Nanoscale Biosensors Based on Luminescent Quantum Dots

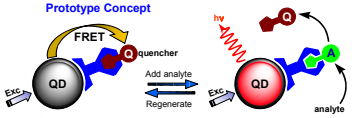
Hedi Mattoussi and Ellen R. Goldman

Optical Sciences Division and Center for Bio/Molecular Science and Engineering (CBMSE)

Objectives

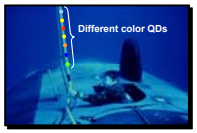
- To develop QD multianalyte biosensors
- Sensors capable of long-term environmental monitoring

Prototype Concept



Payoffs

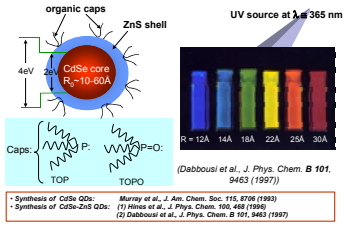
- **Unexploded Ordnance Detection:**
  Continuous monitoring for underwater detection of explosives
- **Biological Screening of Toxins (Force Protection):**
  Sensing systems for monitoring of drugs, toxins, pathogens, and environmental contaminants



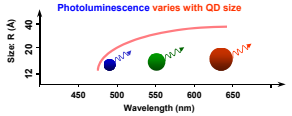
Approaches

- Design and implement new syntheses of highly luminescent QDs
- **Utilize QDs with bioreceptors to assemble multi-analyte biosensors for long-term environmental monitoring**
  - Assembly of biomolecular receptors onto luminescent QDs
  - Control FRET between a QD and dye-labeled receptor upon interaction with target analyte

Unique features of Quantum Dot fluorophores

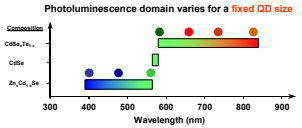


Binary CdSe QDs



- Tunable photoemission:
  - size
  - choice of group II or VI elements
- Maintain the same composition but vary the size across the range of accessible wavelengths

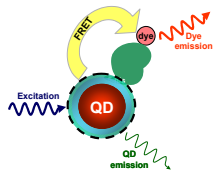
Design of Alloyed QDs



- Homogeneous core formation
- Tunable photoemission:
  - % composition
  - choice of group II or VI elements
  - size
- Maintain uniform size across wide wavelength domain

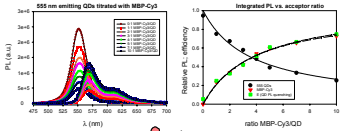
Design of QD nanoscale TNT sensor based on Fluorescence Resonance Energy Transfer (FRET)

1. FRET concept



- FRET Involves the non-radiative exciton transfer from a donor to an acceptor
- Transfer efficiency varies as ~ (1 / r⁶)
- Proximity driven
- It is a powerful sensing tool, used to detect binding events
- Requires spectral (or energy) overlap

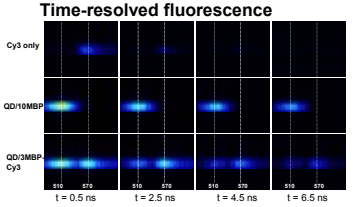
2. Advantages of QDs in FRET



- J(λ) = 8.91x10⁻¹³ cm³/M
  => R_0 = 58.6 Å
- Tunable QD excitation
  => Choose a minimum for the dye

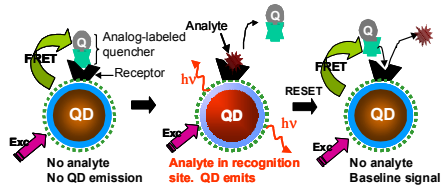
System predisposed for multiplexing (multiple analytes can be targeted simultaneously)

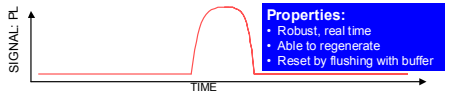
3. Illustration of energy transfer : Time-resolved fluorescence



I. Medintz et al., Nature Materials 2, 630 (2003) and A. Clapp et al., J. Am. Chem. Soc., In press

4. FRET-based sensor concept

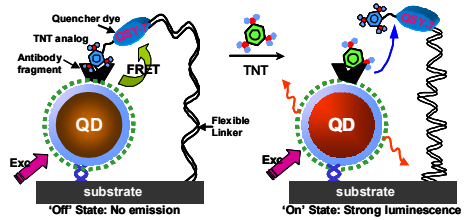




Properties:
- Robust, real time
- Able to regenerate
- Reset by flushing with buffer

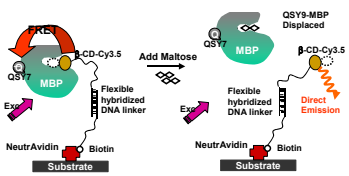
5. TNT monitoring system

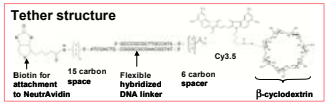
- **Recognition elements:** withstand nonstandard matrixes (*seawater*)
- **Robust reporters:** photo- and chemically stable QDs
- **Easily identifiable:** 'On' or 'Off' luminescence

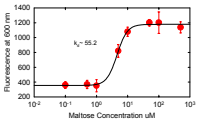


Already constructed and tested: a prototype of a fixed-tether assay

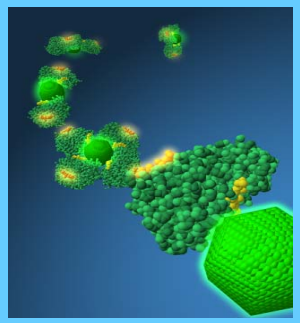
- Assay is based on competition displacement
- Employs reverse quenching as the transduction signal







Titration of P1-Cy3.5-B-CD on NeutrAvidin plate with MBP-95C-QSY7 added versus Maltose concentration



Key research milestones

- Design and develop new QDs with broad emission wavelengths
- Develop QD-surface ligands for water-compatibility and covalent conjugation
- Optimization of QD-acceptor FRET spectral overlap and separation distances
- Sensor optimization by linker and donor-acceptor pairs
- Design and optimization of multireceptor QD-bioconjugates
- Develop sensors that target analytes of interest to the Navy
  - TNT
  - RDX
  - Toxins
  - Pathogens
  - Environmental contaminant

Acknowledgments:

Collaboration with:
- Professor M.G. Bawendi and his group at MIT
- Professor S. Simon and his group at Rockefeller University

Funding from ONR, Keith Ward program

Publications
- **14 refereed publications, 1 patent, 9 proceedings, and 3 book chapters**

Work highlighted in Science, Nature Biotechnology, and Small Time magazine

Seminal papers:

- H. Mattoussi, J.M. Mauro, E.R. Goldman, G.P. Anderson, V.C. Sundar, F.V. Mikulec and M.G. Bawendi, *J. Am. Chem. Soc.* **122**, 12142-12150 (2000).
- E.R. Goldman, G.P. Anderson, P.T. Tran, H. Mattoussi, P.T. Charles, and J. M. Mauro, *Analytical Chemistry* **74**, 841-847 (2002).
- J.K. Jaiswal, H. Mattoussi, J.M. Mauro, and S.M. Simon, *Nature Biotechnology* **21**, 47-51 (2003).
- I.L. Medintz, A.R. Clapp, H. Mattoussi, E.R. Goldman, and J.M. Mauro, *Nature Materials* **2**, 630-638 (2003).