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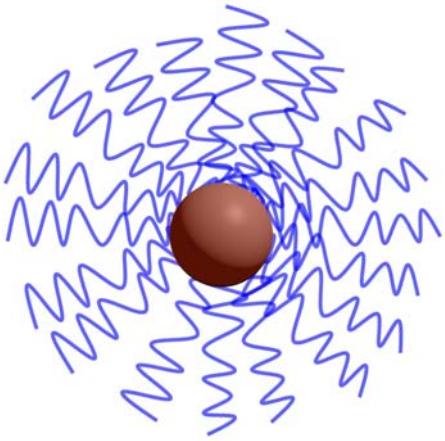
Left to right: Prof. Dr. Axel Müller, Dr. Holger Schmalz and Dipl.-Chem. Alexander Majewski, Department of Macromolecular Chemistry II; Dr. Valérie Jérôme and Prof. Dr. Ruth Freitag, Department of Process Biotechnology.

Dipl.-Chem. Alexander Majewski is a student in the PhD programme “Polymer Science“ within the Bayreuth Graduate School of Mathematical and Natural Sciences (BayNAT). He is the first author of the recent publication in “Biomacromolecules“. The synthesis of the new magnetic PDMAEMA stars is an important aspect of his thesis work.

‘Premium Vectors’ for the Life Sciences: Magnetic Nanoparticles

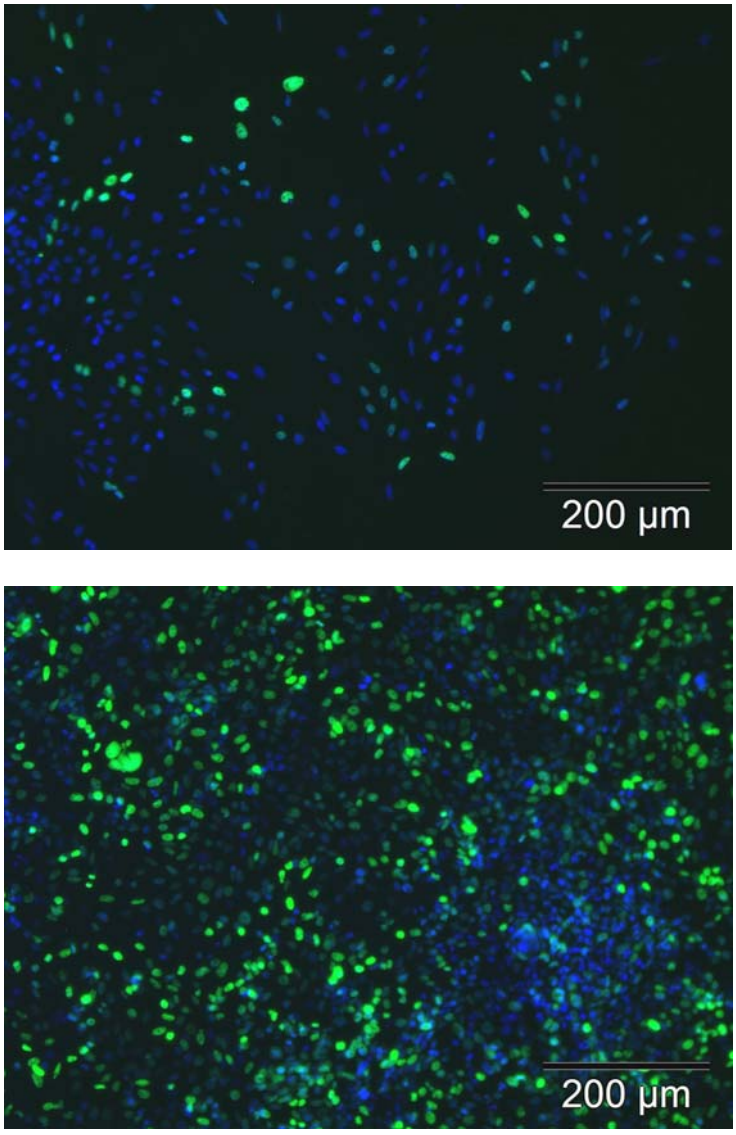
Positively charged star polymers containing a magnetic core are particularly suitable as DNA-delivery vectors. They show extremely high gene transfer efficiency and afterwards enable the quick and simple separation of the transfected cells from the transfection pool. A research team from the University of Bayreuth reports this result in the current edition of “Biomacro-molecules”.



Schematic presentation of the new magnetic vectors: PDMAEMA arms attached to a crystalline iron oxide core stretch in all directions. The nanoparticle thus assumes a star-shaped appearance.

Only five months ago a research team from the University of Bayreuth reported a discovery that was internationally acknowledged. The scientists led by Prof. Dr. Ruth Freitag (Process Biotechnology) and Prof. Dr. Axel Müller (Macromolecular Chemistry II) developed large star-shaped polymers that are promising vectors in genetic engineering. Most importantly, the new polymers were capable of introducing genes into a large variety of living cells, including non-dividing and differentiated cells, i.e. cells that up to now typically require viruses for efficient genetic modification. In chemical terms, these molecules can be described as PDMAEMA stars.

Now the Bayreuth team reports a related discovery in the current online edition of “Biomacromolecules”. As the team specifies, similar PDMAEMA stars can be constructed with a magnetic core and then combine the ability for efficient transfection with the potential for easy separation of the transfected from the non-transfected cells. This research success stems from an intensive interdisciplinary co-operation of long standing. The magnetic PDMAEMA stars were produced in the Bayreuth



The fluorescence microscope makes the high transfection efficiency of magnetic nanoparticles visible. DNA molecules were introduced into cells of a cell line originating from Chinese hamster ovaries: either with PEI, the current standard vector (above), or with the magnetic PDMAEMA stars (below). Successfully transfected cells appear in green, cells that were not transfected in blue.

polymer chemistry laboratories. Tests in the Biotechnology group then demonstrated that the novel agents may very well constitute ’premium vectors’ for the genetic modification of cells.

Biotechnological advantages: high transfection efficiency, quick and simple isolation of transfected cells

Like the PDMAEMA stars previously tested, the magnetic PDMAEMA stars are also capable of efficiently introducing

genetic information, i.e. DNA molecules, into living cells, a process called transfection. “When we transfected cells of a cell line originating from the Chinese hamster (CHO cells), we consistently observed transfection efficiencies that largely exceed those we previously obtained using poly(ethylenimine) (PEI)” explains Prof. Dr. Ruth Freitag. Linear PEI has until now been regarded as the “gold standard” in cell transfection and is therefore used in genetic engineering processes worldwide.

The new vectors have another advantage in addition to their unusual efficiency. The PDMAEMA stars retain their magnetic properties when they are within the cells. For this reason, the transfected cells can be separated from all other cells in a very simple manner: a standard strong magnet is sufficient to extract specifically the cells that have taken up the DNA from those that have not. This makes the magnetic PDMAEMA stars the ideal tool to extract successfully transfected cells from the general transfection pool, and thereby prepare in pure form, a genetically modified cell population, be it to introduce a new gene, compensate for a missing gene, to substitute a defect genes or to ameliorate the consequences of such aberrations.

Star-shaped giant molecules containing a magnetic core, syn-thesis using modern polymer chemistry techniques

How are the magnetic PDMAEMA stars produced? Spherical nanoparticles are the starting point of this process. They belong to the class of iron oxides and have magnetic qualities. Due to their particular crystalline structure, they are called “maghemite“ or “gamma-Fe_2O_3“. Initiator molecules are attached to the surface of such a particle, forming the starting points for the star-shaped structure. Each initiator starts the polymerisation of a long PDMAEMA chain, an “arm”. This process (called “grafting

from“) makes the spherical nanoparticle the centre of a large star-shaped molecule.

The chemical formula of this molecule represents this structure by means of the “at” symbol used in email addresses. It is “γ-Fe_2O_3@$(PDMAEMA_{590})_{46}$“ and means: onto a crystalline iron oxide core comprised of gamma-Fe_2O_3 are attached arms of “PDMAEMA“; this abbreviation stands for “poly(2-(dimethyl-amino)ethyl methacrylate)“. When it is finished, the star-shaped molecule has on average 46 of these chain-like arms. Each arm contains nearly 600 repeating molecule groups.

Patent registration

On account of the high application potential for the life sciences, the magnetic PDMAEMA stars have been registered as a patent in the name of the University of Bayreuth by the Bavarian Patent Alliance (BayPAT, the central patent and marketing agency of the Bavarian universities). The Innovation Advisory Service of Bayreuth University, in particular Dr. Andreas Kokott und Dr. Heinz-Walter Ludwigs, made a major contribution to the preparation for the patent registration.

Publication:

Alexander P. Majewski, Anja Schallon, Valérie Jérôme, Ruth Freitag, Axel H. E. Müller, and Holger Schmalz,
Dual-Responsive Magnetic Core-Shell Nanoparticles for Non-Viral Gene Delivery and Cell Separation,
in: Biomacromolecules, Publication Date (Web): Feb 1, 2012
DOI: 10.1021/bm2017756

For suitability of PDMAEMA stars in genetic therapy

see also:
http://www.uni-bayreuth.de/blick-in-die-forschung/31-2011.pdf

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p. 1: Chr. Wißler; free for publication

p. 2 and 3: Department of Process Biotechnology, University of Bayreuth; free for publication when references are included.

Photo and images in high resolution for download:
http://www.uni-bayreuth.de/presse/images/2012/138