Newsletter

Volume 6, Number 1

February 2012

Phospholipid
Forschungszentrum/Research Center
Heidelberg

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Introduction - Managing Director

On January 1st 2012, PD Dr. Peter van Hoogevest took over the position as Managing Director of the Phospholipid Research Center.

Peter van Hoogevest studied pharmacy at the State University of Utrecht in the Netherlands and did his PhD thesis at the Biochemistry Department of the same University. He started his industrial career in 1984 at Ciba-Geigy Ltd., Basel, Switzerland in the area of drug delivery and especially liposomes. He was responsible for the technological pharmaceutical development of the MTP-PE (muramyltripeptide-PE) liposomes. He worked with Chiron Corp. (USA) at the R&D department on adjuvants for vaccines and was cofounder and CEO of the company ADD Advanced Drug Delivery Technologies AG, Muttenz, Switzerland. After 2000 he joined Phares Drug Delivery AG in Muttenz, Switzerland as managing director and COO. In parallel to his industrial activities, Peter van Hoogevest took care of at least 40 PhD theses in pharmaceutical technology as co-referee and gave regularly lectures at the Universities of Basel, Muttenz and the ETH Zürich. Since 1993 he is Privat Dozent at the University of Basel.

Dr. Peter van Hoogevest
pvanhoogevest@phospholipid-institute.com

Phospholipid Research Center News

a) New Internet-Domain

In August 2011 the Research Center changed its Internet Domain. From now on the website can be visited under following address:
www.phospholipid-institute.com
Please send emails in future to:
info@phospholipid-institute.com

b) Meeting of the Scientific Board, July 11, 2011 in Heidelberg

Participants:
Prof. Alfred Blume (Scientific Board)
Prof. Gert Fricker (Scientific Board)
Dr. Frank Martin (Scientific Board)
Prof. Christel Müller-Goymann (Scientific Board)
Dr. Ralf-Olaf Quinkert (Scientific Board)
Mr. Michael Brugger (PRC)
Dr. Herbert Rebmann (PRC)
Mr. Armin Wendel (PRC)
Dr. Jürgen Zirkel (PRC)

The Phospholipid Research Center received 8 proposals for projects to be funded. The Scientific Board asked for further information and made suggestions for the modification of the project scope in 6 cases. One of these projects will be discussed again during the next Board Meeting. For the other projects only minor modifications are required. One further project was approved.
The next Board Meeting will be on July 9 in Braunschweig. Proposals should be sent in until May 2012.

c) Overview: funded projects

In the following section an overview of all projects funded by the Phospholipid Research Center is provided:

Completed projects:

Prof. U. Massing, Tumor Biology Center Freiburg: "Hydrogenated Phospholipids as anti-metastatic agents"

Prof. N. Skalko-Basnet, Faculty of Health Sciences, University of Tromsø: "Liposomal delivery of curcumin and Curcuma extract as the anti-inflammatory and anticancer agents intended for vaginal therapy"

Prof. A. Blume, Martin-Luther-University Halle-Wittenberg: "Physico-chemical properties of mixed micelles and vesicles composed of phospholipids and surfactants"

Prof. G. Fricker, Institute of Pharmacy and Molecular Biotechnology Ruprecht-Karls-University Heidelberg: "Oral bioavailability screening of new drug compounds: comparison of the phospholipid vesicle based model with the Caco-2 model"

Prof. G. Fricker, Institute of Pharmacy and Molecular Biotechnology Ruprecht-Karls-University Heidelberg: "Phospholipid/Tetraether-lipid based liposomes for controlled drug delivery"

Prof. M. Brandl, Department of Physics and Chemistry, University of Southern Denmark, Odense: "Permeability of Poorly Water Soluble Drugs in the Phospholipid Vesicle-Based Permeation Assay (PVPA): The Influence of Non-Ionic Surfactants"

Dr. M. Abdel-Tawab, Central laboratory of German pharmacists, Eschborn: "Structural properties of NSAID-phospholipid-complexes"

The results of these projects will be published in scientific journals. Coming Newsletters will keep you up to date.

Ongoing projects:

Prof. F. Scholz, Universität Greifswald, Institut für Biochemie: "The effect of foreign molecules (pore forming peptides, and tensides) on the physico-chemical properties of phospholipid bilayer membranes (liposomes). New applications of phospholipids for in-vitro toxicity studies of chemicals"

Dr. S. Ristori, University of Florence: "Using Liposomes as Carriers for Plant Derived Polyphenolic Antibacterial Compounds"

Dr. F. Keyhanfar, Iran University of Medical Science, Teheran: "Study of oral bioavailability of Mebudipine and Dibudipine upon administration in novel PhytoSolve formulations in rats"

Prof. R. Schubert, Albert-Ludwigs-University Freiburg, Institute of Pharmaceutical Sciences: "Investigation of the effect of lipid formulations on transport processes in CaCo2 cell layers"

Dr. G. Pütz, Universitätsklinikum Freiburg, Medizinische Klinik: „Phosphatidylcholines in Anticancer Drug Delivery: Mere Innocent Bystanders?"

Dr. V. Reichel, Ruprecht-Karls Universität Heidelberg, Institut für Pharmazie und Molekulare Biotechnologie: "Stability of cationized Albumin coupled liposomes"

Prof. U. Massing, Tumor Biology Center Freiburg: "Hydrogenated Phospholipids as anti-metastatic agents"

Prof. A. Fahr, Friedrich-Schiller-University, Lehrstuhl für Pharmazeutische Technologie; -- Investigation of cochleate formation and cochleate-cell membrane interactions"

Five further projects will be funded after signing the contract.

d) Proposals and reports

(i) The proposal (4-5 pages in length) should be divided into the following parts:

1. Abstract
2. Introduction: extensive review of the state of the art (latest literature) and comparison with interests and activities of applicant
3. Aim of the project and description of impact of the proposal on the knowledge on and applicability of phospholipids
4. Methods
5. Work plan
6. Timeline
7. Costs

(ii) Funding of future projects will be standardized:

1. Salary PhD Students: up to 50% TVL 13
2. Salary Postgraduates: up to 100% TVL 13 (about € 54 000)
3. Consumables up to € 8 000 p.a. in general
4. Further costs will be discussed if submitted

(iii) Annual reports should document the progress of the funded project. It should contain the following paragraphs:

1. Introduction
2. Aim
3. Preliminary results
4. Conclusions
5. Future perspectives
6. Publications
7. References

For more information about the funding of projects, please visit our website:
www.phospholipid-institute.com

Symposium 2011

Symposium "Phospholipids in Pharmaceutical Research", Heidelberg September 12-13, 2011

In its 5th year the Phospholipid Research Center Heidelberg, organized its "2nd Symposium on Phospholipids in Pharmaceutical Research". From 12th to 13th of September 2011, 170 researchers from all over the world jointed the meeting with the contribution of 18 presentations and about 50 posters, covering many aspects like production and analysis of phospholipids, their physical properties and the experience with their use in pharmaceutical products as useful additives.

The meeting was very successful. We had good discussions and a pleasant social program with the visit of the Castle of Heidelberg.

During the symposium the best three posters received an award. The winners were:

1. Award (500 €) Mrs. Annette Peters, Med. Universitätsklinik, Freiburg/DE
2. Award (300 €) Dr. Agnes Csiszar, FZ Jülich/DE
3. Award (200 €) Mrs. Sarah Fischer, University of Southern Denmark/DK

Britta Merz / Michael Brugger

The winners of the poster awards.
From left to right: Mrs. Peters,Dr. Csiszar and Mrs.Fischer.

Dinner in the castle.

Participants on the balcony at the castle of Heidelberg.

The beautiful castle by day

Sightseeing tour with guides in historical costumes.

and by night.

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Industry NewsHighlights

Lipid Therapeutics Announces Positive Topline Phase IIb Results with LT-02 in Patients with Ulcerative Colitis

Lipid Therapeutics (Germany), a biotechnology company focussing on novel treatments for inflammatory bowel disease, today announced positive topline results from a Phase IIb clinical trial with its lead product, LT-02, in patients with ulcerative colitis. LT-02 is a controlled release formulation of phosphatidylcholine as active moiety that has been specifically designed to treat ulcerative colitis by improving the barrier function of the mucosal layer of the colon, a concept that has now been successfully tested in several clinical trials. The Phase IIb trial met the primary end point, change in SCCAI, for patients refractory to standard first-line intervention who were treated with LT-02 at 0.8g four times a day (51% reduction with LT-02 vs 33% reduction with placebo; $p < 0.05$). Patients who received one of two lower doses of LT-02 also showed a positive benefit. The excellent safety profile of LT-02 treatment was comparable to placebo at all three doses.

Gilead Sciences, Inc. Gilead Sciences and World Health Organization Establish New Five-Year Initiative to Prevent Deaths from Visceral Leishmaniasis

Gilead Sciences, Inc. (Nasdaq:GILD) announced today that it will donate 445,000 vials of AmBisome® (amphotericin B liposome for injection) over five years to help the World Health Organization (WHO) treat more than 50,000 patients with visceral leishmaniasis (VL), also known as kala-azar. These initiatives are part of the Gilead Access Program, which aims to provide wider access to the company's medications to affected populations in the developing world. The Access Program is currently delivering branded or generic versions of Gilead's HIV therapies to 1.8 million patients in developing countries.

Pacira Pharmaceuticals, Inc. Provides Update on Commercial Launch and Product Availability Timing for EXPAREL®

Pacira Pharmaceuticals, Inc. (NASDAQ: PCRX) today provided an updated timing for its commercial launch of EXPAREL® (bupivacaine liposome injectable suspension), a non-opioid analgesic that was approved by the U.S. Food and Drug Administration (FDA) for administration into the surgical site to produce postsurgical analgesia.Due to commercial manufacturing challenges, which Pacira is confident it can address, the company projects product availability in April 2012, by which time Pacira expects it will have manufactured sufficient product to meet customer demands at launch.

Compilation of literature: Dr. Torsten Kromp

Selected Literature and Patent News

Celecoxib loaded liposomes: Development, characterization and in vitro evaluation

Begum M.Y. et al., IJPSR, 2012; Vol. 3(1): 154-161

The potential of liposomes for encapsulation of celecoxib was evaluated to overcome problems associated with the oral application of the drug.
The influence of the drug-lipid ratio on encapsulation was studied as well as the effect of cholesterol and other process parameters on the liposomes. The results indicated, that liposomes with optimized drug content, good stability and controlled drug release (retention) could be obtained.

Preparation and evaluation of drug phospholipids complex for increasing transdermal penetration of phyto constituents

Zaveri M. et al. - International Journal of Institutional Pharmacy and Life Sciences 1(3), 201:80-93

Curcumin is poorly soluble in water. In order to improve the bioavailability of curcumin, its complexation with phospholipids (in 1: 2 molar ratios) was explored. The formation of complex was confirmed by IR spectroscopy and DSC analysis. *In vitro* skin penetration rate of curcumin-phospholipid complex was compared with that of curcumin. Curcumin-phospholipid complex showed almost 60% increasedr permeation of curcumin through rat skin as compared to that of plain curcumin. It was concluded that the complexation of curcumin with phospholipid results in an increased transdermal penetration of curcumin.

WO Pat. 2011157428; December 22, 2011
In-situ lecithin microemulsion gel formulation

The patent application claims an in situ lecithin microemulsion gel formulation. The microemulsion is characterized by a gel-forming phase containing lecithin in a concentration of 0.1% to 50% by weight, based on an apolar continuous phase and optionally a polar agent. The polar agent is present at a concentration lower than the concentration needed for complete gelling. The formulation is intended for use as a therapeutic agent or diagnostic agent in ophthalmology and/or rhinology and/or in the ENT field.

US Pat. Appl. *20110305752; Dec. 15, 2011*
Liposome-encapsulated glutathione for oral administration

The patent application deals with an oral liposomal composition to provide systemic glutathione (reduced). The administration of a therapeutically effective amount of oral liposomal glutathione reduced symptoms in disease states related to glutathione deficiency such as Parkinson's disease and cystic fibrosis. Compounds enhancing the effect of the liposomal glutathione are contemplated such as Selenium, EDTA, carbidopa, and levodopa. The liposomes are made of lecithin or soybean phosphatidylcholine.

US Pat. 8,071,127; Dec. 06, 2011
Dual action, inhaled formulations providing both an immediate and sustained release profile

The patent application claims pharmaceutical compositions comprising phospholipids for inhalation such as for treating respiratory tract infections caused by a variety of microorganisms. In particular a biphasic release formulation which provides for immediate and sustained release of a drug such as anti-infectives delivered by inhalation for the treatment of cystic fibrosis. The preferred phospholipid for the preparation of the liposomes is hydrogenated soy phosphatidylcholine.

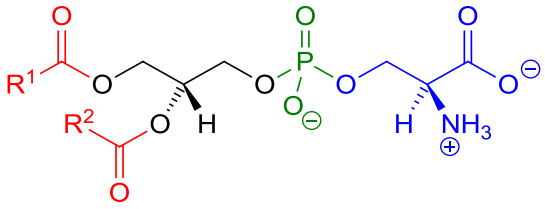
US Pat. Appl. 20110293707; Dec. 01, 2011
Use of the cathelicidin LL-37 and derivatives thereof for wound healing

The patent application deals with the use of the antimicrobial cathelicidin peptide II-37, N-terminal fragments of LL-37 or extended sequences of LL-37 having 1-3 amino acids in the C-terminal end, for stimulating proliferation of epithelial and stromal cells and thereby healing of wounds, such as chronic ulcers. The cytotoxic effect of LL-37 may be reduced by including a bilayer-forming polar lipid, especially a digalactosyldiacylglycerol, in pharmaceutical compositions and growth media comprising LL-37. As phospholipids soybean or egg phosphatidylcholine and DOPC are used.

Compilation of literature: Dr. Torsten Kromp

An introduction to Phosphatidyl Serine

Phosphatidylserine



Phosphatidylserine (PS) is a naturally occurring phospholipid which was discovered 70 years ago in cephalin preparations from ox brain.[1] PS (1,2-Diacyl-*sn*-glycero-3-phosphoserine) consists of a glycerophosphate skeleton conjugated with two fatty acids (phosphatidic acid), to which an L-serine residue is bound *via* a phosphodiester linkage.

PS has three ionisable groups: a phosphate, an amino and a carboxyl group. At pH 7, all of them are ionised – the phosphate and the carboxyl group are negatively charged and the amino group is positively charged, resulting in one net negative charge.[2] The negatively charged PS is able to bind and chelate divalent calcium ions, which is an important factor in the biological function of PS.[2]

The two acyl groups may vary and their nature depends on the PS source. PS from bovine brain contains mainly saturated fatty acids, oleic acid and long chain-polyunsaturated fatty acids (DHA, arachidonic acid). As in most phospholipids, saturated fatty acids are concentrated in position *sn*-1 and unsaturated in position *sn*-2.[3] In plants, the fatty acid composition seems to be similar to that of phosphatidylethanolamine. Apart from extraction from natural sources, PS can also be synthesised from phosphatidylcholine by enzymatic head group exchange using phospholipase D and serine.[4] As bovine brain is not regarded as being a safe source of PS anymore (in particular since the advent of BSE), PS from vegetable sources (mainly from soybean) is produced in large amounts *via* this route. In the resulting products, the fatty acid composition is almost identical to the raw material; therefore the main fatty acid here is linoleic acid. PS with a defined fatty acid composition is manufactured by chemical synthesis.

PS is a structural component of the cell membranes of all animals and plants. It constitutes a large part of the anionic phospholipids of mammalian cell membranes[2], where it is located entirely on its inner surface.[5] In humans, PS is most concentrated in the brain where 15 % of the total phospholipids is PS.[6]

As all animal and plant cell membranes contain PS, it is present in every food derived from plants and animals. Daily intake in western countries is estimated to be 80–130 mg/person/day. Specifically high in PS is brain and some fish like mackerel. Relatively high amounts of PS can also be found in meat, whereas the vegetables' PS content is generally low.[7]

As PS is of such high importance especially for brain and nerves, it has been used as a nutritional supplement since many years. Exogenous PS administration is believed to be beneficial with regards to age-associated memory impairment[8,9], stress[10], and AD/HD symptoms in children[11].

PS is also being used in form of 1,2-dioleoylphosphatidylserine as excipient in the EMEA approved drug product Mepact (liposomal muramyl-tripeptide-phoshphatidylethanolamine). PS can also be used in drug delivery vehicles called cochleates.[12] When dispersions of PS in the sodium form are treated with calcium ions, they form lipid bilayer sheets that are rolled up in a spiral. During this process, drug molecules can be incorporated between the lipid bilayer sheets, where they are effectively protected from degradation. Cochleates have been shown to be highly effective in drug delivery.[13,14]

Recent studies suggested PS-containing liposomes (PSL) as a potential anti-inflammatory agent. PS is translocated from the inner to the outer layer of the

cell membrane at the early stage of apoptosis[5], thereby initiating PS-dependent apoptotic cell phagocytosis. After phagocytosis of apoptotic cells, phagocytes induce the secretion of anti-inflammatory mediators like prostaglandin E_2. This effect can be mimicked by the PSL.[15]

Dr. Christoph Heidecke

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Lipid-Analytics

Phospholipids and Mass Spectroscopy

Nowadays mass spectroscopy is a well established method for analysis of chemical substances. It is used for a wide spectrum of applications like structure determination, trace analysis of pharmaceuticals and derivatives, elemental analysis with ICP-MS, mass spectrometry imaging and many more.

To generate a mass spectrum of a substance, two principal steps have to be done. First, ions of the substance need to be generated, and second, the mass to charge ratio (m/z) of these ions has to be measured. Beside ionization techniques (ESI, APCI, APPI, FAB, MALDI, etc.), there are different techniques to measure m/z. The main three methods are quadrupole mass filters, ion traps, and TOF (time of flight). Further discussion as part of this short communication is focussed on the ESI / quadrupole combination because this is the most popular way to measure the mass spectra of phospholipids.

Electrospray Ionization (ESI) is a technique for ionization of compounds dissolved in a solvent. This is used for the direct analysis of substances as well as for the combination of HPLC with a mass spectrometer as a detector. As solvents often methanol, acetonitrile, water, and mixtures of them are used together with small amounts of acidic or basic compounds like formic acid, acetic acid, ammonium acetate, ammonia and others. This solution is nebulized and simultaneously electric charges (positive or negative) are placed on the small droplets. While the solvent evaporates the charges are transferred to the analyte and positively or negatively charged ions are generated. These ions are directed into the mass spectrometer by means of electric fields.

A quadrupole mass spectrometer works like an adjustable filter for ions of different mass/charge (m/z) ratio. Four rod-like electrodes generate high frequency electromagnetic fields in such a way, that only ions with a specific m/z ratio can travel through the quadrupole and reach the detector where the ions are counted. To generate a mass spectrum, different m/z values are scanned over a period of time.

A very powerful enhancement of this quadrupole technique is the use of three sequential quadrupole filters where the middle one is used as a collision cell. This collision cell allows the controlled fragmentation of ions and the subsequent analysis of the fragments. Depending on the modes in which the different quadrupoles are operated, several mass spectroscopic experiments can be performed to gain specific information about the analysed compounds.

In the case of phospholipids there are several compound specific fragmentation patterns which can be used for the identification and quantification of single phospholipids even in the presence of complex mixtures of other phospholipids. The following table shows a short summary of the typical mass spectroscopic behaviour of some phospholipid (PL) classes.

PL class	ESI	typical fragmentation reactions
PC	pos.	M+1 → 184, +PREC(184)
	neg.	M-15 → fatty acid anions
PE	pos.	M+1 → M – 140, +NL(141)
	neg.	M-1 → fatty acid anions
PG	pos.	M+1 → M – 171, +NL(172)
	neg.	M-1 → fatty acid anions
PA	pos.	M+1 → M – 97, +NL(98)
	neg.	M-1 → fatty acid anions
PS	pos.	M+1 → M – 184, +NL(185)
	neg.	M-1 → fatty acid anions M-1 → M – 88, -NL(87)

All phosphatidylcholines (PC) show a fragmentation of the positively charged molecular ions (M+1) to an ion with m/z = 184 which represents the phosphocholine cation. This fragmentation scheme can be used in a so called precursor experiment (PREC) to specifically detect only those substances which generate the 184-mass. But this is not only specific for PCs, sphingomyelins also show up in a +PREC(184) experiment but they have M+1 ions with odd mass-numbers in contrast to PCs which show M+1 ions with even mass-numbers.

With negative ionization PCs generate, instead of the expected M-1 ions, the corresponding M-15 ions and on fragmentation of these M-15 ions the fatty acid anions are generated.

Phosphatidylethanolamines (PE) show with positive ionization the M+1 ions which generate fragments with M-140. For a selective detection of PEs this can be used by performing a "neutral loss" experiment where only those substances will be detected, which show a mass difference of 141 before and after fragmentation (+NL(141)). In negative mode the M-1 ions are detected and on fragmentation the fatty acid anions are generated.

This applies also for many other phospholipids. With negative ionization the M-1 ions generate the corresponding fatty acid anions and with positive ionization the loss of the polar headgroup can be observed. In the case of phosphatidylserines (PS) also with negative ionization a neutral loss of parts of the polar headgroup is observed (-NL(87)).

Dr. Ralf-Olaf Quinkert

[back]

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