Medicines for the XXI Century

by
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Where I come from

Born in Mexico, in a small town, Pahuatlán (pop. 20,000)

Grew up in Mexico City (pop. 20,000,000)
Whom I live for

Met my wife Cecilia in Mexico City we studied in the same school. We married in 1988 in Tucson Arizona.

David (20) was born in Lake Forest Illinois near Chicago, came to California when he was 2 months old

Luis (15) was born in California at El Camino Hospital in Mountain View

We like to spend our vacation time in Mexico in a small beach town or visiting my parents in the small town I was born
Where I’ve been

Went to school at the National University in Mexico. Studied Pharmaceutics (1984)

Came to the USA in 1987 to pursue graduate studies on a Mexican government scholarship

Started graduate studies at the University of Arizona, completed credit units for a M.S. in Chemical Engineering

Earned Ph.D. in Pharmaceutics at the University of Michigan.

My wife Cecilia also got her M.S. and Ph.D. in Chemistry from the University of Michigan
My first job at Parke Davis (Pfizer) where Lipitor was discovered worked on gabapentin an antiepileptic medicine (1993)

Abbott
Worked in Abbot in Chicago developing AIDS medicines (1994-1996)

My current job at Pearl Therapeutics (AstraZeneca) developing inhaled medications for asthma and COPD

Pearl

inhal
Moved to California to work at Inhale, a start up, that later became Nektar where I helped develop inhaled insulin to treat diabetes, inhaled antibiotics and pegylated medicines for pain treatment (1996-2007)

AstraZeneca

Worked at Aridis, a start up, in South San José where I developed thermally stable vaccines (2007-2009)
MEDICINES

http://www.blacktriangle.org/blog/images/slide1.jpg
The drug development process

Research team formed and objectives set
Novel chemical or biomolecule discovered
Efficacy and safety test “in vitro” and “in vivo” to inform selection of lead candidates
Dosage form design, formulation, stability, scale-up, quality control, chronic safety in animals
Company files Investigational New Drug (IND) application with FDA

Drug is approved for marketing
FDA reviews New Drug Application (NDA) with FDA
Phase III clinical studies in large group of patients
Phase II clinical studies in small group of patients to demonstrate efficacy
Phase I studies in healthy humans (volunteers) to test for safety

http://www.nature.com/nrd/journal/v3/n10/fig_tab/nrd1523_F1.html

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Conventional Drug Delivery
> 80% are oral dosage forms

Tablets and capsules

Injections (parenteral Dosage forms)

Suppositories

Eye or Ear drops

MDI

DPI

Fast dissolve films or tablets

Nasal Spray

Inhalers

Ointments and creams

Patches

http://www.pharmaceutical-technology.com

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Formulation/Device/Route of Administration
Nicotine Pharmacokinetic Profile

![Chart showing nicotine levels over time for different routes of administration.]

- Cigarette, inhalation
- Nasal
- Chewing gum
- Patch
- MDI inhalation

**Time [min]**

**Nicotine venous plasma [ng/mL]**

**SMOKING KILLS**

Patent Application US20060018840 A

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FDA Approved products I have helped developed

- Inhaled insulin for the treatment of diabetes
- Protease inhibitor for the treatment of AIDS
- Inhaled antibiotic for the treatment of lung infections in CF patients
- Opioid antagonist for the treatment of opioid induced constipation during pain management
- Inhaled bronchodilators for the treatment of asthma and COPD
low solubility required lots of “educated” trial and error which end up in a complicated recipe to make it work

Class II
Low solubility
High permeability

Ritonavir
HIV protease inhibitor

Dissolve Ritonavir at 70 °C in Ethanol Glycerin Gelucire (PEG-32 glyceryl palmitostearate) Labrafil (Oleoyl polyoxyxyl-6 glycerides)

Fill Capsule in high speed filling machine while warm (softening point 58 °C)

Close and apply band

Polish

Packaging

Semisolid filled hard shell capsule

Secret recipe

Problem solved through formulation!

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Ritonavir is manufactured as Norvir by Abbott. The Food and Drug Administration (FDA) approved ritonavir on March 1, 1996, making it the seventh approved antiretroviral drug and the second approved protease inhibitor in the United States. Within 2 years of the approval of ritonavir (and of saquinavir a few months earlier), the U.S. HIV-associated death rate fell from over 40,000 per year to about 17,000.
PEGylated naloxol a peripherally-selective opioid antagonist for the treatment of opioid-induced constipation

PEGylation prevents BBB penetration avoiding suppression of opioid CNS effect (including analgesia). Naloxegol is available to compete with GI opioid receptors.
PEGylated naloxol is a honey-like liquid, had to be made into crystals to be able to make a tablet.

Combining naloxegol with all acid counterions available (salt selection)

Problem solved through formulation!
Formulation to discourage addiction

Coated to slow down uptake, reduce “high”

Problem solved through formulation!

Coated granules to low down uptake, reduce “high”

DON’T DO DRUGS
MAKE MEDICINES
Fluidized bed coating
New Therapeutic Agents
Biotechnology: Medicines for the 21st Century

Protein therapeutics

Immunotherapy mAb

Nanoparticles

Vaccines

Nanomachines

PEGylated Proteins

Nanocrystals

Virosomes
Drug Delivery of Biotechnology Products

• Novel Biotechnology therapeutic approaches:
  – peptides, proteins, hormones, oligonucleotides, antibodies, siRNA, vaccines (polysaccharides, proteins, attenuated viruses and bacteria)

• Old time delivery solution: needle
  – Pain, fear of needles leads to poor compliance

• New delivery solution: transdermal, inhalation, nasal, needle-less injection
The future of drug delivery: Fantastic Voyage

As exciting and futuristic the images may look, they still need a “low tech” needle to be delivered into the body...
Drug delivery via *microparticles*

- Protein bound drug
- Liposomes
- Virosomes
- PEGylated Proteins
- Nanomachines
- Nanocrystals
- Spray dried composite particles
- Spray dried particles
Pulmonary Delivery of Proteins

Bioavailability = \eta_{\text{process}} \cdot \eta_{\text{delivery}} \cdot \eta_{\text{deposition}} \cdot \eta_{\text{abs}}
Pulmonary deposition is driven by the Aerodynamic Particle Size

Byron, P.R. J Pharm Sci, 1986, 75, 433-438
The Deep Lung Provides a large surface area to access the blood stream
EXUBERA Pulmonary delivery of insulin: a first in the industry

Innovation
The Impossible Made Possible
Kerry A. Dolan 05.22.06

The Exubera insulin inhaler is a tiny triumph of engineering and persistence.

“Lechuga-Ballesteros’ group hunted for a recipe for dried insulin, a daunting trick because insulin is biologically active only in a liquid state. To make insulin powder that could be safely rehydrated, they had to find ingredients to surround the molecule to prevent it from turning useless in its dry state--what Lechuga-Ballesteros calls "the dough that surrounds the insulin raisins."…

Inhaled Insulin


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Microparticles provides room temperature stability and enable alternative routes of delivery for insulin

- Spray dried microparticles have appropriate characteristics for pulmonary deliver
- Proteins are room temperature stable for more than two years in dry amorphous powders


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Exubera the first non invasive delivery of insulin

Inhaled Insulin
TOBI PODHALER: Antibiotic carrying spray dried micro particles for inhalation improves quality of life of cystic fibrosis patients

FDA approved in 2013
Inhaled antibiotic in powder form
Faster administration, more effective than IV infusion

IV infusion: 70 mg/day over 30 minutes

Nebulized solution inhalation: 600 mg/day 2 inhalation sessions over 30 minutes

Dry powder inhalation: 224 mg/day 8 inhalations over 10 minutes

Inhalation achieves 10X Tobi concentrations in sputum and reduces systemic exposure 7X

Pulmonary drug delivery via spray dried microparticles in a Metered Dose Inhaler

Low solubility in propellant (Hydro Fluoro Alkanes) and low adhesive nature of porous particles results in longer flocculation, creaming times.

Conventional MDI

0 seconds → 5 seconds

Pearl MDI

0 seconds → 15 seconds → 30 seconds
Drug delivery via microparticles is more consistent than existing products

Combination inhalation product provides bioequivalency in combination therapy: a great advantage to rule out interactions and investigate combination synergy in clinical studies.

Bevespi FDA approved for the treatment of COPD

In 2013 AstraZeneca acquired Pearl Therapeutics formulation technology for $1.1B
Bringing vaccines to every corner of the world
The WHO has made a priority to break the cold chain

NEED: Heat resistant vaccines
Rotavirus is a common cause of severe diarrhea and vomiting in children, leading to about 600,000 deaths annually. Most of these occur in developing nations, where medical services to treat intestinal distress are not widely available. Rotavirus vaccine to prevent this illness is currently produced in a liquid or freeze-dried form that must be chilled for transport and storage, making it very expensive for use in impoverished areas. In addition, newborns sometimes spit out the liquid, a problem that is less likely to occur with a strip that sticks to and dissolves on the tongue in less than a minute.
Encasing Spray Dried Live Rotavirus Vaccine in Quick-Dissolving Oral Thin Films

Vaccine Titer (Log FFU/g) vs. Weeks of Storage at 25 °C, 37 °C, and 45 °C

- Liquid Vaccine
- Quick dissolving oral thin film

Breaking the cold chain

VACCINE & PLASTICIZER STABILIZERS

SPRAY DRY

RT stable powder

FILM-CASTING EXCIPIENTS

Solid dispersion film extrusion

Quick dissolving oral thin film
Nanomachines: R-Type Pyocins bactericidal protein complexes

DNA-free protein based structures naturally produced by bacteria as a mechanism defense against hostile bacteria

Figure 1. Scanning electron micrograph (left) of an R-type pyocin showing four of the six tail fibers, and a cartoon (right) indicating the major components of an R-type pyocin. The tail fibers are the major determinant of the pyocin’s killing spectrum and can be engineered to change target specificity.

www.avidbiotics.com
Williams et al. Retargeting R-Type Pyocins To Generate Novel Bactericidal Protein Complexes, APPLIED AND ENVIRONMENTAL MICROBIOLOGY, June 2008, Vol.74, No. 12, p. 3868–3876
Nanomachines: R-Type Pyocins

Killing mechanism

**Figure 2.** Cartoon of a pyocin landing on the surface of a sensitive bacterium, drilling thru the bacterial cell wall with its core, and killing the bacterium as the result of escaping vital bacterial molecules through its open core.
Enabling nanomedicine drug delivery via microparticles
How can you prepare for a career in Pharmaceutics (Ph.D. highly recommended)

Chemistry
- Organic Chemistry
- Physical Chemistry
- Analytical Chemistry
- Bioanalytical Chemistry
- Biochemistry

Mathematics

Biology

Chemical Engineering

Cooking!

Material Sciences

Pharmacology

Formulations!

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Where can you get a Ph. D. degree in Pharmaceutics
Thank you for your attention

“For I know the plans I have for you,” declares the LORD, “plans to prosper you and not to harm you, plans to give you hope and a future.” Jer. 29:11