Newsletter

Volume 8, Number 1

December 2014

Phospholipid
Forschungszentrum/Research Center
Heidelberg

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Introduction

This year the Phospholipid Research Center focussed on the assembling of a special issue of the European Journal of Lipid Science and Technology devoted to "Phospholipids in Pharmaceutics" covering our International Symposium on Phospholipids in Pharmaceutical Research held in Heidelberg, Germany, September 16–17, 2013. The Special Issue can be accessed online at http://onlinelibrary.wiley.com/doi/10.1002/ejlt.v116.9/issuetoc . We were very pleased by the many contributions made by researchers in the phospholipid research field and would like to acknowledge their contributions. A summary of this special issue you will find in this Newsletter.

In addition, a Researchers Meeting was organized at the University Braunschweig on 17th July 2015 (hosted by Prof. Müller-Goymann). The researchers funded by the PRC were invited to present theirs results: You will find a summary of this event below.

We have had two Scientific Advisory Board meetings in 2014. You will find the major decisions of these meetings in this Newsletter.

In the past, systematically phospholipid species, analytical methods to analyse the quality of the phospholipids and their use in specific dosage forms were systematically discussed. In the last Newsletter, these series were concluded and the theoretical basis to understand the essentials on phospholipid excipients has been created. In future Newsletters, we will focus on the latest news in these areas and (critically) assess these findings.

In 2015 our biannual Symposium in Heidelberg is on the program. Please, reserve the 20th and 21st September 2015 for this occasion! This time also the General Assembly of the Phospholipid Research Center will take place during these days in Heidelberg.

We wish you a Happy and Successful 2015!

Peter van Hoogevest

Phospholipid Research Center News

Meetings of the Scientific Advisory Board

The Meetings of the Scientific Advisory Board took place on January 27, 2014 (University Heidelberg, hosted by Prof. Fricker) and on July 18, 2014 (University Braunschweig, hosted by Prof. Müller-Goymann).

Participants:

Prof. Dr. Alfred Blume (Scientific Board)
Prof. Dr. Gert Fricker (Scientific Board)
Dr. Frank Martin (Scientific Board)
Prof. Dr. Christel Müller-Goymann (Scientific Board)
Dr. Ralf-Olaf Quinkert (Scientific Board)
PD Dr. Peter van Hoogevest (Managing Director, PRC)
Dr. Herbert Rebmann (President, PRC)
Mr. Armin Wendel (Vice President, PRC)
Dr. Jürgen Zirkel (PRC)

The Phospholipid Research Center received in total 24 proposals for projects to be funded in 2014: The Scientific Board approved 7 proposals.

The next meeting will take place on January 19, 2015 in Köln and will be hosted by Phospholipid GmbH. Proposals should be sent before December 31, 2014.

For more information about the funding of projects, and how to submit a research proposal, please visit our website: www.phospholipid-institute.com .

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Ongoing funded projects

The following projects are at present ongoing:

"Phospholipid Based Solid Dispersions for Enhanced Oral Absorption of Poorly Soluble Drugs".
Prof. Annette Bauer-Brandl; University of Southern Denmark, Odense, Denmark.

"Investigation of cochleate formulations and cochleate-cell membrane interactions".
Prof. Alfred Fahr; University of Jena, Germany.

„The investigation of the interaction of liposomal formulations containing poorly water soluble drugs with human plasma".
Prof. Alfred Fahr; University of Jena, Germany

"Phospholipid/Tetraetherlipid based liposomes for oral administration of Hepatitis B Virus-derived lipopeptides for hepatocyte-specific drug delivery".
Prof. Gert Fricker, PD Dr. Walter Mier, Prof. Stephan Urban; University of Heidelberg, Germany.

"Distribution of phospholipid based drug carriers into organs and tumors – monitoring by mass spectrometry imaging".
Prof. Carsten Hopf; University Mannheim, Germany.

"Investigations on the retention of lipophilic drug compounds within liposomal drug carriers".
Dr. Stephan Hupfeld, University Oslo, Norway, Prof. Martin Brandl; University of Southern Denmark, Odense, Denmark.

"Interactions of the tumor-targeting vector peptide pHLIP with phospholipids".
Prof. Sandro Keller; University Kaiserslautern, Germany.

"Study of mono-acyl lecithin complexes of poorly water soluble compounds; which compounds benefit particularly from dissolution enhancement regarding improved BAV?"
Prof. Martin Kuentz; University of Applied Sciences and Arts Northwestern Switzerland, Muttenz, Switzerland.

"In vivo detoxification of alcohol using phospholipid supported bioreactors".
Prof. Jean-Christoph Leroux; ETH Zurich, Switzerland.

"Oral anticancer-indirubins: Solubility enhancement, permeability and bioavailability assessment of phospholipid containing (SMEDDS) formulations".
Dr. Anne Mahringer, University Heidelberg, FRG, Prof. Gerhard Eisenbrand, University Kaiserslautern, FRG and Prof. Martin Brandl; University of Southern Denmark, Odense, Denmark.

"Assessment and better prediction of acute hypersensitivity and complement involvement upon administering liposomal drug products to human subjects".
Dr. Bart. Metselaar; University Twente, The Netherlands, Prof. Janos Szebeni. Semmelweis University, Budapest. Hungary.

"Elucidating the use of lyso-phospholipids in oral self-nano-emulsifying drug delivery systems".
Prof. Anette Müllertz; University Copenhagen, Denmark.

"Inhibitory effect of phospholipids on the efflux transporter P-glycoprotein".
Prof. Rolf Schubert; University Freiburg, Germany.

„Mechanistic action and adverse event of therapy with delayed release - Phosphatidylcholine in a genetic mouse model of ulcerative colitis".

Prof. Wolfgang Stremmel; University Clinic of Heidelberg, Germany (till July 2014).

"Impact of Phospholipid Oxidation on Biophysical Properties of Membranes".
Prof. Motomu Tanaka; University Heidelberg, Heidelberg, Germany.

Approved projects

The Board approved the following projects as requested or after minor revision:

"Improving treatment of pediatric sarcoma through targeted liposomal drug delivery".
Dr. Michele Bernasconi, University Childrens Hospital Zurich, Switzerland.

"Inhibition of Akt by polyunsaturated phosphatidylcholine – a novel approach for anti-cancer therapy.
Dr. Andreas Koeberle, University Jena, Germany.

"Interaction of phospholipids with the skin in human subjects",
Dr. M. Lane, University London, United Kingdom.

"Phospholipids as functional excipient in solid oral dosage forms".
Prof. Roland Bodmeier/Dr. Martin Koerber, FU Berlin, Berlin, Germany.

"Phospholipid liquid fill formulations for hard gelatin capsules".
Prof. Heike Bunjes, University Braunschweig, Germany.

"Design of well-defined liposomes to target tumor associated M2 macrophages".
Dr. Jai Prakash, University Twente, The Netherlands.

"Development of NLCs and nanoemulsions with monoacyl-phospholipids and investigation of their skin Interaction".
Prof. Claudia Valenta, University Vienna, Vienna, Austria.

Country of Origin of Projects

As derived from the presently approved projects, the universities that are being funded are located in:
Austria (1), Denmark (3), Germany (12), Hungary (1), Norway (1), The Netherlands (2), United Kingdom (1), Switzerland (3).

Workshop proposal

The Board approved a request of Prof. Sandro Keller (University Kaiserslautern) for a grant of 3000 € to support a workshop on Molecular Membrane Biophysics: International biennial meeting of the section "Membranes, Cells, Networks" of the German Biophysical Society. This workshop was held at the St. Bonifatiuskloster in Hünfeld, Germany on March 3-5, 2014.

Publications

Following publications, related to projects supported by the Phospholipid Research Center were made during 2014:

Deszi, L., Fülöp, T., Meszaros, T., Szenasi, G., Urbanics, R., Vazsonyi, C., Örfi, E., Rosivall, L., Nemes, R. Kok, R.J., Metselaar, J.M., Storm, G. & Szebeni, J., Features of complement activation-related pseudoallergy to liposomes with different surface charge and PEGylation: Comparison of the porcine and rat responses, J. Control. Rel. 2014 (accepted for publication)

Hinna, A., Steiniger, F., Hupfeld, S., Brandl, M. & Kuntsche, J., Asymmetrical flow field-flow fractionation

with on-line detection for drug transfer studies: a feasibility study. (2014) Analytical and Bioanalytical Chemistry, pp. 1-13.

Oral Presentations:

Hinna, A., Hupfeld, S., Kuntsche, J., & Brandl, M., Asymmetrical flow field-flow fractionation with on-line detection for drug transfer studies, a feasibility study, 23rd Mountain/Sea Liposome Workshop. Oberjoch, Germany, March 24th- 28th, 2014.

Weinheimer M., Institute of Pharmaceutical Sciences, Evaluating efficacy and safety of P-gp inhibiting phospholipids by a simplified in vitro digestion simulation", International Liposome Workshop Oberjoch, Germany, March 24th- 28th, 2014.

Posters:

Hinna, A., Hupfeld, S., Kuntsche, J. & Brandl, M., Asymmetrical flow field-flow fractionation with on-line detection for drug transfer studies: Investigating transfer kinetics of a lipophilic model drug between liposomal bilayers, CRS Nordic Chapter Bi-annual meeting, Helsinki Finland, August, 26th-27th, 2014, and the Global Pharmaceutical Education Network Meeting, Helsinki Finland, August 27th-30th 2014 and at the 10th Central European Pharmaceutical technology Meeting, Portorož Slovenia, September 18th-20th, 2014.

Klingler, J., & Keller, S., Interactions of amphiphilic peptides with phospholipid membranes, The Wilhelm und Else-Heraeus-Seminar „Physical Approaches to Membrane Proteins", Bad Honnef, Germany, May 25th-28th, 2014.

Researchers Day

On July 17, 2014 the second Researchers Day of the Phospholipid Research Center took place in Braunschweig, Germany. The meeting was hosted by Prof. Müller-Goymann and the scientific guidance was made by the members of the Scientific Advisory Board. Almost all researchers, who are supported by the Phospholipid Research Center, attended the meeting and gave a presentation on their either ongoing project or on their research intentions, when the project still had to be started.

It was generally felt that the meeting stimulated the contacts between the researchers and gave the Scientific Advisory Board and management of the Phospholipd Research Center an excellent overview on the progress made with the individual projects and allowed the other researchers to comment the presentations.

With permission of the presenters, the seminar slides were distributed among the attending researchers. In order to foster the communication between the researchers, especially when they, for instance, work in the same research area, like oral administration of phospholipids, the Researchers Day event will be regularly repeated.

Selection of Phospholipids

The Phospholipid Research Center issued, as part of the special issue of the European Journal of Lipid Science and Technology devoted to our Symposium, the following publication: Van Hoogevest, P. & Wendel, A., The use of natural and synthetic phospholipids as pharmaceutical excipients. Eur. J. Lipid Sci. Technol. **116,** 1088–1107(2014). This publication is an open access publication: http://onlinelibrary.wiley.com/doi/10.1002/ejlt.201400219/full .

This publication addresses the selection of phospholipid excipients for drug formulations. It is shown that only in very limited product segments, i.e. parenteral liposomal dosage forms and pulmonary administration, synthetic phospholipids are being used. In general, natural phospholipids play a dominant role in all

other administration routes and types of dosage forms.

Most synthetic phospholipids can be replaced by natural phospholipids, in case they have comparable properties. An exception may be synthetic phospholipids like PEG-ylated lipids, but in the past it was found that the incorporation of phosphatidylinositol also prolonged the circulation time of liposomes (Huang, L., Stealth Liposomes, Ninja Liposomes, or Cryptosomes: Are They Really Sterically Stabilized Liposomes? J. Liposome Res, **2**, 451-454 (1992) and Wassef, N.M., Matyas, G.R. & Alving, C.R. Complement-dependent phagocytosis of liposomes by macrophages: suppressive effects of "stealth" lipids, Biochem. Biophys. Res. Commun. **176**, 866-874 (1991).

Unfortunately, pharmaceutical companies lacking abundant development experience tend to select synthetic phospholipids which are, compared to natural phospholipids more expensive and available at lower quantities. The synthetic phospholipids require synthesis with more solvents, chemicals, catalysts compared to natural phospholipids. Since natural phospholipids are extracted from renewable sources like soybeans and egg yolks, natural phospholipids are available in much larger quantities at lower costs compared to synthetic phospholipids.

Sometimes, the decision has been made to perform clinical research with synthetic phospholipids and a reformulation using natural phospholipids, causing development delays, is out of the question. Since, however, only major pharmaceutical companies have the capabilities to perform extensive and expensive Phase III clinical trials and market the successful product in many countries, the company developing the product needs to license out their product to one of these major pharmaceutical companies. Unfortunately, the chance is very high that the major pharmaceutical company will critically assess the development criteria of the selected lipids and may come to the conclusion that the selected lipids are not suitable for large scale production and the costs of good are too high. As a result, the out-licensing company will receive considerably reduced license fees and upfront payments or the product will not be developed at all. In addition, either the scale up of the synthetic phospholipid or reformulation with natural phospholipids in combination with the performance of some additional clinical trials to prove the similarity of performance, will delay the introduction of the product on the market.

The performance of clinical research with a dosage form comprising “suboptimal” lipids may find its justification in the wish to assess the toxicity and efficacy of the drug substance in patients as soon as possible. When this clinical research demonstrates a major clinical breakthrough, resulting in block buster potential for the bigger licensing partner, the considerations above may be overruled by the sales potential of the new drug product. However, clinical breakthroughs with blockbuster potential are very rare and obtained clinical improvements may be marginal. Therefore, often the l out-licensing company will end up in a scenario that the necessary investments (to be made by the bigger licensing partner) do not outweigh the advantages of the envisaged product and the out-licensing company may not find a licensing partner.

The preceding discussion is made with the assumption that the selected synthetic phospholipid excipients are at least known to regulatory authorities. It sometimes, however, happens that synthetic phospholipids are used in clinical dosage forms for the very first time in patients. The selection of such a new lipid excipient means for the lipid supplier an additional effort, because the synthesis method (from small scale to kg scale) and corresponding quality control methods have to be developed and corresponding registration documentation have to be

compiled. By selecting a disease indication for which no adequate therapy exists (for example brain tumors or pancreas cancer) regulatory authorities are inclined to accept only minimal preclinical (in animals) toxicity data on the new lipid excipient to allow clinical testing.

Mostly, the toxicity of the new excipient is pragmatically explored in combination with the other excipients in the formulation with the drug substance and without drug substance (placebo control). In case of promising results in the clinic, the clinical product may be considered for a wider patient population. In practice, only large pharmaceutical companies are able to explore the clinical benefits in larger patient populations. In addition to the general issues related with synthetic phospholipids described above, the larger pharmaceutical company has to consider developing a product containing a new excipient, which has not been used in larger patient populations for a longer period of time in an extended patient population. For such scenarios regulatory authorities require that the toxicity profile of the new excipient is being tested like a new drug substance (see Guidance for Industry–Nonclinical studies for the safety evaluation of pharmaceutical excipients, FDA, May 2005).

As a result, the company taking care of the worldwide distribution and sales has to deal with a liability issue related to the unknown use of the new lipid excipient and this company, afraid for possible side effects related to the use of the new excipient may hesitate to bring the products on the market and take responsibility for the safety of the product. So, seemingly, the company, which needs to out-license the drug product, has expeditiously developed the product. However; at the very end this company may have problems to sell larger volumes of the product. In order to reduce/eliminate its liability, the required licensing partner to boost the sales volume, may only become interested after demonstration of a long track record of safe use of the new excipient in a large patient population.

On the other hand, it should be realized that the selection of new (synthetic) lipid excipients for pharmaceutical development gave rise to the introduction of innovative liposome products on the market. Although, the resulting products are relatively small compared to blockbusters, it is clear that these developments made a major contribution to the popularity and acceptability of lipid carriers in the pharmaceutical industry.

It is therefore wise, to carefully select the phospholipids for development processes and to consider to use natural phospholipids (and to avoid when possible new excipients), taking ecological, large scale availability, acceptability by regulatory authorities and price considerations into account and, in case of doubt, to consult the lipid supplier.

Even when a less suitable lipid for development has been selected for the clinical dosage form, it should be considered by the developing company to reformulate the clinical product using natural lipids. The loss in development time may be more than compensated by the elimination of further development hurdles and licensing-out obstacles to pharmaceutical companies.

Peter van Hoogevest

Industry news

Lipid Therapeutics' European Partner Dr. Falk Pharma GmbH Enrolls First Patients Into Pivotal Phase III Trial With LT-02, a Novel Therapy for Ulcerative Colitis (UC), Press release, 29 October 2014.

Lipid Therapeutics announces that its European co-development partner Dr. Falk Pharma GmbH has enrolled the first patients into a pivotal Phase III trial with LT-02, a novel barrier function therapy for mild-moderately active ulcerative colitis not responding to standard doses of 5-ASA.

LT-02 is a first-in-class highly purified phosphatidylcholine targeted to improve the barrier function in the colon through a proprietary delayed release formulation. Loss of barrier function in the colon in patients with ulcerative colitis has been linked to inflammation due to prolonged bacterial contact with the gut mucosa. Clinical efficacy of the approach has been demonstrated in several clinical trials, most recently in a Phase IIb trial where LT-02 achieved the primary study endpoint (reduction of disease activity in patients with mesalazine-refractory ulcerative colitis) with statistical significance.

Comment of PRC: this therapy modality shows that oral administration of phosphatidylcholine may have in certain specific disease indications a therapeutic effect.

Celator(R) Pharmaceuticals Announces Phase 3 Clinical Study of CPX-351 Achieved Target. Enrollment in High Risk (Secondary) Acute Myeloid Leukemia, Press release, 27 October, 2014.

Celator Pharmaceuticals, Inc., a biopharmaceutical company announced that the target enrollment of 300 patients has been achieved in the company's multicenter, randomized, open-label Phase 3 study of CPX-351 (cytarabine:daunorubicin) Liposome for Injection versus the current standard of care, conventional cytarabine and daunorubicin therapy (7+3) in patients with untreated high-risk (secondary) acute myeloid leukemia (AML). The study randomized the 300th patient ahead of schedule and will remain open for a short time to enable all patients currently in the process of referral and evaluation to complete enrollment into the study.

Cellectar Biosciences Announces Publication of Findings Demonstrating Efficacy of Its Phospholipid Ether Analog Platform in Detecting Colorectal Cancer, Press release 15 October, 2014.

Cellectar Biosciences, Inc. announced that an article reporting the efficacy of its proprietary phospholipid ether (PLE) analog agents for the detection, imaging and real-time visualization of colorectal cancer was published in PLOS ONE, an international, peer-reviewed publication. Cellectar is developing a novel drug delivery and retention technology engineered to specifically target and accumulate in malignant tissue. Recent preclinical and clinical evaluations assessed the efficacy of two of Cellectar's PLE-based agents to successfully accumulate in and illuminate malignant tissue in colon cancer, the results of which are detailed in the current edition of PLOS ONE in an article entitled: "Phospholipid Ether Analogs for the Detection of Colorectal Tumors."

Merrimack Pharmaceuticals Announces Initiation of Phase 1 Clinical Study of MM-398 for Brain Cancer UCSF Investigator-Sponsored Trial Uses Novel Technique for Administration of Highly Concentrated Formulation of MM-398 Into Brain Tumors, Press release 6 November, 2014.

Merrimack Pharmaceuticals, Inc. announced that the first patient has been enrolled in a Phase 1 clinical study of MM-398 (nanoliposomal irinotecan injection) in a highly concentrated formulation in patients with recurrent high grade glioma, a type of aggressive brain tumor with poor prognosis. The Phase 1, dose-escalating, open label study will assess the safety of highly concentrated MM-398 when administered by convection-enhanced drug delivery in patients with recurrent high grade glioma. In this study, MM-398 will be administered with gadoteridol, an MRI imaging agent to enable the real time visualization of drug distribution in the brain, through a small catheter that allows for the drug to be injected directly into the brain tumor - an approach called convection-enhanced drug delivery. Due to the small injection volume required for this method of deliv-

ery, a highly concentrated formulation of MM-398 was specifically developed by Merrimack. The study is being conducted at a single center at the University of California, San Francisco and will enroll up to 36 patients with recurrent high grade glioma.

Pacira Pharmaceuticals Inc. Announces New Data on the Use of EXPAREL to Treat Postsurgical Pain Following Total Knee Arthroplasty, Press release 6 November, 2014

Pacira Pharmaceuticals, Inc. announced results of an independent, physician-initiated study designed to evaluate the difference in postsurgical pain and opioid consumption between patients who received EXPAREL versus a multi-drug analgesic cocktail for pain management following total knee arthroplasty (TKA). The data, presented at the annual meeting of the American Association of Hip and Knee Surgeons (AAHKS), found that patients treated with EXPAREL reported significantly lower patient-perceived pain scores and morphine sulfate equivalence consumption, and reported higher satisfaction with pain control and overall experience, compared with patients who received the multi-drug analgesic cocktail. EXPAREL (bupivacaine liposome injectable suspension) is indicated for single-dose infiltration into the surgical site to produce postsurgical analgesia. The product combines bupivacaine with DepoFoam, a proven product delivery technology that delivers medication over a desired time period. EXPAREL represents the first and only multivesicular liposome local anesthetic that can be utilized in the peri- or postsurgical setting in the same fashion as current local anesthetics. By utilizing the DepoFoam platform, a single dose of EXPAREL delivers bupivacaine over time, providing significant reductions in cumulative pain scores with a 45% decrease in opioid consumption; the clinical benefit of the opioid reduction was not demonstrated.

Literature alerts

Gol, D., & Shah, V. Nano-cochleates: A novel approach for drug delivery World J. Pharm. Res. 3, 1920-1944 (2014).

This review points to the possible use of special structures obtained when phosphatidylserine is mixed with divalent ions like Ca^{2+}. It is claimed that the formed cochleates are better than liposomes regarding chemical and physical stability. This statement still has to be proven. In addition, many liposomal products are on the market underscoring that chemical and physical problems can be solved. Nevertheless, these unique structures may have a potential in drug delivery and more research to investigate the potential is warranted.

Cullis, P.R., Jigaltsev, I.V., Taylor, J.R., Leaver, T., Wild, A.& Belliveau, N.M. Limit size lipid nanoparticles and related methods. US patent application, US2014/0328759 A1

This patent application describes very small liposomes and nanoemulsions (10-100 nm) prepared using a solvent dilution method. The equipment, suitable for preparation of very small liposome batches for laboratory use is available at www.nanoassemblr.com .

Henry, B.D., Neill, D.R., Becker, K.A., Gore, S., Bricio-Moreno, L., Ziobro, R., Edwards, M.J., Mühlemann, K., Steinmann, J., Kleuser, B., Japtok, L., Luginbühl, M., Wolfmeier, H., Scherag, A., Gulbins, E., Kadioglu, A., Draeger. A. & Babiychuk, E.B. Nature Biotechnology Engineered liposomes sequester bacterial exotoxins and protect from severe invasive infections in mice (doi:10.1038/nbt.3037 Published online 02 November 2014.

Gram-positive bacterial pathogens that secrete cytotoxic pore-forming toxins, such as Staphylococcus aureus and Streptococcus pneumoniae, cause a substantial

burden of disease. Inspired by the principles that govern natural toxin-host interactions, we have engineered artificial liposomes that are tailored to effectively compete with host cells for toxin binding. Liposome-bound toxins are unable to lyse mammalian cells in vitro. We use these artificial liposomes as decoy targets to sequester bacterial toxins that are produced during active infection in vivo. Administration of artificial liposomes within 10 h after infection rescues mice from septicemia caused by S. aureus and S. pneumoniae, whereas untreated mice die within 24–33 h. Furthermore, liposomes protect mice against invasive pneumococcal pneumonia. Composed exclusively of naturally occurring lipids, tailored liposomes are not bactericidal and could be used therapeutically either alone or in conjunction with antibiotics to combat bacterial infections and to minimize toxin-induced tissue damage that occurs during bacterial clearance.

Ye, T., Xu, W., Shi, T., Yang, R., Yang, X., Wang, S. & Pan, W. targeted delivery of docetaxel to the metastatic lymph nodes: A comparison study between nanoliposomes and activated carbon nanoparticles , Asian J. Pharm. Sci. (2014), http://dx.doi.org/10.1016/j.ajps.2014.08.004

The objective of this study is to compare the targeting ability of activated carbon nanoparticles and nanoliposomes, which are used as carriers for delivering docetaxel (DTX) to the metastatic lymph nodes. In this study, the DTX-loaded activated carbon nanoparticles (DTX-AC-NPs) were prepared by modifying the activated carbon with nitric acid oxidation and absorbing DTX in the concentrated nitro-oxide nanocarbon. Then DTX-loaded nanoliposomes (DTX-LPs) were prepared by the proliposome method. The physiochemical properties of DTX-AC-NPs and DTX-LPs were evaluated in vitro. The metastatic lymph node uptake and the (subcutaneous) injection site retention were investigated by analyzing the DTX concentration in metastatic lymph nodes and injection sites. The result showed that DTX-AC-NPs and DTX-LPs with suitable and stable physicochemical properties could be used for in vivo lymph node targeting studies. DTX-AC-NPs significantly increased DTX-AUC(0e24) and prolonged DTX-retention in metastatic lymph nodes compared to DTX-LPs and non-modified activate carbon in vivo. This study demonstrated activated carbon nanoparticles may be potential intralymphatic drug delivery system to preferentially target regional metastatic lymph nodes.

Comments PRC: Because of the advent of nanotechnology increasingly materials are being explored coming from material science. Although it is interesting (from academic point of view) to compare these new materials with existing approaches using liposomes, it should be realized that these new, inorganic materials, are not biodegradable and possibly toxic. In addition, the treatment with nitric acid may make the carbon particles more homogeneous but also more toxic.

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