [3].

The Portioning-Mixing method circumvents the problem of competing coupling reactions by segregation of the solid support into multiple aliquots to which separate reactions are performed. This method involves the splitting of the resin support into n equal aliquots, coupling a single activated monomer or performing separate reactions on each individual fraction, and then mixing the resin aliquots together. The repetition of this protocol for a total of x cycles produces a collection of n^x different molecules. The method, firstly applied to the preparation of peptide libraries, can be easily extended to the synthesis of libraries of organic compounds [4].

Libraries, distinguished by the format in which the diversity is presented, can be grouped in two main categories: Soluble Libraries and Tethered Libraries. The library format is very important since it, in turn, imposes the type of biological assays that can be utilized in the screening step, influences the strategy followed for ligand structure elucidation and determines the size of the library that can be practically screened.

Soluble libraries are tested in solution, after cleavage from the solid support. Since they are handled as a single compound in solution they are amenable for any kind of biological assays. The identification of the active component in the mixtures is then achieved by an iterative process of screening and re-synthesis [5, 6] or using the Positional Scanning (PS) format (only for peptides) [7] or applying the tagging techniques [8], depending on the synthetic history of the library.

Tethered libraries are assayed while still attached to the solid support on which they have been synthesized [9] and also in this case the decoding process is linked to the synthetic strategy used for the library preparation. Successful synthesis and screening of libraries bound on paper, glass or resin have been reported [2, 9, 10].

The solid phase synthesis methods of molecular libraries in different formats will be discussed in this lecture, underlying the close relationship between the different synthetic approaches and the screening assays to be performed.

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COMBINATORIAL CHEMISTRY: A CASE STUDY
Identification of a Synthetic Ligand for the Affinity Purification of Antibodies

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Monoclonal antibodies are becoming an important class of therapeutic agents useful for the treatment of a vast array of diseases. Many monoclonals are waiting for FDA approval, and they represent almost 30 % of biotechnology derived drugs under development. Production of MAb's by hybridoma technology or transgenic animals can be easily scaled up, but still immunoglobulins purification from crude feedstocks poses several problems. Main difficulties are due to the low antibody concentration in cell culture supernatants or milk of transgenic animals and the high amounts of contaminating proteins.

Purification by affinity chromatography of monoclonal antibodies for therapy is based on the use of protein A or protein G immobilized on appropriate supports [1], as a first step to capture and concentrate the immunoglobulin from diluted feedstocks. These two proteins, which bind to the constant portion of the immunoglobulins, and so can be used to purify the majority of antibodies, are obtained from microorganisms or genetically modified bacteria, through complex and expensive procedures, requiring in addition time consuming analytical controls to check for the presence of contaminants such as viruses, pirogens, or DNA fragments, which may affect the safety of the purified MAb for clinical purposes. Given the importance of the application of MAb's for therapy, and given the role of the purification process in assuring the quality, consistency and safety of the products, it is clear that the availability of synthetic ligands able to mimic protein A or G in the purification of antibodies is of remarkable industrial importance, since it may lead to less expensive production costs and reduced risks of contamination. A synthetic ligand [TG19318], able to mimic protein A in the recognition of the immunoglobulin Fc portion, has been previously identified in our laboratory

through the synthesis and screening of multimeric combinatorial peptide libraries [2]. Its applicability in affinity chromatography for the down stream processing of antibodies has been fully characterized, examining the specificity and selectivity for polyclonal and monoclonal IgG derived from different sources. Ligand specificity was broader than protein A, since IgG deriving from human, cow, horse, pig, mouse, rat, rabbit, goat, and sheep sera, as well as IgY deriving from egg yolk, were efficiently purified on TG19318-affinity columns. Adsorbed antibodies were conveniently eluted by a buffer change to 0.1 M acetic acid or 0.1 M sodium bicarbonate pH 9, with full retention of immunological properties. Monoclonal antibodies deriving from cell culture supernatants or ascitic fluids were also conveniently purified on TG19318-affinity columns, even from very diluted samples. The ligand is useful not only for IgG purification from different sources, but also for IgM [3], IgA [4], and IgE [5] isolation from sera or crude cell supernatants.

Affinity constant for TG19318:IgG interaction was 0.3 □M, as determined by plasmon resonance experiments. Antibody purity after affinity purification was close to 95 %, as determined by densitometric scanning of SDS-PAGE gels of purified fractions, and maximal column capacity reached 30 mg Ig/ml support under optimized conditions. In vivo toxicity studies in mice indicated a ligand oral toxicity > 2000 mg/kg, while intravenous toxicity was close to 150 mg/kg [6]. Validation of antibody affinity purification processes for therapeutic use, a very complex, laborious, and costly procedure, is going to be simplified by the use of TG19318, which could reduce considerably the presence of biological contaminants in the purified preparation, a very recurrent problem when using recombinant or extractive biomolecules as affinity ligands.

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BIOLOGICAL LIBRARIES

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Biological methods for library preparation are mainly limited to peptide or oligonucleotide libraries. For peptide libraries, methods are based on the construction of a pool of clones each one expressing a different peptide on its surface [1-9]. The peptides are fused to proteins

normally expressed on the surface of the microorganism used. Phage display libraries are the most commonly used. Screening is accomplished by incubation of the target molecule, adsorbed to a solid support, with the phage population. Active phages will bind the target even after extensive washing steps. Target-bound phages are isolated and propagated by infection of E. coli and subjected to an additional round of adsorption to the immobilized target. This procedure increases both the number of active phages and the stringency of selection, since harsher condition may be employed in the washing steps to reduce the number of non-specifically bound phages. As for the case of synthetic libraries, iterative cycles of adsorption, washing, elution and propagation in E. coli are performed to enrich the phage population in the active or in few active sequences. Active phages may then be subjected to DNA sequencing in order to decode the active peptide sequence. In a very similar way, also oligonucleotide libraries can be screened for immobilized targets using the polymerase chain reaction (PCR) methodology to expand the number of active sequences after each selection cycles.

The construction of biological display libraries requires the introduction into a microorganism of the genetic information necessary for the peptide synthesis. For the construction of a random peptide display library it is necessary to synthesize pools of DNA fragments that are then inserted into specific vectors. The DNA fragments are chemically synthesized as a mixture of single-stranded degenerated oligonucleotides containing constant regions and one or more degenerated stretches of DNA. DNA consists of sequences of 4 different nucleotides and each trinucleotide codes for a corresponding amino acid. Because of the codon degeneracy, most of the amino acids are coded by more than one triplet. Since in fully degenerated oligonucleotides there is the possibility to introduce stop codons that will interrupt protein synthesis, the oligonucleotides are synthesized using different mixtures of nucleotides especially in the third position of each triplet. The DNA fragments to be cloned must be in a double-stranded form, at least at the end of each fragment. This is normally done by annealing short oligonucleotides to a complementary constant region inserted during the synthesis and by enzymatically completing the complementary DNA strand. After compatible ends are prepared by restriction enzyme digestion, the fragments are ligated into an appropriate vector and then introduced into the microorganism.

The most common microorganism used for peptide display is the *E. coli* filamentous bacteriophage. Bacteriophages are viruses that infect bacteria by injecting their single-stranded DNA genome into the bacterial cells. Once inside the cell, they start to replicate their DNA. By using the host protein synthesis machinery, their coat proteins are synthesized and the DNA packaged into phage particles across the bacterial membrane and secreted into the medium from which they are easily recovered by precipitation. In order to be accessible to the target molecule, the peptides must be exposed to the medium and anchored to the viral coat or bacterial external membrane. For this reason, the DNA fragments coding for the peptides are inserted within a coat or membrane protein gene. The insertion is usually at one end of the fusion protein, in a region that does not change the conformation of important domains and without disrupting the protein coding sequence. For filamentous phage display, the most commonly used proteins are pIII and pVIII. The minor coat protein pIII is present at 3-5 copies per virion and is responsible for the binding to the F pilus and infection of male bacteria. pVIII is the major coat protein present at about 2700 copies and aggregates around the phage DNA.

The entire phage genome is usually used as a vector, after specific modifications have been introduced. First, it is necessary to genetically engineer specific restriction sites at the

point of insertion of the DNA fragments. Some times new genes or regulatory regions are introduced, or existing genes are mutated. When the entire phage genome is used as a vector, the library is constituted of viral particles displaying a number of peptide molecules equal to the number of fusion coat protein molecules. Alternatively, a defective phage vector, called phagemid, can be created. A phagemid is a vector that contains the genetic information for packaging into virions, but does not encode viral genes, which must be supplied by a helper phage for the production of viral particles. In this case, phages will display a mixture of peptide-coat protein fusion and the corresponding wild-type coat protein. This system was created mainly for the display of larger protein fragments and for fusion proteins that do tolerate very short peptides only. In the phagemid system, the library can be propagated as bacterial colonies, but, in the presence of a helper phage, it will be constituted of phage particles. Several phage and phagemid vectors have been engineered for the display of random peptides.

The ligand selection process is called ***Biopanning***. The target molecule must be bound to a solid support, usually a microtiter plate or a small Petri dish. Less common alternative supports are magnetic particles, column with solid matrices, cells, mammalian organs. In a typical experiment, the number of phages that are incubated with the target corresponds to about 100 to 1000 times the complexity of the library. After the unbound clones are washed away, the bound ones are eluted by different methods, like low pH, high concentration of free target, direct infection of bacteria cells. The eluted phages are grown, purified and submitted to a new cycle of selection. Usually 3 to 4 rounds of selection are sufficient, and the entire process can be completed in about a week. At the end, several clones are isolated and their DNA extracted and sequenced. The DNA portions coding for the peptides are translated into amino acids and the sequences compared. If a consensus sequence can be identified, the screening may have been successful. One or more peptides are chosen and chemically synthesized in order to verify their binding affinity, outside of the microorganism system.

Compared to chemical libraries, biological display libraries have several advantages and disadvantages. Some of the major advantages are the possibility to use a library for many different selection processes (even 100s), the easy propagation of the library and of the selected clones. The possibility to build larger size libraries is another advantage together with simple selection and sequencing procedures. On the contrary, a disadvantage is the fusion of peptides to a microorganism protein, and, therefore, the binding site can be extended to the fusion protein or the fusion protein may influence the peptide conformation.

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COMPUTATION METHODS IN LIBRARY DESIGN

Anneliese F. Appleton
Molecular Simulations, Sydney, Australia.

Drug discovery projects have traditionally required testing hundreds or perhaps thousands of individually synthesized and characterized chemicals; the new techniques of robotic synthesis, combinatorial chemistry, and high-throughput screening (HTS) offer the possibility of rapidly preparing and testing hundreds of thousands or more samples. This increased throughput dramatically increases the probability of finding a lead compound with the proper balance of activity, specificity, safety, bioavailability, and stability to result in a successful new drug.

One of the major goals of combinatorial chemistry, or the rational design of combinatorial libraries, is to design compound libraries with maximum diversity, enhancing the potential of finding active compounds in the initial rounds of high-throughput screening programs. During the last five years many of the computational tools which had been used in the rational design of new molecules have been adapted to assist with the combinatorial chemistry approach. Computational methods have been developed to assist the chemist with:

(1) library specification
(2) library design and analysis
(3) library data management
(4) library structure activity relationship (SAR) determination

This presentation will attempt to illustrate how software can assist the chemist answer questions such as:

Which combinatorial library should I make first?
Can I screen effectively with a subset of the library?
Are my libraries diverse or well focused?
What library should I make or purchase next to screen around a lead compound?

During the talk the concept of virtual libraries will be introduced and a description of how library design can assist with pruning a large library down to one which is synthetically feasible will be given. Core-based versus reaction based library specification methods will be discussed. The computational concepts of molecular diversity and similarity and the way theoretically designed libraries may be chosen based on maximum diversity, to optimize property distributions and minimize deconvolution effort will be addressed as well as strategies designed to simulate virtual high throughput screening (VHTS) studies.

SOFTWARE FOR COMBINATORIAL TECHNOLOGIES

Anneliese F. Appleton
Molecular Simulations, Sydney, Australia.

This presentation will interactively show how the Combinatorial Chemistry Software available from Molecular Simulations[1] can assist with combinatorial library design and analysis. Demonstration of how a broad set of 2D and 3D properties, including topological and information-content indices and electronic, thermodynamic, and geometric descriptors can be calculated and how these descriptors can be used to assess a particular libraries characteristics. The optimum set of model descriptors to be used in the selection of the best fragments or side chains for a combinatorial library most likely depends on the specific ligand-receptor system that is the target of the library. Descriptors that are relevant in some systems and help differentiate active from in active compounds may be irrelevant in other systems.

This interactive software demonstration will should how the user can build large theoretical libraries, calculate a variety of molecular properties or descriptors for theoretical libraries and how these properties can be used to calculate the relative diversity or similarity of a particular library. These descriptors can also be used to compare libraries and to identify where holes in a particular library might be.

[1] *For more information about Molecular Simulations Software see http://www.msi.com*

BIOASSAY DESIGN

Franciscus Th. M. van Amsterdam
GlaxoWellcome, United Kingdom

Bioassay design is all about identifying an interesting target, validating the target, design the assay to be used for further studies and validate the assay.

This presentation will focus on the main areas of bioassay design, starting with new approaches in bio-informatics and molecular biology, which are today indispensable tools to identify new targets from genetic and genomic information. With the completion of the Human Genome Initiative, this role is only destined to further increase.

Various assay technologies will then be discussed, from enzymatic and radioligand binding to reporter gene technologies and whole cell screens, and their potential use in the drug discovery process. Attention will be paid to the criteria used to convert an assay into a screenable assay, i.e. into an assay that can be used in high throughput, automated screening systems.

HTS in Drug Discovery

Franciscus van Amsterdam
GlaxoWellcome, United Kingdom

High Throughput Screening is much more than testing a large number of samples, using a bioassay. HTS starts with a validated bioassay, but requires that the assay be integrated with a robotic system that is run by a good scheduler, an infrastructure of compound and library synthesis and management, and good analytical chemical capacities. All of this should be embedded in an IT environment that is able to quickly analyse the screening data and store the results in a meaningful way in an accessible database. The cycle is completed with a series of Chemo-Informatics tools, which are needed to model the data and develop the right hypothesis for improving from hit to lead to developable compound to a marketable medicine.

The presentation will describe most aspects of the screening cycle, based on the developments of the RoboLab in GlaxoWellcome Verona (Italy). Examples will be shown of hardware, robotics, data analysis and management as well as the characteristics of various assay formats for low, medium or high throughput screens.

NATURAL PRODUCTS AND COMBINATORIAL TECHNOLOGIES

Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

The use of natural products as relevant, novel and promising new scaffolds for the generation of combinatorial libraries will be discussed. Decoration methods, where a natural, biologically active scaffold is submitted to a combinatorial semisynthetic modification approach will be presented; then, the use of natural products as inspiration starting point for the design of libraries (construction of a natural scaffold via synthetic organic chemistry) will be presented and commented. Other sources of natural products-derived libraries will also be presented: combinatorial biosynthesis, combinatorial biotransformation and biological libraries will be briefly touched during this contribution.

CASE STUDY 10: COMBINATORIALIZATION OF NATURAL PRODUCTS

Pierfausto Seneci
Lead Discovery Director
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Two examples will be described and critically evaluated during this contribution: first, an example of decoration of a pre-existing natural scaffold (derived from taxol, from IRORI researchers including Czarnik) will be presented, then an example of combinatorial construction of a complex natural product-derived scaffold (derived from epothilone, by Nicolaou's group) with concomitant diversification of the scaffold to give a library will be presented.

PATENTING ISSUES IN COMBINATORIAL TECHNOLOGIES

Pierfausto Seneci
Lead Discovery Director
GlaxoWellcome, Italy

The crucial issue of patent protection of chemical diversity generated through combinatorial libraries will be thoroughly covered through this contribution, presenting and commenting the published opinion of patent experts but also providing the opinion of big pharma companies regarding the level of protection required during each stage of library synthesis and screening. The patenting of key technologies aimed to improve the productivity and proficiency of Combinatorial Technologies will also be covered in this contribution.

ECONOMICS OF COMBINATORIAL CHEMISTRY AND TECHNOLOGY

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The time and cost needed for the development of new drugs have increased steadily during the past three decades. Estimated costs for introducing a new drug in the market now reach around 200-300 millions USD, and this process takes around 10-12 years after discovery. This increase in time and cost is due mainly to the extensive clinical studies of new chemical entities required by competent regulatory agencies, such as the FDA, and to a lesser extend to the increased costs associated to research. The time and cost required for clinical and preclinical evaluation of new drugs is not likely to decrease in the near future, and as a consequence, a key issue for pharmaceutical companies to stay in the market has been to increase the number of new drugs in the development pipeline. Drug discovery in the past has been based traditionally on the random screening of collection of chemically synthesized compounds or extracts derived from natural sources, such as microorganisms, bacteria, fungi, plants, of terrestrial or marine origin or by modifications of chemicals with known physiological activities. This approach has resulted in many important drugs, however the ratio of novel to previously discovered compounds has diminished with time. In addition, this process is very time consuming and expensive.

A limiting factor was linked to the restricted number of molecules available or extract samples to be screened, since the success rate in obtaining useful lead candidates depends directly from the number of samples tested. Chemical synthesis of new chemical entities often is a very laborious task, and additional time is required for purification and chemical characterization. The average cost of creating a new molecular entity in a pharmaceutical company is around 7500 USD/compound. Generation of natural extracts, while very often providing interesting new molecular structures endowed with biological properties leads to mixtures of different compounds at different concentrations, thus making activity comparisons very difficult. In addition, once activity is found on a specific

assay, the extract needs to be fractionated in order to identify the active component. Quite often, the chemical synthesis of natural compounds is extremely difficult, thus making the lead development in to a new drug a very complex task. While the pharmaceutical industry was demanding more rapid and cost effective approaches to lead discovery, the advent of new methodologies in molecular biology, biochemistry, and genetic, leading to the identification and production of an ever increasing number enzymes, proteins, receptors, involved in biological processes of pharmacological relevance, and good candidates for the development of screening assay, complicated even more this scenario. The introduction of combinatorial technologies provided an unlimited source of new compounds, capable to satisfy all these needs.

This approach was so appealing and full of promises that many small companies started to flourish financed by capitals raised from private investors, and once combinatorial technologies clearly demonstrated the potential to identify new leads with a previously unknown speed, big pharmaceutical companies started to invest heavily in this sector.

NATURAL PRODUCTS: A BRIEF HISTORY AND NEW PERSPECTIVES FOR THE DISCOVERY PROCESS

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Natural products are a notable source of useful compounds with medical, agricultural and industrial significance such as antinfectives, immunosuppressants, herbicides, enzyme inhibitors. In the last century over 1300 natural compounds such as theophylline, morphine, colchicine, digitalis, salicin, atropine were discovered and used as drugs. Natural sources may include plants, sponges, insects and microbes. The last class of producers represents the easiest scalable and renewable source of compounds. Plants instead represent the source of folk and shamanic medicines including Aztec, Chinese, Ayurvedic and Kampo. The first documented therapeutic uses of plant and other natural materials was in 3000 BC.

The term natural product is often used synonymously of "secondary metabolite". A primary metabolite is an intermediate or a product of primary metabolism, it is essential to growth and life, it utilizes a limited number of biochemical pathways. For example essential amino acids, D-ribose, ATP are primary metabolites.

Secondary metabolites are not essential to growth and the life of the producing organism but perform functions that confer a selective advantage. They are synthetised from the primary metabolites by a much wider variety of biochemical pathways.

More than ten thousand secondary metabolites are known but medicine, science and industry still need new ones. Scientific strategies for the study of natural products have changed substantially in the past few years for a number of reasons, including advances in technology, new molecules of substantial interest, changing ethical principles for organism collection and the need to find new molecules.

The aspects concerning the identification, isolation, characterization and scaling up of an active compound from natural sources nowadays will be illustrated.

Moreover, knowledge of genetics and molecular evolution helps us understand how biosynthesis of many classes of secondary metabolites evolved and suggest how manipulate this. One proposed hypothesis is termed inventive evolution. Steps of inventive evolution can be mimicked in several ways for the purpose of drug discovery. For example libraries of chemical compounds of any imaginable structure may be produced by combinatorial synthesis. Out of these libraries new active compounds can be selected. It could be possible to produce unnatural natural products from which new drugs can be selected.

COUNTRY REPORTS

DEVELOPMENT OF COMBINATORIAL CHEMISTRY AND COMBINATORIAL TECHNOLOGIES IN HONG KONG

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To the turn of the millenium, there is a rapid change in Hong Kong to cope with the challenge of the new millenium and to restore her to be one of the prosperous cities in region after Asian economic crisis. The government has planned two main projects in order to increase the quantity and quality of the Hong Kong industries: they are the Science Park and Cyber-Port projects. The Science Park project will emphasis in technology development and application. It will accommodate many local and overseas ventures for research and development (R & D) in the high technology such as information technology, material science, biotechnology and traditional Chinese medicine (TCM), etc. The bioactive compounds or drugs will be the major products of in biotechnology and TCM industries. The major effort will focus on the use of molecular biology technology to develop new drugs and screening of new medicinal compounds from Chinese herbs, and the application of combinatorial chemistry/combinatorial technologies (CC/CT) will be a very small portion of the efforts to be employed in the development of biotechnology and TCM industries in Hong Kong.

Combinatorial chemistry was introduced in early 1980 and application of CC/CT becomes a major subject in many developed countries in this decade. However there are only few studies in the application of CC/CT in developing countries/cities including Hong Kong and most of the studies focus on the productions of new catalysts and few on new drugs. The importance of CC/CT in medicinal chemistry and drug discovery is still not well-recognized by the government and the public in Hong Kong. In order to make biotechnology and TCM industries in Hong Kong to remain competitive and economically viable in the coming decades, there is an urgent need to emphasis the application of CC/CT in these industries.

The present presentation will first report the projects in different areas of CC/CT in Hong Kong. Then the potential development of the application of CC/CT in Hong Kong at the beginning of next millenium will be discussed.

THE STATUS OF RESEARCH ON COMBINATORIAL CHEMISTRY/ COMBINATORIAL TECHNOLOGY IN THAILAND

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The role of combinatorial chemistry and technology, especially in the field of natural products, in the development of the country is well recognized. The fact that research work in this field might be applied in public health, agriculture and industry would enhance the value of natural products which are abundant in Thailand. The application of combinatorial chemistry had improved the standard and quality of the utilization of natural products, especially in drug development.

This lecture will present an overview of the research on combinatorial chemistry/ combinatorial technology, especially the application to natural products in promoting and utilizing strategies.

Some examples related to the application of combinatorial chemistry, which concerns the utilization of natural products directly or even indirectly, in the improvement of the quality of food production and in drug development.

COMBINATORIAL CHEMISTRY IN MALAYSIA

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The introduction of combinatorial chemistry in Malaysia is very recent and in the very beginning stage. A large number of phytochemical research and pharmacological research are currently being conducted in various research institutes and universities. These are mainly conventional studies on chemical identification and structural elucidation. The development of high throughput and mass screening is in developmental stage. The government has initiated a Development and Technology working group: Natural Bioactive Compounds, Malaysian Industry-Government Group for High Technology (MIGHT) in order to speed up the progress on the rapid and high throughput screening and the use of combinatorial chemistry in medicinal plants and pharmaceutical research. This has led to the emergence of many groups of workers and laboratories showing interests in combinatorial chemistry. There is a critical need to expose and promote this new innovation and technique to developing countries ike Malaysia in order to promote the growth of new noble compounds and chemicals which could indirectly promote the growth of industrial and agricultural sector in the country.

PLASTIC INDUSTRIES AND DEGRADABLE POLYMERS DEVELOPMENT IN TAIWAN

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Taiwan's plastic industry experienced a relatively last year in 1998. In the first quarters of 1998, the prices of plastics start to weaken under the Asian financial crisis. Prices further dropped to a low ebb due to a weakening of oil prices as well as downstream demand. For the prices of plastic products, although PVC, LDPE and LLDPE will start to recover, PP, HDPE, PS and ABS should follow the 1998 trend and remain weak. We forecasted 1999 prices and 2003 supply and demand balance for various plastic products in Taiwan.

Under the requirements of the ISO 14000 standard, only environmentally friendly packing materials will be permitted. As such, in 1999 environmentally friendly degradable plastics will be emphasized.

AN OVERVIEW ON STATUS OF WATER QUALITY OF SOME INDUSTRIALIZING CRAFT VILLAGES IN THE DELTA OF NORTHERN VIETNAM AND THEIR IMPACT ON THE NATURAL WATERBODIES

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Vietnam National Center for Natural science and Technology

A large countryside in the Red river delta of northern Vietnam has been used for culturing water-rice . This is main profession and occupied a considerable proportion in income of rural people. However, beside of agriculture, there were also many traditional - industrializing craft villages had been existing here for a long time ago. According to statistic, there are about 200 industrial villages on surrounding catchment area of the Cau river, such as paper-mills, iron forging , laminate steel, plastic recycle, cast bronze and aluminum etc. In rural area, industrial villages made many jobs for farmers during idle time. Products of many industrializing craft villages are also economic value with high utilization. However, all these are small factories as family industry, scattered every village. Those factories are often with backward-old machines, techniques, and almost of these have not any measure for treatment of industrial waste waters. Because of that there is a large amount of waste water untreated of these industrial villages was discharging daily into natural waterbodies. Untreated industrial waste waters polluted natural surface waters, particularly waterbodies directly received waste waters. Pollution of water environment effected on aquatic ecosystem, specially ecosystem of Cau river.

This report represents an overview on status of water environment of two industrializing craft villages such as Duong O village (paper-mill craft village), and Da Hoi village (metallurgy village icluding laminate steel, iron forging, and plate iron wire).

At Duong O, It has about of 2,000 m^3 /day waste water of paper-mill factories with high concentration of pollutants such as total solid ranged 1,470 -2,648 mg/l, plant oil (resin)(31.06 - 35.45 mg/l), COD (970 - 1,260 mg/l). These waste waters untreated drain into channels and then discharge directly into the Cau river through sewers. Organic pollution is occurring in some waterbodies received waste waters. Water environment of channels is being mostly polluted, concentration of dissolved oxygen drops very low (0.3-05 mg/l), and being in anaerobic condition. Bacteria consume the organices and deplete disolved oxygen. When oxygen levels here become very low, anaerobic bacteria take over, breaking down what's left but producing foul-smell and toxic gases (methane, hydrogen sulfide) in the process.

Water quality of Cau river is considerably impacted also by waste waters of paper mills. In water area surrounding sewer gate of waste water's outflow, concentration of phenol, resin, COD, BOD, coliform are high and exceed many times over limitation value of surface water quality standard of Vietnam. In addition, waste waters drain into Cau river with color reddish-violet of dye Rhodamine B used for dying paper..

At Da Hoi village, among waste waters, waste waters of iron wire plating factories are concerning because of plating solution using with high concentration of heavy metal such as Zn (88.65 mg/l), CN (16.74 mg/l). Concentration of these metals in waste waters may be lower. Waste waters of other factories as metallurgy, metal forging with high concentration of mineral oil (1.5 - 1.8 mg/l), and phenol (0.09-0.11 mg/l) exceeded limitation value of industrial waste

water quality standard of Vietnam. These waste waters drain directly into Cau river. Fortunately, up till now, recent analyses show that concentration of heavy metals of the Cau river's waters are lower than limitation value of surface water quality standard of Vietnam.

At two villages as above, pollution of surface water impacted on quality of ground waters (supplying waters). In some wells, concentration of ammonia, nitride, coliform in water are higher than limitation value of ground water quality standard of Vietnam.

Analyses on hydrobilogical fauna in some typical water bodies show that in waterbodies received waste waters, aquatic species composition are less abundant than others. The water bodies are strongly affected by waste waters, as oxygen levels drop, fish and other aquatic organisms were killed, and aquatic biodiversity was degraded as well as. In rainy season, waste waters of paper-mill factories overflow into rice fields, rice seedling can be killed and productivity and quality of rice crop can be decreased.

After everyone, some recommendations on improve water environment and aquatic ecosystemd of peper mill villages in particularly and genarally managing policy of environment in industrializing craft villages located on drainage basin of the Cau river that are given also in the report.