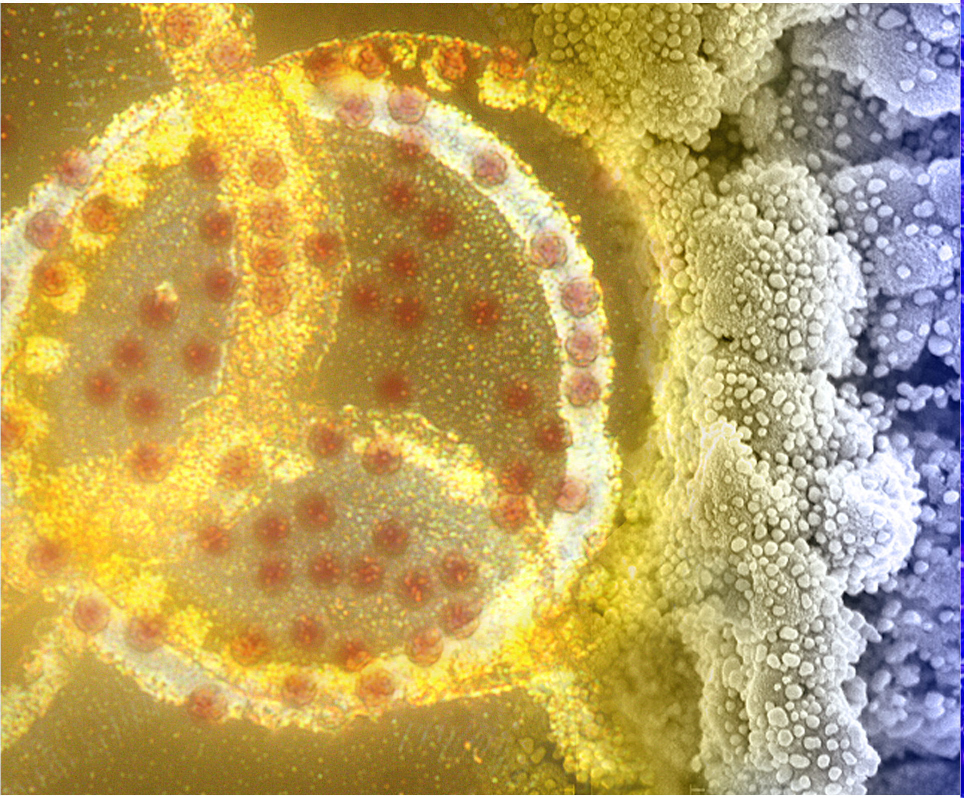
# Плазмонные структуры для биомедицинской диагностики



Е.А.Гудилин, А.А.Семенова, Н.А.Браже, Г.В.Максимов

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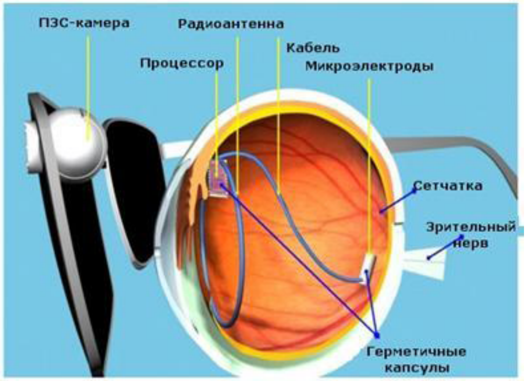
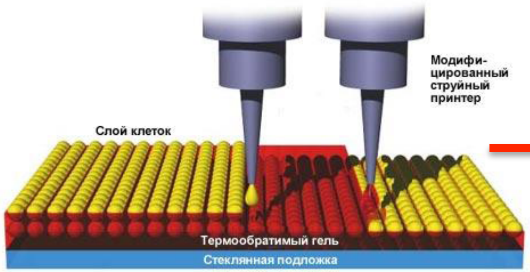
www.nanometer.ru
www.fnm.msu.ru

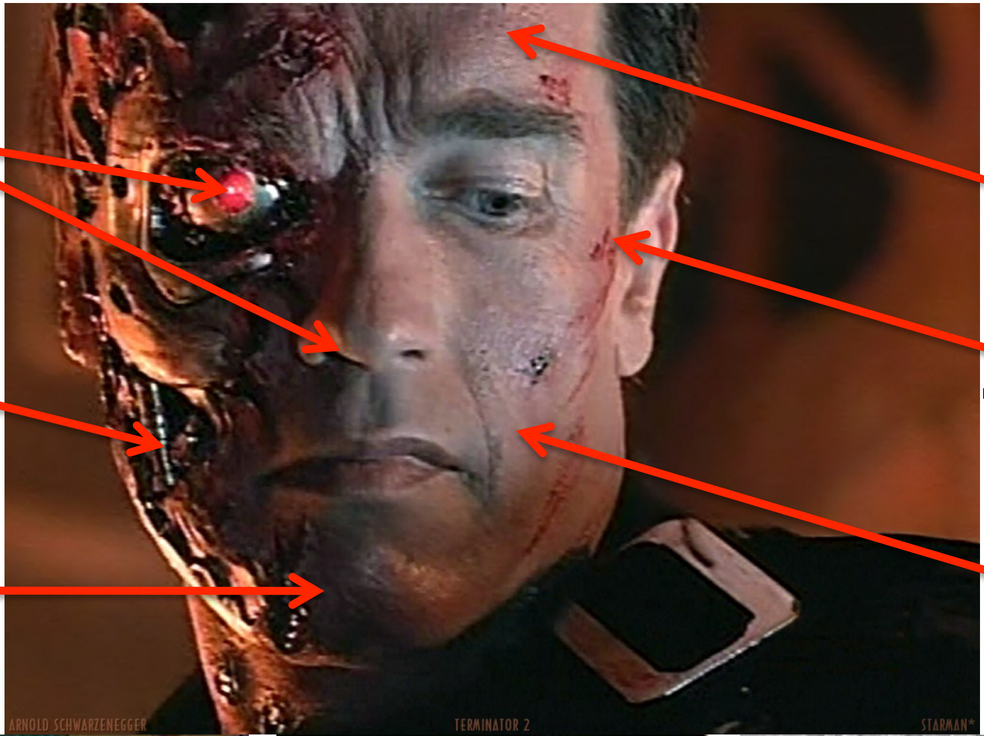
# Материалы для биологии

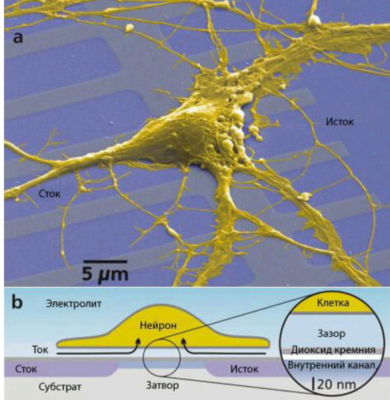



Сенсоры

Нанокерамика и сплавы



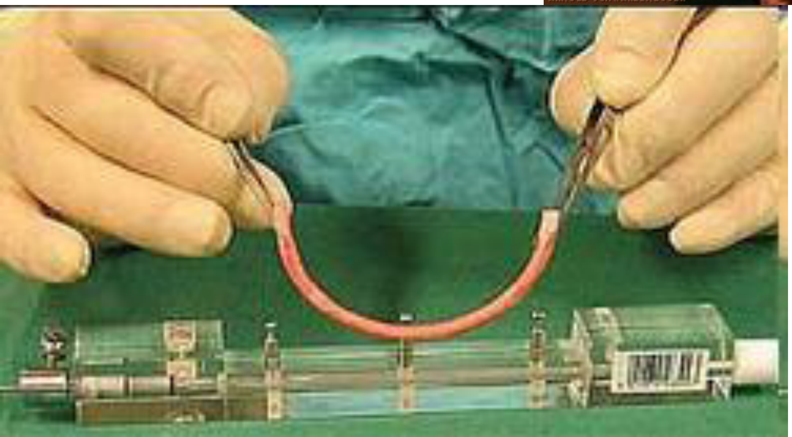



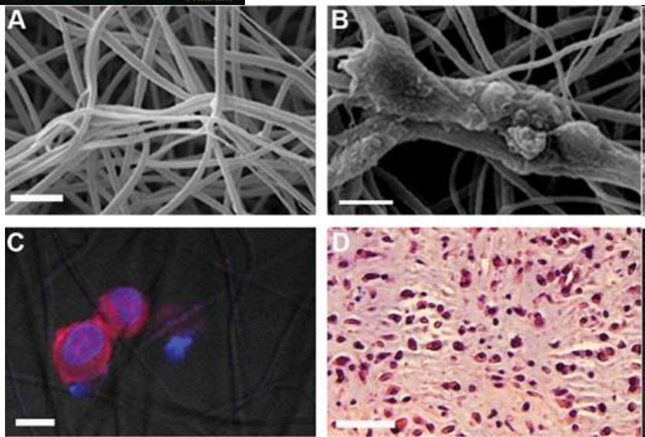




Гибридные материалы

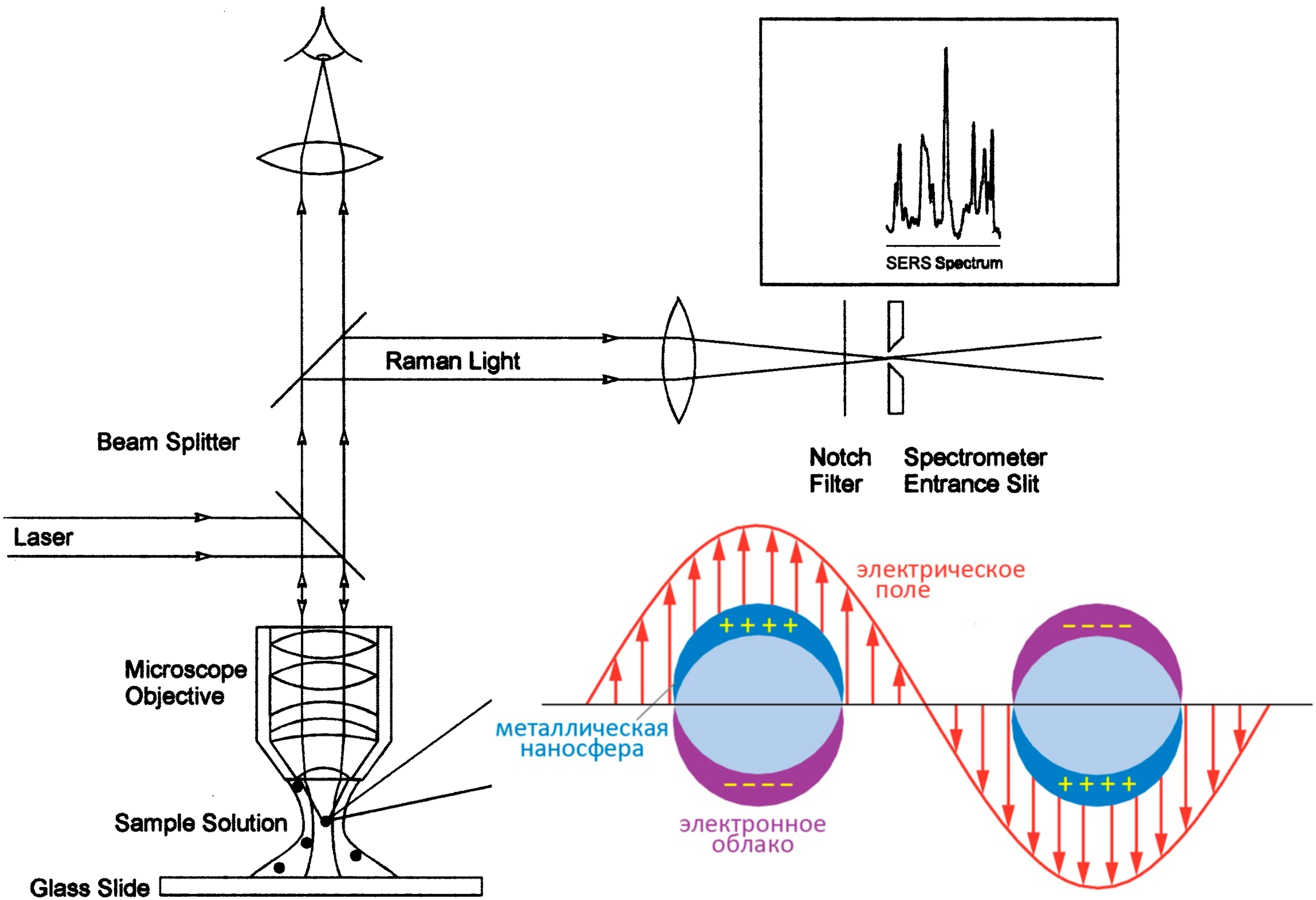
Терапевтические, диагностические наночастицы

Полимеры, нанокомпозиты

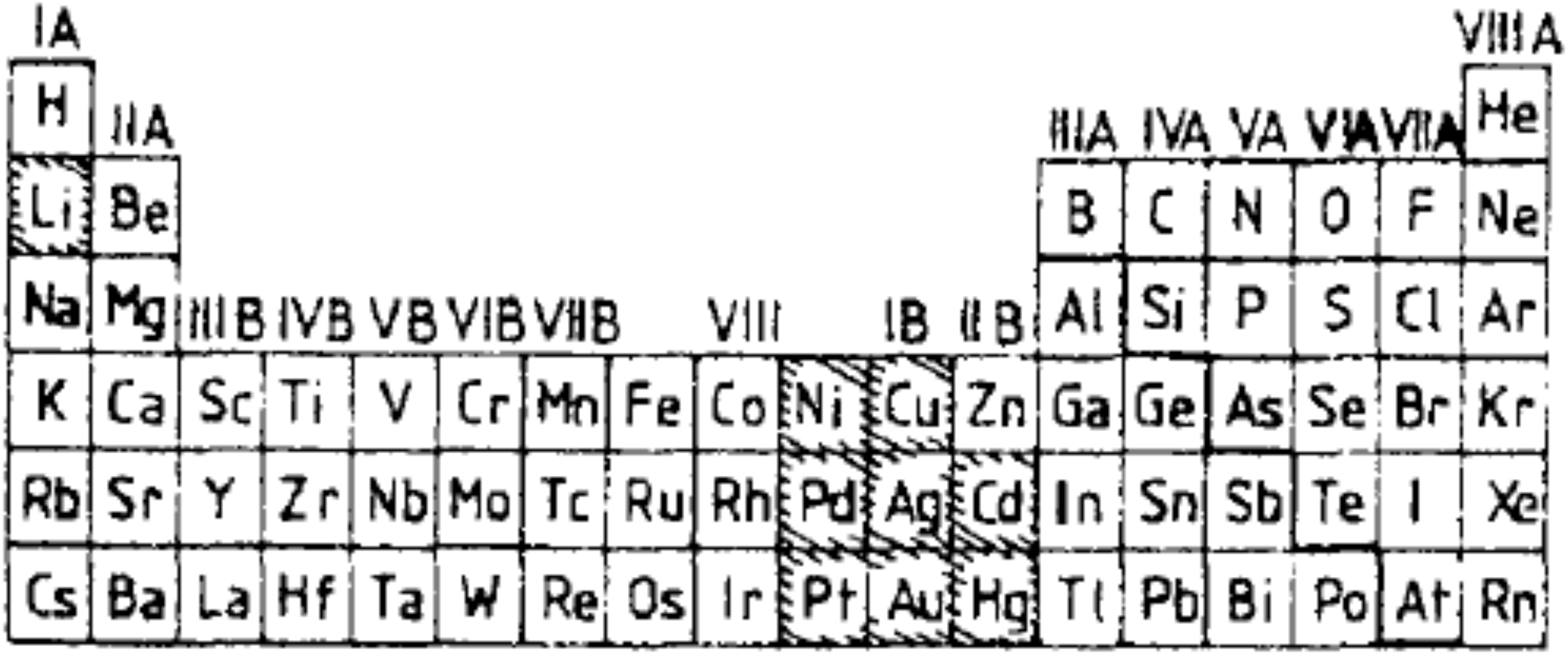




# Surface-Enhanced Raman Scattering/Spectroscopy




K. Kneipp, et al. Bioimaging. 1998. 6. 104–110.



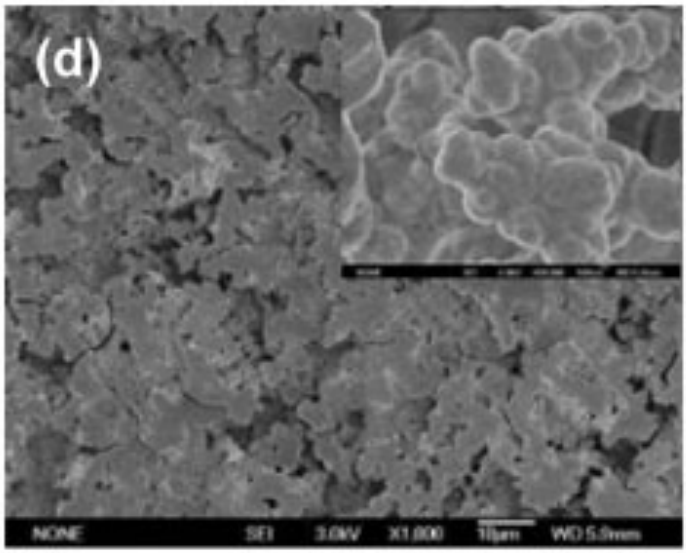

Для SERS используют:

- коллоидные растворы;
- структурированные подложки
- голографические решетки.

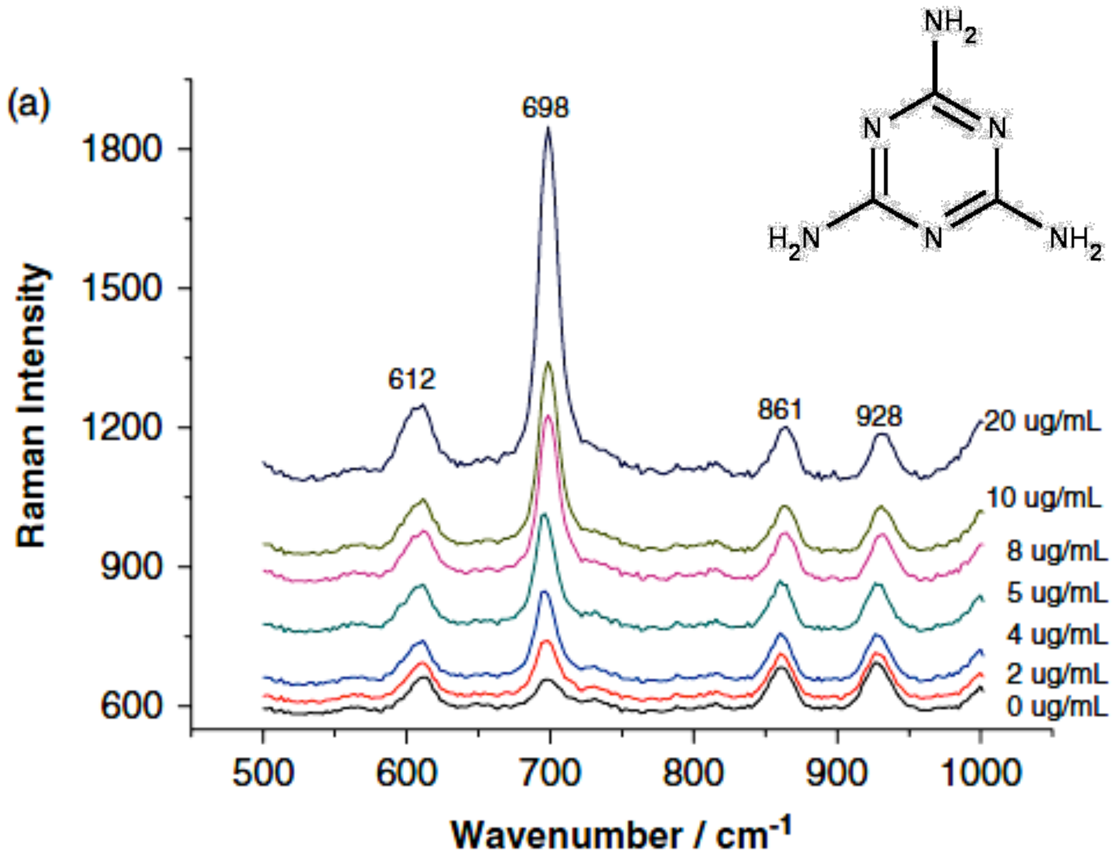

*R. Dornhaus. Festkörperprobleme. 1982. XXII. 201–228.*
*R. Alvarez-Puebla, et al. Small. 2010. 6 (5). 604–610.*

# Детектирование меламина в молоке

$AgNO_3$, цитрат натрия ($Na_3C_6H_5O_7$) [нагревание до 100$^oC$] {*Lee, Meisel, 1982*}




РЭМ-изображение частиц Ag

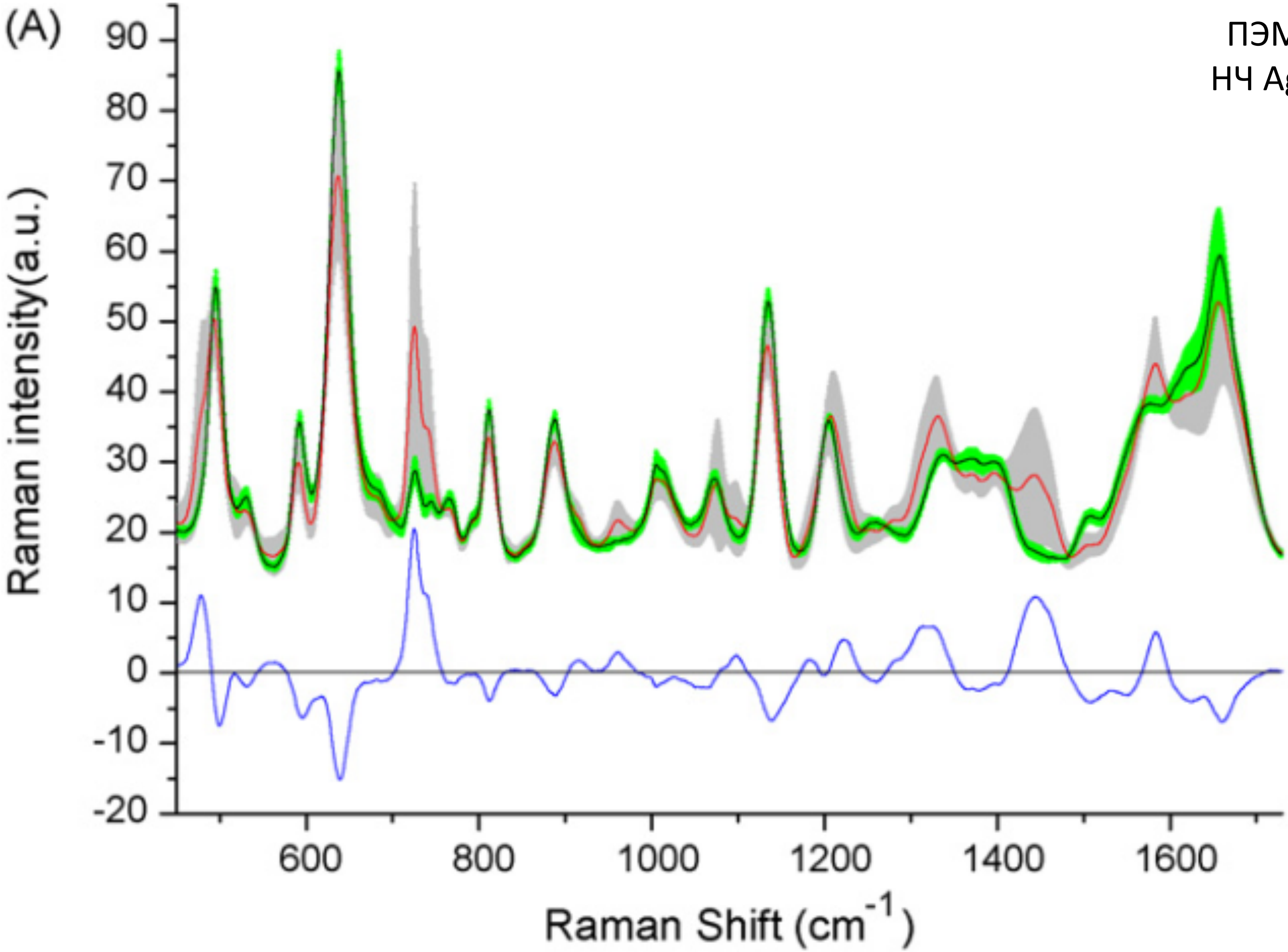



SERS-спектры меламина в молоке при различных концентрациях

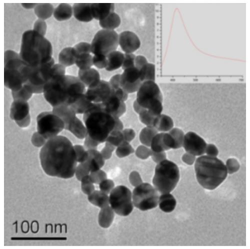

*X.-F. Zhang, et al. J. Raman Spectrosc. 2010. 41. 1655–1660.*
*P. C. Lee, et al. J. Phys. Chem. 1982. 86. 3391–3395.*

# Диагностика онкологических заболеваний

$AgNO_3$, гидрохлорид гидроксиламина ($NH_2OH \cdot HCl$), NaOH {*Leopold, Lendl, 2003*}



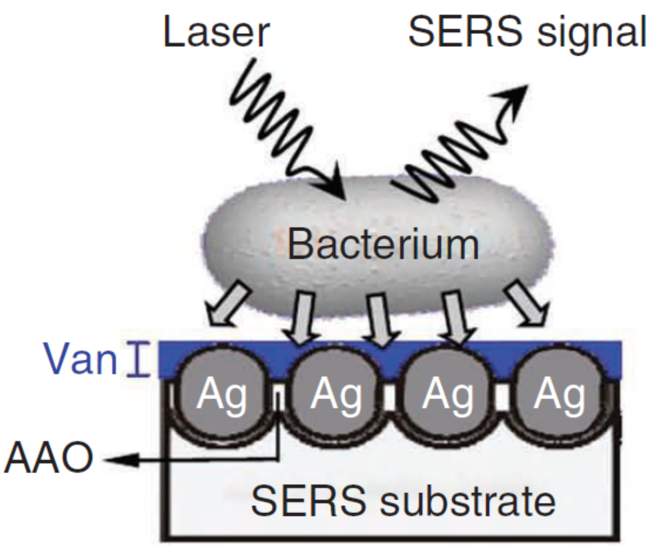

ПЭМ
НЧ Ag

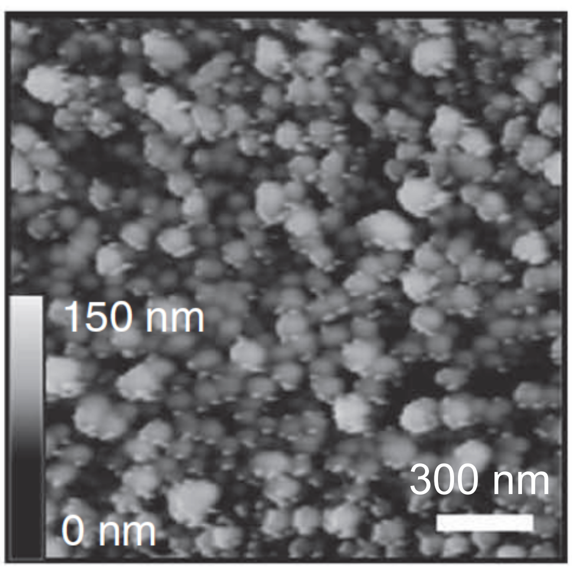


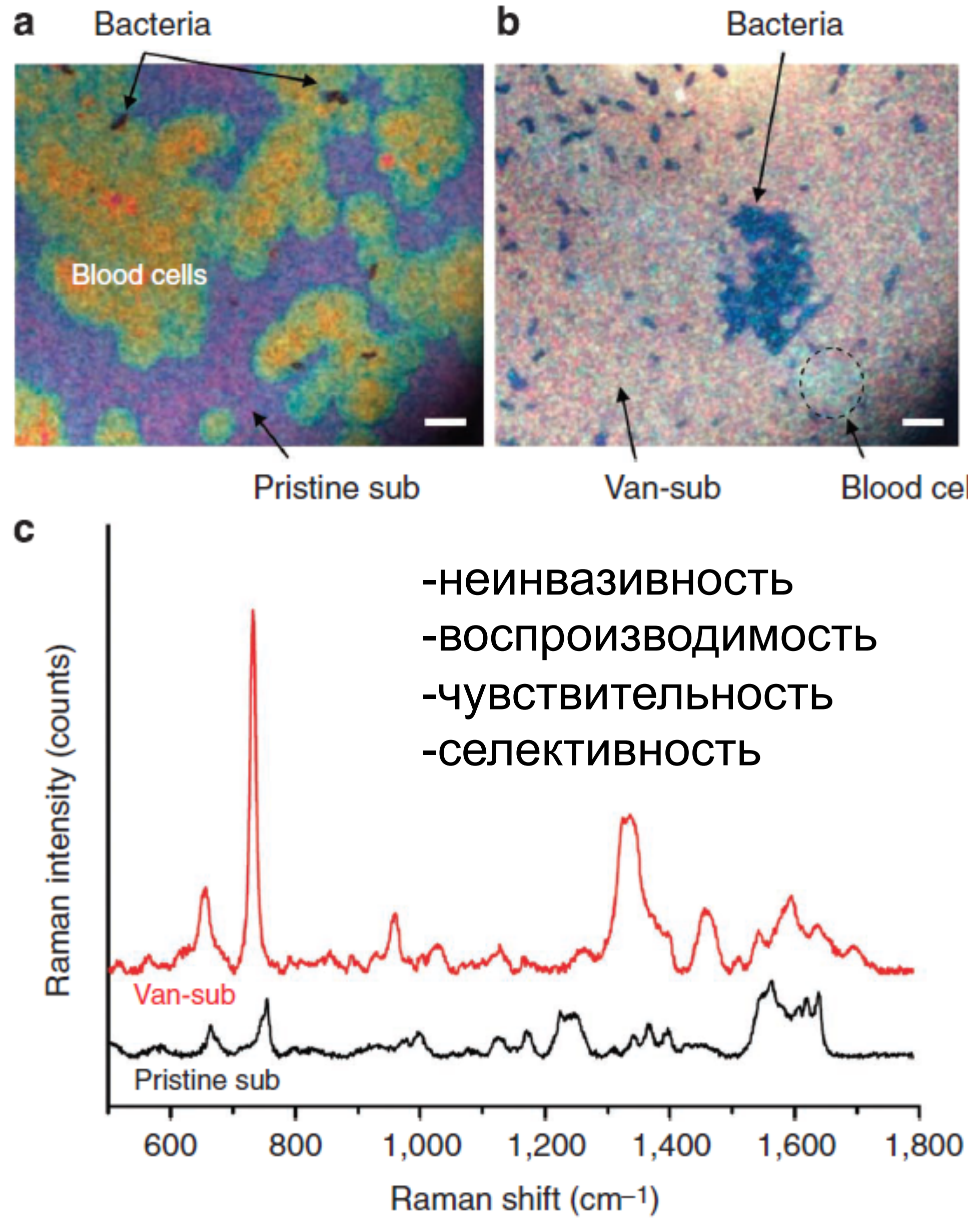

SERS-спектры плазмы крови здорового (*черная линия*) и больного (*красная*) человека. Затемненные области (*зеленая* и *серая*) – стандартное отклонение от спектров. Разность между спектрами приведена внизу (*синяя линия*)

*S. Feng, et al. Biosensors and Bioelectronics. 2010. 25. 2414–2419.*
*N. Leopold, et al. J. Phys. Chem. B. 2003. 107. 5723–5727.*

# Актуальность



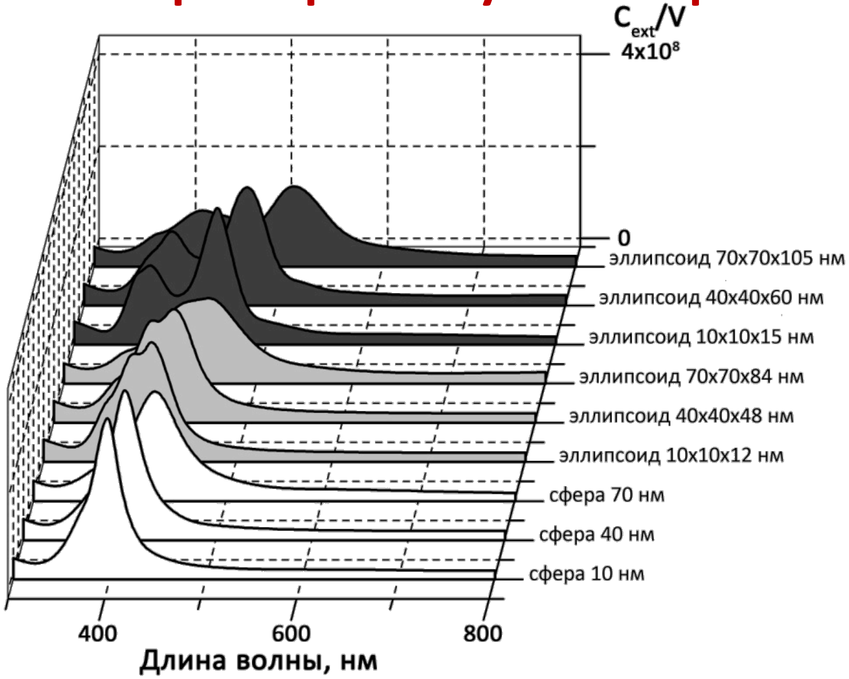



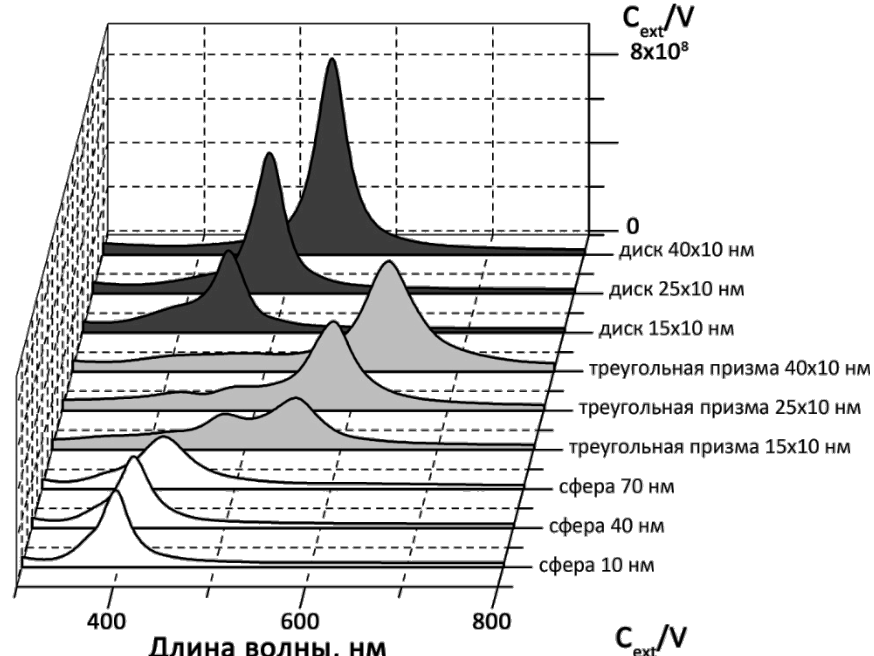



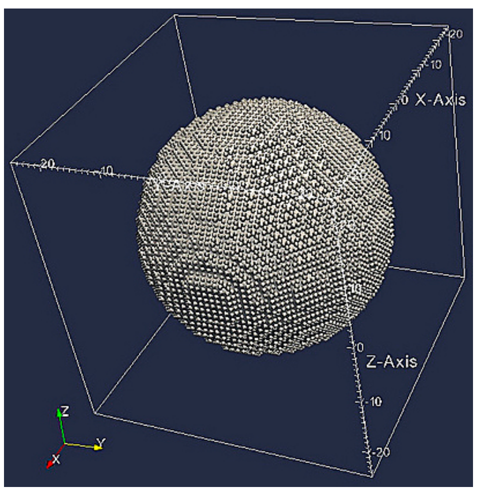

-неинвазивность
-воспроизводимость
-чувствительность
-селективность

*T.-Y. Liu, et al. Nature Communications. 2011. 2. 1–8.*

# Серебро – универсальный материал для ГКР



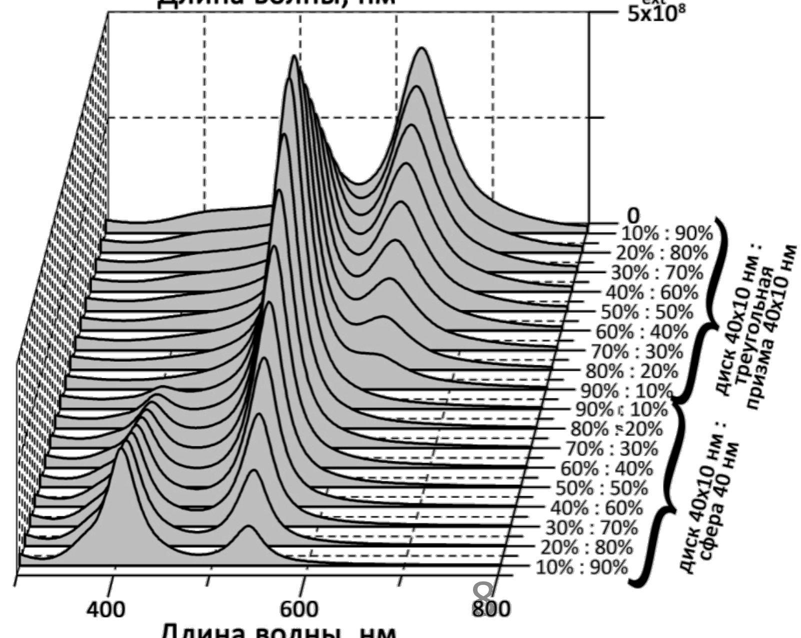
Метод дискретно-дипольного приближения (ДДП)

ПО DDSCAT 7.1

[*Draine B.T., Flatau P.J., 1994*]

$C_{ext}$ – эффективное сечение экстинкции

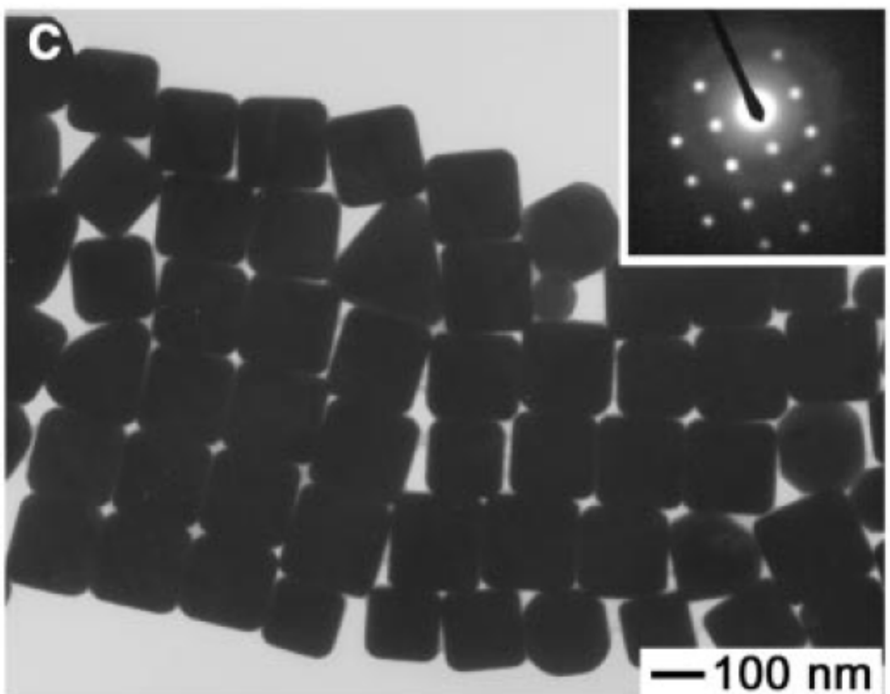
$V$ – объем частицы

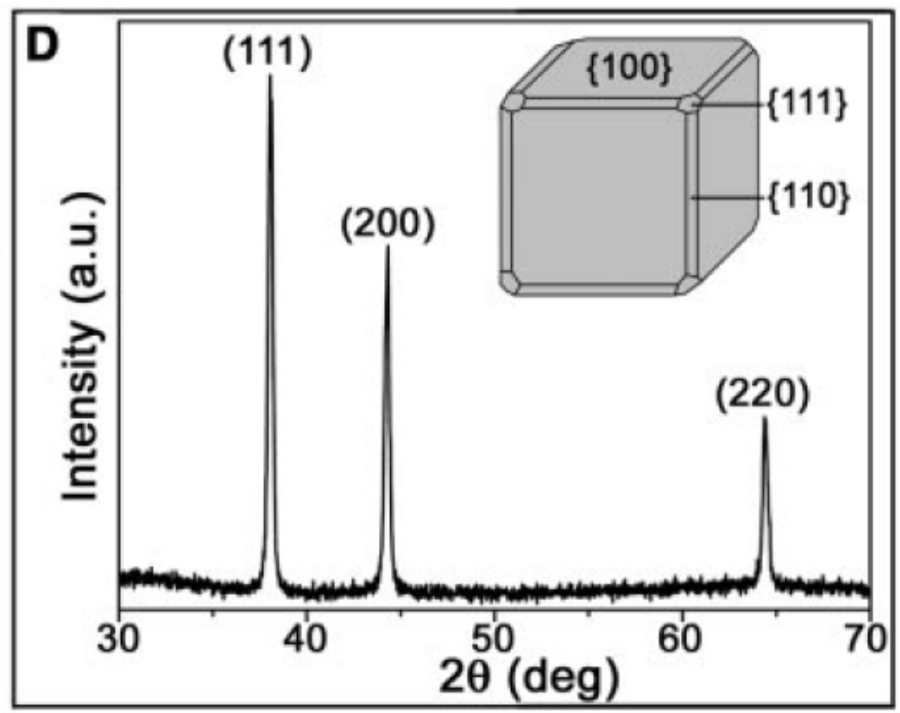


# Схема синтеза

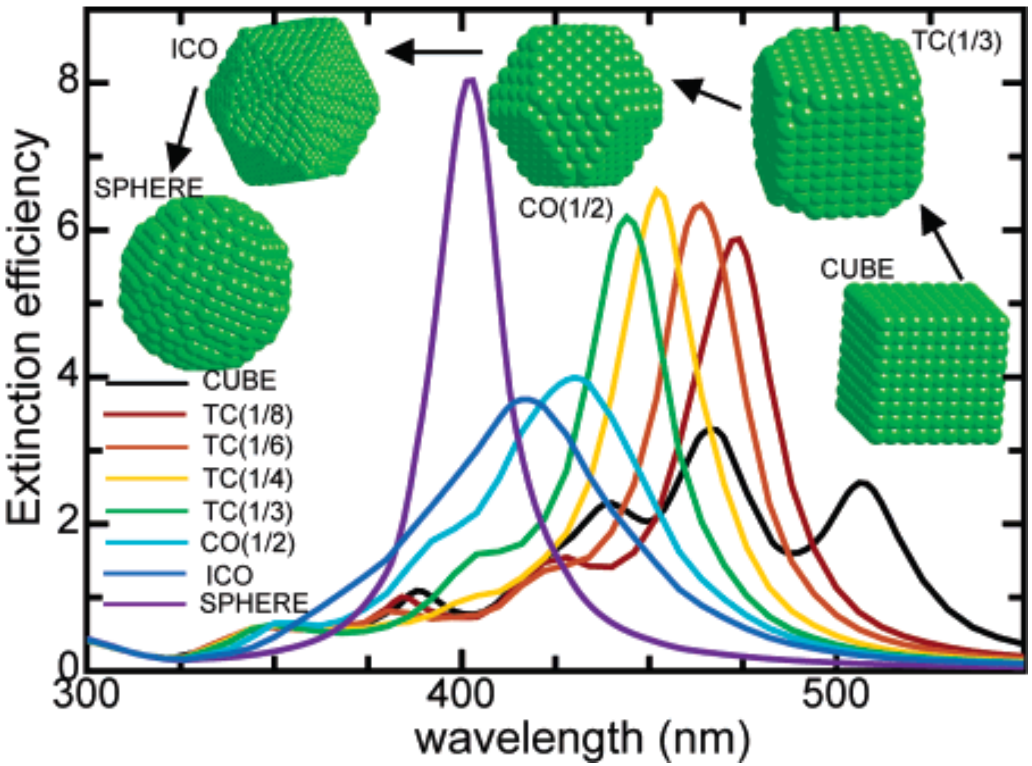
R – соотношение между темпами роста в направлениях <100> и <111>

- R = 1,73 – октаэдры и тетраэдры {111}
- R = 0,58 – кубы {100}
- R = 0,7 – усеченные кубы

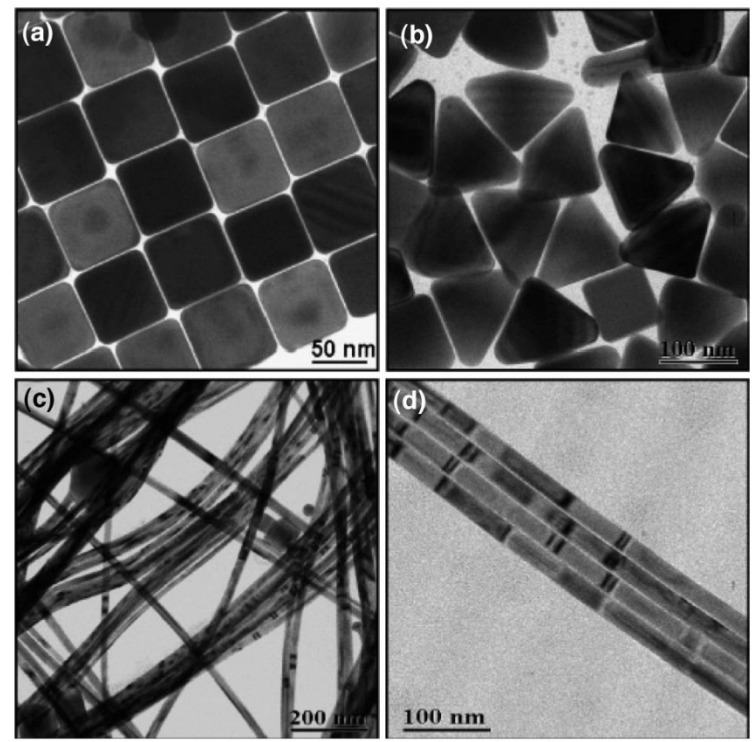


# Частицы серебра с различной морфологией




Зависимость коэффициента экстинкции от длины волны падающего излучения для НЧ Ag разной формы (куб, усеченный куб, сфера)



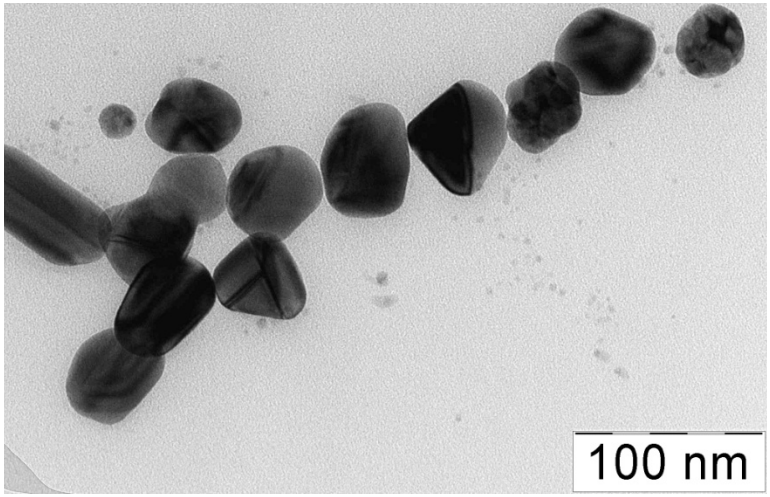

ПЭМ-изображения НЧ Ag: кубики (*a*), треугольные пластинки (*b*), нити (*c, d*)

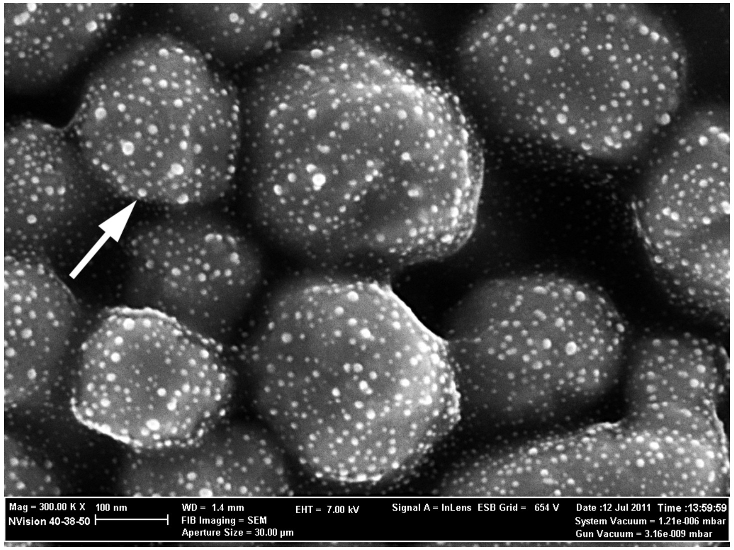

*C. Noguez. J. Phys. Chem. C. 2007. 111. 3806-3819.*

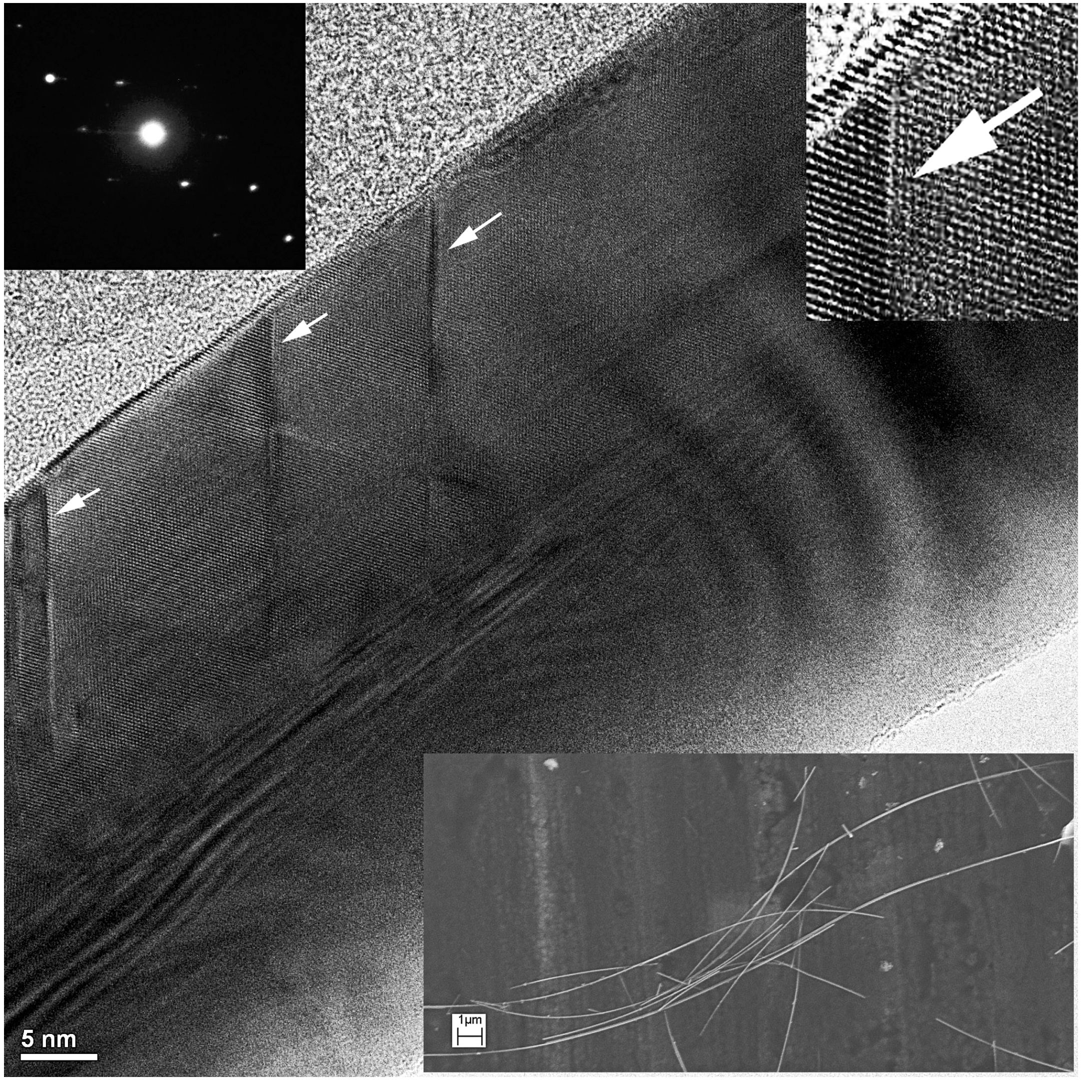
*D. Yu. J. Phys. Chem B. 2005. 109 (12). 5497–5503.*

# Полиольный синтез

$AgNO_3$, ПВП, этиленгликоль (HO – $(CH_2)_2$ – OH)[нагревание до 160°C] [*Wiley B., 2005*]



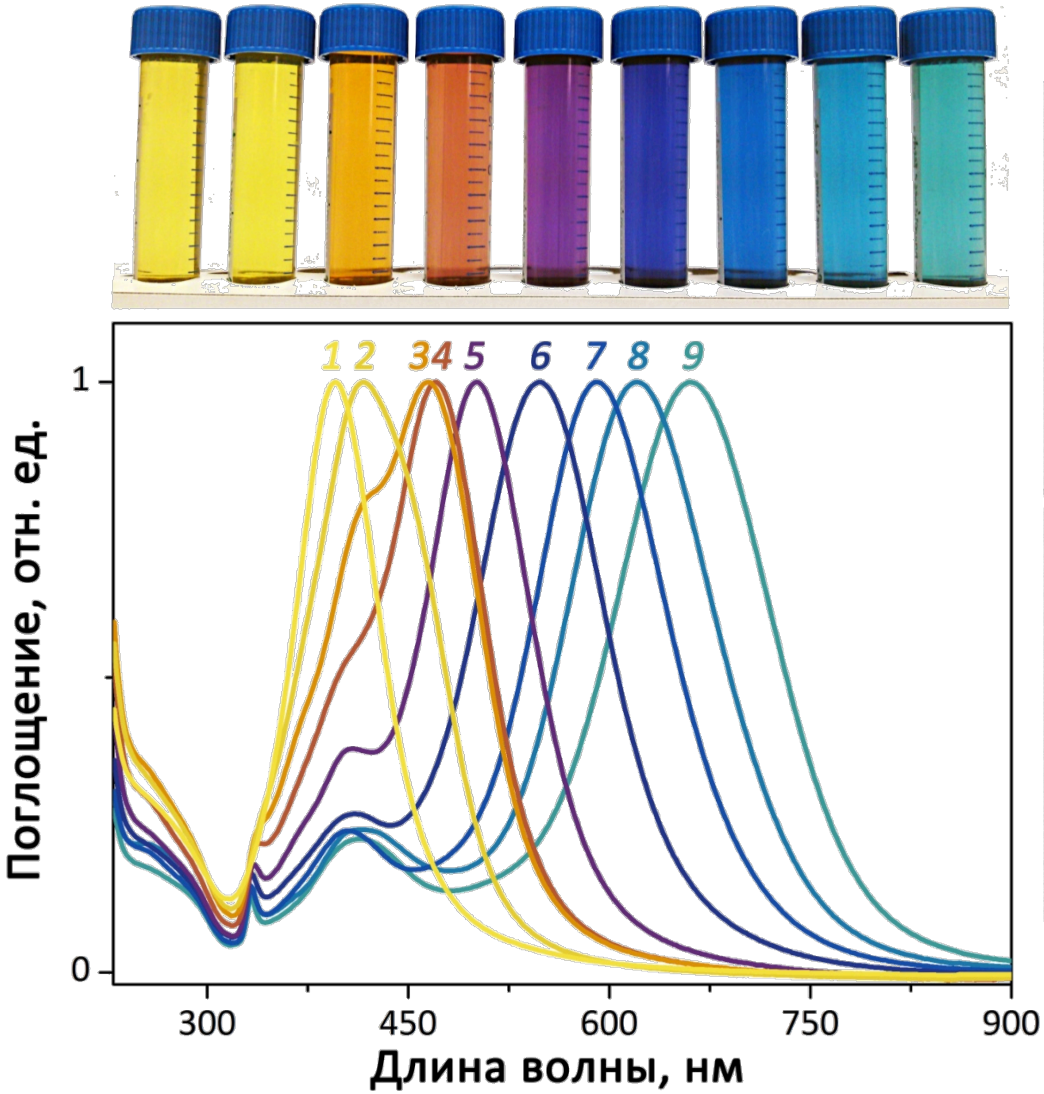



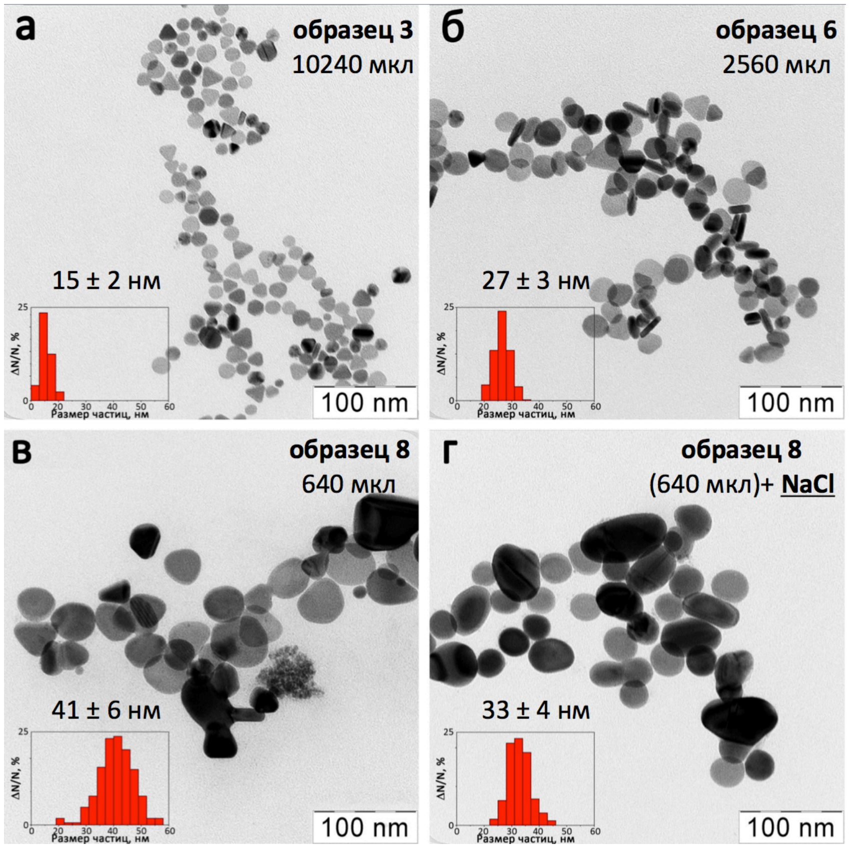
# Анизотропные наночастицы серебра

I (затравки): $AgNO_3$, цитрат натрия ($Na_3C_6H_5O_7$), $NaBH_4$

II: аликвота I (затравок) + ПВП, $Na_3C_6H_5O_7$, аскорбиновая кислота ($C_6H_8O_6$, АА) [*Zeng J., 2011*]

$2AgNO_3 + 2NaBH_4 + 6H_2O = 2Ag + 2H_3BO_3 + 2NaNO_3 + 7H_2$ *(I)*  $2AgNO_3 + C_6H_8O_6 = 2Ag + C_6H_6O_6 + 2HNO_3$ *(II)*




*A.A.Semenova и др.*

# Нам уже годик!

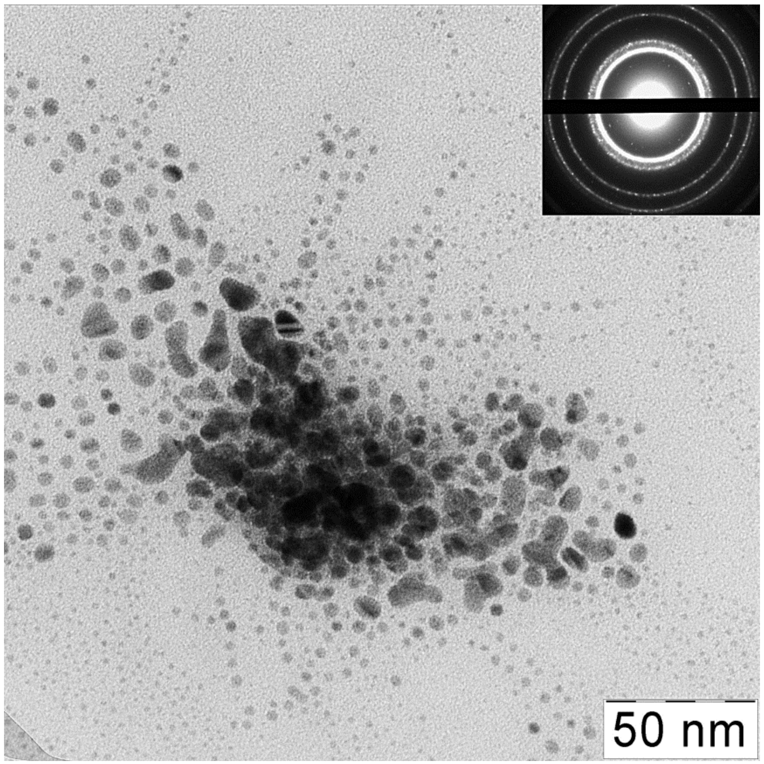
2011

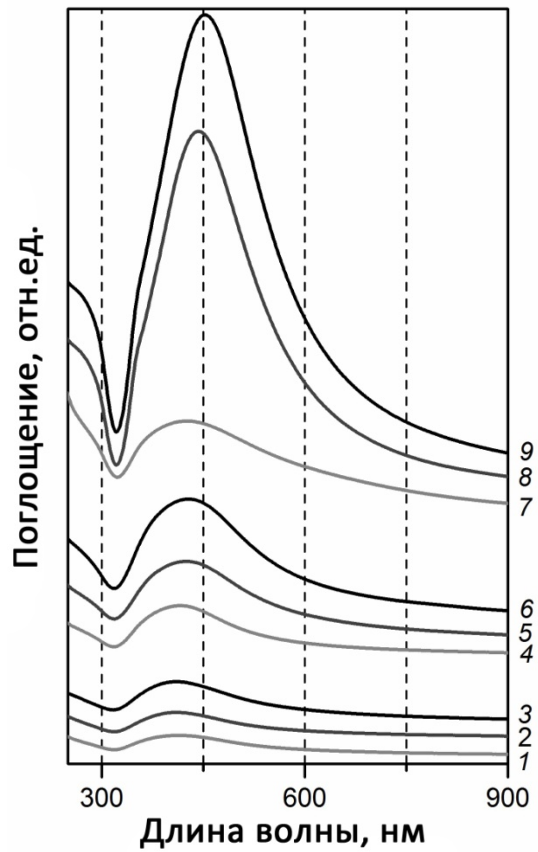

2012

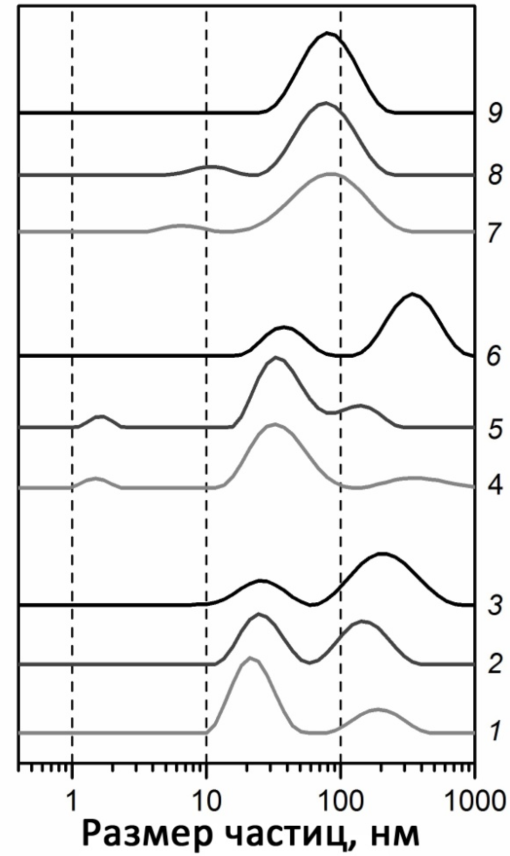
# «Чистые» гидрозоли серебра

$2AgNO_3 + 2NaOH = Ag_2O + 2NaNO_3 + H_2O$ *(1)*  $Ag_2O + 4NH_3 + H_2O = 2[Ag(NH_3)_2]OH$ *(2)*

$4[Ag(NH_3)_2]OH = 4Ag + 8NH_3 + O_2 + 2H_2O$ *(3)*

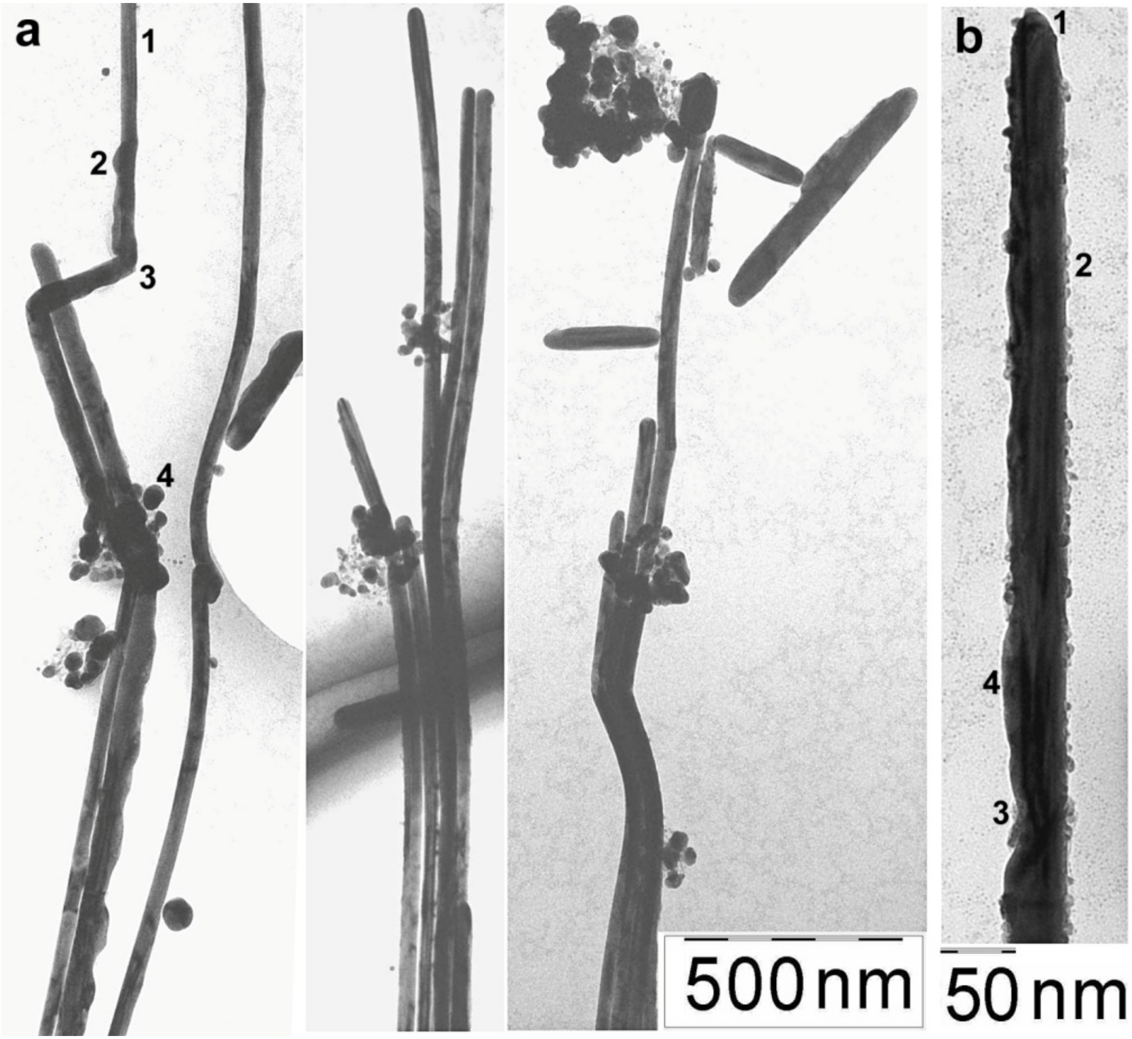


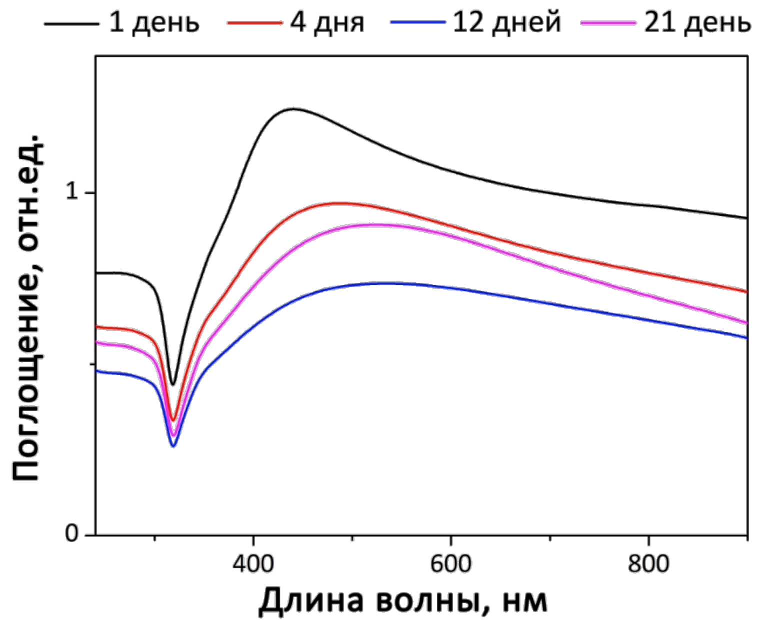



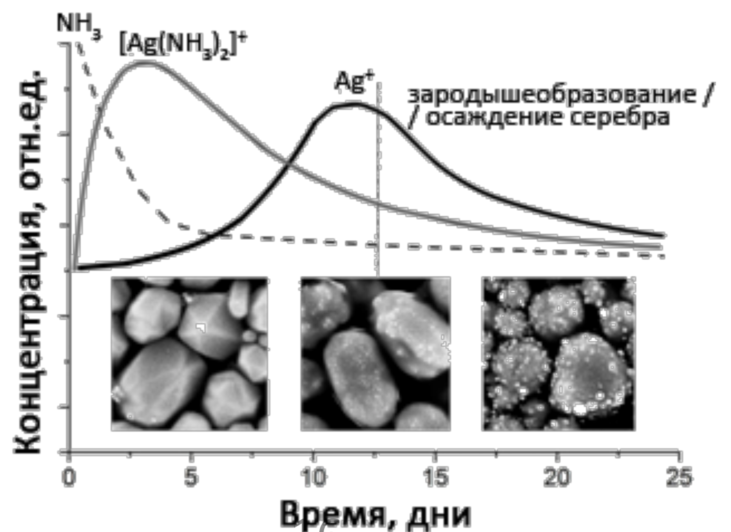




| № образца | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* |
|---|---|---|---|---|---|---|---|---|---|
| Объем комплекса, мл | 0,1 | 0,1 | 0,1 | 0,5 | 0,5 | 0,5 | 2,5 | 2,5 | 2,5 |
| Время протекания реакции, мин | 20 | 30 | 60 | 20 | 30 | 60 | 20 | 30 | 60 |

# Растворение – осаждение ($NH_3*H_2O$)

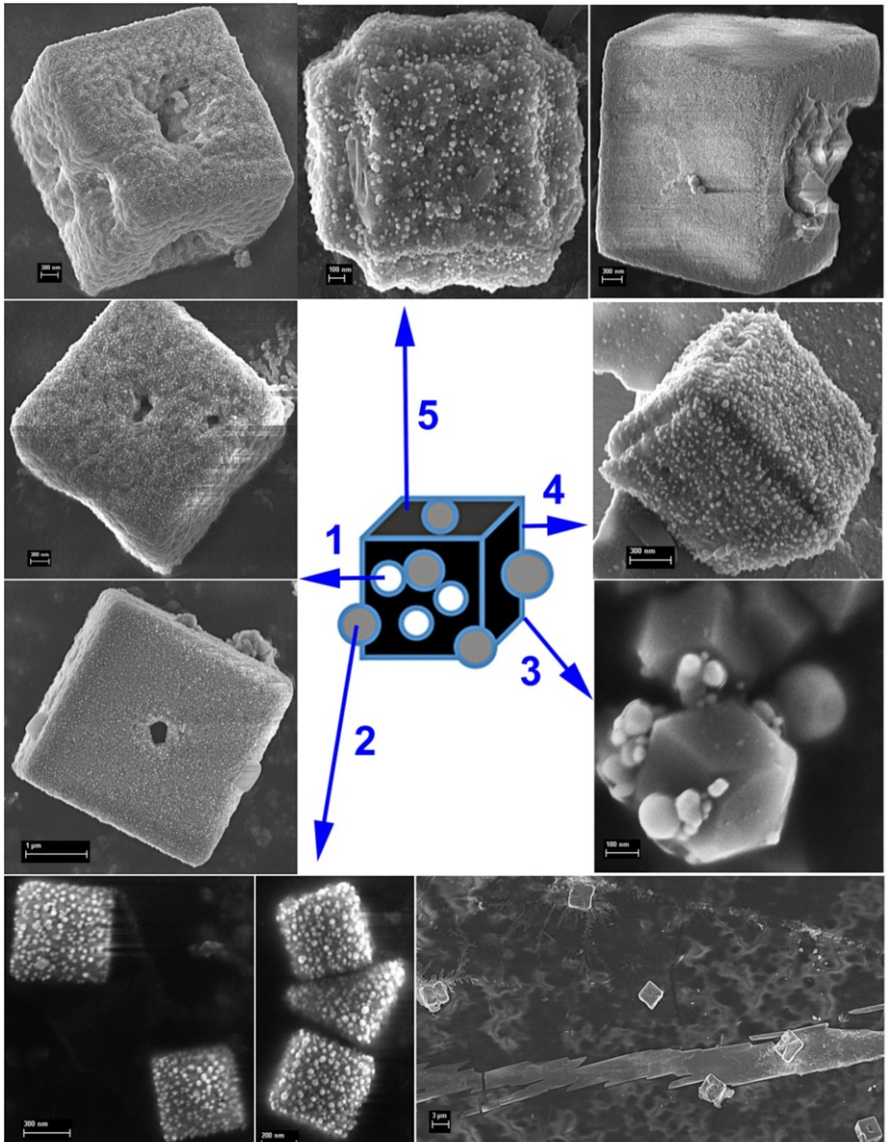


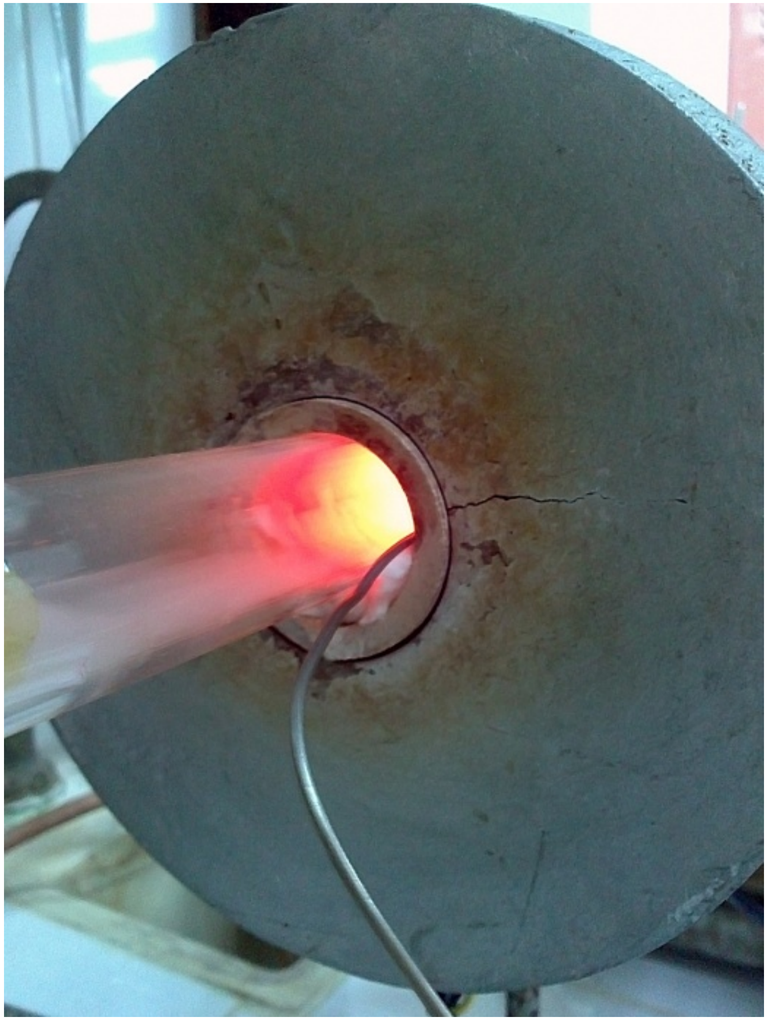



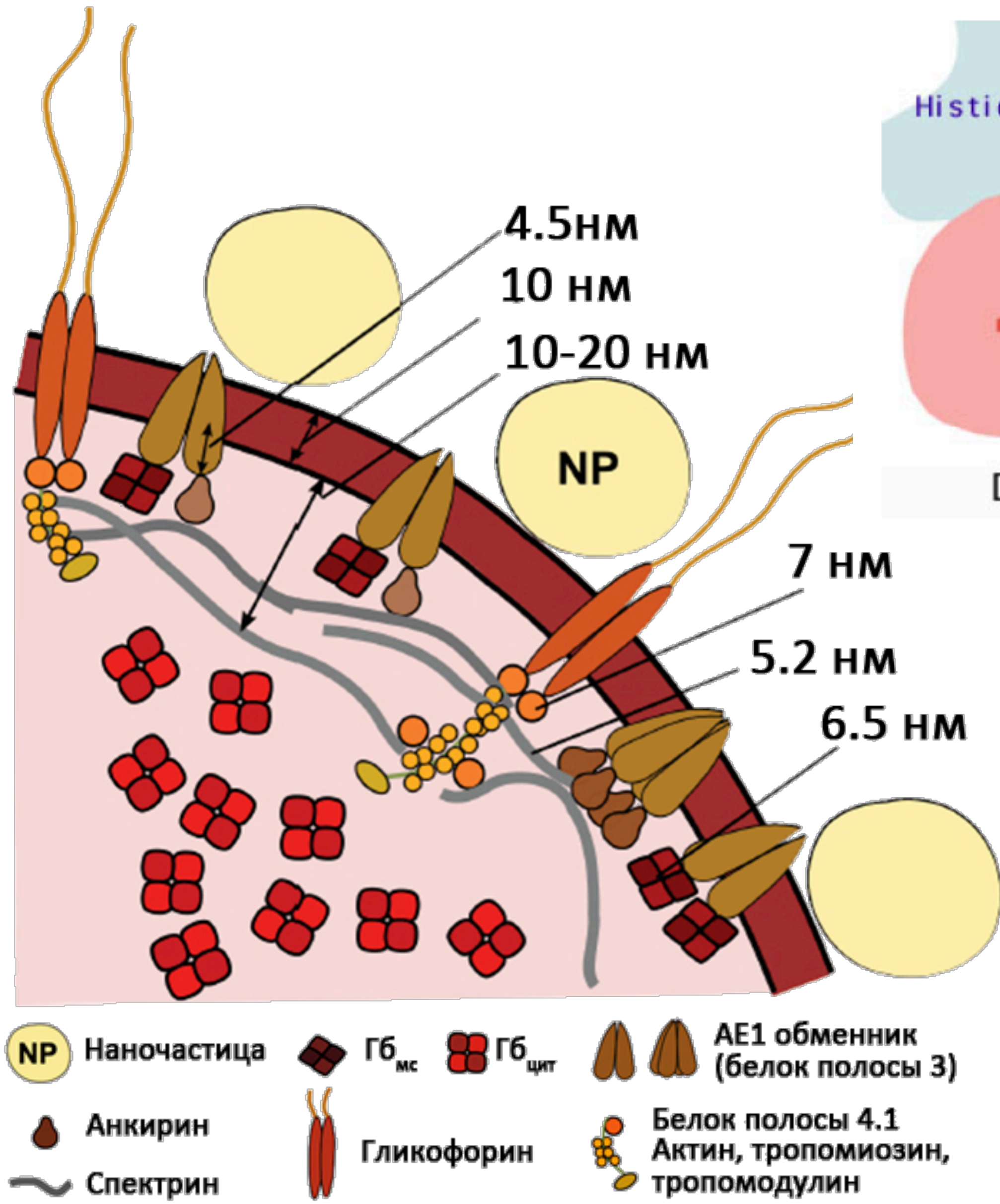



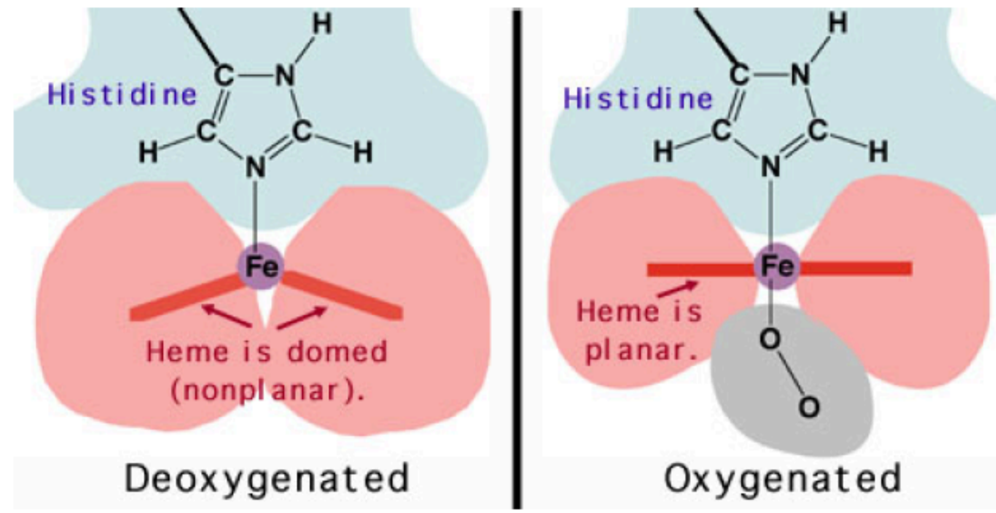
# Пиролиз аэрозолей

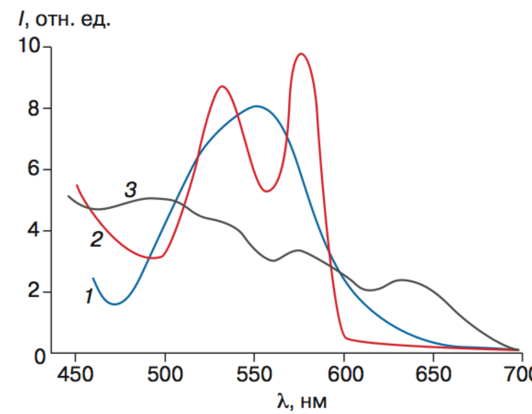
$2[Ag(NH_3)_2]OH = Ag_2O + 2NH_3 + H_2O; 2Ag_2O = 4Ag + O_2$





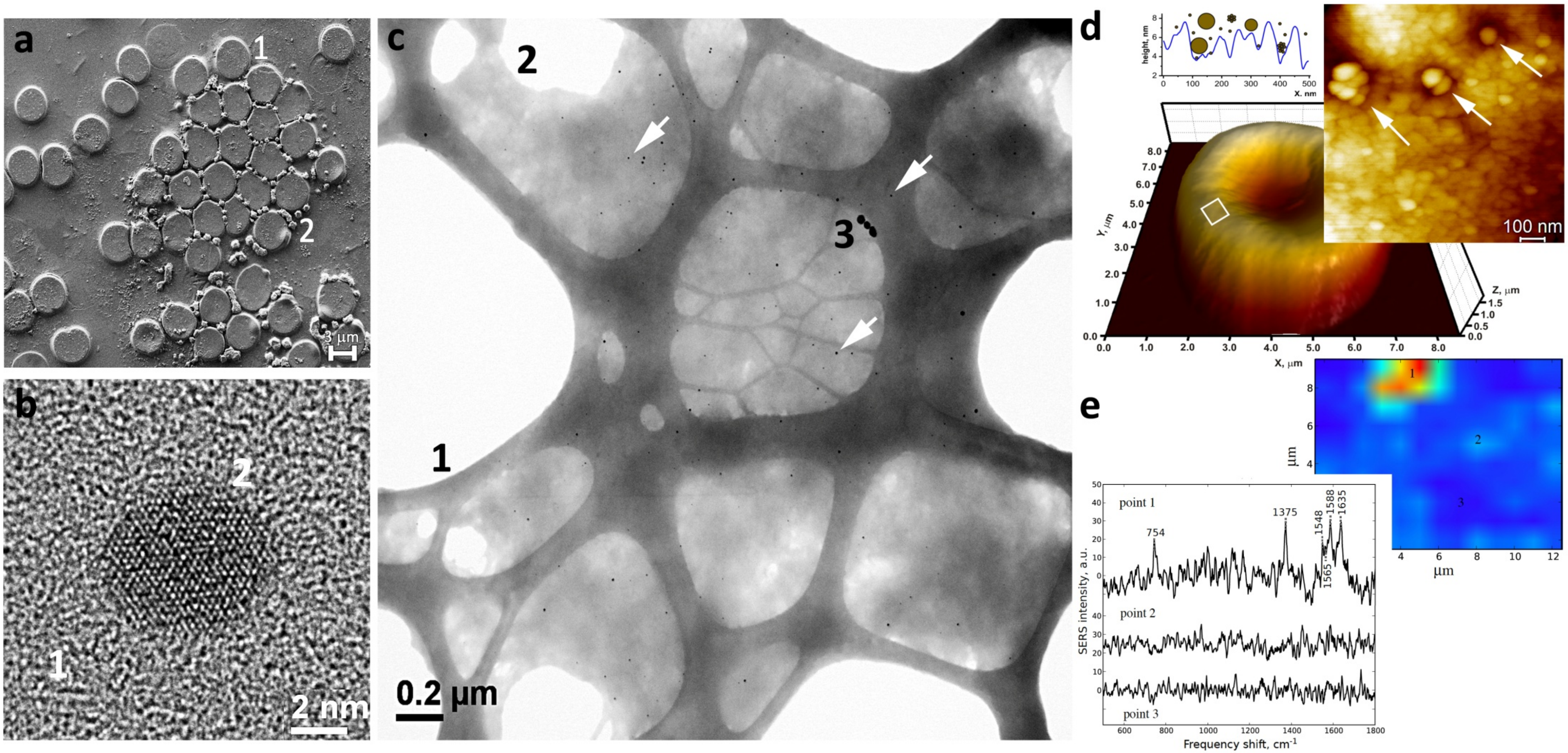




Спектры поглощения дезоксигемоглобина (*1*), оксигемоглобина (*2*) и ферригемоглобина (*3*)

*N. Brazhe, et al. Biophys. J. 2009. 97 (12). 3206–3214*

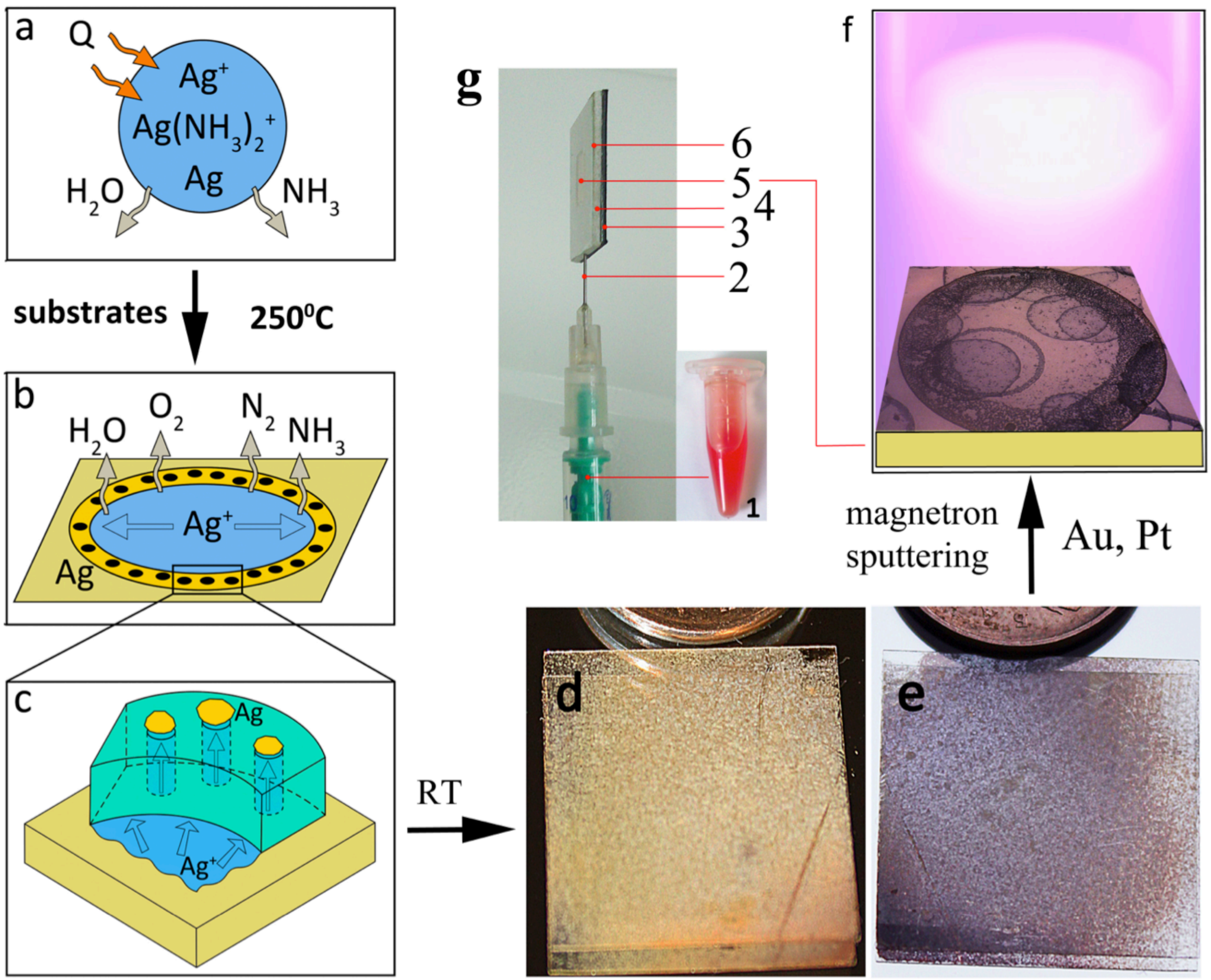
# Серебро и клеточная мембрана




*A.A.Semenova и др.*

# Аэрозольное осаждение

## USSR (UltraSonic Silver Rain), «серебряный дождь»




*A.A.Semenova и др.*

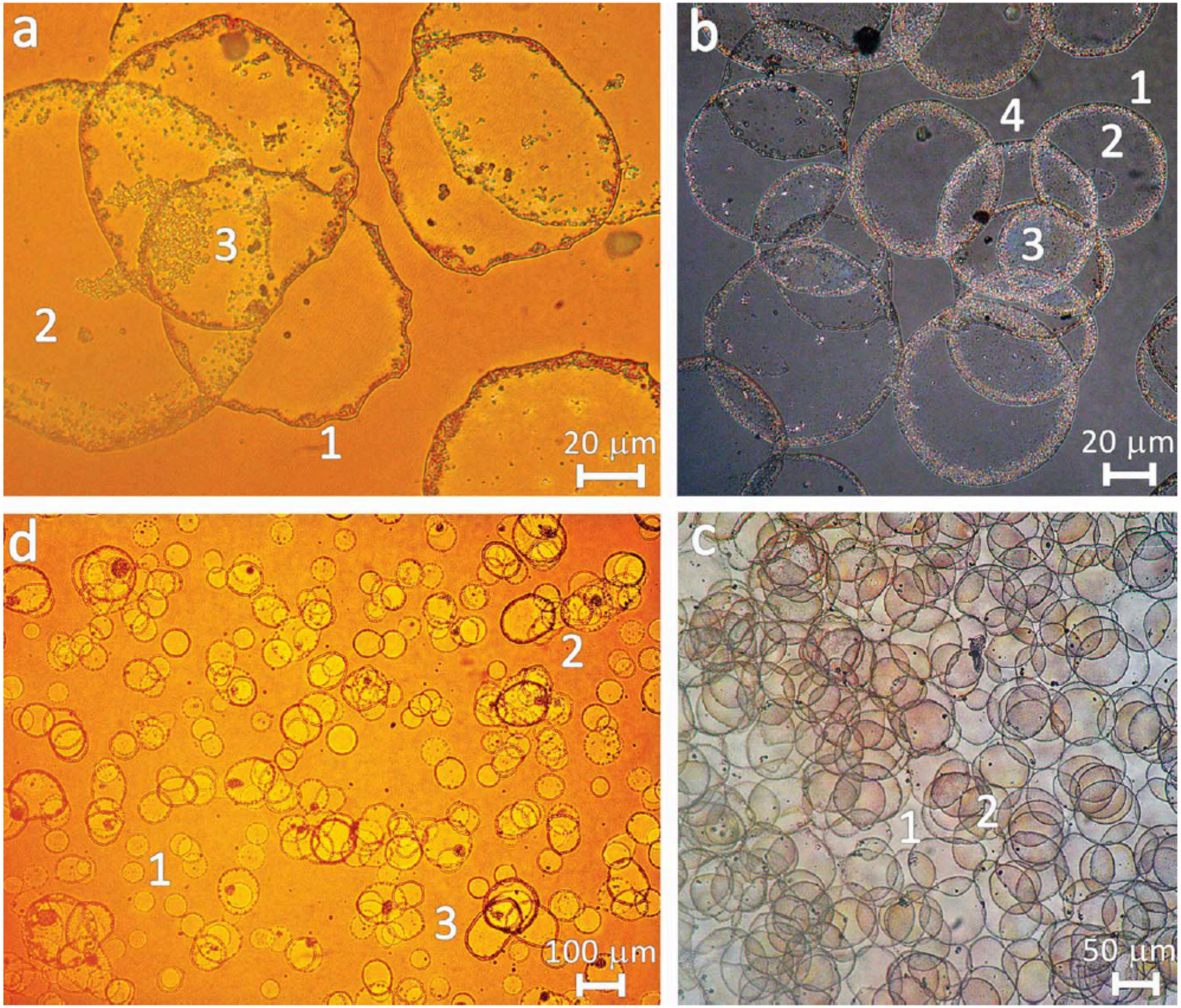



**Fig. 2** Typical optical images of the surface of USR substrates. (a) Stochastically intersecting silver rings on a glass substrate preliminarily sputtered by a magnetron with a 5 nm gold layer; (1) concave rims of transformed silver complex droplets; (2) visually smooth area of the ring; (3) silver clusters in the region of ring intersection; (b) a group of silver rings on a bare glass substrate; (1) rounded silver rim; (2) silver clusters inside the ring; (3) intersecting area with a thicker layer of deposited silver; (4) a silver string between two neighboring rings; (c) a final layer of stochastic silver rings forming a continuous coating with rare naked areas (1) and usual groups of heavily intersecting rings (2); (d) beginning of silver deposition after some induction time; (1) individual silver rings; (2) chains of silver rings; (3) initial growing groups of silver rings.

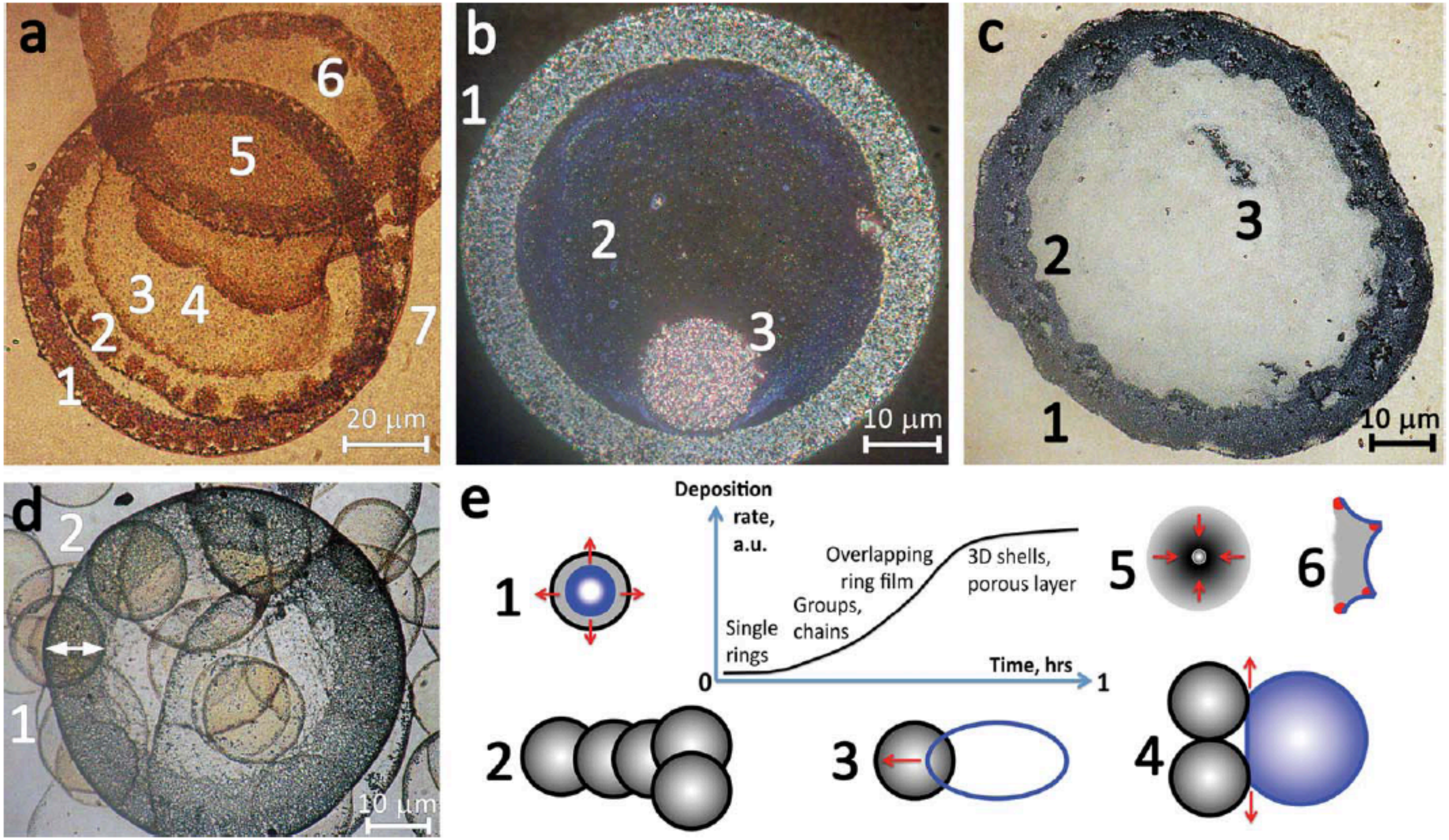



**Fig. 3** Magnified optical images of "coffee ring" features of USR substrates. (a) overlapping silver circles, (1) a primary circle, (2)–(4) secondary waves of liquid producing nanostructured silver, the morphology of their rims are irregular due to pinning of the moving liquid front onto preceding silver clusters, (5) a thicker layer of silver clusters in the overlapping area of expanding circles, (6) an elongated segment of a silver circle, (7) an aligned part of the elongated circle, (b) a perfect silver ring; (1) a wide rim; (2) silver clusters; (3) a spot of silver upon residual solution evaporation; (c) a typical irregular ring on a gold sputtered glass substrate; (1) wavy outer rim; (2) structured inner rim; (3) a film of silver inside the rim; (d) a large perfect ring formed on top of a group of first circles of silver on a bare glass substrate; (1) initial rings; (2) circular rim of the large ring with an expanded boundary (marked with a double arrow); (e) a hypothetical scheme of droplet ensemble evolution and a schematic drawing of basic phenomenological events; (1) wetting of inner areas of silver rings with new solution droplets (a circular group of rings); (2) consecutive pinning of droplets on a substrate producing a chain of silver rings; (3) soaking and elongation of a secondary droplet deposited on a substrate with a primary silver ring due to its better wetting; (4) a string rim of fallen droplets originated from wetting of two neighboring silver rings; (5) substrate dewetting and formation of silver clusters; (6) silver rim polygonization due to pinning of shrinking droplets on occasionally formed silver clusters.

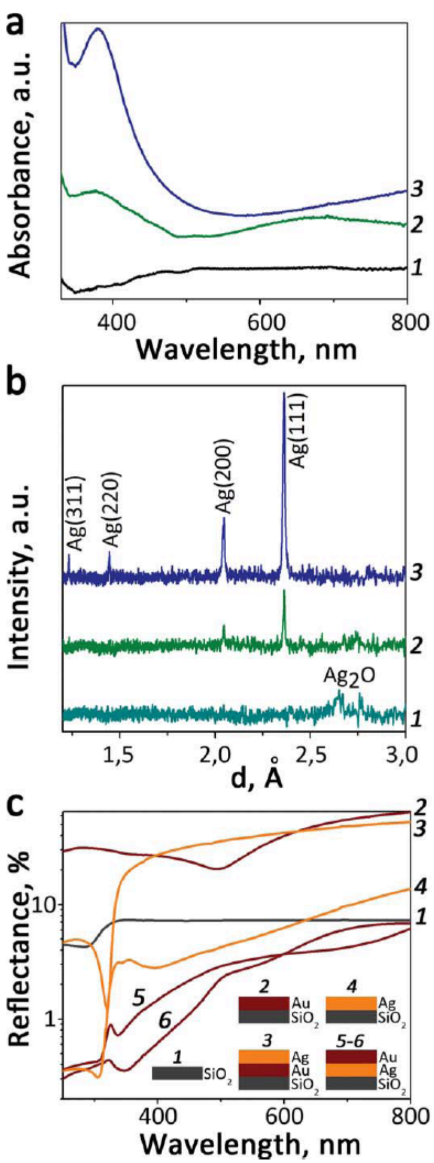



**Fig. 5** Phase composition and optical properties of nanostructured samples. (a) Diffuse reflectance UV-vis spectroscopy and (b) XRD data for the substrates preheated up to 60 °C and kept under an aerosol stream for 40 min ("1"); the temperature is kept at 270 °C, same deposition time ("3"), an intermediate sample obtained after the treatment of the sample ("1") at 270 °C for 5 min ("2"); (c) reflectivity data (8° incidence angle) for finally treated substrates, (1) bare glass, (2) a glass substrate with magnetron-sputtered gold (5 nm); (3) a glass with sputtered gold and then covered chemically with silver by USR; (4) a glass coated with pure silver rings by USR; (5) and (6) the same with additional gold sputtering onto the silver ring layer, 5 and 15 nm of gold, respectively.

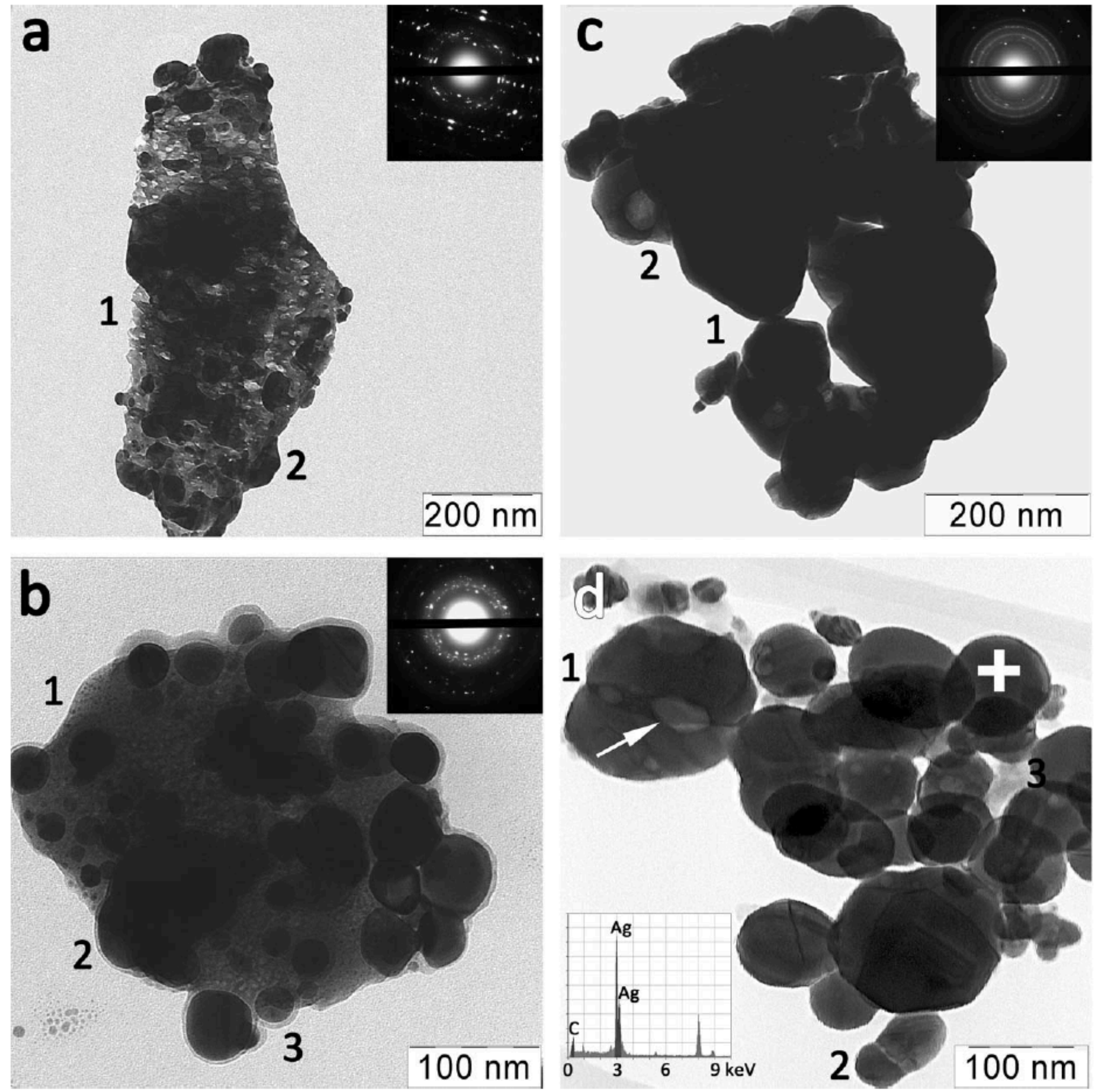
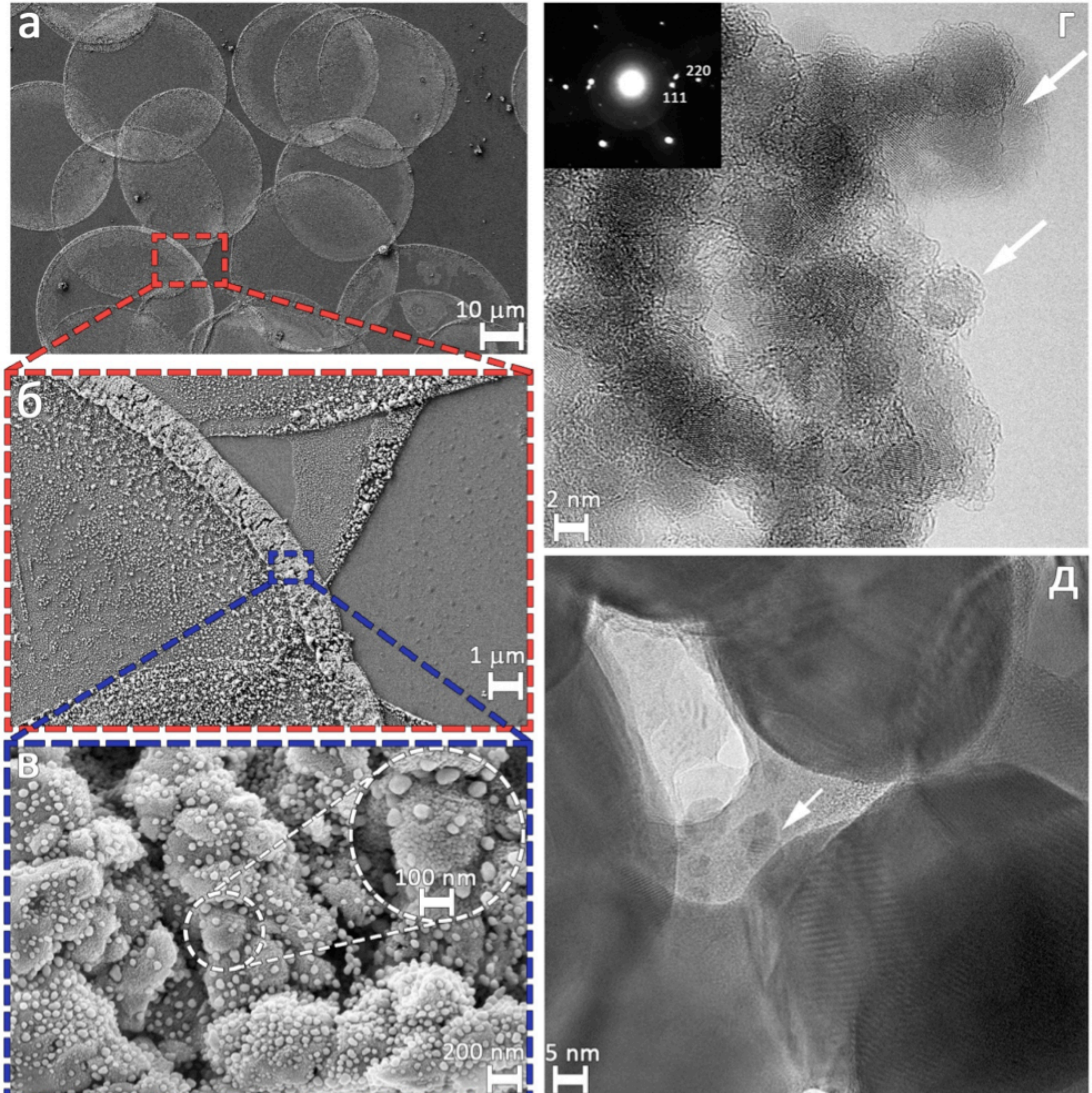



**Fig. 6** Typical TEM images of fragments of nanostructured silver coating formed under different conditions; the substrates are preheated up to 60 °C and kept under an aerosol stream for 40 min (a); (c) the temperature is kept at 270 °C, same deposition time, (b) an intermediate sample obtained after the treatment of the sample (a) at 270 °C for 5 min. The insets show electron diffraction patterns for the samples. "1" denotes a piece of silver(I) oxide with an oriented porous structure and some metallic nanoparticles ("2") for the sample "a", a matrix of porous precursor with tiny clusters of as-formed silver ("1") or larger nanoparticles of silver ("2", "3") for "b", silver nanoparticles ("1") becomes larger while pores ("2") still remain for "c"; (d) a magnified STEM view of porous joint AgNPs composing the crater walls, the inset shows local chemical analysis data; 1–3 – points of HREM investigation.


а
10 μm
б
1 μm
в
100 nm
200 nm
г
220
111
2 nm
д
5 nm

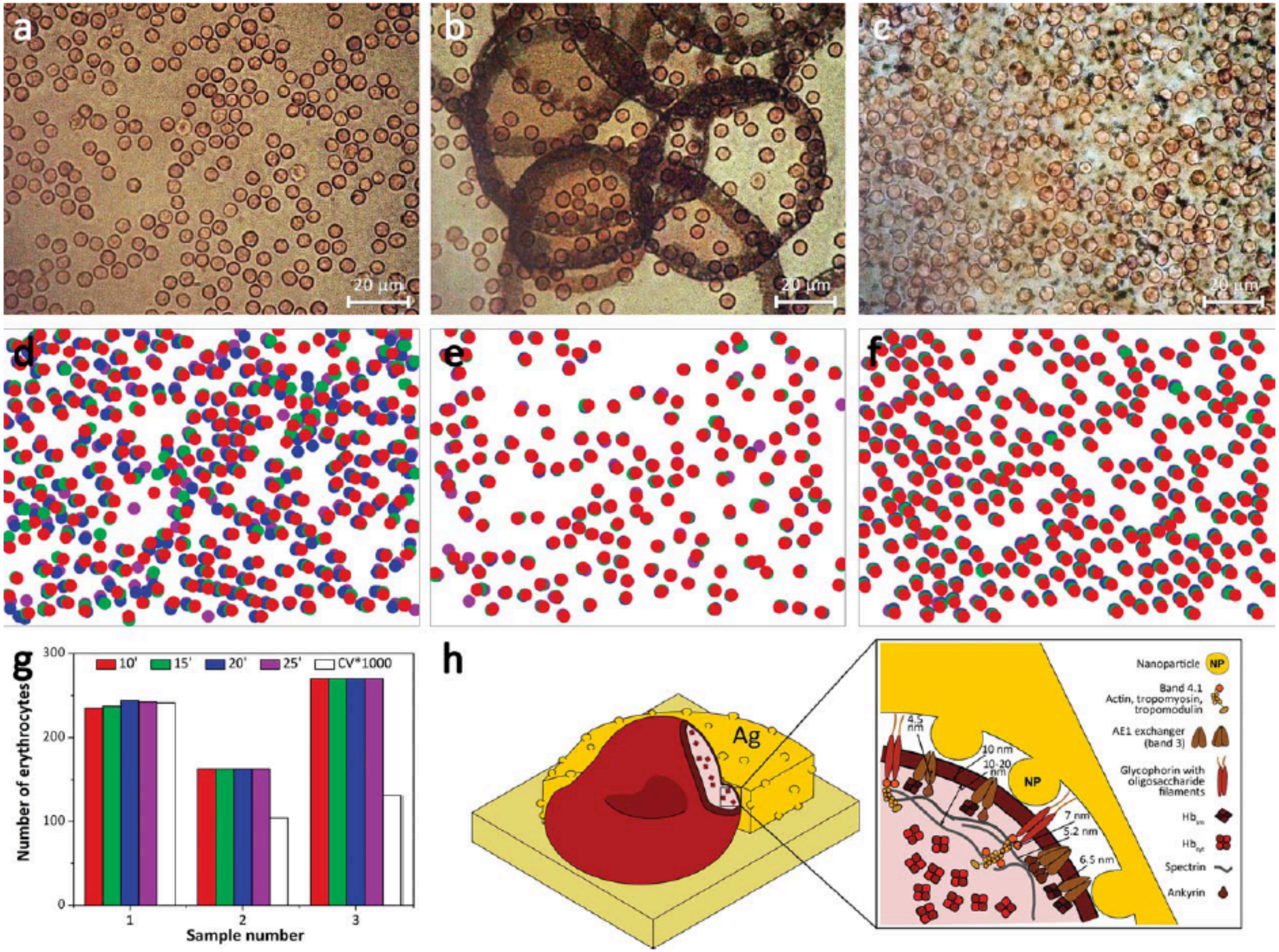



**Fig. 8** Counting of erythrocytes onto USR substrates. Erythrocyte deposition from the Alen's buffer onto a bare glass (a), and "coffee ring" silver substrates with distinct silver circles (sample "b", produced at 270 °C for 5 min) or heavily overlapping circles (sample "c", produced at 270 °C for 40 min). The (d, e, f) maps visualize each counted erythrocyte for the (a, b, c) substrates; "red", "green", "blue" and "magenta" spots correspond to 10, 15, 20 and 25 min periods of erythrocyte physical contact with the substrates under a layer of biological buffer. Note that the observed multiple spots around a fixed point evidence for red blood cell migration with respect to the substrate. (g) Reflects the counting statistics, "sample number" "1", "2, "3" are the samples "a", "b" and "c", respectively; color bars correspond to colored spot counts in the images "d", "e", "f" while white bars are given for variation coefficients ("CV" in the figure) of cell quantities. (h) A model of an erythrocyte near a nanostructured silver wall on the USR substrate, an erythrocyte cross-section and its magnified view show the submembrane structure of the bended erythrocyte with $Hb_{sm}$ approaching closely towards the silver wall.

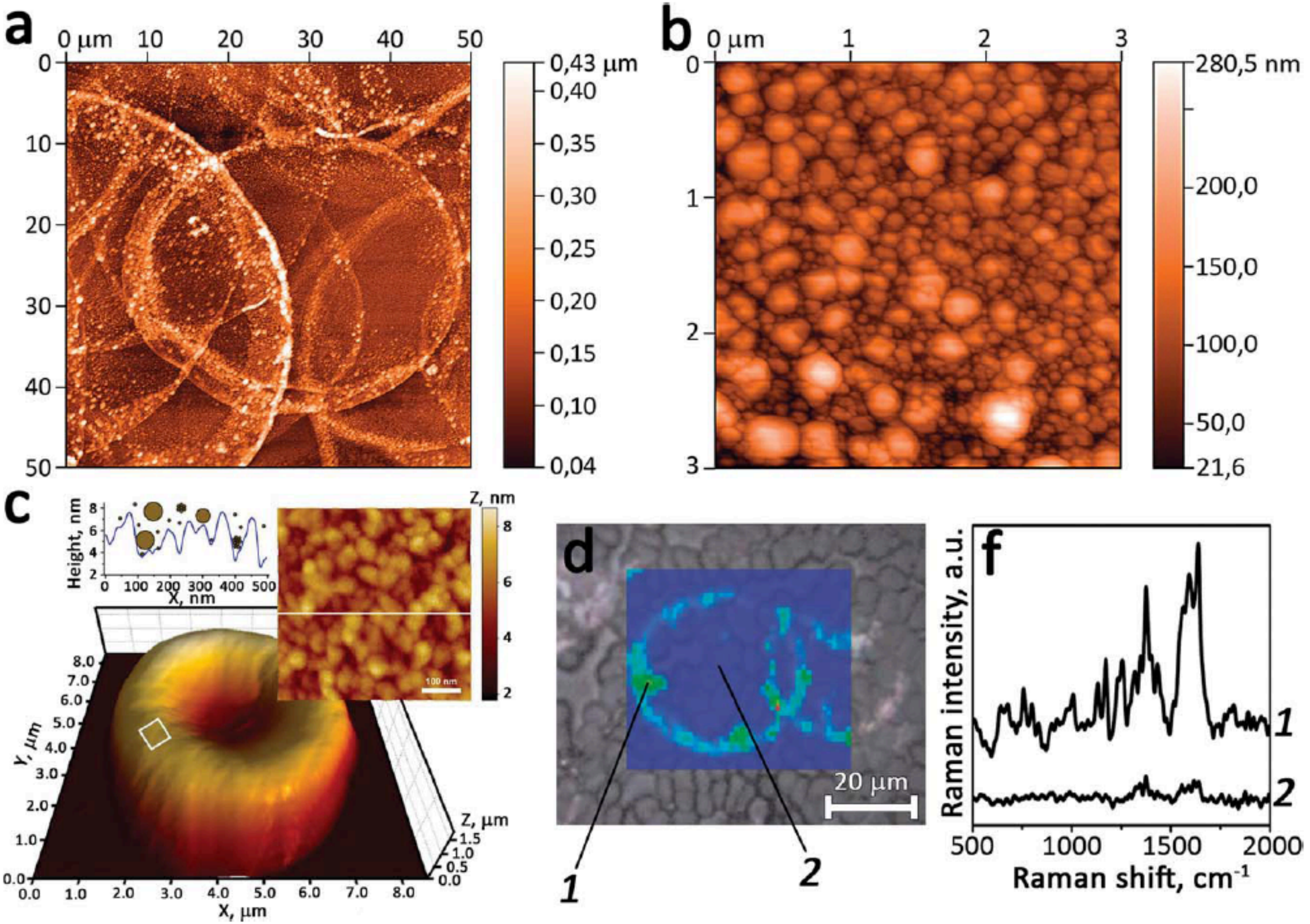
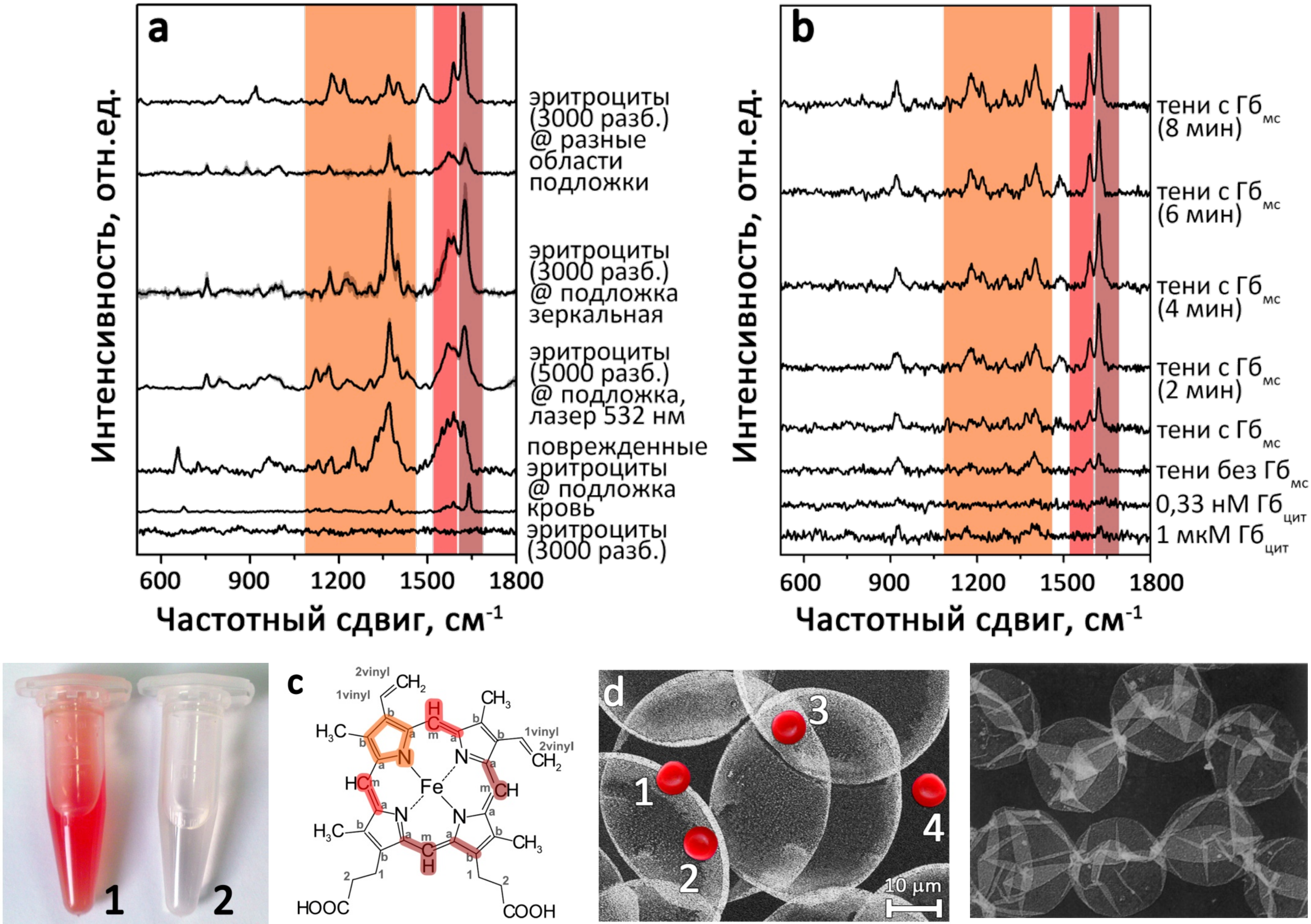
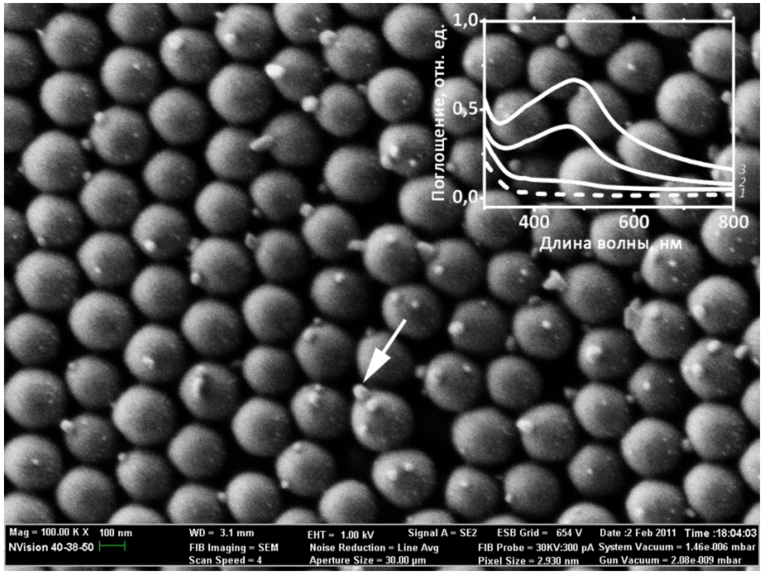


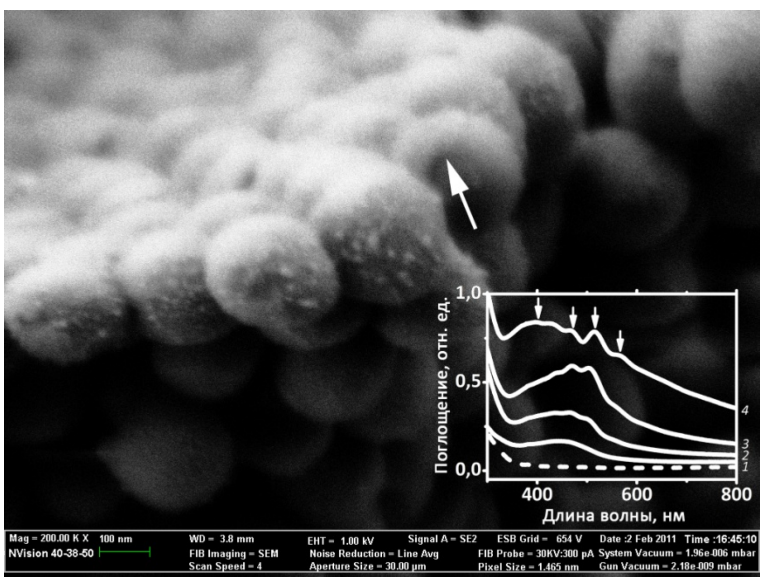

**Fig. 10** The lock and key concept of successful SERS of living erythrocytes on USR substrates. (a) AFM image showing typical sizes of silver crater walls concentrating plasmonic silver; (b) AFM image of silver wall surfaces with elements suitable in their sizes ("key") for penetrating in erythrocyte membrane invaginations ("lock"); (c) AFM image of a single erythrocyte showing nanoscale details of its external surface; the profile graph is given for the white rectangular area, the spheres show hypothetically silver wall elements attempting to enter invaginations; (d) SERS mapping of erythrocytes on the USR substrate and typical SERS spectra measured from different points: on a crater wall and on a flat surface.



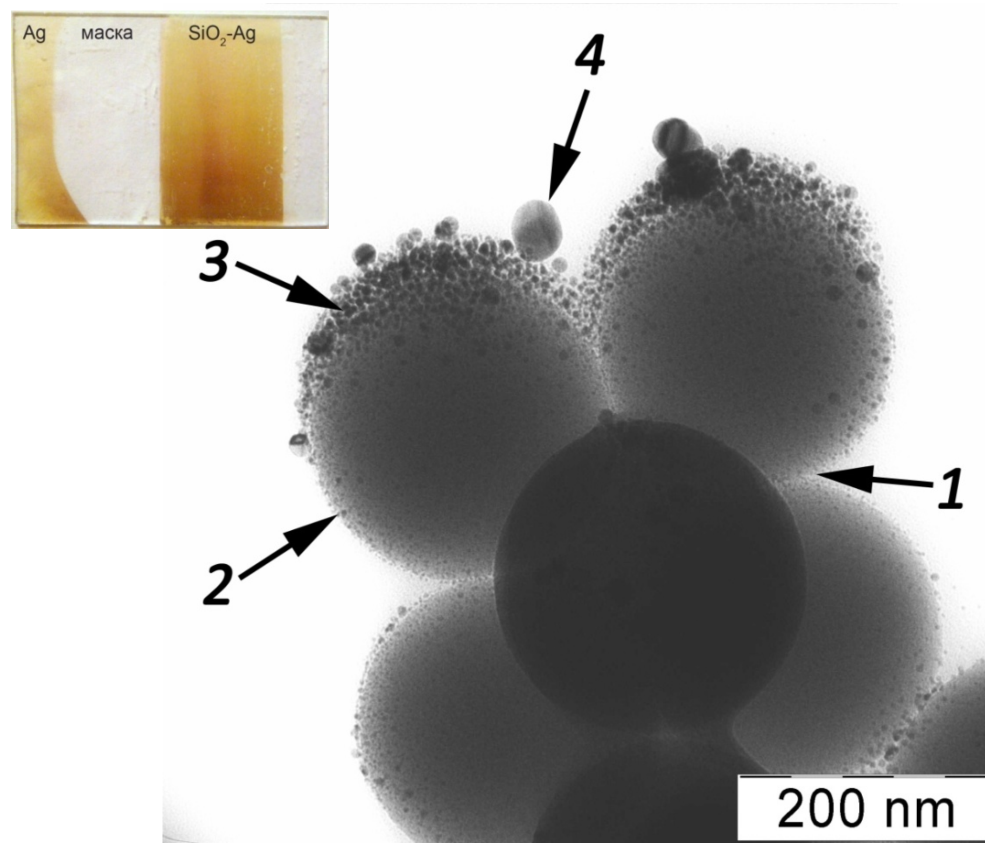

*A.A.Semenova и др.*

# Подложки $SiO_2$–Ag

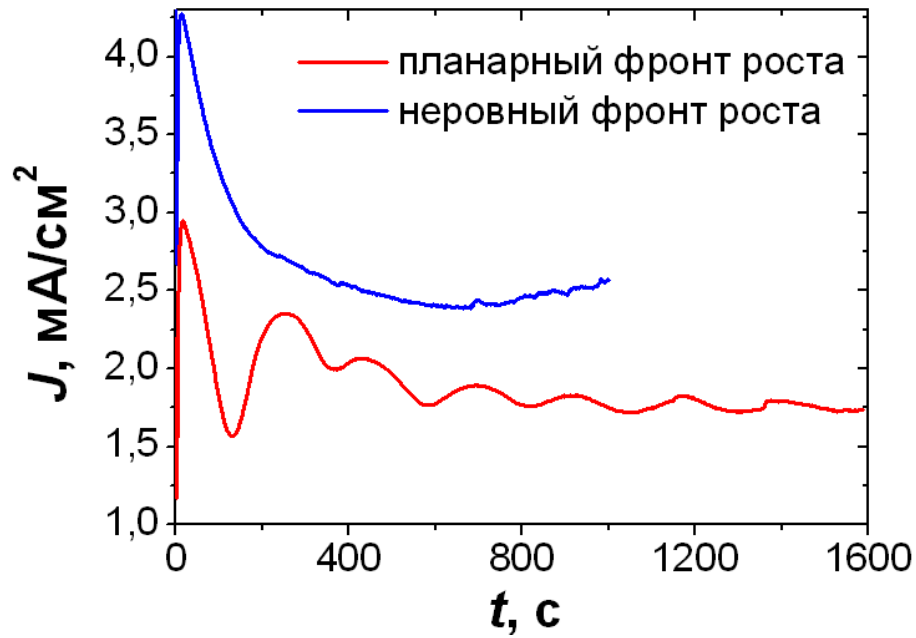


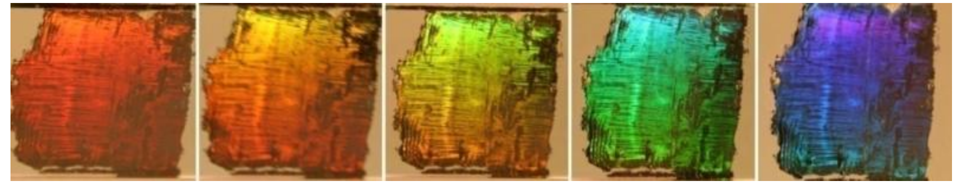



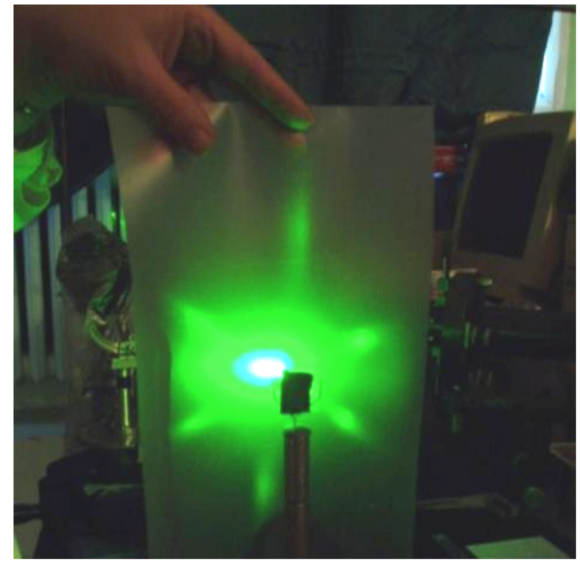

РЭМ подложек (угол – 90° (*вверху*) и 0° (*внизу*), время напыления – 10 мин). На вставке: спектры поглощения образцов при различном времени напыления: 1 (*1*), 5 (*2*) и 10 (*3*) мин – *вверху*, 0.5 (*1*), 1 (*2*), 3 (*3*) и 10 (*4*) мин – *внизу*. Штриховая линия – подложка $SiO_2$

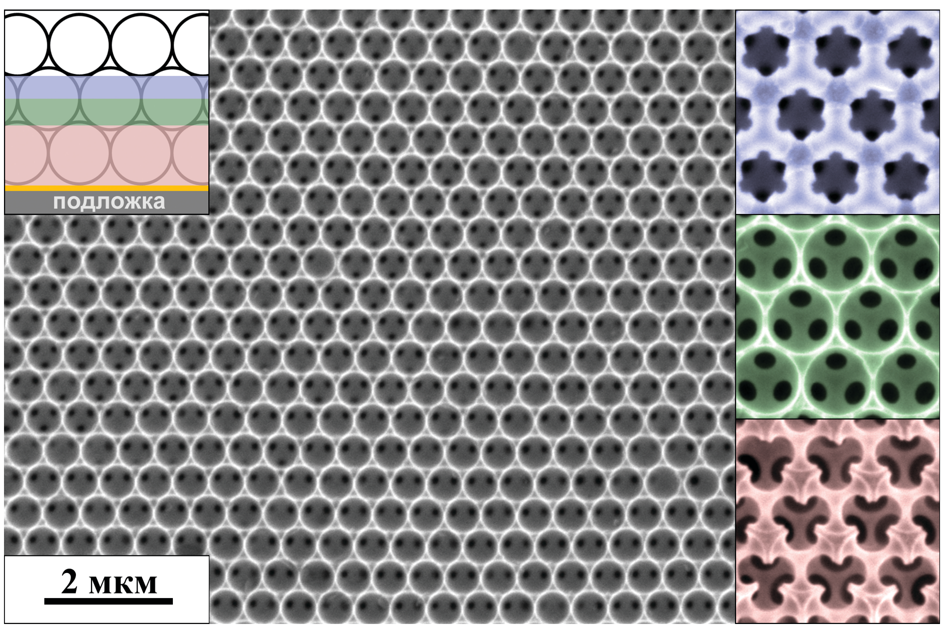


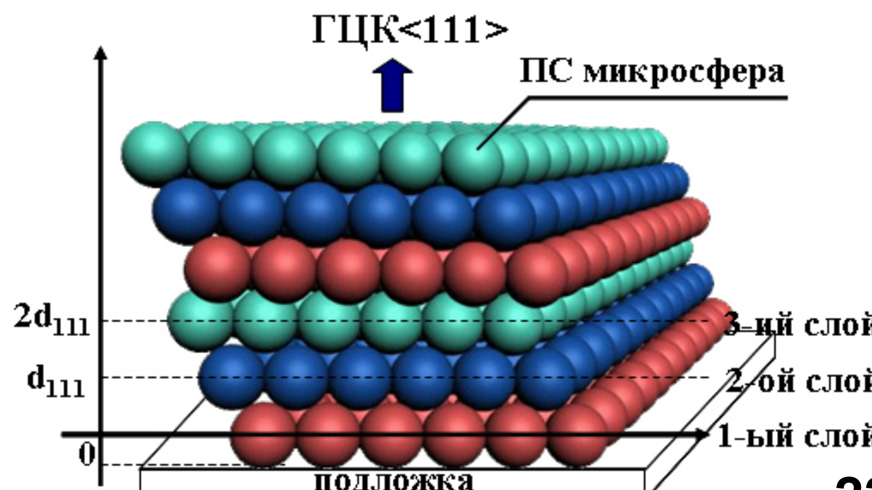

ПЭМ-изображение композитных частиц $SiO_2$–Ag


планарный фронт роста
неровный фронт роста
4,0
3,5
3,0
2,5
2,0
1,5
1,0
0
400
800
1200
1600
J, мА/см²
t, с






подложка
2 мкм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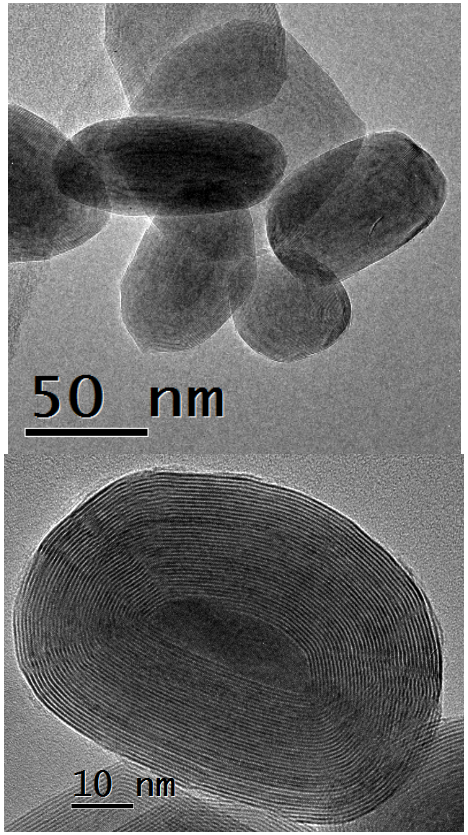
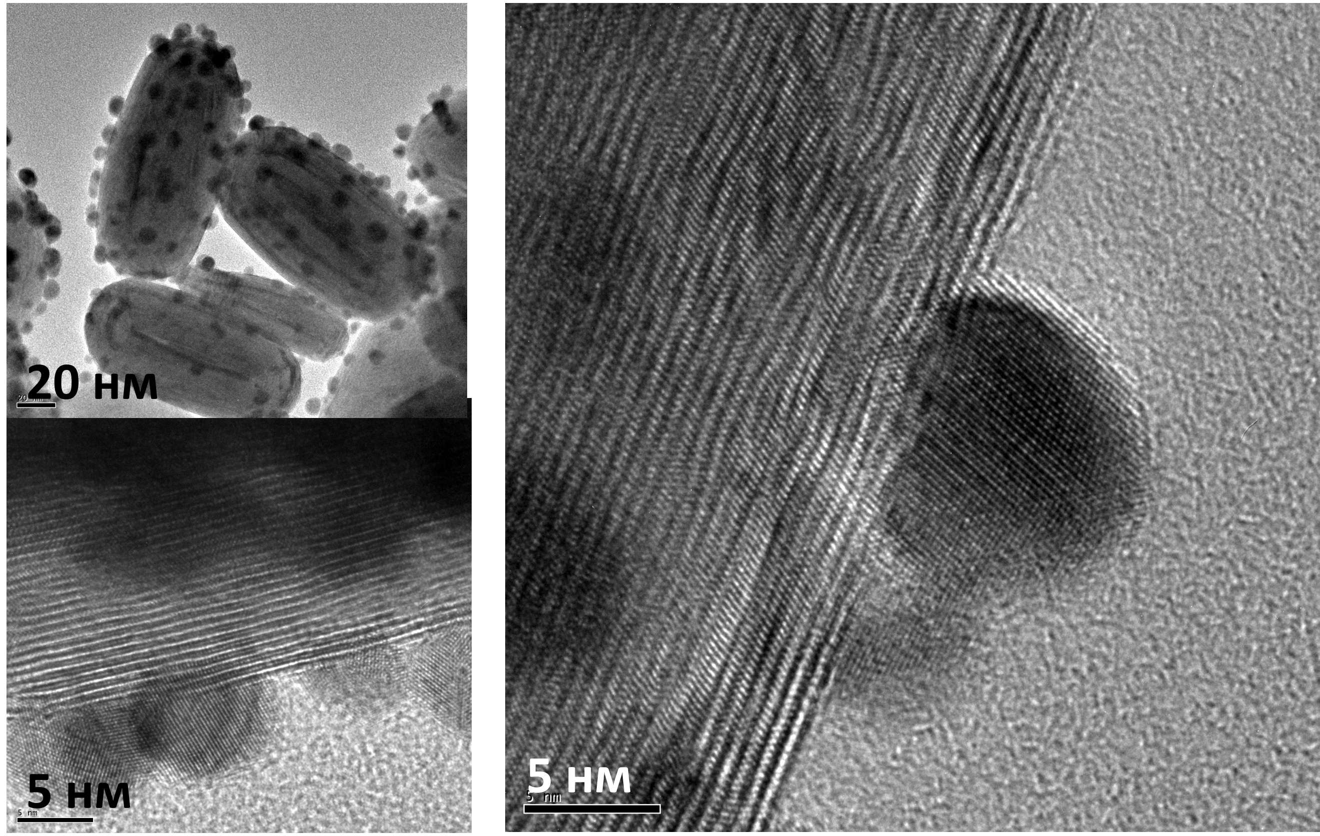
1-ый слой
подложка

# Нанокомпозит Au - ФПЧ-$MoS_2$



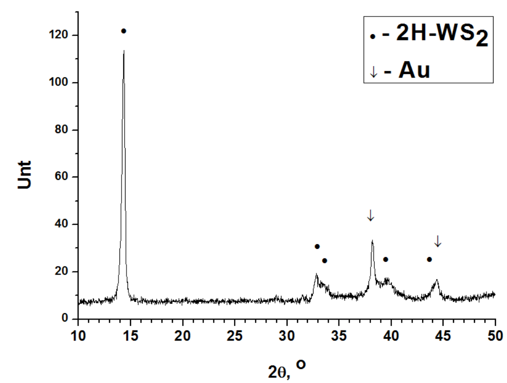

Исходные ФПЧ-$MoS_2$

ФПЧ-$WS_2$, модифицированные наночастицами Au

**Кристаллографическое соотношение:**

**(103) 2H-$MoS_2$ (2.28Å) II (111) Au (2.35Å)**

**Рассогласование 3.1%.**



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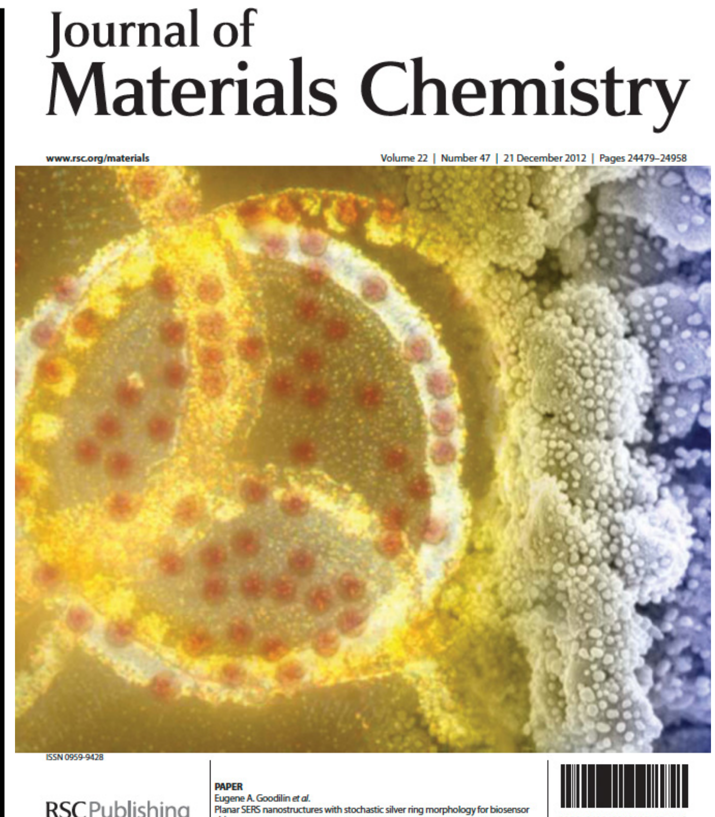


**http://www.nanometer.ru/2013/05/23/prosto_o_slozhnom_331850.html**