DOI: 10.1002/ange.200804429

Photoinduced Drug Release

Magnetically Guided Titania Nanotubes for Site-Selective Photocatalysis and Drug Release**

*Nabeen K. Shrestha, Jan M. Macak, Felix Schmidt-Stein, Robert Hahn, Claudia T. Mierke, Ben Fabry, and Patrik Schmuki**

The nanoscale encapsulation of ferromagnetic structures has received a great deal of attention because of the exciting possibilities to use these materials in various applications that range from novel electromagnetic[1] to biomedical devices.[2,3] For example, nanoscale magnetic entities could be transported and concentrated at pretargeted locations or organs within the human body by means of an external magnetic field in order to exert a specific function with high local and temporal precision. Therefore, functionalized magnetic nanodots, nanowires, or nanotubes have a high potential for in vivo applications such as magnetic resonance imaging[4,5] or site-selective drug delivery systems,[2,3] if the magnetic property is combined with an appropriate drug loading and release mechanism.

TiO_2 nanotubes are a highly promising encapsulating material for a magnetic core as a high degree of biocompatibility[6] can be combined with a broad range of other functionalities. Since the pioneering work of Fujishima and Honda in 1971,[7] it has been established that TiO_2 is a highly active photocatalyst; this is based on the ability of TiO_2 to produce electron–hole pairs upon light irradiation and thereby create highly reactive radical species.[8–13] This property of TiO_2 has been intensively explored in the form of photoelectrodes for the decomposition of various organic pollutants in water[14–16] and air,[17–19] and it has been used in self-cleaning,[20–22] disinfecting,[23,24] and anticancer[24,25] materials. The photocatalytic ability of TiO_2 can be enhanced by using nanosized TiO_2 materials because of their large specific surface area. Herein, we describe a simple way of embedding magnetic properties into TiO_2 nanotubes and demonstrate their different site-selective photocatalytic applications. Not only can these tubes be used as a magnetically guided photocatalyst for the decomposition of organic matter but also the photocatalytic mechanism can be exploited to release an active species (a model drug). Among the various synthetic routes used to prepare TiO_2 nanotubes,[26–28] anodization approaches have gained significant attention[29,30] as they lead to highly ordered nanotubular arrangements. During the past few years, our research group has contributed several generations of anodically grown self-organized TiO_2 nanotube layers by anodization of Ti in aqueous[31–33] and organic electrolytes.[34–37]

In our approach, we use nanotube layers (Figure 1 a) that were produced in ethylene glycol/NH_4F electrolytes[36–38] (see Section S1 and Figure S1 in the Supporting Information). These TiO_2 nanotubes were filled with magnetic nanoparticles by sucking a droplet of ferrofluid placed on the top of the nanotube layer using a permanent magnet (see the Supporting Information). Figure 1 b shows top- and side-view SEM images of the nanotubes that are loaded with the magnetic nanoparticles. It is clear from these images that the majority of the inside tube walls were coated relatively uniformly with the magnetic particles leaving a hollow space inside the tubes. In contrast to other established but time-consuming and

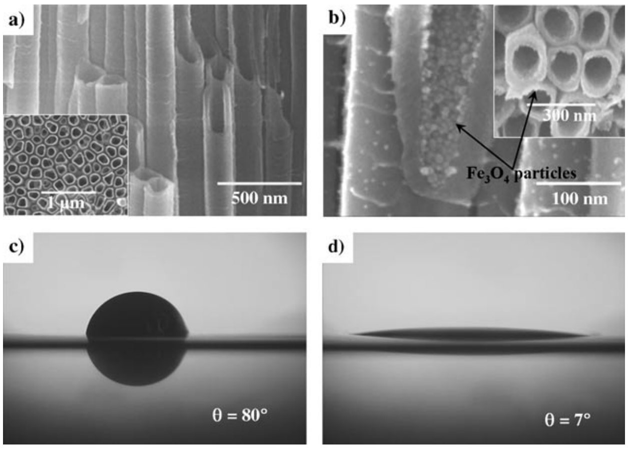


Figure 1. SEM side view of the TiO_2 nanotubes a) before and b) after loading with the magnetic particles. The insets show the top view of the corresponding samples. Optical images of nanotube layers coated with octadecylophosphonic acid to make surface hydrophobic c) after dropping the ferrofluid and d) the same sample shown in (c) after exposure to a magnetic field from underneath the sample.

---

[*] Dr. N. K. Shrestha, Dr. J. M. Macak, F. Schmidt-Stein, R. Hahn, Prof. Dr. P. Schmuki
Department of Material Science WW-4, LKO
University of Erlangen-Nuremberg
Martensstrasse 7, 91058 Erlangen (Germany)
E-mail: schmuki@ww.uni-erlangen.de

Dr. C. T. Mierke, Dr. B. Fabry
Center for Medical Physics and Technology
Department of Physics, University of Erlangen-Nuremberg
Henkestrasse 91, 91052 Erlangen (Germany)

[**] We would like to acknowledge financial support from the Alexander von Humboldt Foundation (for N.K.S.), the German Science Foundation (DFG), and in particular the Cluster of Excellence "Engineering of Advanced Materials" at the University of Erlangen-Nuremberg. S. Berger is acknowledged for his invaluable help with experiments. Prof. Dr. R. Fink, Dr. K. Petukhov, Dr. M. Kalbacova, U. Marten-Jahns, and Hans Rollig are also acknowledged for providing the magnetic particles, help with the magnetic measurements, cell measurements, XRD measurements, and technical help, respectively.

All experimental details and characterization are provided in the Supporting Information for this article, which is available on the WWW under http://dx.doi.org/10.1002/anie.200804429.

expensive techniques to incorporate ferromagnetic structures inside nanotubes, including chemical vapor deposition,[39] ion-beam sputtering,[40] and the arc-discharge reaction,[41] this simple approach that uses a permanent magnet allows an effective and quick filling of the nanotubes.

Figure 1 c,d shows an optical image sequence of droplets of the magnetic suspension (10 μL) on the nanotube layer. Without applying a magnetic field, the liquid wetted the surface with a contact angle of approximately 10° (see Figure S2a in the Supporting Information), which reflects the surface's hydrophilic and oleophilic nature.[42,43] In this case, the magnetic particles can enter the tubes only because of capillary forces, and only a small fraction of the nanotubes can successfully be filled. However, when a magnetic force is applied by a magnet placed underneath the samples, the entire volume of the magnetite suspension can enter the nanotubes within a fraction of a second (see Figure S2b in the Supporting Information) and the contact angle thus becomes virtually zero. It is particularly noteworthy that this magnetically assisted tube filling even works very well with tubes that are made hydrophobic by coating them with a monolayer of octadecylphosphonic acid.[43] In this case, the contact angles on such nanotube surfaces without (Figure 1 c) and with an external magnetic field (Figure 1 d) were approximately 80° and 7°, respectively. This result shows that, if desired, the nanotube layers can be modified with virtually any organic functionality and thereafter "magnetic filling" is still possible.

Magnetic measurements carried out with loaded tubes also confirmed that they exhibit ferromagnetism at 5 K and paramagnetism at 300 K (see Figure S3 in the Supporting Information). As the tubes were annealed at 420 °C for 3 hours to remove the residual organic component from the ferrofluid, the crystalline structure of the tubes was also altered to an anatase structure, as shown by the XRD results (see Figure S4 in the Supporting Information). An anatase structure of TiO_2 is desirable as it represents the most active crystal form for photocatalytic efficiency. Furthermore, the XRD results show that the same crystalline structure of the magnetic particles was observed before and after annealing, which suggests that no oxidation of the loaded magnetic particles occurred and, thus, the magnetic property of the particles remained unchanged after annealing. Additionally, we also performed energy dispersive X-ray analysis (EDS) to confirm the presence of magnetic particles inside the tubes (see Figure S5 in the Supporting Information).

In order to demonstrate the use of these nanotube layers as magnetically guided photocatalysts, that is, to achieve photocatalytic reactions at desired spatial locations, the Fe_3O_4-filled TiO_2 nanotubes were separated by bending the substrate, and photocatalytic experiments were carried out in an Acid Orange 7 (AO7, $C_{16}H_{11}N_2O_4SNa$) dye solution. A set of images of the magnetic TiO_2 nanotubes (0.02 g) placed in the middle of a petri dish before UV light exposure and after UV light exposure for 160 minutes are shown in Figure 2 a and b respectively. After UV light irradiation, a white patch around the nanotube bundles that arises from the photo-induced oxidation of the dye could be seen. To demonstrate the ability of the magnetic nanotubes to act as a movable photocatalyst, we installed a magnet underneath the petri dish, just below the nanotubes (Figure 2 b), and moved it along one direction. After this guided movement, the white patch on the original reaction was even more easily visible (Figure 2 c, d, a movie of the nanotube movement is shown in Figure S6 in the Supporting Information). It should be noted that no significant photocatalytic degradation of the organic dye other than in the vicinity of the nanotube bundles was observed.

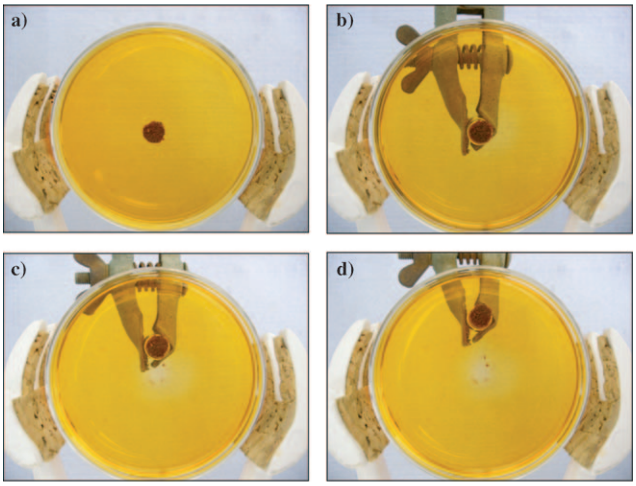


Figure 2. Magnetically guided photocatalytic activity of Fe_3O_4 particles loaded into TiO_2 nanotubes, as demonstrated by a photocatalytic degradation sequence of Acid Orange 7 by magnetic TiO_2 nanotubes in aqueous agar solution. Images are shown a) before, b) after illumination with UV light for 160 min, and c), d) after moving the nanotube bundles at increments of 1 cm on each step guided by a permanent magnet.

The photocatalytic effect can be exploited to release highly defined molecular entities (for example drugs) from the nanotubes. To demonstrate this effect, magnetic nanotubes were prepared and separated from the substrate, then a violet-blue (402 nm) fluorescent marker, a model drug that can be activated with UV light, was attached to the TiO_2 nanotubes by using a silane coupling agent as a cross-linker. The release concept is based on the fact that the UV-induced hole generation in the valence band of the TiO_2 will lead to chain-scission of a monolayer attached to TiO_2. As outlined in Figure 3 a, the cleavage takes place at the anchoring siloxane groups,[42] which causes the release of the model drug (the fluorescent molecule in the present study). Figure 3 c–g shows that when the dye-functionalized nanotubes (surrounded by water) were irradiated with a UV laser, the expected violet-blue fluorescence from the marker could be observed. After few seconds of irradiation with UV light, the release of the fluorescent marker into the electrolyte was clearly visible. This result not only provides proof of the release principle, but also provides evidence that chain-scission indeed occurs much faster than photoinduced degradation of the fluorescence marker, that is, the fluorescence marker escapes the range of the photogenerated radicals before they can destroy the active molecule. The ability to guide the system was again confirmed by moving a permanent magnet placed underneath the petri dish. As shown in Figure 3 c–g (see also the movie in Figure S7 in the Supporting Information), the nanotubes

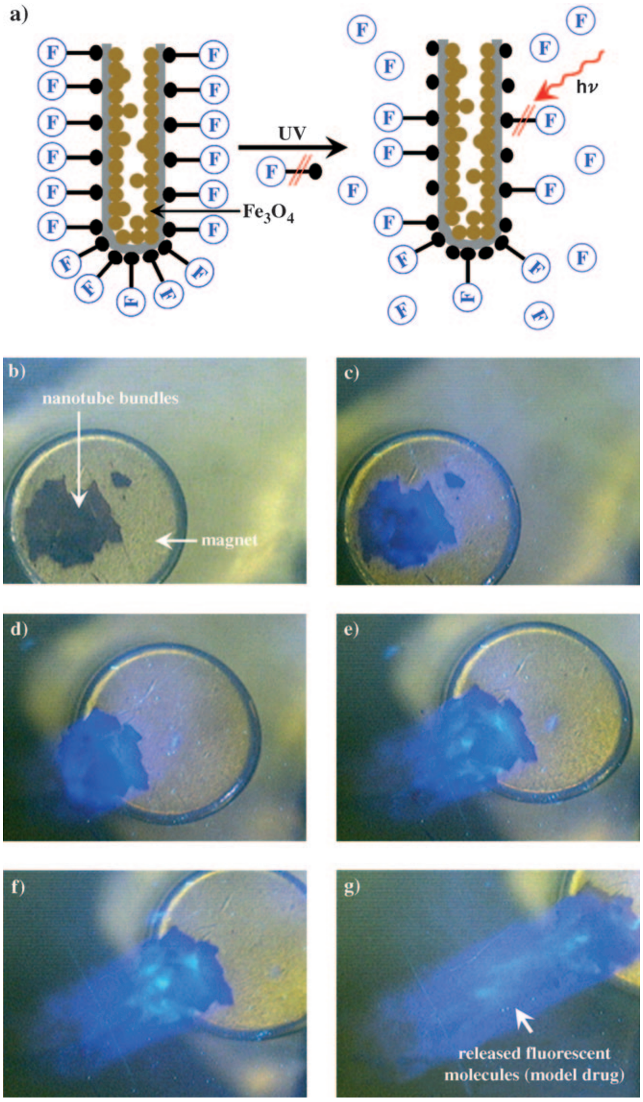


Figure 3. a) Diagram showing the release principle of active molecules (model drug) from the functionalized magnetic TiO_2 nanotubes upon irradiation with UV light. A fluorescent dye (active molecule) was attached to the TiO_2 nanotubes with a siloxane linker. b)–g) Sequence of images showing the release of the fluorescent dye into the surrounding system by the dye-functionalized magnetic TiO_2 nanotubes. The UV light was "off" in (b) and was "on" in (c)–(g). The movement of the tube layers in water was guided by a permanent magnet underneath the petri dish.

followed the magnet and continuously released the fluorescent dye as long as UV light irradiation was continued. In a similar experiment, the nanotubes were repeatedly washed with water and reilluminated in fresh water with the UV laser. In all the repetition cycles, the nanotubes continued to fluoresce and showed a fluorescence track as shown in Figure 3. When illumination was stopped, release of the fluorescence was also terminated. The results were further confirmed by additional release kinetics studies by using fluorescence microscopy (see Section S5 and Figure S8 in the Supporting Information). Overall, the results show that a highly temporally and spatially controlled photoinduced drug release can be realized by using the principle presented here.

It should be pointed out that this release approach is almost unique to TiO_2, as its bond-breaking ability for attached linker molecules occurs because of the relative position of the TiO_2 valence band relative to the water redox levels.

The photocatalytic activity of the magnetic TiO_2 nanotubes may additionally be directly exploited to kill unwanted cells in the human body. An example of the photoinduced killing of cancer cells by using the TiO_2 nanotubes is shown in Figure 4 (for details, see Section S6 and Figure S9 in the Supporting Information and Ref. [44]). In view of in vivo biomedical applications, it should be pointed out that super-band-gap excitation of TiO_2 to stimulate photocatalytic activity can be achieved not only by UV light but also by X-ray sources,[45,46] thus opening up possibilities for a non-invasive therapy in the living body.

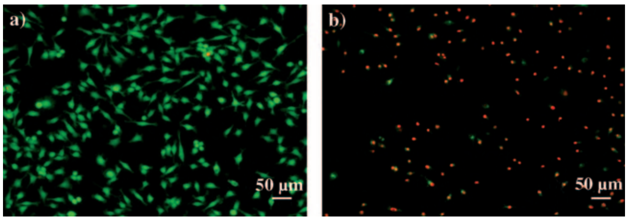


Figure 4. Fluorescence microscopy images demonstrating UV-induced cancer cell killing by using HeLa tumor cells cultured on TiO_2 nanotube layers. The image shows cells a) without and b) after UV light irradiation. Live cells were detected with calcein (green) and dead cells were detected with EthD-1 (red).

In summary, we have presented a simple approach to the fabrication of magnetic TiO_2 nanotubes that can be magnetically guided in three dimensions. We have shown two key applications of these magnetic nanotubes: 1) as a photocatalyst for the photooxidative decomposition of organic species (such as cancer cells) at selected locations and 2) for site-specific photoinduced release of active molecules such as drugs.

Received: September 8, 2008

Keywords: drug delivery · magnetic properties · nanostructures · photocatalysis · photooxidation

---

[1] N. Grobert, W. K. Hsu, Y. Q. Zhu, J. P. Hare, H. W. Kroto, D. R. M. Walton, *Appl. Phys. Lett.* **1999**, *75*, 3363 – 3365.
[2] S. J. Son, J. Reichel, B. He, M. Schuchman, S. B. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 7316 – 7317.
[3] I. Mönch, A. Meye, A. Leonhardt, K. Krämer, R. Kozhuharova, T. Gemming, M. P. Wirth, B. Büchner, *J. Magn. Magn. Mater.* **2005**, *290–291*, 276 – 278.
[4] A. K. Gupta, M. Gupta, *Biomaterials* **2005**, *26*, 3995 – 4021.
[5] A. F. Thünemann, D. Schutt, L. Kaufner, U. Pison, H. Möhwald, *Langmuir* **2006**, *22*, 2351 – 2357.
[6] J. Park, S. Bauer, K. von der Mark, P. Schmuki, *Nano Lett.* **2007**, *7*, 1686 – 1691.
[7] A. Fujishima, K. Honda, *Nature* **1972**, *238*, 37 – 38.
[8] B. O'Regan, M. Grätzel, *Nature* **1991**, *353*, 737 – 740.

[9] M. Grätzel, *Nature* **2001**, *414*, 338 – 344.

[10] K. Hara, H. Sugihara, Y. Tachibana, A. Islam, M Yanagida, K. Sayama, H. Arakawa, G. Fujihashi, T. Horiguchi, T. Kinoshita, *Langmuir* **2001**, *17*, 5992 – 5999.

[11] J. M. Macak, H. Tsuchiya, A. Ghicov, P. Schmuki, *Electrochem. Commun.* **2005**, *7*, 1133 – 1137.

[12] A. Ghicov, J. M. Macak, H. Tsuchiya, J. Kunze, V. Haeublein, L. Frey, P. Schmuki, *Nano Lett.* **2006**, *6*, 1080 – 1082.

[13] Y. Kondo, H. Yoshikawa, K. Awaga, M. Murayama, T. Mori, K. Sunada, S. Bandow, S. Iijima, *Langmuir* **2008**, *24*, 547 – 550.

[14] A. Fernández, G. Lassaletta, V. M. Jiménez, A. Justo, A. R. González-Elipe, J.-M. Herrmann, H. Tahiri, Y. Ait-Ichou, *Appl. Catal. B* **1995**, *7*, 49 – 63.

[15] M. Muneer, H. K. Singh, D. Bahnemann, *Chemosphere* **2002**, *49*, 193 – 203.

[16] M. Makita, A. Harata, *Chem. Eng. Process.* **2008**, *47*, 859 – 863.

[17] I. Sopyan, M. Watanabe, S. Murasawa, K. Hashimoto, A. Fujishima, *J. Photochem. Photobiol. A* **1996**, *98*, 79 – 86.

[18] O. d'Hennezel, P. Pichat, D. F. Ollis, *J. Photochem. Photobiol. A* **1998**, *118*, 197 – 204.

[19] H. Ichiura, T. Kitaoka, H. Tanaka, *Chemosphere* **2003**, *50*, 79 – 83.

[20] R. Wang, K. Hashimoto, A. Fujishima, M. Chikuni, E. Kojima, A. Kitamura, M. Shimohigoshi, T. Watanabe, *Nature* **1997**, *388*, 431 – 432.

[21] R. Wang, K. Hashimoto, A. Fujishima, M. Chikuni, E. Kojima, A. Kitamura, M. Shimohigoshi, T. Watanabe, *Adv. Mater.* **1998**, *10*, 135 – 138.

[22] T. Yuranova, D. Laub, J. Kiwi, *Catal. Today* **2007**, *122*, 109 – 117.

[23] P. Evans, D. W. Sheel, *Surf. Coat. Technol.* **2007**, *201*, 9319 – 9324.

[24] D. M. Blake, P. C. Maness, Z. Huang, E. J. Wolfrum, J. Huang, *Sep. Purif. Methods* **1999**, *28*, 1 – 50.

[25] A. Fujishima, T. N. Rao, D. A. Tryk, *J. Photochem. Photobiol. C* **2000**, *1*, 1 – 21.

[26] A. Michailowski, D. AlMawlawi, G. Cheng, M. Moskovitz, *Chem. Phys. Lett.* **2001**, *349*, 1 – 5.

[27] T. Kasuga, M. Hiramatsu, A. Hoson, T. Sekino, K. Niihara, *Langmuir* **1998**, *14*, 3160 – 3163.

[28] M. S. Sander, M. J. Côté, W. Gu, B. M. Kile, C. P. Trip, *Adv. Mater.* **2004**, *16*, 2052 – 2057.

[29] V. Zwilling, E. Darque-Ceretti, A. Boutry-Forveille, D. David, M. Y. Perrin, M. Aucouturier, *Surf. Interface Anal.* **1999**, *27*, 629 – 637.

[30] J. M. Macák, H. Tsuchiya, A. Ghicov, K. Yasuda, R. Hahn, S. Bauer, P. Schmuki, *Curr. Opin. Solid Sate Mater. Sci.* **2007**, *11*, 3 – 18.

[31] R. Beranek, H. Hildebrand, P. Schmuki, *Electrochem. Solid-State Lett.* **2003**, *6*, B12 – B14.

[32] J. M. Macák, H. Tsuchiya, P. Schmuki, *Angew. Chem.* **2005**, *117*, 2136 – 2139; *Angew. Chem. Int. Ed.* **2005**, *44*, 2100 – 2102.

[33] A. Ghicov, H. Tsuchiya, J. M. Macak, P. Schmuki, *Electrochem. Commun.* **2005**, *7*, 505 – 509.

[34] J. M. Macak, H. Tsuchiya, L. Taveira, S. Aldabergerova, P. Schmuki, *Angew. Chem.* **2005**, *117*, 7629 – 7632; *Angew. Chem. Int. Ed.* **2005**, *44*, 7463 – 7465.

[35] H. Tsuchiya, J. M. Macak, L. Taveira, E. Balaur, A. Ghicov, K. Sirotna, P. Schmuki, *Electrochem. Commun.* **2005**, *7*, 576 – 580.

[36] S. P. Albu, A. Ghicov, J. M. Macak, P. Schmuki, *Phys. Status Solidi RRL* **2007**, *1*, R65 – R67.

[37] J. M. Macák, S. P. Albu, P. Schmuki, *Phys. Status Solidi RRL* **2007**, *1*, R181 – R183.

[38] J. M. Macak, P. Schmuki, *Electrochim. Acta* **2006**, *52*, 1258 – 1264.

[39] A. Leonhardt, S. Hampel, C. Müller, I. Mönch, R. Koseva, M. Ritschel, D. Elefant, K. Biedermann, B. Büchner, *Chem. Vap. Deposition* **2006**, *12*, 380 – 387.

[40] T. Hayashi, S. Hirono, M. Tomita, S. Umemura, *Nature* **1996**, *381*, 772 – 774.

[41] R. Lv, F. Kang, W. Wang, J. Wie, X. Zhang, Z. Huang, J. Gu, K. Wang, D. Wu, *Phys. Status Solidi A* **2007**, *204*, 867 – 873.

[42] E. Balaur, J. M. Macak, L. Taviera, H. Tsuchiya, P. Schmuki, *Electrochem. Commun.* **2005**, *7*, 1066 – 1070.

[43] E. Balaur, J. M. Macak, H. Tsuchiya, P. Schmuki, *J. Mater. Chem.* **2005**, *15*, 4488 – 4491.

[44] M. Kalbacova, J. M. Macak, F. Schmidt-Stein, C. T. Mierke, P. Schmuki, *Phys. Status Solidi RRL* **2008**, *2*, 194 – 196.

[45] K. Tamura, Y. Ohko, H. Kawamura, H. Yoshikawa, T. Tatsuma, A. Fujishima, J. Mizuki, *Electrochim. Acta* **2007**, *52*, 6938 – 6942.

[46] F. Schmidt-Stein, N. K. Shrestha, P. Schmuki, unpublished results.

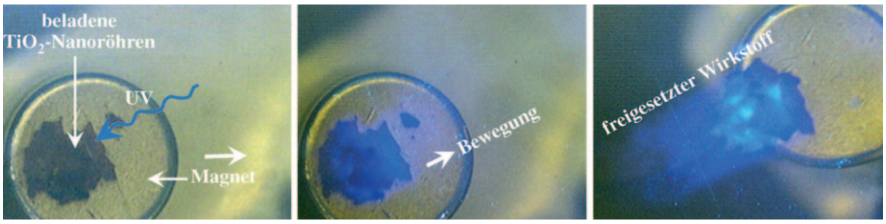
[47] J. M. Macak, S. P. Albu, D. H. Kim, I. Paramasivam, S. Aldabergerova, P. Schmuki, *Electrochem. Solid-State Lett.* **2007**, *10*, K28 – K31.

[48] J. M. Macák, H. Hildebrand, U. Marten-Jahns, P. Schmuki, *J. Electroanal. Chem.* **2008**, *621*, 254 – 266.

Photochemische Wirkstoff-Freisetzung

N. K. Shrestha, J. M. Macak,
F. Schmidt-Stein, R. Hahn, C. T. Mierke,
B. Fabry, P. Schmuki* ——— ■■■■–■■■■

Magnetically Guided Titania Nanotubes for Site-Selective Photocatalysis and Drug Release



Nichts wie raus! Die zeitlich und räumlich gesteuerte Freisetzung von Farb- oder Wirkstoffmolekülen gelingt mithilfe photokatalytisch aktiver TiO_2-Nanoröhren (siehe Bild). Die Bindung zwischen den aktiven Molekülen und den Nanoröhren, die mit magnetischen Fe_3O_4-Nanopartikeln gefüllt sind, wird durch UV-Bestrahlung gespalten. So entweicht die Ladung, bevor photochemisch erzeugte Radikale sie zersetzen können.