Methodologies for Drug Delivery

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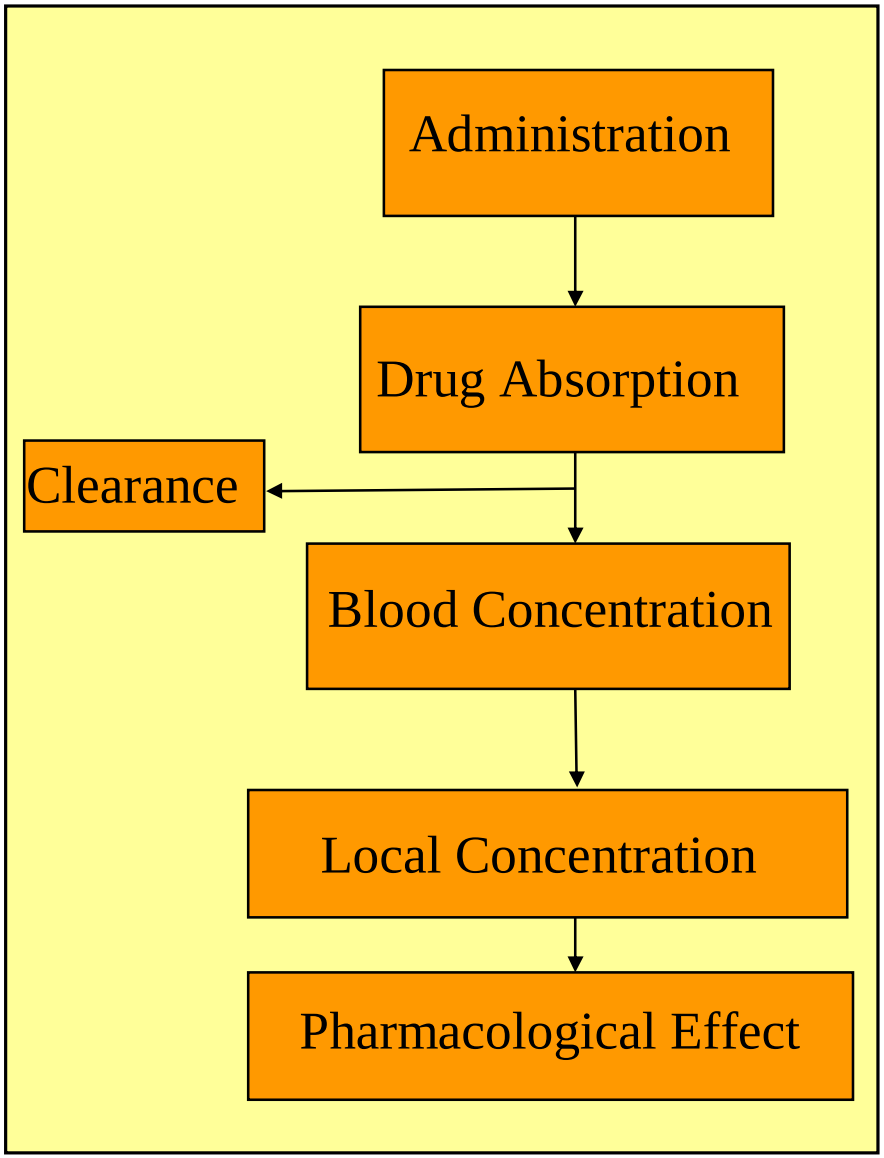
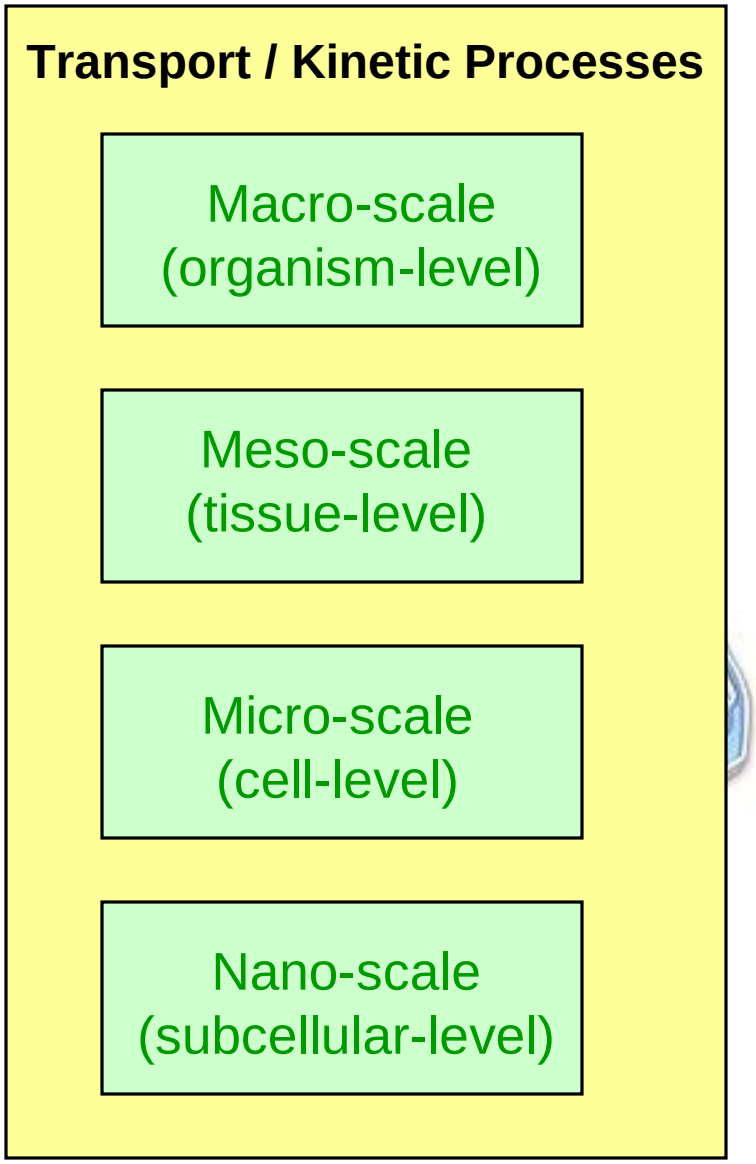
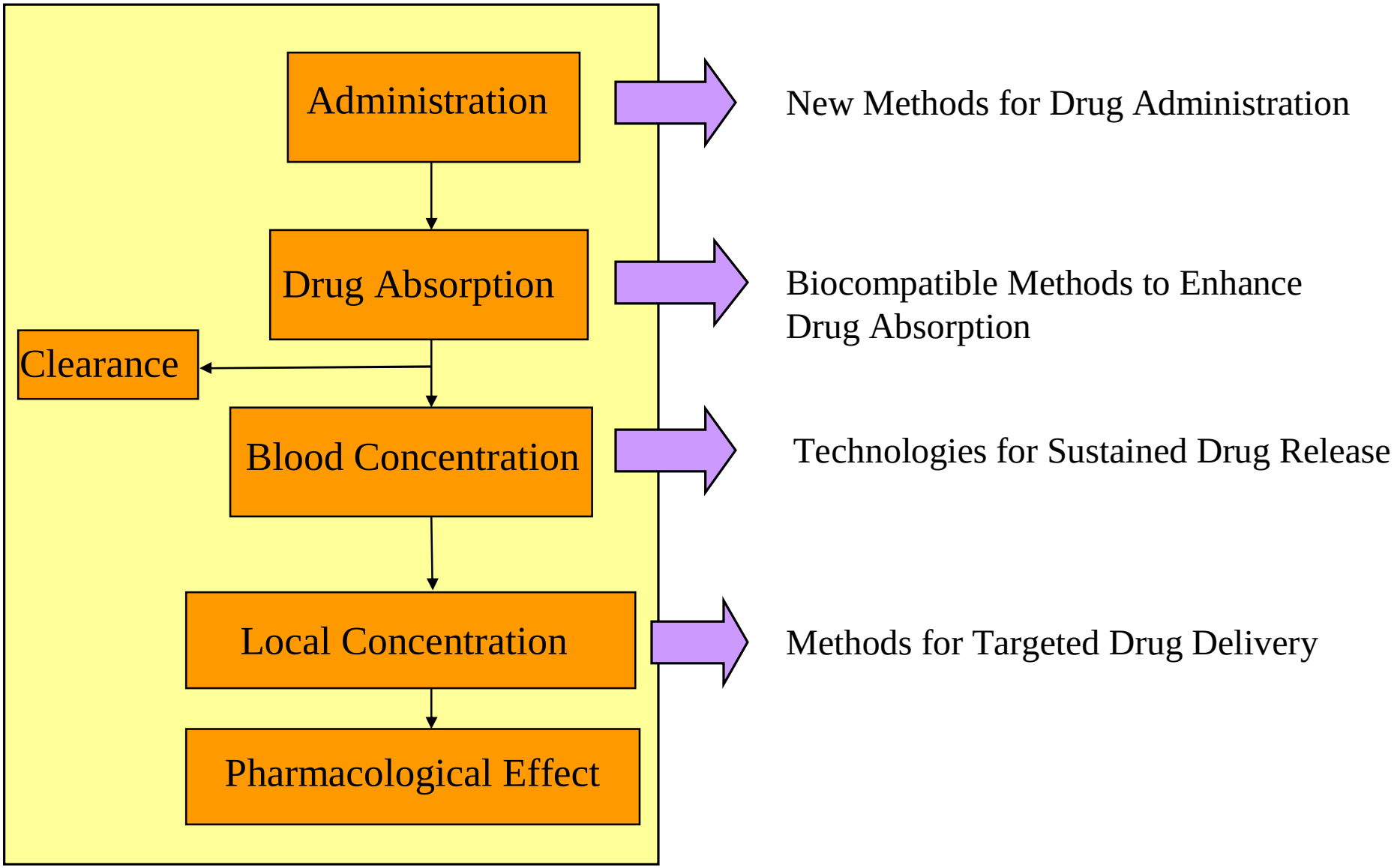
Drug Delivery: Converting Molecules into Therapies





Drug Delivery: Technology Development



Drug Administration: Pills and Injections

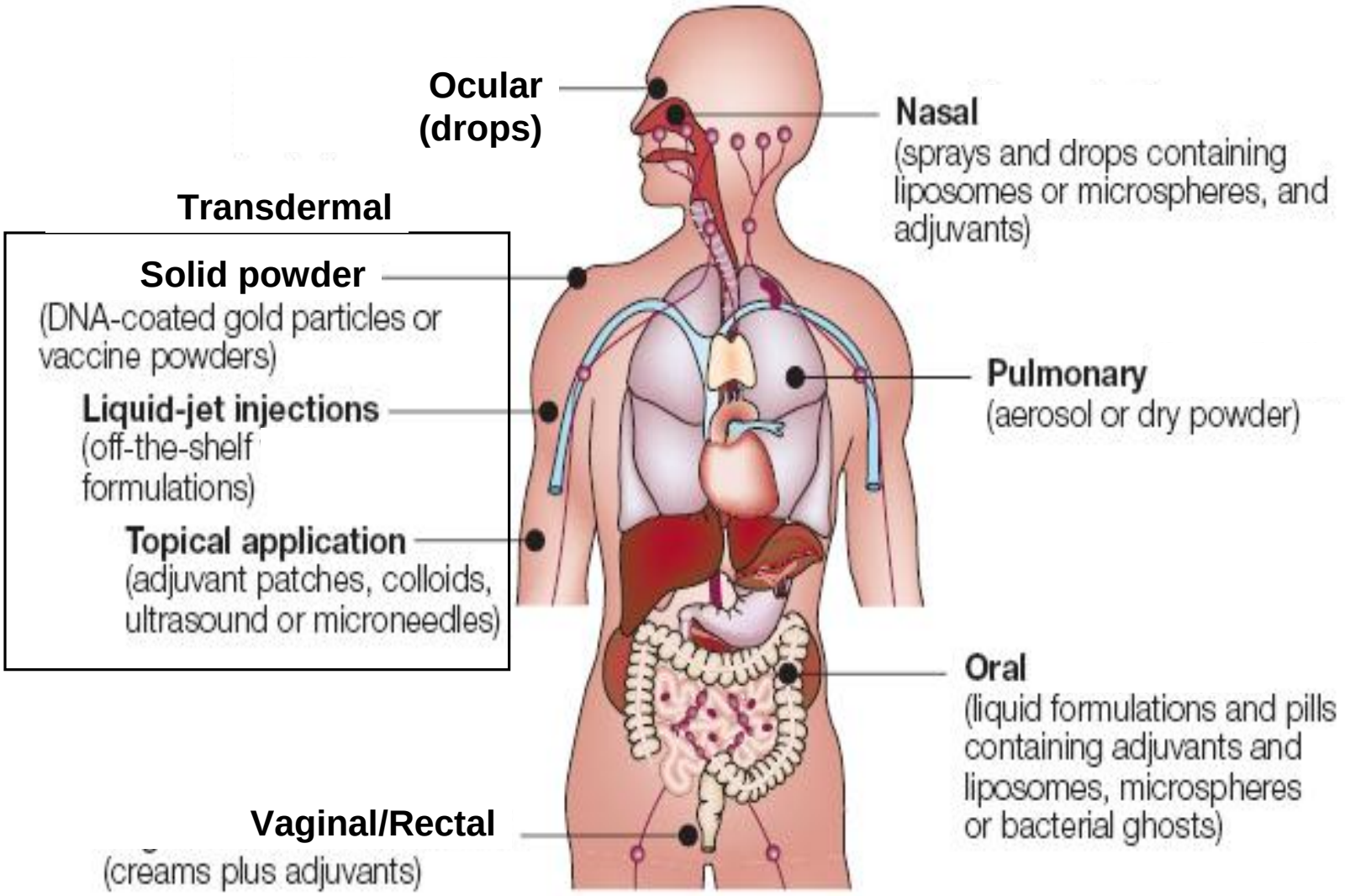
- Injections: Only route for protein drugs
  - Vaccines, Insulin, Growth Hormones
  - 12 billion injections performed annually

- Issues with needles
  - Pain and anxiety
  - Non-compliance (> $100 billion per year)
  - Inappropriate use (millions of cases of HBV/HIV)

- New Methods
  - Non or Minimally Invasive
  - Easy-to-use
  - Minimal Patient Attention

Popular Mechanics, June 2003

Alternate Routes of Drug Administration



Mitragotri, Nature Reviews Immunology, 2005

Transdermal Drug Delivery

- Advantages

  - Painless Method of Drug Administration
  - No Stomach degradation
  - Easy Termination

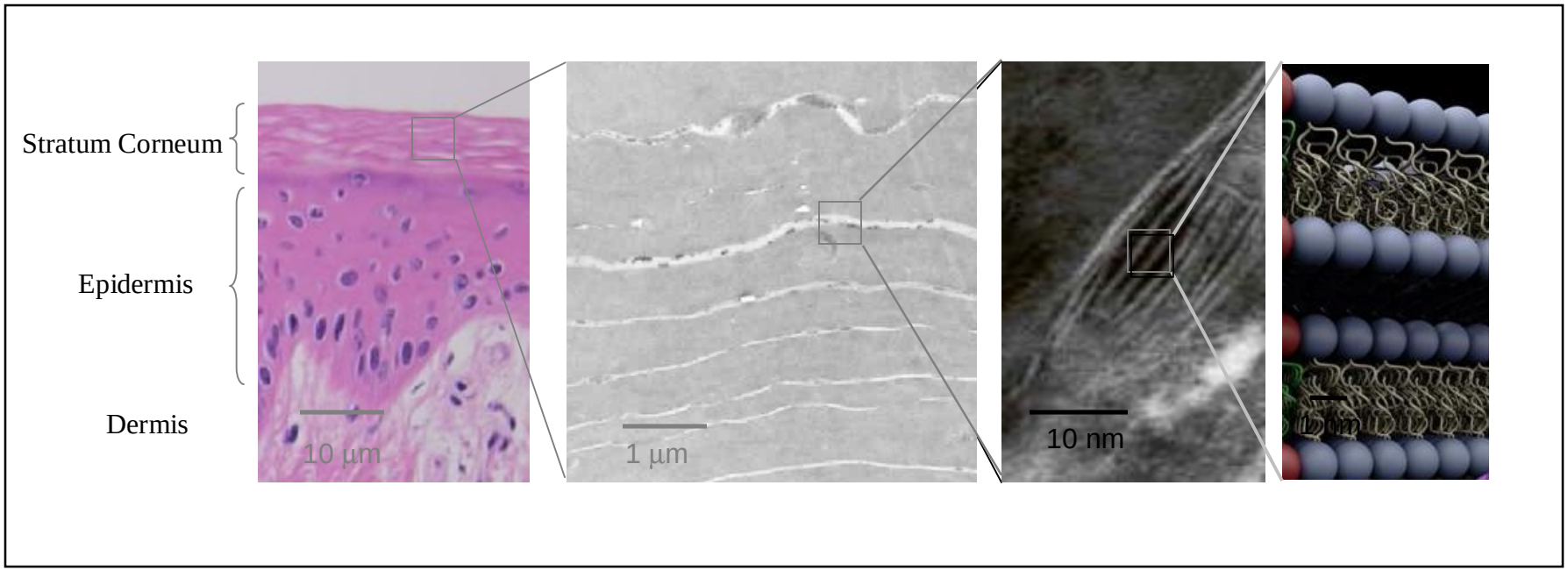
- Limitations

  - Low Skin Permeability
  - Used for only a few Drugs (MW< 400)

    Nicotine, Estradiol, Testosterone, etc.

Prausnitz, Mitragotri, Langer, Nature Reviews Drug Discovery, 2004

Skin is an Outstanding Barrier to Molecular Transport

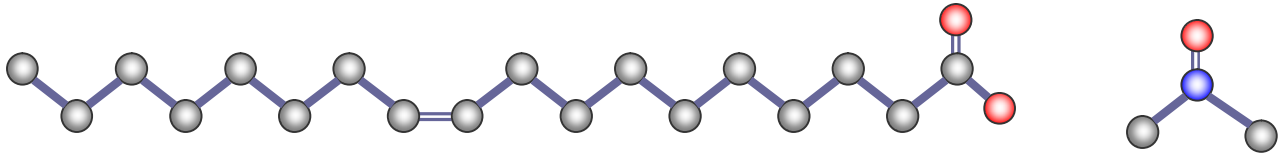


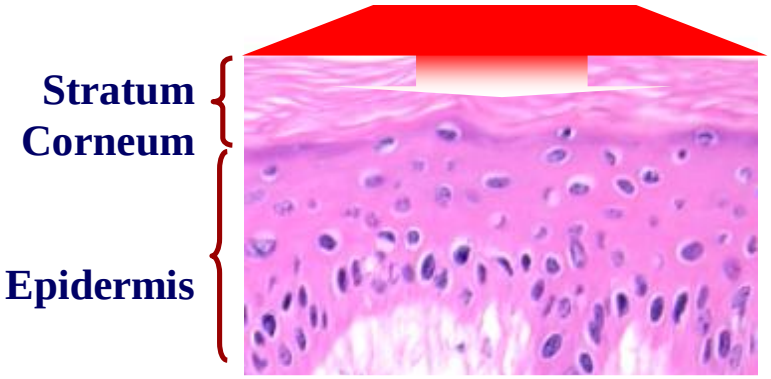
Stratum Corneum (topmost 15 mm layer) is the main barrier

Lipid bilayers are the primary building blocks of the barrier

Goal: Develop Strategies to Increase Skin Permeability to Drugs

Chemicals to Enhance Skin Permeability



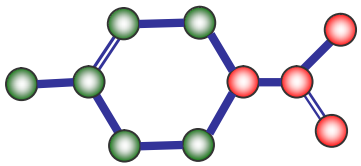


Safe, but not potent

Potent, but not safe

Can we design chemicals that are both safe and potent?

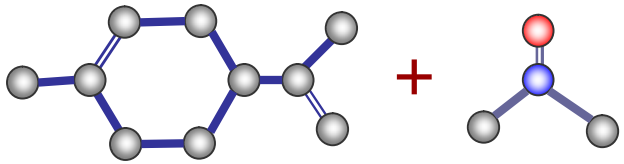
Approach I



Design and discovery of new Chemicals from first principles

Karande, Jain & Mitragotri, PNAS, 102:4688, 2005

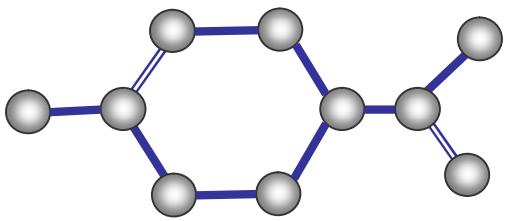
Approach II



Combining specific Chemicals to form mixtures

Karande, Jain & Mitragotri, Nature Biotechnology, 22:192, 2004

Design of Potent and Safe Mixtures of Chemicals



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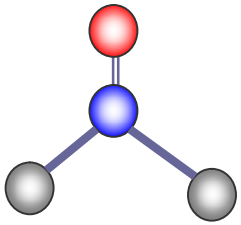
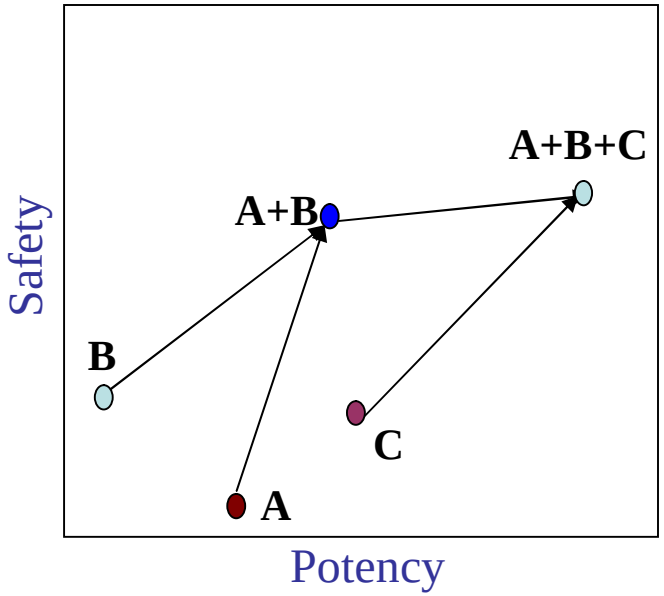
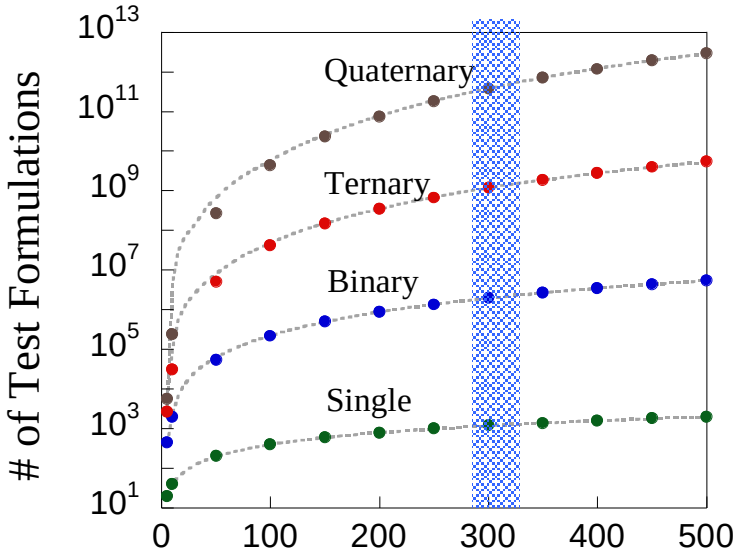






Performance of mixtures is difficult to predict
-Strong interactions

Massive Experimental Space

- High throughput methods are required to screen the experimental space

- Such methods have been developed and have led to the discovery of novel formulations

Ultrasound to Enhance Skin Permeability

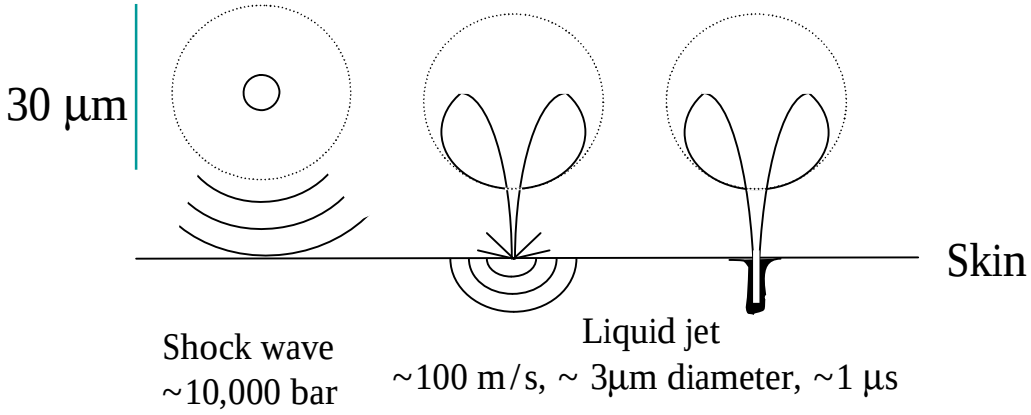
- Ultrasound Pretreatment for a Short Time to Permeabilize Skin
- Skin Remains Permeable for Several Hours (12 hours)
- Drug is Placed on the Skin for Sustained Delivery

- Drugs delivered (pre-clinical)
  - Insulin, heparin, vaccines

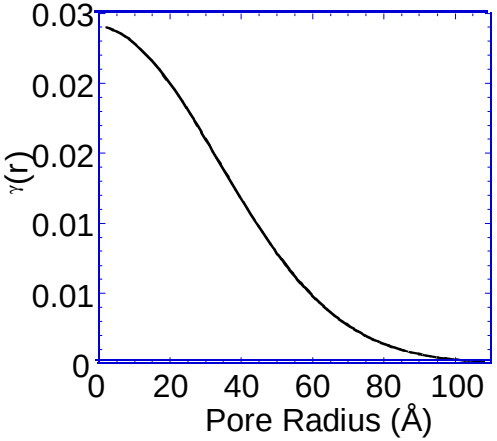
- Approved for use in humans for local anesthesia

Mechanism: Cavitation-mediated Changes in Skin

• Cavitation on the skin surface generates shock waves on the skin surface and temporarily disrupts skin structure

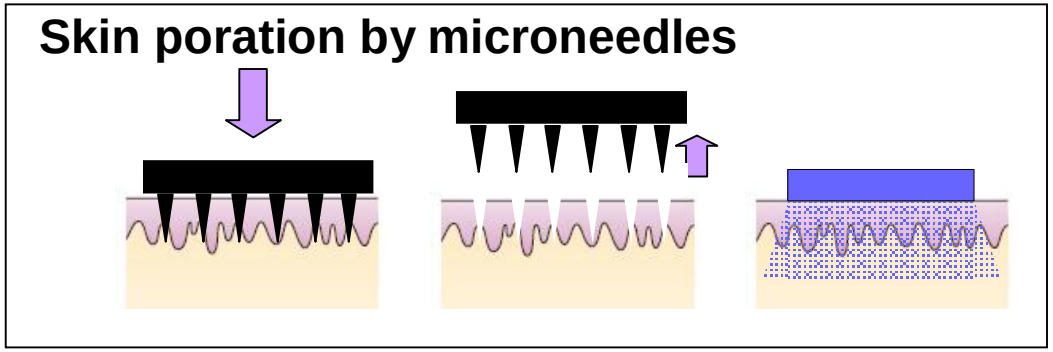


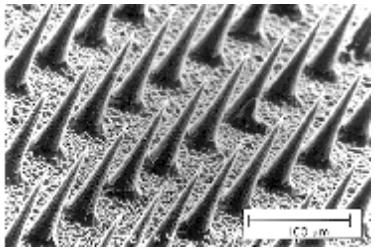
• Structural changes in the skin are molecular in nature

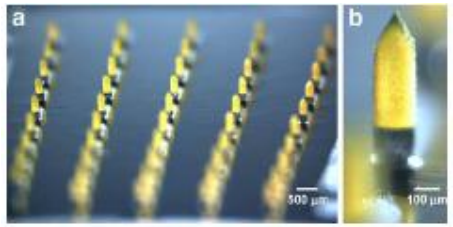


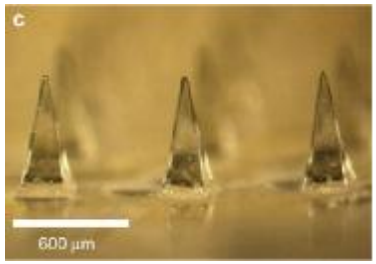
>99% pores are smaller than 100 angstroms in radius

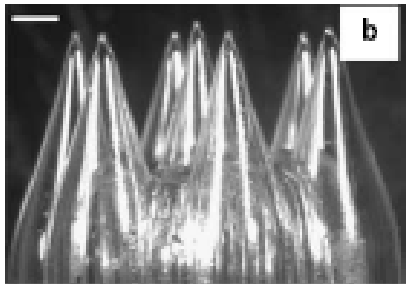
Microneedles for Skin Penetration







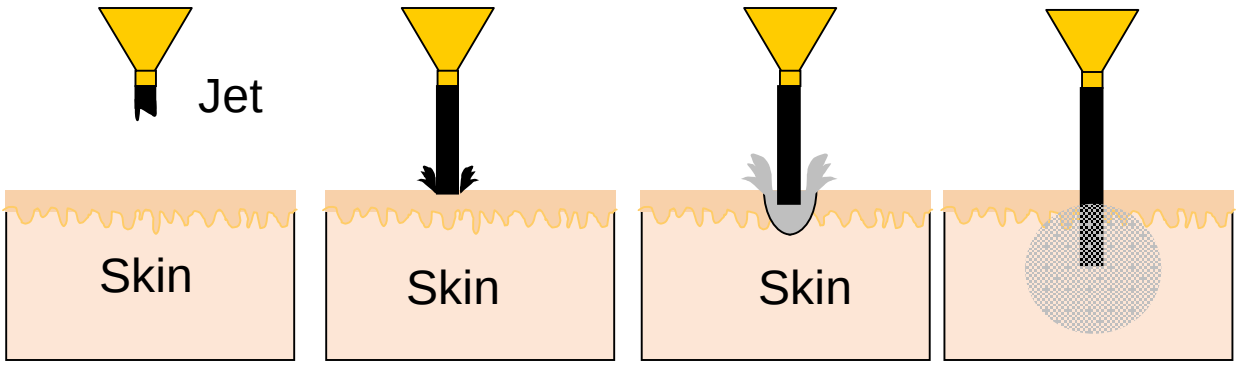




Images: Mark Prausnitz

Needle-free Jet Injectors

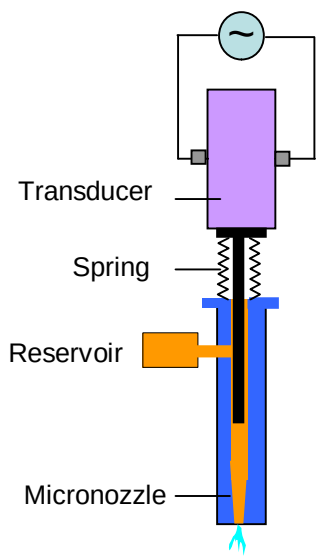
- Attractive Alternative to Needles
  - Around since 1950
  - Used extensively for mass vaccination in 1960's
  - Not very popular for delivery of drugs (pain/bruising)
  - Mechanism



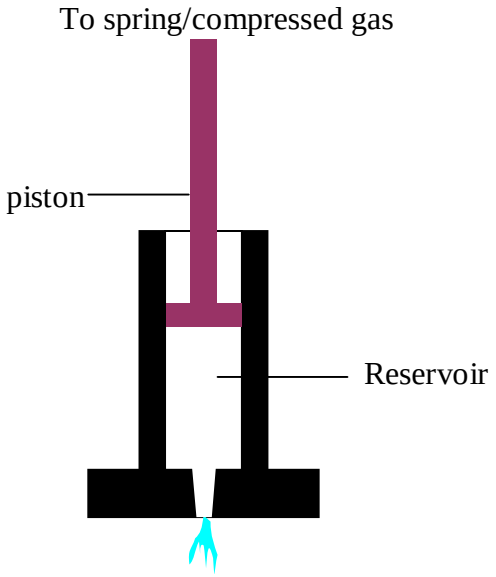
  - New designs of jet injectors are required
    - Smaller, gentler yet effective devices

Mitragotri, *Nature Reviews Drug Discovery*, 2006

Nanoliter Pulsed Microjet



(a) Microjet Injector



(b) Conventional Jet Injector

Mode of Operation:	Continuous	Discrete
Nozzle diameter:	50-100 µm	75-200 µm
Exit velocity:	>100 m/s	>150 m/s
Target tissue:	Epidermis	Dermis/subcutaneous tissue
Dose Precision:	2-15 nl	30-100 µl
Injection volumes:	1µl/min	0.1-1 ml
Penetration depth:	200-400 µm	2-20 mm
Active control:	yes	No

- Pulsed microjet injector is a hybrid device between a conventional jet injector and a conventional transdermal patch
- Delivery of macromolecules (insulin) at a pre-clinical level

Mitragotri et al. *PNAS*, 2007

Summary

• Better methods of drug delivery represent a large unmet need

• Several technologies for needle-free delivery have demonstrated their capabilities

• The challenge now is make these technologies user-friendly and facilitate their integration