August 12, 2023

Quantum dots (QD) hold promise in advancing medicine. This research project will explore the various applications of QD, compare it to the current method of those such medical applications, and examine how QDs can be implemented

Quantum dots (QD), hold promise in advancing different areas in science such as medicine. This research project will explore ,

Topic: How will quantum dots enhance the efficiency of solar cells and contribute to sustainable energy solutions?

* What are quantum dots: properties, behaviour, makeup, everything you can find about them
* How do solar panels work: how does solar energy conversion work, their principles, their drawbacks in the traditional solar cells
* How quantum dots would be better as solar cells: explain how with detail
* Explain how they would be used, how you can make quantum dots into a solar cell, how they would be manufactured as solar cells, how they would be better than traditional cells (with statistics if you can)
* World impacts:(Compare the pros and cons of both traditional and quantum dot solar cells) talk about how quantum dots would impact renewable energy, benefit our environment. → Try to find ways to explain how to get these more in the market and use them as solar cells more recently than a futuristic thing – steps to take to go down this path more efficiently and faster (figure it yourself the best you can)

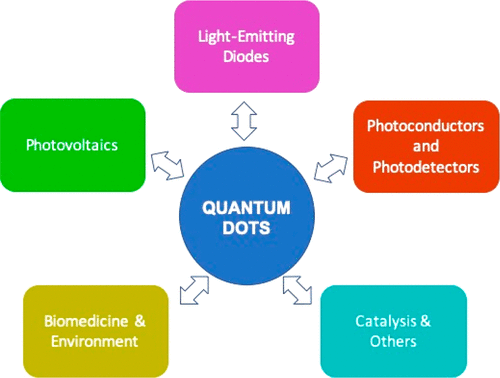
Copy word for word - have to later rephrase

definition

**Quantum Dots**

<https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiRhJSmr9uAAxWlADQIHRXlDn0QFnoECC8QAQ&url=https%3A%2F%2Fpubs.acs.org%2Fdoi%2F10.1021%2Facsanm.0c01386&usg=AOvVaw1BEvWUB8mvRR4xT4UlyDwB&opi=89978449> (aug. 16)

* Quantum dots: also called artificial atoms
* Are semiconductor nanocrystals - nanosize diameters
* Have quantum size effects in their optical and electronic properties
* Are used in a lot of devices
* Still dont know much about them so active area of research
* Applications based around light and optical properties: role in light emission, conversion and detection



**APPLICATIONS:**

QD for LED and Display Application:

* Use epitaxial QD
* However, the high temperature of the growth process can introduce problems to interface control, due to In desorption,

<https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiRhJSmr9uAAxWlADQIHRXlDn0QFnoECCkQAQ&url=https%3A%2F%2Fwww.news-medical.net%2Flife-sciences%2FWhat-are-Quantum-Dots.aspx&usg=AOvVaw1xeDn2m-vOSZFpaT3dVQ8n&opi=89978449> (August 16)

* Semiconductor nanocrystal – (unique from bulk semiconductor or discrete molecules )
* Exciton confined – leads to QD’s optical and electrical properties
* Useful for biomedical imaging, electronic devices, solar energy

**Properties:**

* QD not all the same – so properties differ from their own size and shape
* Smaller crystals are = larger their band gaps (the distance between valence band of electrons and conduction band – lowest energy the electron needs to move up to the conduction band to do conduction) = greater energy level differences in crystal
* QD (extra small) = more energy needed to excite and more energy released when back to resting state
* Affects the way dots emit signals

**Use in Medical Imaging**

* More precise and accurate results with QD
* Can control the production of the crystals so then we know the size and shape = knowing conductivity properties → helps intercept results from imaging then
* Regulating size (also potential energy) → can be used for specific purposes

**Use in Photovoltaic Cells:**

* Traditional solar cells: made of silicon → convert solar energy to electrical
* Quantum dot voltaic cells: QD absorb light from sun from different frequencies, get excited – that excitation energy used to harness and convert to electrical current
* Right now: quantum dot photovoltaic cells exist, but not as efficient as traditional solar cells
* Only convert 9% of sun’s energy into electricity → could be improved with further research

**Use In Computing:**

* Could increase speed of computer calculations

**Production of Quantum Dots:**

Ways to make QD:

* Colloidal Synthesis: A process involving transformation of precursors into monomers, which become supersaturated causing the growth of the nanocrystal via nucleation.
* Fabrication: used to make stronger quantum dots that have outer shells
* Viral Assembly: Genetically engineered bacteriophage viruses used to form the nanocrystal.
* Electrochemical Assembly: ionic reaction between metal and electrolyte → makes spontaneous formation of quantum dots

<https://www.news-medical.net/life-sciences/Quantum-Dots-in-Photovoltaics.aspx> (August 20)

* Traditional solar cells: made of silicon
* Technology of solar cell is advancing – quantum dots are promising for future
* QD: used to line solar cells with a thin coating
* Have natural ability to absorb solar light → specific band gaps = frequencies of sunlight: light is absorbed to excite nanocrystal particles – used to convert to electrical energy

**Advantages:**

* QD as solar cells: low cost, lightweight and versatile nature
* Are durable : don’t need high temperatures or inert atmosphere to create energy – don’t show degradation signs after 5 months in normal air conditions
* Manufacturing process: requires “considerably” less energy
* Entire cell (minus electrodes ) can be deposited at room temperature in normal conditions (no solution needed)
* Minimizes manufacturing process with the transport of materials

**Disadvantages**

* Not efficient (less than industrial standard rates) – 9% converted to electrical
* ^^ understandable because quantum dots havent been used much as solar cells for very long though regular silicon cells have been used for 6 decades
* More research might improve efficiency

**Further Development**

* Stability of quantum dots still not understood (more research needed)
* More research has become popular in this
* Potential they carry for the future is undeniable

<https://www.news-medical.net/life-sciences/Quantum-Dot-Production.aspx>

Ways to produce quantum dots:

**Colloidal Synthesis:**

<https://www.edn.com/quantum-dots-explained/>

* Semiconductors
* Size: 2- 10 nm
* So small..quantum effects give them unique light emitting properties
* Emit light: electrons absorb energy..some absorb an efficient amount to escape atomic orbit and move around freely (be able to conduct in that region that it can move around). When it goes back to atomic orbit..it loses energy in the form of light (colour of light depends on amount of energy)
* Because the dots are so small, energy released from electrons is pretty consistent : so emissions are of the same colour
* Large dots (5-6 nm) give low energy emissions (red and oranges) .. small dots (2-3 nm) give high energy emissions (blue and violet) → sometimes called “quantum confinement” (constraints at atomic level are predominant)
* Because they’re monochromatic.. Many potential and existing applications like in solar cells, medical imaging, quantum computing, QLED TV
* Quantum dots in TV: red, green, blue dots arranged in layers, protected by a film from environmental degeneration. Dots are stimulated by a blue LED backlight to emit the red, green and blue (which combine to give different colours). PRO: improving colour quality by making sure not much light is absorbed by colour filters, and reduce overlap of green and blue

<https://www.techtarget.com/whatis/definition/semiconductor> *What are Semiconductors (August 22)*

* Substance with specific electrical properties that are important for computers and electrical devices
* Typically: solid chemical compound that conducts electricity in certain conditions (not all the time → that’s why *semi*conductor) – ideal for controlling electrical currents
* Conductor = conduct electricity. Insulator = not conduct electricity Semiconductor = in between
* Conductance depends on: current. Voltage, intensity of radiation of infrared, visible light, ultraviolet or X-ray
* Specific properties depend on: impurities (aka dopants) added to it

**How do Semiconductors Work?**

* Semiconductors made up of crystal
* Valence electrons of atoms bind with other atoms to make covalent bonds (conductors usually have one valence electron, semiconductors usually with 4)
* If both atoms have same number of valence shells, electrons bind and organize into crystal structures

**Difference Between N-type and P-type Semiconductors:**

* N-type: usually negative charge electrons like current in a wire
* P-type: carries current in holes (electron deficiencies) – holes have positive charge
* Flow of holes is opposite to flow of electrons
* Elemental semiconductors: antimony, arsenic, silicon, boron, carbon, selenium, sulfur, etc
* Semiconductor: controls and manages the flow of electrons
* Semiconductor optical amplifier (SOA): element found in semiconductors to amplify light

<https://www.sigmaaldrich.com/CA/en/technical-documents/technical-article/materials-science-and-engineering/biosensors-and-imaging/quantum-dots>

* Tiny particles (nanocrystals) of semiconductor materials
* Diameter (2- 10 nm) = 10-50 atoms
* Different and unique properties from large bulky semiconductors because of the high surface area to volume ratio of QD → most apparent result of this is the colours they show based on the size of the particles (quantum confinement)
* Because so small: electrons confined in small space (quantum box) …when radii of semiconductor nanocrystals is smaller than the exciton of Bohr radius (radius of average distance between electron in the conduction band and the hold it leaves behind in the valence band), there is quantization of the energy levels according to Pauli’s exclusion principle
* These quantized energy levels make them more similar to atoms than bulk materials…so nicknamed “artificial atoms”
* Generally , as size decreases, difference of energy of highest valance band and the lowest conduction band increases → more energy needed to excite and more released when grounded
* QD can emit any colour light from the same material just by changing dot size → a lot of control over the size of dot manufactured
* Classified based on types based on composition and structure:

**Core-Type Quantum Dots**

* Single component materials of uniformed internal composition
* Properties of these can be changed by changing the size of crystals

**Core Shell Quantum Dots (CSQD)**

* Luminance properties of QD comes from recombination of electron-hole pairs (exciton decay) by radiative pathways
* Non radiative can also do exciton decay but reduce fluorescence quantum field
* To improve efficiency and brightness: grow shells of other higher band gap semiconducting material around the dots
* Ex. quantum dots with CdSe in the core and ZnS in the shell – 50% greater quantum yield
* Coating QD with shells improves quantum yields by “passivizing nonradiative recombination sites” and stronger against processing conditions by different applications
* Explored as way to improve photophysical properties of QD

**Alloyed Quantum Dots**

* Changing crystal size to get different properties could be a problem in some applications due to size restrictions
* Alloyed quantum dots change the composition and internal structure of the crystals without changing the size to get different properties
* Alloying materials that have different band gap energies creates even more interesting properties different from bulk semiconductors and their parent semiconductors

**Applications:**

* Optical properties like bright, pure colours, ability to emit rainbow of colours, high efficiencies, longer lifetimes, high extinction — great for LEDs, solid state lighting, displays, and photovoltaics
* Zero dimensional makes them have sharper density than higher dimensions. Small size also means electrons don’t have to travel so far so electronic devices work faster — great for transistors, solar cells, ultrafast all-optical switches and logic gates, quantum computing
* Small size makes them able to go anywhere in the body – great for biomedical imaging, biosensors. Right now…fluorescence based biosensor used organic dyes with broad spectral width But limits their effectiveness to just a few colours and shorter lifespan. QD emit whole spectrum, longer lifetime, brighter, little degeneration overtime,

<https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiRhJSmr9uAAxWlADQIHRXlDn0QFnoECC0QAQ&url=https%3A%2F%2Fwww.britishcouncil.org%2Fvoices-magazine%2Fwhat-quantum-dot&usg=AOvVaw2iJx7JWC0bZTHbYL8qv1lC&opi=89978449>

* QD: specks of material — so small some people say they dont have any dimension (1/10,000 of human hair)
* That small particles called nanoparticles
* QD: nanoparticles with semiconducting properties — quantum effects because they are so small ( electrons are trapped and can only be in defined energy levels)
* Confined, discrete energy levels = good for optical and electrical (electron’s motion confined in all 3 dimensions)

Look like:

* small cluster of atoms
* Can come in different combination of elements (example: cadmium, selenium, zinc)
* When buying them.. they come in a protective shell of semiconducting material — shell keeps it confined, stable and protected
* When making it— can control the diameter of core and thickness of shell

Making them:

* Growing them in nucleation site/ make on metal dish using electrochemical approach …to control how big they are: use flowing gas or a drop in temperature (stop them from growing)
* Exciting them with a laser makes them glow different colours (colour based on elements used and size)
* For TV: improves picture quality — when shine light on QD, shines different colours/wavelength based on size and composition (called photoluminescence). Excited QD relaxes: releases energy as light — in TVs, can be used to improve back light to make colours on the screen clearer
* Researchers - combine QD with **LED making light emissions with very narrow wavelength.** Makes colours brighter.
* can capture light and convert it to electricity— can do this efficiently and need less space than other types of materials
* Changing size of dots: change ability to absorb and emit different light (use flowing gas to control size. Big dots = red light. Small dot = blue)
* Dots under radiation emit light — could be used for security to detect radiological material. Good for radiation detections at security and screening
* For medical: certain medical procedures require radiation but need to know patient's doses (QD can be the dosimeter). Can be used in neuroscience as sensor to show if X-ray beam correctly located.
* Can also be used for drug delivery and cell labeling
* Need to explore the physics, ethics and safety of it.. make sure its biologically safe (dissipate or remain in body)
* Cadmium: sometimes used as QD cores BUT…a heavy metal, can cause respiratory problems when inhaled, cardiovascular and renal problems when injected, cadmium poisoning treatment is limited.
* QD uses small amount of cadmium but finding other elements to use instead (cadimum is expensive too so also a motivation to end it)

<https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiRhJSmr9uAAxWlADQIHRXlDn0QFnoECA4QAQ&url=https%3A%2F%2Fwww.nanowerk.com%2Fwhat_are_quantum_dots.php&usg=AOvVaw0LdJ8_lHSa0iq5GhrXKxAX&opi=89978449>

* QD: theorized in 1970, made in early 1980s
* Properties depended on: size, shape, composition, structure (solid or hollow)
* To use QD across a lot of areas effectively: need a large dependable manufacturing technology to always make large quantities of QD of all the same parameters — ensures each batch has predictable, same and reliable properties for whatever use

(*Didn’t take many notes from here but if more info needed, can use this)*

Using it for Solar Cells:

* Why use QD:
  + Can be made in energy saving room temperature area
  + Made from abundant, inexpensive materials
  + Material doesn’t need extensive purification (save time and more money) —> compared to silicon
  + Can be used for more application — (flexible and inexpensive = lightweight plastics)
* Attempts haven’t worked: not as efficient yet for converting sunlight
* Promising route: replace the old layer by layer method —> instead, semiconductor ink with the goal of letting the coating of large areas of solar cells substrates be in single deposition instead of 10 depostiions steps as the original

Graphene Quantum Dots:

* Graphene: unrolled plane of carbon nanotubes → highly considered for nanoscale electronics. Research shows..possible to carve out nanoscale transistors from a Graphene QD (aka a single graphene crystal)
* Unlike other substances..Graphene: highly conductive + stable even when cut into 1 nanometer wide
* Considering it for photovoltaics cells, **bio sensing**, photoelectric, **bioimaging**,: b/c
  + special photoluminescent property,
  + low toxicity,
  + biocompatible,
  + very stable against photo bleaching and photoblinking
* Still figuring out efficient + universal ways to synthesize GQDs with high stability, controlled surface properties, and tunable PL emission wavelength

Perovskite quantum dots:

* Luminescent quantum dots (LQD): have high photoluminescence quantum fields, flexible emission colour controlling, solution processability
  + Promise in lighting systems (warm white light without UV or infrared) + high quality display

- Production held back b/c …expensive production costs,

December 25, 2023

**New Topic: In what ways do quantum dots play a crucial role in advancing the field of medicine? (the application of quantum dots in the field of medicine)**

* ~~Talk about quantum dots (explain what they are, their pros/cons, etc)~~
* ~~Tell about the different applications of quantum dots briefly (tech, medicine, renewable energy – bullet point list them)~~
* ~~Dive into the medical aspect of it and what areas QDs can help with (first just list them, then dive into each later)~~ 
  + ~~When diving into each one: explain what that thing is first (ex. What is drug delivery), how it is currently being done, then how we can do it with QDs AND make a list of the pros and cons of using QDs for that medical aspect → do this for all the aspects of medicine~~
* ~~Show examples of how QDs are already being used in medicine? (Charts + Graphs?)~~
* CONCLUSION: (*make this better)*
  + ~~Why QDs are the needed advancement/ the future of medicine~~
  + ~~The overall pros and cons of using QDs in medicine~~
  + ~~How we can start the implication /use QDs more~~

<https://www.brighthubengineering.com/manufacturing-technology/89345-quantum-dots-advantages-and-disadvantages/> (pros and cons of quantum dots in general)

* QDs: artificial clusters of semiconductor atoms
* Have ability to confine their electrons’ motions due to their small size
* Can tune their bandgap = control their light absorption and emission frequencies
  + Done through quantization of energy levels
  + Makes it possible for their light + electrical properties to be adjusted for their different applications/purposes

Pros of QD:

* Can easily control their properties (specifically for the emission spectrum):

→ Can easily control the size of the dot produced

→ QD formation absorb photons and then re-emit longer wavelengths of light for a period of time

→ This means..that with being able to also control the size of the dots, we can then control the wavelengths of the re-emitted photons

→ Therefore: can manipulate the light that is emitted without significant cost or high-end technology

→ Can make a full range of QDs each with distinct emission spectrum

* Can be excited with very little energy = lower costs

→ only need a single blue or ultraviolet light beam to excite the QD, no matter it’s size

* have high photostability + brightness

→ good for high sensitivity applications (ex. Fluorescent tagging , live-cell imaging)

→ Fluorescent properties + high resistance to metabolic degeneration allows them to be used for a wide range of experiments with ignoring time barriers

* Can be used in various forms (crystals dissolved in liquid solution quantum dusts, beads)

→ Makes their application range wider

* Multiple manufacturing methods …all are cost effective + easy (ex. Lithographic techniques, epitaxial techniques, colloidal synthesis. )

Cons of QDs:

* In biological applications: possible that due to large physical size, they can’t diffuse through cell membranes…making drug delivery difficult
  + Delivery process of QD may be dangerous for cell..could also destroy cell
  + QD could be toxic for cell
* Their long lifetimes could be problematic/limit certain applications in which QD should biodegrade immediately after use
  + Some case: possible to remove QD by washing cell with proper solutions
* Can blink and become invisible
  + Could cause quantum yield distortion (ie. ratio of emitted: absorbed energy is rather low
  + Their low transmittance could stay undetected or could require high-sensitivity detection systems
* For display + monitor systems: QD’s are used in LEDs called QD-LED…Problem: manufacturing of blue emitting QDs is difficult
  + For blue…requires smaller sizes + amplified emission compared to the other colors for it to be detectable by human eyes
* Despite the cons..QDs still versatile + flexible

December 26, 2023

<https://www.sciencedirect.com/science/article/abs/pii/S1773224720315975> (Quantum Dots in general)

* QD: fluorescent type of semiconductor nanoparticles
* Made of a core + a shell that is another semiconductor material with diameter of 2-10 nm (10-50 atoms)
* First discovered : by Alexey Ekimov and Louis Brus in 1980 in a glass matrix in colloidal solution
* Size of QD = different optical + absorption + photoluminescent properties
* The name QD ..shows quantum confinement and optical properties
  + Makes them good for bioimaging + other functions (ex. Imaging, sensing, tracking, real time monitoring)
* QD: also called artificial atoms b/c their energy level are similar to individual atoms
* Outershell made of heavy or inorganic material like cadmium, selenium, zinc oxide, silica, etc which are coated with shell material → create a site for conjugation + reduces toxicity
* Type of QD used depends on application
  + Ex. Drug delivery: use biocompatible QDs like carbon QD (preferred for delivery of mitomycin - anti cancer agent), zinc oxide QD, graphene QD
  + For imaging + sensing: semiconductor QD’s used like ZnCuln/ZnS QD and CdTe QD
  + QD’s coated with organic acid: used for *in-vivo* (means within the living in latin) cellular imaging of tumors + *in-vivo* cell staining
* QD= have rigid structure = large surface area for drug conjugation (drug isn’t encapsulated by QD, instead: absorbed/binds onto surface
  + QD groups functional for drug binding = free -COOH and free -NH2

Pros of QD:

* Less degeneration compared to other imaging probes → allows for longer tracking of cellular processes
* 10-20 times brighter + longer photo stability than organic dyes
* Stable fluorophore (*fluorescent chemical compound that can re-emit light upon light excitation)* b/c made of inorganic materials
* Nano size = large surface area = higher drug load capacity + tagging of nanocarriers in biological systems
* Can easily be modified (different shapes, sizes, coatings) → can make it suitable for biological systems (ex. coating can be of a bioactive molecule)
  + Modifications change the charge, solubility, and size
* Chemically inert
* Can encapsulate hydrophobic and hydrophilic drugs + exhibit long durations of blood circulation
* Low cost
* Good stability
* Good flow ability
* Exhibit narrow + sharp peaks with broad excitation peaks
* Quantum confinement effect caused by: splitting of energy levels in quantum dots…creates increase in semiconductor band gaps with decrease in size of nanocrystal
* Classified in 3 ways (based on size, material used for preparation, composition/structure):

1. Core-Type QD
2. Core Shell QD
3. Alloyed QD

* Other way to divide them is into 2 types:

1. Larger QD (diameter of 5-6 nm, emit longer wavelengths of red and orange. Ex: photovoltaic and LED)
2. Smaller QD (diameter of 2-3 nm, emit shorter wavelengths of blue and green. Ex. imaging, bio application, bio sensing)

* Other way to divide into 2 types:

1. Semiconductor QD
2. Carbon based QD

* For preparation of QD for drug delivery, drug should:
  + Have a free amino or carboxyl group
  + Have aromatic ring and free for adsorption
  + Have a charge (positive or negative) for electrostatic interaction
  + Have low molecular weight b/c after attachment, QD’s weight + size increases
* Various applications in:
  + Sensor
  + Bio-imaging
  + Drug delivery
  + Theranostics (a method of diagnosing and treating cancer through radiotracers)

Main Con of QD = toxicity of materials (like lead and cadmium) → material selection is based on application

* 1 QD = 100- 1000 atoms all of various elements with different applications:
  + In periodic table: Group II-VI elements (CdTe, CdS, CdSe), Group IV-VI elements (PbS, PbSe) and Group III-V (InP, InAs) used mostly in solar cells + sensors since they have heavy metals
    - Major limitation: toxicity, quenching effect (fluorescence reduces with time or in presence of other chemicals) = not good for biological applications
  + Group III-V elements limitations: no chemical stability in aqueous solutions. Synthesis of these elements requires harmful substances = not good for biological applications
  + Non-toxic quantum dots invented to overcome those limitations. Which are
    - Group I-III- V12 elements and Group IV (not toxic, don’t need harmful substances for synthesis) + carbon and silicon = good for biological applications
      * carbon : non-toxic, easy to synthesize = good for biomedical + biological applications b/c of aqueous solubility
      * Group I-III- V12 (Cu, Al, Ag, S, Se, Te): lifetime photoluminescence property + low toxicity = good for light emitting devices
      * Silicon: produces non-toxic silicic acid = good for bioimaging (dependent on size, shape and surface modification of the QD)

December 27, 2023

<https://www.studyiq.com/articles/quantum-dots/>

* Discovered by Moungi G. Bawendi, Louis E. Brus, and Alexei I. Ekimov

**What is a Quantum Dot:**

* Called “artificial atoms”
* Semiconductor nanocrystals that have quantum mechanical properties
  + Properties influenced by size. Nanoscale = quantum confinement occurs
* Made mainly of Group II-VI or III-V elements like cadmium selenide (CdSe) or indium arsenide (InAs) → differences come from their size which scientists can control for different applications

**Chemistry Perspective:**

* Optical properties (like tunable fluorescence) = great for labeling and tracking molecules in biological systems
* researchers use them as fluorescent probes to see cellular processes
* Sensors + detectors: QD are sensitive to surrounding environment (like pH, temperature) = highly accurate + responsive sensors
  + Good for environmental monitoring, medical diagnosis, industrial quality control

**In Quantum Physics:**

* Quantum computing = since QD’s electrons are confined in discrete energy levels …similar to behavior of electrons in atoms..could use QD to make quantum bits or qubits (fundamental unit of quantum computing)
* QD = have ability to trap and manipulate electrons = would help create stable qubits for quantum computers

**Applications of QD:**

* Biomedical imaging (fluorescent labels to track and visualize molecules + cellular processes in living things )
  + Provides visualization for biology, medicine and drug development b/c of their stability, brightness and resistance to photobleaching
* Cancer diagnosis and treatment (track cancer cells for early diagnosis and precise drug delivery to only the cancerous cells (less damage to healthy cells = chemotherapy becomes more effective)…can target the cancer cells)
  + Improves cancer treatment + detection
* Environmental Monitoring (real time sensing of pH, temp, pollutants, and other parameters)
  + Ex. monitoring water and air qualities
* Optoelectronic devices: improves solar cell efficiency + creates brighter LEDs
  + More efficient solar cells ..capture broader rays of light wavelengths
  + Better/more accurate LED colours ..good for display technology + lighting solutions
* Quantum computing (potentially use them as stable qubits)
  + Revolutionize cryptography and simulations
* Telecommunication: used to make high speed semiconductor lasers for data transmission
  + Faster + more reliable data transfers
* Security: creates authentic + secure tags/labels that have unique fluorescent markers
  + Combats counterfeits
* Energy storage: improves battery + supercapacitors performance
  + Faster charging, higher capacity, more energy density b/c of nanosize
* QD Televisions: enhances colour + brightness on TVs
  + Brighter and higher quality TVs
* Drug delivery: more targeting drug delivery to cells which minimizes side effects
  + Safer and more effective drug therapy
  + Maximizes the effect of the medication

**Pros to Quantum Dots:**

* Improve display quality (enhance colour and brightness of displays)
* Energy efficiency (can emit more light efficiently = possibly reduced power consumption)
* Can produce a wider range of colours
* Highly durable and less degradation over time ( longer lifespan of materials that use QD)
* QD have a lot of applications and flexible/can be manipulated for all different things
* Reduced environmental impact: energy efficiency + longer lifespan of materials means less carbon emissions

**Cons to Quantum Dots:**

* Cost: could be expensive to implement and initially makes the products very expensive
* Toxic materials: some QD are made of toxic metals like cadmium which could be an environmental and health concern if not handled and disposed properly
* Limited research: still a new technology that requires more research to know all the risks and benefits

January 26, 2024

**Medical Applications of QD:**

**The ones I 100% will do**

**Ones I’m considering on doing**

* **Bioimaging - live cell imaging and in vivo imaging**
* **Drug delivery**
* **Biosensors**
* **Photodynamic therapy → for Cancer therapy**
* **Targeted gene delivery**
* **Biomarkers – for diagnostics**
* Intracellular tracking
* Fluorescence-activated cell sorting (FACS)

**Bioimaging**

**What is Bioimaging**

<https://cab.ku.dk/what_is_bioimaging/#:~:text=Bioimaging%20relates%20to%20methods%20that,outside%2C%20i.e.%20without%20physical%20interference>.

* bioimaging : non-invasive method to visualize biological processes in real time
* Helps to know the 3-D structure of observed specimen
* Can observe: subcellular structures, entire cells, tissues, entire multicellular organisms
* Uses: photons, electrons, fluorescence, ultrasound, X-ray, magnetic resonance, positrons to observe
* Use to: follow cellular processes, quantify ion or metabolite levels, measure interaction of molecules when they are happening

<https://blog.rbiq-qbin.qc.ca/2020/01/27/what-is-bio-imaging/>

* Bioimaging: describes any scientific technique to that can be used to look at or inside biological tissues and organisms

Types:

Positron Emission Tomography (PET) = used to observe metabolic processes and molecular targeting in body

* + How: ingesting/inhaling/injecting a very small radiotracer (biologically active molecules ..labeled with small amounts of radioactive material. Made to bind with specific proteins and sugar in the body). Radiotracer distributes itself in the body/organ and is traced+detected by the PET scan → 3-D image of the tracer concentration is constructed by computer analysis
  + Used: cancer diagnosis+monitoring it. Mapping human heart/brain

Computed Tomography (CT)

* Used to get detailed internal images of the body (body tissues and bones, blood vessels, organs)
* How: uses x-ray tech to take series of images from different angles..combines them together via computer processing to produce a 3-D image → similar to an X-ray but is in 3-D

<https://my.clevelandclinic.org/health/diagnostics/4808-ct-computed-tomography-scan>

* used to detect: blood clots, cancer, tumors, fractures, kidney stones, etc

Magnetic Resonance Imaging (MRI)

* Uses 2 large powerful magnets + radio waves
* How: When exposed to strong magnetic fields: spins of the hydrogen atoms (from the water in our body) changes – all the spins then line up towards where they feel the strongest magnetic pull. MRI sends radio-frequency impulse which affects the spins …a special coil in the MRI machine measures the changes. Measurement used to make the 3-D image
* Types:
  + Structural MRI (see the structure/anatomy of that organ or body part)
  + Functional MRI (fMRI) = indirectly measure brain activity by seeing which areas become active ie. get more blood flow
  + Cardiovascular MRI = used to study the function of heart and vascular system
* Cons: can’t use it on people with metal transplants or pacemakers, is very loud, person has to be lying down perfectly still for a long time
* Used: identify injuries or tumors, study brain activity to know which parts of brain are activated in certain tasks/to certain stimuli, diagnosis for cardiac disease, etc

Ultrasound Imaging:

* How: uses very high frequency sound waves to visualize internal organs/tissues (similar to bat’s echolocation)
* Used: check the health+heartbeat of fetuses in the uterus, image any type of body tissue
* Microscopes

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9541884/#:~:text=It%20has%20to%20do%20with,provide%20information%20on%20anatomical%20structure>.

* Strong tool for seeing function of internal organs and their disorders
* CT = useful for observing bone density in osteoporosis
* Aids illness management and therapy + detect, diagnose, and characterize the problems in clinical settings

January 27, 2024

**Bioimaging with QD:**

<https://www.sigmaaldrich.com/CA/en/technical-documents/technical-article/materials-science-and-engineering/biosensors-and-imaging/qd-in-bioimaging-and-bioassays>

* Used for both homogeneous assays (solution based detections) and heterogeneous assays (assays on solid supports). Assay = to analyze something, like a metal ore, for one or more specific components
* QD good for bioimaging because of detection sensitivity because of their unique optical properties (of brightness and large Stokes shift → Stokes shift = the difference between the band maxima of the absorption spectra and the emissions spectra of the same electronic transition)

**Biomarkers:**

* QD = can be conjugated to target ligands (molecules that bind to another - usually larger - molecule) like small molecules, antibodies, peptides, etc
* QD + ligand conjugate: used to label the targeted molecules that are immobilized on paper strips, membranes, biochips, gels, cells
* Molecular recognition happens when: target molecule + its ligand interact (ex. Antibody + antigen, complementary DNA strands) . Then the target location and abundance is revealed by fluorescence (by the QD)
* Normally without QD: only a few (2-3) organic dyes can be used in parallel because of spectral overlap + hard to accurately quantify fluorescence signals because they photobleach quickly
* QD pro: small enough to diffuse into cells + improve staining to 5-10 colours
* QD cons: 5-10 colours –not enough for comprehensive molecular profiling. + labor-intensive to make so it is costly

Sigma-Aldrich (a company) made QD biomarkers as followed

* Made a multicolor, multicycle, molecular profiling (M3P) addresses those QD cons listed above)
* Combined 5-10 colour QD-antibody conjugates together. Then incubated the mixture with cells and tissue sections to see parallel multiplexed staining
* Stain then removed and samples used again for another round of multicolour staining (have a method of completely destaining the cells without having signal carryover, affecting cell morphology nor the biomarker antigenicity (the ability of an antigen to bind to, or interact with, the products of the final cell-mediated response like a B-cell or T-cell receptors) → allows for next round of staining to identify different subset of biomarkers
* In each staining cycle: 10 biomarkers analyzed with 10 spectrally distinct QD
* 10 staining cycles x 10 subsets of biomarkers in each = molecular profile of 100 distinct biomarkers
* To reduce labor required: replaced low yield covalent QD-antibody conjugations with a non-covalent self-assembly protocol by joining a universal QD-protein A platform with a variety of intact antibodies Pro: requires no chemical reaction or purification for end users, easy and quick preparation, adapter protein+primary antibody are stable during staining and don’t cross react

***In Vivo* Imaging:**

* First use of in vivo imaging with QD was a frog embryo
* Chemical + photostability of QD helps track cell lineage + allows comparative embryology studies for up to 4 day (without abnormalities arising during embryonic development)
* For *in vivo* targeting: QDs guided by peptides will concentrate at tumor blood vessels in ex vivo histology sections (method was first used to non-invasively image tumors in mice using QD-antibody conjugates:
  + Needed to use hyperspectral imaging to delineate QD fluorescence from the mice’s very high skin fluorescence. Red QD (which is long wavelength with large Stokes shift) was still not powerful enough. To improve light penetration depth + reduce autofluorescence, researchers prepared QDs whose core valence + conduction band edges were lower/higher than the shell = QD emission near infrared. → these QD: injected into mice and pig intradermally and it quickly drains into nearby lymph nodes = image-guided surgery )

**Perspectives:**

* QD: promise a leap for bioassays and bioimaging
* Con: majority of bioapplication of QD require technology development or proof-of-concept use in model systems
* In immunotherapy research: high multiplexed molecular profiling of the cell genome, transcriptome, and proteome in native microenvironment…expected to reveal more about the human immune system
* QD: aid in development of immunotherapy that could help those affected by various immune diseases
* QD compared to MRI or PET or other imaging: have higher sensitivity, higher resolution and lower cost
* QD: can be used in nanoengineering of nanomaterial (by learning about the effects of their size, shape, charge, surface coating, and targeting ligand)
* For *in vivo* use: benefits need to outweigh risks but this has to still be shown. QD toxicity is a concern

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3733675/>

* Diffusion of several neurotransmitters in the synapses have been studied by QD that were attached to glycine neurotransmitters and AMPA glutamate receptors
  + This revealed rapid fluctuations in diffusion rates in different membrane domains
  + Ex. neuronal growth factor (NGF) receptor: internalized into cell once binded to a specific ligand → can be studied in detail now because of photostability of QD
  + QD that are conjugated to NGF bind to the NGF receptors in axon terminals = endocytosis of receptor-ligand pair in vesicular structures (QD imagining shows that the vesicles have only 1 NGF receptor and are moved great length to the cell body)
* For intracellular transport:
  + Used peptide-conjugated QDs to see nanoparticle behavior in live cells
  + Peptide-conjugated QD was internalized by macropinocytosis..triggered by the QD binding to the cell membrane
  + Once inside: QD entered into a vesicle…vesicle actively transported by molecular machines (like dyneins) through microtubule tracks..then reach an asymmetric perinuclear region (outside the nucleus) known as microtubule organizing center (MTOC) → steps and speed similar to those of purified filaments + QD was tracked for extended period of time without loss of signal so we could follow the molecular motor
  + Challenge right now: delivering freely diffusing + monodispersed QD into living cell’s cytoplasm
    - Way to solve it: inject QD into cells with a microneedle. Con: each cell needs to be injected at a time
    - Another way to solve it: try to temporarily permeabilize the cell membrane by making microscopic pores on it (with brief electric pulses or use of bacterial toxins)
* MAJOR CONCERN: toxicity of the QD

**Diagnostics:**

Biomarkers (IHC = immunohistochemistry) – immunostaining:

* Toxicity is not a concern for in vitro or ex vivo samples (using QD as ultrasensitive probes in this way may be the most clinically relevant application for them)
* IHC = useful for biomarker detections b/c..preserves morphology of tissue = important for many diagnoses → but IHC: only minor improvements for diagnostics in last 50 years
* Using QD enhanced IHC diagnostic potential + lets you detect multiple disease markers in a single slide → can transform IHC in pathology

Cancer Diagnostics:

* Most common biomarker used = ER/PR/Her2 (used to diagnose breast cancer + most effective treatment for such patients)
  + Currently: markers measured individually with immunoassays (like HercepTest and traditional IHC techniques → do a subjective assessment of protein marker expression visualized by standard chromogens)
  + QD-based method’s results correlate closely with results of traditional IHC, Western blot analysis, FISH
  + Researchers used 5 QD colors at once on tissue specimen = 5 unique markers (ER/mTOR/PR/EGFR/Her1) → QD have high molecular profiling potential
* QD-based immunostaining =
  + higher detection sensitivity
  + Increased accuracy + sensitivity (supported by Li and colleagues -> performed a detailed examination of QD staining for the Her2 protein)
  + Helps identify more subgroup of biomarkers to improve diagnostics ie. more people will be able to be diagnosed sooner than later (proof = Li and colleagues’ work)

January 29, 2024

Single-Cell Analysis

* QD can be used to analyze single, rare cells (ex. Circulating tumor cells, isolated malignant cell when observing a tumor tissue or biological fluids)
* QD analysis: keeps specimen structurally intact → preserving morphological info to correlate it with the molecular profiling data
* QD-based molecular profiling technique allows: mapping of molecular and cellular variation in heterogeneous tissues + identification of isolated malignant cells within predominantly benign prostate glands → better than other methods for analyzing distinct regions b/c allows molecular and morphological data to be extracted without physically removing the region of interest (ex. Liu et al. identified prostate glands with a single cancerous cell before the whole gland became malignant)
* Ex 2: Reed-Sternberg (RS) cells are hallmarks of Hodgkin’s lymphoma BUT are only 1% of infiltrated cells in the lymph nodes.
  + QD probes: identify individual RS cells with 4 biomarkers (CD15/ CD30/CD45/Pax5) and differentiate them from other immune cells
  + Compared the QD staining results with the determined pathological examination results → QD-based method quickly identified those confirmed with the disease + showed presence of the disease in patients who were “suspected” to have it (RS cells amount was very low in “suspected” …too ambiguous for the pathological examination to pick up) + showed no RS cells in patients who had reactive lymph nodes but not Hodgkin’s lymphoma
  + Results show: QD probes’s detection sensitivity + bio diagnostic assays with multiplex QD can diagnose patients at an earlier stage than with conventional methods = possibly improved therapeutic success rate

Solution-Based Diagnostics

* Numerous assays using QDs as ultrasensitive and multiplexed probes for analyte detection have been developed.
* QD’s increased multiplexing capability can be used in flow cytometry in the characteristics of cellular immune responses → ex. Can help diagnose complex diseases like cancer. Help identify T cells in HIV characterizations

Analysis of Genes:

* A major application of molecular profiling (like gene chips and PCR)
* QD’s unique optical properties make them ideal to use as probes
* Han et al: first to report a technology using QD-tagging microbeads for the optical coding of biomolecules
  + 6 different QD colours x 10 intensity levels = 1 million unique theoretical combo to be abstained
  + Coupling microbeads to DNA recognition sequences → authors easily detected + identified target molecules (coding + target signals can be read at the single-bead level -> QD can be used to rapidly analyze DNA)
  + Single QD: useful for DNA analysis
  + QD probes: ultrasensitive detection of DNA and genetic mutation
* QD-DNA conjugates: can be used for detection of single-nucleotide polymorphism (SNPs) (a sequence varies by just one base) → can detect SNP + single base deletions in mins (at room temperature) with high specificity
* Wang and colleagues: developed a DNA nanosensor system using single QDs with bioconjugated capture sequence + separate dye-conjugated reporter sequence
  + QD sensor binds to target DNA sequence…reporter sequence binds that to a sandwich assay = reporter dye close to nanocrystal, which helps form a FRET donor-acceptor pair for target detection at femtomolar (having a concentration of 10^-15 moles/liter) sensitivity
  + Allows detailed detection from just a small sample (don’t need so many DNA samples…can identify with only one DNA strand) = reduced cost + time for gene analysis

Conclusion:

* In future: have doped and strain-tuned QD
* For biomedical applications:
  + make sure to minimize overall size of bioconjugated nanocrystals
  + reduce steric hindrance (the slowing of a chemical reaction due to steric bulk) and non-specific protein adsorption
  + Develop chemically active + photoswitchable nanocrystals
  + Understand the potential toxic effects of QD
* Goal for QD in the future:
  + Make them monovalent
  + Free from nonspecific adsorption
  + Compact in size
  + Bright for single-molecule imaging
* To reach goals: need development in Qd structures, new surface-coatings, molecular tagging, and strategies for cellular delivery

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9076002/>

* QD: amazing optical properties → like high quantum yield, high brightness, high extinction high extinction coefficient, high stability against photobleaching, and blinking (randomly switching between On (bright) and Off (dark) states for an emitter)
* QD’s emission spectra correlates with their size (can tune their optical properties by changing the particle’s size)
* QD’s emission wavelength = directly proportional to average particle diameter …Ex. CdSe QDs emit fluorescence at various points in the visible range (400-600 nm) by changing its size from 2-10 nm
* Particle size + emission spectra can be adjusted by manipulating the core composition…Ex. QD with CdS cores have average diameter of 1-6 nm + emission spectra in ultraviolet-visible range (UV-VIS) depending on particle size. QD with InAs core have similar diameter but emission spectra in infrared
* Live cell imaging and in vivo imaging: above features help with bioimaging
* QD used to visualize intracellular components
  + Incubate QD with desired cells → QD easily taken up by the cell because of fine particle size
  + Then excited .. emissions spectra detected by fluorescence microscopes
  + Blinking feature: helps detect *individual* QD events which helps visualize individual cellular components like proteins … different from conventional fluorescent probes with continuous fluorescence emissions (all the events merge into one..can’t differentiate between the events)
* QD used for in vivo visualization for organs and tissues
  + Administer it by combining QD with certain ligands → increases affinity to the organ/tissue so that it isn’t rejected

Fluorescence-Activated Cell Sorting (FACS)

* FACS used in: evaluation of drug uptake in cells, isolation of cell populations, characteristics of certain diseases, detecting cellular markers, mapping immune cells
* QD: great potential ask FACS because:
  + Compared to organic dyes, QD have narrow emission spectra → reduces overlapping + increases possibility of including multiple labels for polychromatic (multiple color) cell sorting by FACS
  + Have broad excitation spectra – helps excite multiple QD probes with a single laser beam = increases the capacity of individual FACS equipment
  + Higher brightness than most organic dyes = increased detection accuracy
* One research to study blood groups: used CdTe QDs as fluorescent probes conjugated to monoclonal antibodies against A and B antigens on red blood cells.
  + Bioconjugate showed high efficiency + was stable for over 6 months
  + QD : potential to replace the antibodies taht are normally used for staining cell surface markers because of their higher stability + economic prices (if binded with specific targeting ligand to recognize target markers)
  + Unlike antibodies, QD can be taken up by cells = staining of intracellular markers = no need for permeabilization buffers which affect cell viability, fluorophore efficacy, + increase complexity of FACS experiments

Photodynamic Therapy (PDT)

* PDT: Promising technique for treating cancers (ex. Skin, head, neck, tongue, breast)
* In PDT: chemical compound called photosensitizer is activated by light irradiation → transfers that energy to intercellular oxygen leading to the in situ generation of reactive oxygen species (ROS) → then induction of apoptosis (process of programmed cell death) in target tumor cells (kills cancer cells)
* QD: have ability to be the photosensitizer or energy donor for other photosensitizer
* QD’s advantages compared to organic photosensitizers:
  + Potent light absorption
  + Strong emissions
  + High photostability
  + Water solubility
  + Tunable optical properties
  + High tissue accumulation
  + Size and composition can be altered to optimize emissions in near infrared (NIR) region → allows for deep tissue penetration to treat deep-sited tumors
* One experiment: investigating the potential of graphene QD (GQD) and graphene oxide QD (GOQD) as photosensitizers:
  + QD irradiated with 290 μW power UV tube light
  + QD could then kill 90% of B16F10 melanoma cells and MCF-7 breast cancer cells in 5 minutes → shows high potency and efficiency
* Recent reports suggest: carbon QD could be used in PDT for Covid-19 viadual mechanism of ROS generation and type 1 interferon (proteins that are part of your natural defense system – tell your immune system that there are pathogens/cancer cells present) response stimulation

Drug Delivery

* QD great for drug delivery because of their:
  + Ease of fabrication
  + Capacity to conjugate to many types of drugs
  + Tuned physico-chemical (physics and chemistry) properties
  + Unique optical properties → makes them traceable/easy to monitor
  + Ultra small → important for extravasation and penetration through the stroma rich environment of tumors like hepatocellular carcinoma and pancreatic cancer + 10 nm size holds promise for tumor penetration
  + Can have many physical and chemical modifications like…Decoration (covalently coated with on QD’s surface) with targeting ligands, functional coating to adjust biodistribution and pharmacokinetic properties. Ex. folic acid: widely-used ligand…targets overexpressed folate receptors on cancer cell’s surface
* How the targeted drug delivery happens:
  + QD taken up by cell via receptor- mediated endocytosis (this gives ligand-modified QD 3 pathways into the cell - pathway determined by the ligand, target receptor, and composition of QD):
  + 1) Clathrin-mediated Endocytosis:
    - QD concentrate at target receptor site
    - QD engulfed by cell membrane (membrane coated in a protein called clathrin to make a clathrin-coated vesicle)
    - Membrane protein (dynamin) dissociates the vesicle from the cell membrane and into cytoplasm by making an endosome
    - If QD can escape endosome: will be released into cytosol + become accessible to release the drug
    - if can’t escape endosome: then will face lysosomal degradation
  + 2) Caveolae-mediated Endocytosis:
    - Caveolae = cholesterol-rich flask-shaped membrane invaginations
    - QD binds to target receptor site
    - QD enters the target cell via caveolae which then break off from the cell membrane to form a caveosome
    - caveosomes: considered less-destructive vesicles than endosomes = maximizes drug delivery efficiency to the cell
  + 3) Macropinocytosis:
    - QD binds to target receptor
    - certain ligands that can be used on the QD trigger cell membrane ruffles to form
    - ruffles engulf the QD into the cytosol, making a macropinosome
    - QD leaks the ligand out into the cytosol
* Studies/Experiments:

- Abdellatif et al: functionalized Cd/Se QDs with vapreotide → an agonist for somatostatin receptors in blood cells (holds potential for treating blood cancer)

- Liu et al: prepared doxorubicin-loaded PEGylated MoS₂ QDs (purpose: traceable doxorubicin delivery to cancer cells). Those QDs had blue photoluminescence + had pH-responsive drug release —> whole process they showed good stability + bio safety

February 17, 2024

QD in the Health Market

* global market for QD: estimated to be between 4-8 billion USD
* NANOCO™: major company for healthcare market of QD
  + addressed market size of 1 billion USD in 2022
  + Example of marketed product (HEATWAVE™): made QD biosensor that works in electromagnetic spectrum of 100 - 1650 nm (very broad range) —> for non-invasive quantification of molecules in blood (ex. Hemoglobin (detected at 575 nm), bilirubin (at 455 nm), glucose (1650 nm)
  + Another product (VIVODOTS ®): QD used to map tumorous cells during surgery with avoiding the unnecessary removal of unaffected tissues
* NN-Labs ® : products include cadmium-based + cadmium-free QD for cellular imaging, in vivo imaging, making molecular labeling probes
* QD LASER™ = Japanese based QD company
  + innovation made called VISIRIUM ® Technology —> 50 g-weight eyeglasses that project images onto retina to help those with visual disorders

Clinical Translation Challenges

* clinical trealastion is still slow
* only 6 registered clinical trials with QD as of December 2021 (according to the National Institute of Health)
* Challenges with QD:
  + 1) Pharmaceutical Issue: from this scope:
    - QD: ultra-fine colloids particles + large SA + metallic nature = susceptible to aggregation (formation of a number of things into a cluster), degradation, hygroscopicity (phenomenon of attracting and holding water molecules), or chemical redox alterations
    - Any change to physcio-chemical properties of QD = potentially dramatic changes to optical properties
    - Way to solve the problem and improve the stability of QD (specifically for PbS QD which are susceptible to degradation through oxidation of surface chalcogen atoms) : using trioctylphosphine for passivation (coating a material so that it is less readily affected/corroded by the environment) of the surface S atoms+lead mono-carboxylate → protects QD from oxygen + improves quantum properties no matter the particle’s size or original surface ligands

February 18, 2024

* + 2) Industrial Issues:
    - Mass production of QD: very intricate + multi-step process for all the surface modifications
    - Difficult to maintain consistent physico-chemical properties on mass scale
    - Traces of impurities: negligible on small scale BUT larger scale..have an impact on quality + performance of the QD (Ex. alkyl phosphonic + phosphinic acids impurities in trioctylphosphine oxide (TOPO) used as solvent for CdSe QDs = poor optical performance of CdSe QDs when scaled up
      * To solve the problems: advances in synthesis + purification methods….
        + Ex. The classical hot injection method for CdSe QD synthesis - when scaled up - affects optical properties of the QD b/c injection’s speed and stirring velocity affect particle size distribution. To solve the problem: made a one-pot strategy = all precursors mixed together at room temperature..reaction compounds heated uniformly after...Pros: injection free, robust, better optical properties
    - Large scale production of QD = potential environmental hazard b/c of the toxic heavy metals (Cd, Pb)
      * To solve it: cadmium free QD introduced (ex. Carbon QD, graphene QD, silicon QD)
      * Green methods are being developed: (ex. Dry heating, microwave-based synthesis, using recycled components)
  + 3) In vivo issues:
    - In principle, QD are not organ specific and interact with cellular membranes in a non-selective manner. To solve this: modifying QD with targeting ligands, polymers, antibodies, etc makes them have increased affinity to certain tissues (ex. tumors)
    - Most metallic QDs are associated with intracellular toxicity either through interacting with DNA or oxidative (taking place in the presence of oxygen) damage to cellular bodies → more risk with heavy metals since they accumulate in the bones without significant elimination (ex. Cadmium and lead)
      * Use other materials that aren't heavy metals
      * Surface modifications developed to allow body to clear the metallic QDs that usually accumulate in the body
    - Fine particle size of QD = increased chance of elimination from body through kidneys (renal clearance)..may be filtered out before even doing their job. To solve this:
      * Adjust the size of QD: those with diameter less than 5.5 nm are more likely to be excreted by kidneys … making QD 8-10 nm will help prevent glomerular filtration
      * Reported that QD with neutral or negatively-charged surfaces = less susceptible to glomerular filtration
      * Changing shape + stiffness of QD = can alter their rate of glomerular filtration

QDs versus Other Substitutes

* Organic dyes (ex carbocyanines, phycoerythrin (PE), Fluorescein isothiocyanate (FITC)) used as fluorescent labels for imaging, tracking various drug carriers, etc
* Organic dyes: used a lot because of pros:
  + ease of synthesis
  + cheap prices
  + commercial availability
  + ease of use
* Organic dyes disadvantages/drawbacks:
  + Low molar absorption coefficients
  + Narrow absorption spectra
  + Broad emissions spectra
  + Asymmetric emission profile
  + Short fluorescence lifetime (only lasts for 1-10 ns)
  + High liability to photobleaching = makes it harder to detect single events (like a single molecule)
* Another substance called Tandem dyes.
* Pros of Tandem dyes:
  + Single flow cytometer’s laser can excite multiple dyes while the emitted spectra is captured on different detector = increases applicability of flow cytometers in detecting multiple fluorophores
* Cons of Tandem dyes:
  + Photobleaching
  + Low thermal stability
  + Broad emission spectra = emission spilling over to other detectors = need compensation calculations then and could limit compatibility of some fluorophores to each other
* Pros of QD:
  + Broad excitation spectra = helps them gets excited with various lasers
  + Narrow emission spectra = reduces the spill over phenomenon + don’t need complex calculations or compensation experiments
  + Have 10 times longer fluorescence lifetime than organic dyes
  + Lower susceptibility to photobleaching
  + High thermal stability
  + High brightness
  + Higher molar absorption coefficients
  + Symmetric emission profiles
  + Optical properties can be tuned + can manipulate physcio-chemical properties and surface chemistry
  + Helps detect single events = better detection of cellular component/events with higher accuracy
* QD not used exclusively for biomedical applications because:
  + Limited knowledge of bioconjugation strategies …especially with antibodies
  + Not enough established protocols

Clinical potential of QD and Future Perspectives

* Modification with ligands/antibodies = modulate accumulation in tissues = visualizing only target tissues with high efficiency + biosafety
* Photodynamic Therapy: QD will accumulate in the tumor tissue via passive targeting (because of small size = increased permeability + retention effect) or active targeting (for ligand-modified QD).
* Cancer metastasis: a serious complication in most aggressive tumors
  + In some cases like for lung and breast cancer … metastasis can happen undetected where only few cancer cells are circulating in blood..numbers too low to be detected by MRI or PET or other methods (such small numbers = micrometastasis → occur in 30% of breast cancer cases without detection)
  + QDs can help detect micrometastases in blood 21/26 of cases of non-small cell lung cancer patients….promising clinical potential
* Can help track vaccination record for at least 9 months (follow pathway of vaccine inside) b/c of resistance to photobleaching

How to Get QD into the biomedical field/Improve the clinical transition:

* Use environmentally friendly and aqueous solvent -based/ biotechnology-based synthetic method = reduces environmental hazard, improves the ability to alter the size, skips unnecessary post-synthetic modifications (= decrease the complexity of making them + lower production costs)
* Use functional coating with smart materials like pH-responsive polymers/biomaterials with self-homing tissue affinity → to replace ligand-based modifications = improve stability and scalability
* Don’t use heavy metals at all to minimize biosafety hazards (ie. heavy metal accumulation in the body)
* Have a balance between body retention + clearance ability of QDs (achieved by manipulating particle size, charge, surface properties) → to help QD stay in body long enough for complete intended applications BUT make sure it clears from body to avoid potential toxicity
* Have enough experimental protocols to see all the diverse applications of QD = expand their usage to be able to compete with the classical methods since those methods already have well-established protocols + wide commercial availability.

**Drug Delivery**

**What It is and How It is Currently Being Done**

<https://www.nibib.nih.gov/science-education/science-topics/drug-delivery-systems-getting-drugs-their-targets-controlled-manner>

* Drug delivery: technology that carry drugs into and throughout the body
* Include methods like pills and vaccines, or “packaged” like in micelle or QD to protect drug from degeneration as it travels in body
* Side effects of most methods: drug interact with the healthy organs/tissues (limit ability to treat cancer, neurodegenerative diseases, infectious diseases, etc)
* 2 types of drug delivery systems: routes of delivery and delivery vehicles

Routes of Delivery:

* Meds can be taken in different ways (ex. Inhaling, swallowing, injecting, absorbing through skin) → pros and cons to each method and appropriate method dependent on the medication

Drug Delivery Vehicles

* The ways in which medications can be packaged so drug travels in your body safely
* Research done to find new ways to package hard to use drugs for reasons like size or fragility

<https://www.gilero.com/news/drug-delivery-overview/>

* Drug delivery: process of administering medications/other pharmaceuticals compounds to achieve therapeutic effects
* A drug’s effectiveness can be affected by the way it's administered … finding the best delivery system for a drug will optimize the drug’s ability

Drug Delivery Devices

* Drug delivery devices: physical agents that help with delivering drugs
* Example of drug delivery devices:
* Prefilled syringes
* Infusion pumps
* Nasal drops
* Eye drops
* Transdermal patches
* Autoinjectors
* Nebulizers

How Drug Delivery Systems Work

* Transports drugs/medication to the body via absorption … each method of drug delivery does it differently
* Some systems: administer drugs locally (ex. Lidocaine injection before a dental procedure, topical ointment to only the rash on your skin)

Types of Drug Delivery Routes

* Differs based on patient’s needs/drug’s purpose
* Oral Route: most common one. Through capsules, tablets, liquids. → this route is usually safe, convenient and inexpensive
* Injection: into a vein (intravenously), muscle (intramuscularly), spinal cord (intrathecally), or under the skin (subcutaneously)
* Inhalation: breathed into lungs by the mouth (inhaled) or mouth and nose (nebulized)
* Nasal: sprayed into nostrils and absorbed through nasal membrane
* Topical: applied to skin for local effect
* Transdermal: delivered to skin via a patch (systemic effect)
* Rectal: inserted into rectum and absorbed into the blood
* Sublingual: placed under tongue for rapid absorption into the bloodstream

Four Drug Delivery Methods

* Important to know how much time it should take for the drug to be released into the body … can control and modify this
* Immediate Release: dosage form makes sure drug is released completely and rapidly
* Non-Immediate Release: The dosage form does not fully release the drug right upon administration
* Site-Specific Release: Dosage form offers targeted delivery of the drug to the specific location it needs to be administered to
* Sustained Release: Dosage form continuously releases a drug slowly/in controlled amounts over a prolonged period
* Delivery methods: enhance performance of drugs by increasing effectiveness, safety + patient compliance = better patient outcomes

<https://www.technologynetworks.com/drug-discovery/articles/drug-delivery-322035>

* Drug delivery system: system used as a “carrier” for administering therapeutic agents/drugs into the patient’s body
* Drugs delivered by different routes…routes classified by their “starting point” (where the drug is first administered):
* Buccal drug delivery: administered through buccal mucosa (lining of cheeks)
  + Pro: Buccal route avoids first-pass effects (rapid drug uptake + metabolism in the specific location of the body)
  + Con: certain barriers in terms of drug absorption so can only use small molecule drugs with lipophilic properties to cross the membrane
  + Used for extended-release drug delivery (drug released for extended period of time but in controlled amounts) BUT formulations that attach to mucosa are usually preferred instead
  + Ex. for mucosa formulations: tablets, gels, lozenges, patches
* Nasal Drug Delivery: drug delivery through the nasal cavity
  + For local diseases affecting upper respiratory tracts (like nasal congestion, allergic rhinitis): nasal spray used
  + Some cases where rapid-onset required (abrupt appearance of signs and symptoms in over a period of hours - days) → systemic delivery used instead for small molecule drugs (ex. The migraine medication olmatriptan)
  + Nasal mucosa: thing + heavily vascularized = rapid transfer to systemic blood circulation
  + first -pass metabolism can be avoided
* Ocular Drug delivery:
  + Difficult to do b/c of eye’s anatomy and barriers (static, dynamic, metabolic barriers to prevent/delay absorption of drugs)
* Oral Drug delivery: the preferred route
  + Ease-of-use, cost effective, highly absorptive properties of the gastrointestinal GI tract
  + To work: need to make sure drug has aqueous solubility in the GI system
  + Not suitable for all patients ex. Younger or older populations, those with cognitive impairments
* Pulmonary Drug Delivery: via inhalation through the mouth and into the airways
  + Effective for treating localized disease in lungs
  + Pro: unaffected by dietary complications + interpatient metabolic variations
  + Has potential for admission of systemic diseases b/c of large absorptive surface area + high permeability of alveolar membrane
* Sublingual drug delivery: drugs given under the tongue
  + Absorbed into bloodstream via tongue’s ventral surface and the floor of the mouth
  + Is rapid absorption, avoids first-pass metabolism
  + Con: disrupt talking, eating, and drinking
  + Absorption affected though by smoking due to vasoconstriction of vessels (not recommended for smokers)
* Transdermal Drug Delivery: applying formulation onto the skin
  + Drug penetrates the stratum corneum → deeper epidermis and dermis → absorbed via the dermal microcirculation
  + Is non-invasive + suitable for unconscious/vomiting patients
* Vaginal/Anal Drug Delivery: faster onset of action compared to oral route + higher bioavailability
  + Rectal meds: used for local effects (ex. laxatives) or systemic effects (ex. Analgesics when other routes are contraindicated (anything that prevents a person from receiving a specific treatment/procedure because it may be harmful))
  + Vaginal: (usually to give hormones + address women’s health issues) avoids first-pass metabolism + unaffected by gastrointestinal disturbances

Targeted Drug Delivery: way of delivering drugs that enhances the concentration of that drug to a particular part of the body compared to others

* Increase efficacy + reduce off-target effects
* 2 mechanism of targeting a drug:
  + Passive Targeting: only takes into advantage tissue permeability. Biological (e.g changed properties of the diseased tissue) and pharmacological factors (properties of the drug–carrier system) will affect the accumulation of the drug to a particular location
  + Active Targeting: done by conjugating the delivery vehicle with a targeting moiety (part of a chemical structure of a molecule/compound) → lets drugs accumulate in a specific location. Works b/c of interaction between moiety/carrier and receptor/ligand target

Drug Delivery Vehicles

* For drug molecules that have low bioavailability and need protection from degradation from inside the body (degradation from enzymatic or acid-catalyzed reactions) → 40% of novel active pharmaceutical ingredients (API) are rejected by the pharmaceutical industry because of low bioavailability
* Carrier systems invented: increase bioavailability + defend drug molecules against degradation
* Nanoparticles: type of carrier-based delivery
  + Modifying properties = optimize bioavailability, decrease clearance, increase stability → makes them ideal “carriers” for drug delivery to target-tissues
  + Have good solubility
  + Small size + large surface area = increased bioavailability
  + Good for drug carries because of ability to cross the blood-brain barrier, enter the pulmonary system, pass through tight junctions of endothelial cells
  + Can enter the body by 3 routes: injection, inhalation, oral
  + Can adjust the surface properties of the particle so that body’s immune response does not see it as a foreign threat → one way is to incorporate polymer complex onto the surface so that it binds to plasma proteins = increase clearance
  + Explored for being good drug carriers to treat cancer, neurological disorders, AIDS, etc

<https://www.youtube.com/watch?v=emEua2eJp1U>

* Tumor marker: substance found in body tissues that can be elevated in cancer cells (ex. CA 15-3 breast cancer, )
* Nanoparticles designed to conjugate to various molecular markers
* Ex. DDX = most effective anti-cancer drug BUT can kill healthy cells too
* Nanoscale capsules can deliver DDX to only inside cancer cells
* Consists of: DNA-origami shell, covered in immune factors + molecular binding sites on surface

1. Nanoparticle travels through the bloodstream
2. The DDX nanoparticle penetrates through the cancer cells because of the cancer markers on its surface
3. Shell opens up to release DDX inside
4. The cancer cell is killed by the direct release of DDX

<https://www.youtube.com/watch?v=aFU5Qx-cLu8>

* Nanoparticles can be modified to be able to attach to cancer cell and be carried inside
* Engineered to only bind to the cancer cells and not neighboring healthy cells
* QD taken into the cancer cell by the cell membrane making a vacuole around it to let it enter inside
* Cellular proteins wrap around the particle and take it into the cell → this vesicle wrapped in protein takes the particle to the center of the cell
* Proteins go away, the vesicle travels further deeper to fuse with the endosome (the digestive system of the cell. Inside endosome is acid to digest incoming material)
* Nanoparticle gets degraded inside the endosome, releasing the drug
* Drug kills cancer cell
* Nanoparticle based drug delivery helps kill cancer cells without the side effects of other methods like chemotherapy

<https://news.nus.edu.sg/understanding-drug-delivery/>

**Quantum dots for Drug Delivery**

<https://link.springer.com/article/10.1186/s11671-016-1394-9#:~:text=QDs%20possess%20unique%20optical%20properties,%2C%20adsorption%20and%20coupling%2C%20etc>.

* QD drug delivery: potential for early detection, monitoring and localized treatment
* QD carriers can: improve stability of the drugs, lengthen circulation time in vivo, enhance targeted absorption, improve distribution + metabolic process of drugs

Review

* Many anti-tumor drugs that are in clinical tests have side effects (ex. Non-selectivity, toxicity, poor targeting)
* Side effects in application happen when classical cancer therapeutics (because of nonspecific nature of the drugs) cause high toxicity in non cancer cells which are dividing rapidly
* Tumors: hard to locate (b/c of lack of bioluminescence) and remove (especially smaller scale ones) → so we want a method that can target only cancer cells with high specificity + be imagined in vivo at the same time
* Many types of nano-vehicles for nano-carriers for drugs (types include polymer nanoparticles, microemulsion, micelles, AND quantum dots
* QD: good for drug carriers b/c of optical properties as luminescent nano-probes/carriers
* Drug loaded onto QD vis dissolving, dispersing, adsorption, coupling
* The physical and chemical properties, physical response, and biological characters of drug can be altered for the carrier’s role = absorption, distribution, metabolism + excretion of drug is affected
* QD nan-carrier for drugs: enhance efficacy + reduce side effects of drug reaction = improve therapeutic index of the drug (can also help with absorption of small molecule drugs)
* Surface modification with targeting ligands = common for increasing drug-delivery efficiency

Advantages of QD as Nano-Carrier in Targeted Drug Delivery

(compared to conventional drug carriers, nano-carriers have)

* Smaller size
* Greater surface area
* Higher + more reactivity activity center
* Stronger adsorption capacity

Pros as Drug Carriers

* Can target to specific organs by modifying the antibodies, aptamer, folic acid + other biological molecules used
* Have a unique mode of controlling and releasing drugs. In the beginning: the control/release of the drugs is usually an outbreak release then shows constant release for a long period of time. Therefore:
  + Extend effectiveness of drugs at limited concentrations
  + Deliver at fewer intervals
  + Lower doses for the patients = reduce side effects for the patient
* Because QD drug carriers have adhesive properties + small size:
  + Can extend how long the drug stays in the local tissue/organ
  + Increase the contact areas for the drug
  + Improve absorption + bioavailability of oral drugs
* Can prevent rapid degradation of drugs by body’s digestive enzymes
  + Improves stability + utilization of the drug
* Can alter mechanism of membrane transport → improve permeability of the drugs → improve absorption rate of drugs in cells
* Can modify the original drug to
  + Enhance water-solubility
  + Have targeted + sustained release
  + = enhance efficacy of anticancer drugs + reduce side effects

Applications of QD Nano-Carriers for Drugs

The Ideal QD nano-carrier materials for drugs would have the following properties:

* Don’t react with the drug
* Have high drug loading capacity + encapsulation efficiency
* Has appropriate preparation + purification methods
* Good biocompatibility
* Low toxicity
* Certain mechanical strengths + stability and appropriate particle size + shape
* Longer residence time in vivo
* (commonly used anticancer nano-carriers for drugs right now are: liposome, chitosan, silica nanoparticles, polymer nanoparticles)

QD’s beneficial properties: (unique optical properties because of):

* Quantum effect and size effect
* Nanoscale =
  + quantum confinement effect
  + size effect
  + dielectric confinement effect
  + Macroscopic quantum tunneling effect
  + Surface effect
* Important part of modifying QD is their selective targeting
* Currently: tumor cell targeting focused only on few candidate ligands that’s receptors are overexpressed in tumor cells (overexpressed meaning the receptors that usually found in cancer cells that are making nutrients for that cell = causing the cancer cell to grow) (receptors like folic acid and delivery of siRNA)
* Folic acid = widely used as a targeting ligand b/c of high binding affinity with folate receptor (FR)
* Studying siRNA delivery in cells: good choice to use QD to study this b/c of QD’s florence + unique optical properties (tunable emissions, brightness, photostability)

Folic Acid-Quantum Dot Complexes

* Folic Acid (FA) : a needed vitamin for everyone…important for the biosynthesis of nucleic acids, amino and pantothenic acid
* Researchers found: series of receptors associated with tumor growth on surface of tumor cells/tumor-associated blood vessels → receptors: high affinity to combine with its ligand =
  + Ligands can be used as the targeting molecules in drug carriers…will enhance therapeutic efficacy with a receptor-mediating mechanism = targeted therapy
* Folic acid: targeting ligand of folic receptor (FR)... (FA binds to FR,..delivering FA to cells that express the folic receptor)
* FR: highly expressed in most tumor cells (ex. Ovarian cancer, cervical cancer, endometrial cancer, breast cancer, colon cancer, lung cancer, etc)
* FA: a low weight targeting molecule
* Making FA complexes with protein toxins, small molecule chemotherapeutic agents, radio-therapeutic agents, etc = better targeting ability + therapeutic effects than original drug = higher potential for drug delivery system
* FA: good guiding molecule for anti-tumor drugs because they have:
  + Low cost
  + High chemical stability
  + Good receptor affinity
  + Small size conducive to enter tumor cells through blood vessels
  + Can completely infiltrate tumor tissues
* FA complexes: can target the tumor cells well. = better diagnosis and treatment of cancers
  + Ex of a breakthrough of this: FA complex coupled with radioactive elements → used for clinical diagnosis of ovarian cancer
  + Still needs more research b/c FA complex structure + composition, metabolism + excretion in vivo, physiological function, stability, toxicity all uncertain

QD in RNA Interference (RNAi) Applications

The Use of Quantum Dots in Studying Drug Release

* Traditional methods of tracking nano-drug release in vivo make it difficult to:
  + Quantify free drug and encapsulated drugs separately
  + Quantifying certain trace drugs under the background of complex organisms
* QD-FRET (Forster resonance energy transfer) created ..could solve those problems
* QD-FRET works when fluorescence emission spectrum of QD + the excitation spectrum of fluorescent receptors OVERLAP + spatial distance b/t donor and acceptor is close enough (1-10 nm) = QD’s state of excitation can be used as fluorescence donor → transfer the florence energy to the acceptor = fluorescence quenching of QD donor + fluorescence enhancement of acceptor
* The closer the two molecules, = higher the FRET efficiency
* QD-FRET: successfully used in interaction studies in macromolecules, immunoassay, non-sensor designs, + some more
* QD-FRET system could be used to release Dox into cells:

1. A10 RNA aptamer (an Identified prostate-specific membrane antigen) coated onto QD surface
2. Mixed in with Dox solution → Dox inserts into the inner aptamer duplex = QD-aptamer (Dox) complexes
3. Donor-acceptor of Dox and QD + donor quenching body double FRET system of Dox and aptamer = reversible fluorescence self-quenching of complexes
4. Complexes are incubated + recognized and taken by prostate tumor cells
5. Dox is released from complex…fluorescence signals of QD and Dox are significantly increased in cells
6. Tumor cell is localized and intracellular Dox release can be tested by measuring the fluorescence signal changes

* Wide variety of water-soluble + insoluble drugs can be combined with nanoparticles with high efficiency + modified drug loadings
* QD used as drug models + imaging labels/agents for drugs: already developed
* QD: efficient detection + precise quantization of cellular uptake of particles
  + QD-PNPs: used as a model to monitor position of used polymer + evaluate efficacy of the delivery system
  + QD can be used as model for non-fluorescent drugs
  + QD; can create visible ring around microparticles to study microparticle theranostic delivery formulations
* FRET-based QD-PEG-Dox delivery system used: effective + facile → monitored in real time the release of loaded drug (ADM)
* FRET signals and drug release can also be monitored+detected in varying pH environments
  + Give us a versatile + sensitive + efficient method for monitoring drugs release in real time (pH versatility = can track in various physiological microenvironments)

February 24, 2024

**Biomarkers → for Diagnostics**

**What are biomarkers and how do they work**

<https://www.fda.gov/drugs/biomarker-qualification-program/what-are-biomarkers-and-why-are-they-important-transcript>

* Biomarkers: characteristics of the body that we can measure (ex. Blood pressure is a biomarker)
* X-rays and CAT scans = also biomarkers because they tell how the body is doing + they’re measurable
* Biomarkers: important for drug development b/c measure the effect of experimental drugs on people during trials
  + Knowing the effect of the drug is by seeing the effect on the biomarkers = important to have a wide range of biomarkers to use to know the full effect of drugs
* Drug development right now: many problems, specifically with getting it onto the market
  + Ex, a drug can pass the preclinical process, all the animal testings, all the types of assays but once in people…have 1/10 chance of going to the market. 9/10 of drugs may fail during the stage of testing on people
  + To improve success rate of drugs developed: need a whole new generation of biomarkers that are more informative + can tell earlier/sooner if a drug is going to work or not/any toxicity
  + Improving drug delivery success rates + efficiency = accelerate the process of making treatments = more treatments available + lower costs of drug development

<https://www.webmd.com/a-to-z-guides/biomarkers-overview>

* Biomarkers: traits doctors use to measure blood, body fluids, tissues
  + Any measurable factor that lets doctors know about your body’s health
* Also called molecular markers/ signature molecules
* Can show signs of conditions, disease, normal body functions, or if something is going wrong
* Can only use biomarkers to see how body reacts to treatments for a disease

Types of Biomarkers

* Diagnostics biomarkers: tells doctors if you have a specific type of condition → to make more specific diagnosis
* Monitoring biomarkers: to see how a condition progresses → review these set of biomarkers over time to see if condition improves, worsens or stays the same
* Predictive biomarkers: helps doctors know beforehand on whether on not you will respond well to a certain treatment
* Susceptibility or risk biomarkers: do figure out how likely you are to get a condition → can do this before a disease is even in your body
* Prognostic biomarkers: to see how a disease may progress

Examples of Biomarkers:

* Blood pressure
* X-ray results
* CAT scan results
* Pulse
* Lab tests of blood and tissues
* Molecules made by tumors in the body that are related to cancer

Why are Biomarkers Important:

* Help doctors have information on different parts/systems of your body
* A comparable factor to how a normal system in your body should be to an abnormal one
* For cancer, biomarkers like proteins, genes and other molecules can:
  + Find some early-stage cancers: early detection = better/faster treatment and recovery
  + Predict how serious a cancer is: how far along the cancer is
  + See how one responds to a cancer treatment: to find the best/proper treatment for the individual..see how the treatment will work in the person over time. Looking at biomarkers could replace CT scans and MRIs
  + Monitor/predict the likelihood of the cancer reoccuring: in some cases, can take cells from a tumor, look at the biomarkers, and give a recurrence risk score (how likely the cancer is to return)
* Many names for biomarker testing for cancer (ex. Molecular testing, tumor testing, somatic testing, genomic profiling, etc)
* Can use biomarkers in clinical trials to see how new drugs will affect people (look at the changes the medications have on the biomarkers) → help them make new medications
* Biomarkers for psychiatry: researching on how biomarkers can be used for the prevention, diagnosis, medication response, + drug development for mental health disorders
  + Can help make treatments more specific to the person’s condition (instead of a one-fits-all treatment)

<https://www.news-medical.net/health/What-is-a-Biomarker.aspx>

* Biomarkers (short for biological markers) : biological measure for a biological state
* “Indicator of normal biological processes, pathogenic processes, or pharmacological response to a therapeutic invention”
* Each body system (cardiovascular, immune, metabolic) have their own biomarkers
* An ideal biomarker is:
  + Safe + easy to measure
  + Cost efficient to follow up
  + Modifiable
  + Consistent across genders and ethnic groups
* Biomarkers: show state of disease/health , show how healthy a person is, make diagnostics if they need to

Biomarkers in cancer detection and drug development

* Used to detect, screen, diagnosis, treat + monitor cancer
* Usually: anti-cancer drugs kill cancer + healthy cells
* Targeted therapy can help kill only cancer cells → find/use the typical biomarkers in cancers to do so so therapy only targets the cells that match the biomarkers
  + Will minimize risk of toxicity + reduce cost of treatment
* For cancer research: genetic studies important b/c genetic abnormalities usually underlie development of cancers → finding certain DNA or RNA markers could help in detection + treatment of certain cancers

<https://www.acobiom.com/en/biomarkers-diagnostics/#:~:text=They%20are%20measured%20from%20a,be%20either%20quantitative%20or%20qualitative>.

* Biomarkers: can be molecular or cellular (DNA, RNA, protein, metabolites)
* Measured from tissue biopsy or a liquid biopsy (blood, urine, saliva)
* Can be either qualitative (involves a pathogenic process detection with only a yes/no analysis) or quantitative (pathogenic process detection with a threshold effect)
* Biomarkers used to:
  + Diagnosing diseases/predicting risk of diseases
  + Determining if a treatment is efficient or not
  + Monitoring healthy people for signs of a disease
  + Targeting groups of people to see if the drug will be useful for them
  + Producing safer drugs by predicting their risks/effects earlier
  + Giving researches a global view of everything that occurs inside a cell

Biomarkers to develop Diagnostics

* All in-vitro diagnostics based on biomarkers
* Step 1 of diagnostic development: identifying one or more biomarkers associated with the normal biological/pathological process OR with patient’s response to a predetermined treatment
* To determine which marker/combo of marker is reliable, relevant + specific to the predetermined measurements of a process/the patient’s response to a therapy: need to know the biological, physiological or morphological properties of markers
* Precision medicine: requires identification + clinical validation of a lot of biomarkers to predict the course of a disease, monitor disease evolution, identify different sub-populations of patients, and to predict + monitor patient response to therapies
* Some therapies (ex. Pancreatic cancer and Alzheimer’s disease) still need identification of biomarkers to find a pathological biological process
* Some pathologies (ex. Solid tumors): diagnosis would be more accepted/made changes to using liquid biopsies for the biomarker base

Biomarkers in routine: an objective still difficult to reach

* Usually…diagnostic tests done to clarify + support clinical decisions. In recent years: diagnostic process now driven to pre-select patients (targeted therapy + personalized treatments)
* Shift happened because of following factors:
  + Advancing technology (can measure more specific markers now)
  + A greater understanding of the disease process
  + Greater appreciation of the uniqueness of each person’s phenotypes at the molecular level
* Trying to move on from a “one size fits all” medical approach → trying to have personalized medicine = diagnosis + treatment becomes faster + cheaper + more accurate + more effective
* Payers: have emerging interest in making sure drugs are administered to the right patient → this interest will also help us move forward in biomarkers + diagnostics to a personalized/targeted medical way

The challenge of cancer biomarkers in clinical practice

* Traditionally: drugs given to cancer patients were of low toxicity OR high tolerance (regardless of drug’s efficacy in the patient, as long as the drug worked in experimental + clinical trials). Now: trying to give more “personalized” treatment
* Personalized treatment would:
  + Minimize risk of toxicity
  + Minimize side effects
  + Reduce cost of treatment
* Currently 32 valid biomarkers listed by the FDA across spectrum of therapeutic areas (cancer being the most)
* Chemotherapy: an Ex. of current treatment that is prescribed to many patients despite uncertainty in the degree of their response to therapy
  + Some cases…overtreatment. Others…is a “trial and error” approach
  + Carries many side effects
  + Lacks precision (effects whole body)
  + Could cause potential progression of disease
  + Expensive
  + → biomarkers could be use to guide the decision of whether or not chemotherapy would be the best decision
* Challenges for moving from biomarker discovery → clinical utility:
  + Lack of making different selections before initiating the discovery phase
  + Lack in biomarker characterization/validation strategies
  + Robustness of analysis techniques used in clinical trials
* Parameters to check for when choosing useful biomarkers:
  + Sensitivity
  + Specificity
  + Predictive value
  + Clinical correlation
* But biomarkers with ideal specificity + sensitivity: difficult to identify + validate in clinics
* However…advances in DNA/RNA give opportunity to do simultaneous analysis of a lot of different biomarkers in a single experiment

**Quantum Dots for biomarkers:**

<https://www.team-consulting.com/insights/quantum-dots-new-dimension-diagnostics/>

* Prevention is always better than cure
* early/better detection = simpler resolution, reduced trauma for patient, cost-effective treatment, faster treatment
* QD: specks of matter so small that they are concentrated into a single point (a dot) → zero dimensional
* Not always just a single atom..usually a cluster of atoms in crystal structures that are 2-10 nm in size
* QD follow quantum confinement:
  + If you give an atom energy, it will get “excited” = the electrons of the atom will boost up to a higher energy level. When electron goes back down to original energy level, the electron “gives away” that excitation energy = emits a photon of a slightly lower energy + longer wavelength than what the atom originally absorbed. → since wavelength + frequency of light = different colors…different atoms emit different colors. 1 way to determine atom’s colour: the way their energy levels are arranged…energy levels in atom have set values = quantized
  + QD same as atoms with their quantized energy level behavior. BUT: materials of QD (ex. silicon) can produce different colours based on its size = ‘tunable’ light emission property. Small QD = generally emits blue light…large QD: generally red light…different sized QD can produce different colours)
* Medical diagnostics: science of finding the cause of someone’s symptoms
  + Requires finding the problem. ex. Biomarkers in blood or urine…biomarkers show the presence of a specific medical condition
  + Immunoassays: type of tests done to identify the specific biomarker and how much of it is present in the sample. Ex. is home pregancy tests . immuno= the use of antibodies during assay. Adding chemical probe/label to an antibody that emits light (a fluoresce known as fluorophore) = easier to detect what’s happening (ie. the biomarkers present + how much of it)

QD vs. Organic dyes:

* Brightness:
  + QD a magnitude brighter than organic dyes. This is because QD have a larger molar absorption coefficient (ie. larger capacity for absorbing light) and higher fluorescent quantum yield (the ratio of photons produced per photon received) in visible range + infrared.
  + Organic dyes: smaller molar absorption coefficient. High quantum yield in only the visible range. Brightness dependent on size, rigidity, + covalent structure of organic dye → structure could make the dye more likely to lose energy in ways that doesn’t produce light.
  + Increased Brightness: important for in-vivo diagnostics → brighter emissions could compensate for light lost on dye’s way to the detector due to light scattering, absorption, and/or autofluoresce
* Sharpness:
  + QD: emission peaks (coloured spectrum emitted) are narrow and sharp with little overlap (they don’t emit at the same wavelengths) happening between the peaks of multiple QD when excited (ie. their emissions are extremely distinct from one another) = QD clearer + easier to spot = easier to measure the light emitted by multiple QD at once because their emission spectra can be separated out easily
  + Organic dyes: spectra of light emitted is broad and can overlap (two different dyes can emit lots of different colours but some of those colours may be the same with the same intensity) = harder to distinguish emission signals from each other
* Optical stability:
  + Photobleaching: phenomenon where a chemical reaction occurs between a fluorophore and its immediate environment = fluorophore will start to degrade and lose ability to fluoresce → occurs in most organic fluorophores
  + QD: inorganic = less susceptible to photobleaching effect → huge advantage for in vivo diagnostics
* Excitation:
  + QD: to emit light, QD need to absorb an incident (ie. excitation) light. QD have broad absorption spectrum which increases towards the shorter wavelengths (the blue hues) + very similar absorption spectrum for all QD = (1) large choice of incident light in the shorter wavelength to choose from b/c have enough energy to excite a QD (2) QDs have similar absorption spectra (they overlap in the lower wavelengths of their absorption spectra) = one excitation light can excite multiple QD at once, usually light in the UV range.
  + Organic dyes: absorption spectra of organic dyes don’t usually overlap enough to excite them all simultaneously
* Multiplexing in assays: can help develop rapid + low cost diagnostic platforms. Complicated medical conditions…accurate diagnosis not fully possible on detection of just one analyte. In theory…possible to detect multiple analytes at the same time which are labeled with QD of different sizes using a single excitation light source
* Benefits of using QD: DNA sequencing, cancer diagnosis and treatment
* Advantages of using QD in real-time when operating on a patient: QD migrate slowly in an organ + can fluoresce for many hours = more accurate and prolonged luminance of the tumor. QD can be tuned to emit light at desired wavelength to see through body tissues (ex. Using infrared to see through fat tissues)

Possible Cons/why QD aren’t on the market yet:

* New technology = more reluctance to use it
* Organic dyes: comparatively cheaper
* Toxicity of Material: heavy metal could leak while illuminating or on oxidation…heavy metal QD would need coating to meet biocompatibility requirements
* Toxicity accumulation in body: QD size is 6-60 nm in diameter…organic dyes are 0.5 nm in diameter = risk of the kidneys not being able to clear QD out
* Manufacturing: less data on reproducibility, characterization, comparability, etc when compared to organic dyes (they’re produced in large scale and reproducibility/consistency is known)
* Super-biomarkers made: QD based … can outperform conventional dye-based biomarkers

**Photodynamic Therapy**

<https://www.cancer.org/cancer/managing-cancer/treatment-types/radiation/photodynamic-therapy.html>

* Photodynamic therapy (PDT) : treatment that uses special drugs called photosensitizing agents + light = kill cancer cells
* Drugs only work once they are activated by certain wavelengths of light
* Other names: photoradiation therapy, phototherapy, photochemotherapy
* Depending on place being treated…photosensitizing agent either put into bloodstream via a vein or on skin
* After some time…drug absorbed by the cancer cells. Light then applied to the area → light causes drug to react and form a special type of oxygen that kills cancer cells
* PDT could also help by destroying blood vessels feeding the cancer cells + alerting immune system to attack the cancer
* Drug-to-light interval: time between when the drug is given to when the light is applied → time could be b/t hours - days depending on drug used
* Light used for PDT: comes from LEDs or certain lasers → light used depends on type of cancer and location in the body
* PDT: usually used as outpatient procedure (ie. don’t have to be in the hospital) or sometimes combined with chemotherapy, surgery, anti-cancer drugs, or radiation therapy
* PDT: good for localized cancers

Pros of PDT:

* No long term effects when properly used
* Less invasive than surgery
* Takes short time + often done as outpatient procedure
* Precise targeting
* Can be repeated multiple times at the same site (unlike radiation therapy)
* Usually little to no scarring after area heals
* Costs less than other cancer treatments

Cons of PDT:

* Can only treat areas that light can reach → used to treat problems that are on or just under the skin, or lining of organs (that light can reach). Can’t be used to treat large cancer or cancers deep into skin or organs
* Can’t treat cancer that spread in many places
* Drug used causes people to become very sensitive to light for some time..certain precautions need to be taken after procedure
* Can’t be used on people with certain blood diseases

Potential Side Effects:

* Photosensitivity reaction: sensitive to bright light and sunlight. Skin could be red, and experience tingling or burning sensation. Need to take precautions to prevent skin’s exposure to light
* Skin changes: skin might turn red and swell for a bit of time depending on type/location of treatment
* Swelling and pain in treated area
* Immune system changes: could stimulate the immune system to work more or weaken it for a period of time

<https://www.mayoclinic.org/tests-procedures/photodynamic-therapy/about/pac-20385027>

* PDT: 2 step process..uses light + a drug (photosensitizer) to destroy cancer or precancerous cells
* Photosensitizers activated by certain wavelengths of light (usually a laser)
* Photosensitizer: nontoxic until activated by light → then becomes toxic to the targeted tissue
* PDT can trigger body’s immune system to help fight cancer/precancerous cells
* Used to treat:
  + Pancreatic cancer
  + Bile duct cancer
  + Esophageal cancer
  + Certain skin cancers like precancerous skin changes and nonmelanoma skin cancer
  + Lung cancers

<https://www.yalemedicine.org/conditions/photodynamic-therapy>

<https://www.nhs.uk/conditions/photodynamic-therapy/>

* On its own, the drug is harmless..when activated with light, will damage surrounding cells
* treat wherever light can go (ex. Skin, eyes, mouth, esophagus, lungs)
* Besides, cancer, holds promise in treating warts, acne, extramammary Paget’s disease (precancerous condition that affects the anus and genitals)
* PDT done in 2 ways:
  + Using light from a lamp or laser (called conventional PDT)
  + Using natural daylight (called daylight PDT)
* Conventional PDT steps:

1. Preparation: need to go to a hospital/clinic to be given light-sensitive medicine. Depending on the area treated, medicine can be a cream, injection or special drink. After taking medicine, asked to go home but come back after few hours/days so that medicine has time to build up in the abnormal cells
2. Light treatment: asked back to the clinic for the light therapy. Involve a lamp/laser being shone on the area for 10-45 minutes. Sometimes might give anesthesia to numb the area

* Daylight PDT: used for some skin conditions. Medicine is a cream you put on affected area, then spend 2 hrs outdoors in the sun to activate the medicine (still need sunscreen on while doing so)

<https://www.cancer.gov/about-cancer/treatment/types/photodynamic-therapy#:~:text=Photodynamic%20therapy%20uses%20a%20drug,therapy%20is%20also%20called%20PDT>.

February 25, 2024

**Quantum Dots for photodynamic therapy:**

[**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9405672/**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9405672/)

* Global cancer statistic: 10 million cancer deaths worldwide in 2020
* Most cancer drugs: have severe side effects because of the circulation of the drug molecules in the body
* Photosenizter gets excited to a higher energy level when it absorbs a photon when exposed to light…the excited electrons can do two things: (1) it can emit the light back (fluresce) back to its ground state or (2) it can go to a relatively stable excited triplet state (the electron that got promoted has the same spin orientation as the other unpaired electron <https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Chemistry_Textbook_Maps/Map%3A_Physical_Chemistry_for_the_Biosciences_(Chang)/14%3A_Spectroscopy/14.07%3A_Fluorescence_and_Phosphorescence> ) → if excited triplet state: will relax back down to ground state = transferring the energy to oxygen to make a singlet oxygen species (¹O₂ → the reactive oxygen species) → singlet oxygen readily oxidizes biomolecules like protein, lipids, DNA, RNA = killing cancer cell
  + The triplet state photosensitizer can lose a hydrogen = make a radical and/or anion radical (radical = atom, molecule, or ion that has at least one unpaired valence electron) → stars the therapeutic effects
* PDT: have varying efficacies depending on drug used, dose of drug, light source, tissue type, availability of oxygen
* 3 ways cell death can be triggered by PDT:

1. PDT can cause vascular constriction + platelet aggregation
2. Cause direct cellular oxidation = cause apoptosis (programmed cell death) and necrosis (death of a body tissue due to lack of blood flow aka oxygen supply)
3. Could stimulate an autoimmune and inflammatory response to the area

* Pros of PDT:
  + No surgical intervention (less invasive)
  + Can be localized at the tumor site = less systemic toxicity

Photosensitizers (PS)

* Ideal PS are:
  + Chemically pure
  + Easy to synthesize
  + Have long shelf life
  + Have a strong absorption …preferably between 600-800 nm to have enough energy for singlet oxygen excitation
  + Have minimum dark toxicity
  + Possess high renal clearance rate (filter easily through the kidneys) → prevents toxicity and accumulation
  + Able to selectively localize at the tumor tissue
* Three generations of PS …each generation getting more advanced. Third generation is most advanced: has PS conjugated to specific proteins, amino acids, antibodies carbohydrates for specific targeting
  + Third generation also has classical PS encapsulated/conjugated to nanoparticles
  + Problems with the current second generation PS:
    - tend to accumulate in the skin and eyes = phototoxicity + photosensitivity for a long period of time → not fully tumor selective
    - Most have hydrophobic tendencies so might agglomerate (collect into a large mass) in aqueous medium
    - Not very successful for deep or bulky tumors or tumors that have spread to multiple organs
  + Research is going into third generation PS which can overcome the drawbacks of solubility + phototoxicity in healthy cells. → nanotechnology (QD) being used now to help target photosensitizers better

Nanotechnology in PDT

* Can target tumor cells because of enhanced permeability + retention properties = more targeted photodynamic action = limiting the phototoxicity to normal/healthy cells
* Nanocarriers for PS for PDT:
  + Localize the PS to the tumor site
  + Delivery high concentration to PS
  + Improve biodistribution by having surface modifications

Quantum Dots

* Nanomaterials;: classified based on number of degrees of freedom experienced by the electrons
  + Quantum wells: 2-D nanomaterial → confinement in only one direction
  + Quantum wires: 1-D nanostructure → confinement in two directions
  + Quantum dots: 0-D nanocrystals → confinement in all three directions

Quantum confinement: → the effect that gives QD their unique electronic + optical properties

* Bohr radius: the distance between the electron in the conduction band (where an electron can bounce up to when excited) and its corresponding hole in the valence band (where the valence electron’s resting energy level is at)
  + A characteristic of each semiconductor
  + Quantum confinement happens at dimensions smaller than the Bohr radius
* Large semiconductor materials are larger than Bohr radius = continuous electronic energy levels
* QD: excited by photon → electrons in valence band gain energy and make an exciton (exciton = the combo of an electron + a hole pair that is free to move through a non-metallic crystal as a unit) → size of exciton = size of QD = discreet atomic like energy levels + the exciton is ALSO then confined in all three dimensions…discreet atom like energy levels = longer lifetime in that excited state
* Emission spectra of QD can be modified → can emit then between the UV - near infrared region (more than conventional photosensitizer which can only do visible region) → just need to keep changing the QD’s size
* Can control QD’s size by: changing reaction parameters (ex. pH, temperature, time, concentration) during synthetic processes
* Having near infrared (NIR) range available → the light can diffuse quickly = deep tissue penetration = use QD to target deep rooted tumors
* QD can induce ¹O₂ production: transfer the energy from the excited QD state to the ground state triplet oxygen
* QD: more photostable + biocompatible than organic dyes → can improve biocompatibility + intracellular delivery with simple surface modifications
* QD for PDT: still being discovered and explored . holds promise especially with carbon dots, graphene dots, and bimetallic dots
* Fluorescence resonance energy transfer (FRET): coupling of acceptor and donor dipoles…when donor is excited by a photon, it relaxes back to lowest level of excited singlet stage…if acceptor is very close by, the energy released by the donor relaxing to ground state could excite the acceptor (this energy exchange called resonance) . if acceptor is fluorescent too…FRET enhances acceptor’s fluorescence
  + QD FRET: used to enhance PDT action
  + QD: can be made to enhance water solubility + conjugated with conventional PS/target molecules to improve therapeutic results
  + QD: can be effective drug carriers for PS → combat solubility + aggregation issues
  + QD: can enhance fluorescence emissions of PS drug by FET interactions (QD-PS conjugates synthesized in na way that the QD emissions overlap with PS excitation = lets excitation of PS be at lower wavelengths + enhance fluorescence emission by the PS)

Prooxidant and antioxidant properties of QD

* Some QD: can cross over from antioxidant nature to prooxidant nature upon laser irradiation
* Study 1 by Christensen et al. : used bimetallic and carbon dots in in vitro
  + Reported that: QD inhibited oxidation of the radical probes used but when irradiated with blue light…catalyzed the oxidation process
  + Generation of ¹O₂ : enhanced A LOT by D₂O solution
  + = QD are like “oxygen scavengers” in the dark but when shone with blue light = induce production of singlet oxygen
* Study 2 by Chong et al. used graphene quantum dots
  + Concluded that: in no light…graphene QD protected cells from oxidative damage by scavenging free radicals
  + But when irradiated with blue light = generated a lot of reactive oxygen species
* Studies show that: can make “smart” QDs that first protect cell but then can kill it..all with controlling it by a light switch (= QD accepted into cancer cell easily but later, kill it)

Cell Penetration Mechanism

* Cellular uptake of QD dependent on size, composition, surface modification , charge
* Many studies done to see the localization of different types of QD in different cellular organelles in different cell lines . found that:
  + Most QD localize in the lysosomes → some concentrations in the mitochondria and endoplasmic reticulum
  + Exocytosis of internalized QD is very fast → but only 40% was discharged
  + Metallic QD: avoided for biological applications b/c of toxicity risk BUT graphene QD reported to be nontoxic + biocompatible . Graphene QD…known to localize in the nucleus + in cytoplasm
  + Carbon based QD : well tolerated + very little toxicity risk for therapeutic concentrations
* QD usually follow endocytosis for cell penetration → and like to accumulate in the cytoplasm BUT can be made to target other cellular organelles too
* Carbon + Graphene QD: the MOST looked at in terms of biocompatibility + safety b/c have showed the least toxicity risk → explored the most for clinical applications (including PDT)

Carbon QD for PDT ([Zheng et al., 2016](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9405672/#B137))

Good because:

* Biocompatible
* Non-toxic
* Can be easily synthesized
* Have high water dispersibility
* Have non-blinking fluorescence properties
* Surface is usually made of -NH2, -COOH, -OH groups = easy surface modifications

Study of Carbon QD for targeting hypoxia in tumors using PDT (by Zheng et al.)

* Hyperoxia: common characteristics in tumors → usually results in resistance against PDT
* Developed a carbon nitride doped carbon dot to photo catalyze the water splitting reaction to generate oxygen in vivo upon irradiation with 630 nm laser
* Carbon dot then conjugated with the PEGylated protoporphyrin PS for PDT → conjugate downregulated hypoxia related proteins + improved the therapeutic effect of PDT

Graphene QD for PDT ([Ramachandran et al., 2022](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9405672/#B87)).

Good because:

* Environmentally friendly
* Easy synthetic routes
* Tunable optical and electrical properties
* Incredible luminesce properties
* Reported good cell penetration + uptake properties

Study to see the synthesis and PDT application of titanium dioxide nanoparticles and N-doped graphene QD composites (GQDs/TiO2 NCs):

* The nano composite created significant amount of ROS + had cytotoxic effects against the highly aggressive MDA-MB-231 breast cancer cells after irradiation with NIR light

Conclusion:

* Can transform cancer therapy + imaging
* Surface of QD: can be functionalized to help attach specific antibodies/proteins to cause site specific localization of the PS = reduce phototoxicity that is usually seen with conventional PS
* QD for PDT can eliminate most drawbacks with current methods
* But need more data on pharmacokinetics + pharmacodynamics of QD
* Need more data on long term toxicity of QD in humans + environment
* More data on metabolism + excretion of QD from the body
* More data on lethal doses + inhibitory concentration of each QD in vivo models

Cancer information

<https://ourworldindata.org/causes-of-death#:~:text=Now%2C%20non%2Dcommunicable%20diseases%20%E2%80%93,of%20death%20can%20fall%20further>.

<https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588>

<https://www.statista.com/topics/4334/cancer-in-canada/#topicOverview>

<https://www.cancerresearchuk.org/about-cancer/what-is-cancer/why-some-cancers-come-back#:~:text=These%20days%2C%20doctors%20are%20able,you%20have%20any%20cancer%20left>.

<https://www.cancerresearchuk.org/about-cancer/treatment/cancer-drugs#:~:text=There%20are%20many%20different%20types,have%20a%20combination%20of%20drugs>.

<https://www.verywellhealth.com/what-does-in-vivo-and-in-vitro-mean-2249118#:~:text=The%20terms%20%22in%20vivo%22%20and,developing%20drugs%20or%20studying%20diseases>.