Serendipity and Uncertainty in Pharmaceutical Research

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Cortona
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‘That’s Dr Arnold Moore. He’s conducting an experiment to test the theory that most great scientific discoveries were hit on by accident.’

Drawing by Hoff; © 1957
The New Yorker Magazine, Inc.
Topics to Discuss

- Drug discovery in the past
- Some examples for role of serendipity in drug discovery
- Current drug discovery
- Serendipity and uncertainty: opportunities and challenges
Historical Medicines

- Mostly mixtures and extracts

Drimia maritima (sea onion)  

Colchicum autumnale (autumn crocus)  

Papaver somniferum (opium)
Many Historical Medicines still being used today

- Codein
- Colchicin
- Thrombin Inhibitors
- Digoxin
From Dyes to Drugs

Methylene Blue
- first synthesized in 1876
- Active against malaria
- Phase III clinical trial for Alzheimers ongoing

\[
\text{Chlorpromazine (Antipsychotic)}
\]
Chlorpromazin and the number of patients in psychiatric hospitals in the US

“The effect of this drug in emptying psychiatric hospitals has been compared to that of penicillin and infectious diseases.”

Number of patients in state and governmental hospitals in the United States 1946-1967

From: F.H. Clarke, How modern medicines are discovered, 1973, p. 57
Leo Sternbach and the Discovery of Diazepam (Valium)
“During the 1970s <Valium> Roche was the most frequently prescribed drug. It is a safe, potent anxiolytic with pronounced muscle-relaxant properties, and is the best-known tranquilizer of its kind”

First sentence from “Leo Sternbach, The Benzodiazepine Story”, 1970
Discovery of the Benzodiazepines

Quinazoline 3-oxides

Chlordiazepoxide (Librium)
Clinical Development of the first Benzodiazepines

- Librium
  - Synthesized in 1955
  - Tested in May 1957
  - Launched in 1960 (2.5 years from first pharmacological testing to introduction)

- Valium (Diazepam)
  - Tested in 1959
  - Launched in 1963 (4 years from first pharmacological testing to introduction)
Benzodiazepine Agonists Introduced By Roche

Chlordiazepoxide (Librium, 1960)
Diazepam (Valium, 1963)
Nitrazepam (Mogadon, 1965)
Medazepam (Nobrium, 1968)
Flurazepam (Dalmadorm, 1970)
Bromazepam (Lexotanil, 1974)
Clonazepam (Rivotril, 1975)
Flunitrazepam (Rohypnol, 1975)
Midazolam (Dormicum, 1982)
Benzodiazepines Enhance the Inhibitory Action of GABA
Proposed therapeutic effects of subtype selective GABA\(\text{A}\) ligands

**Agonism: Sedation**

**Agonism: Anxiolytic**

**Agonism: Anxiolytic**

**Inverse Agonism: Cognition enhancement**
Average Life Expectancy at Birth in Switzerland

Ten Great Public Health Achievements
United States, 1900-1999

- Vaccination
- Motor-vehicle safety
- Safer workplaces
- Control of infectious diseases
- Decline in deaths from coronary heart disease and stroke
- Safer and healthier foods
- Healthier mothers and babies
- Family planning
- Fluoridation of drinking water
- Recognition of tobacco use as a health hazard

Source: CDC 1999
Major impact of antivirals on public health

Estimated Numbers of AIDS Cases, Deaths, and Persons Living with AIDS, 1985–2007—United States and Dependent Areas

- **Cases**
- **Deaths**
- **Prevalence**

**Year of diagnosis or death**

- **Invirase approval 1995**
- **1st PI-based HAART**

Note: Data have been adjusted for reporting delays.
The Discovery and Development Process

Description of R&D phases

**Research**
- **New Med Proposal**
- **Target Assess**
- **Lead Id**
- **Lead Opt**
- **EIH Enable**

**R&D**
- **Phase I**
- **Phase II**
- **Phase III**
- **GLP studies**
- **Optimize a lead series**

**Development**
- **Reg**
- **On Market**
- **Clinical phases**

**Idea**
- Evaluate the target (incl 3D structure) and develop a screening process
- Conduct screening / design / virtual screening on a target
Cornerstones for Innovation and Differentiation

We know what to target (Understanding disease, new pathways, Biomarkers, PHC)

We have a safe and efficacious compound (Therapeutic Modalities)

World-Class skills in Translational Medicine (PoM & PoC) and Non-clinical Safety

- Small Molecules
- Therapeutic Proteins
- Peptides
- Oligonucleotides
FDA Drug Approvals since 1993

Renin (2REN) and the inhibitor Aliskiren
Discovery of Sildenafil (Viagra)

- Sildenafil synthesized at Pfizer
- Potent inhibitor of PDE-5
- Initial clinical studies for hypertension and angina pectoris failed.
- However: compound induced marked penile erections
- Approved by FDA for erectile dysfunction in 1998
PDE-5 Inhibitors Sildenafil and Vardenafil

Sildenafil

Vardenafil
Serendipity and Uncertainty in Current Drug Discovery

- Prediction of molecular properties
- Prediction of efficacy in humans
- Long timelines and high attrition rates
- Portfolio management and goal setting
The Discovery and Development Process

Dwell times and success rates

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time (years)</th>
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<tr>
<td>Phase I</td>
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<tr>
<td>Phase II</td>
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<tr>
<td>Phase III</td>
<td>1.2</td>
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<tr>
<td>Reg</td>
<td>1</td>
</tr>
<tr>
<td>On Market</td>
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**Research**
- New Med Proposal
- Target Assess
- Lead Id
- Lead Opt
- EIH Enable
- Phase I
- Phase II
- Phase III
- Reg
- On Market

**Development**
- 57
- 36
- 22
- 14
- 8
- 4.5
- 2
- 1.2
- 1
The Pharma R&D Pipeline

PFIZER PIPELINE SNAPSHOT AS OF August 2, 2016
Included are 64 NMEs, 20 additional indications, plus 8 biosimilars

10 Programs advanced or are new
3 Projects discontinued since last update

<table>
<thead>
<tr>
<th>DISCOVERY PROJECTS</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>IN REGISTRATION</th>
<th>TOTAL</th>
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<td>38</td>
<td>16</td>
<td>29</td>
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Dealing with Serendipity and Uncertainty in Current Pharmaceutical Research

- Opportunities
  - High Throughput Screening of compounds in assays
  - Big data analysis (genetic and clinical data)
  - Drug Repurposing
New Indications for old Drugs

- Aspirin
  - Old: analgesic
  - New: antiplatelet

- Gabapentin
  - Old: antiepileptic
  - New: neuropathic pain

- Minoxidil
  - Old: hypertension (candidate)
  - New: hair loss
Drug Repurposing

**Drug repurposing** is the application of known drugs and compounds to new indications or diseases

- Success also demonstrated with older compounds via a use-patent and external licensing:
  - Tecfidera / Dimethyl-fumarate for MS (Biogen)
  - Thalidomid for myeloma (Celgene)
- Some small biotechs focus on this approach (Biovista, Melior, SOM) and large cap pharmas now highly interested
Serendipity and Uncertainty in Pharmaceutical Research

Summary

- It takes a very long time to develop a new drug.
- Large uncertainty due to the low success rate of research projects.
- Despite scientific progress, serendipity still plays a significant role.
- Good experimental data plus reasonable working hypothesis maximise the chance to identify "pleasant surprises".

„Chance favors the prepared mind“

Louis Pasteur
Thank you