Diabetes and Drug Development
Metabolic Syndrome (Syndrome X)

- Hyperinsulinemia
- Insulin Resistance
- Hyperglycemia
- Obesity (↑ visceral fat)

- Hypertension (↑ blood pressure)
  - ↑ LDL
  - ↓ HDL
  - ↑ Lipoproteins
  - ↑ Triglycerides
  - ↑ FFA
  - Dyslipidemia

Cardiovascular Disease

- Atherosclerosis
- Type II Diabetes
- Complications
  - Retinopathy
  - Renal failure
  - Circulatory
Pathogenesis of Type II Diabetes

Genetic Factors

Environmental Factors
- Obesity
- Physical Inactivity
- Age

Insulin Resistance

Impaired Glucose Tolerance

β-cell Failure

Liver
- Increased glucose production

Pancreas
- Impaired insulin secretion

Peripheral Tissues (Muscle)
- Insulin resistance

Type II Diabetes
**PPARs Are a Sub-family of Nuclear Receptors Involved in Metabolic Regulation**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Disease Indication</th>
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<tbody>
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<td>Fibrates</td>
<td>Hypertriglyceridemia</td>
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<tr>
<td>TZD</td>
<td>Hyperglycemia</td>
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*Taken from Rosen and Spiegelman (2001) *J. Biol. Chem.* **276**:37731-37734*
Avandia® Forms Direct Hydrogen Bonds with the AF2 Helix
Contemporary Drug Discovery

🌟 How has drug discovery process changed?
🌟 What significant advances in drug development?
🌟 How did molecular biology, genomics etc influence?
🌟 Will it deliver new, better drugs?
🌟 Why does it cost so much?
Different Types of Therapeutic Strategies

- Small synthetic or natural product drugs (aspirin)
- Biologics (vaccines, insulin, Antibodies, DNA/RNA)
- Gene Therapy (replace or insert new gene sequences)
- Stem Cell derived organ replacement
Early Pharmaceuticals -1950’s

- Originated as chemical companies
- Science largely driven by chemists
- Emphasis was exclusively on small molecules derived from medicinal chemical synthesis or natural product cpds
- No well defined molecular targets
- Little biological knowledge
- Used direct animal testing-few biochemical or cell-based assays
Modern Pharma / Biotechs - 1980’s

- Relies on cloning, sequencing, 3D structures
- Emphasis on protein based drugs - biologics (GH, insulin, tPa, interferon)
- Clone, express, over-produce target proteins and sell directly as drugs
- Largely limited to extracellular targets
- Delivery requires injection - not oral pills
Two Distinct Classes of Drug Products

**Small Molecules**
- Synthetic or natural cpds
- MW < 1Kd
- Oral, bio-available
- Both intra - extracellular Targets
- The classic Pill

**Biologics**
- Peptides, proteins, Antibodies, RNA, DNA
- MW > 5Kd - 200Kd
- Injectable - not oral
- Extracellular targets
- The Needle
New Hybrid Drug Discovery Strategy - 1990’s

- Use mol. Biol., genomics, bio-informatics to identify specific molecular targets

- Develop novel bio-assays to screen for small molecule agonists and antagonists - intra or extracellular targets

- Use high throughput robotics to screen > million cpds

- Establish huge diverse chemical libraries by conventional organic chemistry and new combi-chem methods

- Even use “virtual screens” in silico

- Use reverse genetics and pharmaco genomics to get at function, structure and disease indication
A Powerful Drug Discovery Engine

1-2 yrs  .5-1 yrs  .5-1 yrs  1-2 yrs  1-3 yrs  5-8 yrs
Find Target  Dev Bio-assay  Screen Library  SAR  Animal tests  Human clinicals

Step 1 → Step 2 → Step 3 → Step 4 → Step 5 → Step 6
Mol. Biol genetics  Biochem Cell biol  Robotics  Synthetic chemistry  Tox-pharmaco  Phases I, II, III

$1-2 mil  1-2 mil  2-3 mil  2-4 mil  5-20 mil  50-500 mil
Modern Drug Discovery Requires Automated, High-throughput Capability

Automation allows drug discovery laboratories to work faster, more accurately and more efficiently

**Compound Libraries**
- Large collections (>10^6 compounds)
- Ensure accessibility, integrity and diversity

**Automated systems for High Throughput Screens (HTS)**

**Integrated work stations**
- Liquid handling
- Plate washing
- Plate-based assays/detection
- Sample processing and preparation
**HTS Drug Discovery Strategy**

- **High Through-put Screening**
  - Partially purified target from rat liver
  - 96 or 384 well bioassay by Robotics

- **Confirmation of Hits**
  - Recombinant human target

- **Cell based Assay / $^3$H-uptake**
  - Differentiated L6

- **Structural Analysis**
  - MS, HPLC confirmation

- **Specificity Analysis**
  - PKA & PKC
  - Assorted kinase assays

- **Pharmacokinetics**
- **Cytotoxicity**

- **Ex vivo Efficacy**
- **Mechanism of Action**

- **SAR / In vivo PoP**

**HTS Flow Chart**

- **Primary Screen**
  - 956,560
- **Secondary Screen**
  - 1481
- **Confirmation**
  - 9
- **Potential Hits**
  - 6
- **Drug Hit**
  - 2
Profile of an Ideal Therapeutic

★ Specific for just one target molecule that is disease linked
★ High potency / affinity for target (< 1nM Kd)
★ No general or specific toxicity
★ Reasonable half-life and liver clearance
★ Not a covalent modifier or mutagenic
★ Oral bio-available once a day pill
★ Easy to synthesize and stable on the shelf
Bottlenecks Along the Drug discovery Pathway

- No specific - functional bio-assays
- Inadequate cpd chemical libraries
- Poor pharmacological properties
  oral bioavailability, clearance, metabolites
- No valid animal model for disease
- Sporadic human toxicity due to polymorphism in the population
Modern Tools that Facilitate Drug Discovery

- Genomics, bio-informatics and molecular function
- Gene expression profiling - microarray technology
- Proof of concept - animal models using mouse knock-outs and transgenes
- High resolution 3D structures by X-ray and NMR
- Virtual in silico screens and better SAR
Micro Arrays in Drug Discovery

- Drug  +Drug

mRNA

Hybridize Probes To 30K Gene Chip

A snapshot of genes turned UP and Down by the drug
Using KO mice to Aid Drug Development

- Test consequence of inhibiting a specific Target Gene (ie. Is inhibition of a specific gene product detrimental)

- Properties of KO can inform gene function and disease indication (ie. -/- animals provide proof of concept)

- KO animals are critical for testing specificity of drugs

- KO phenotype can sometimes reveal related gene function

- KO’s - transgenes can also provide disease animal model
The Economics of Drug Discovery and Development

- Cost of bringing a new Drug to market ($500-800 mil)
- Average time for drug development & approval (10-12yrs)
- Market share of a good product ($0.5-5 billion)
- Do pharma co. charge too much? Why are US prices high?
- How to provide expensive drugs to poor nations?
Major Points

1. Targeting NR PPARg to treat Type II diabetes is a good example of novel therapeutic strategies directed against specific Txn factors.
2. TZD’s bind the AF2 domain of PPARg and alter its ability to recruit specific co-activators or co-repressors.
4. Phase I of the biotech revolution led to development of protein-based therapeutics (i.e., insulin, GH, B-interferon, tPA and monoclonal Ab’s).
5. Phase II led to use of sophisticated molecular genetics, genomics and biochemistry to identify novel human gene products that can be modulated by small synthetic chemicals (oral-bioavailable pills).
6. Modern arsenal of drug development includes: combi-chem libraries, genomics, proteomics, micro-arrays, bio-informatics, virtual screens, KO & transgenic mice, designer genes and cells, stem cells etc.
7. Difficult factors to overcome in drug development: time (15 yrs) and cost ($200-400 mil) for novel, efficacious and safe drugs.