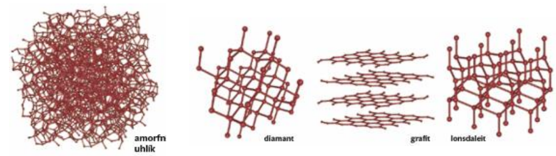
Nanotechnologie uhlíku pro transport léčiv

Kamil Záruba, Tomáš Bříza

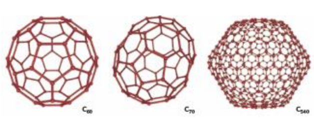
2018

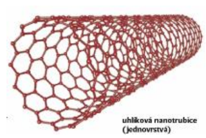
Alotropické modifikace uhlíku

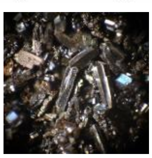


Vesmír, 2011

Allotropické modifikace uhlíku



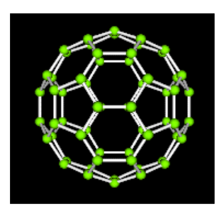



Krystalický fulleren

Vesmír, 2011

1. Fullereny

- fullereny byly nazvány po americkém architektovi Buckminsteru Fullerovi
- nejstabilnější známý fulleren obsahuje 60 atomů uhlíku. Jeho čistá krystalická forma, která je tvrdší než diamant a dostala název **fullerit**



Fullereny - příprava

- elektrický oblouk mezi dvěma uhlíkovými elektrodami

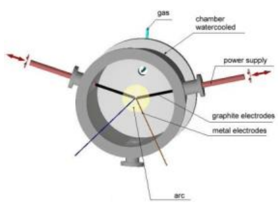


Schéma Krätschmer-Huffmann fullerenového generátoru

Fullereny - příprava

- elektrický oblouk mezi dvěma uhlíkovými elektrodami
- laserové odpařování

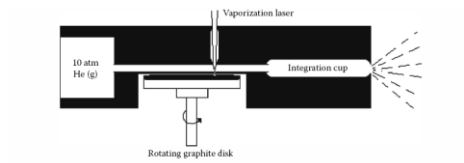
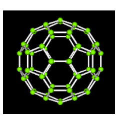
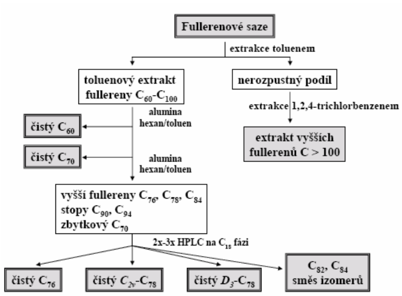


FIGURE 5.2 Original schematic diagram of the pulsed supersonic nozzle used to produce fullerenes. (Adapted from Kroto, H.W. et al., *Nature*, 318(6042), 162, 1985.)

Nanobiomaterials Handbook

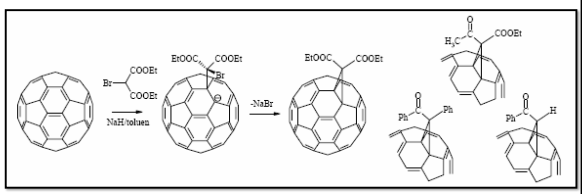
Fullereny - izolace





www.uochb.cas.cz/Zpravy/PostGrad2004/7_Lhotak.pdf

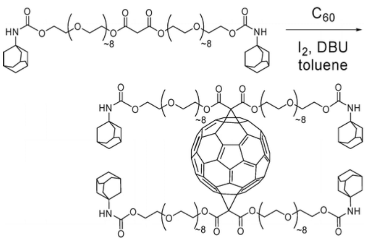
Fullereny - modifikace



www.uochb.cas.cz/Zpravy/PostGrad2004/4_Lhotak.pdf

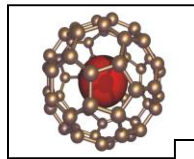
Fullereny - modifikace

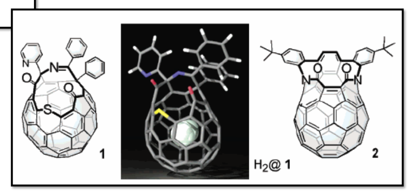
- příprava vodorozpustných fullerenů na bázi glykolu



J. Org. Chem., 2005, 70 (7), pp 2660–2666

Endofullereny

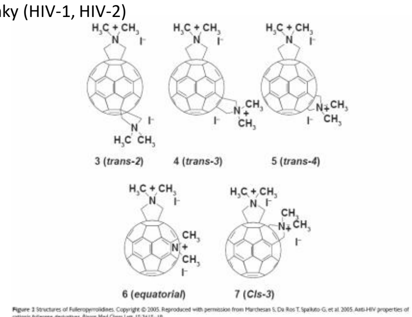




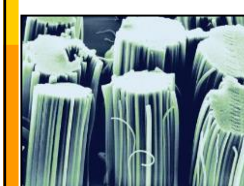
Murata et al. J. AM. CHEM. SOC. 2003, 125, 7152-7153

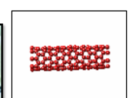
Fullereny

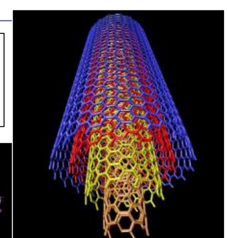
- antivirální účinky (HIV-1, HIV-2)

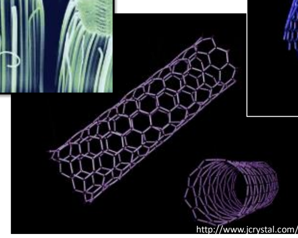


2. Nanotrubice



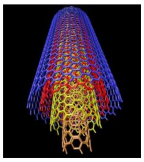


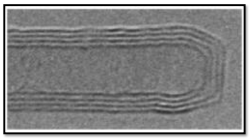


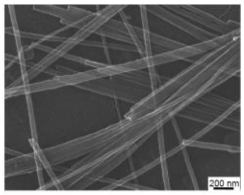


Nanotrubice

- jedno (SW-CNT) a vícestěnné (MW-CNT) nanotrubice

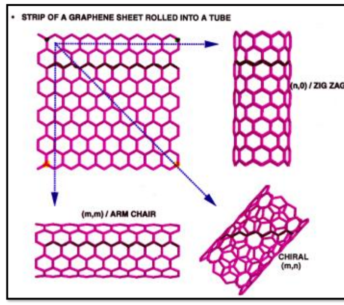


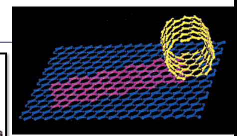


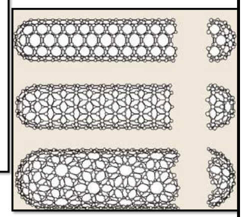


http://idea.library.drexel.edu/bitstream/1860/2797/1/Korneva_Guzeliya.pdf

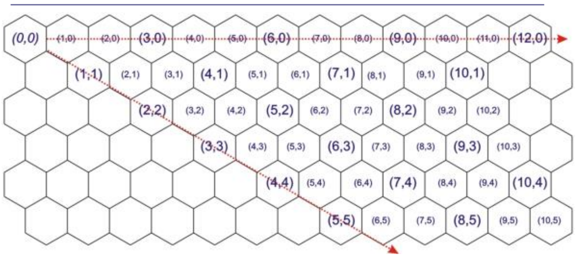
Nanotrubice







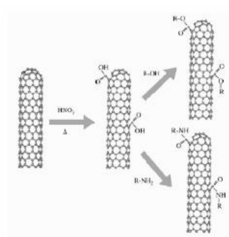
Nanotrubice – elektronická struktura



Různé směry „stočení“ plochy grafenu vedou ke vzniku **CNT s vodivými** (indexy (*n*, *m*) větším písmem) **a polovodivými** ((indexy (*n*, *m*) malým písmem)) **vlastnostmi**. Stočení ve směru obou šipek vede k **achirálním CNT**, stočení ve směru mezi vyznačenými šipkami vede k **chirálním CNT**.

Převzato z ***Carbon Nanotubes***. Smith B. W., Luzzi D. E. v knize *Introduction to Nanoscale Science and Technology*, Di Ventra, M., Evoy, S., Heflin Jr, J. R., Eds.; Springer: New York, **2004**.

Nanotrubice - funkcionalizace



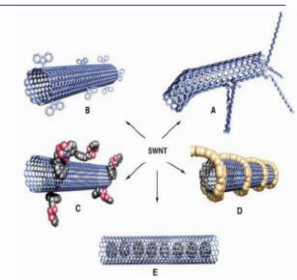
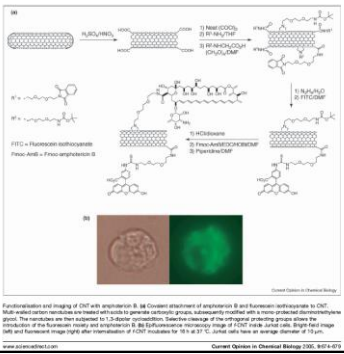


Figure 2.7. Functionalization possibilities for SWNTs: A) defect-group functionalization, B) covalent sidewall functionalization, C) noncovalent functionalization with surfactants, D) noncovalent exohedral functionalization with polymers, and E) endohedral functionalization.[38]

Nanotrubice - funkcionalizace



modifikace Amfotericinem B (antimykotikum)

Nanotrubice

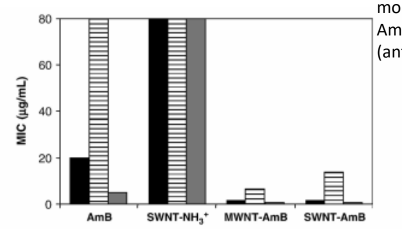
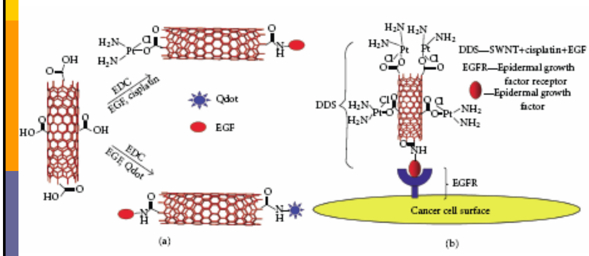


Fig. 5. Antifungal activity of AmB conjugated to carbon nanotubes (CNT 2). The MIC corresponds to the lowest concentration of compound that inhibits visible growth on the pathogens. *Candida parapsilosis* (black bar); *Candida Albicans* (dashed bar); *Cryptococcus neoformans* (grey bar).

modifikace Amfotericinem B (antimykotikum)

Biochimica et Biophysica Acta 1758 (2006) 404 – 412

Nanotrubice



J. Drug Deliv. 2012, doi:10.1155/2012/837327

Nanotrubice

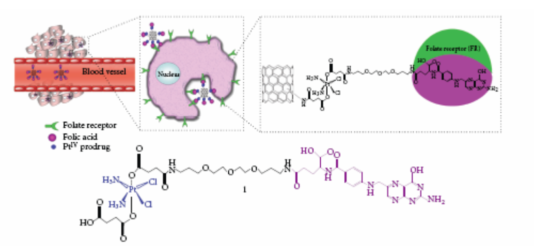


FIGURE 5: The "longboat" anticancer system in which the chemotherapeutic agent cisplatin is attached from one end to the FA derivative and from the opposite end to a SWNT via an amide link [20].

J. Drug Deliv. 2012, doi:10.1155/2012/837327

Nanotrubice

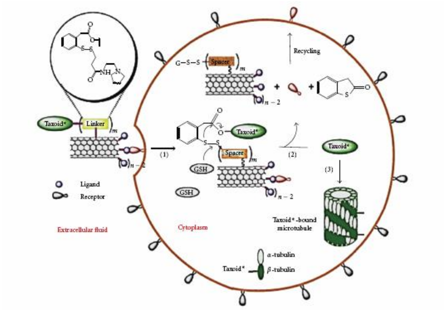


FIGURE 6: (1) Internalization of the CNTs carried conjugate into the tumour cell via receptor-mediated endocytosis. (2) Taxoid was released by the cleavage of the chemical linker. (3) The free taxoid molecules were bound to microtubules to form stabilized microtubules, resulting in arrest of cell mitosis and induction of apoptosis [31].

J. Drug Deliv. 2012, doi:10.1155/2012/837327

Nanotrubice

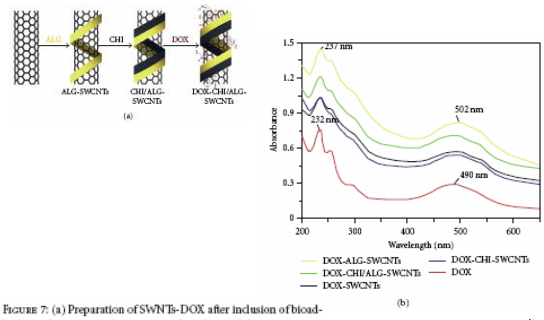
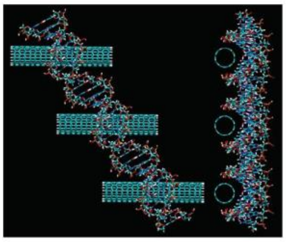


FIGURE 7: (a) Preparation of SWNTs-DOX after inclusion of bioadhesive polymers to enhance nanotubes dispersability in aqueous phase. (b) UV absorption spectra of DOX formulations [32].

J. Drug Deliv. 2012, doi:10.1155/2012/8373271

Biologické aplikace: DNA sequencing

- nanotrubice odpovídají velikostí velkému žlábku DNA
- páry bází různě ovlivňují velikost proudu protékajícího nanotrubicí po vložení určitého potenciálu
- použití různých nanotrubic by umožnilo rychlé paralelní sekvenování DNA

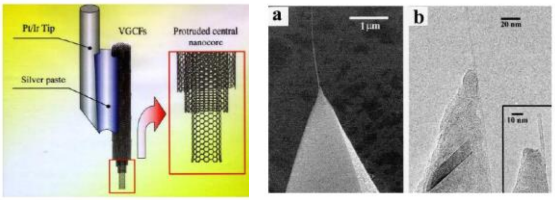


Pohled shora a ze strany na supra-molekulární komplex DNA s nanotrubicemi

Biologické aplikace: Sondy AFM

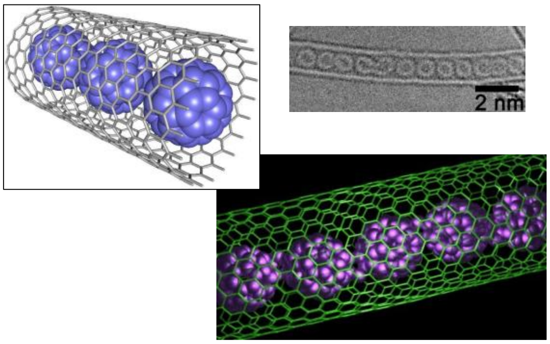
Nanotrubice jako hroty (vzorkovací sondy) AFM:

1. malý průměr – maximální rozlišení
2. vynikající chemická a mechanická odolnost

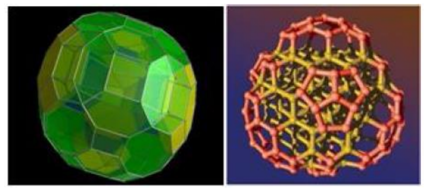


rozlišení až ca 12 nm

3. Nanolusky



4. Nanodiamanty (ND)



ND - velikost

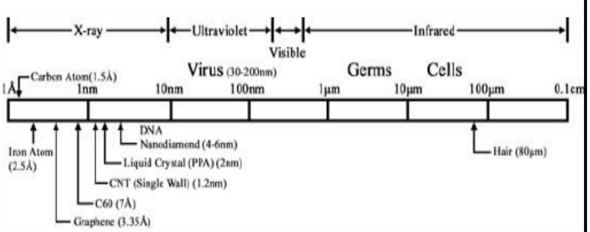


Fig 8: The relative scale of ND compared to microbes and cells.

ND – srovnání vlastností s jinými materiály

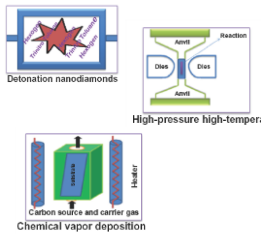
Properties	CVD diamond	Titanium	Stainless steel
Hardness(kg/ mm^2)	10,000	230	210
Young's modulus(GPa)	1000	120.2	215.3
Bulk modulus(GPa)	442	108.6	166
Thermal conductivity(watts/cm *C)	20	0.21	0.16
Thermal expansion(×1 0-8 K-1)	1.1	1.8	17.2

S. Kazi, *Int. J. Pharm. Sci. Inv.* 2014, 3, 40-45

Nanodiamanty – příprava

- detonační nanodiamanty
- laserová ablace
- vysokoenergetické mletí
- deposice chemických par
- superkritické tekutiny
- ...

- výtěžky až 90 %



R. Kaur, I. Badea, *Int. J. Nanomed* 2013, *8*, 203-220

ND – příprava

- vysoká teplota a tlak
  => např. řízená detonace

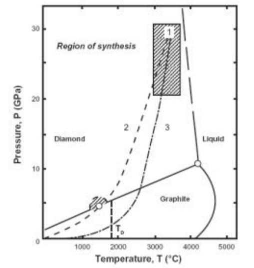
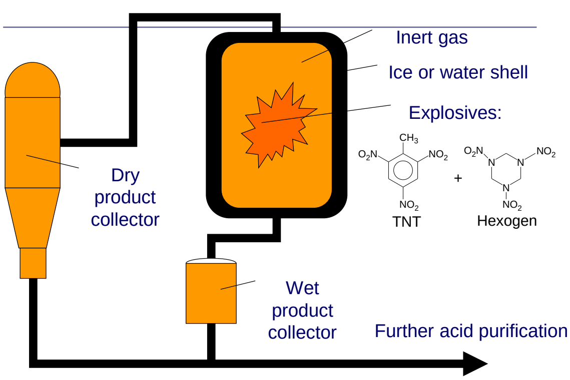


Figure 3 Phase diagram for carbon depicting the pressure and temperature requirements for synthesis of detonation nanodiamond (1); cooling profile of products produced by wet detonation synthesis (2) and dry detonation synthesis (3).[29]
Notes: "T_D" represents Debye temperature.
Reproduced courtesy of IOP Publishing Ltd, from: Baidakova M, Vul A. New prospects and frontiers of nanodiamond clusters. *J Phys D Appl Phys.* 2007;40(20):6300–6311.

Detonační ND



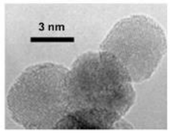
Vliv parametrů detonace na kvalitu ND

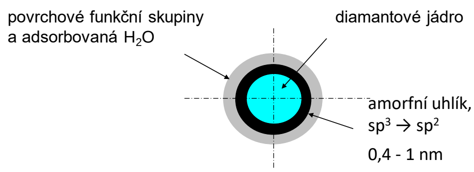
Růst teploty, tlaku, doby reakce a obsahu uhlíku

Fractal aggregates of monocrystalls	Porous polycrystalls	Polycrystalls
Single point binding	Multi point binding	Full binding
Nanoseconds	Microseconds	Milliseconds

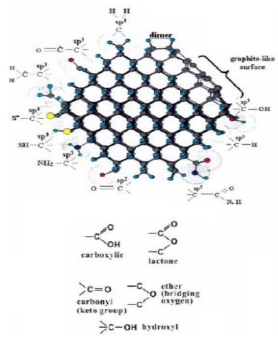
Struktura částice ND

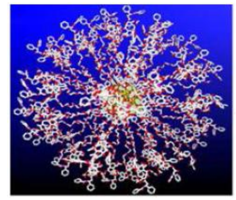
- sférické částice, *d* = 2-8 nm
- jádro sp^3
- povrchová vrstva $sp^3 \rightarrow sp^2$, amorfní uhlík

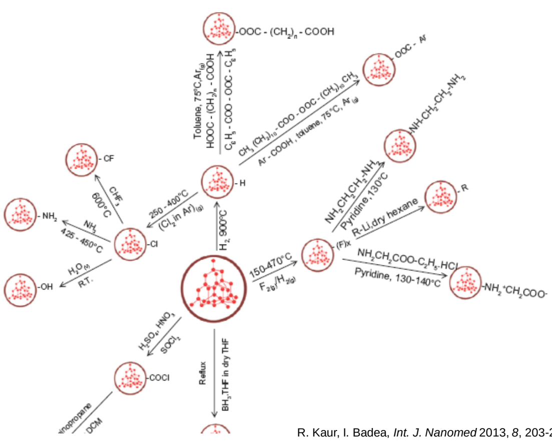




ND – modifikace

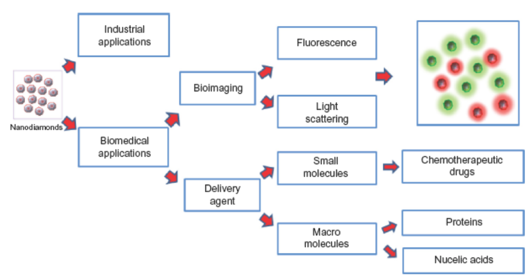






R. Kaur, I. Badea, *Int. J. Nanomed* 2013, *8*, 203-220

ND – aplikace



R. Kaur, I. Badea, *Int. J. Nanomed* 2013, *8*, 203-220

ND s léčivy

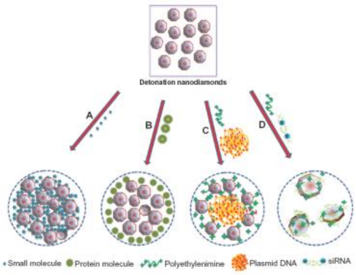
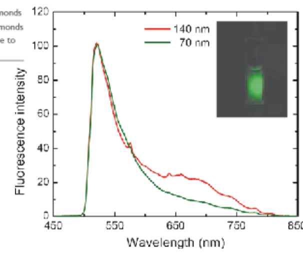


Figure 7 A schematic diagram representing the binding of detonation nanodiamonds with (**A**) small molecules,[72,73] (**B**) proteins,[72] (**C**) plasmid DNA,[46,109] and (**D**) siRNA.[110]
©2012 Dove Medical Press. Adapted with permission from Kaur R, Chitanda JM, Michel D, et al. Lysine-functionalized nanodiamonds: synthesis, physiochemical characterization, and nucleic acid binding studies. *Int J Nanomedicine*. 2012;7:3851–3866.

Nanodiamanty – fluorofory

Table 1 Highlights of the unique fluorescence properties of nanodiamonds

Property	Advantage
High quantum efficiency	Bright fluorescence
Photostability over longer periods	Long-term tracking of nanodiamonds in cells
Emission wavelength > 690 nm	High-contrast imaging of nanodiamonds
Longer fluorescence lifetime	High-contrast imaging of nanodiamonds
Deeper location of nitrogen vacancy centers	No alteration in fluorescence due to surface modification



Nanodiamanty – fluorofory

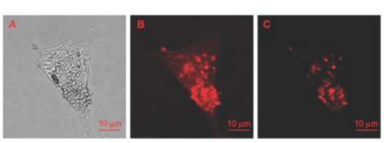


Figure 9 Images of a single HeLa cell treated with ND-transferrin complex: (**A**) bright-field image, (**B**) confocal scanning image obtained by collecting all the fluorescence emissions above a wavelength of 550 nm, and (**C**) confocal scanning image obtained by collecting only the fluorescence emissions at wavelengths of 663–738 nm.
Note: A 514.5 nm laser was used as excitation source.
Reprinted from: Weng MF, Chiang SY, Wang NS, Niu H. Fluorescent nanodiamonds for specifically targeted bioimaging: application to the interaction of transferrin with transferrin receptor. *Diam Relat Mater*. 2009;18(2–3):587–591.[128] Copyright (2008), with permission from Elsevier.

Nanodiamanty – fluorofory

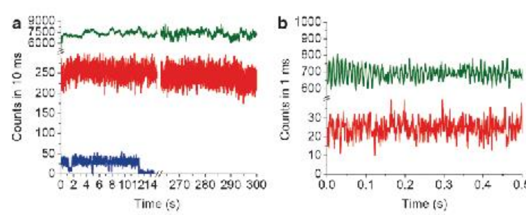


Fig. 6.9 Spectroscopic characterization of 35-nm and 140-nm rFNDs. (a) Typical time traces of the fluorescence from a single 140-nm rFND (*green*), a single 35-nm rFND (*red*), and a single Alexa Fluor 546 dye molecule attached to a single dsDNA molecule (*blue*). (b) Time traces of the fluorescence from a single 140-nm rFND (*green*) and a single 35-nm rFND (*red*) acquired with a time resolution of 1 ms, showing no photoblinking behavior. (c) Plot of the fluorescence

Nanodiamanty – fluorofory

- monitoring pohybu jediné nanočástice

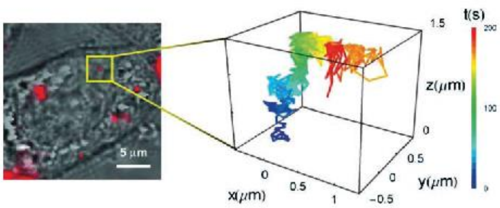


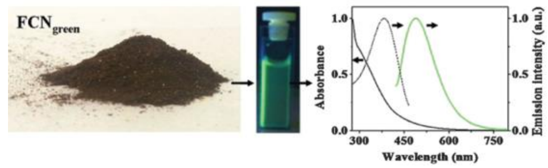
Fig. 6.14 Three-dimensional tracking of a single 35-nm rFND in a live cell. Overlay of bright-field and epifluorescence images (*left*) shows the existence of 35-nm rFNDs in the cytoplasm of a live HeLa cell. The fluorescence intensity is sufficiently high and stable to allow tracking of a single rFND in three dimensions over a time span of 200 s (*right*). Adapted from [22]

Jiné fluorescenční nanočástice

- uhlíkaté nanočástice

Table 1 Properties of fluorescent carbon nanoparticles (FCNPs) with blue, green, yellow and red emission; containing between 10 and 33% oxygen and 1 to 8% of nitrogen. From ref. 75

FCNP	Molecular mass or particle size	Composition (C:H:N:O; in %)	Emission peak and (excitation) wavelength	Molar absorbance at excitation wavelength	Quantum yield (%)
$FCNP_{blue}$	400–2200 Da	65:6:8:21	440 nm (370 nm)	$\sim 2 \times 10^3$	6–30
$FCNP_{green}$	2500–14 000 Da, 2–4 nm	75:10:5:10	500 nm (400 nm)	$\sim 5 \times 10^4$	14
$FCNP_{yellow}$	1–4 nm	50:15:2:33	560 nm (425 nm)	$\sim 4 \times 10^3$	12
$FCNP_{red}$	~4–10 nm	70:5:1:24	600 nm (385 nm)	$\sim 7 \times 10^5$	7



Wolfbeis O. S., *Chem. Soc. Rev.*, 2015, 44, 4743

- od příštího týdne přednáší prof. Švorčík