Implementing Actuation-Navigation-Sensory Capabilities in Cancer-Fighting Nanorobotic Agents

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From Medical Robotic Platforms Dedicated to Surgery to the Next Medical Robotic Platforms Dedicated to Cancer Therapy (Medical Nanorobotics)

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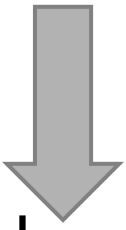
NanoRobotics (Nano + Robotics)



Nanotechnology

How to exploit phenomena at the nanoscale in the context of drug delivery…

Motivation

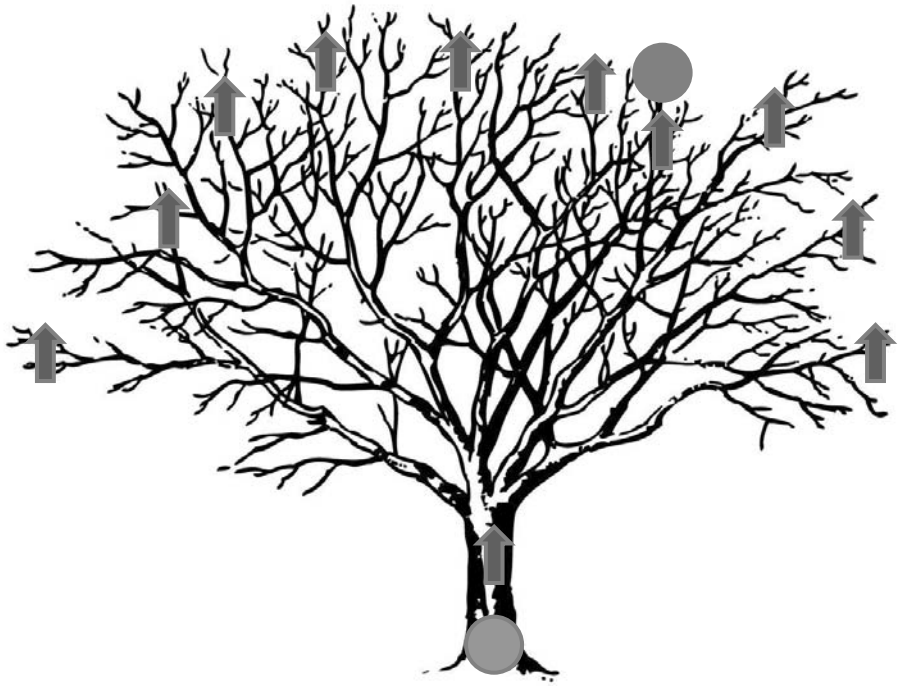
- For 2013 in US alone: an estimated 1,660,290 new cancer cases.
- This results to approximately 580,350 deaths – almost 1,600 people per day or 1 every 54 seconds.
- With an estimated today's world population of 7.119 billion individuals with US population representing only 4.45%, one can easily realize the importance of finding new or improved treatment modalities.

Robotic Approach to Tumor Targeting

- FACT: More than 80% of cancers are localized in the form of a solid tumor
  - So why going everywhere (systemic circulation) instead of delivering the therapeutics using the most direct physiological routes (non-systemic delivery)

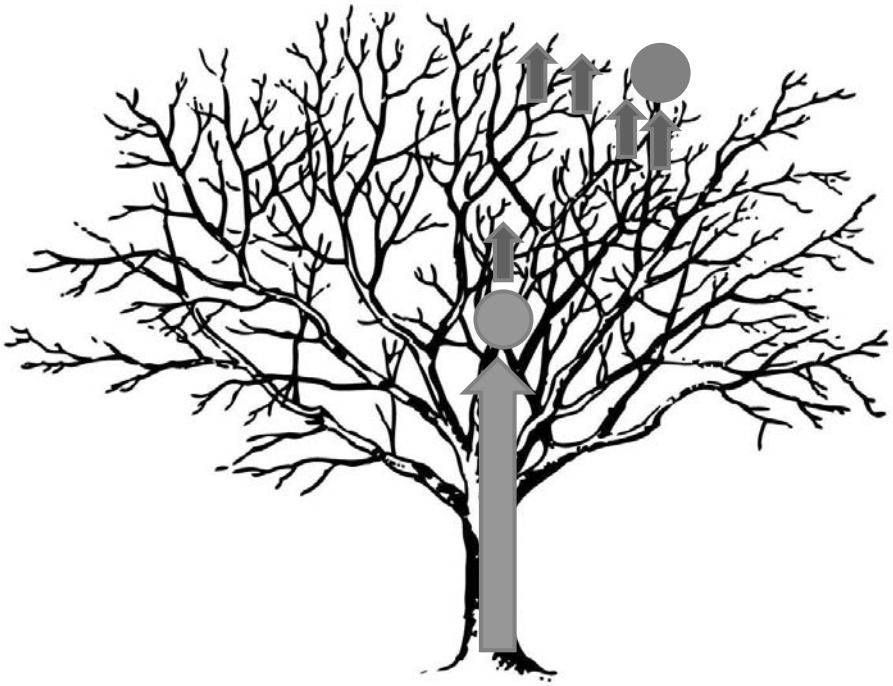
- **Direct targeting** (new concept)
  - Pharmaceutical carriers or agents (nanobots) being navigated directly from the injection site to the targeted area
  - Avoid or at least reduce systemic circulation
  - Can be combined with passive or active targeting

Without Direct Targeting



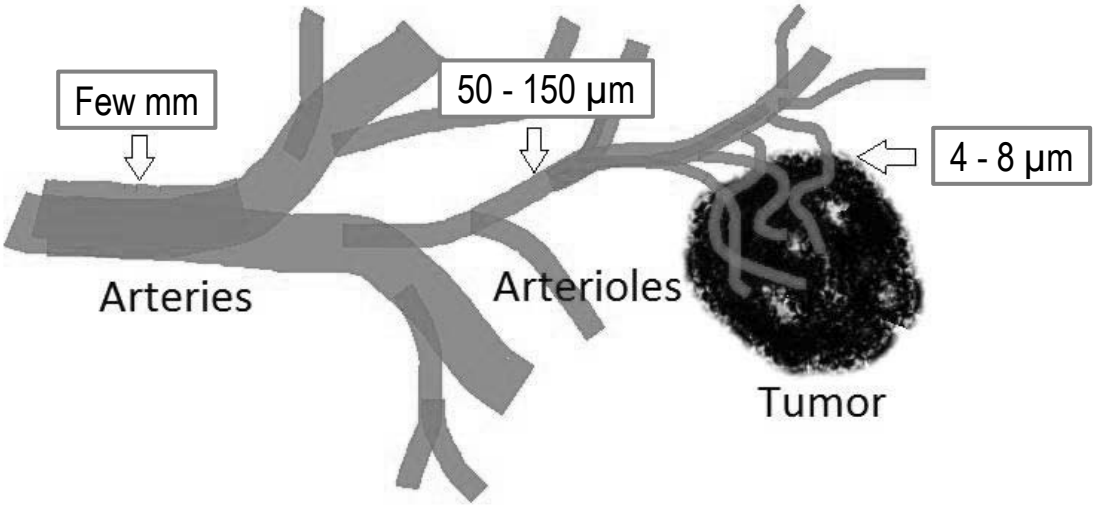
Low therapeutic index
(low therapeutic efficacy + high toxicity)

Increasing Direct Targeting

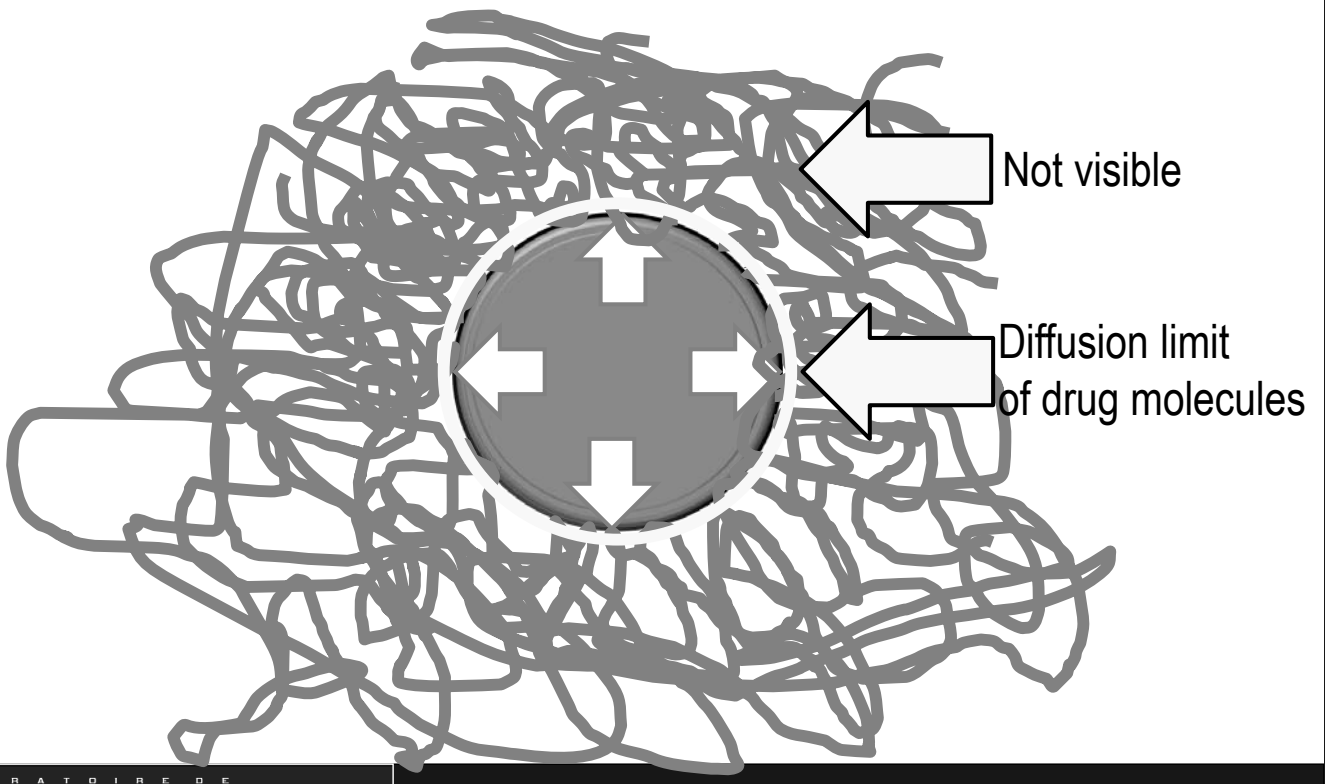


Reduced toxicity and improved targeting

Solid Tumors
(more than 80% of all cancers)



The Main Challenges

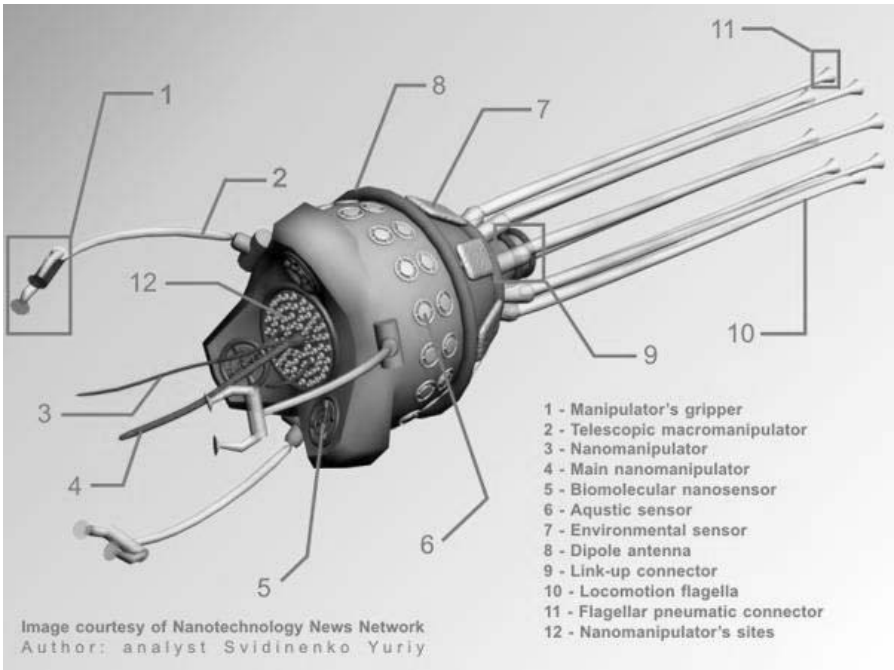


How to resolve that – An engineering approach:

Providing a therapeutic agent having the following general robotic capabilities:

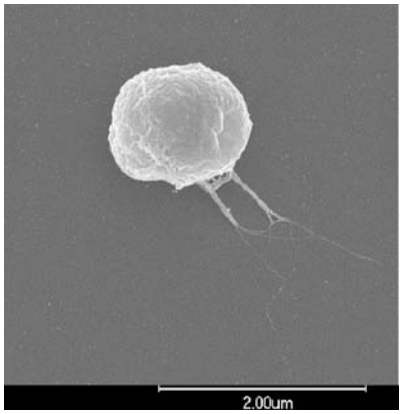
- Navigation
  - *Non-systemic circulation*
- Actuation (propelling thrust force)
  - *Deeper in the tumor volume passed the diffusion limit*
- Sensory capability
  - *To target non-visible hypoxic zones in tumors*

One potential solution… in a far, far future



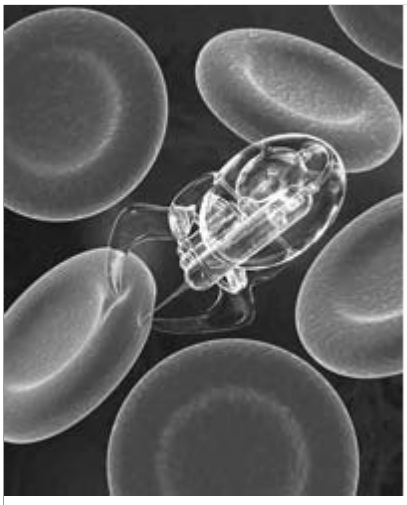
MC-1 Magnetotactic Bacterium

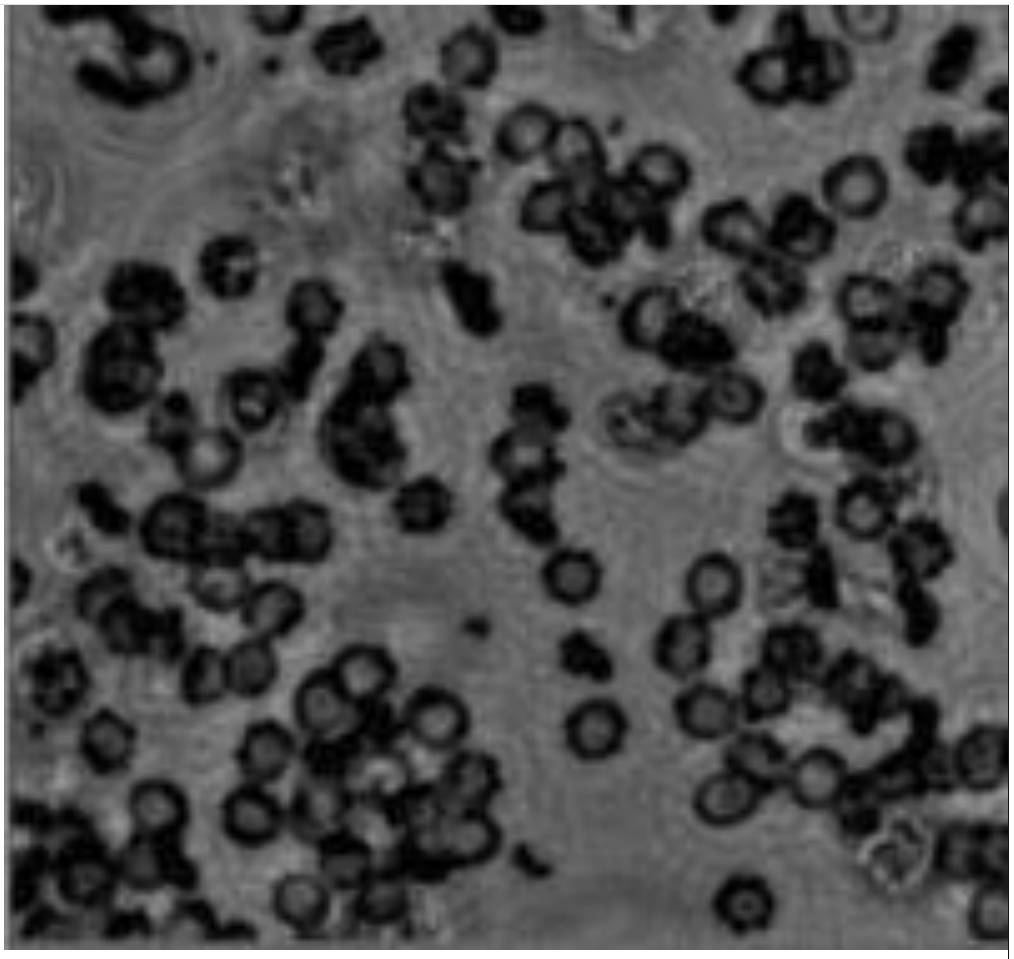
- Since an artificial implementation is far beyond technological feasibility, a potential strategy was to identify a microorganism that has all these specifications and to harness it to act as a "nanorobot" for drug delivery applications



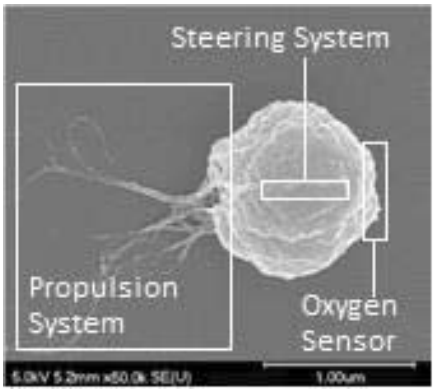
Gram-negative procaryotes

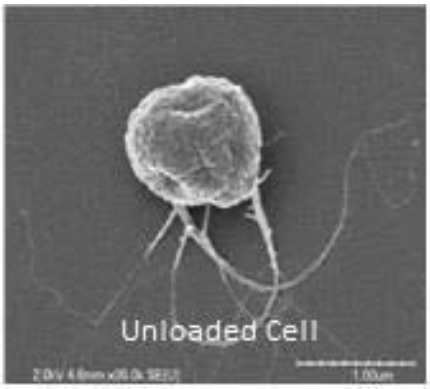
Pettaquamscutt Estuary in Rhode Island, USA

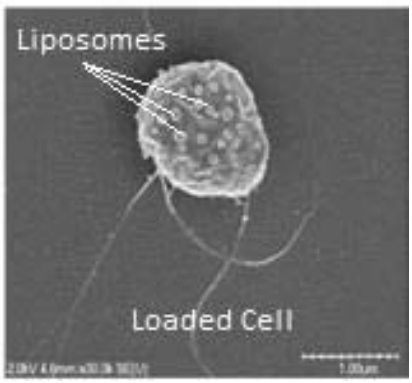


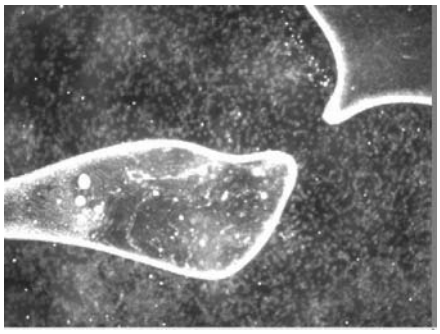


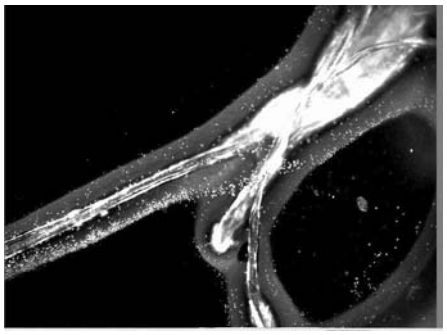
Harnessing What Nature Already Provides

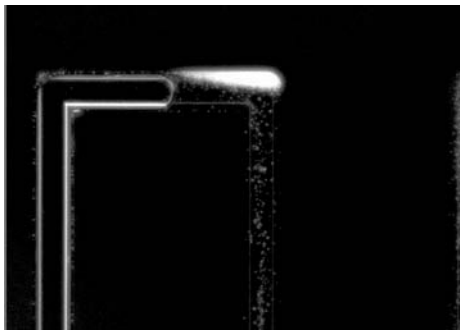




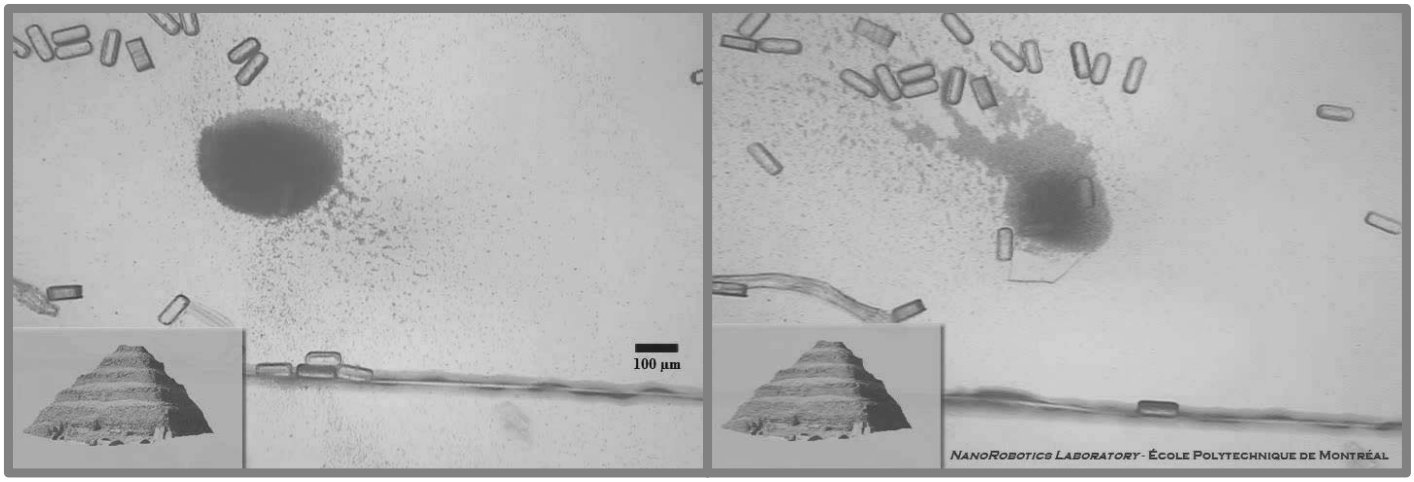


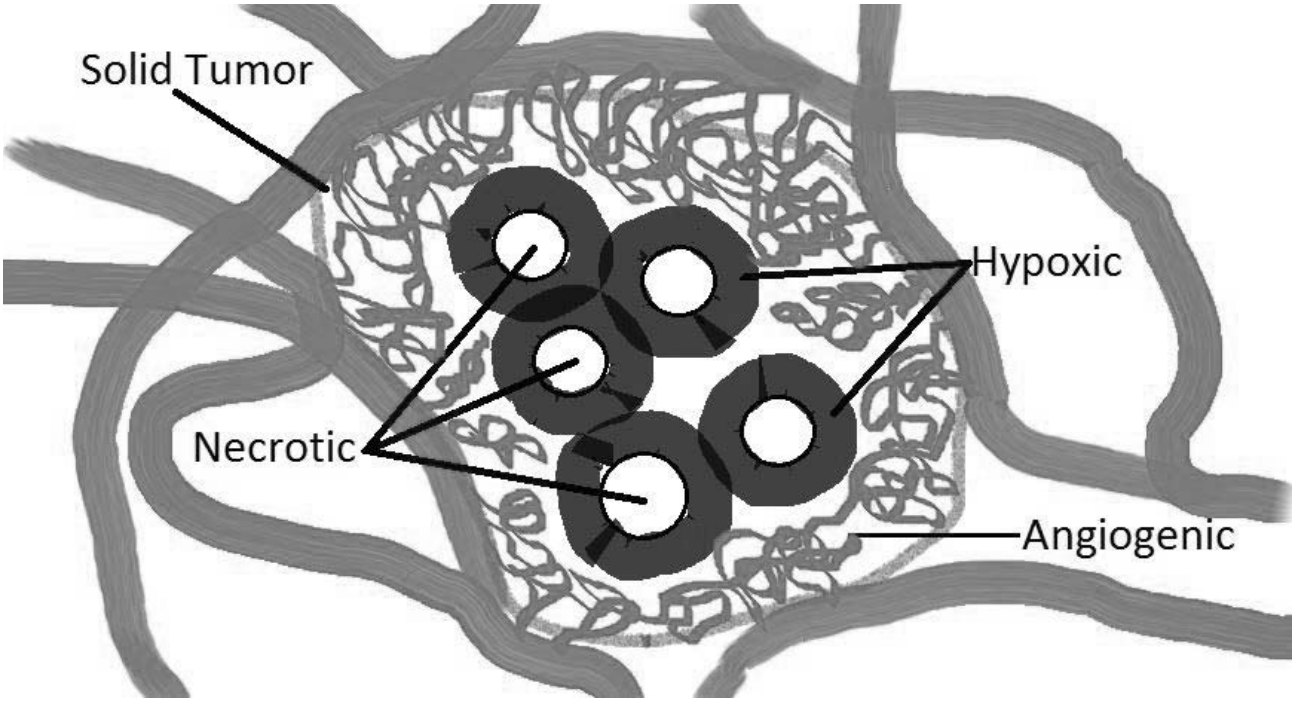




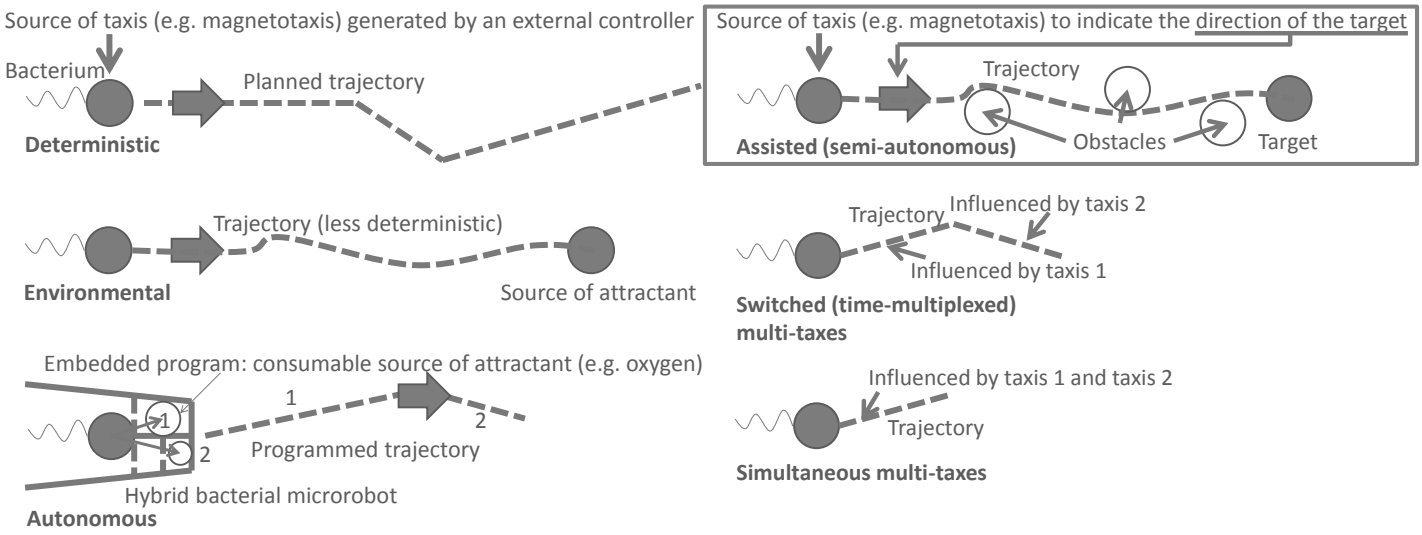


Full (Deterministic) Control

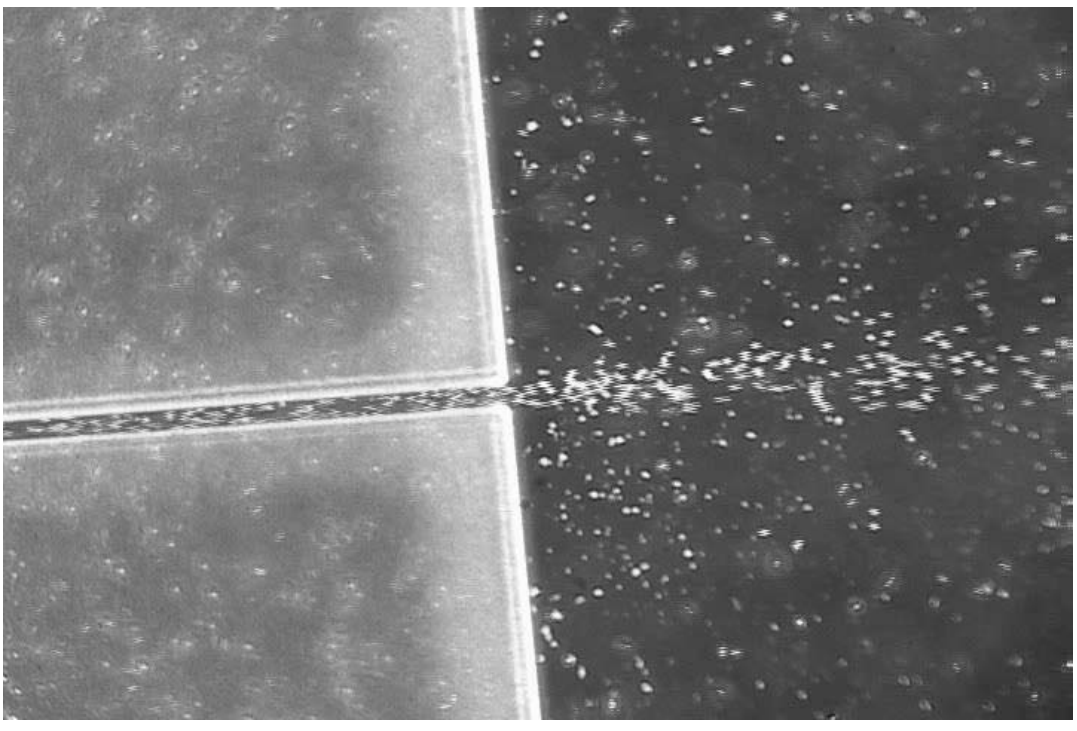




Taxis-based Directional Control

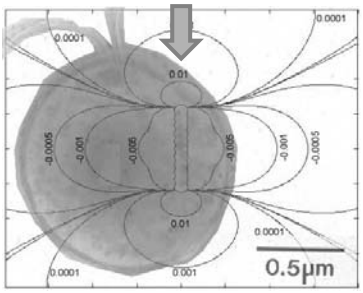


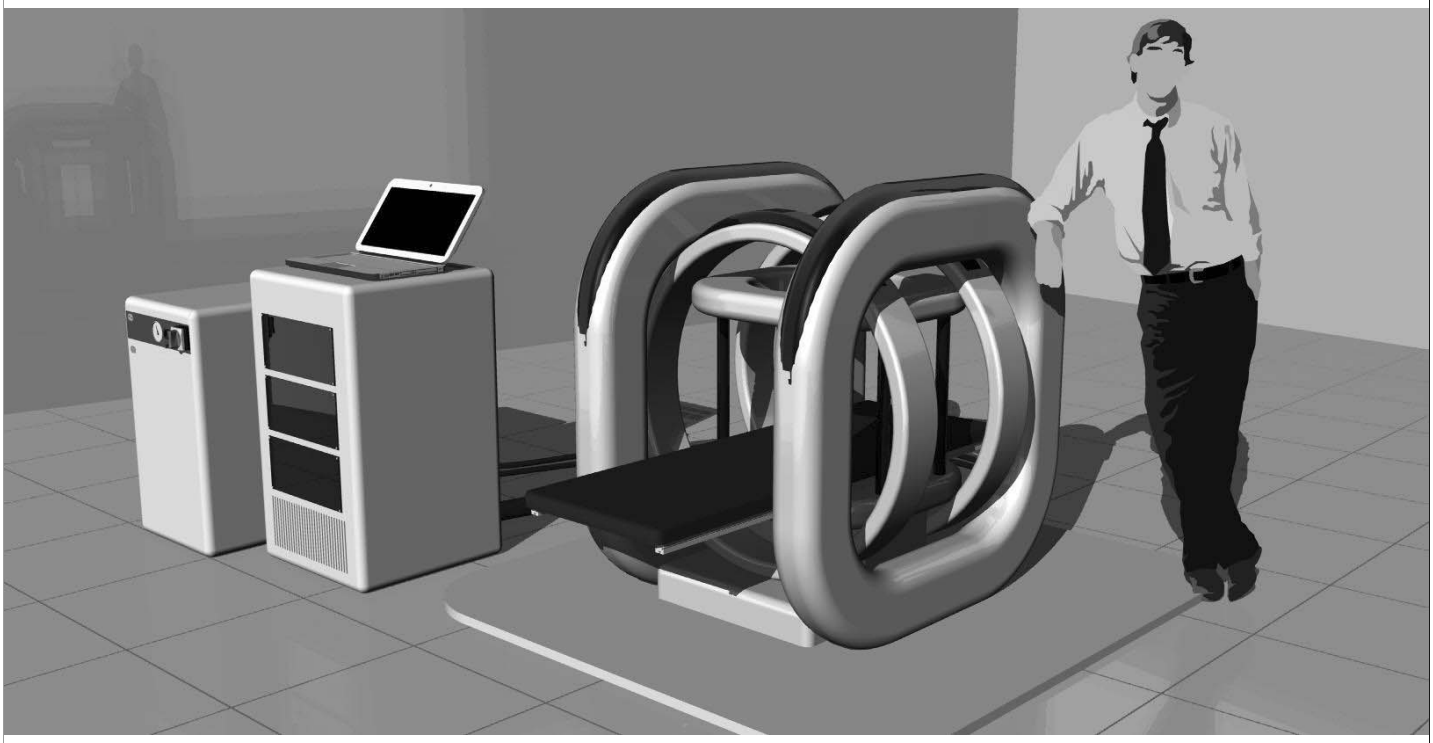
Reference: S. Martel, "Bacterial Microsystems and Microrobots," *Biomed. Microdevices*, 2013

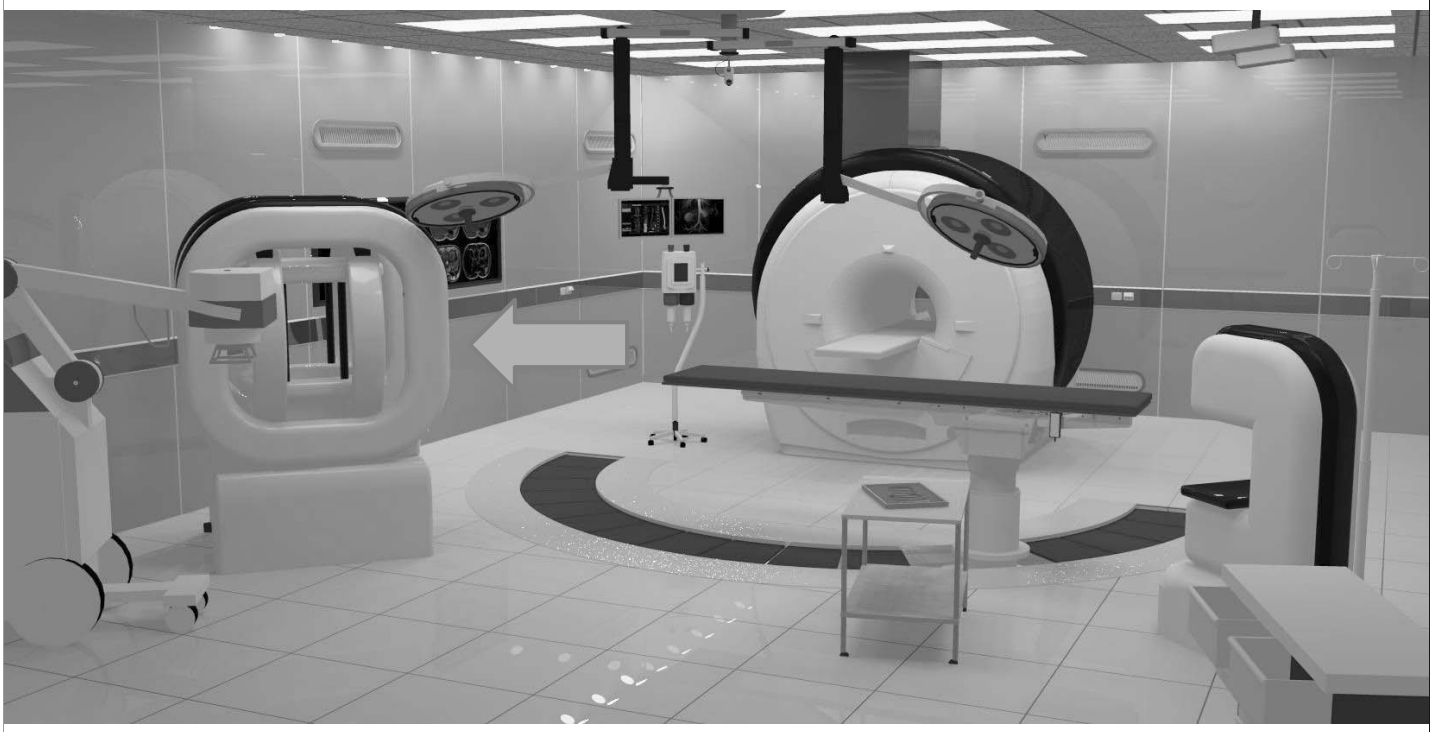


MC-1 Strain Magnetococcus Marinus Natural Migration Behavior

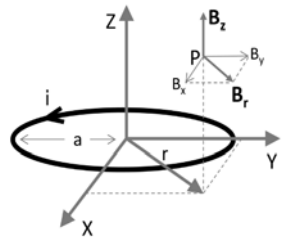
- Contains a chain of magnetic iron-oxide (Fe_3O_4) nano-crystals enclosed in membranes known as magnetosomes acting like a nano-compass needle.
- Downward migration along geomagnetic field lines in conjunction with aerotaxis to efficiently migrate to and maintain position at their preferred low oxygen concentrations.
- Such magnetically-assisted aerotaxis known as magneto-aerotaxis results in the formation of microaerophilic bands of MC-1 cells at O_2 concentrations equivalent to the ones observed in the hypoxic regions of solid tumors.

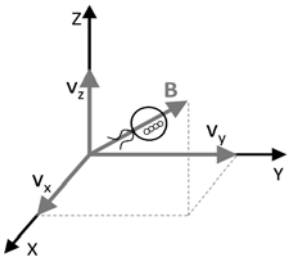


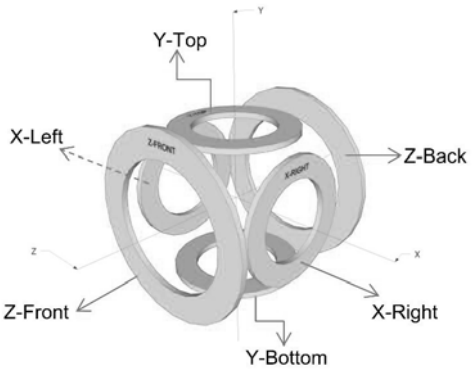


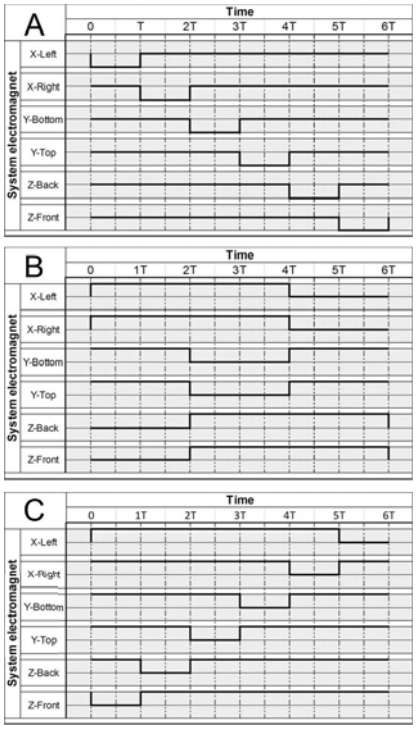


Magnetic Pole



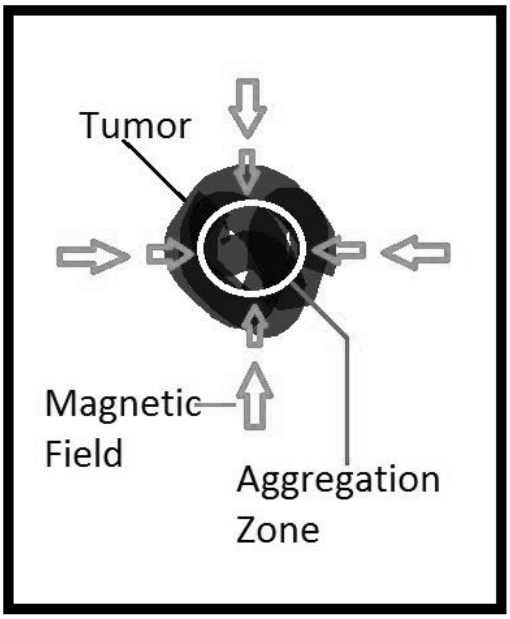


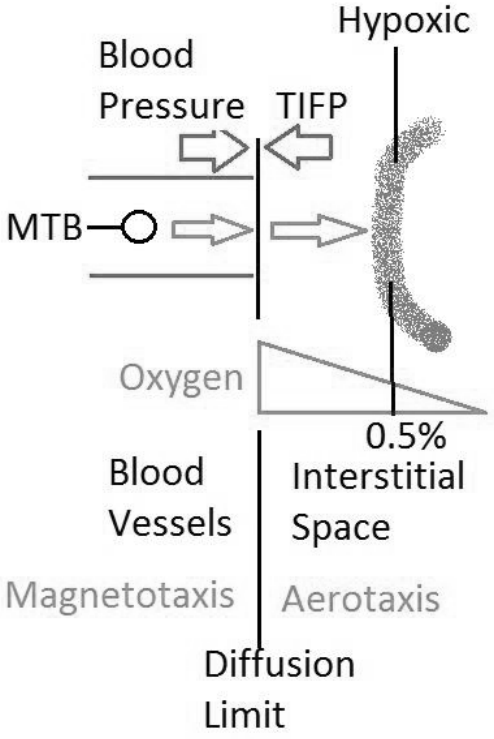


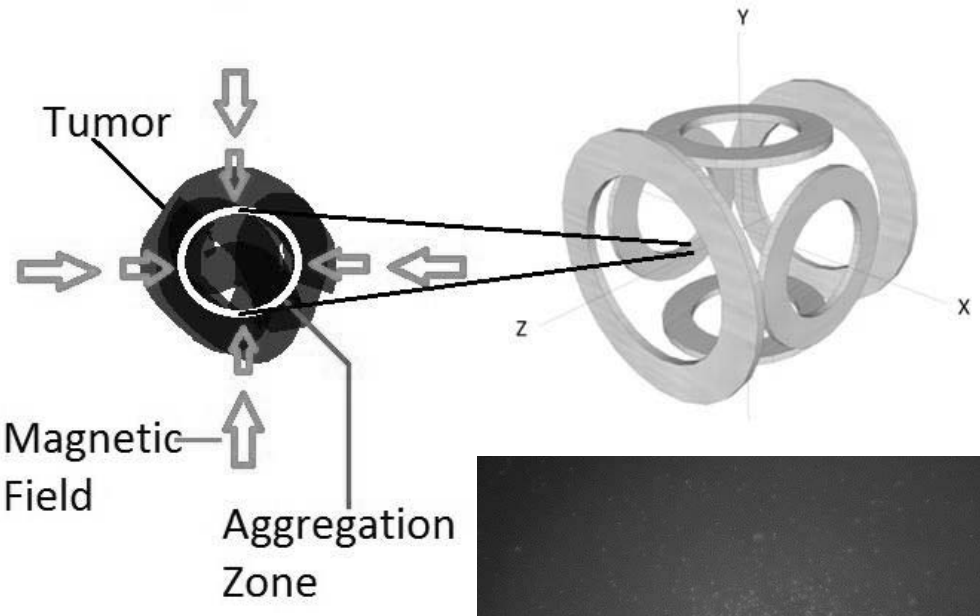


$$B_Z = \frac{\mu_0 I}{2\pi a\sqrt{(1+\alpha)^2+\beta^2}}\left[E(k)\,\frac{1-\alpha^2-\beta^2}{(1+\alpha)^2+\beta^2-4\alpha} + K(k)\right]\ldots$$

Basic Principle

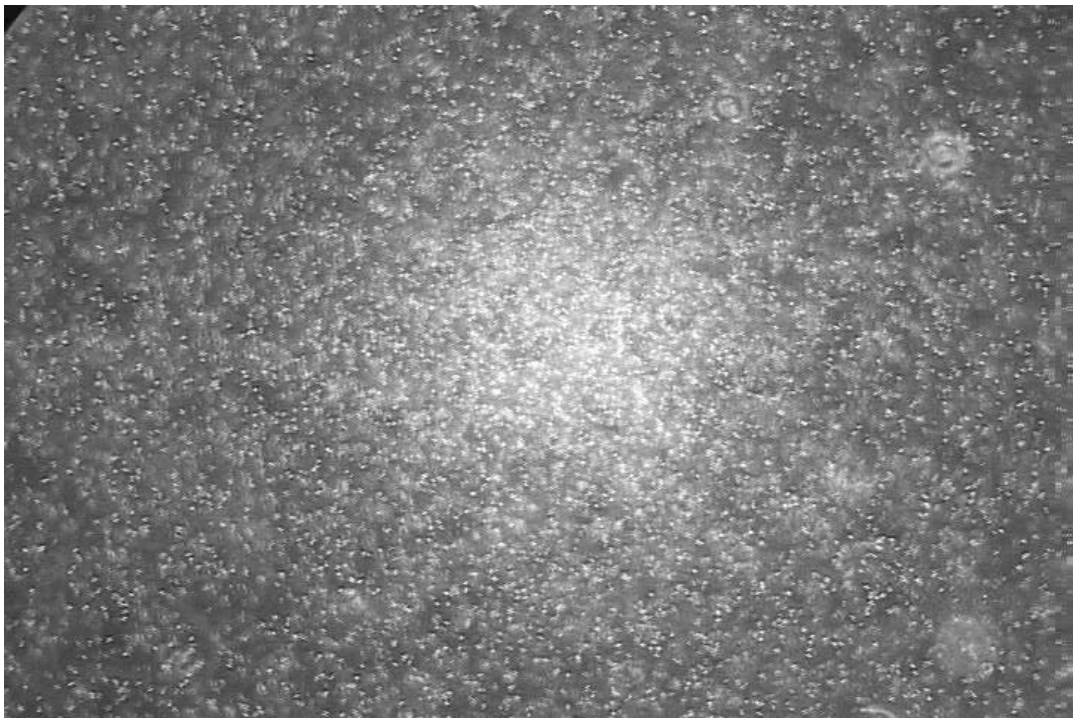


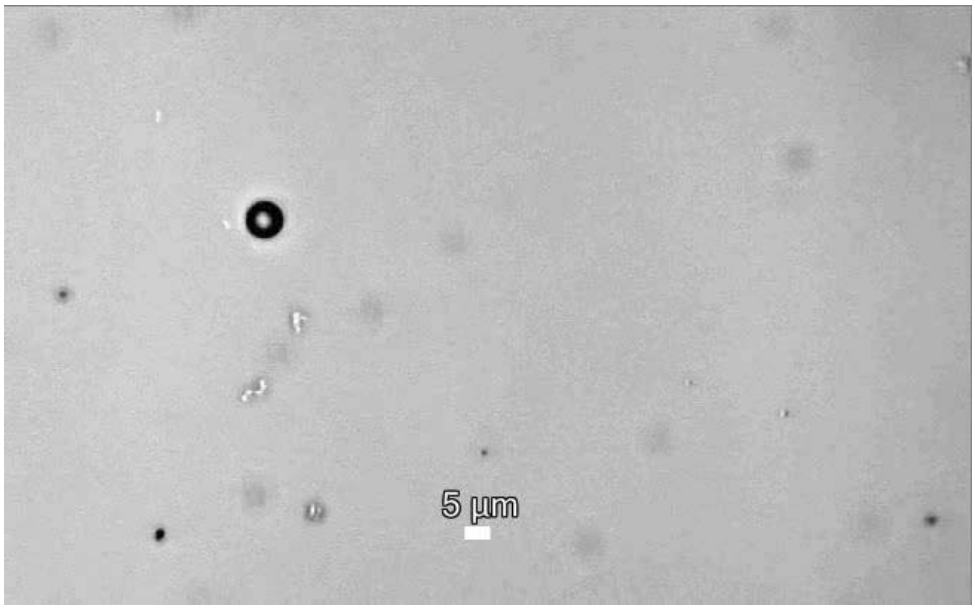




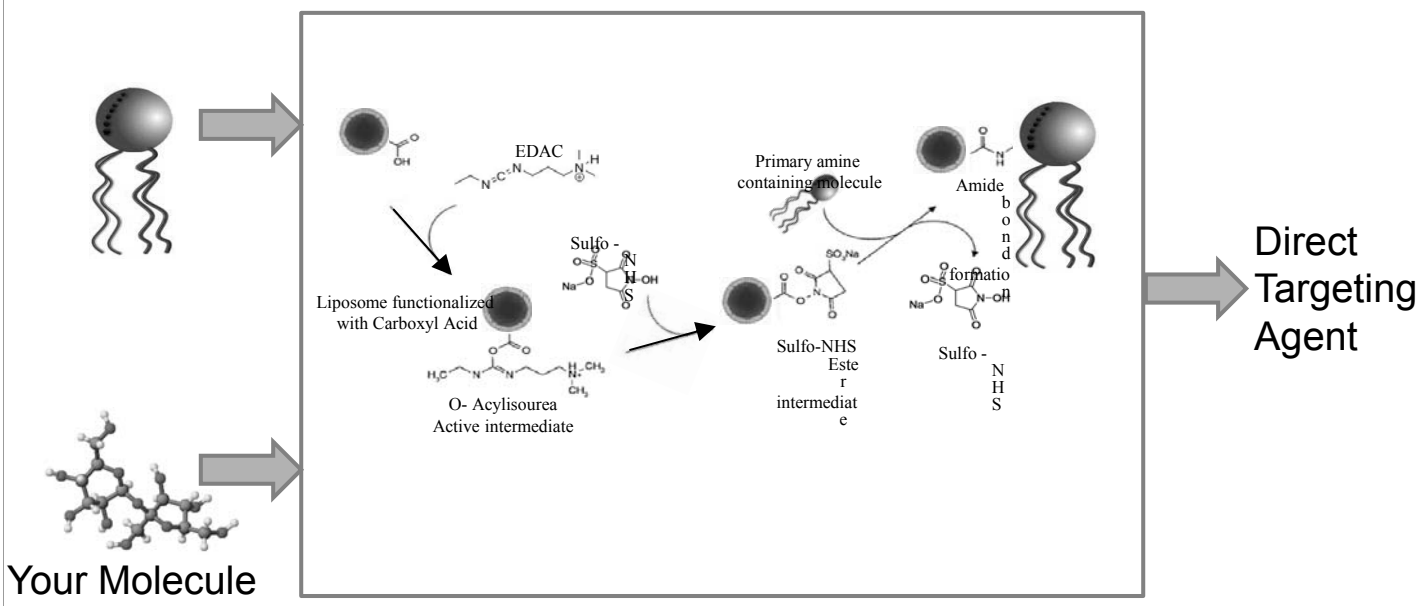
Oxygen Sensors – Microaerophilic Behavior

(Objective: Autonomous Targeting of Tumor Hypoxic Zones)



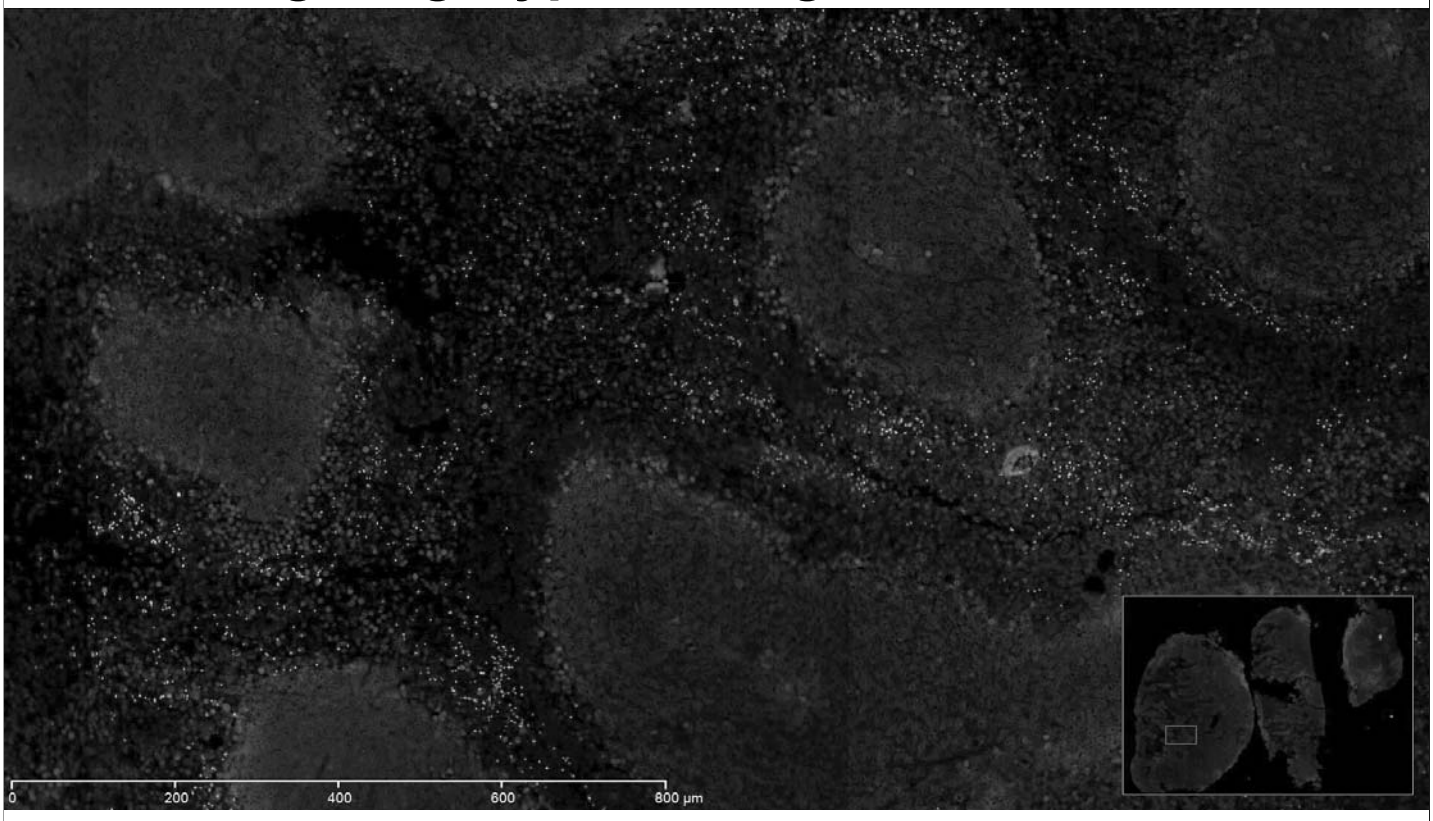


Attachment of activated drug-loaded liposomes (or polymeric containers) to functional groups of MC-1 cells using carbodiimide chemistry



Taherkhani S., Mohammadi M., Daoud J., Martel S., and Tabrizian M., Covalent binding of nanoliposomes to the surface of magnetotactic bacteria acting as self-propelled target delivery agents," *ACS Nano,* 2014 (DOI: 10.1021/nn5011304)

Targeting Hypoxic Regions in Tumors



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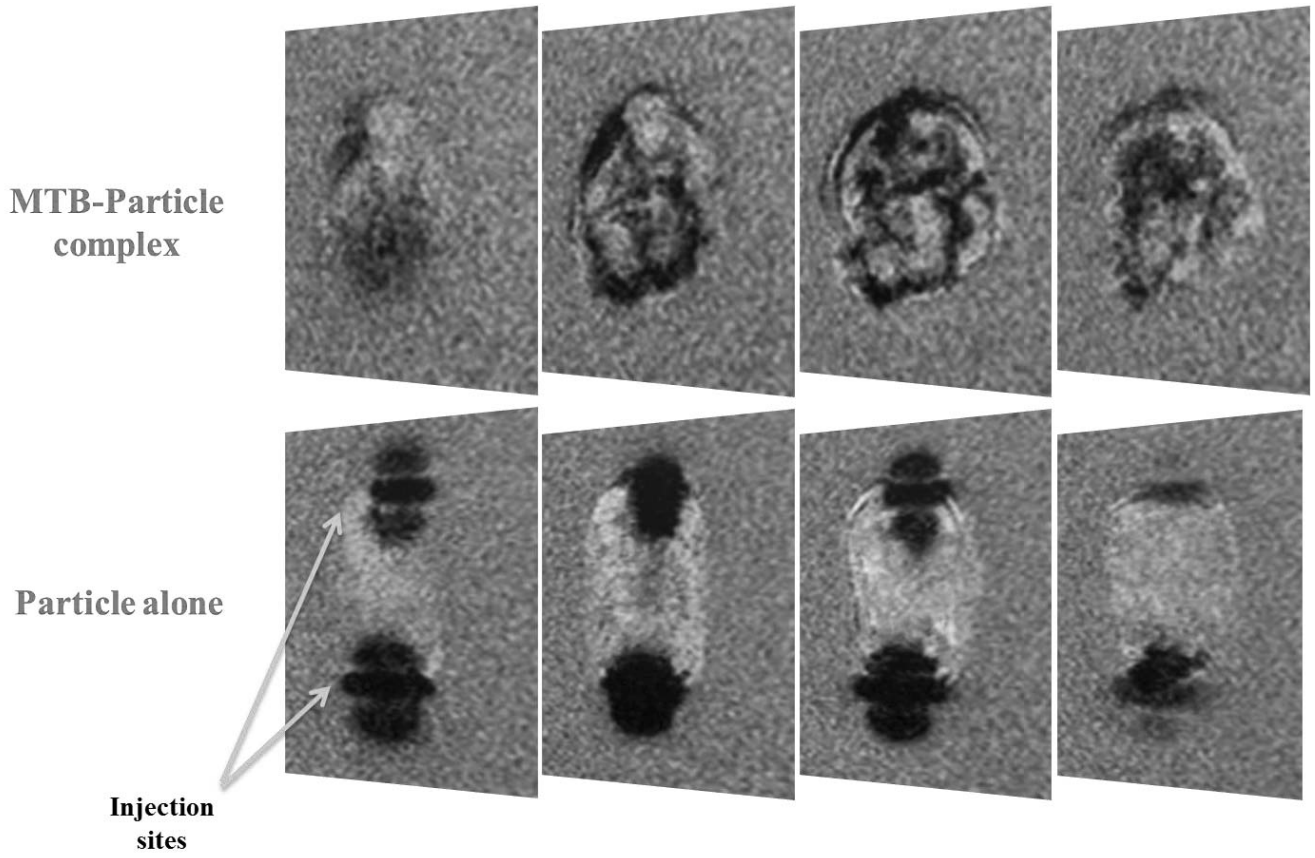

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- In alphabetical order (current immediate collaborators in medical applications only):
- G. Batist – Oncologist, McGill University
- N. Beauchemin – Biochemist, McGill University
- G. Beaudoin – Medical Physics and MRI sequencing, University of Montréal
- F. Cheriet – Medical imaging, Polytechnique Montréal
- L. Gaboury – Pathologist, University of Montréal
- S. Kadoury – Medical image registration, Polytechnique Montréal
- M. Lafleur – Chemist, University of Montréal
- M. Mohammadi – Biologist, bacterial culture, Polytechnique Montréal
- D. Radzioch – Immunologist, McGill University
- G. Soulez – Interventional Radiologist, University of Montréal
- M. Tabrizian – Biomaterials and Bio-interfaces, McGill University
- T. Vuong – Radio-oncologist, McGill University

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