Natural products inspired drug discovery

A highly simplified depiction of drug discovery

**Target Selection**
- Genomics
- Proteomics
- Bioinformatics

**Lead discovery**
- Synthesis and isolation
- Combinatorial chemistry
- Assay development
- High-throughput screening

**Medicinal chemistry**
- Library development
- SAR studies
- In Silico screening
- Chemical syntheses (process chemistry)

**In vivo studies**
- Affinity and selectivity testing
- Disease models
- Lead candidate refinement

**In vitro studies**
- Animal models
- Behavioural studies
- Functional imaging

**Clinical trials and therapeutics**

**General timeline of drug discovery**

<table>
<thead>
<tr>
<th>Drug Discovery</th>
<th>Preclinical</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>10,000 - 30,000 compounds made and screened</td>
<td>1% ca. 100-300 compounds</td>
<td>Phase 1 20-100 volunteers Phase 2 100-500 volunteers Phase 3 1000-5000 volunteers</td>
</tr>
<tr>
<td>3 - 6 years</td>
<td>6 - 7 years</td>
<td>0.5 - 2 years</td>
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</tbody>
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**FDA Approval**

**Scale-up and manufacturing**

**Market**

This group meeting will cover:
- The evolution of selected drug classes from their parent natural product motifs to their current pharmacophores
- Syntheses of selected drugs and natural products

This group meeting will not cover:
- SAR studies of druglike molecules
- Biochemistry of drugs

Key reviews:
Statins inhibit cholesterol synthesis in the body and that leads to reduction in blood cholesterol levels, which is thought to reduce the risk of atherosclerosis and diseases caused by it.

Discovery timeline of statins:
- Cholesterol (1950s)
- Compactin (1970s)
- Lovastatin (1980s)
- Atorvastatin (1990s)
- Pravastatin (1990s)
- Rosuvastatin (2000s)

Selected syntheses of compactin:
- TMSO + \( \text{Me}_2\text{SiCH}_2\text{O} \) (75%) \( \rightarrow \) OTBS \( \text{Me}_2\text{SiCH}_2\text{O} \) \( \rightarrow \) 7 steps \( \rightarrow \) compactin \( \text{JACS. 1985, 3731} \)
- \( \text{Ac}_2\text{O} \) \( \rightarrow \) OTMS \( \text{Me}_2\text{SiCH}_2\text{O} \) \( \rightarrow \) 11 steps \( \rightarrow \) Tgt \( \text{JACS. 1983, 1403} \)
- \( \text{MeO}_2\text{C} \) \( \rightarrow \) 17 steps \( \rightarrow \) 7 steps \( \rightarrow \) \( \text{OH} \) \( \rightarrow \) JACS. 1981, 6538.

Cholesterol controversy, P1:
- Compactin withdrawn. Lovastatin suspended.
- Lovastatin trial resumes.
- Lovastatin available for prescription.

Cholesterol controversy phase 2:
- Atorvastatin
- Pravastatin 4-5 y clinical outcome trials showed red. of adverse effects.

Heart protection study confirms safety of simvastatin in 5-y trial in 20,000 patients and demonstrates clinical benefits in a broad array of patient types.

Selected syntheses of simvastatin:
- \( \text{NMe}_2 \) \( \rightarrow \) iPr \( \text{NMe}_2 \) \( \rightarrow \) 6 steps to lovastatin
- \( \text{MeN} \) \( \rightarrow \) iPr \( \text{NMe}_2 \) \( \rightarrow \) 5 steps to lovastatin
- \( \text{MeN} \) \( \rightarrow \) iPr \( \text{NMe}_2 \) \( \rightarrow \) 6 steps to lovastatin
- \( \text{MeN} \) \( \rightarrow \) iPr \( \text{NMe}_2 \) \( \rightarrow \) 6 steps to lovastatin

Selected syntheses of rosuvastatin:
- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA
- \( \text{NMe} \) \( \rightarrow \) iPr \( \text{NMe} \) \( \rightarrow \) 96% mCPBA
- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA
- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA

Selected syntheses of cerivastatin:
- \( \text{MeO} \) \( \rightarrow \) iPr \( \text{MeO} \) \( \rightarrow \) 96% mCPBA
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Selected syntheses of fluvastatin:
- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA
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- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA

Selected syntheses of pravastatin:
- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA
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Selected syntheses of simvastatin:
- \( \text{CHO} \) \( \rightarrow \) iPr \( \text{CHO} \) \( \rightarrow \) 96% mCPBA
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Selected syntheses of cerivastatin:
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Direct Xa Inhibitors

Direct Xa inhibitors are a class of relatively new oral anticoagulant drugs that inhibit factor Xa. They have a fast onset, predictable pharmacokinetics and don’t require as strict monitoring as the older anticoagulant drugs.

Apixaban. JMC. 2007, 5339.

Discovery timeline of Direct Xa inhibitors

- 1916: Heparin
- 1920s: Dicoumarol
- 1936: LMWH developed
- 1938: Warfarin approved as the 1st anticoagulant drug.
- 1948: Naturally occurring compounds antistasin & TAP (Tick anticoagulant peptide) discovered.
- 1980s: YM-6082b
- 1997: Edoxaban
- 2008: Rivaroxaban

Outbreak of haemorrhagic cattle disease in Canada and US. 6 years

- 1930s: Warfarin
- 1935: DX-9065a

Apixaban

- 1. NaNO₂, HCl then NaOAc
- 2. TFA (71%)

Edoxaban. US 20050020645

- 1. (R) (α-MBA)
- 2. I₂, KI, NaHCO₃
- 3. NaN₃, NH₄Cl

(better way to make this compound?)
NS5A Inhibitors & HCV drugs

NS5A Inhibitors belong to a class of antiviral drugs called protease inhibitors. They are direct acting antiviral agents (DAAs) that target viral proteins, and their development was a culmination of increased understanding of the viral life cycle.

Discovery timeline of NS5A Inhibitors

- Discovery of interferons - naturally occurring substance. Approved to treat hairy cell leukemia and Kaposi's sarcoma
- 1970s
- 1980s
- 1990s
- 1998
- 2001
- 2007
- 2010
- 2016

Blood tests developed to test Hep B (1963) and Hep A (1973). Many blood samples still tested negative for A and B, however.

Hepatitis C virus identified. In 1992, a blood test was perfected to eliminate HCV from the blood transfusion supply.

Ribavirin

Telaprevir (VX-950)

Boceprevir

Peg-Intron, Peg-Intron + Rebetol and Pegasys approv.

Scientists discovered the connection b/n HCV and the brain, how fat is involved in the replication process and many studies of exp. drugs were started and completed.

Fluorination and phosphoamidation of sofosbuvir (nucleoside chemistry see O'Hara GM)

Early stage nucleofluorination

DAST or Deoxyflur (51%)

DIPEA

Selectfluor (71%)

CO2Et

(1:1)

Late stage fluorination

Pharmasset. 2006012, 440 A2

BzO

NHBz

OMs instead of OBz

A not observed, 41% desired pdt.

BzO

NHBz

50% EtOH DBU

jPr

Holy reaction (quant.)

TL. 2006, 315.

Phosphoamidation

Ar = pNO2(C6H4)

rt. 72 h

>99.7% purity

>80% conv.

Gilead 2010135,569 A1

R = OH, imid

NFSI

KHMDS

Nucleoside

(81%)

Boc

Cl

2. NH3OAc

then

1. Pd(OAc)2

1. HATU DIPEA

2. HCl

JMC. 2014, 2033.

Ledisapvir

Harvoni

Sofosbuvir

Me2CONH2

Me

Me

NHCO2Me

Me

Me

Me

Me

PhO

NHCO2Me

JMC. 2014, 2033.

Ledisapvir

1. Pd(OAc)2

2. HCl

JMC. 2014, 2033.
Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) are enzyme inhibitors that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4). They are used in the treatment of type 2 diabetes. Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins that play an important role in insulin secretion and blood glucose control regulation.

Efficient synthesis of berberine alkaloids and analogs. ACIE. 2014, 14783.

Discovery timeline of DPP-4 inhibitors

First inhibitors characterized primarily 5 membered heterocycles

1967
- Berberine
- Lupeol
- Cyano-pyrrolidines

1990s
- 1990s
- Novartis discovers N-substituted glycyl cyanopyrrolidines

1994
- Vildagliptin

1995
- Alogliptin

1998
- Sitagliptin

1999
- Omarigliptin

2005
- Teneligliptin

2010s
- Linagliptin

OPRD. 2015, 1760.

Discovery route to N-pyrazole sulfonylation

BocN

Regioselective mesylation

BocN

Pyranone synthesis

BocHN

Efficient synthesis of berberine alkaloids and analogs. ACIE. 2014, 14783.
Relief from chronic pain remains a recognized unmet medical need. Consequently, the search for new analgesic agents is being intensively studied by the pharmaceutical industry. The TRPV1 receptor is an ion channel that has been implicated in mediation of many types of pain and therefore studied most extensively.

**Discovery timeline of TRPV1 antagonists**

- **1919**: Capsaicin
- **1990**: Capsazepine
- **1997**: RTX

**As of late 2009**

**Active compounds**
- AstaZeneica
- Bayer
- F. Hoffmann-La Roche
- Johnson & Johnson
- Novartis
- Others

**Preclinical**
- Rottweil-Phizer
- Sanofi-Aventis
- AstraZeneca
- AstraZeneca/Novartis
- AstraZeneca/Bayer
- GlaxoSmithKline

**Phase I**
- AstraZeneca
- Bayer
- Janssen
- Johnson & Johnson
- Novartis
- Pfizer

**Phase II**
- AstraZeneca
- Bayer
- Janssen
- Johnson & Johnson
- Novartis
- Pfizer

**Phase III**
- AstraZeneca
- Bayer
- Janssen
- Johnson & Johnson
- Novartis
- Pfizer

**AbbVie TRPV1 OPRD 2014, 303.**

1. LDA, DFB 80%
2. TFAA, py.

**AbbVie TRPV1 synthesis?**

1. HCl, MeOH
2. L-prolylglut.

**TRPV1 antagonist OPRD. 2016, 227**

5 steps sequential coupling + SnAr
Antiandrogens antagonise the androgen receptor (AR) and thereby block the biological effects of testosterone and dihydrotestosterone (DHT). Antiandrogens are important for men with hormonally responsive diseases like prostate cancer, benign prostatic hyperplasia (BHP), acne, seborrhea, hirsutism and androgen alopecia.

**Discovery timeline of antiandrogens**

- Charles Huggins treated patients by androgen ablation with castration or estrogen therapy (1941)
- Charles Huggins wins Nobel Prize in physiology (1966)
- Nilutamide (1967)
- Flutamide (1969)
- Bicalutamide (1995)
- Abiraterone acetate (2008)
- Sinokamide (2011)
- Enzalutamide (2012)
- Ataric acid (2012)
- n-butyl Phsulfon

**Chemical Structures**

- **Cyproterone acetate**
- **Flutamide**
- **Nilutamide**
- **Bicalutamide**
- **Enzalutamide**
- **Sinokamide**
- **Cyproterone acetate**
- **Flutamide**
- **Nilutamide**
- **Bicalutamide**
- **Enzalutamide**
- **Sinokamide**

**Chemical Reactions**

- **ACS Med. Lett. 2015, 908.**
  - Reaction 1: HOAc, 110 °C (88%)
  - Reaction 2: MEMO₂C, Me, MEMO₂C (50%)
  - Reaction 3: HOAc, 110 °C (88%)
- **JOC. 1989, 5180.**
  - Reaction 1: HOAc, TsOH (98%)
  - Reaction 2: H₂, Pd/C, H₂O, 2 steps (83%)
- **JMC. 2010, 2779.**
  - Reaction 1: TMSOTf, 77% (77%)
  - Reaction 2: H₃O⁺ (83%)
Drug classes by mechanism of action

Statins
- Compactin
- R = H, Lovastatin
- R = Me, Simvastatin
- Pravastatin

Direct Xa inhibitors
- Dicoumarol
- Heparin

Tubulin inhibitors
- Vinflunine
- Colchicine
- Edoxaban
- Apixaban
- Rivaroxaban
- Combretastatin

Natural products/natural product-like
vs. Synthetic drugs

Baran GM
7/26/17
Drug classes by mechanism of action

TRPV1 antagonists

- Capsaicin
- RTX
- Capsazepine
- SAR-115740
- AMG517
- ABT102
- SB-706498
- MK-2295

Antiandrogens

- Cypionate acetate
- Spironolactone
- n-butylPhosulfon
- Abiraterone acetate
- Ataric acid
- Sinokamide

NS5A inhibitors

- Interferon
- Ribavirin
- Teiprevir (VX-950)
- Boceprevir

Proton pump inhibitors

- Omeprazole
- Lansoprazole
- Rabeprazole
- Pantoprazole
- Boceprevir
Drug classes by mechanism of action

**DPP4 inhibitors**
- Berberine
- Lupeol
- Vildagliptin
- Sitagliptin
- Alogliptin
- Omarigliptin
- Teneligliptin
- Linagliptin

**HIV protease inhibitors & antiretrovirals**
- Withanolide A
- Prostratin
- Indinavir
- Tipranavir
- Amprenavir
- Darunavir

**Some (Well-known) natural product derived drugs**
- FLOVENT
- Latanoprost
- Imipenem
- Doxycycline
- Quinine

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Drug classes not covered:
- Proton pump inhibitors
- Tubulin inhibitors
- NK1 inhibitors
- Bcr-Abl TK inhibitors
- NNRT inhibitors
- PDE5s inhibitors
- Cephalosporins
- HIV protease inhibitors
- Angiotensin inhibitors