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Jena, 18. Dezember 2018

EINLADUNG

Am Montag, **28. Januar 2019**, spricht um **14:00 Uhr**
im Hörsaal des ZAF, Philosophenweg 7, 07743 Jena

Herr Dr. Lutz Nuhn

Max Planck Institute for Polymer Research
Mainz

zum Thema

"Functional Unfolding Nanogels for Immunotherapy"

Alle Interessenten sind herzlich eingeladen.

gez. Prof. Dr. Ulrich S. Schubert

Es handelt sich um eine Veranstaltung des SFB 1278 - POLYTARGET

Functional Unfolding Nanogels for Immunotherapy

Lutz Nuhn
Max-Planck-Institute for Polymer Research, Mainz (Germany)

Nano-sized particles with stimuli-responsive properties provide unique opportunities to address unmet medical needs, especially for immunotherapy.[1] However, facile and straightforward access to multifunctional as well as biodegradable carriers remains a key requirement. Self-assembling amphiphilic block copolymers often meet those criteria by forming micellar nanoparticles readily, yet, with limited degree of functionalization, drug load or stability under physiological conditions. To that respect, we utilize reactive precursor block copolymers that are functionalized and stabilized during self-assembly, e.g. by covalent incorporation of hydrophilic cross-links, fluorescent dyes or drugs into the micellar core affording functional degradable nanogels.[2]

One of the most versatile reactive precursor block copolymer system we have been elucidated over the past is based on RAFT polymerized pentafluorophenyl methacrylate (PFPMA) with tri(ethylene glycol) methyl ether methacrylate (MEO_3MA). The perfluorinated PFPMA reactive ester assures phase separation in polar aprotic solvents and, thus, triggers micellar self-assembly with amine reactive cores.[3] During conversion with hydrophilic bis-amine crosslinkers under anhydrous conditions, the nanostructures are covalently stabilized while omitting PFP-ester hydrolysis. Moreover, by sequential addition of mono-amine entities further functionalities are introduced into the resulting core-crosslinked nanogel system, which amplifies its versatility for drug delivery: For instance, we applied cationic cross-linkers affording positively charged nanogels for siRNA delivery in antifibrotic therapy[4] or CpG delivery in antitumor vaccination.[5]

By introducing disulfide or ketal-crosslinks the resulting nanogels are able to unfold into single polymer chains under reductive or acidic conditions present after cellular nanoparticle internalization.[6-8] Interestingly, subcutaneous injection of non-charged ketal-crosslinked nanogels shows an enhanced accumulation in tissue draining lymph nodes. This feature promotes local maturation of antigen-presenting cells, when TLR7/8 small molecule agonists are covalently ligated to the nanogels.[9] Consequently, such nanogels can successfully be applied as adjuvants during vaccination against e.g. tuberculosis or RSV,[9,10] or even as immunotherapeutics against cancer.[11]

In addition, the RAFT block copolymerization approach guarantees access to well-defined end groups which can be exploited towards particle surface bioconjugation with peptides or proteins through vinylsulfone or click chemistry.[5,12] Site-specific ligation of targeting single chain antibodies (nanobodies) promotes nanogel delivery into special immune cell subpopulations (e.g. tumor-associated macrophages TAM) in the tumor micromilieu.[13] Altogether, such core- and corona-functional unfolding nanogels can be considered as versatile platform to address and resolve multiple needs in (cancer) immunotherapy.

Short CV:

Lutz Nuhn graduated in biomedical chemistry at the Johannes Gutenberg-University Mainz (Germany) in 2010. In 2008/09 he practiced first research experience at MIT with Robert Langer and Daniel G. Anderson. For his PhD he joined the groups of Rudolf Zentel (Mainz, Germany) and Prof. Kazunori Kataoka (Tokyo, Japan) to obtain his degree in 2014. Afterwards, he worked as postdoctoral associate in the group of Bruno G. De Geest with Richard Hoogenboom at Ghent University (Belgium). In summer 2017 he joined the group of Tanja Weil at the Max Planck Institute for Polymer Science (Mainz, Germany) as junior group leader.

Lutz Nuhn received scholarships from the German National Academic Foundation (Studienstiftung des deutschen Volkes), the Max Planck Graduate Center (MPGC), the Fonds der Chemischen Industrie (FCI), the Alexander von Humboldt Foundation (AvH) and the Research Foundation Flanders (FWO). He is currently a Liebig fellow of the FCI and Emmy-Noether group leader supported by the German Research Foundation (DFG). His research focuses on novel polymer-based therapeutics for immunoengineering.

References:

[1] E. Lepeltier and L. Nuhn, C.-M. Lehr, R. Zentel, *Nanomedicine (Lond.)* **2015**, *10*, 3147-3166.
[2] N. Leber, L. Nuhn, R. Zentel, *Macromol. Bio. Sci.* **2017**, *1700092*, 1-15.
[3] L. Nuhn, M. Hirsch, B. Krieg, K. Koynov, M. Schmidt, M. Helm, R. Zentel, *ACS Nano* **2012**, *6*, 2198-2214.
[4] L. Kaps and L. Nuhn, M. Aslam [...], D. Schuppan, R. Zentel, *Adv. Healthcare Mater.* **2015**, *4*, 2809-2815.
[5] S. Hartmann and L. Nuhn, B. Parlitzsch [...], H. Kunz, R. Zentel, *Adv. Healthcare Mater.* **2015**, *4*, 522-527.
[6] L. Nuhn, L. Braun, I. Overhoff [...], K. Koynov, R. Zentel, *Macromol. Rapid Commun.* **2014**, *35*, 2057-2064.
[7] N. Leber, L. Kaps, M. Aslam [...], L. Nuhn, R. Zentel, D. Schuppan, *J. Controlled Release* **2017**, *248*, 10-23.
[8] L. Nuhn, S. Van Herck [...], K. Koynov, B. N. Lambrecht, B. G. De Geest, *Angew. Chem. Int. Ed.* **2018**, *57*, 10760-10764.
[9] L. Nuhn, N. Vanparijs [...], S. De Koker, B. G. De Geest, *Proc. Natl. Acad. Sci.* **2016**, *113*, 8098-8130.
[10] L. Nuhn, L. Van Hoecke [...], S. A. David, X. Saelens, B. G. De Geest, *Biomaterials* **2018**, *178*, 643-651.
[11] L. Nuhn, S. De Koeker, S. Van Lient [...], S. A. David, J. Tavernier, B. G. De Geest, *Adv. Mater.* **2018**, *1803397*, 1-9.
[12] N. Vanparijs, L. Nuhn [...], H. D. Maynard, B. G. De Geest, *Nanomedicine (Lond.)* **2016**, *11*, 2631-2645.
[13] L. Nuhn, E. Bolli, [...], J. A. Van Ginderachter, B. G. De Geest, *Bioconjugate Chem.* **2018**, *29*, 2394-2405.

Dr. Lutz Nuhn

Lutz Nuhn graduated in biomedical chemistry at the Johannes Gutenberg-University Mainz (Germany) in 2010. In 2008/09, he practiced first research experience at MIT with Robert Langer and Daniel G. Anderson. For his PhD, he joined the group of Rudolf Zentel in Mainz (Germany) working on multifunctional carriers for peptide and oligonucleotide delivery by reactive precursor polymers. After a research stay with Prof. Kazunori Kataoka at Tokyo University (Japan), he obtained his doctoral degree in 2014. Afterwards, he became a postdoctoral associate in the group of Bruno G. De Geest at Ghent University (Belgium) working on multifunctional nanogels for lymph node focused immune activation. Since summer 2017, he has joined the group of Tanja Weil at the Max Planck Institute for Polymer Science (Mainz, Germany) as a young group leader.

Lutz Nuhn received scholarships from the German National Academic Foundation (Studienstiftung des deutschen Volkes), the Max Planck Graduate Center (MPGC), the Fonds der Chemischen Industrie (FCI), the Alexander von Humboldt Foundation (AvH) and the Research Foundation Flanders (FWO). He is currently a Liebig fellow of the FCI and a project leader in the DFG Collaborative Research Center SFB-1066 "Nanodimensional Polymer Therapeutics for Tumor Therapy" (Project B4: "Polymer induced tumor-

Research interests:

At the interface between materials chemistry and life science we want to design novel polymeric drug delivery systems and study their potency to improve pathologic phenomena in living cells and tissues. Thereby, our primary research interests focus on the design of nano-sized vaccines and anti-cancer immunotherapeutics. For this purpose, we develop well-defined block copolymers with self-assembling and responsive properties. The resulting nano-sized carriers can sense various stimuli including temperature, pH or light and provide reactivity to amino acid residues as well as specific receptor binding properties. Key feature of them is their biodegradability towards nanoparticle disassembly under physiologically relevant conditions over time.

Towards the development of vaccines against insidious intracellular pathogens and cancer, we utilize these nanocarriers for engineering selective immune-responses *in vitro* and *in vivo*. Moreover, novel strategies to modulate immune regulatory properties of the tumor microenvironment are investigated in order to combat cancer via next generation nano-immunotherapeutics.

Selected Publications:

L. Nuhn, M. Hirsch, B. Krieg, K. Koynov, K. Fischer, M. Schmidt, M. Helm, R. Zentel "Cationic Nanohydrogel Particles as Potential siRNA Carriers for Cellular Delivery", *ACS Nano* **2012**, *6*, 2198-2214.

L. Nuhn, S. Hartmann, B. Palitzsch, B. Gerlitzki, E. Schmitt, R. Zentel, H. Kunz "Water-Soluble Polymers Coupled with Glycopeptide Antigens and T-Cell Epitopes as Potential Antitumor Vaccines", *Angewandte Chemie International Edition* **2013**, *52*, 10652-10656; *Angewandte Chemie* **2013**, *125*, 10846-10850.

L. Kaps, L. Nuhn, M. Aslam, A. Brose, F. Foerster, S. Rosigkeit, P. Renz, R. Heck, Y. Ook Kim, I. Lieberwirth, D. Schuppan, R. Zentel "In Vivo Gene-Silencing in Fibrotic Liver by siRNA-Loaded Cationic Nanohydrogel Particles", *Advanced Healthcare Materials* **2015**, *4*, 2809-2815.

S. Hartmann, L. Nuhn, B. Palitzsch, M. Glaffig, N. Stergiou, B. Gerlitzki, E. Schmitt, R. Zentel, H. Kunz "CpG-Loaded Multifunctional Cationic Nanohydrogel Particles as Self-Adjuvanting Glycopeptide Antitumor Vaccines", *Advanced Healthcare Materials* **2015**, *4*, 522-527.

L. Nuhn, N. Vanparijs, A. De Beuckelaer, L. Lybaert, G. Verstraete, K. Deswarte, S. Lienenklaus, N. M. Shukla, A. C. D. Salyer, B. N. Lambrecht, J. Grooten, S. A. David, S. De Koker, B. G. De Geest "pH-Degradable Imidazoquinoline-Ligated Nanogels for Lymph Node Focused Immune Activation", *Proceedings of the National Academy of Sciences* **2016**, *113*, 8098-8103.