# Challenges for Advanced Drug Delivery

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**WORKSHOP ON INNOVATIONS IN PHARMACEUTICAL MANUFACTURING**

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**Washington, DC**

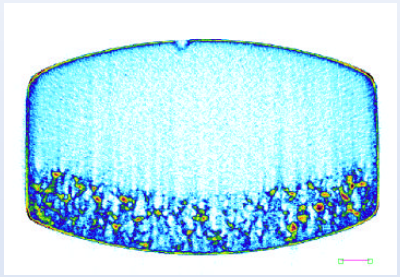
# Outline

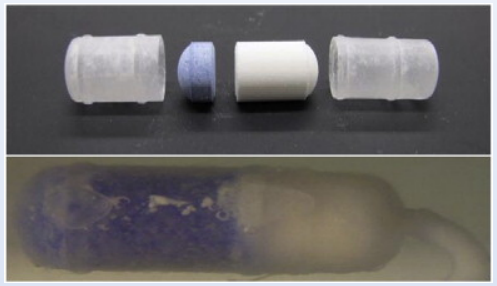
- Background – Dosage Form Innovation
- Scope of this talk
- Nature of the Challenges
- Dealing with complexity
- Potential Future Manufacturing Approaches

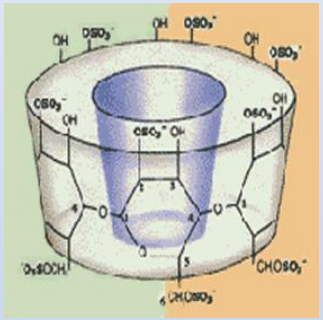
# “Traditional” Innovation

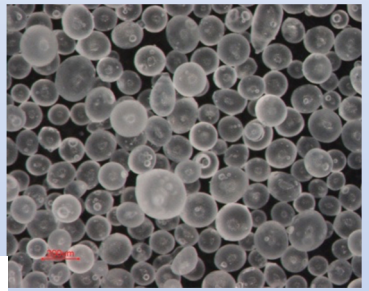
# 1990’s-2000’s

- Oral Controlled Release
- Solubilization
- Injectable Sustained Release
- Pulmonary Delivery
- Taste Masking
- Devices
  - Inhalation
  - Injection
  - Other (e.g. ophthalmic)










Genotropin Pen

Exubera

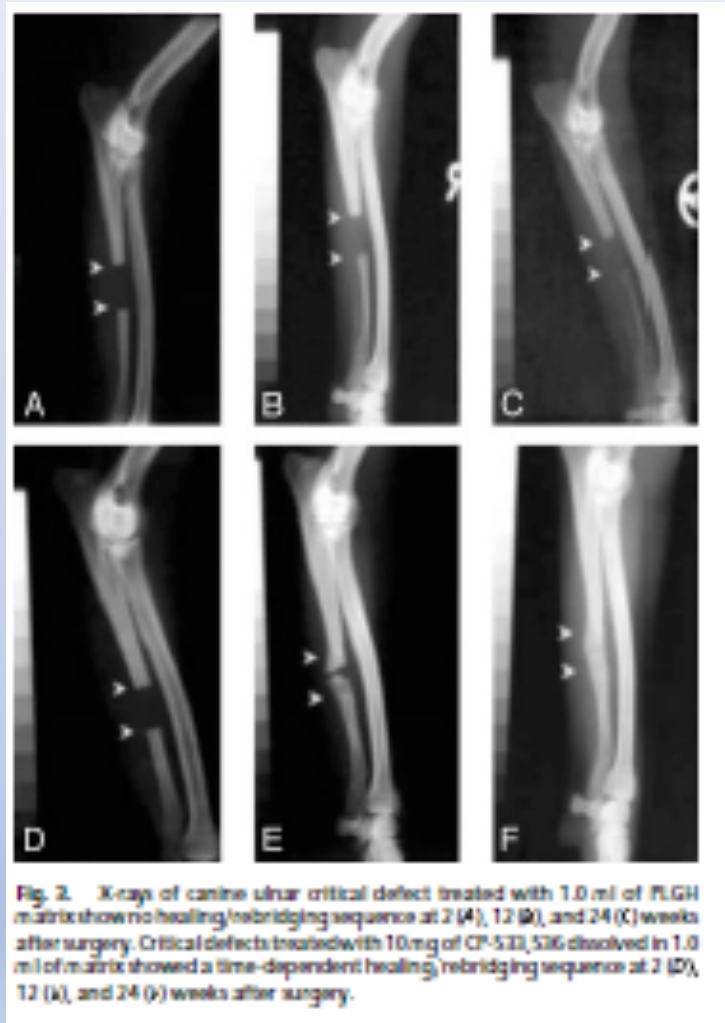



Fig. 2. X-rays of canine ulnar critical defect treated with 1.0 ml of PLGH matrix show no healing/rebridging sequence at 2 (A), 12 (B), and 24 (C) weeks after surgery. Critical defects treated with 10 mg of CP-533,536 dissolved in 1.0 ml of matrix showed a time-dependent healing/rebridging sequence at 2 (D), 12 (E), and 24 (F) weeks after surgery.

# Taking it to a new level

- Combine microelectronics and microfabrication technology with drug delivery.
- **Much enabling technology already exists**
- Prototypes in development.
- **Looking for right application to justify sophistication.**

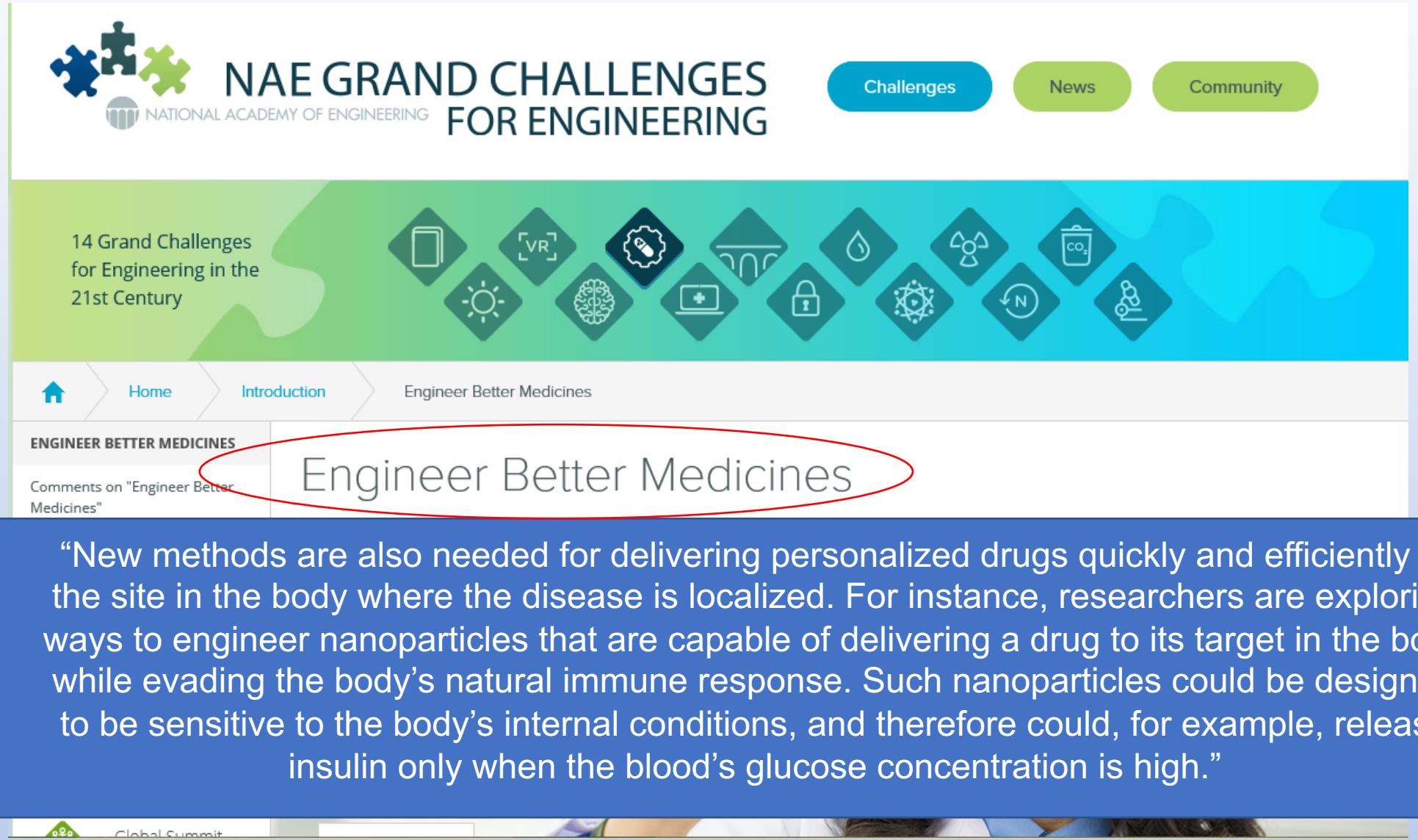
Limited by ***Ideas***

Proteus ingestible event marker (microchip)
http://www.proteusbiomed.com/technology/


http://www.mchips.com/products_drugdelivery.html
http://web.mit.edu/newsoffice/2012/wireless-drug-delivery-0216.html#


Nano Chip Inside

http://www.nanomedsys.com/



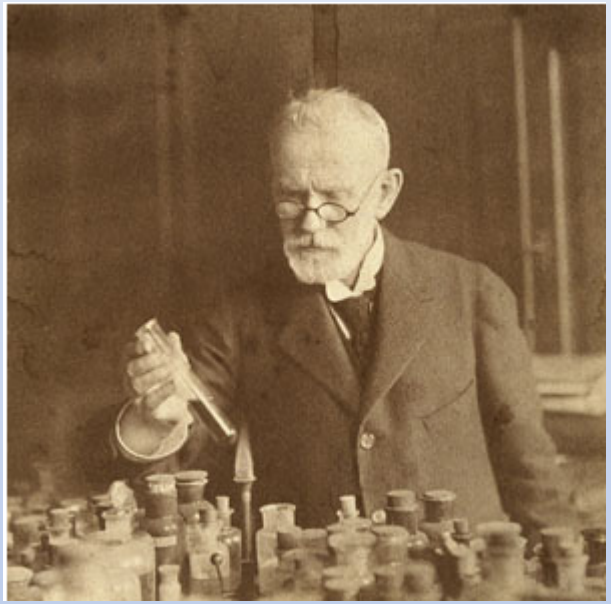

"New methods are also needed for delivering personalized drugs quickly and efficiently to the site in the body where the disease is localized. For instance, researchers are exploring ways to engineer nanoparticles that are capable of delivering a drug to its target in the body while evading the body's natural immune response. Such nanoparticles could be designed to be sensitive to the body's internal conditions, and therefore could, for example, release insulin only when the blood's glucose concentration is high."

Sounds like The Magic Bullet

http://www.engineeringchallenges.org/9129.aspx

# Is a “Magic Bullet” possible?

- Concept dates from late 1800’s.
- The term “magic bullet” coined by Paul Ehrlich ca. 1907, inspired by the story, *“Der Freischutz”.*
- A magic bullet would hit only its intended target.  (6 out of 7 times)
- **We should also ask: “Is there a magic target?”**
  - **Many of the cell-surface proteins used for targeting are present in almost all cells.**
    - **Challenge is to hit a subset of targets.**
  - **What are the best targets?**



# Why are nanocarriers the Magic Bullet?

- Size: **Small** enough to go where needed. Comparable to cellular components
- **Multifunctional** – large enough to include needed features
- **Versatile:** Many variables to work with, therefore almost limitless possibilities.
- Has been an area of **intense** interest, generating **thousands** of publications, and launching many small companies.

2015 search:

Search History (3 searches) *(close)*

| | # ▲ | Searches | Results |
|---|---|---|---|
| ☐ | 1 | (nanoparticles or nanocarriers).mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, bc, bo, bt, cb, cc, ds, ge, gl, gn, mc, mi, mq, or, ps, sq, st, tm, tn, id, sh, dm, mf, dv, kw] ▸ | 258180 |
| ☐ | 2 | drug delivery.mp. [mp=ti, ab, ot, nm, hw, kf, px, rx, ui, an, bc, bo, bt, cb, cc, ds, ge, gl, gn, mc, mi, mq, or, ps, sq, st, tm, tn, id, sh, dm, mf, dv, kw] ▸ | 240131 |
| ☐ | **3** | **1 and 2** ▸ | **36060** |

2020 *Science Direct* search:
"Nanoparticles .AND. Targeting": 131,561 results
.AND. Cancer: 48,908
.AND. Manufacturing: 9,531

Yet, there are **very few** products!

# Nanoparticles in the Clinic (2019)

- FDA or EMA **Approved** Products: 29
- Current Clinical Trials (including approved products): 75
- New technologies since 2016: 15
- Ratio of academic publications to clinical trials ~ 1000—prob not bad

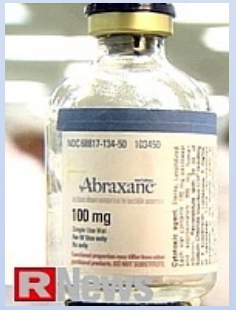
➢ But much of the academic research concerns concepts that are ***much more complex*** than the current clinical trial materials.

Anselmo AC, Mitragotri S.
Nanoparticles in the clinic: An update. Bioeng Transl Med. 2019;4:e10143. https://doi.org/10.1002/btm2.10143

# **Reformulating "old" drugs with** nanotechnology can improve safety

- Doxil™;
  - Reformulation of doxorubicin (liposomes)
  - Decreased cardiotoxicity compared to free drug
  - Marketed drug


- Abraxane™
  - Reformulation of paclitaxel (albumin bound)
  - Decreased immunotoxicity compared to free drug
  - Marketed drug

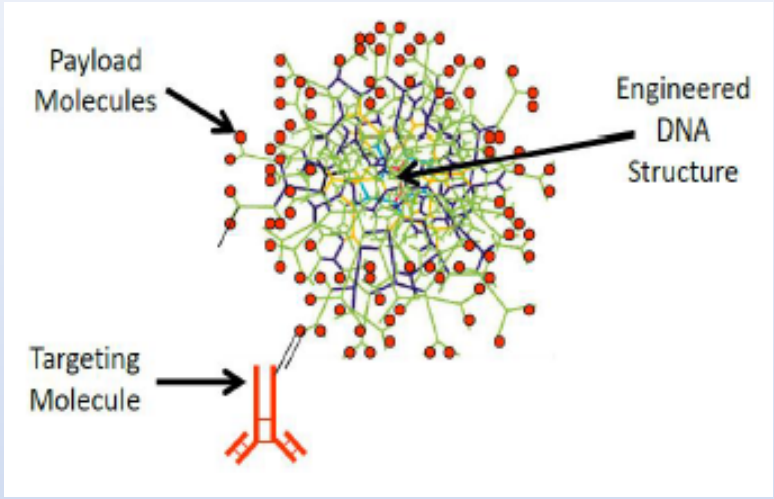


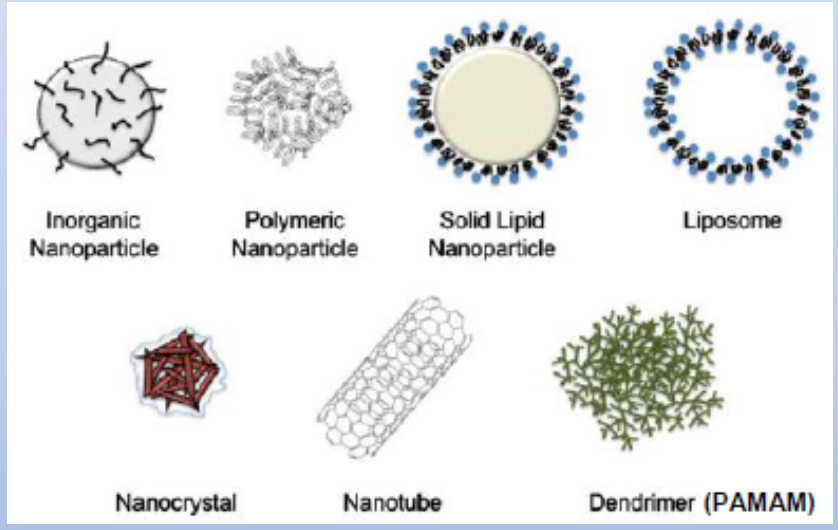

- Aurimune™
  - Reformulation of TNFα (Au nanoparticles)
  - Immunotoxicity decreased by 3-fold
  - In phase II clinical trials.


But **none** of these have been shown to be **more effective** than the original product.

# Tissue Targeted Delivery

- Science is still emerging
  - Vast published literature but
  - Few products
- Heavy biology and chemistry components; goes well beyond normal concept of formulation
- Interdisciplinary collaboration (Med Chem, Biology, Metabolism, Clinical, Formulation, Tox,…) absolutely essential from beginning
- Potential partners include academic and start-ups, with some small companies becoming established



# What does Big Pharma find frightening about targeted nanoparticles?

1. Complexity: Good in-vivo performance depends on overcoming multiple barriers, avoiding clearance mechanisms, and hitting targets precisely without unacceptable off-target effects.
2. Complexity: Multiple engineered parts, including an active molecule, the base particle, targeting ligands, linkers, excipients, …
3. Complexity: Multiple scientific disciplines needed to design and develop nanoparticles, and their activities are more inter-dependent than for conventional products. Often new skills and techniques are required.
4. Complexity: Manufacture of a very complex product is likely to be expensive.

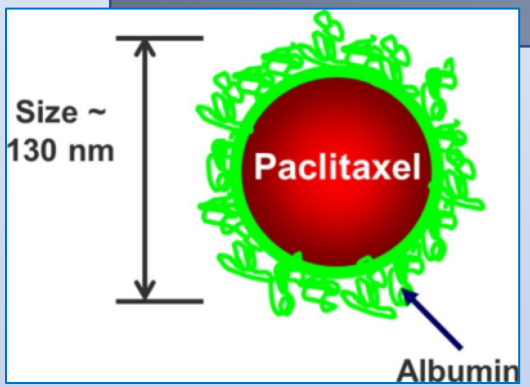
Right now, all approaches are seen as high risk.

# How complex does it have to be?

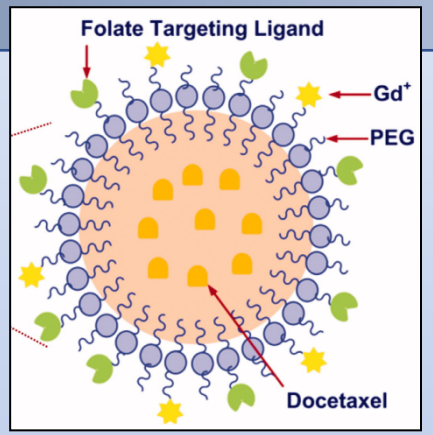
*"Everything should be made as simple as possible, but not simpler."*

- *Paraphrased from Einstein*

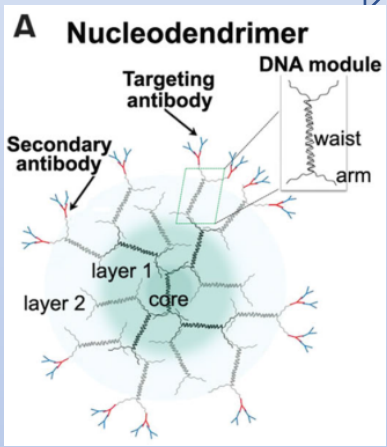
## Increasing Complexity



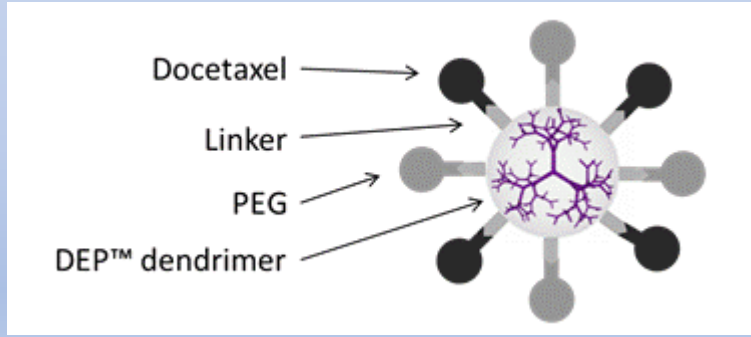

Desai, Neil. *AAPS Journal* 14.2 (2012): 282–295




Ganta *et al.*, Drug Deliv. 2015 Jul 21:1-13.




S.Muro, *Adv. Funct. Mater.* **2014**, *24*, 2899–2906




www.starpharma.com

Future

?

# How can we deal with this complexity?

Although a "simple" design might have only a few parts, separation of functions into different parts greatly simplifies optimization. There is a fundamental choice to make at the design stage.

*Traditional Formulation*:

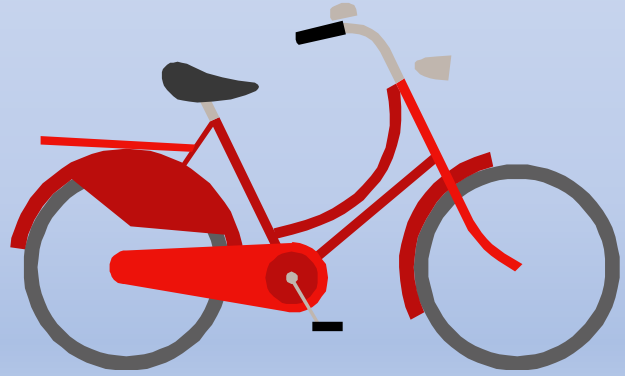
- A mixture of components is optimized to achieve a performance objective.
  - Used for most drug products
  - Hard to make improvements to individual components.

How many components are <u>required</u>?

1. Payload
2. Nanoparticle "skeleton"
3. Targeting ligand
4. Linker?
5. Stealth component?
6. Cell-penetrating component?
7. Imaging agent?
8. Release-triggering mechanism?
9. Other?

*Traditional Engineering Approach*:

- Functions are separated and assigned to different components, which can be improved separately.



# On the positive side…

- Better understanding of cellular mechanisms and barriers should enable more deliberate design of functionalized nanoparticles.
  - Complex, but not more complex than required.
- There is an opportunity to engineer small-scale processes for early studies that can be scaled up.
  - ➢ In many cases small-scale processes can supply clinical studies or small patient populations
- Wise use of evolving tools for studying and imaging biodistribution of nanoparticles can provide early feedback on whether they are going where they are supposed to.
- The National Cancer Institute has a dedicated Nanotechnology Characterization Laboratory that is resourced to help develop new nano-therapeutics.

# Common observed problems with engineered nano**materials**

- Pyrogenicity and endotoxin contamination
- Sterility and terminal sterilization
- Opsonization and MPS uptake
- Hemolysis
- Complement activation
- Thrombogenicity
  - Disseminated Intravascular Coagulation
- Cytokine storm

Common issues to all injectables

Expected with NP

Frequently observed with NP; can be problematic

*Highly undesired!*

"Nanoparticle Interactions with the Immune System" *Nanomedicines Alliance Industry Symposium,* Marina A. Dobrovolskaia, Ph.D. Nanotechnology Characterization Lab, March 7, 2013

# Nanoparticles aren't just drugs

- Have all the issues associated with drugs, but also
  - Carrier particles
  - Chemical linkers (if used)
  - Targeting moieties (if used)
  - Imaging moieties (if used)
  - Stealth technology (if used)
  - Etc.
- These are complex structures that have a ***surface that interacts with biological components*** (e.g. clotting mechanisms, immune system).
  - Need to think of them as ***biomaterials***.
- Do surface properties depend on ***process***?
  - Can they be independent of process?
    - ➢Implications for design and manufacturing.

# Gap between academic preparation and manufacturing

A typical prep in an academic publication from a reputable lab:

*"…Next 0.2, 1 or 2ml of this solution were pipeted into vials containing 100mg blend polymers and volumed up to 2ml with chloroform…*

*….ultracentrifugation….lyophilization…"*

➢Obviously, process would be re-worked in industrial development.

*PLGA-PEG nanoparticles for targeted delivery of mTOR/PI3 kinase inhibitor dactolisib to inflamed endothelium*, Gholizadeh *et al.,* Int. J. Pharm. **548**(2) 747-758 (2018)

# Can these sophisticated systems be manufactured?

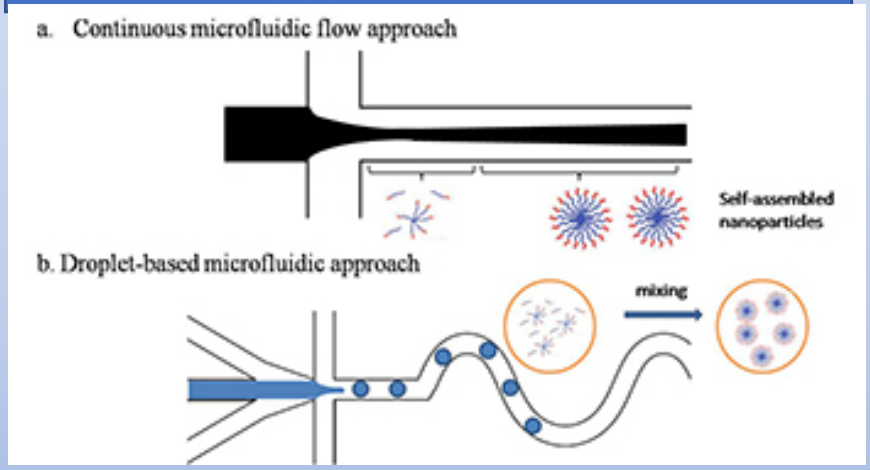
- **Yes**, but process design must be planned early in development. Consider:
- Difference between lab scale and commercial scale
- Most lab glassware operations are “batch” mode
- Continuous operations offer some attractive features for scale-up.
- Is it possible to do “screening” experiments at small scale but using processes that can be scaled up?
  - Microfluidics or “small” fluidics may offer some opportunities

Understand variables and dynamics and do traditional scale-up

Syrris Ltd.

Can scale-up be avoided entirely?

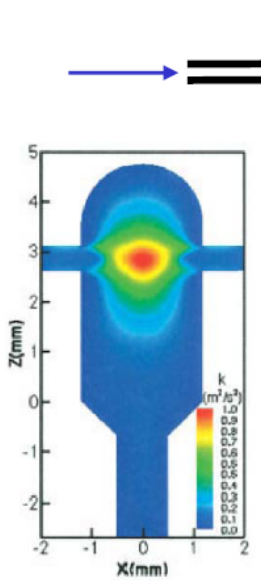
Create massively parallel equipment and run at “same” scale as for early experiments




Chun-Xia Zhao, http://www.aibn.uq.edu.au/microfluidic-platform-technology

Top-down vs. bottom-up: Control by chemistry/thermodynamics or by process?

# One possibility: Confined impinging jet micro-reactors



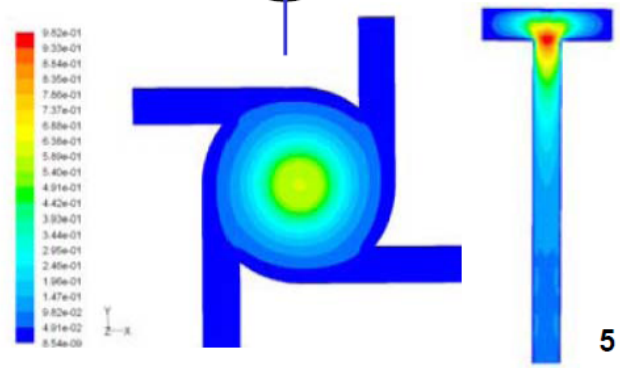

$$\mathrm{Re} = \frac{\rho V D}{\mu}$$

Micro-mixing by impinging streams of equal momentum

Micro-mixing by tangential streams of equal/non-equal momentum

$$\mathrm{Re} = \sum_{i=1,N} \frac{\rho_i V_i D_i}{\mu_i}$$

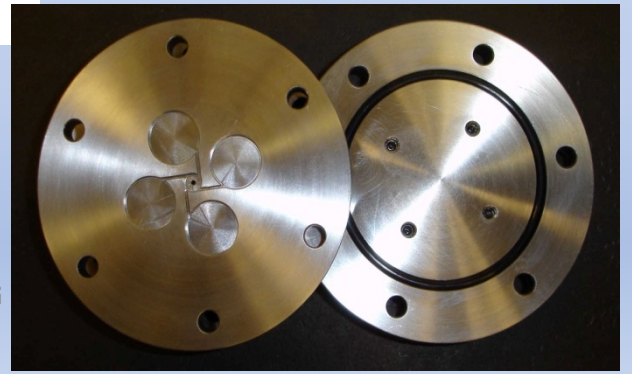
Re = Reynold's Number
ρ = density
V = velocity
D = characteristic dimension
μ = viscosity



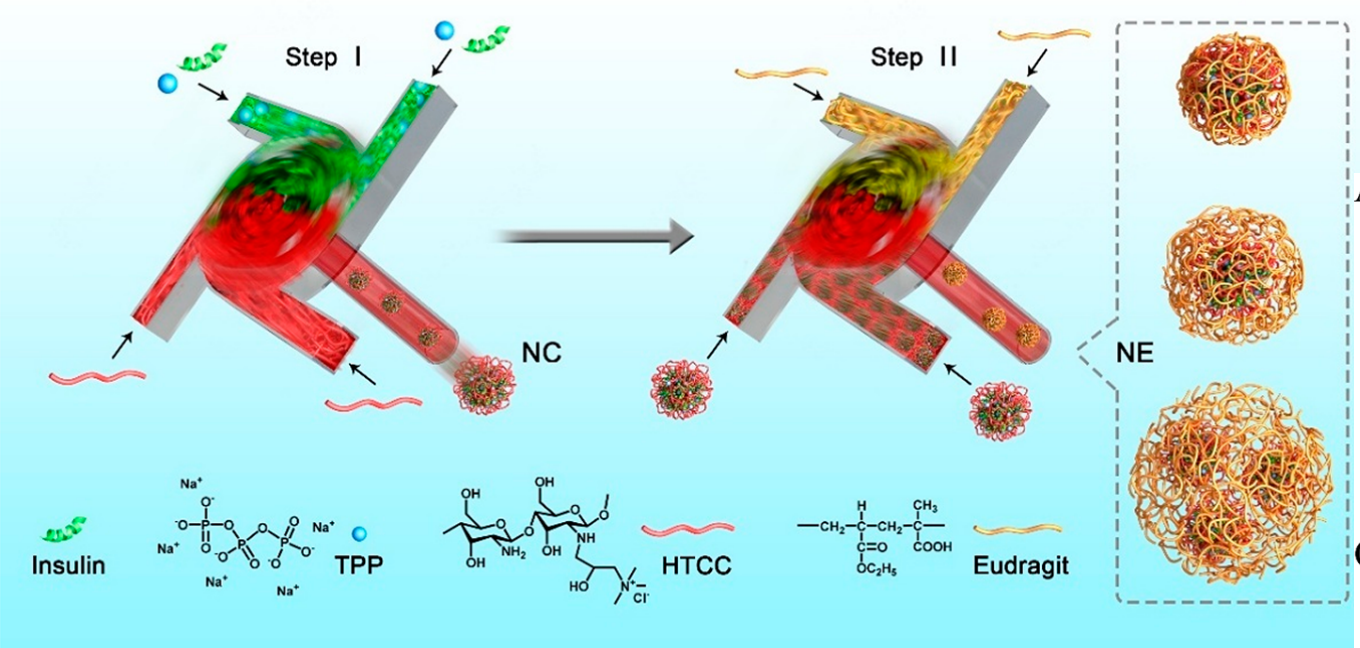
Y. Liu, R.K. Prud'homme *et al.*, *Chem. Eng. Sci.* 63 (2008) 2892-2842
B.K. Johnson and R.K. Prud'homme, *AIChE J.* 49(2002) 2264-2282

5

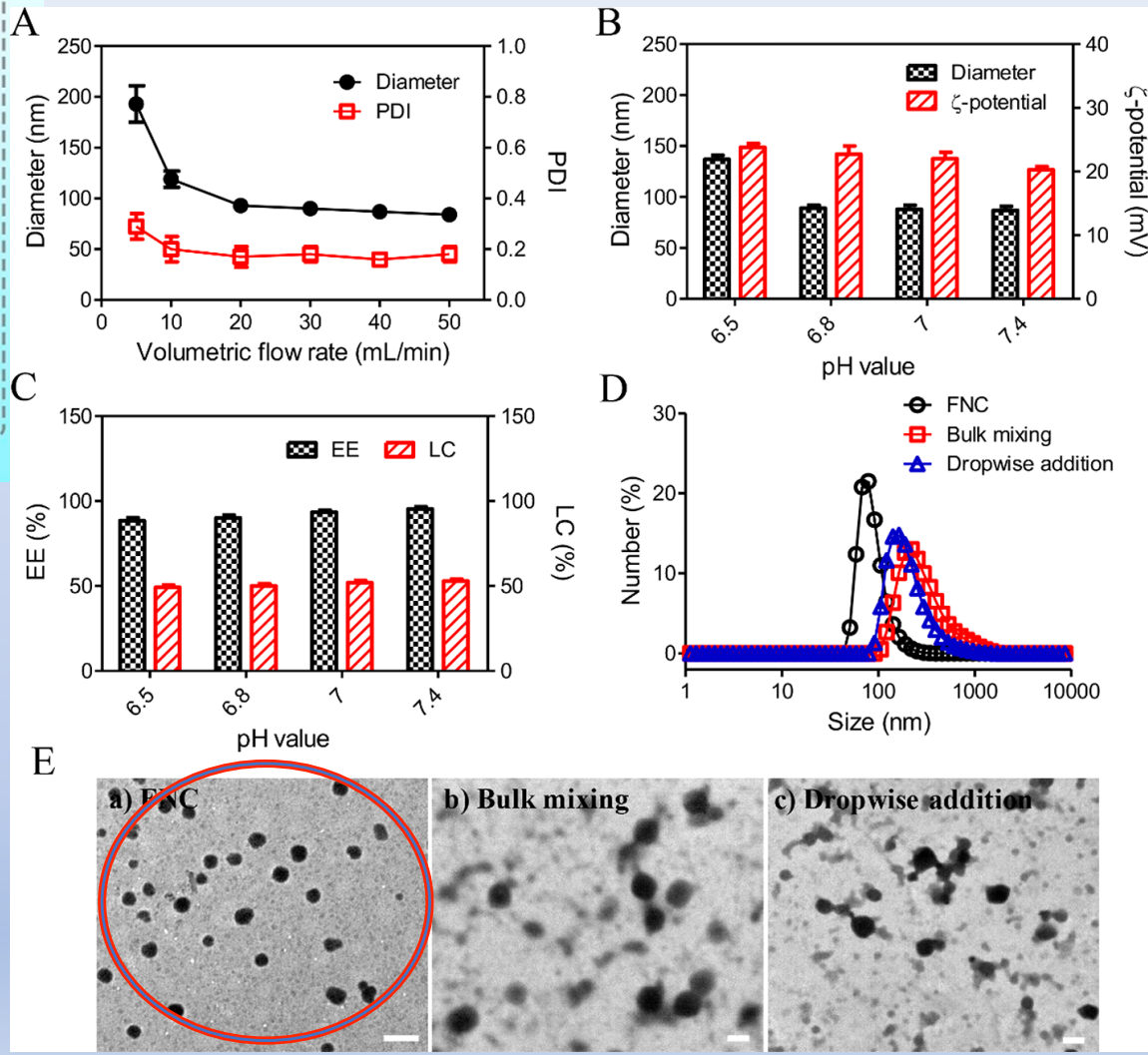
Has been scaled to tons per day.
(Slide courtesy of Robert Prud'homme)



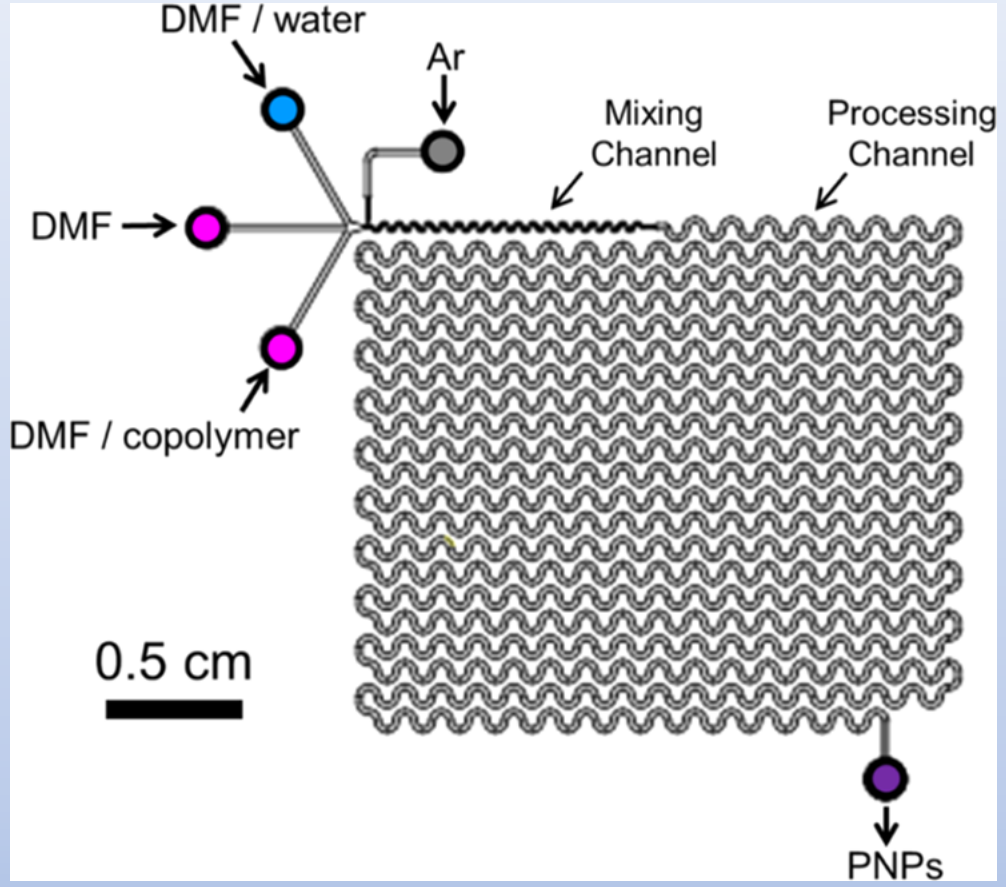
# Example: Flash Nano-Complexation

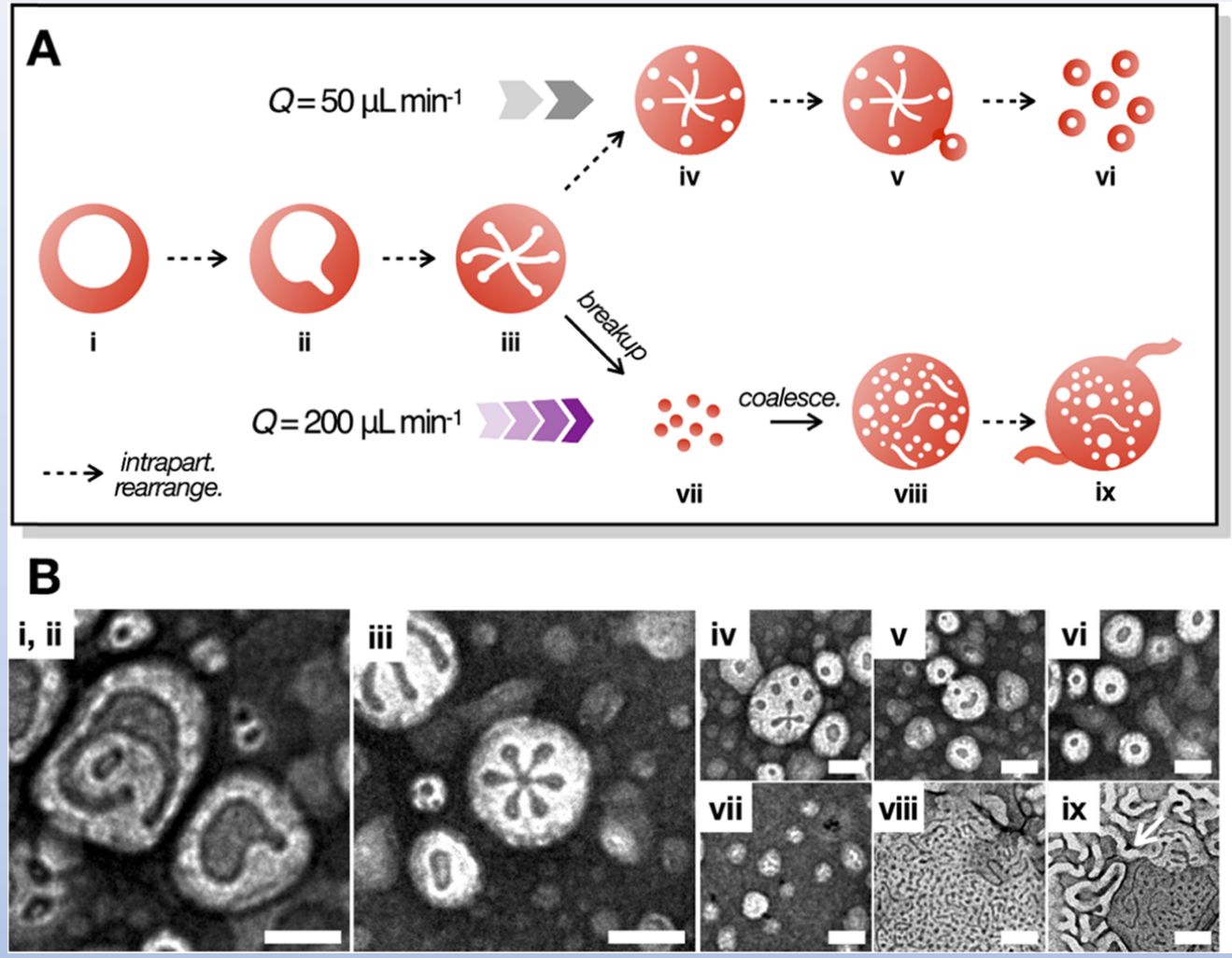



Sun *et al.,* Biomacromolecules 2019, 20, 528−538



# Microfluidic approach




Huang *et al.,* ACS Appl. Mater. Interfaces 2020, 12, 177−190

# Key investments needed for these manufacturing approaches

- Sensors & Analytical Techniques
- Controls
- Data analytics
- Computational modeling
- Workforce planning:  Unfamiliar approaches will require up-skilling of personnel in various functions
- Strategy to go from lab bench to clinical manufacturing to commercial.
  - Platform technologies?

# Summary

- With a small number of approved products and a slightly larger number of products in clinical trials, it is reasonable to assume that nanoparticle approaches to therapy will continue to increase in importance.
- Intense academic interest in nanoparticle approaches (targeted or otherwise) makes it likely that some highly complex products could reach IND stage in the next 5-10 years.
- These new products could challenge the ability of Pharma to manufacture them.
- Thoughtful design of products and processes at early stages should ease development
- Nanoparticles are *materials* with *surfaces* that affect behavior and performance
- Industry and Regulatory Authorities should be receptive to alternative manufacturing paradigms that could enable manufacture of these challenging products.