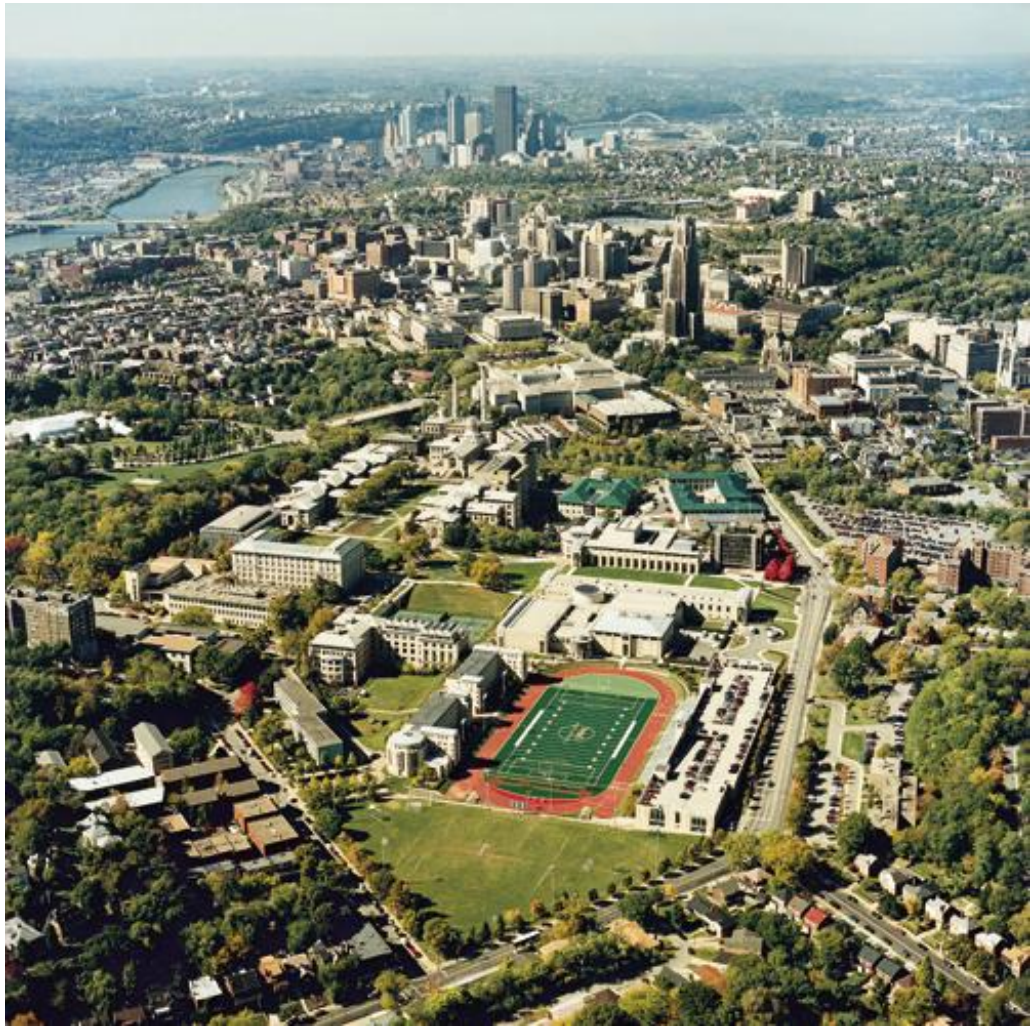

Commercialization and future developments in nanobiotechnology.

Marcel Bruchez
Visiting Associate Research Professor and Program Manager
Pittsburgh Technology Center for Networks and Pathways
Molecular Biosensor and Imaging Center

Carnegie Mellon University
Quantum Dot Corporation (former)

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An Apology

2003, 100 patents

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

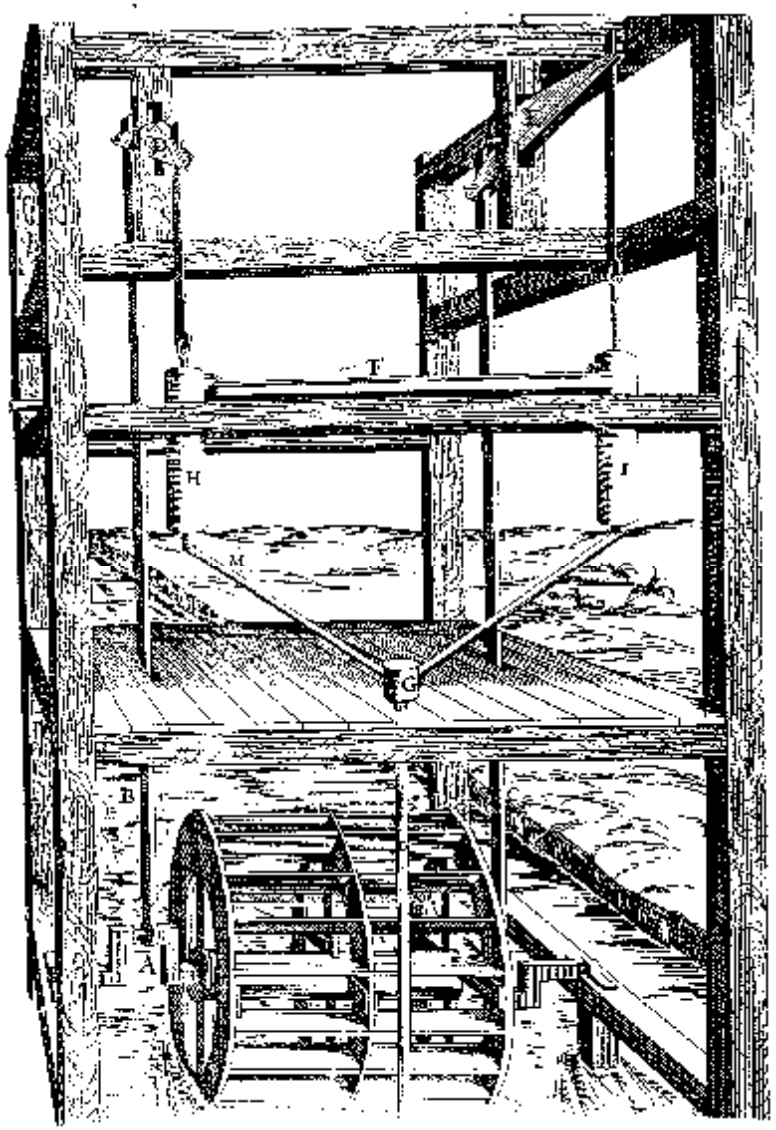
Koppikar et al,
Nano. Law and
Business. 1(1), 2004

Quantum Dot Patents Issued per Year

Estimates as high as ~90,000 nano patents...

QuickTime™ and a
H.263 decompressor
are needed to see this picture.

A 3.5 billion year old water wheel?



But how?

Nature innovates...
When there is a need

Generations of selection, not design.

Nature "does"
Nature "doesn't" understand how.

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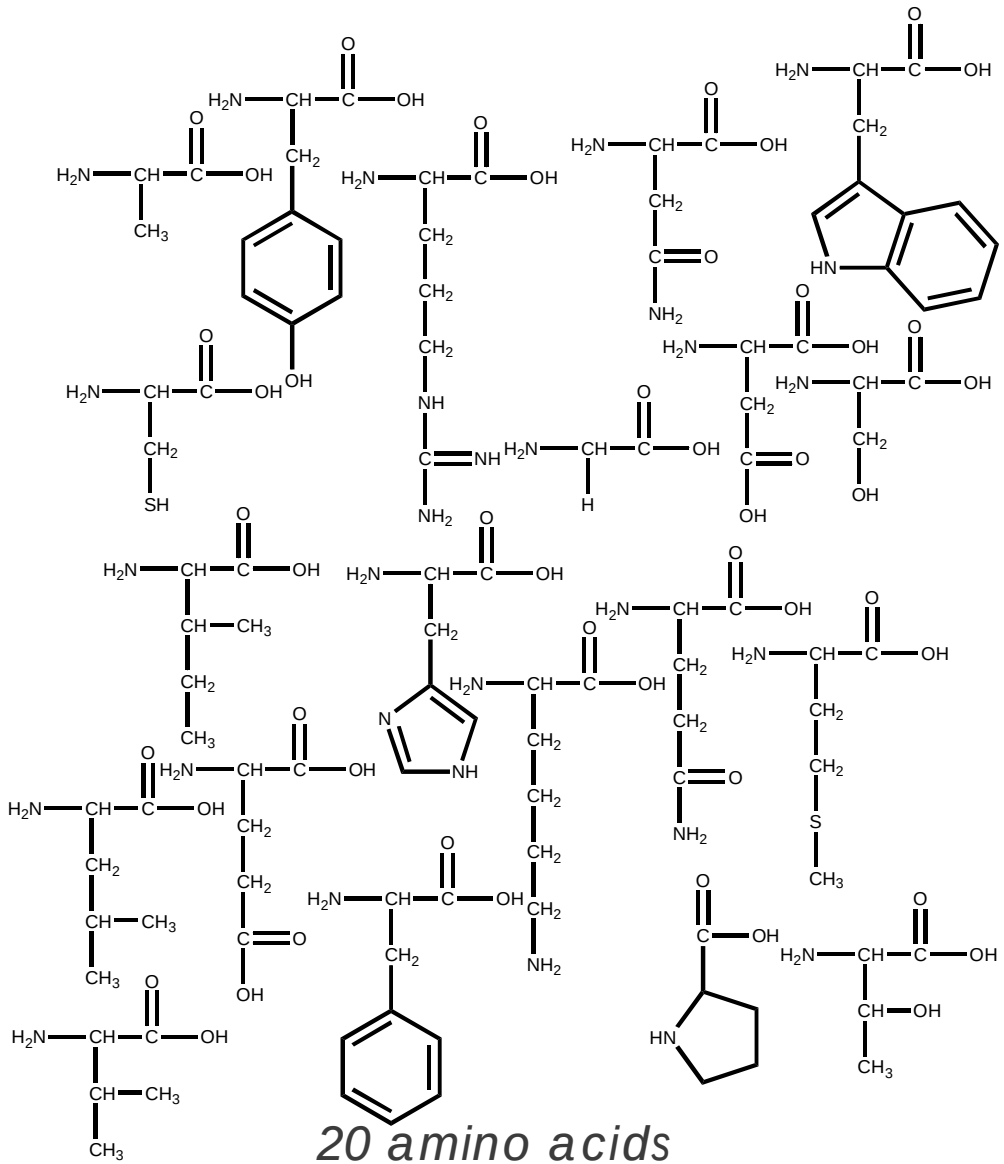
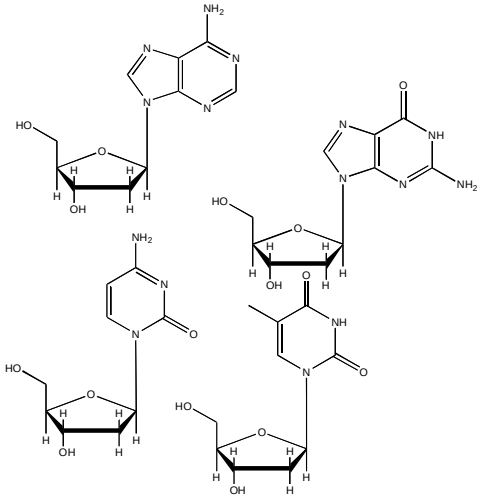
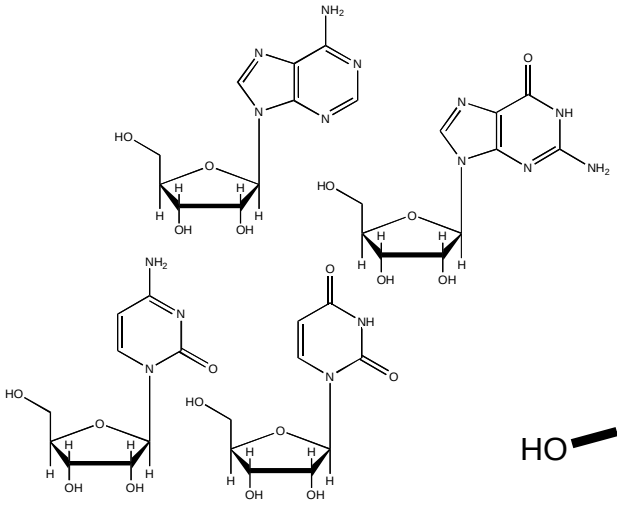
Limited tools in Her arsenal

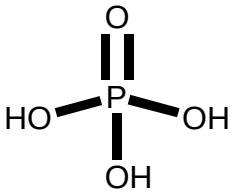


20 amino acids



4 (deoxy)ribonucleic acids





Nanobiotechnology expands the toolset...

Expanding the toolset

- Application of innovations in materials and chemistry into biological systems
- Application of materials and chemical processes to solve biological problems

- “Un natural capabilities”
  - Detection
  - Repair/treatment
  - Maintenance

- We are neither as fast, nor as patient as nature.
- We “need” to understand in order to design.

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Commercialization in Nanobiotechnology

- Context--
  - Healthcare is a worldwide market with diverse geographical market needs
    - Per capita spending in US: 1999 $6280 (Nat. Coalition on Health Care)
    - Per captia spending in India: 2004 $650 (US Commercial Service)
  - And this results in diverse technology needs

- US: Drugs: $286B, Diagnostics: <$20B, Research Tools, <$5B. (19% GDP)
- India: Drugs $8.8 B, Diagnostics: $115M, Researc Tools n/a. (5.1% GDP)

- Focus in US: Outcomes
- Focus in India: Costs

Nanotechnology Size Scale

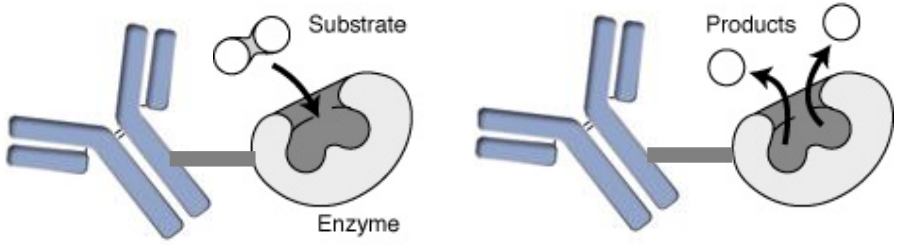
QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

Fullerene *Quantum Dot* *Nanoshell* *Dendrimer* *Liposome*

Size is comparable to biological scale---biology is possible

Example Nanobiotechnology Developments

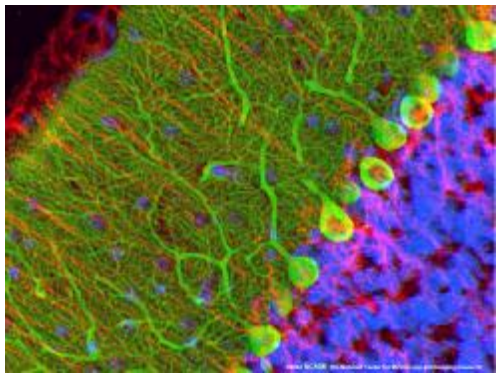
- Therapeutics--Antibody Directed Enzyme Prodrug Therapy



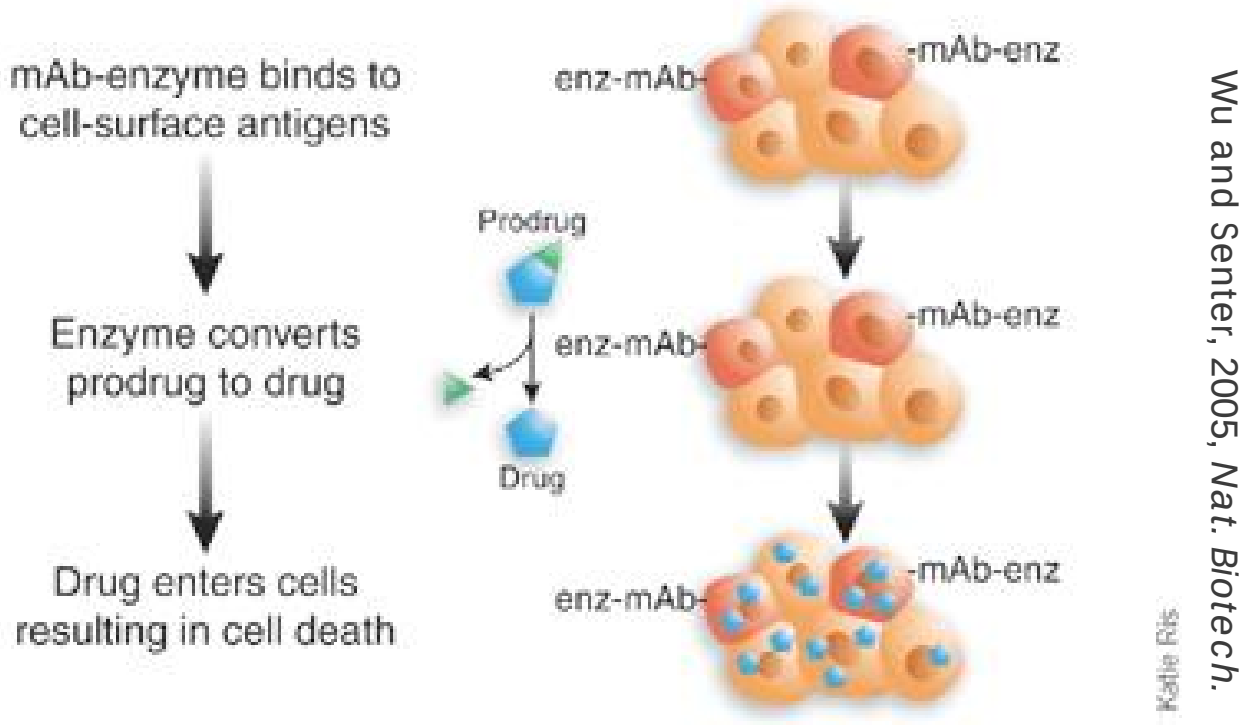
- Diagnostics--Combidex (dextran coated iron oxide nanopartcles)

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

- Research Products--Quantum Dots for Biological Detection



ADEPT (Antibody Directed Enzyme Pro-drug Therapy)



Wu and Senter, 2005, *Nat. Biotech.*

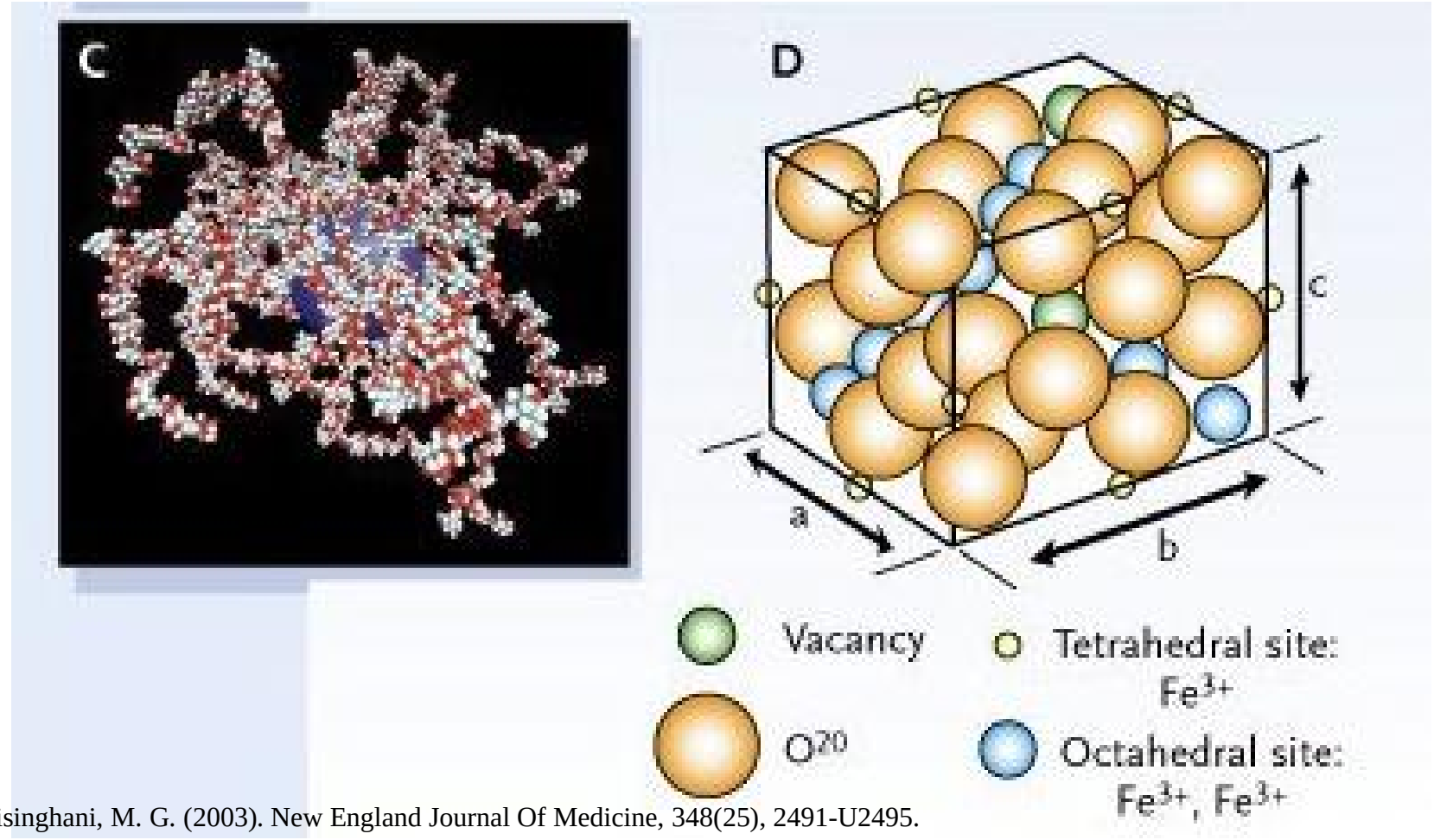
- The Problem: Many drugs are toxic (especially for cancer)
- Impossible to maintain high dose for long time without risk to patient
- The Solution: Deliver a small factory to the specific "bad" cells
- Treat patient with "nontoxic" drug at lower dose for long period
- The factory will "open" the drug at the target site and nowhere else

ADEPT State of the Art

- Animal models show effectiveness
- Clinical results reported in 2000, 2002
  - Inadequate clearance of antibody-enzyme conjugate
  - Long persistence of activated drug
  - Immunogenicity (mouse monoclonal)

- Enter Seattle Genetics (Senter) and Genencor (Schellenberger).
  - Humanized antibody (decreased immunogenicity)
  - Engineered protein production
  - 2005--Effective in immunodeficient mice…

- Key challenges remain---and this system is fully characterized
  - Sequence, structure, activity, kinetics, stability, specificity…
  - It was first published and demonstrated in mice in 1990
    - Bagshawe, Biochem. Soc. Trans. 1990.



Harisinghani, M. G. (2003). New England Journal Of Medicine, 348(25), 2491-U2495.

Superparamagnetic (no residual magnetism) iron oxide with dextran coating. Particles are passive--taken up by cells through phagocytosis and leaky vessels.

Combidex Safety

Contrast Media	Overall AE Rate	Serious AE Rate
Combidex® **(ferumoxtran-10)** Proposed dose and method of administration	**15.8%**	**4/1236 (0.3%)**
Ultravist® **(iopromide)**	**32%**	**8/708 (1.1%)**
Comparators to Ultravist: (iohexol, iopamidol, ioversol)	**"Similar" to Ultravist**	**4/659 (0.6%)**
Oxilan® **(ioxilan)**	**14.3%**	**8/531 (1.5%)**
Comparator to Oxilan: Omnipaque™ **(iohexol)**	**"Similar" to Oxilan**	**6/542 (1.1%)**

Figure from Gerald Faich--Safety Presentation to Oncology Drug Advisory Board, 2005.

Combidex for "sentinel node" detection

- Sentinel Nodes are essential to staging and grading tumors.
  - The are the sites of fluid drainage from primary tumor
  - They are the likely sites of first metastasis
- Patient prognosis and treatment options depend on accurate stage/grade.
- Accurate node identification would reduce "morbidity" from radical lymph node removal.

- But…tricky indication. They went for "broad" rather than specific indication.
- Healthy patients--risk averse.
- Clinical trial was not compelling for approval of broad (too few patients for each disease) OR for approval of specific indication.
- The "drug" may be safe but unmarketable. Redo the trial.

The FDA's Take on Combidex

" I would like to draw your attention to the fact that this is a broad indication. If granted, this agent can be used for almost all cancers regardless of type, size, clinical stage, whether patient has been previously treated with drug, biologic, radiation, or surgery.

One objective of today's presentation is to show you why the Agency has concerns for such a wide or broad indication given the level of efficacy and safety observed from clinical trials...

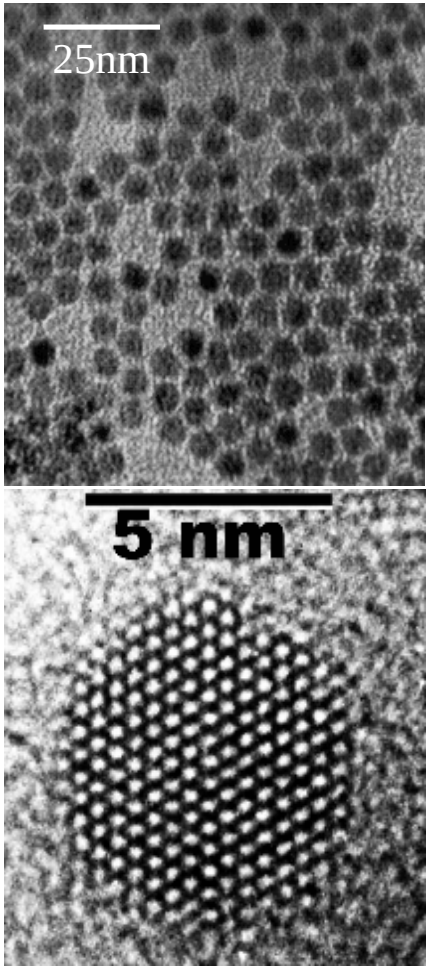
Our position is that dilution and slow infusion are not entirely free, and also we disagree that the Combidex, the safety profile resemble that of iodinated contrast agent."

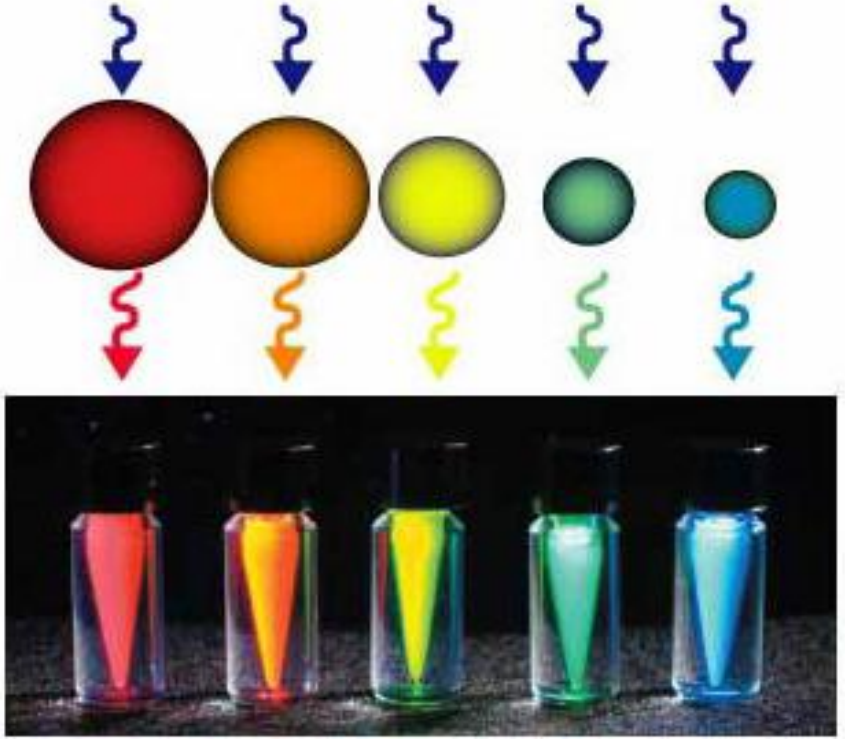
- Dr. Zili Li, Medical Team Leader Medical Imaging and RadioPharm.
- www.fda.gov/OHRMS/DOCKETS/ac/05/transcripts/2005-4095T1.DOC

The FDA clinical trials

Full transcript of discussion available

Highly fluorescent, nanometer-size, single crystals of semiconductor materials





655 605 585 565 525 nm

Multicolor, stable materials
Long-term traceability in live cells and animals
Longitudinal study possible after fixation
Compatibility with GFP and other intrinsic probes

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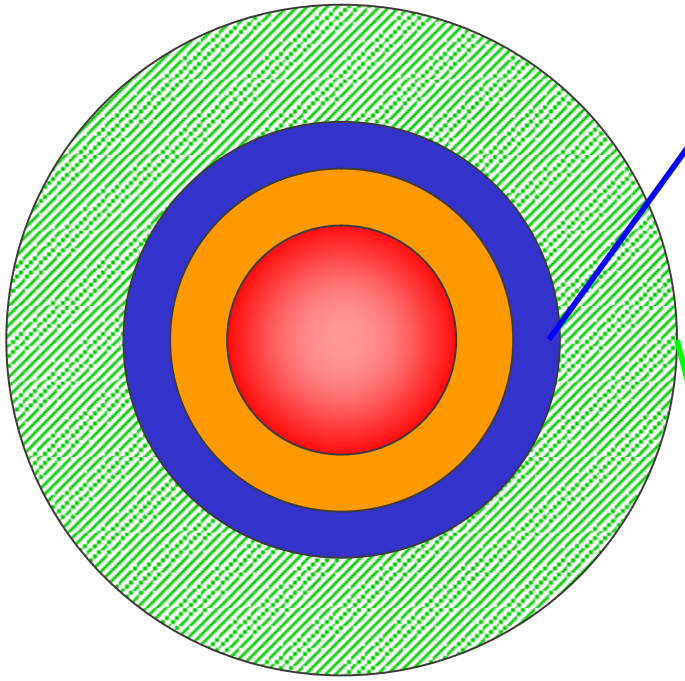
Commercial Challenges

Particle Synthesis
Reliable
Consistent
Stable
Bright
Scalable



Surface Modification
Stable
Specific
Manipulable
Scalable

Conjugate Preparation
Irreversible
Versatile
Activity Preserving

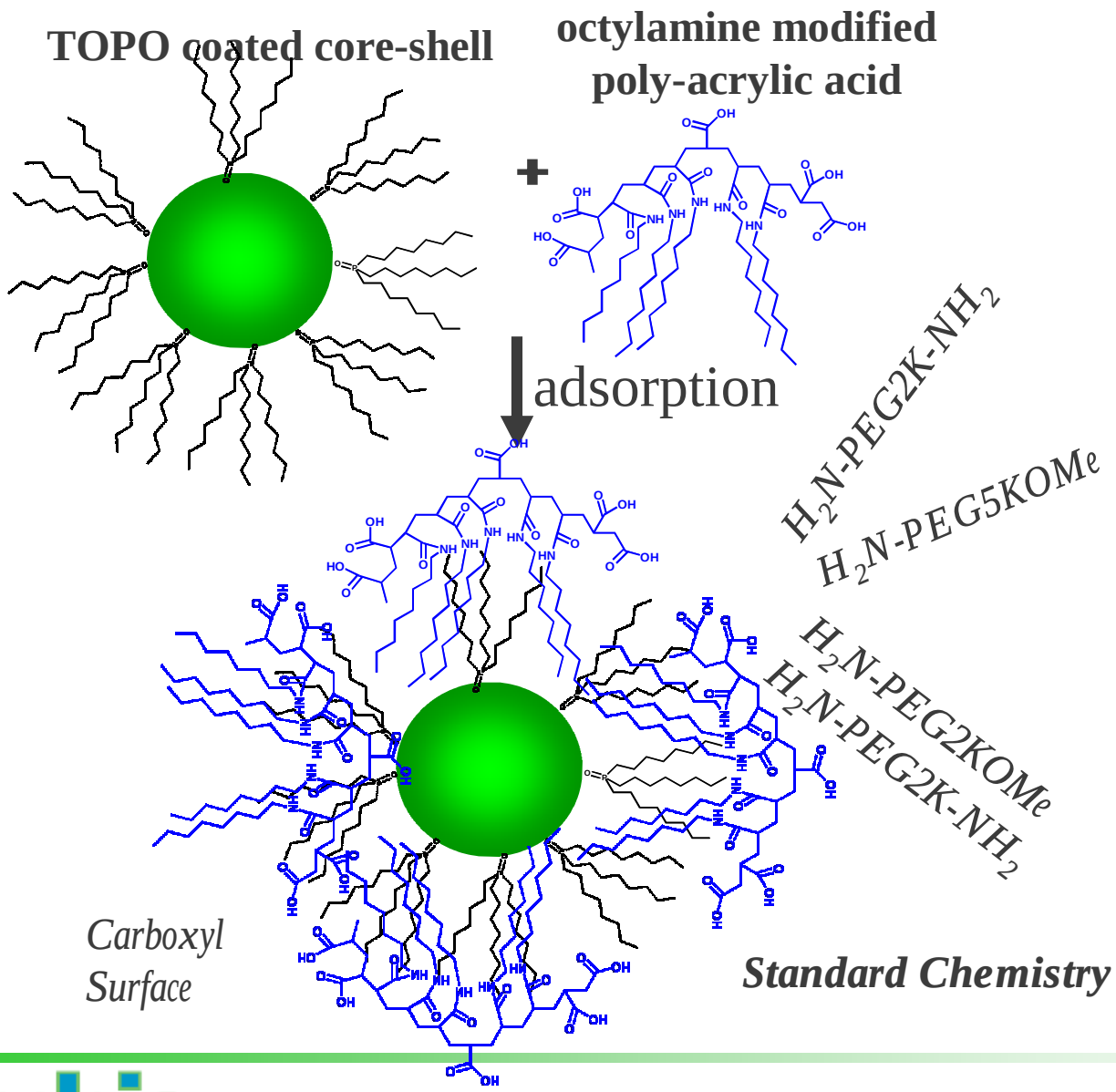
Critical Properties
Bright
Stable
Active
Reproducible

A little clever, a lot lucky…

Still room for improvements…

Very limited modularity…

Amphiphilic Stabilization



Macrophage uptake

Vascular Imaging

Conjugation without aggregation.

Empirical observations yielded applications

The Right Materials Have Great Impact

QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

Real-time studies of relevant ligand receptor dynamics & interactions enabled by commercial quantum dot conjugates.

QuickTime™ and a
Cinepak decompressor
are needed to see this picture.

Epidermal Growth Factor

Important Cancer Marker Her-2/neu

New Phenomena Yield New Treatments

Cell Body

Lidke, et.al. Journal of Cell Biology 2005 (August 15th), 170(4), 619-626. MPI Goettingen Jovin/Arndt-Jovin.

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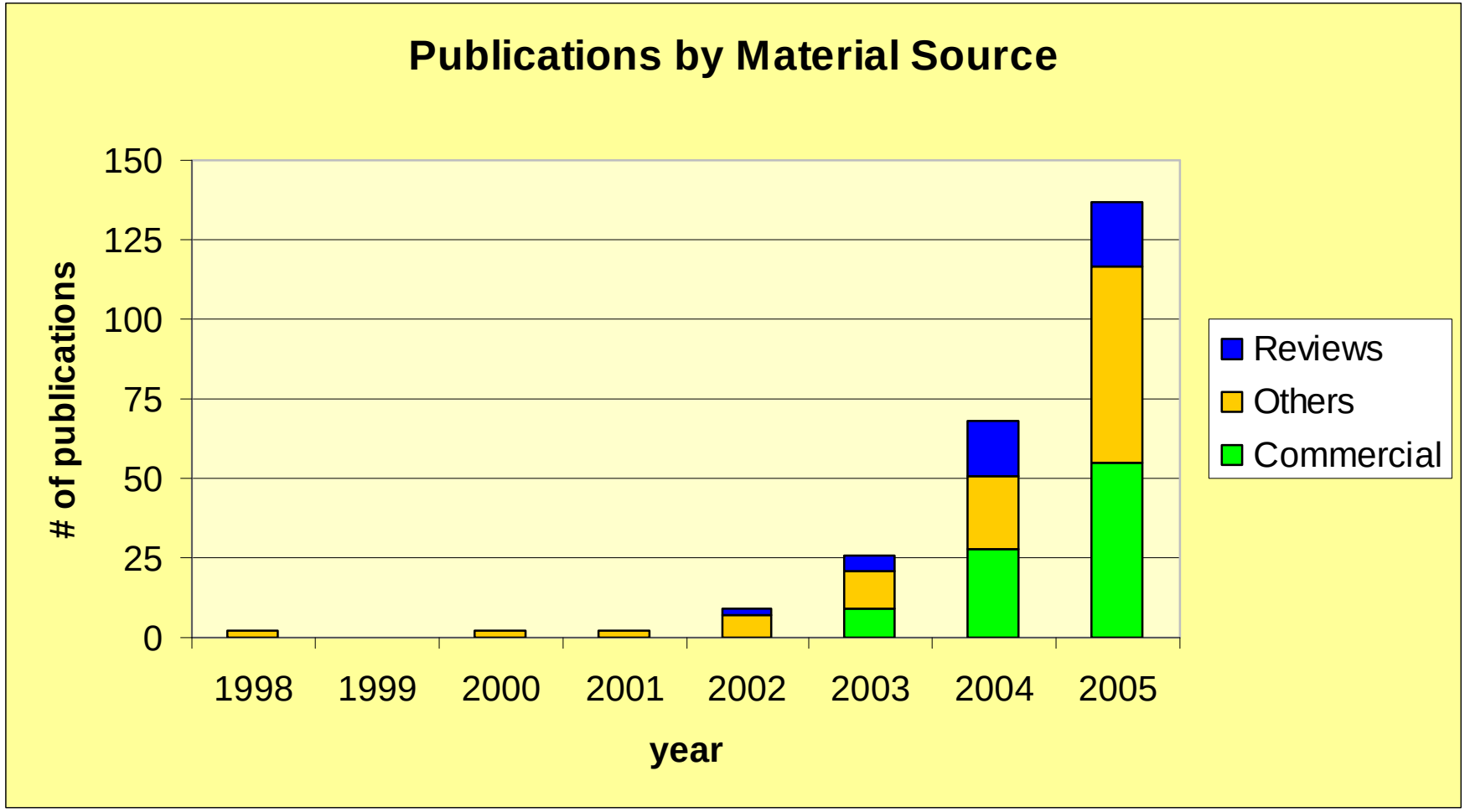
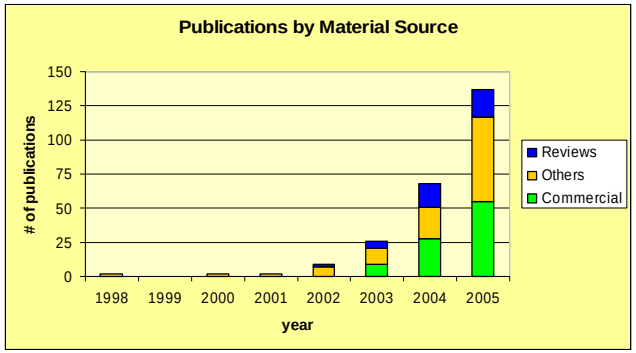
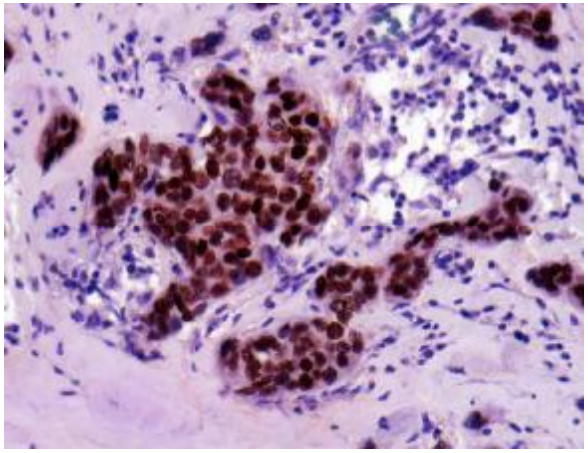
Literature Trends Indicate Growing Impact



Impact focused in basic method development and research—Foundations.

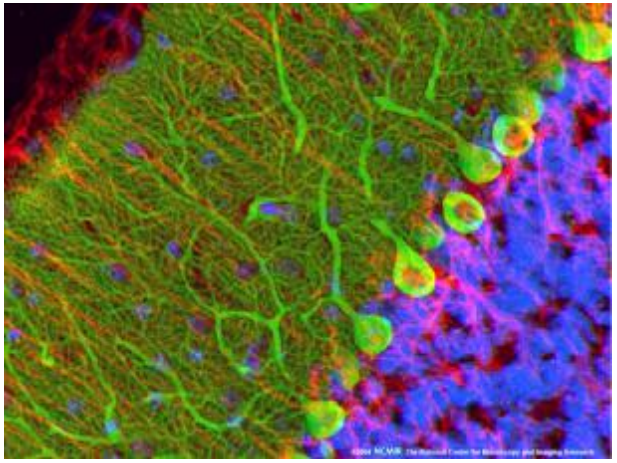
On the Edge…Poised for Dramatic Expansion





- New Probes + New Systems + Existing Needs

- New Capabilities



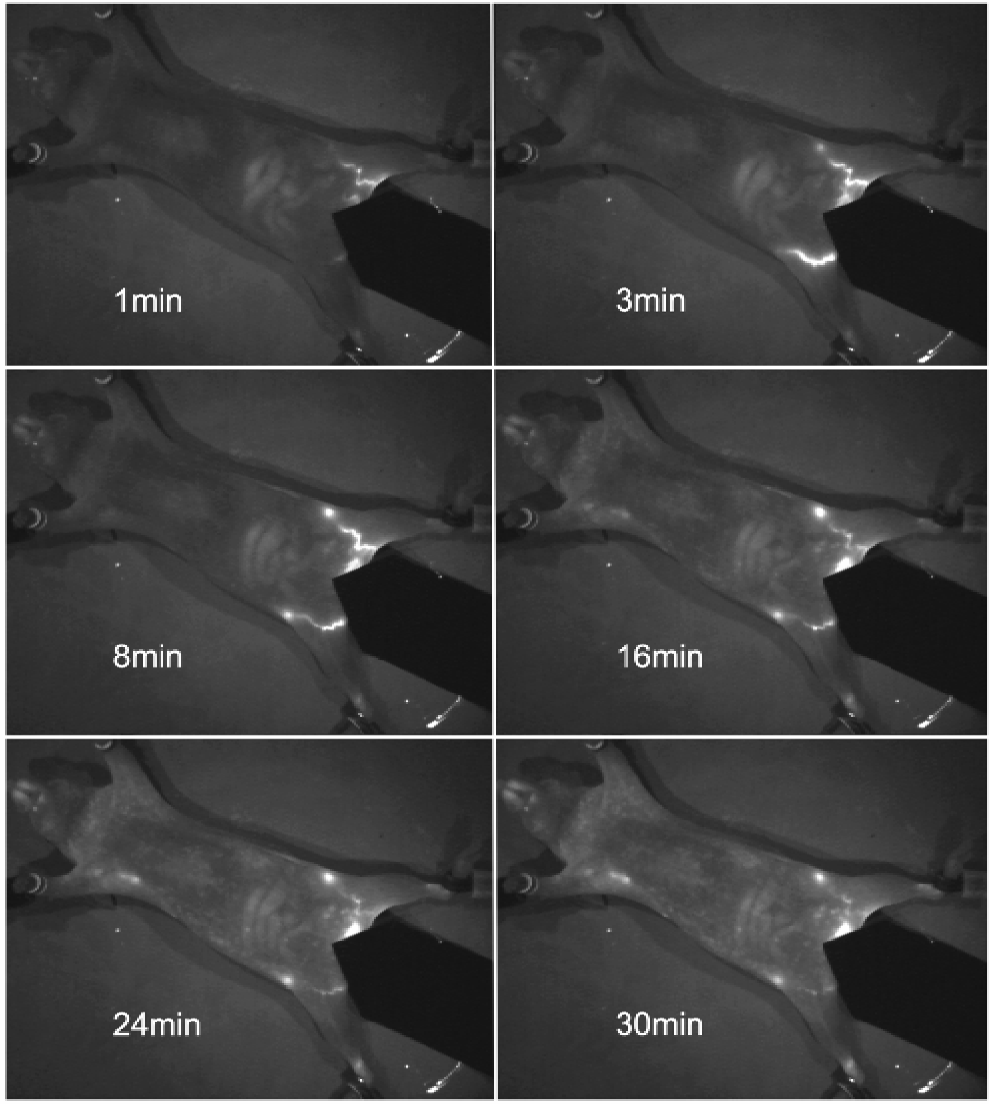
Innovation, not displacement builds business

A word about safety.

- You can not “establish the safety” of a material.
- Safety has a context.
- Nanomaterials are devices--they are chemically ill-defined.
- Characterization of product by process, designed for application.

- We do not know if Qdots will be safe, because we do not know how they will be used.

- Route, Dose, Version?



They are well tolerated in mice at high dose IV, for at least 2 years.

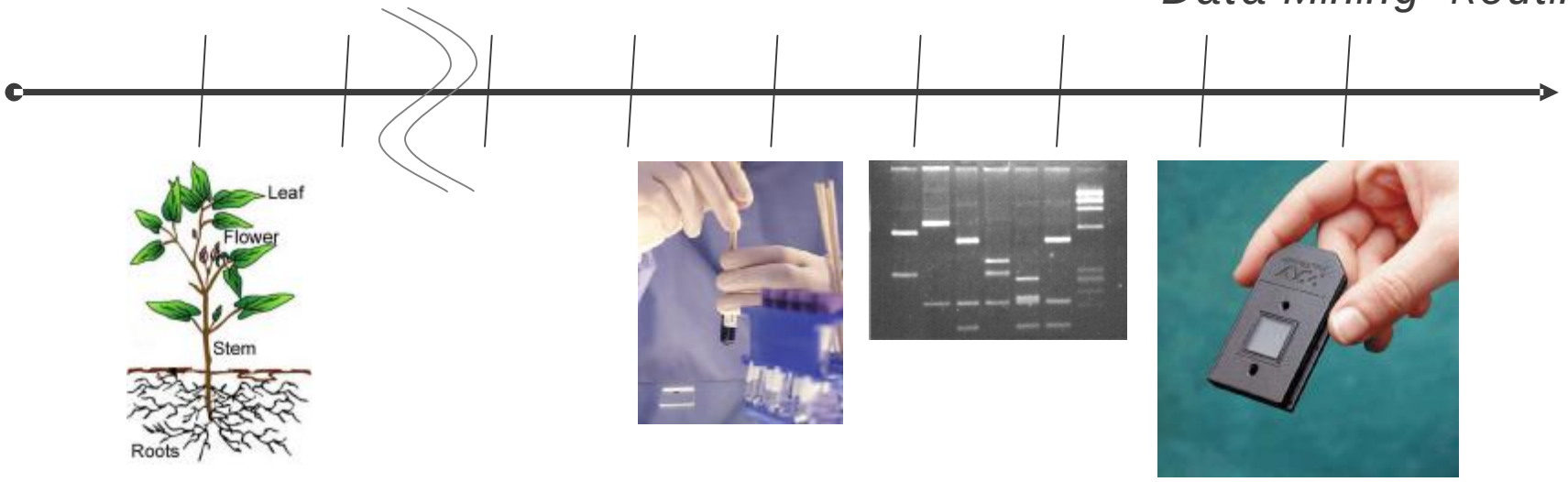
First Clinical Applications—Pathology

- Initial products for research on the market
  - Ventana Medical Systems (leader in clinical pathology)
- Initial trials underway in academic centers
- Used in major drug discovery centers in industry

- Initial clinical products in 2-3 years
- Future in Molecular (Personalized) Medicine

The past and the future.

Descriptive
Phenomenological
Quantitative
Molecular
Biochemical
High-Throughput
Data Mining--Routine



- Tools gap is filled as technology matures.
- Biology solves problems without regard to tools--we don't.

Tools Gap In NanoBiotechnology

Test and measurement
QC each device
Video microscopy
Six Sigma

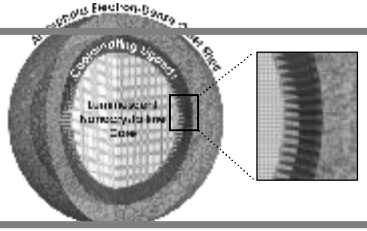
cm

mm

Grain size
Rheology
Phase Behavior

µm

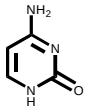
Characterization is a research problem



nm

Homogeneous Pop.
Purity
Sequence
Structure/Activity

Å



Molecular Purity
Solution analytical

Characerization tools lacking--Scale, Size, Materials

Development Challenges

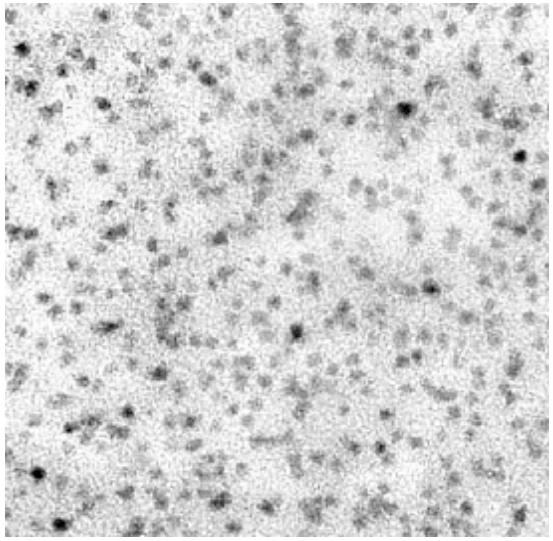
- Systems approaches required
- Weak specifiability--detailed design capability
- Propagation of uncertainty

- Ill defined properties
- Population properties

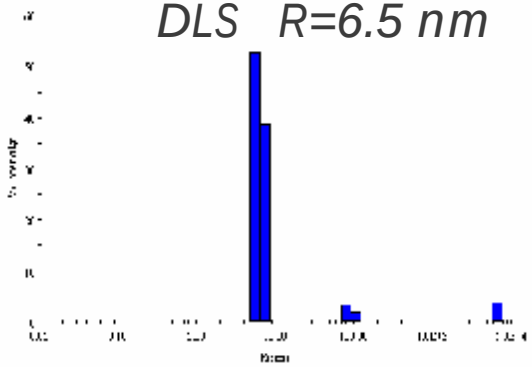
- In-vivo uses?
  - 1 dose is 10^{14} “devices”
  - How to QC?

Size?

TEM 5 nm



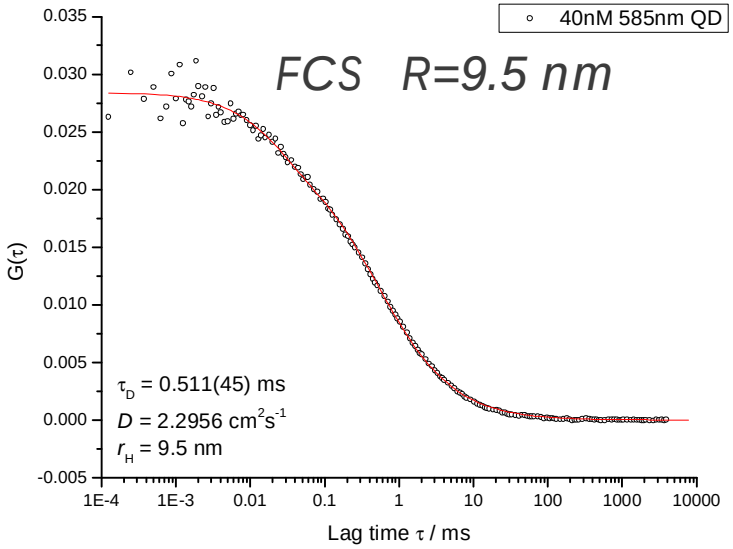
DLS R=6.5 nm



GFC R=6.7

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

FCS R=9.5 nm

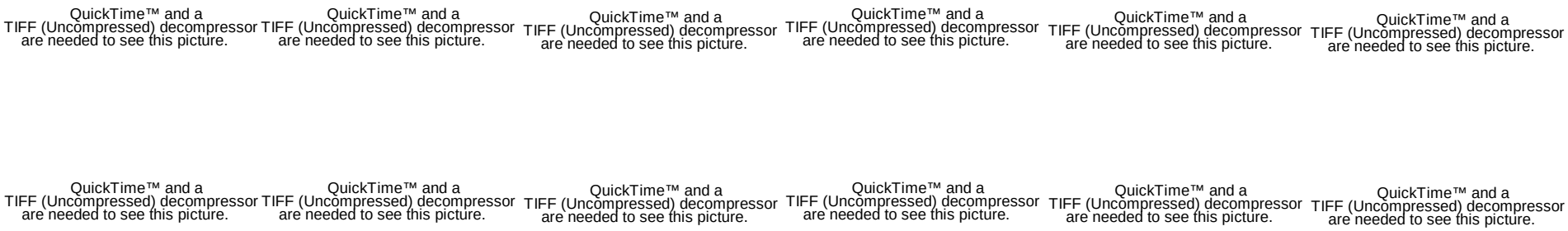


We should know what we mean when we say "size."

Predicting the future

- Progress will slow. Tools will be needed to accelerate.
- Infrastructure and discussion is critical to get the right tools.
  - What are the missing pieces?
  - How to effectively measure them?
- Basic science still needed (impact of size on bio-properties).

- Or, we could get more efficient at testing.
  - Evolutionary approaches needed.



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  - Dr. Joel Martin
  - Dr. Charles Hotz
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  - Donald Zehnder
- Collaborators

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