NANO-THERANOSTICS WITH PLASMONIC NANOPARTICLES - GOD EXISTS IN THE SMALL DETAILS

NANOISRAEL2016
The 5th International Nanotechnology Conference & Exhibition
February 22-23 ,2016 | Smolarz Auditorium Tel Aviv University, Tel Aviv, Israel

23 Feb. 2016

Dror Fixler
Faculty of Engineering Institute of Nanotechnology and Advanced Materials, Bar-Ilan University

Group research

Diagnostics: Spectrally and Time resolved encoded imaging

- Diffusion Reflection
- Spectral imaging
- Phase retrieval
- Time resolved fluorescence imaging

Therapy: Surface Plasmon Resonance

- Arterial Vascular Disorders
- Cell & tissue manipulations

Bar-Ilan University

Outline

- Motivation – nanoparticle guided therapy;
- New imaging techniques based on plasmon coupled probes for medical applications;
- Perspective;
- Conclusions.

Bar-Ilan University

Outline

- **Motivation – nanoparticle guided therapy;**
- **New imaging techniques based on plasmon coupled probes for medical applications;**
- **Perspective;**
- **Conclusions.**

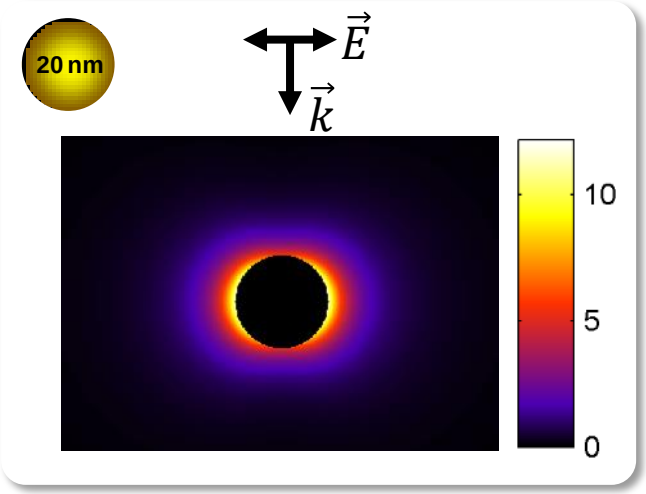
Laser-tissue interaction

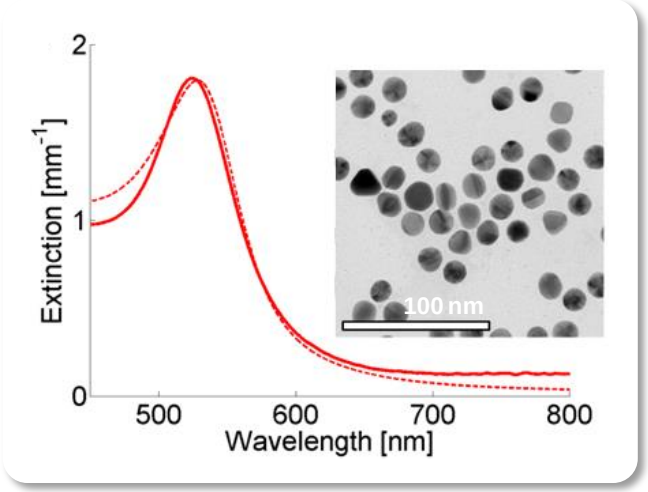
- Scattering and fluorescence → visibility → diagnosis

  Contrast agents: stains, fluorophores, quantum dots

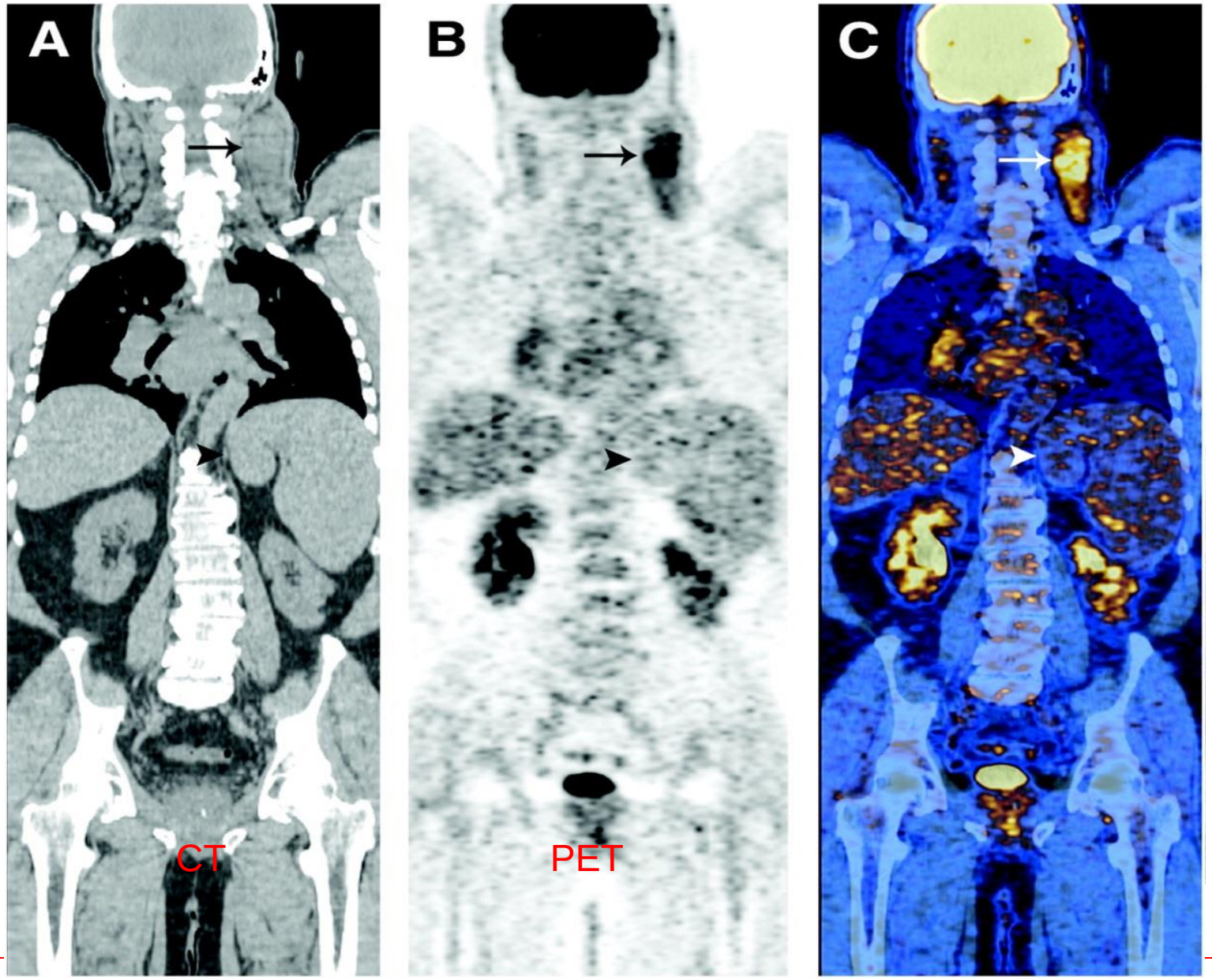
- Absorption → heat/chemistry → therapy

  Mediating agents: photosensitizers, gold nanoparticles



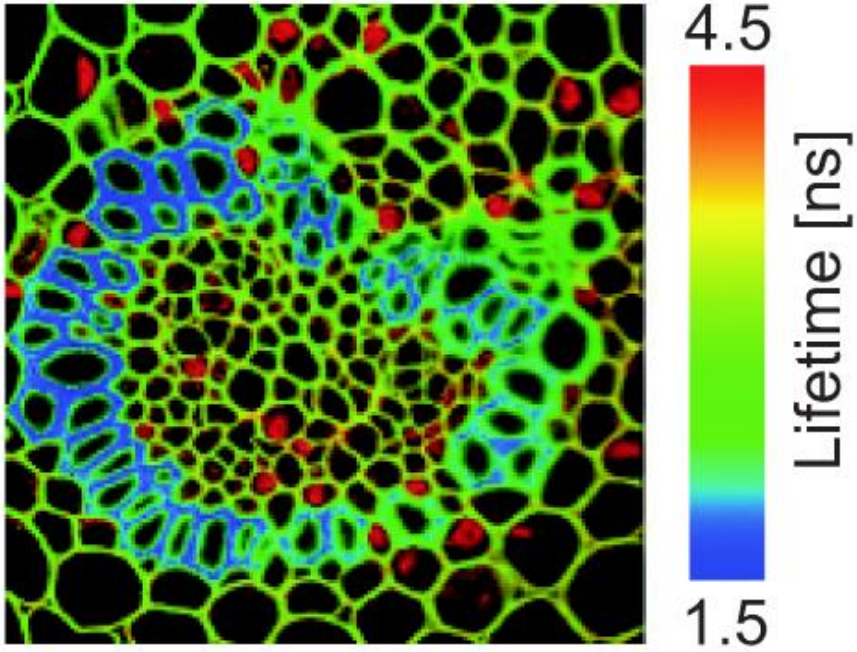


Structural and Functional Imaging

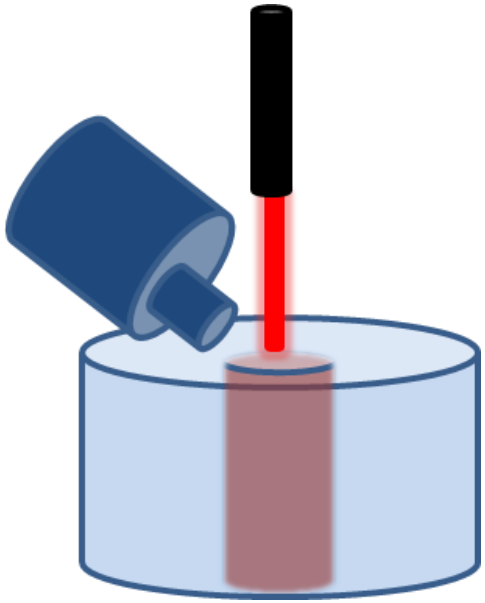


Structural and Functional Imaging

Fluorescence Lifetime Imaging Microscopy (FLIM)



Diffusion Reflection (DR)



Goal

Manipulate cells and tissue on a nanometric scale for theranostic applications

Approach

Localized area of interest using gold nanoparticles and Fluorescence Lifetime imaging

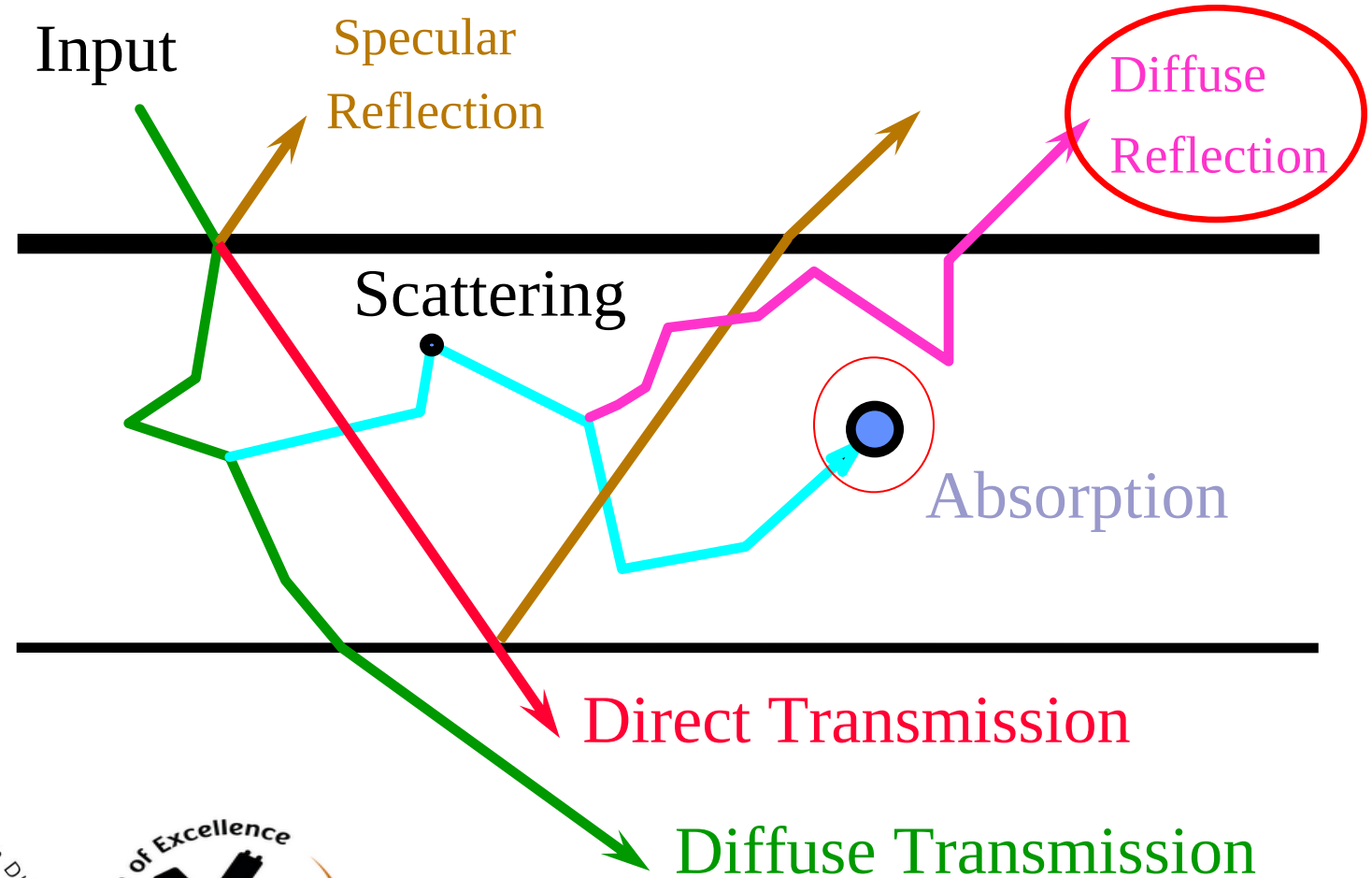
Bar-Ilan University

Outline

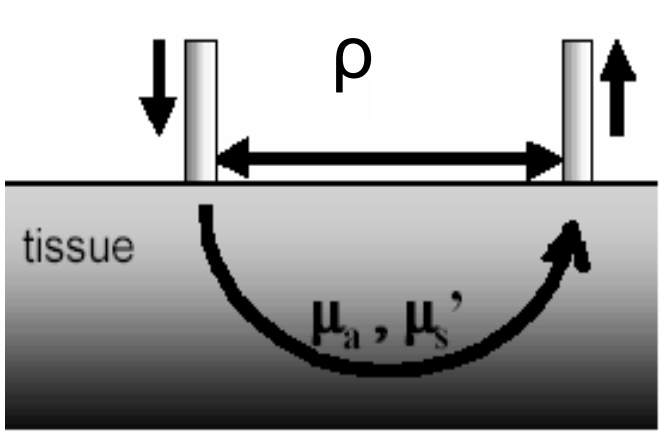
- Motivation – nanoparticle guided therapy;
- New imaging techniques based on plasmon coupled probes for medical applications;
- Perspective;
- Conclusions.

“Fantastic Voyage” Isaac Asimov (1966)

Light Interaction with a Turbid Medium



Light Path in Irradiated Tissues

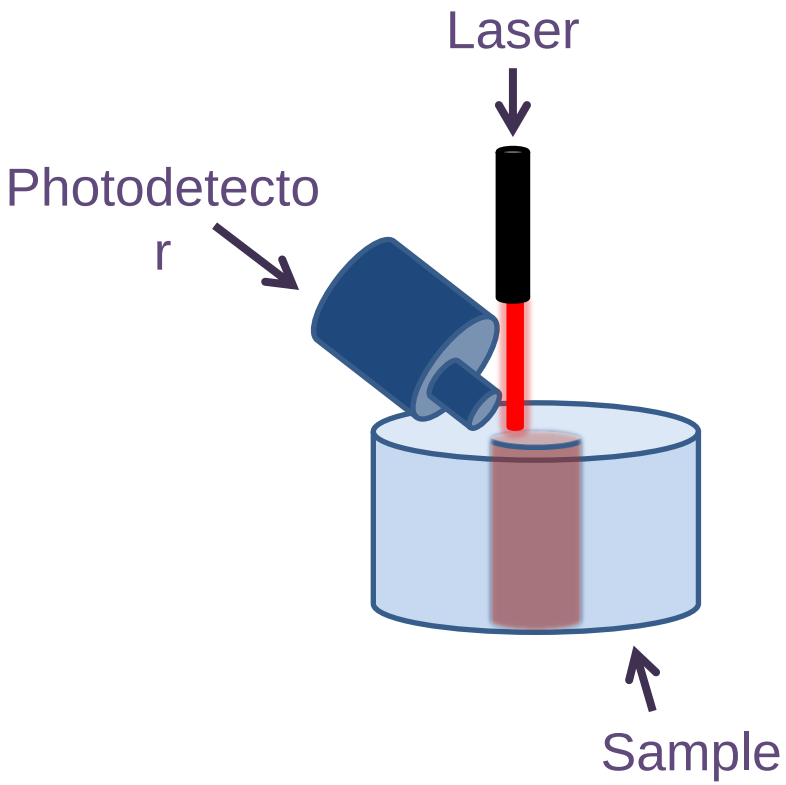


$$\Gamma(\rho) = \left(\frac{c_1}{\rho^m} \right) \exp(-c_2 \rho)$$

ρ<1 mm	→	m=0.5,	*Groenhuis et al.,* 1983
ρ>1 mm	→	m=1,	*Schmitt et al.,* 1990
large ρ	→	m=2,	*Bonner et al.,* 1987

Ankri, Taitelbaum and Fixler, Reflected Light Intensity Profile of Two-Layer Tissues - Phantom Experiments, J. of Biomedical Optics, 16:8 (2011).

Diffusion Reflection (DR)



Intensity

Spectral Properties

$$I(\rho) = \frac{c_1}{\rho^2} e^{-\mu\rho}$$

Separation Distance

$$\ln[\rho^2 \mathrm{I}(\rho)] = c_2 - \mu\rho$$

Surface plasmon resonance

When a nanoparticle is much smaller than the wavelength of light, coherent oscillation of the conduction band electrons is induced by interaction with an electromagnetic field. This resonance is called Surface Plasmon Resonance (SPR).

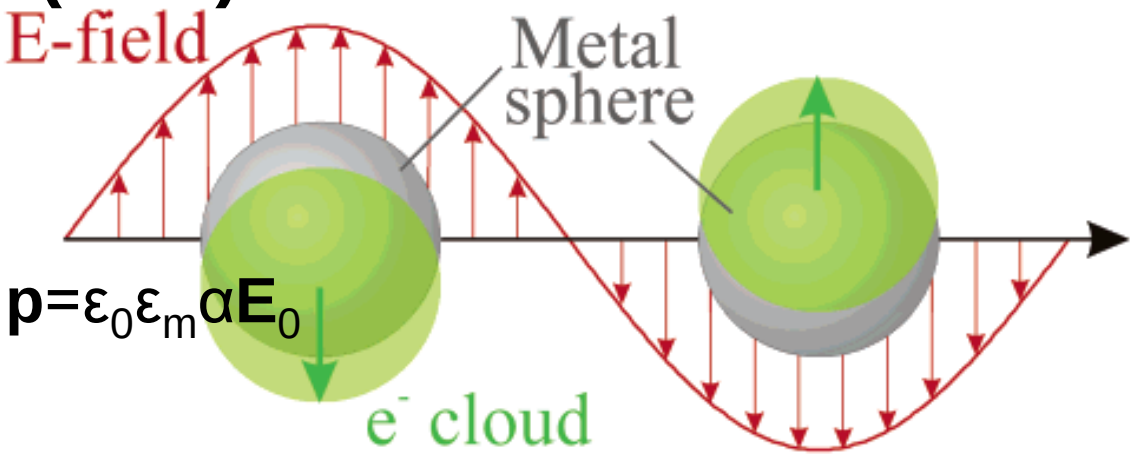
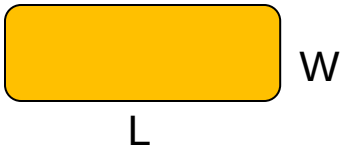


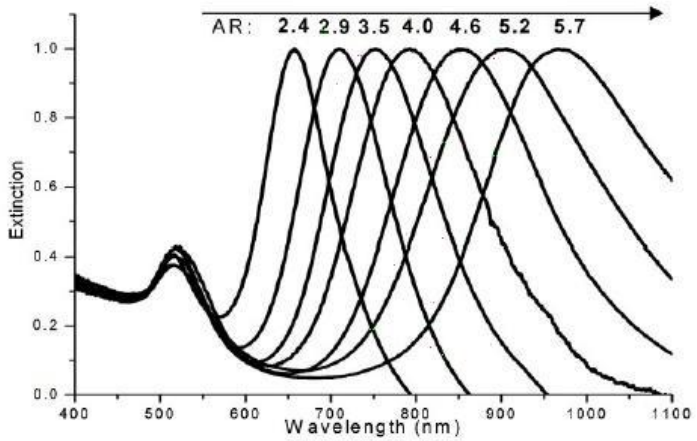
Figure: Schematic of plasmon oscillation for a sphere, showing the displacement of the conduction electron charge cloud relative to the nuclei.

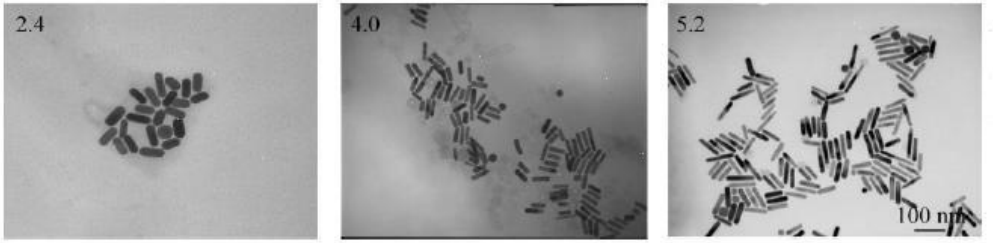
Optical Properties of Gold Nanorods

Gold nanorods have shape and size-dependent optical properties originating from an anisotropic shape and tunable aspect ratio.



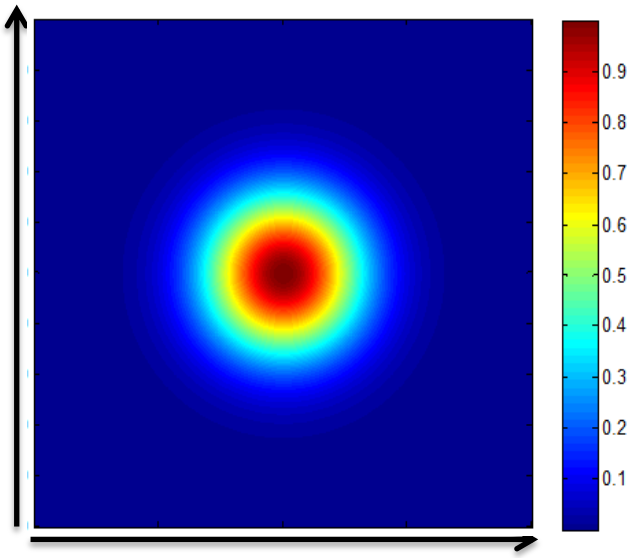
Aspect Ratio (AR) = L/W



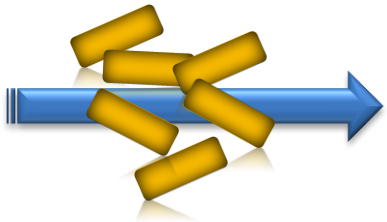


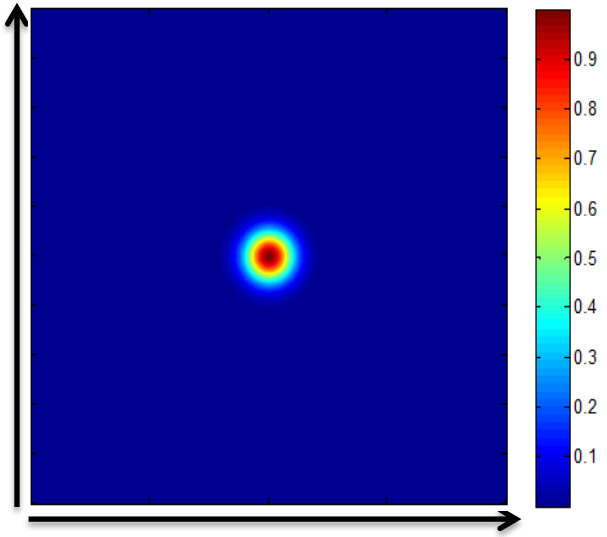
Nikoobakht *et al. Chem Mater.* **2003**, *15*, 1957-1962.

The concept



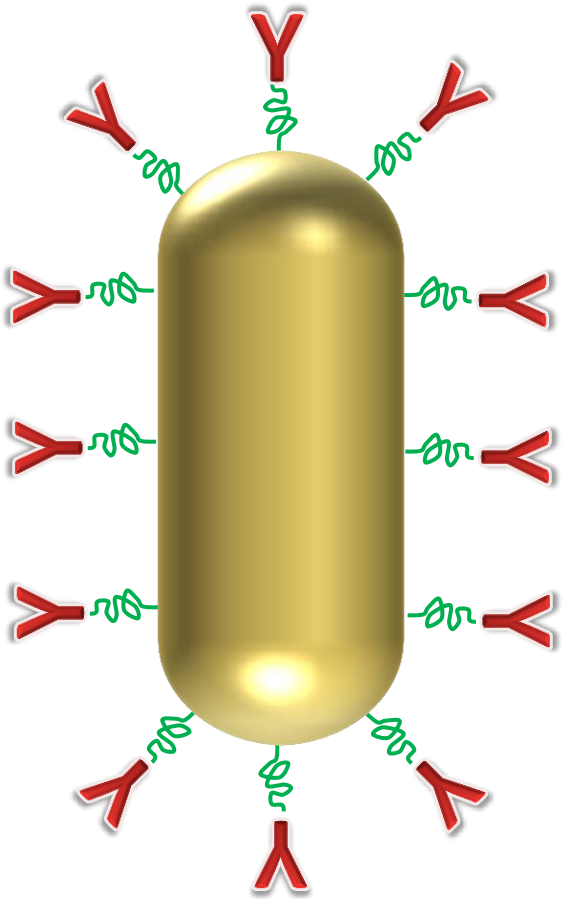
GNRs injection

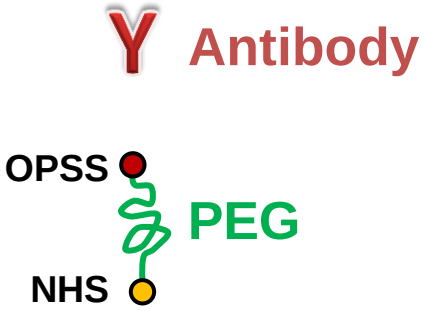




Protocol

1. Particle preparation





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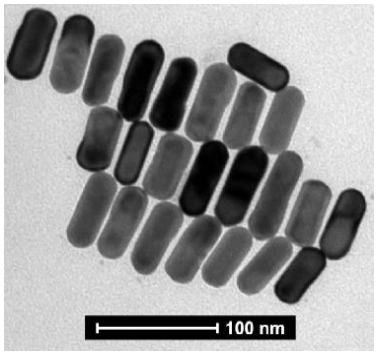
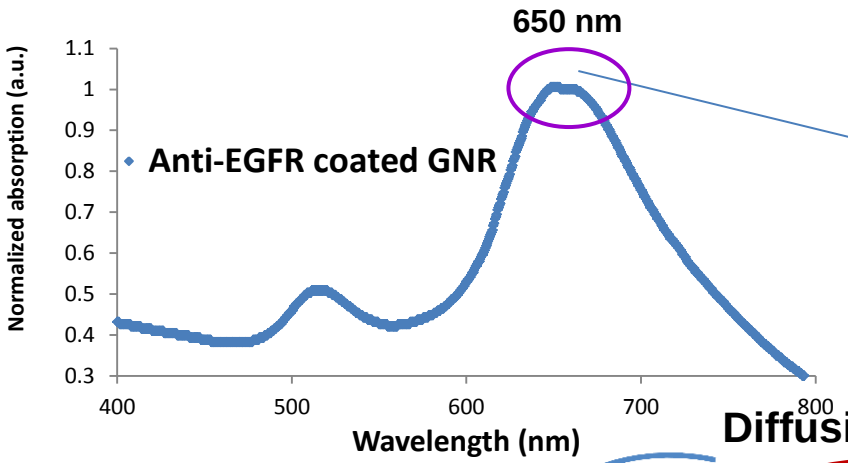
BINA
Tradition of Excellence

Protocol

1. Particle preparation
2. Targeting

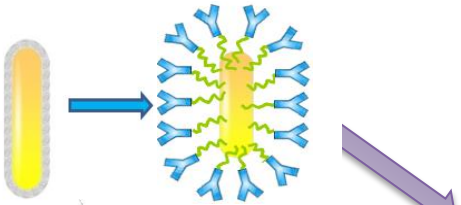
Tumor detection based on DR measurements of targeted gold nanorods (GNR)

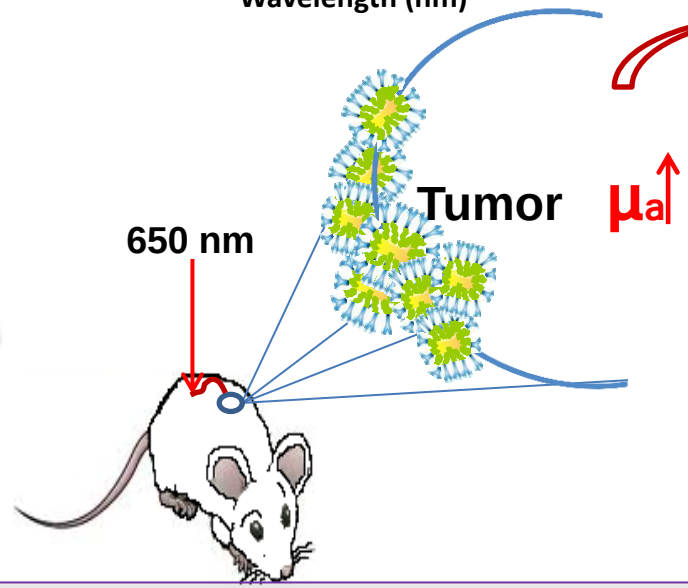


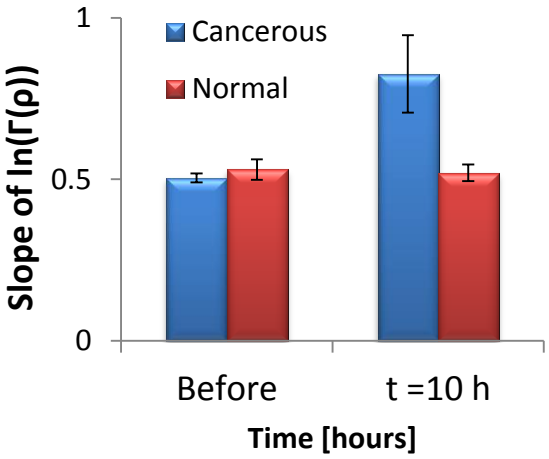


Enhancing the tumor *absorption coefficient* by EFGR labeled GNR injection.

Diffusion Reflection measurements







Fixler; *A New Skin Surface Subcutaneous gold nanoroad detection, J. of Biomedical Optics 18(6), 2013.*

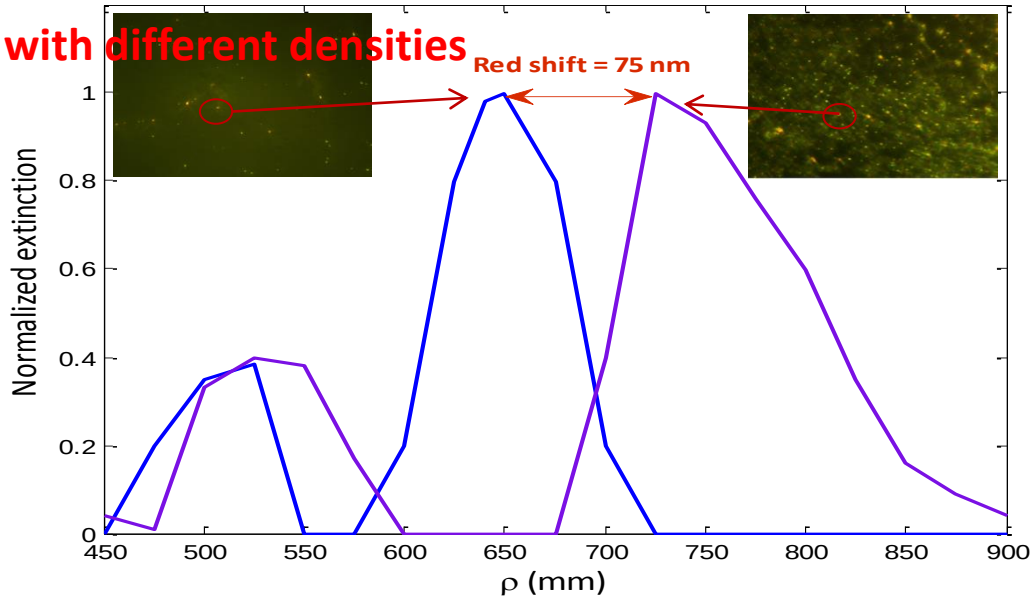
Protocol

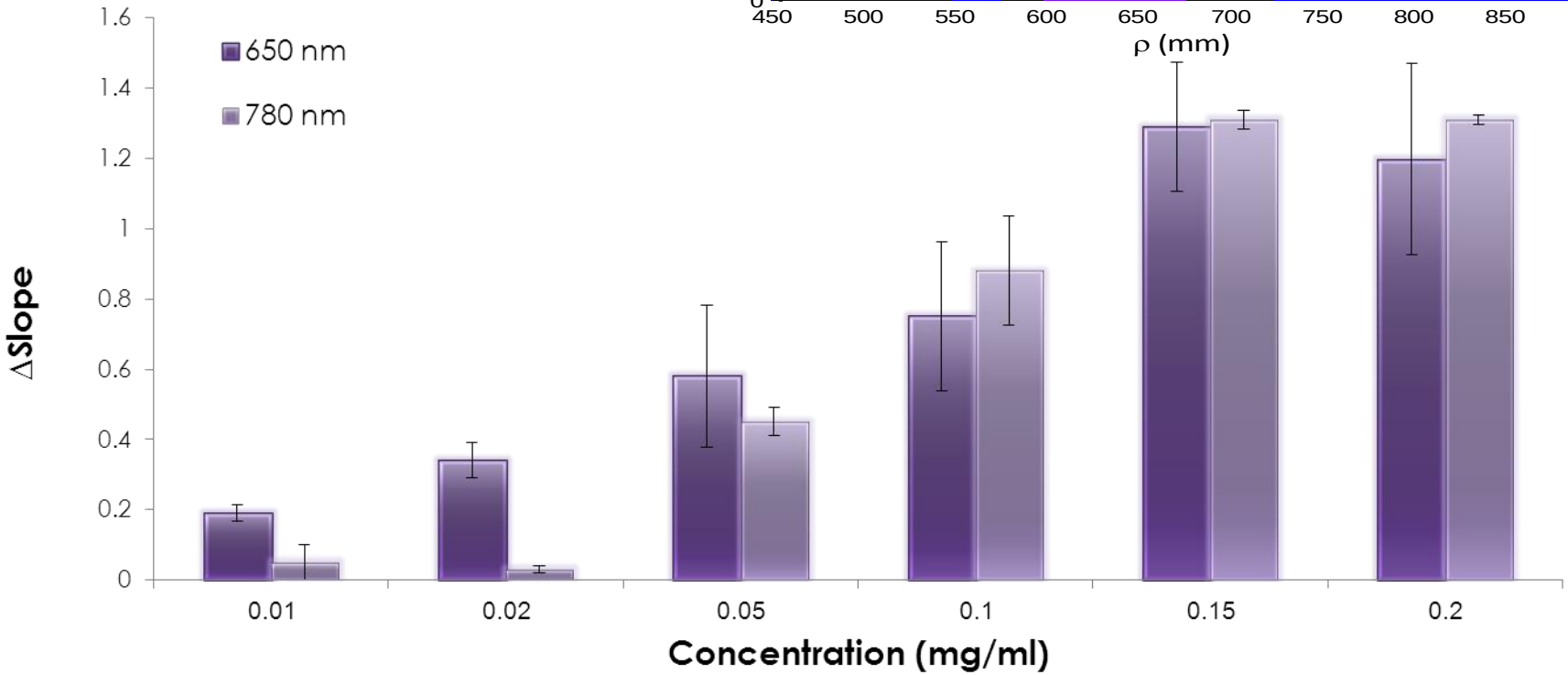
1. Particle preparation
2. Targeting
3. Irradiation

DR measurements of high concentrations of GNR- a *Red shift* is observed

Dark field Microscopy:

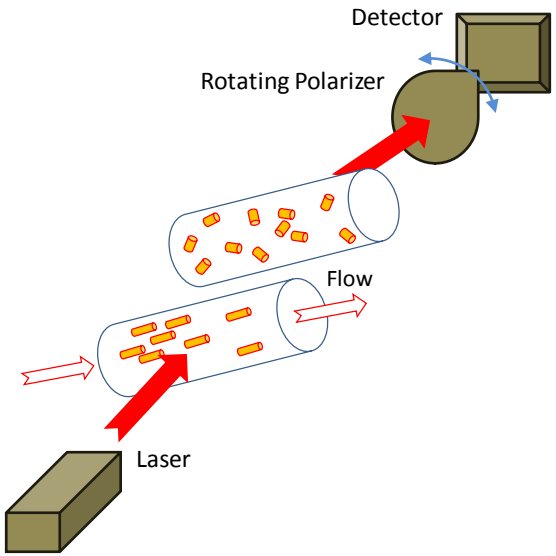
GNR with different densities

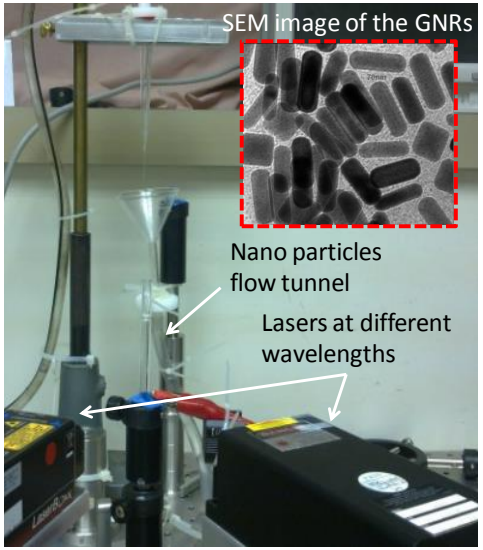


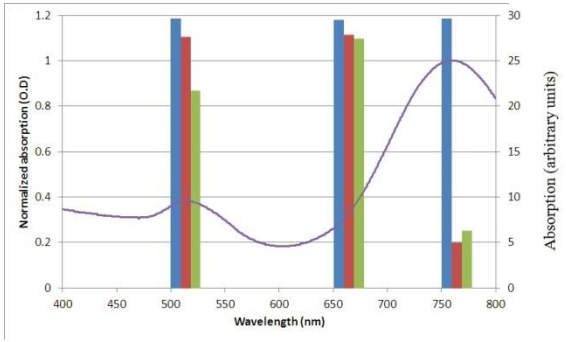


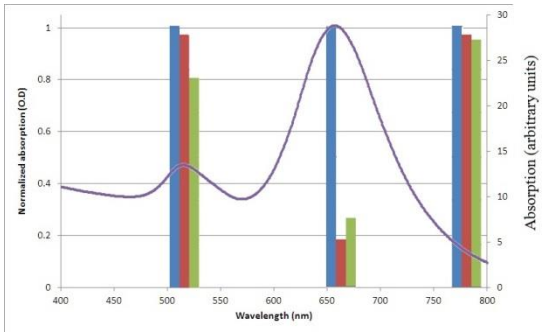
Fixler et al, Intercoupling Surface Plasmon Resonance and Diffusion Reflection Measurements for Real-Time Cancer Detection, J. Biophotonics 6(2):188-196 (2013).

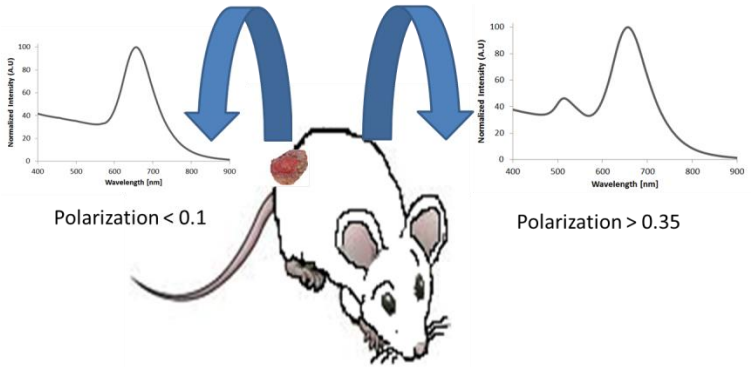
In vivo *Tumor Detection Using Polarization and Wavelength Reflection Characteristics of Gold Nanorods*

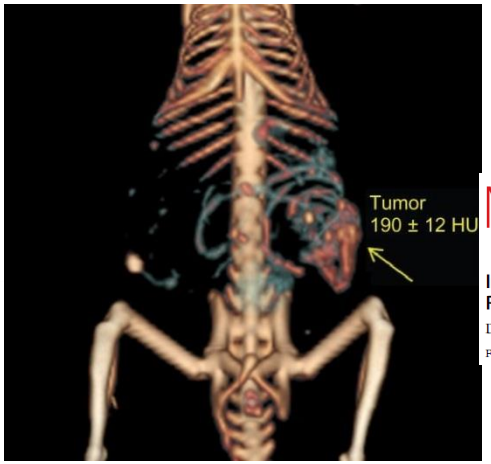


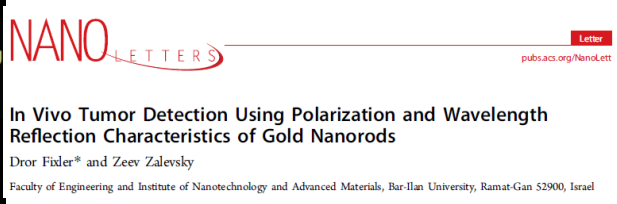











NANO LETTERS

Letter

pubs.acs.org/NanoLett

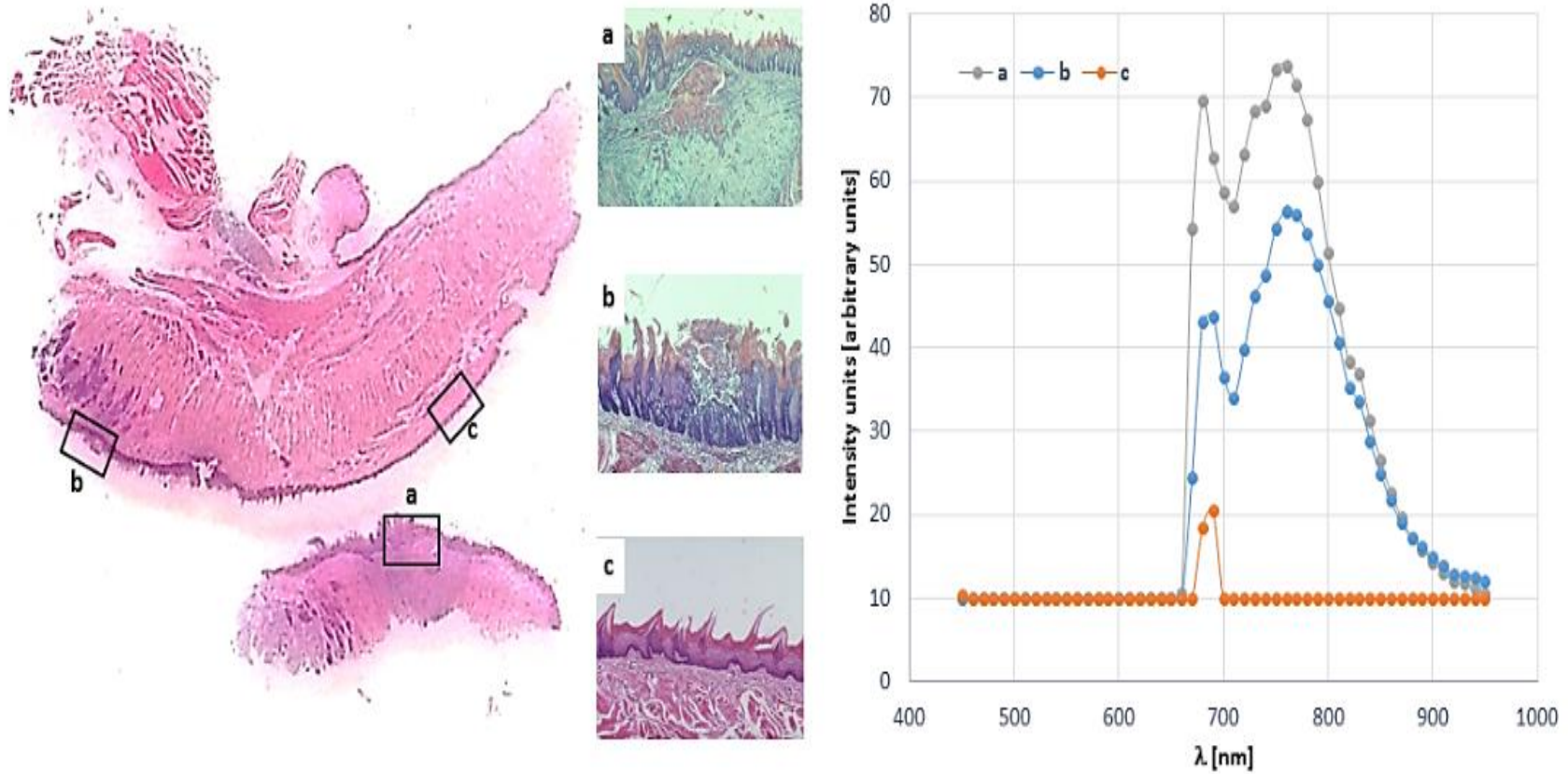
In Vivo Tumor Detection Using Polarization and Wavelength Reflection Characteristics of Gold Nanorods

Dror Fixler* and Zeev Zalevsky

Faculty of Engineering and Institute of Nanotechnology and Advanced Materials, Bar-Ilan University, Ramat-Gan 52900, Israel

D. Fixler et. al, Nano Lett. 2013 13(12):6292-6.

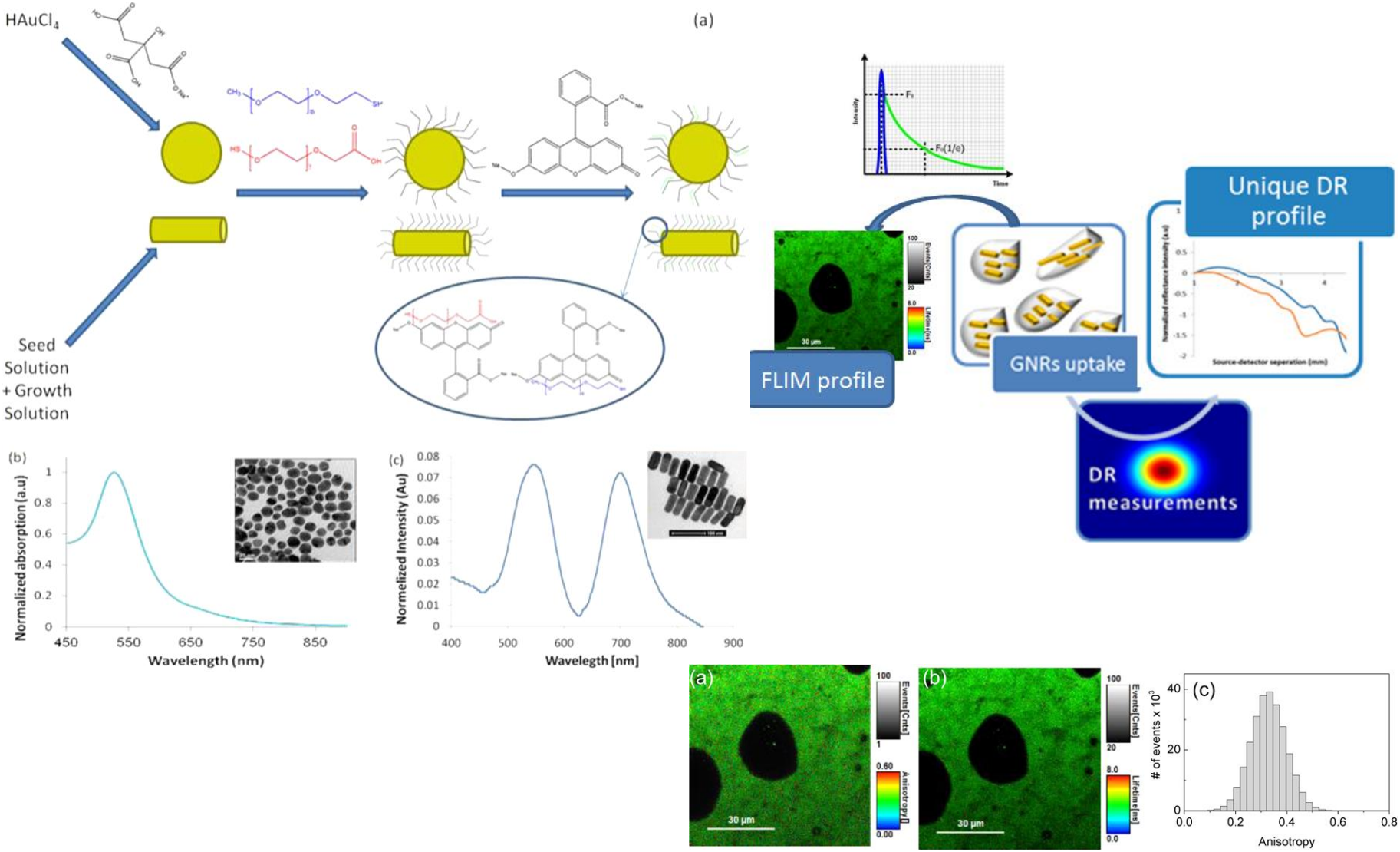
A novel method for early detection of oral cancer



Reflectance spectra and the corresponding histology of the experimental rat tongue at week 37. The area of normal epithelium (area c) lacks the reflectance spectrum at 780nm, the same as in the control rats. High reflectance at 780nm was found in the area identified histologically as squamous cell carcinoma (area a) and moderate reflectance in the area of carcinoma in-situ (area b).

Fixler et.al. Diffusion Reflection: A Novel Method for Detection of Oral Cancer. J Dent Res. 2014;93(6):602-606.

Combining GNRs and Fluorescence

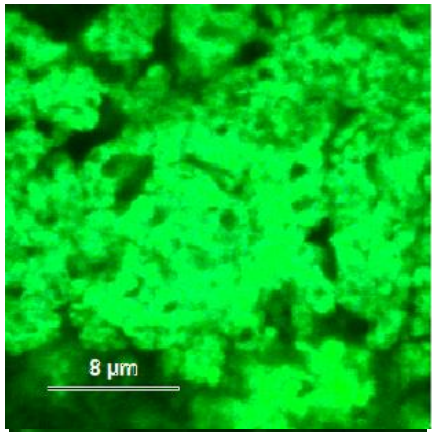


Dror Fixler and Krishanu Ray, Diffusion Reflection and Fluorescence Lifetime Imaging Microscopy Study of Fluorophore-Conjugated Gold Nanoparticles or Nanorods in Solid Phantoms, ACS Photonics (2014)

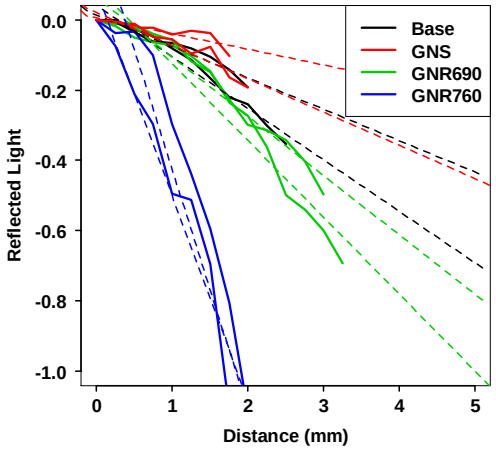
Set Up

FLIM

DR



MEF

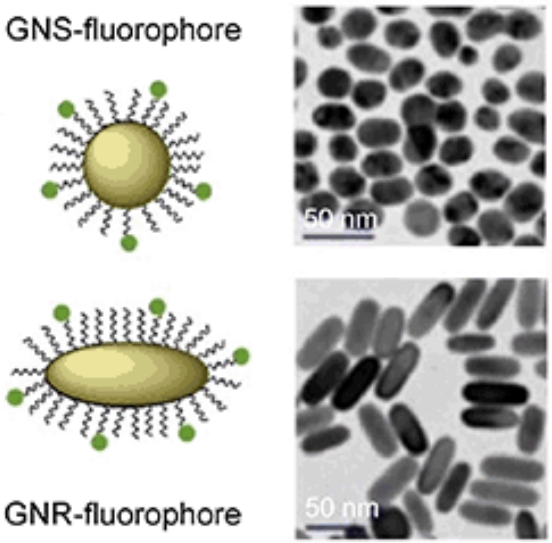


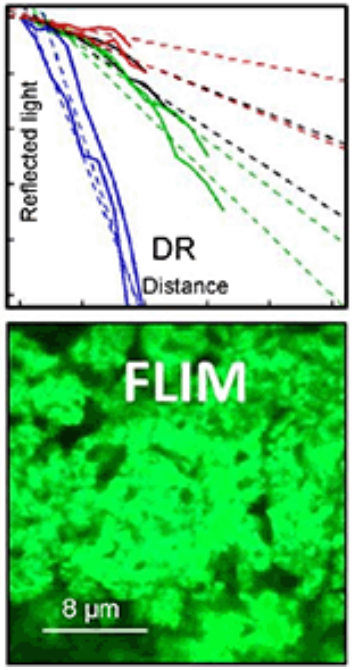
Metal-Enhanced Fluorescence (MEF)

Research Article
Nano Research
pp 1-10

First online: 12 November 2015

DOI 10.1007/s12274-015-0891-y





An ultra-sensitive dual-mode imaging system using metal-enhanced fluorescence in solid phantoms

Eran A. Barnoy, Dror Fixler ✉ , Rachela Popovtzer, Tsviya Nayhoz, Krishanu Ray ✉

The resolution issue

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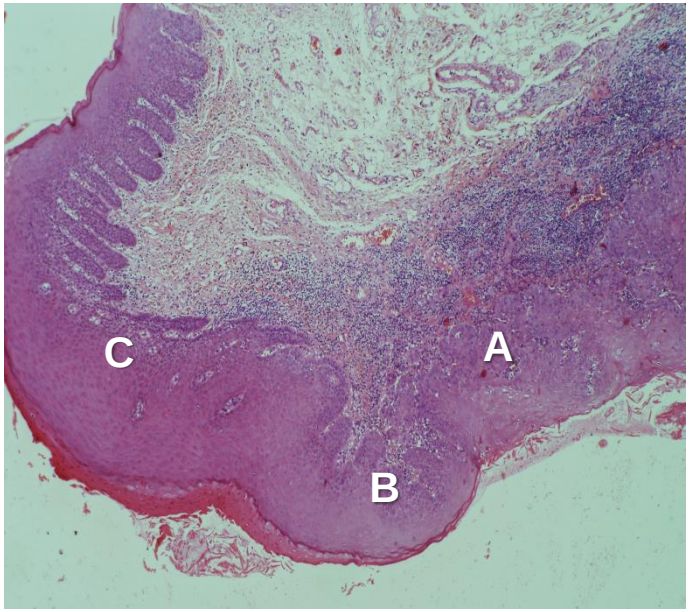
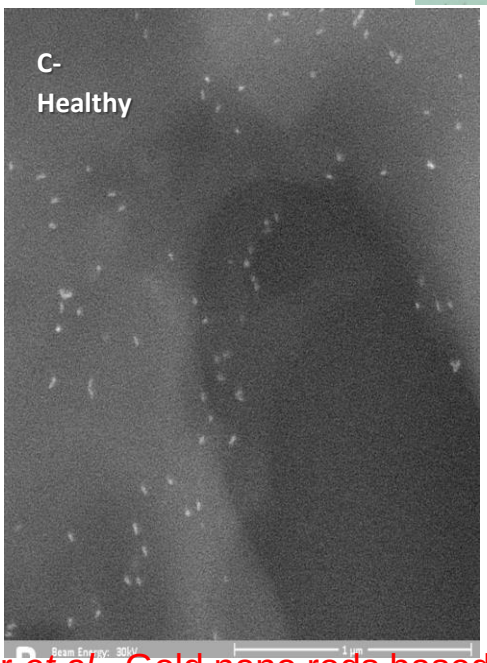
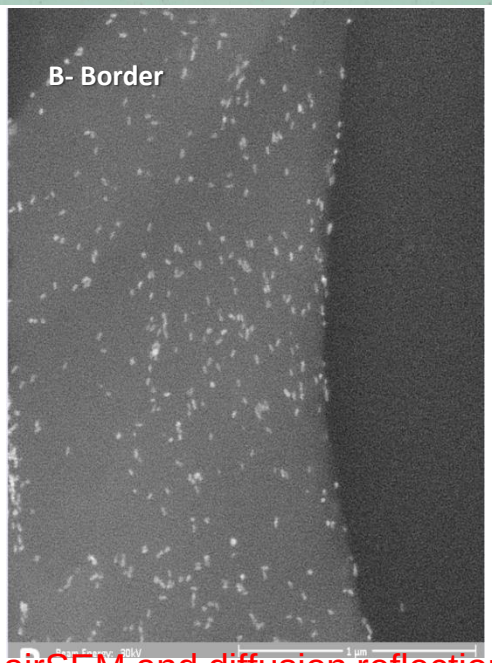
ARTICLE

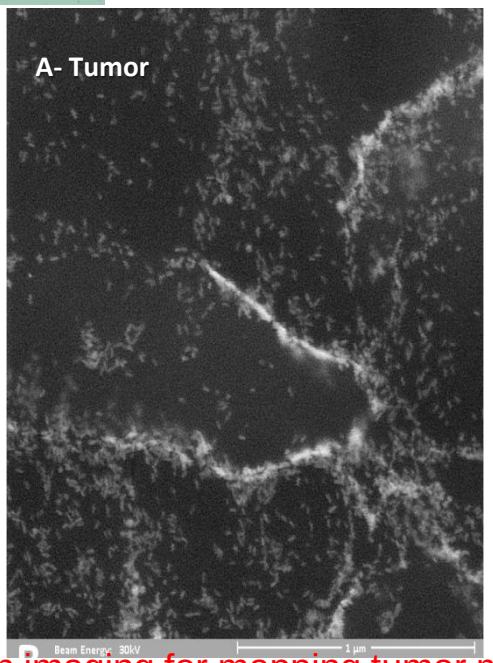
Gold Nanorods Based Air Scanning Electron Microscopy and Diffusion Reflection Imaging for Mapping Tumor Margins in Squamous Cell Carcinoma

Rinat Ankri,[†] Ariel Ashkenazy,[†] Yonat Milstein,[§] Yaniv Brami,[§] Asaf Olshinka,[∥] Nitza Goldenberg-Cohen,[⊥] Aron Popovtzer,[#] Dror Fixler,[*,†,▽] and Abraham Hirshberg[‡,▽]









Ankri, Fixler *et al.*, Gold nano rods based airSEM and diffusion reflection imaging for mapping tumor margins in SCC cells, ACS nano (2016).

As described elsewhere…:

1. Reflected light intensity profile of two-layer tissues - phantom experiments; Rinat Ankri, Haim Taitelbaum and Dror Fixler, *Journal of Biomedical Optics*, 2011.

2. On phantom experiment of the photon migration model in tissues; Rinat Ankri, Haim Taitelbaum, and Dror Fixler, *The Open Optics Journal*, 2012.

3. A new method for cancer detection based on diffusion reflection measurements of targeted gold nanorods; Rinat Ankri, Vital Peretz, Menachem Motiei, Rachela Popovtzer and Dror Fixler, *International Journal of Nanomedicine*, 2012.

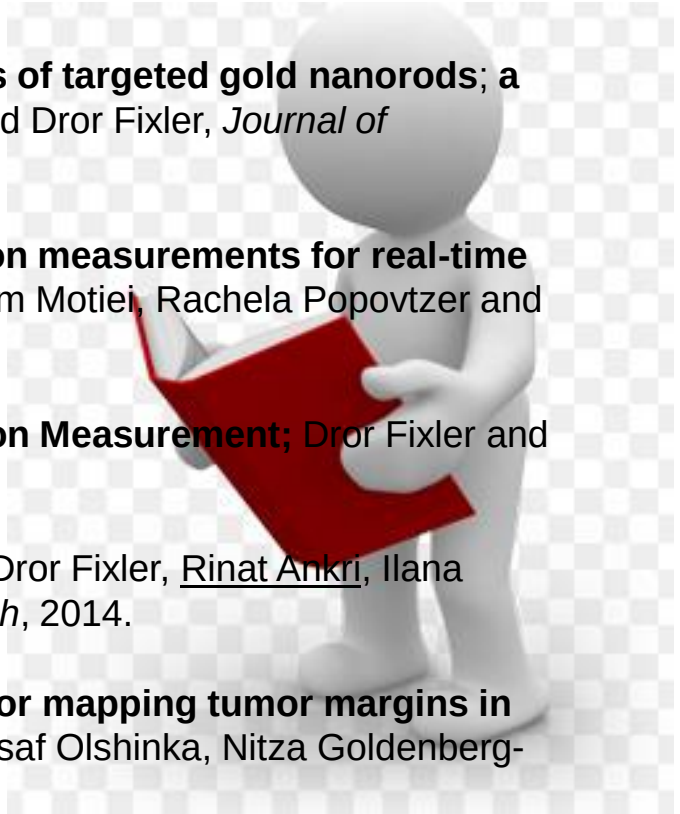
4. *In-vivo* tumor detection using diffusion reflection measurements of targeted gold nanorods; **a quantitative study**; Rinat Ankri, Hamootal Duadi, Menachem Motiei and Dror Fixler, *Journal of Biophotonics*, 2012.

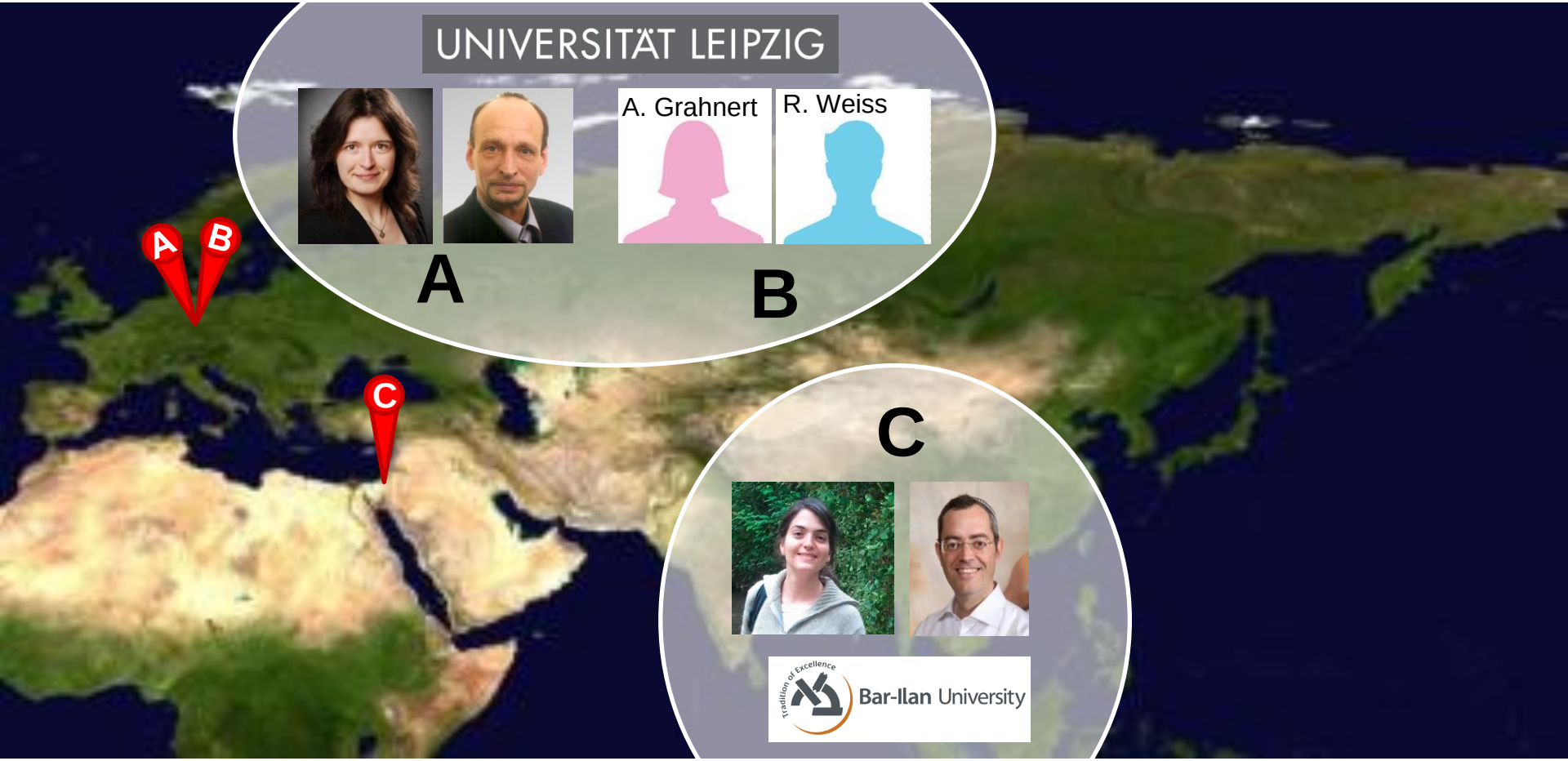
5. Intercoupling surface plasmon resonance and diffusion reflection measurements for real-time cancer detection; Rinat Ankri, Amihai Meiri, Shemuel I. Lau, Menachem Motiei, Rachela Popovtzer and Dror Fixler, *Journal of Biophotonics*, 2012.

6. Subcutaneous Gold Nanoroad Detection with Diffusion Reflection Measurement; Dror Fixler and Rinat Ankri, *Journal of Biomedical Optics*, 2013.

5. Diffusion reflection, a new method for detection of oral cancer; Dror Fixler, Rinat Ankri, Ilana Kaplan, Ilya Novikov and Abraham Hirshberg, *Journal of dental research*, 2014.

7. Gold nano rods based airSEM and diffusion reflection imaging for mapping tumor margins in SCC cells; Rinat Ankri, Ariel Ashkenazy, Yonat Milstein, Yaniv Brami, Asaf Olshinka, Nitza Goldenberg-Cohen, Dror Fixler, Abraham Hirshberg; *ACS Nano*, 2016

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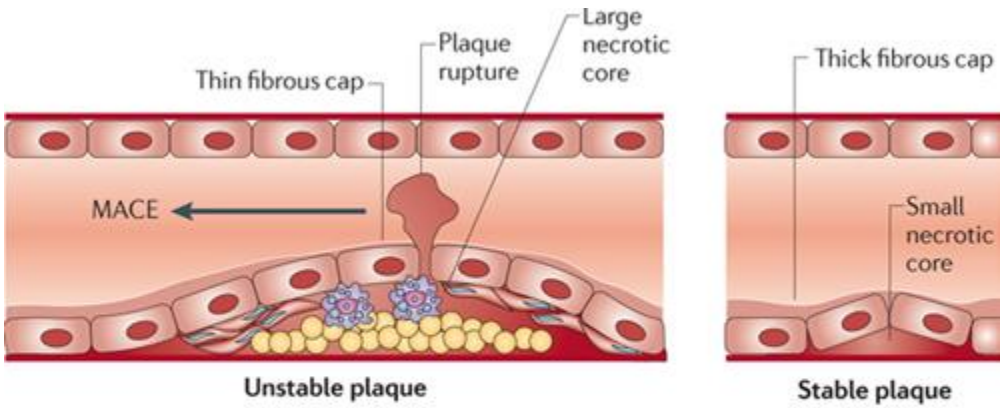
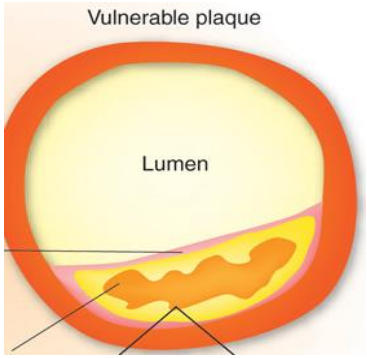
Tradition of Excellence
Bar-Ilan University

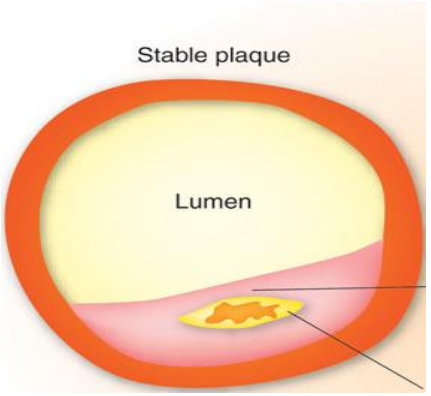
Stable vs. Unstable (vulnerable) Plaques



Nature Reviews | Drug Discovery

NEJM Dec 2013

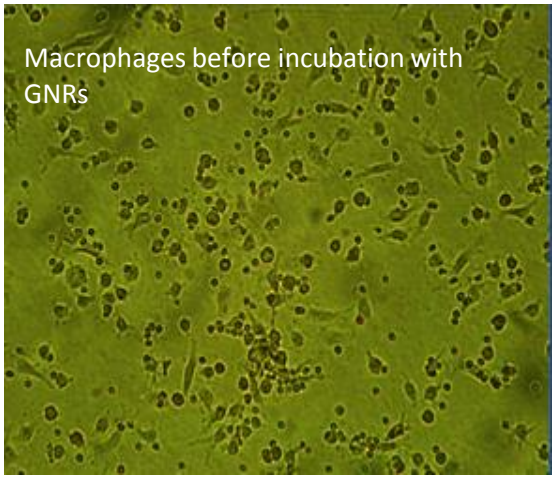


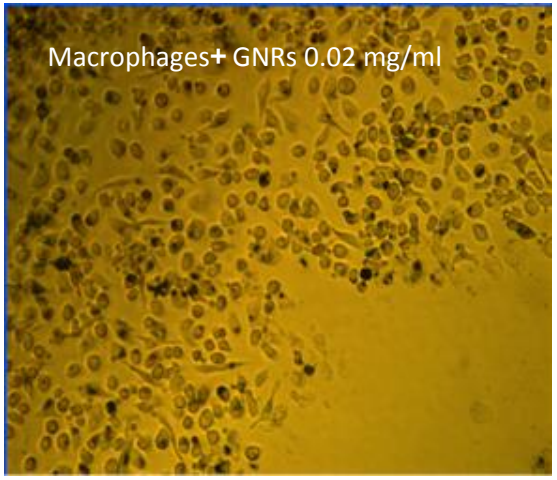


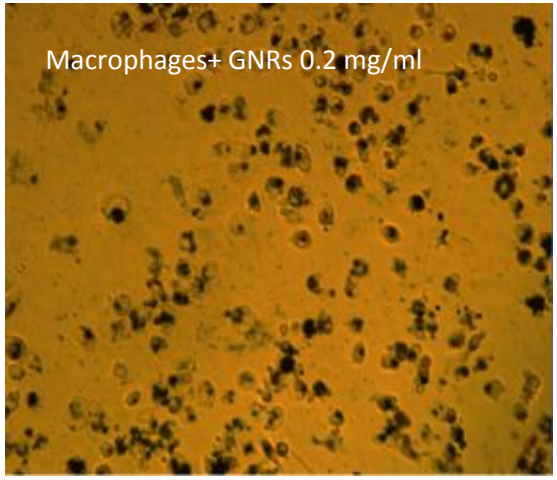
Rich in macrophages, foam cells, inflammatory cells, thin fibrous cap

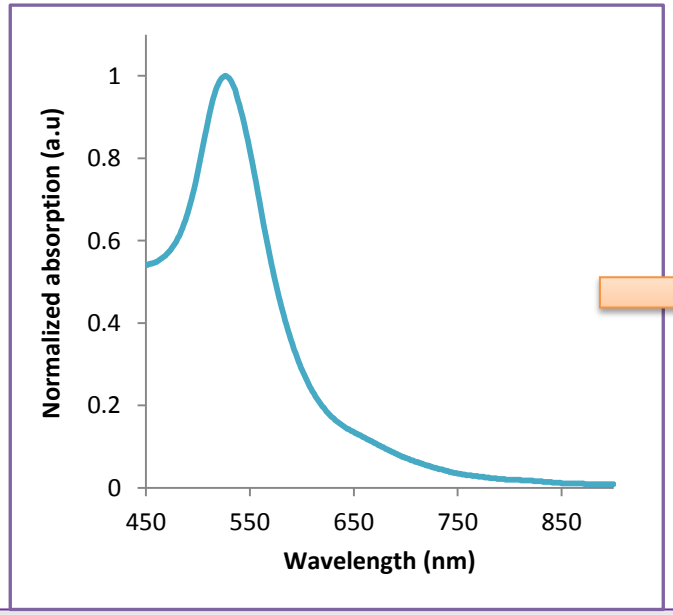
Rich in extracellular matrix smooth muscle cells, thick cap

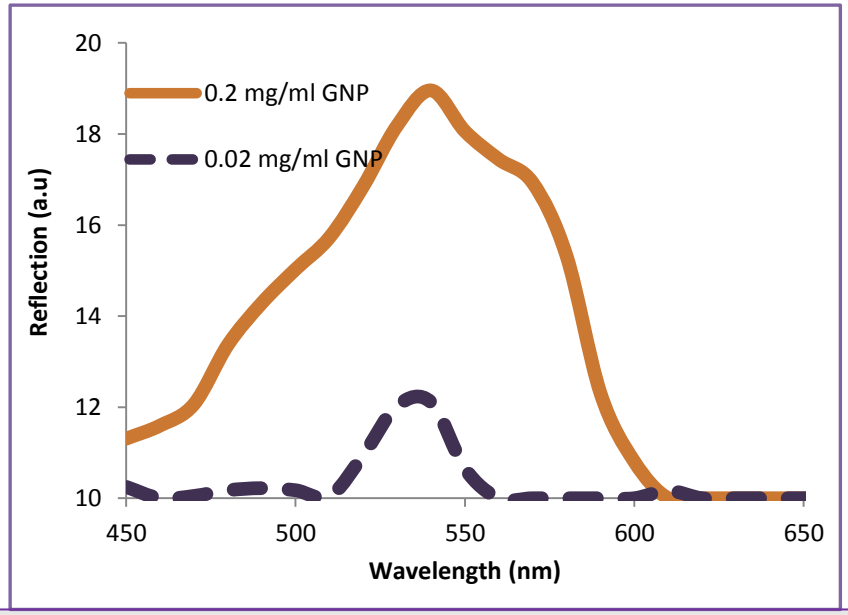
GNPs uptake by macrophages





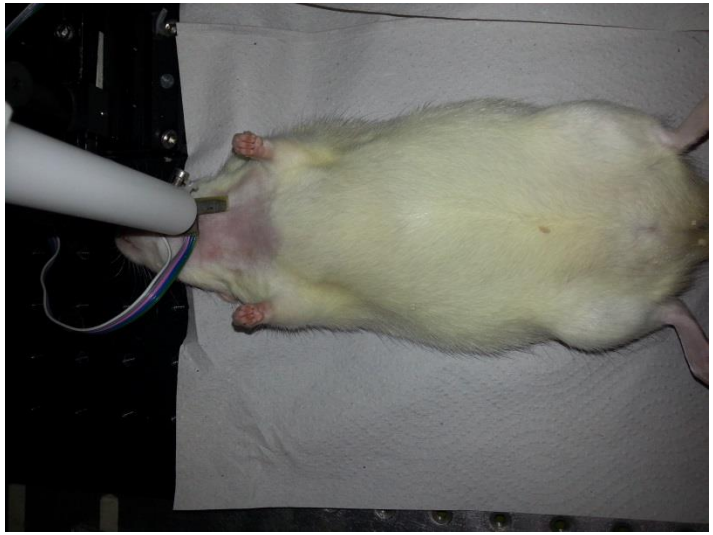


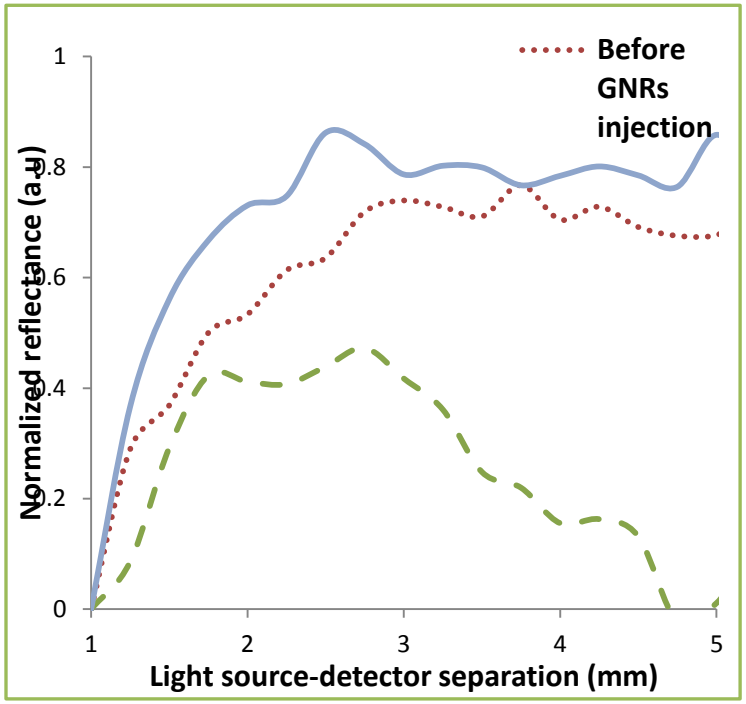


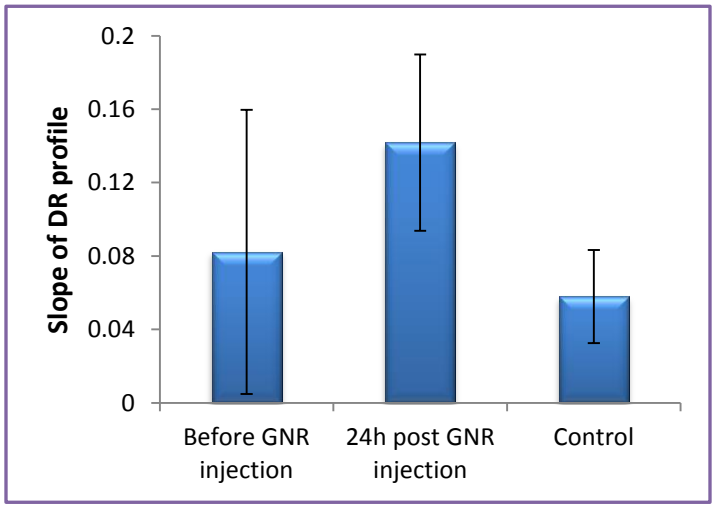


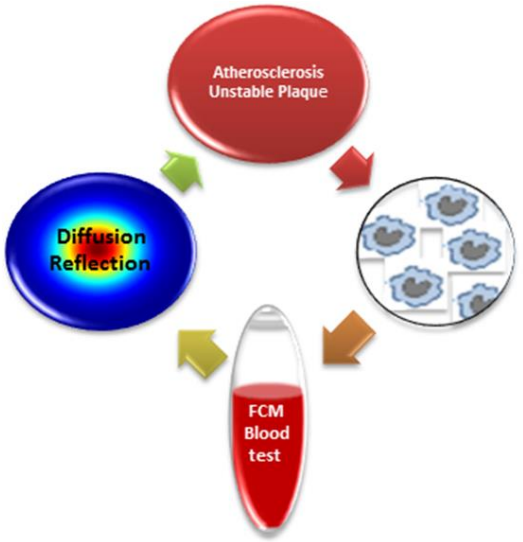
Ankri, Fixler et.al; *Nano letters*, April 2014

In vivo DR measurements of atherosclerosis with GNRs



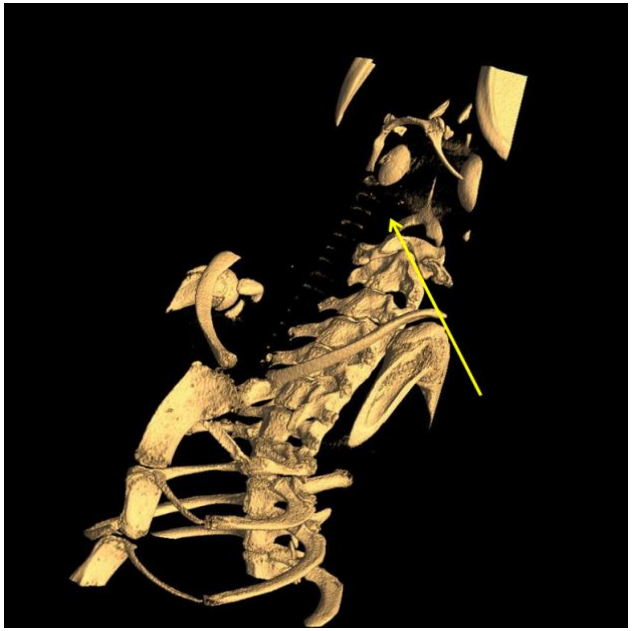




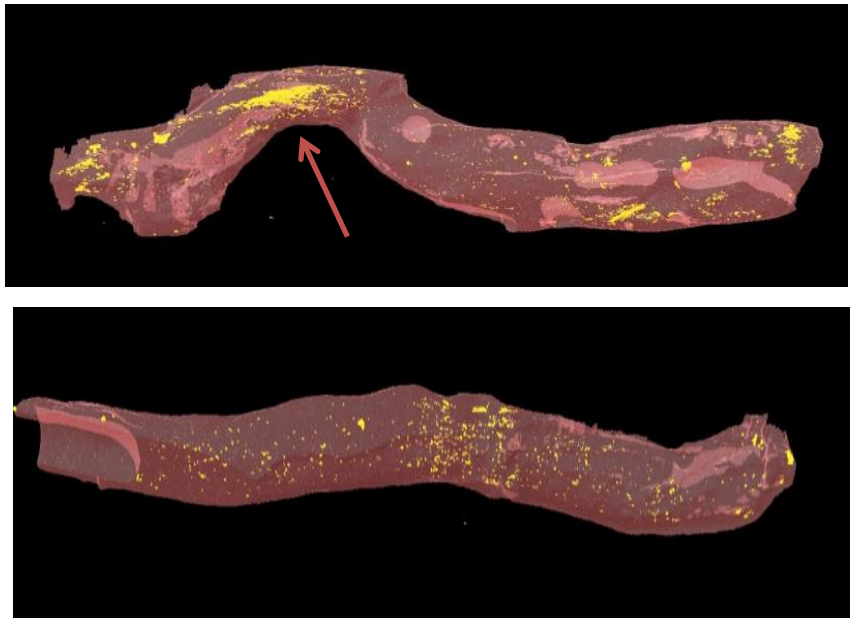


Ankri Fixler et.al; Nano letters, April 2014

In vivo CT injured artery with GNRs



Ex vivo CT injured artery with GNRs



NANO LETTERS

Letter

pubs.acs.org/NanoLett

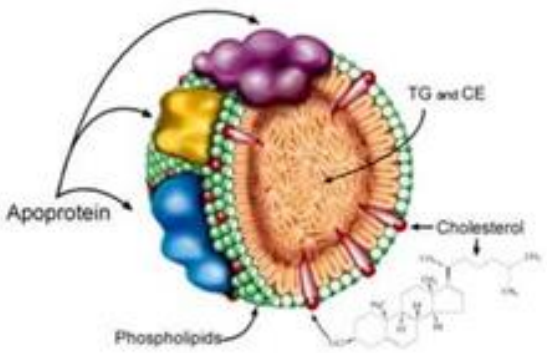
Gold Nanorods as Absorption Contrast Agents for the Noninvasive Detection of Arterial Vascular Disorders Based on Diffusion Reflection Measurements

Rinat Ankri,[†,§] Dorit Leshem-Lev,[‡,§] Dror Fixler,[*,†] Rachela Popovtzer,[†] Menachem Motiei,[†] Ran Kornowski,[‡] Edith Hochhauser,[‡] and Eli I. Lev[‡]

GNR for Atherosclerosis Theranostic

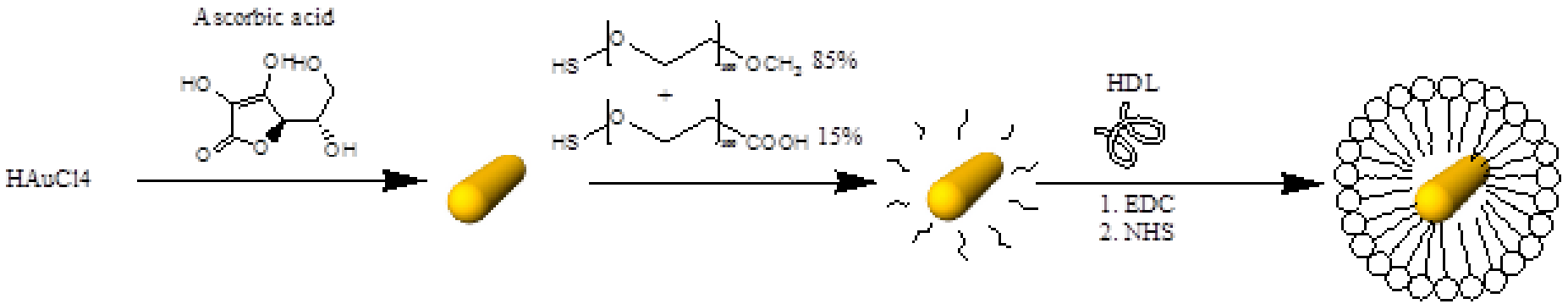
Anti-inflammatory therapy is considered to be a promising approach to treat ASVD. However, most anti-inflammatory therapeutic agents delay the progression of ASVD, rather than prevent its formation.

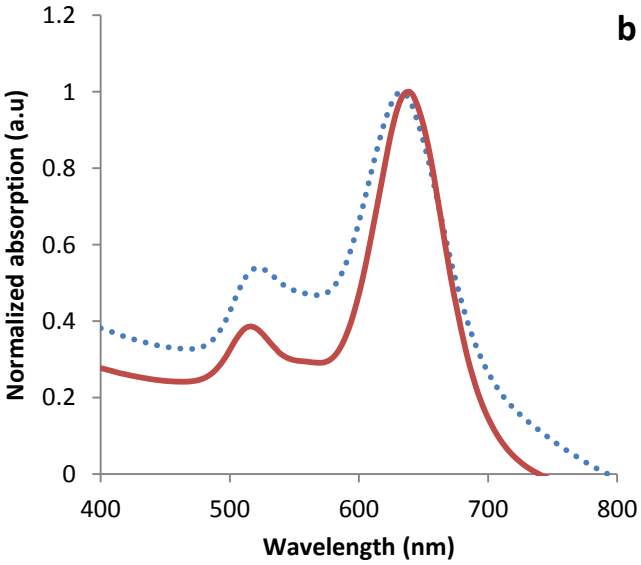
HDL exerts cardiovascular protection by promoting the reverse cholesterol transport (RCT) and other pleiotropic beneficial effects

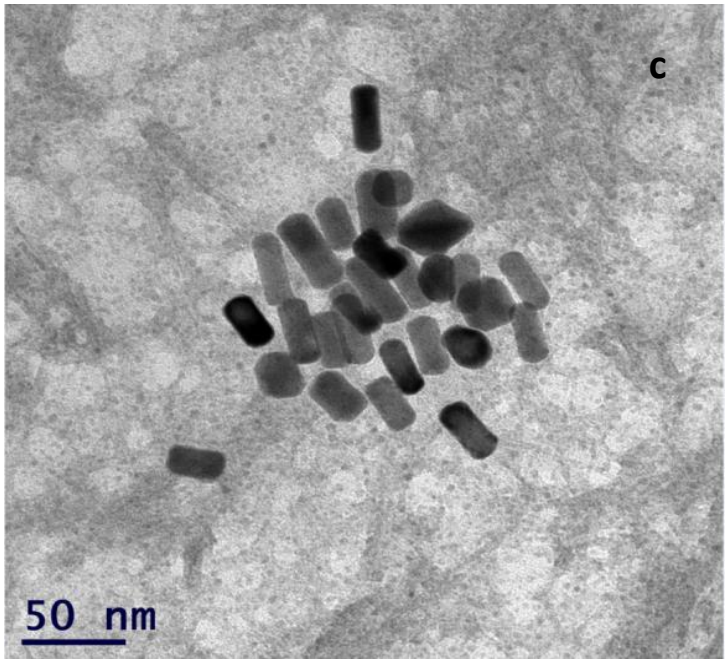


We suggest to use GNR conjugated to high density lipoprotein (HDL) for AS theranostic

HDL coated GNR







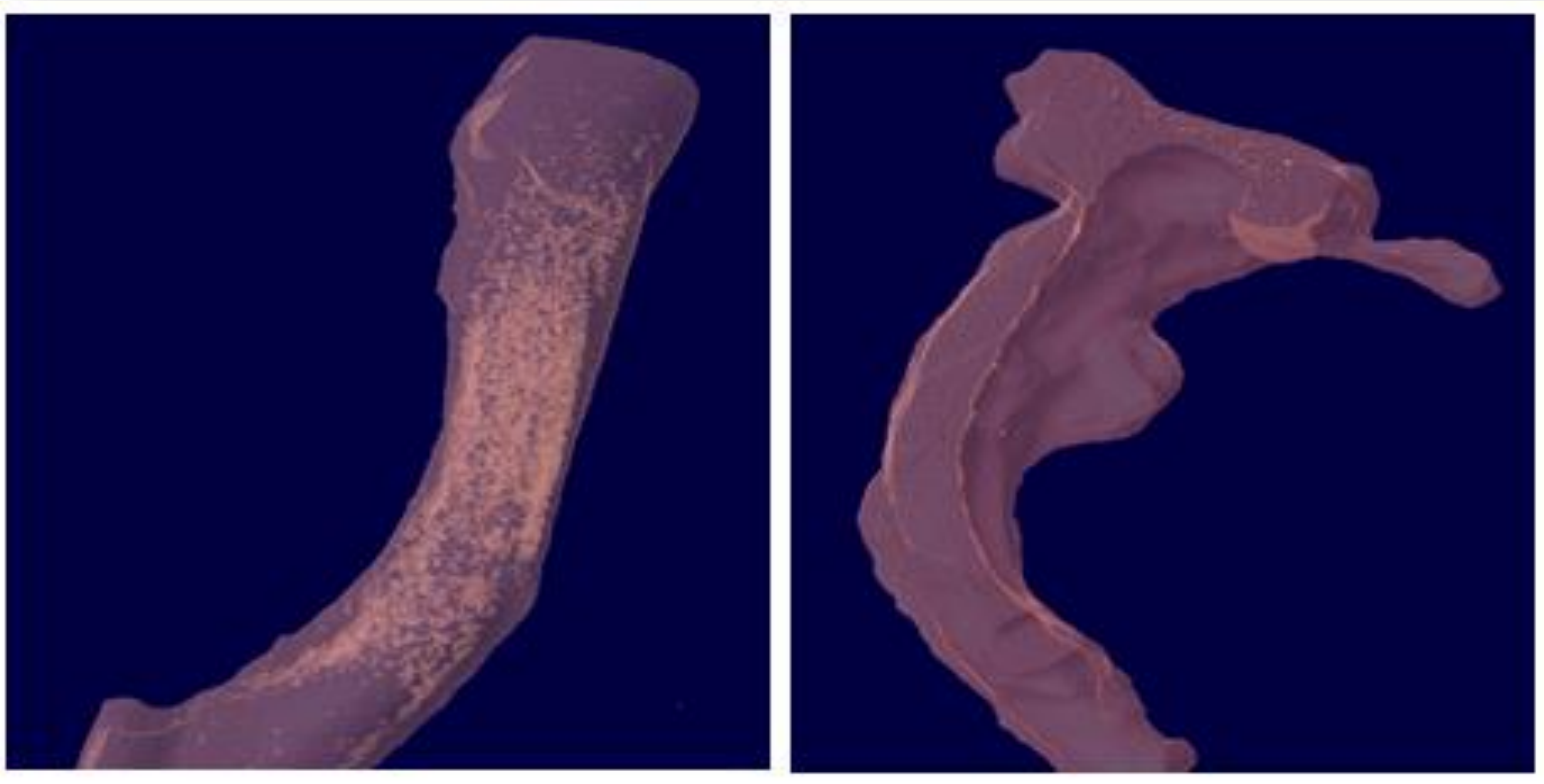
Ankri, Fixler et al.; submitted to *Biomaterials*, 2016

In vivo; Therapy

Carotids CT two weeks post GNR injection

GNR

GNR+HDL

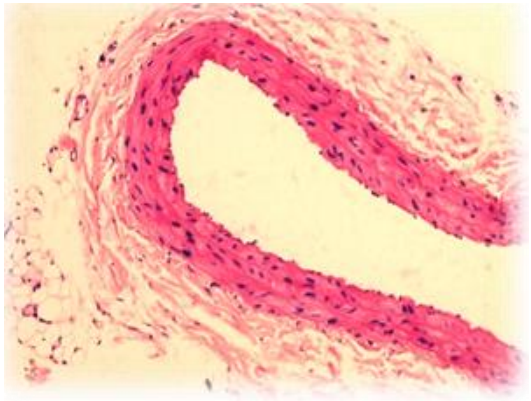


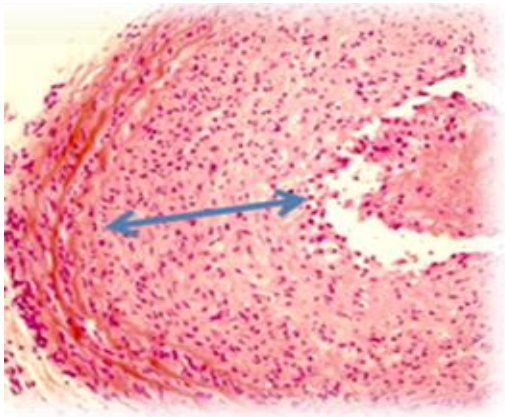
Carotids histology 2 weeks post GNR injection

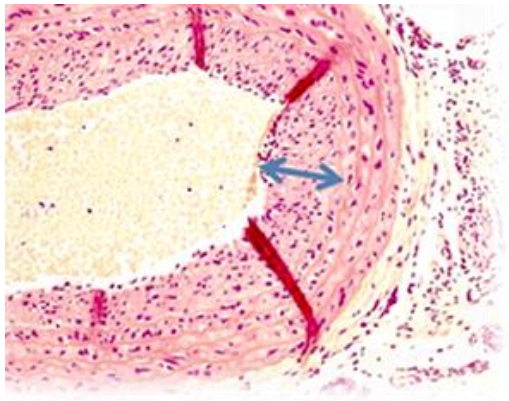
Hematoxylin and Eosin (H&E) Staining

Normal carotid

Balloon-injured carotid artery





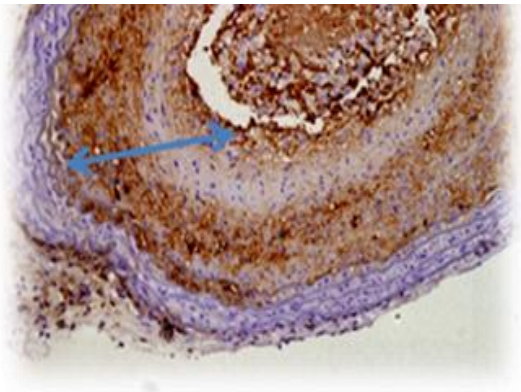


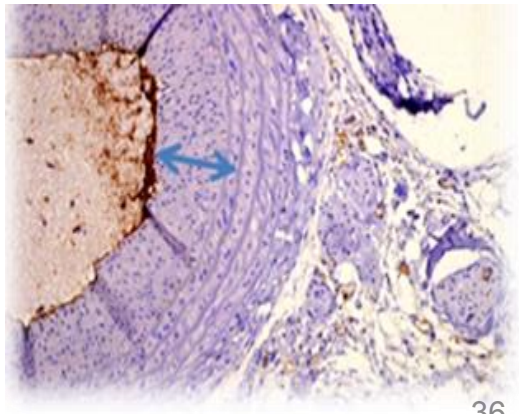
No GNR

GNR

GNR-HDL

CD-68 immunostaining



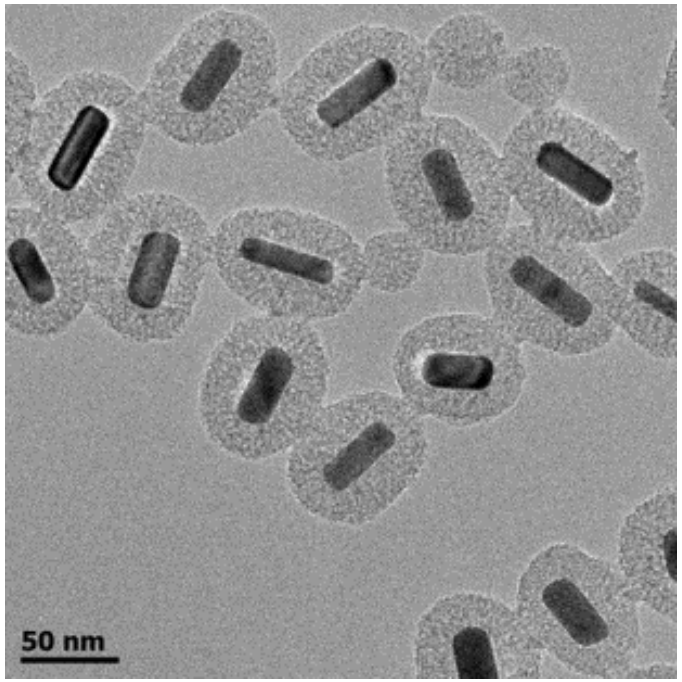


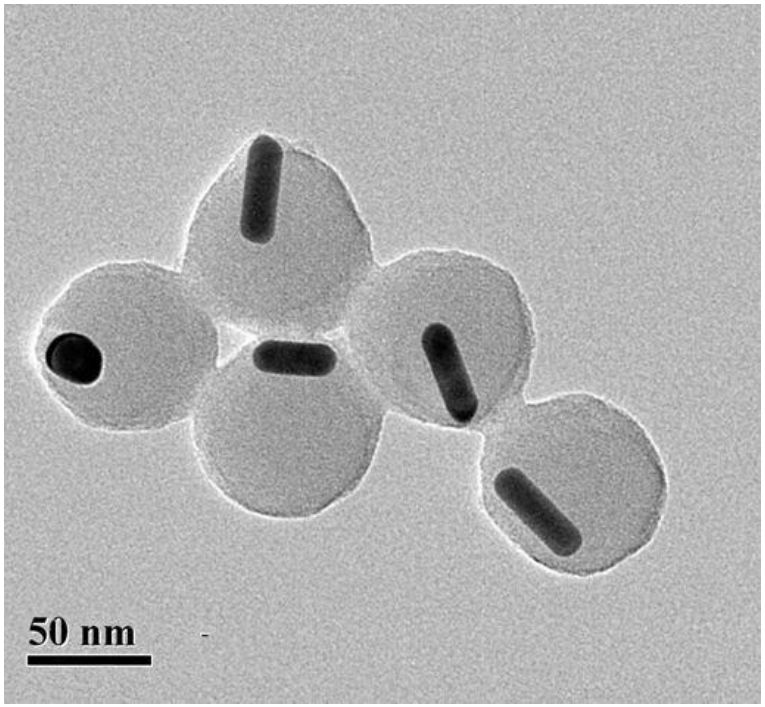
IBA news **12/1/2016**

Outline

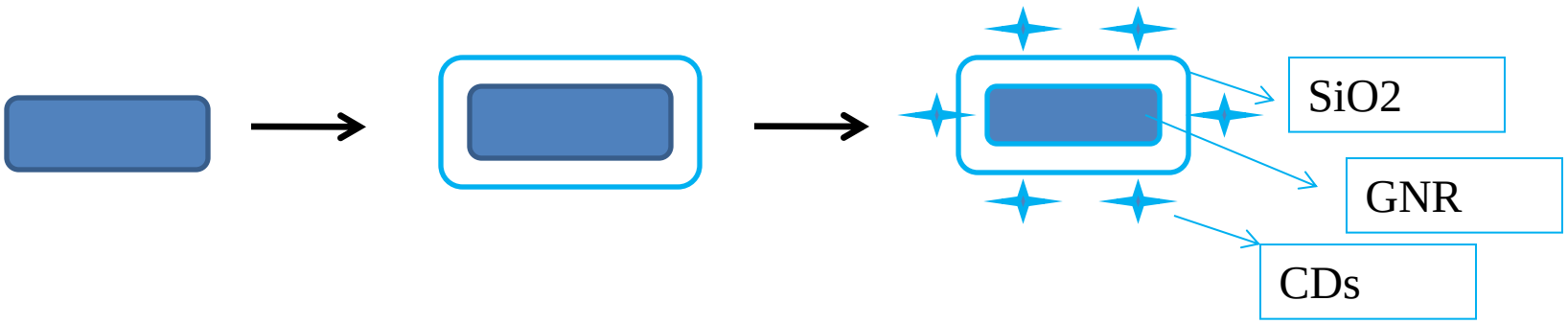
- Motivation – nanoparticle guided therapy;
- New imaging techniques based on plasmon coupled probes for medical applications;
- Perspective;
- Conclusions.

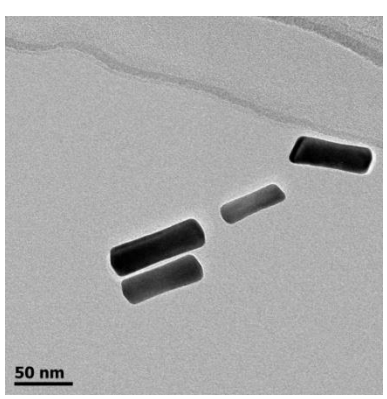
GNR@PEDOT/SiO_2@CDs

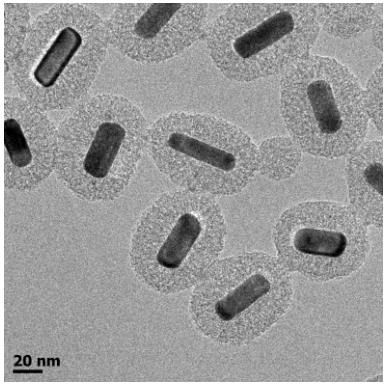


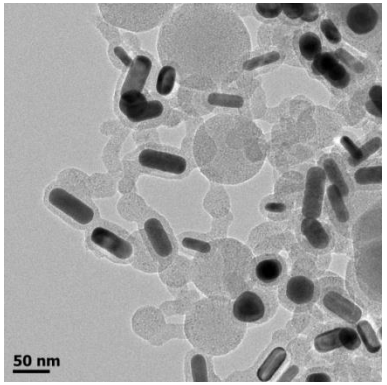


GNR@SiO2 3 ml









GNR：0.2 mg/ml (minimum)

Where is God?

Hand with Ring (Wilhelm Röntgen,1895)

CT of mice

Summary

The diffusion reflection method is highly capable of revealing abnormalities in the tissue based on GNPs injection.

HDL-Au nanoparticles present a novel tool for theranostic of atherosclerosis.

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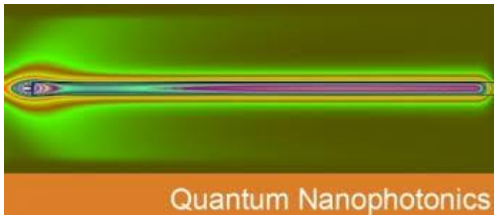
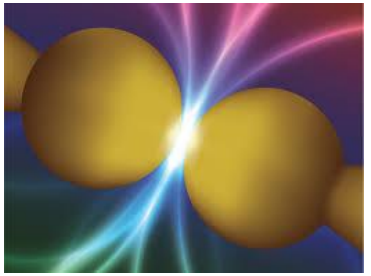
BINA

Special Issue of Cytometry, Part A focused on **Nanoscale Imaging and Sensing for Biomedical Applications**

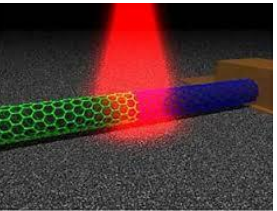
Cytometry PART A

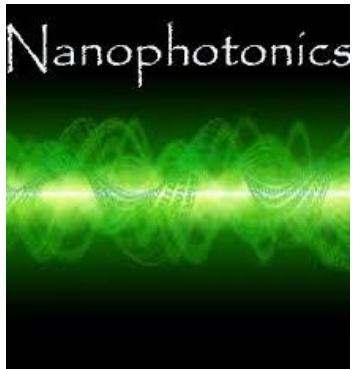




Papers will emphasize fundamentals of nanophotonics and biology including:

- optical imaging using nanophotonics principles (nanostructures, nanoparticles, etc.).
- *in vitro* and *in vivo* applications of nanophotonics (functionalized nanoparticles, surfaces, etc.).
- biomedical instrumentation development (nanosensors or nanoscale imagers).





Summer Program in Nano Photonics

For Postgraduate Students

July 2016

The summer program allows students to create a rigorous academic experience that combines one advanced course with an exciting social and cultural program at Israel's finest department of electrical engineering at Bar-Ilan University. The program centers around one core course which carries 4 academic credits and is taught by Bar-Ilan University.

Course topic:

Optical Super Resolved Imaging and Fluorescent Microscopy

Taught by Prof. Zeev Zalevsky and Prof. Dror Fixler

Acknowledgements

Lab members

- Dr. Rinat Ankri- Post Doc.
- Dr. Hamootal Duadi- Lab manger
- I. Yariv; E. Bar-Noy; S. Abughosh; R. Bauer; I. Feder - Ph.D Stud
- G. Yahav; T. Nayhoz; A. Ashkenazy- 2nd degree student

Collaborators

- Prof. Rachela Popovtzer & Dr. Menachem Motiei

  Faculty of Engineering, Bar-Ilan University
- Prof. Eli Lev, Dr. Dorit Leshem*Rabin Medical Center, Petah-Tikv*
- Prof Krishanu Ray- Univ. of Maryland School of Medicine, Mar
- Prof. Attila Tarnok- Universität Leipzig, Germany
- Prof. Klaus Suhling- Kings college of London
- Prof. Shuyun Zhou, Prof. Zheng Xie- TIPC, CAS, Beijing, China

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Lab web page:
http://www.eng.biu.ac.il/fixlerd/
Email- Dror.Fixler@biu.ac.il

Funding

- ✓ Israel Science Foundation.
- ✓ Israel Cancer Association.
- ✓ Kamin, Magnet, State of Israel.
- ✓ Gassner Fund for Medical Research.
- ✓ D-CURE.

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Questions?