Program

June 9th, 2014	
Social activities	
18:00-20:00	Social Dinner at Restaurant Adler Zürich
June 10th, 2014	
Chairman Christian Wolfrum	
09:20-09:30	Introduction Jean-Luc Wolfender, Karl Gademeann, Jeff Bode, Christian Wolfrum
09:30-10:00	Past, present and future of traditional Chinese medicine in China De-an Guo
10:00-10:30	Plant phenolics: From antinutritional to potential health beneficial compounds Denis Barron
10:30-11:15	**Coffee Break**
Chairman Jean-Luc Wolfender	
11:15-11:45	Fusaruside: Discovery, Function and Biosynthesis 谭仁祥 Renxiang Tan
11:45-12:15	Synthesis of densely phosphorylated natural products Henning Jacob Jessen
12:15-12:45	Collective Total Syntheses of Complex Natural Products Enabled by Au-Catalyzed Reactions 杨 震 Zhen Yang
13:00-14:30	**Lunch**
Afternoon Session	
Chairman Karl Gademann	
14:30-15:00	Phenotypic Screening and the Issue of Target Deconvolution Tackled by Computational and Experimental Complementary Approaches Leonardo Scapozza
15:00-15:30	Natural Products and Protein Targets - Why Nature Does Polypharmacology Jürg Gertsch
15:30-16:00	Novel compounds discovery from Chinese herbs: from bench to beside Yi Zhun Zhu
16:10-17:00	**Coffee Break**
17:00-17:30	Decoding Ligand-Receptor interactions

	Bernd Wollscheid
17:00-17:30	tbd Lixin Zhang
19:00-20:30	**Social Dinner at the Uniturm Zürich**
June 11th, 2014	
Chairman Jeff Bode	
09:30-10:00	Identification of bioactive compounds responsible for therapeutic benefits of traditional herbal medicine 叶阳 Yang Ye
10:00-10:30	Decoding cell circuits and processes through the application of multiparametric life-cell imaging and 3D tumor microtissue-based screening approaches Willy Krek, Claudio Thoma
10:30-11:15	**Coffee Break**
Chairman Bernd Wollscheid	
11:15-11:45	New Developments in Fragrance Chemistry - A Sino-Swiss Experience Andreas Goeke
11:45-12:15	Searching for cellular protein targets for sesquiterpene lactones Peng George Wang
12:15-12:45	Innovative strategies for the efficient isolation of natural products at the preparative scale and discovery of potential new leads Emerson Ferreira Quieroz
13:00-14:30	**Lunch**
Afternoon Session	
Chairman Michael Ristow	
14:30-15:00	Structural studies of GPCRs, important drug targets Qiang Zhao
15:00-15:30	Library-based discovery of bioactive natural products – from screening to medicinal chemistry Matthias Hamburger
15:30-16:00	Lysine glutarylation is a protein modification regulated by SIRT5 Minjia Tan

16:10-17:00	**Coffee Break**
Chairman Erick Carreira	
17:00-17:30	C. elegans as a screening organism to identify novel health-promoting compounds and phytochemicals Michael Ristow
17:30-18:00	Potential therapeutic roles of natural Sirtuin modulators Fan Peihong
19:00-20:30	**Social Dinner at the Waid Zürich**

June 12th, 2014	
all day	**Departure of guests**

Past, present and future of traditional Chinese medicine in China

De-an GUO

Shanghai Research Center for TCM Modernization, Shanghai Institute of Materia Medica,

Chinese Academy of Sciences, Shanghai 201203, P.R. China

Abstract

Traditional Chinese medicine (TCM) has over 3000 years of history to treat diseases in China and has played a pivotal role in the Chinese health system. In the past 20 years or so, great progress has been achieved on the modernization of traditional Chinese medicine. Government launched a number of “heavy-weight” programs and allocated central budget for the development of TCM. Chemistry of Chinese herbal medicines was thoroughly investigated and over 3000 new chemical compounds were isolated and some of them have been in the process of new drug development. TCM pharmaceutical industry is on the rise and growing rapidly with respect to the yearly gross sale and modern facilities. In this lecture, TCM resources, related research institutions and education systems, recent development in Chinese Pharmacopoeia, TCM new drug registration regulations by CFDA, TCM-based drug discovery, government funding sectors, recent research progress achieved will be briefly overviewed, which may help the audience to understand where TCM stands in China. In addition, the current research on the quality standard construction of traditional Chinese medicines will also be introduced with some concrete examples. The future perspective of TCM modernization will be briefly projected.

Plant phenolics: From antinutritional to potential health beneficial compounds.

Denis Barron

Natural Bioactives & Screening Department, Nestlé Institute of Health Sciences, EPFL Innovation Park, 1015 Lausanne, Switzerland.

Abstract

Until fairly recently, plant phenolics were rather considered as antinutritional compounds. However, most of them are metabolized in the body into simpler structures which are the real forms potentially inducing a biological response. This is only since the late 90's that the animal and human metabolism of plant phenolics have extensively attracted the interest of the scientific community. The main advances in this topic since the last 10 years will be reviewed in this seminar.

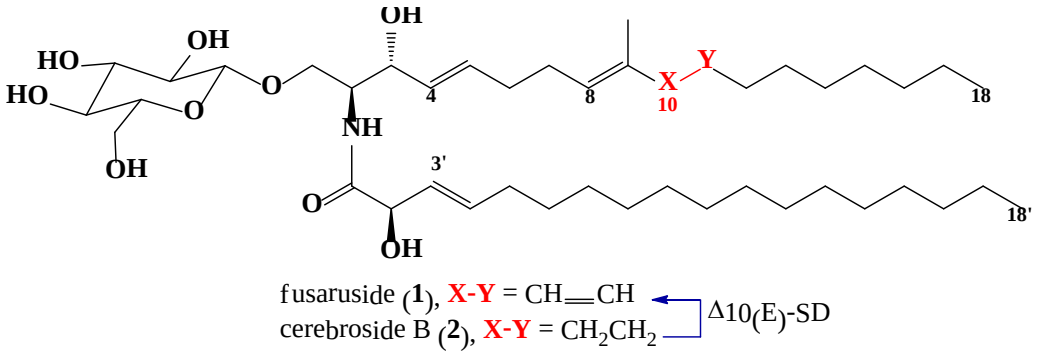
Fusaruside: Discovery, Function and Biosynthesis

Ren Xiang Tan

State Key Laboratory of Pharmaceutical Biotechnology, Nanjing University, Nanjing 210093, P. R. China

ABSTRACT

Under an urgent global necessity of selective immunosuppressive agents, fusaruside (**1**) has been characterized as a sphingolipid-based immunosuppressant. Distinct from its congeners, compound **1** carrys a 9-methyl-4,8,10-sphingatrienine chain involved in its effective protection of mice from ConA-induced liver injury. Attention to its mode of action has addressed that it inhibits proinflammatory immune response in T cells, prevents hepatocyte from apoptosis, and contributes to rebuilding the balance between STAT1 (in inflammatory T cells) and STAT3 (in hepatocytes) signalings. Such a unique action of **1** on T-cell-mediated immune reactions suggests that it is a novel immunomodulatory drug candidate more selective than the prescribed immunosuppressants. The biosynthetic pathway of **1** was clarified to find a novel Δ10(E)-sphingolipid desaturase (Δ10(E)-SD) that fundamentalizes its eco-friendly and renewable production from an abundant sphingolipid (**2**). Moreover, the Δ10(E)-SD gene was demonstrated to confer upon fungal strains the ability to survive in harsh environments characterized by low temperature or high salinity. In aggregation, the fusaruside story that will be presented may exemplify the symbiosis-inspired identification of new biomolecules and distinct motif-motivated discovery of new biocatalysts.



fusaruside (**1**), **X-Y** = CH═CH
cerebroside B (**2**), **X-Y** = CH_2CH_2 ← Δ10(E)-SD

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Synthesis of Densely Phosphorylated Natural Products

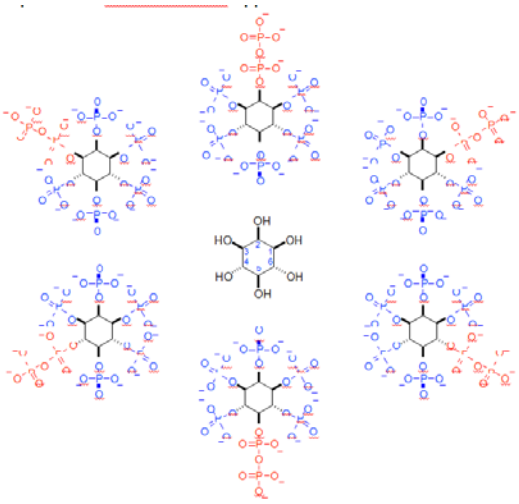
H. J. Jessen, Zürich/CH, S. Capolicchio, Zürich/CH, D. Thakor, Zürich/CH, I. Pavlovic, Zürich/CH, A. Hofer, Zürich/CH

Henning Jacob Jessen

University of Zurich, Winterthurerstrasse 190, Zürich/CH

ABSTRACT

One of the most abundant modifications in nature is phosphorylation, which lies at the heart of cellular signaling and function. Many highly phosphorylated secondary messengers directly transmit information and contribute to the viability of cells. Some of them are well understood, as e.g. InsP3 , but some of them much less, for example, diphosphoinositol polyphosphates (X-PP-InsP5).
We have chosen the intriguing structures of diphosphoinositol polyphosphates X-PPInsP$_5$ as valuable targets for a total synthesis program. Besides their biological importance in such diverse processes as telomere length regulation, apoptosis, vesicle trafficking, cellular signaling and transphosphorylation, X-PP-InsP$_5$ are also interesting synthetic targets: the major challenges lie in the high polarity (up to 13 negative charges!), the instability (phosphate anhydrides and esters), the UV-inactivity and the need to develop concise stereoselective approaches.



In this study we demonstrate, how a novel C2-symmetric P-amidite can be used to desymmetrize myo-inositol followed by efficient introduction of phosphate esters and anhydrides in one-pot transformations.

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Collective Total Syntheses of Complex Natural Products Enabled by Au-Catalyzed Reactions

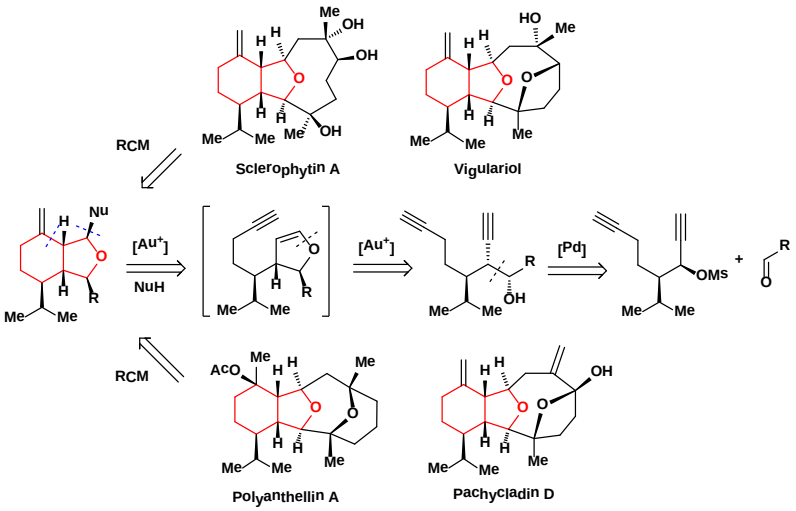
Zhen Yang

[†]*Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen 518055, China*

[‡]*Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Beijing National Laboratory for Molecular Science (BNLMS), and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China.*

ABSTRACT

The cladiellin family of natural products with various biological activities, which includes molecules such as sclerophytin A, polyanthellin A, pachycladin D and vigulariol, continues to invite new synthetic studies. A gold-catalyzed tandem reaction of 1,7-diynes[1] to construct the 6-5-bicyclic ring systems that are present in a number of natural products was developed. This reaction was applied as the key step to realize the formal and total syntheses of nine members of the cladiellin family in an enantio- and diastereoselective manner.[2] This modular and efficient approach could also be used for the construction of other cladiellins, as well as their analogues, for follow-up studies.



Phenotypic Screening and the Issue of Target Deconvolution Tackled by Computational and Experimental Complementary Approaches

Leonardo Scapozza,

Pharmaceutical Biochemistry, School of Pharmaceutical Sciences, University of Geneva

Abstract

Phenotypic screening has regained a lot of interest within drug discovery because of the increased knowledge on cellular molecular events and advances in screening technologies including microscopy and miniaturization. These technological advances give now the opportunity of testing new as well as already known compounds from all different sources – chemicals and natural products in particular – in different biological contexts using a system-based approach. While these assays are extremely useful during the hit discovery and hit to lead optimization phase of drug discovery, knowing the mechanism of action and the targets linked to it remains crucial for developing chemical entities further into drugs. In the past decade several methods for finding target(s) of biological active compounds have been developed and used by us and others. In this presentation I will give you an overview of the available computational and experimental methodologies based on different case studies related mostly to neglected and infectious diseases.

Natural products and protein targets - why nature does polypharmacology?

Jürg Gertsch

$Institute of Biochemistry and Molecular Medicine, University of Bern, Switzerland

ABSTRACT

For centuries the science of pharmacognosy has dominated rational drug development until it was gradually substituted by target-based drug discovery. Pharmacognosy stems from the different systems of traditional herbal medicine and its "reverse pharmacology" approach has led to the discovery of numerous pharmacologically active molecules and drug leads for humankind. But do botanical drugs also provide effective mixtures? Nature has evolved distinct strategies to modulate biological processes, either by selectively targeting biological macromolecules or by creating molecular promiscuity or polypharmacology (one molecule binds to different targets). Widely claimed to be superior over monosubstances, mixtures of bioactive compounds in botanical drugs allegedly exert synergistic therapeutic effects. Despite evolutionary clues to molecular synergism in nature, sound experimental data are still widely lacking to support this assumption.

Using examples from our research on the endocannabinoid system, in this presentation it is shown that a better understanding of a biological network can help to understand biological (i.e. pharmacological) synergy and antagonism as a function of concentration. It will be discussed how this could be exploited for drug discovery and development and whether nature and pharmaceutical industry use opposite strategies to achieve the same goal.

Novel compounds discovery from Chinese herbs: from bench to beside

Yi Zhun Zhu

Fudan University, Shanghai

Abstract

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Decoding Ligand-Receptor interactions

Bernd Wollscheid

Institute of Molecular Systems Biology, ETH Zurich

Abstract

Ligand-induced changes in cell surface receptors result in physiological responses, which constitute the biological activity of various ligands such as proteins, peptides, pharmaceutical drugs, toxins or whole pathogens. However, traditional approaches for the ligand-based identification of corresponding receptors are usually limited to non-transient, high affinity interactions and highly artificial experimental set-ups. Therefore, many signaling molecules remain orphan ligands without a known primary molecular target – invaluable information in understanding the respective mechanisms of signal transduction, drug action or disease.

Previously, we have developed the cell surface capture (CSC) technology for the unbiased identification and quantification of cell surface drug targets by mass spectrometry (MS). This demonstrated the powerful applicability of chemical reagents in the tagging of cell surface glycoproteins at carbohydrate groups and the subsequent purification of the corresponding peptides for MS analysis. Based on these results we now synthesized trifunctional cross-linkers for the ligand-based tagging of glycoprotein receptors on living cells and the purification of receptor-derived peptides for MS analysis. Through quantitative comparison to a sample generated with an unspecific control probe, this ligand-based receptor capturing (LRC) approach allows for the highly specific and sensitive detection of ligand interactions with their corresponding receptors under near-physiological conditions. Experiments with ligands ranging from peptide hormones to clinical antibodies demonstrate the potential of this approach to specifically identify one or more target receptors for a given ligand as the molecular mode of action with great statistical power. Advanced discovery-driven applications reveal potential receptors and receptor panels for ligands ranging from protein domains, small molecules to intact viruses.

Identification of bioactive compounds responsible for therapeutic benefits of traditional herbal medicine

Yang Ye

Shanghai Institute of Materia Medica, CAS, China

Abstract

Decoding cell circuits and processes through the application of multiparametric life-cell imaging and 3D tumor microtissue-based screening approaches

Claudio Thoma

Institute for Molecular Health Sciences, ETH Zurich

Abstract

The underlying basis of tumor development is mutated cancer cells. Large efforts have been taken to characterize these mutated tumor genomes using next-generation sequencing to uncover genetic changes associated with the evolution of the malignant phenotype. Invariably, such genetic changes lead to reprogramming of cancer cell circuits and create different cell-autonomous addictions. Moreover, such cell-intrinsic changes do further lead to systemic changes within the whole tumor microenvironment, which is not only an assembly of mutated cancer cells, but rather can be considered as a conglomerate of a multitude of cross-talking cells.

To embrace this cell-intrinsic as well as systemic complexity, functional screening approaches are needed to discover disease targets and cancer cell vulnerabilities arising indirectly as a result of reprogrammed cell circuits. We embarked on two different screening approaches that aim (i) to discover cancer-cell intrinsic mechanistic changes directly elicited by loss-of-function of tumor suppressor genes and (ii) to screen for cancer cell addictions in a three-dimensional (3D) multicellular tumor spheroid model.

(i) Given the broad role that microtubules (MT) play in cancer-related cellular processes and therapy, we sought to systematically identify tumor suppressors on the basis of their ability to affect MT dynamic instability. We performed a focused high-resolution live cell image-based RNA interference screen targeting a collection of 70 human tumor suppressor genes followed by computational extraction and multi-parametric analysis of MT dynamics from time-lapse image sequences. This allowed to identify the products of the tumor suppressor genes with potent MT-stabilizing activities.

(ii) Since cancer cells in a solid tumor *in vivo* are coordinately influenced by an interactive 3D microenvironment exposing the cells to different intrinsic climates depending on their position, a high throughput-compatible method to discover cancer gene functions and synthetic lethality in a 3D multicellular tumor spheroid model system has been developed and applied to discover hypoxia-induced vulnerabilities to discover potential candidates for combined treatments with angiogenesis inhibitors.

These approaches model key aspects of cancer cell-intrinsic processes and the tumor microenvironment and demonstrate their suitability in discovery science and the screening application for anti-cancer agents.

New Developments in Fragrance Chemistry- A Sino-Swiss Experience

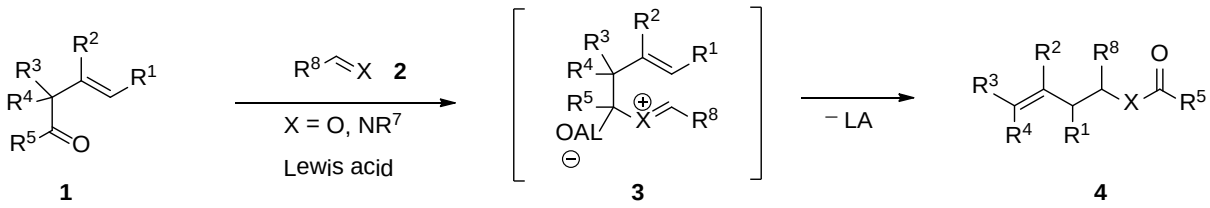
Andreas Goeke

Givaudan Schweiz AG, Fragrance Research, Überlandstrasse 138, CH-8600 Dübendorf, Switzerland;

Abstract

Domino reactions are efficient transformations which enable the generation of structural complexity in one-pot operations. Roughly 150 years after the introduction of organic synthesis to perfumery, this concept is particularly important in modern fragrance industry: for the successful introduction of novel odorants, low production cost of a new material is an essential requirement, although relatively low volumes consumed in the fragrance world represent an adverse economy of scale.

A domino methylenation-Diels Alder-Cope rearrangement sequence of α,β-unsaturated aldehydes with a variety of dienes led to the introduction of Shisolia™, an innovative shisso-leaf-like odorant.[1] Furthermore, the new access of α-vinyl cyclohexene carbaldehydes led to the discovery of unprecedented oxy-oxonia- and azonia-Cope rearrangements.



These reactions represent a non metal organic allylation method of broad scope to afford homoallylic esters or amides **4** through a crossed disproportionation of β,γ-unsaturated carbonyl compounds **1** with another aldehyde or imine **2**. The mechanism was shown to proceed through sigmatropic rearrangements of intermediates **3**.[1,3] By an appropriate choice of substituents, the method was applicable to [N+4] ring enlargement reactions which resulted in macrocyclic lactones, lactams and ketones.[2] Allyl amino acids were also prepared.[5]

Searching for cellular protein targets for sesquiterpene lactones

Peng George Wang

Department of Chemistry, Georgia State University, Atlanta, USA

College of Pharmacy, Nankai University, Tianjin, China

Abstract

Sesquiterpene lactones constitute a large and diverse group of biologically active plant natural products. It was found recently that a series of guaianolide esquiterpene lactones such as parthenolide (PTL) and their derivatives such as micheliolide (MCL) can selectively eradicate acute myelogenous leukemia stem or progenitor cells. We recently designed and synthesized biotin-labeled and fluorescence-labeled MCL, and used them as probes to search for their cellular protein targets. After the targeted proteins were identified, a novel MS-based reaction screening (MSRS) approach was used to illustrate the reactions between the natural products and the protein, the results are surprising …

Innovative strategies for the efficient isolation of natural products at the preparative scale and discovery of potential new leads

Queiroz EF, Guillarme D and Wolfender JL

School of Pharmaceutical Sciences, Phytochemistry and Bioactive Natural Products, University of Geneva, University of Lausanne, CH-1211 Geneva 4, Switzerland

Abstract

In natural product research the isolation of compounds at the milligram scale is key element to assess their bioactivity *in vivo*. Conventional isolation approaches are often time-consuming and employs relatively complex schemes that involve different preparative chromatographic methods. One efficient strategy consists in the transfer of extract profiling gradient conditions from HPLC to semi-prep HPLC. In order to further increase the sample loading, Medium Pressure Liquid Chromatography (MPLC) represents an interesting alternative since grams of crude extract can be separated in one step. For this we have developed models for accurate gradient HPLC-MPLC transfer. A detailed monitoring of this preparative isolation step is achieved post-chromatographically by ultra-fast UHPLC/TOF/MS and provided 2D LC x LC matrices that contain all information for an optimal and rational fraction combination. The improvements of the preparative separations obtained are illustrated with the separation of different crude plant extracts containing potential lead compounds. The approach has been successfully applied to the discovery of interesting bioactive compounds from tropical plants. As a key example the isolation of unusual dimeric flavonoids from a Brazilian medicinal plant will be discussed. These compounds showed an interesting activity against *Trypanosoma cruzi,* the parasite responsible for the Chagas disease *in vitro*. They inhibited the parasite invasion process and its intracellular development in host cells with similar potencies to the reference compound benznidazole. Since enough amount of these interesting leads could be obtained by the isolation strategy developed, *in vivo* biological activity investigation could be performed in *T. cruzi*-infected mice. It was possible to prove that the compound reduced the blood parasitemia *in vivo*. Other examples presenting the possibilities and limitations of the methodology will be presented.

Structural studies of GPCRs, important drug targets

Qiang Zhao

Shanghai Institute of Materia Medica, CAS, China

Abstract

Purinoceptor 12 ($P2Y_{12}R$) is a major clinical target, which regulates platelet activation and thrombus formation. Here we report the crystal structures of human P2Y12R in complex with its non-nucleotide reversible antagonist AZD1283 and agonist 2MeSADP. The structures reveal a distinct straight conformation of helix V, which sets $P2Y_{12}R$ apart from other known class A G protein-coupled receptor (GPCR) structures. The highly conserved disulfide bridge between helix III and extracellular loop 2 (ECL2) appears to be very labile, which is supported by our biochemical analysis indicating that these two cysteines likely exist as free thiols in the native receptor. The structure reveals details of AZD1283 interactions with the receptor, and points to the existence of at least two non-overlapping ligand binding pockets at its extracellular interface. The agonist-bound $P2Y_{12}R$ structure answers long-standing ambiguities surrounding $P2Y_{12}R$-agonist recognition, and reveals interactions with several residues that had not been reported to be involved in agonist binding. As a first example of a GPCR where agonist access to the binding pocket requires large scale rearrangements in the highly malleable extracellular region, the structural studies therefore will provide invaluable insight into the pharmacology and mechanisms of action of agonists and different classes of antagonists for the $P2Y_{12}R$ and potentially for other closely related P2YRs.

Library-based discovery of bioactive natural products – from screening to medicinal chemistry

Matthias Hamburger

Pharmaceutical Biology, Department of Pharmaceutical Sciences, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

Abstract

The efficient identification of bioactive compounds in complex matrices, and the global chemical characterization of extracts remain major challenges in natural products research. Over the past decade, new technologies and tools have become available in the biosciences and in analytical chemistry which enable new approaches in the activity-driven search for natural products. These new possibilities can be summarized with a few keywords such as: miniaturization, on-line analysis of complex samples, chemometric data analysis, study of molecular modes of action, and systems oriented approaches towards the characterization of drug effects *in vitro* and *in vivo*.

We have been exploring some of these in our lab over the past years. As a consequence, we established a technology platform for miniaturized natural products-based lead discovery. This platform includes 2D-barcoded liquid extract libraries, HPLC-based micro-fractionation for off-line bioactivity assessment, simultaneous on-line spectroscopy (PDA, TOFMS, and MS/MS), and off-line NMR spectroscopy with a 1mm microprobe. The platform is generically applicable with mechanism-based and functional assays in the 96-well MTP format and serves as a turntable for collaborative projects in various therapeutic areas.

Use of the technology platform and of different profiling approaches will be illustrated with selected examples, including discovery of new $GABA_A$ receptor modulators, antiretroviral compounds, kinase inhibitors and antiprotozoal natural products. The use of profiling data for medicinal chemistry projects will be highlighted with the example of the $GABA_A$ receptor modulating lead compound SCT-66.

Lysine glutarylation is a protein modification regulated by SIRT5

Minjia Tan

Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Abstract

C. elegans as a screening organism to identify novel health-promoting compounds and phytochemicals

Michael Ristow

Energy Metabolism Laboratory, ETH Zürich (Swiss Federal Institute of Technology Zürich), Zürich-Schwerzenbach, CH-8603, Switzerland

Abstract

Recent evidence suggests that applying various compounds and particularly phytochemicals modulate mitochondrial metabolism to reduce cancer growth, to ameliorate increased blood glucose levels, and to extend life span in various model organisms, including *S. cerevisiae*, *D. melanogaster*, *C. elegans* and mice. In conflict with Harman's free radical theory of aging (FRTA), these effects may be due to *increased* formation of reactive oxygen species (ROS) within the mitochondria causing an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. This type of retrograde response has been named mitochondrial hormesis or *mitohormesis*, and may in addition be applicable to the health-promoting effects of physical exercise in humans, and impaired insulin/IGF1-signaling as well as sirtuin signalling in model organisms. Consistently, abrogation of this mitochondrial ROS signal by antioxidant supplements impairs the lifespan-extending and health-promoting capabilities of physical exercise, as well as lifespan-extending compounds and phytochemicals, respectively. In summary, the findings discussed indicate that ROS are essential signaling molecules which are required to promote health and longevity. Hence, the concept of mitohormesis provides a common mechanistic denominator for the health-promoting effects of physical exercise, as well as lifespan-extending compounds and phytochemicals, and possibly beyond. [1-14]

Potential therapeutic roles of natural Sirtuin modulators

Pei-Hong Fan

Department of Natural Product Chemistry, Key Lab of Chemical Biology and Ministry of Education, School of Pharmaceutical Sciences, Shandong University, Jinan 250012, P.R.China

Abstract

Class III histone deacetylases (sirtuins) are a class of NAD^+ -dependent deacetylases comprising seven members in humans. Sirtuins involved in numerous cellular signaling pathways as key regulators. They are becoming increasingly recognized as important drug targets in cancer, various neurodegenerative diseases such as Alzheimer, Parkinson's disease and others, as well as other metabolic disorders. Modulation of sirtuin activity could provide an interesting and novel therapeutic option. Here, based on recent literatures, we discuss the therapeutic potency and controversies of sirtuins regulation, the discovery of natural Sirtuin modulators and their potential therapeutic roles. We hope to hear experts' opinions about the possibility and significance of developing Sirtuin modulators.