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## **FDA : Application of Nanotechnology to Cosmetics and Foods**

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Office of Cosmetics and Colors

Tuesday, November 24, 2009

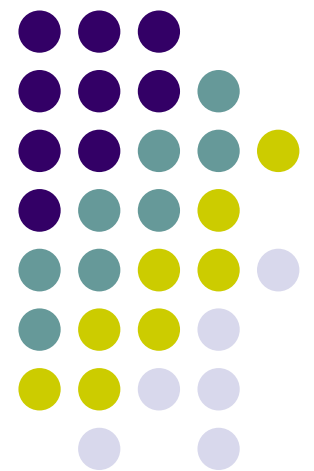
# Outline

- Definitions
- Regulatory authority
- Nanotechnology in food and cosmetics
- Safety/toxicity concerns
- Current research
- Summary



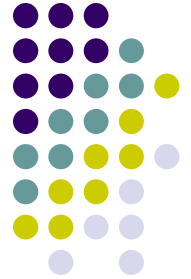
# Section I

# Definitions



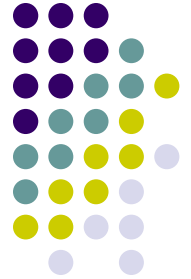


## Poll Question



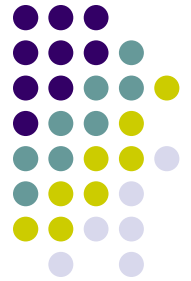
- What does nanotechnology mean?
- A) Use particles that are larger than 1 nm
- B) Use particles that range from 1-100 nm
- C) Use particles that have unique properties
- D) Answers B&C

# Definition

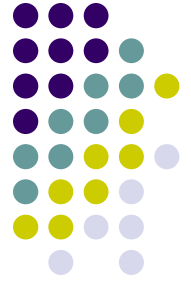


- Nanotechnology
  - No official FDA definition
  - National Nanotechnology Initiative (NNI) definition:  
understanding and control of matter at dimensions of roughly 1 to 100 nm, where unique phenomena enable novel applications

# Scope of Products Regulated by FDA's Center for Food Safety and Applied Nutrition



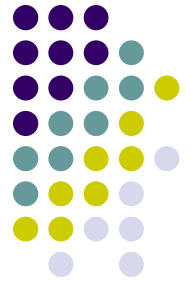
- Food
  - “Conventional food”
  - Infant formula
  - Medical food
  - Dietary supplements
  - Food additives
  - Food contact substances
  - GRAS substances
  - Prior sanctioned substances
- Color Additives
- Cosmetics



# Definitions – Food (201(f))

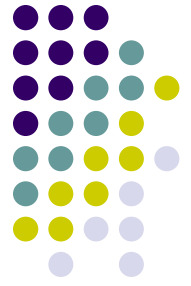
- Articles used for food or drink for humans or animals (includes pet food and animal feed)
- Chewing gum
- Substances migrating to food from food contact articles

# Definition - Dietary Supplements



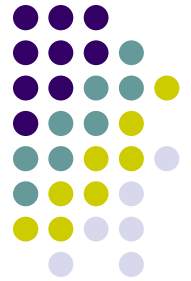
- Product (other than tobacco) that is intended to supplement the diet
- Contains one or more of the following dietary ingredients:
  - Vitamin
  - Mineral
  - Herb or other botanical
  - Amino acid
  - Other dietary substance used to increase total dietary intake
  - A concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients





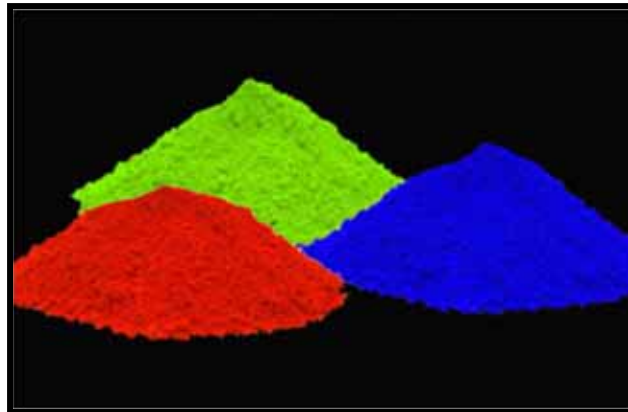
# Definition – Food Additive

- Any substance which may become a component or affect the characteristics of any food
  - Includes substance intended for use in producing, manufacturing, packaging, transporting, or holding food
  - Includes any source of radiation intended for use
  - Under the Food, Drug, and Cosmetic Act and implementing regulations, the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common safe use in food.



# Definition – Color Additives

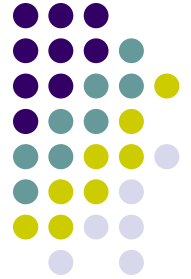
- Dye, pigment, or other substance when added or applied to a food, drug, or cosmetic, is capable of imparting color

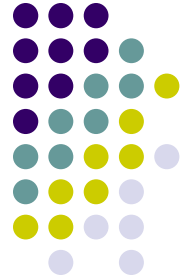


# Definition – Cosmetics

- Articles intended for:
  - Cleansing
  - Beautifying
  - Promoting attractiveness
  - Altering appearance

Excludes soaps





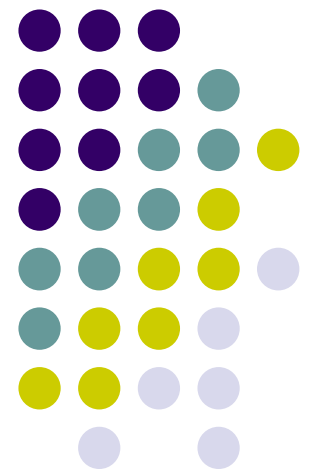
# Let's Pause for Two Questions from the Audience



# Section II

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## Regulatory Authority



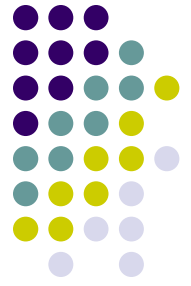


## Poll Question



- Do you think food, dietary supplements, and cosmetics are subject to approval by FDA?

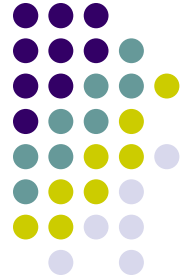
✓ Yes    ✗ No



# Requirements for market

- Food must not be adulterated or misbranded
- Cosmetics must not be adulterated or misbranded
- No pre-market approval of these products with the exception of food additives and color additives

# Question



What do you think might be potential uses of nanotechnology in foods and cosmetics?

1)

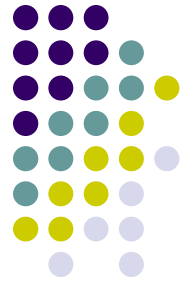
2)

3)

Raise your hand to volunteer!

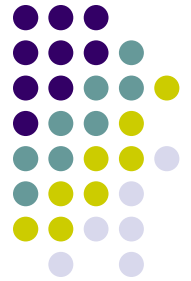


# Potential Uses of Nanotechnology in Foods



- Dietary supplements
  - Nanosized mineral supplements which have dramatically increased absorption
  - Nanoemulsions that increase absorption of botanical ingredients
- Enhance flavor and color

# Potential Uses of Nanotechnology in Foods (continued)

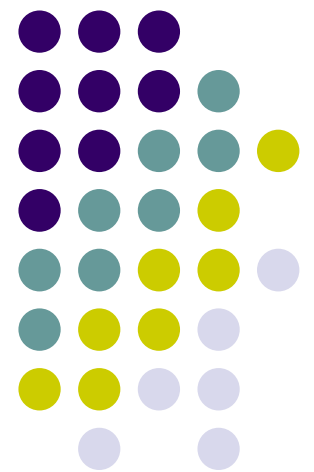


- Decrease microbial contamination in food and improve packaging
  - Barrier to keep microbes out
  - Kill microbes directly
  - Carrier of antimicrobial compounds
  - Sensor to alert consumers or retailers of potential spoilage
  - Tracer to identify the source of contamination

# Section III

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## Nanotechnology in Cosmetics and Foods

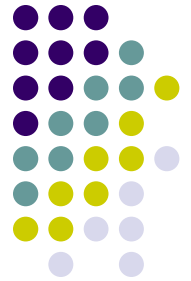


# Current Status in Foods

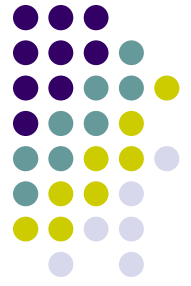


- Titanium nitride was approved as a nanosized recycling aide for polyethylene terephthalate (PET) used as food contact material

# Current Reported Uses of Nanotechnology in Cosmetic Products



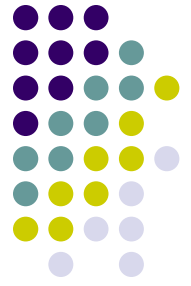
- Nanodispersed Systems
  - Liposomes (nanosomes)
  - Nanoemulsions
  - Solid lipid nanoparticles
- Other Nanoparticles
  - Polymer systems (nanocapsule, dendrimer)
  - Metal Oxide Nanoparticles



# Nanodispersed Systems

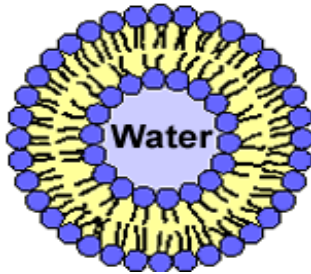
- Liposome technology
  - Hydrophilic vesicles with phosphatidylcholine membrane(s) ranging in size from 15-3500 nm
  - Used to alter optical properties, to increase solubility (transport) cosmetic ingredients, and to alter physical properties
- Other nanodispersions used in cosmetics are lipophilic vesicles
  - Nanoemulsions, solid lipid nanoparticles

# Nanodispersed Systems

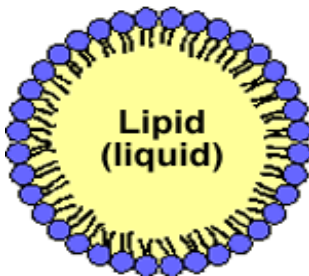


**Figure 1: Structure of nanodispersed systems**

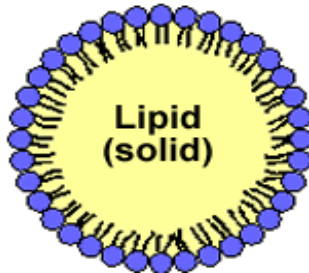
**1a Liposome:** Lipid bilayer enclosing an aqueous core



**1b Nanoemulsion:** Lipid monolayer enclosing a liquid lipid core

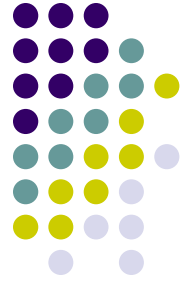


**1c Lipid nanoparticle:** Lipid monolayer enclosing a solid lipid core



- Liposomes – lipid bilayer
- Nanoemulsion and lipid nanoparticles – lipid monolayer
- Core can be hydrophilic or hydrophobic depending on the number of phospholipid layers
- Deliver water or lipid soluble ingredients

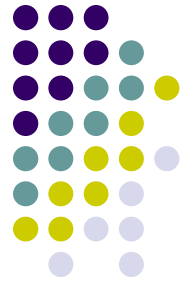
# Cosmetic Nanoemulsions



- Nanoencapsulation of ingredients
- May be found in skin and hair care preparations
- Useful in typical cosmetic formulations
- Light or oxygen sensitive actives can be protected
  - Vitamin A and Vitamin E
- Low biotoxicity of phospholipid

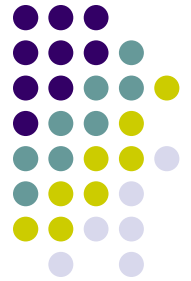


# Potential Lipid Nanoparticle Advantages



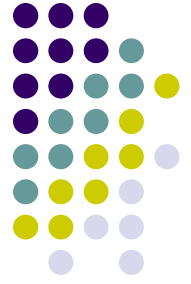
- Improved stability of ingredients
- Controlled release of ingredients
- Improved skin hydration
- Incorporation of lipophilic ingredients
- No or low carrier biotoxicity

# Solid Hydrophobic Nanospheres

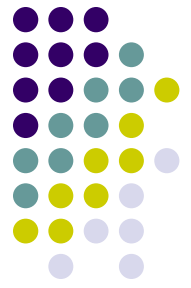


- Highly cationic charge density of surface layer leads to strong interaction with skin/hair
- Solid hydrophobic core protects water soluble and volatile ingredients
- Found in fragrances, vitamins

# Polymer Nanoparticles



- Can lead to burst or controlled release of active ingredient
- Robust compared to liposomal formulations
- Great number of natural and synthetic sources
- Stable in both liquid and powder form
- Nanocapsules, dendrimers



# Metal Oxide Nanoparticles

- Metal oxides, such as  $\text{TiO}_2$  and  $\text{ZnO}$ , are found in many commercial applications

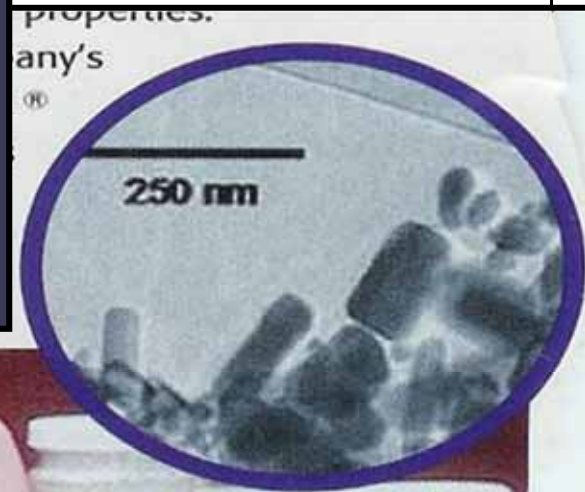


Photo Courtesy Nanophase Technologies

*Nanophase Technologies' zinc oxide nanoparticles (seen in inset photo) are included in the above products. The nanoparticles are transparent and can block UV rays from the skin. They are also antimicrobial, which helps control odor.*

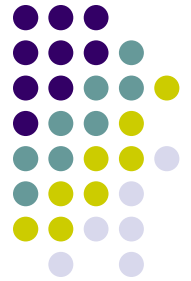


## Poll Question

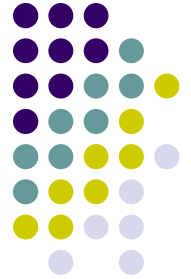


- What advantages would titanium dioxide or zinc oxide nanoparticles have for use as sunscreens?
- A) Transparent on the skin
- B) Protection against UVB rays only
- C) Helps increase penetration of sunscreen deep within the skin

# Potential Advantage of Metal Oxides



- Small crystal size and controlled particle size give excellent dispersibility, make skin feel attractive, and is transparent on the skin
- May increase protection against both UVA and UVB rays



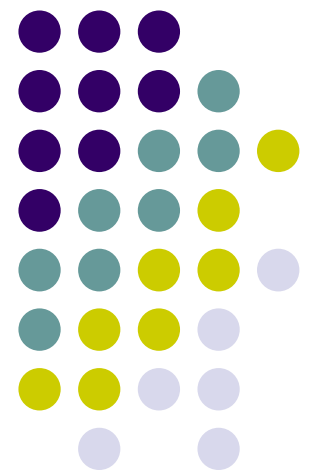
# Let's Pause for Two Questions from the Audience



# Section IV

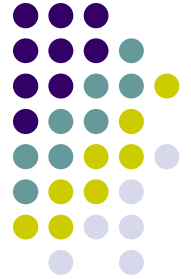
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## Safety/Toxicity Concerns





# Toxicity Concerns

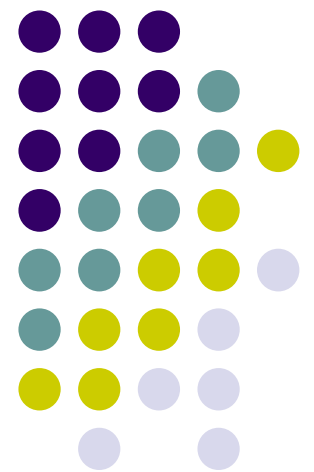


- Similar to that of other FDA regulated products that are not nanoparticles
- Potential for toxicity related to type of nanoparticle used
  - Nanotubes
  - Fullerenes (Buckyballs)

# Section V

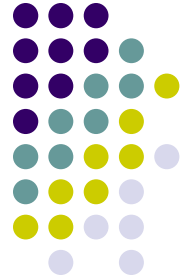
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## Current Research

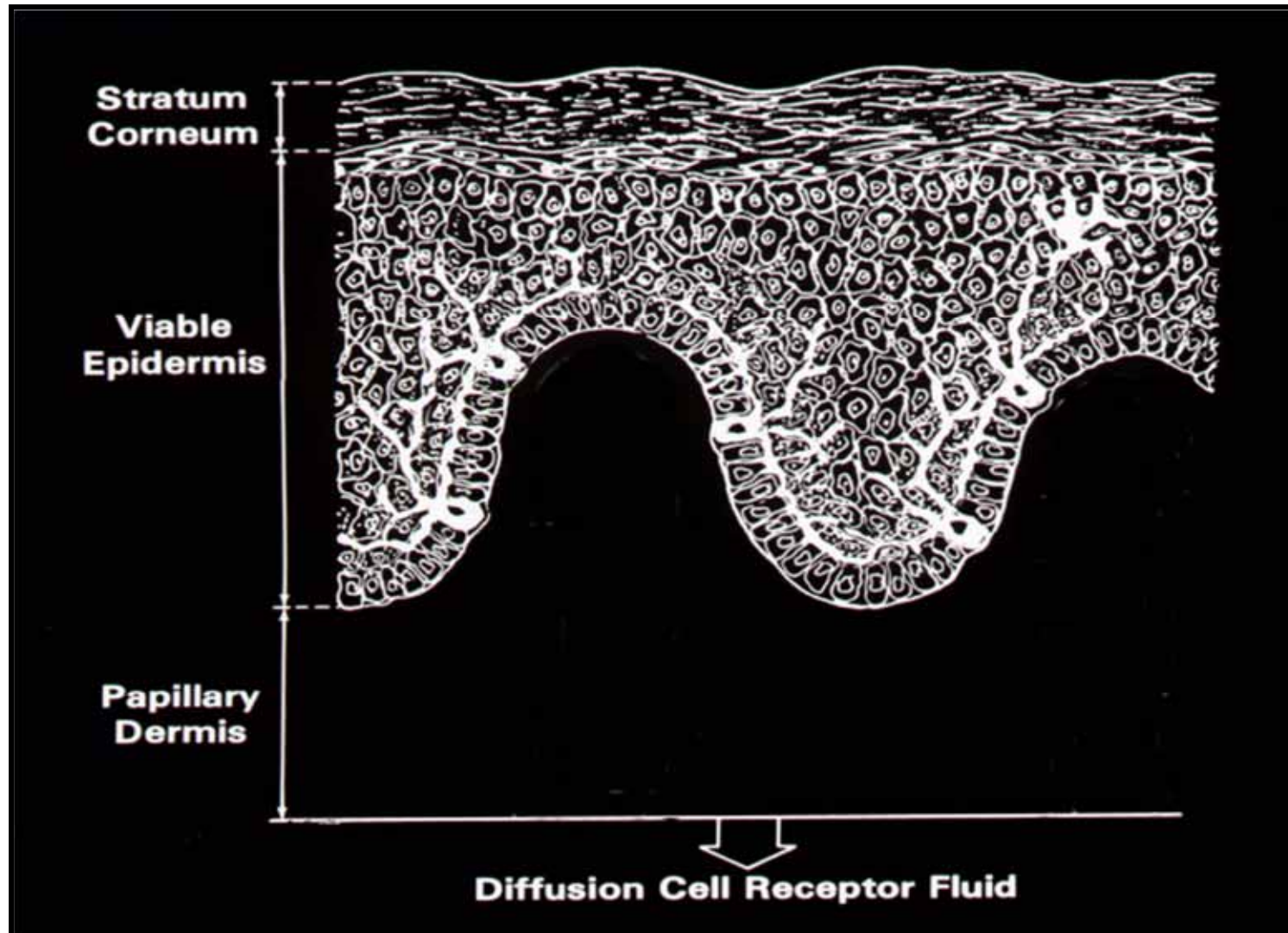
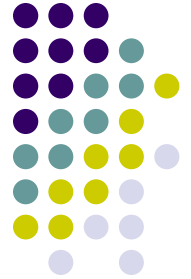


# On-going Research in Cosmetics

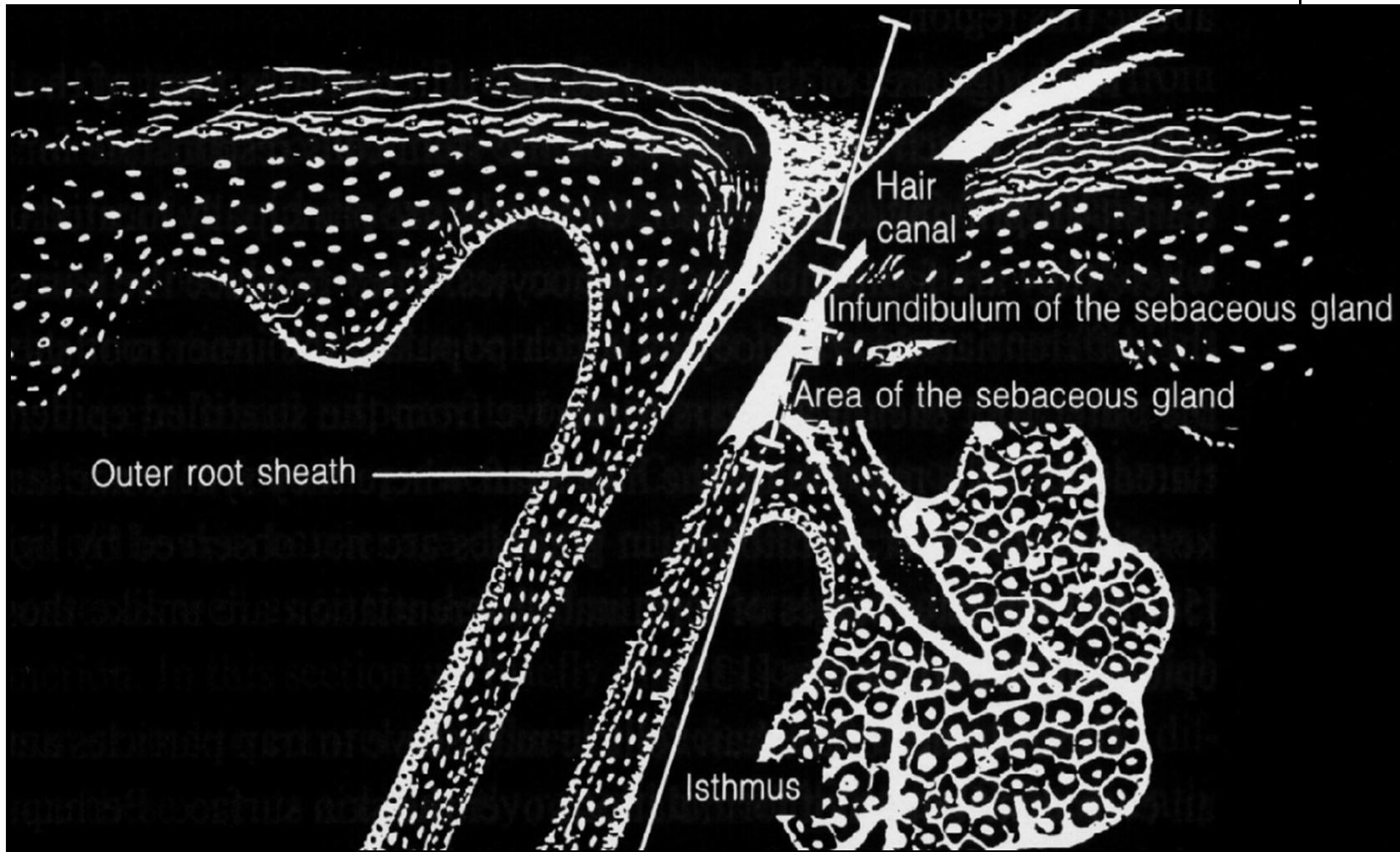
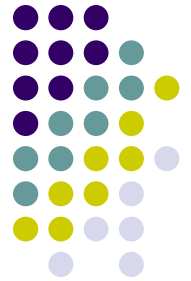
## Skin Absorption Studies



# Barrier Layer of Skin



# Upper Hair Follicle





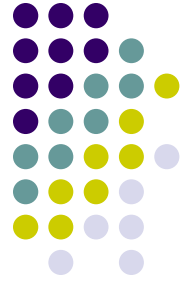


Image from: Toll  
*et al.*, J. Invest.  
Dermatol. 123,  
168-176, 2004.

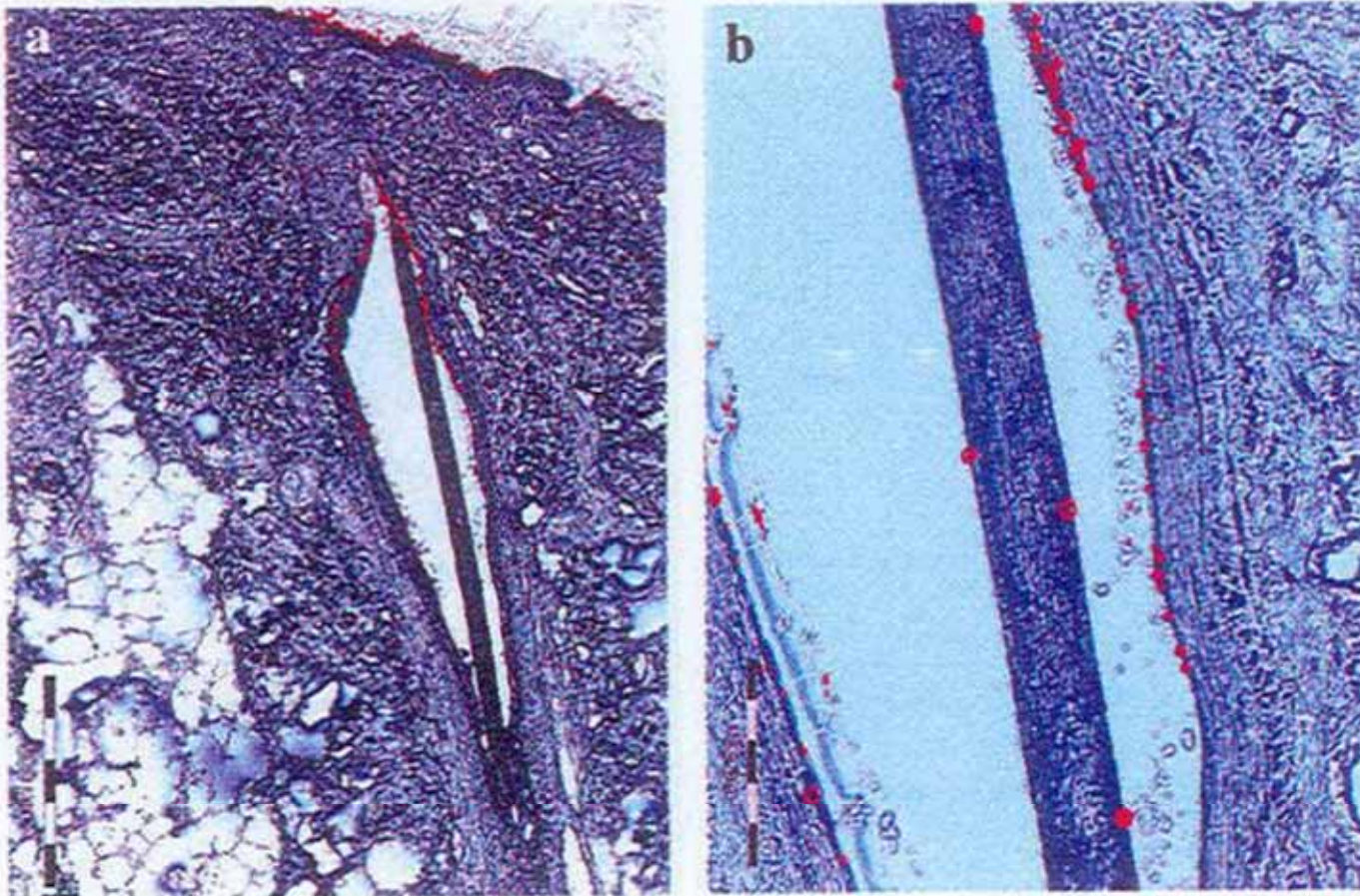
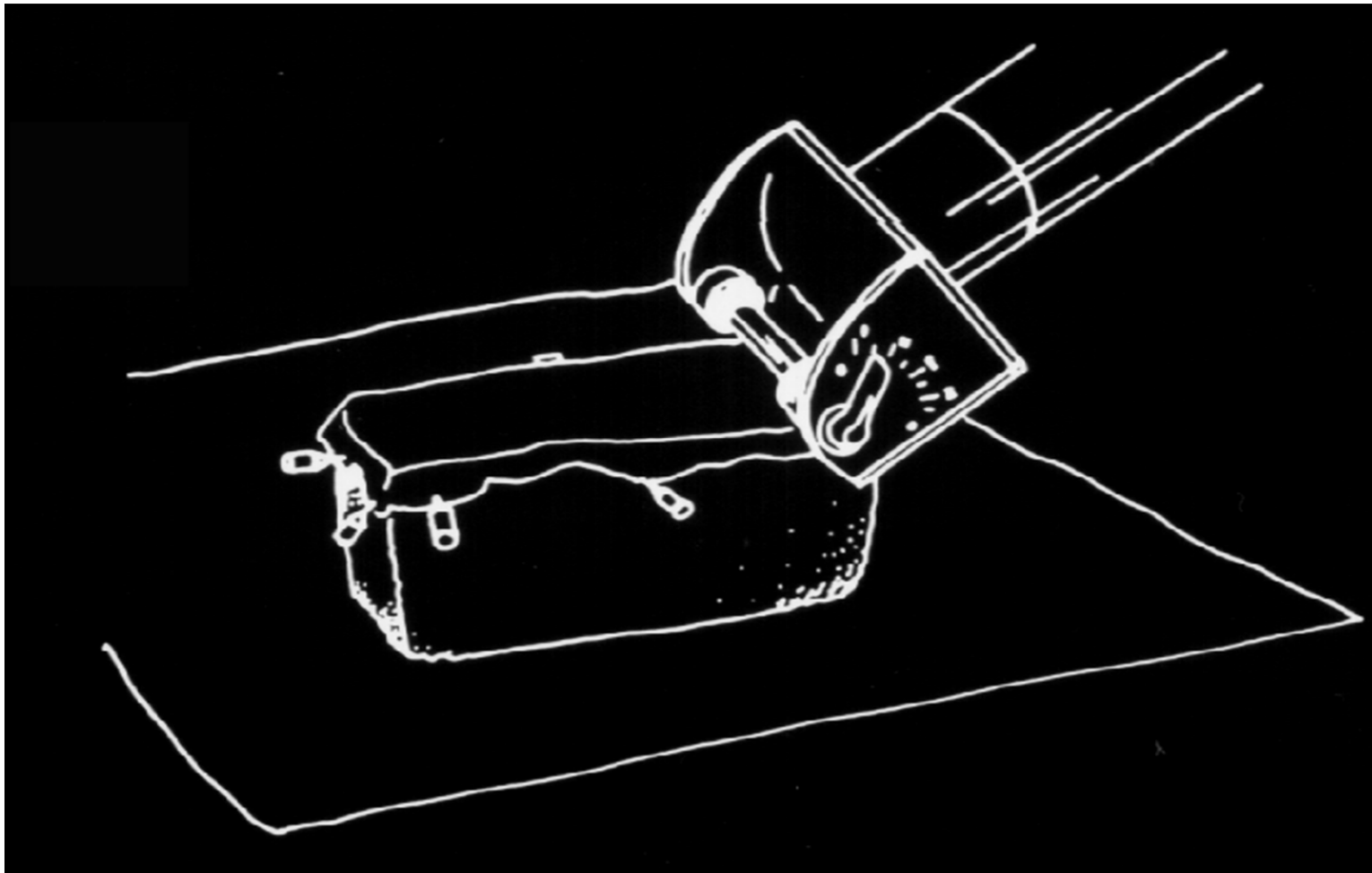
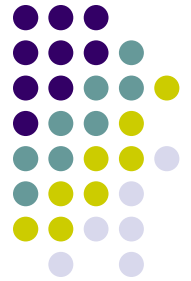
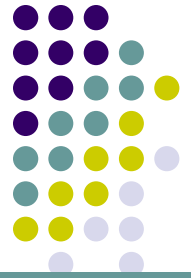


Image shows penetration of microspheres into hair follicle. Authors concluded that penetration was between cuticula of hair shaft and inner root sheath

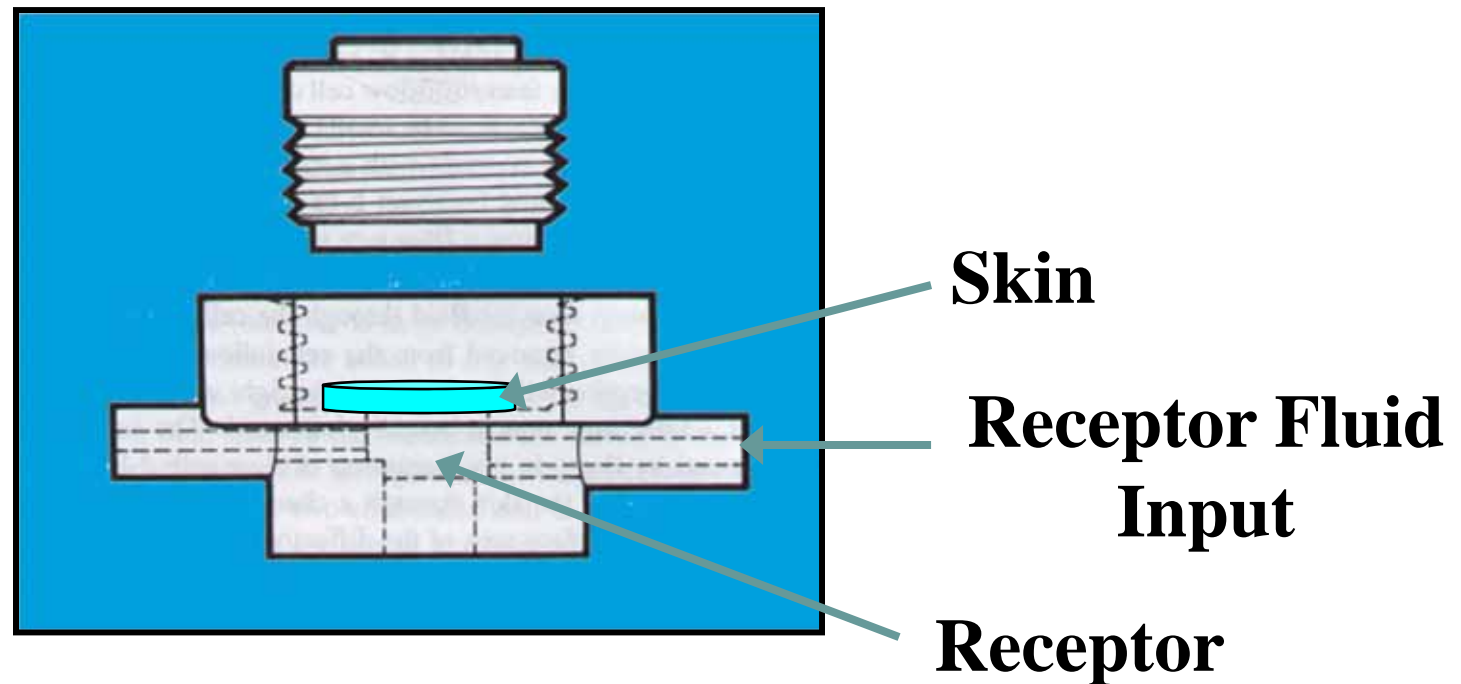
# Preparation of Skin with Dermatome



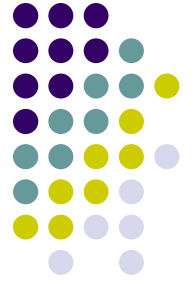
# Percutaneous Absorption Studies



## In Vitro Diffusion Cell

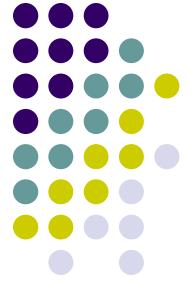






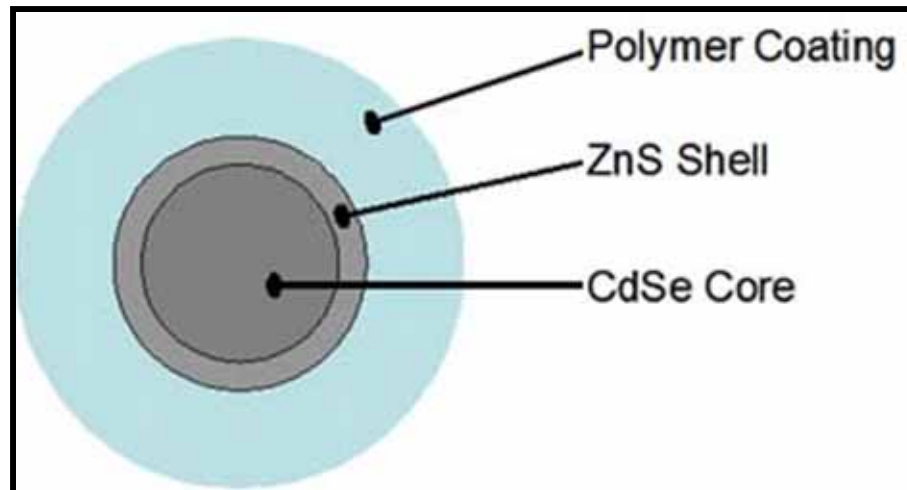
# Let's Pause for Two Questions from the Audience



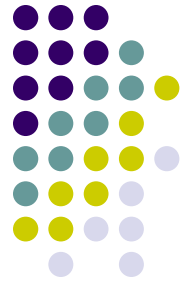


# Quantum Dot Study

- Good model compound for topical products
  - Relatively stable
  - Highly fluorescent

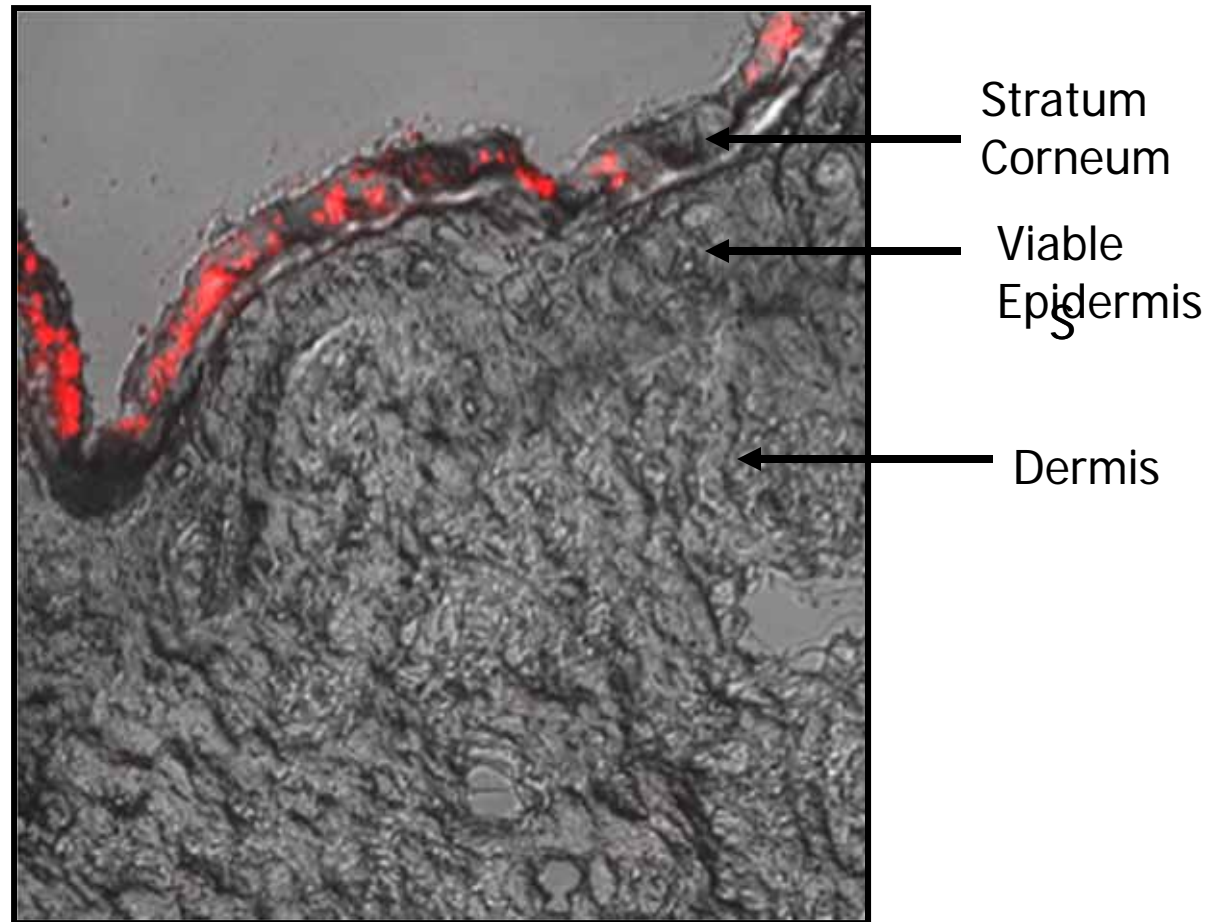


# Skin Penetration Study Details



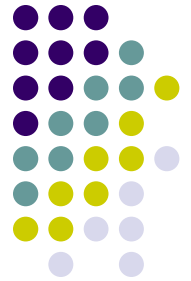
- Human cadaver or surgical specimen skin
- Applied to skin in a borate buffer or in an oil/water emulsion for 8 or 24 hr.
- Skin surface was either washed with soap and water at the end of the study or left unwashed
- Generally, frozen sections made with a cryostat, fixed with formaldehyde vapor and examined for fluorescence at 40X with a Laser Scanning Confocal Microscope

# Evaluation of Quantum Dot Penetration – Human Skin



M.E. K. Kraeling et al., The Toxicologist, March 2007.

# Liposome Study

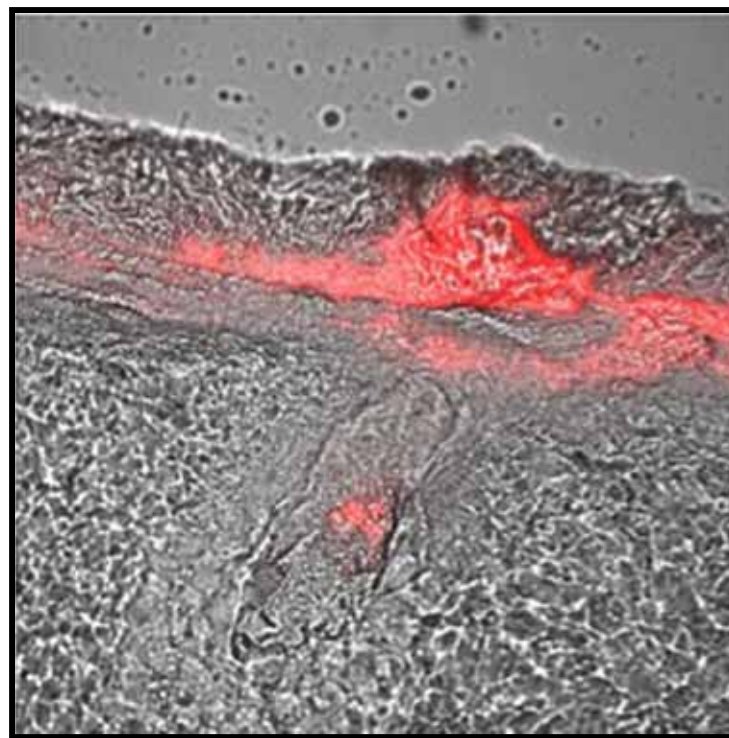


- Liposome Formulations
  - Phosphatidyl choline (egg)
  - Tween 80
  - Oil dye
- Skin absorption studies conducted with hairless guinea pig skin for 24 hr.
- Frozen skin sections examined using confocal microscope

# Confocal Microscopy Analysis Liposome – Micelle Mixtures



- “Flexible” liposome formulations contain a mixture of liposomes and micelles
- Increased concentration of micelles may promote skin penetration



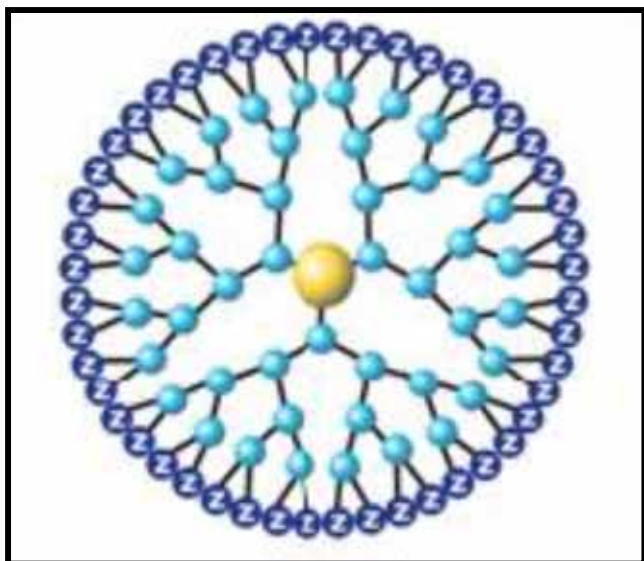
O. Ogunsola et al., ACS Colloid and Surface Science Symposium, June 2007



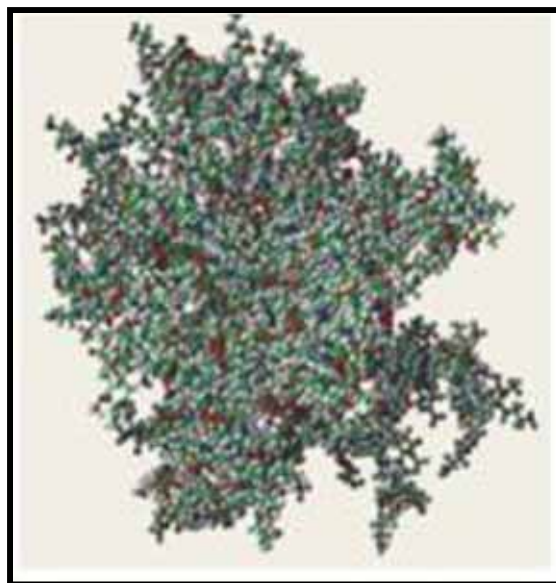


# G4 PAMAM Dendrimer

2D Graphical Diagram

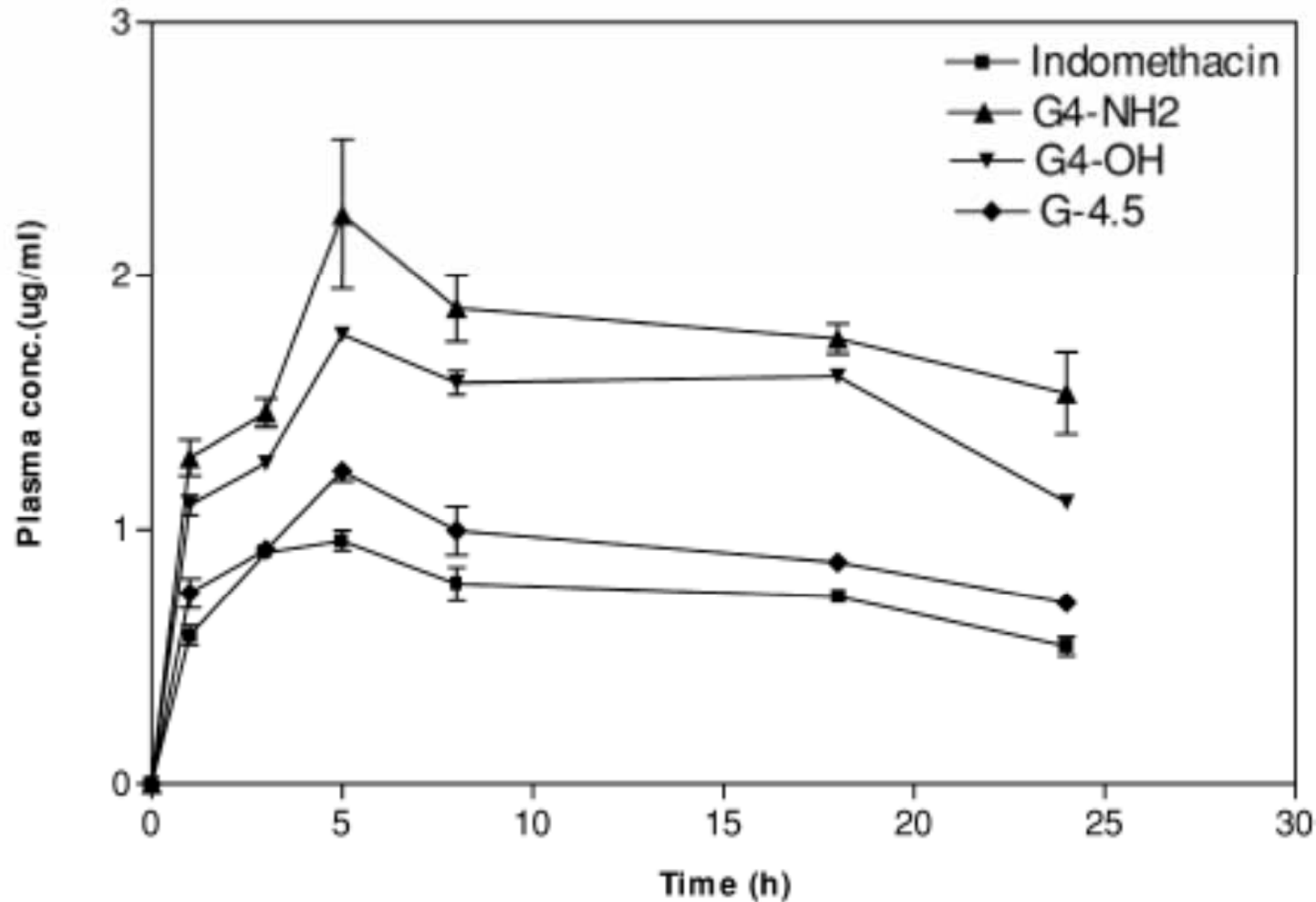
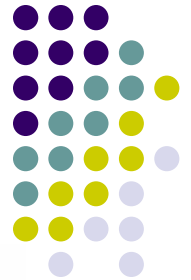


3D Chemical Structure



**48 surface groups, 4.4 nm diameter**

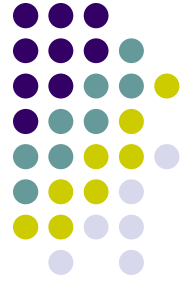
# Effect of Dendrimers on Rat Skin Penetration of Indomethacin from a Transdermal Patch



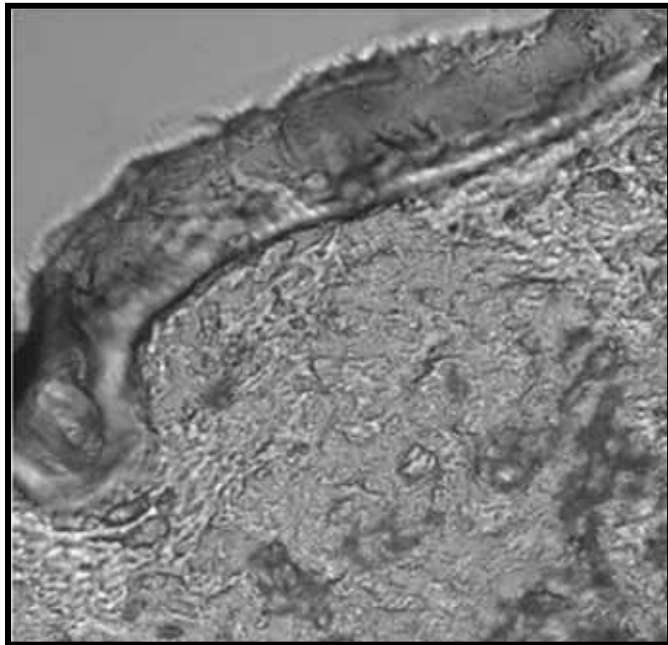
Chauhan et al., J. Control Release, 90, 335-343, 2003



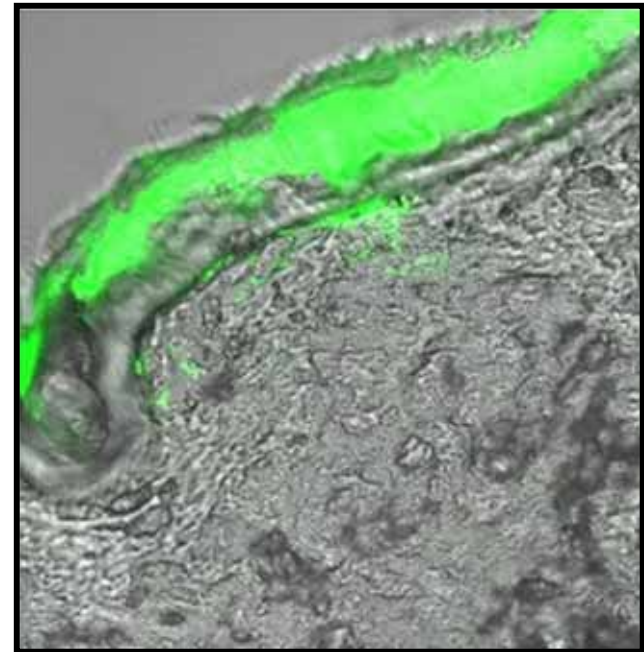
# Penetration of G5 PAMAM Dendrimers into Human Skin



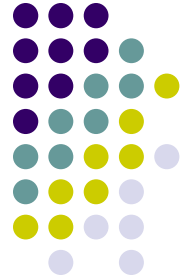
**Bright Field Image**



**Fluorescent Image**



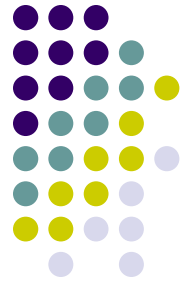
Kraeling, M. E. K., Ogunsola, O. A., Bronaugh, R. L., The Toxicologist, March 2008.



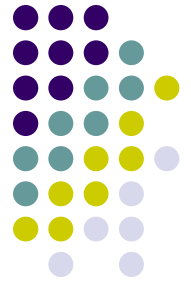
# Let's Pause for Two Questions from the Audience



# Research – Safety of Cosmetic Products Using Nanoparticles



- In vitro penetration studies
  - Little or no penetration into viable skin of 20 nm or 37 nm diameter quantum dots
  - Nanoscale sized liposomes may deliver a fluorescent dye into viable skin tissue
    - Stability
- Using dendrimer nanoparticles to assess skin absorption



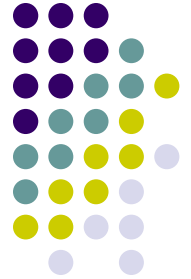
# Some Potential Research Needs

- Types of instrumentation and methods needed to characterize aspects such as the size, stability, and solubility in different solutions/formulations
- Battery of toxicological studies to compare properties of nanoparticles v macroparticles
- Toxicological properties of nanoparticles following different routes of administration
- Information on absorption into and through skin

For a more comprehensive list refer to

[http://www.nano.gov/html/news/EHS\\_research\\_needs.html](http://www.nano.gov/html/news/EHS_research_needs.html)

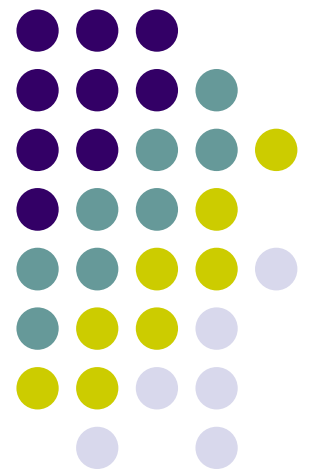
# Summary



- Information available on nanoparticles in foods and cosmetics is scant
- Information is needed regarding methodology for detection and for monitoring safety

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