Serendipitous Target-based Drug Discovery

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Rio de Janeiro (2005) short course
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SERENDIPITY

Definition:
The occurrence and development of events by chance in a happy and beneficial way.
The chance is an event, serendipity is a capacity.

Etymology: Horace Walpole (1717-1797) used this term from the Persian fairy tale *The Three Princes of Serendip*, whose heroes „were always making discoveries by accidents and sagacity, of things they were not in quest of”. Serendip was the Persian name of Sri Lanka (Ceylon).
Highlights of Drug Discoveries in Chronology

1. spironolactone (1954)
2. propranolol (1962)
3. salbutamol (1966)
4. cimetidine (1972)
5. captopril (1976)
6. losartan (1988)
7. trastuzumab (1991)
8. imatinib (1992)
9. exenatid (1993)
10. tofacitinib (1999)
11. sitagliptin (2001)
12. dapagliflozin (2002)
Aldosterone antagonists: spironolactone and eplerenone

aldosterone: steroid hormone (mineralocorticoid)
aldosterone antagonists are used for the treatment of heart failure as diuretics
β adrenergic receptor antagonists

Non-selective beta blocking agents

1962 propranolol (ICI)
1968 timolol (Frosst)
1970 nadolol (Squibb)

β1 selective beta blocking drugs

1967 acebutolol (May & Bakes)
1969 atenolol (ICI)
1970 metoprolol (Hässle)
1976 bisoprolol (Merck KGaA)

For the treatment of hypertension, arrhythmias, glaucoma, angina pectoris. Higher beta-1 selectivity results in less effect on bronchial receptors.
Structure of non-selective beta blocking agents

propranolol (1962, ICI)

timolol (1968, Frosst)

nadolol (1970, Squibb)

Aryloxypropanolamines
Propranolol is the most lipophilic beta-blocker, and enters CNS
Propranolol and nadolol are racemates
Structures of  $\beta_1$-selective beta blockers

acenutrolol  (1967, May & Baker)

atenolol  (1969, ICI)

bisoprolol  (1976, Merck KGaA)

metoprolol  (1970, Hässle)

*atenolol* is one of the most widely used beta-blockers, it does not penetrate BBB thus avoiding CNS side effects

*bisoprolol* has the highest degree of beta-1 selectivity
Drug therapy of COPD
(chronic obstructive pulmonary disease)

1966    salbutamol: short-acting β2-selective agonist
1972 -1983 optimization of long-acting analogues
         formoterol and salmeterol

Salbutamol (Glaxo, 1969) is used for the treatment of bronchial asthma. Natural products, epinephrine and ephedrine, were lead molecules to discover beta-2 agonists. Lipophilic analogues, salmeterol and formoterol have long duration, prevent nocturnal asthma.
Structures of salbutamol, formoterol and salmeterol

salbutamol  (Allen & Hanburys, 1966)
salmeterol  (Glaxo, 1983)
formoterol  (Yamanouchi, 1972)

epinephrine (adrenalin) as reference compound

salbutamol: rapid onset and short duration.
salmeterol: slow onset and long duration
formoterol: fast onset and long duration
Drug therapy of peptic ulcer and GERD
(GERD : gastroesophageal reflux disease)

1971 cimetidine : pioneer H2-receptor antagonist
1976 - 1987 optimization of H2-receptor antagonists ranitidine and famotidine etc.

Cimetidine revolutionized the medical treatment of peptic ulcer disease, hypersecretion of gastric acid, gastroesophageal reflux disease. Famotidine is the most potent member of this drug class.
Structures of cimetidine, ranitidine and famotidine

Cimetidine: cynoguanidine and „thio”-methyl-imidazole
Ranitidine: nitroethene-diamine and „thio”-methyl-furan
Famotidine: sulfamoyl-propanimidamide and „thio”-methyl-thiazol
Drug therapy of hypertension

1976  captopril: pioneer ACE inhibitor
1978 - 1980  optimization of ACE-inhibitors:
enalapril, lisinopril, perindopril etc.
1986  losartan: pioneer AII antagonist
1989 - 1991  optimization of AII antagonists:
valsartan, telmisartan etc.

Renin-angiotensin-aldosterone-system (RAAS) controls blood pressure. Angiotensin-converting enzyme (ACE) cleaves angiotensin I (inactive decapeptide) to give angiotensin II (vasoconstrictor). ACE-inhibitors and angiotensin II antagonists (AII) are important drugs for the treatment of hypertension.
Captopril (pioneer drug) has a short duration of action. It is used in emergencies. Long-acting analogues of captopril are used for the chronic treatment of hypertension.
Structures of losartan, valsartan and telmisartan

Losartan, valsartan and telmisartan are long-acting angiotensin II antagonists. Telmisartan has the longest duration of action.
Targeted drug delivery with antibody - drug conjugate

Trastuzumab (1991, Genentech) is a monoclonal antibody that interferes with HER2/neu receptor. It is used for the treatment of HER2 positive breast cancer.

Trastuzumab emtansine (2004, Genentech) is a drug conjugate of trastuzumab linked to a derivative of maytansine, cytotoxic agent.
Drug therapy of chronic myeloid leukemia (CML)

1992  imatinib : Bcr-Abl tyrosine kinase inhibitor
       pioneer drug
2002  nilotinib : in case of resistance to imatinib

Imatinib and nilotinib are used for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukemia.

It is about 10% of all new cases of leukemias.
Imatinib and nilotinib are pyrido-pyrimidine-amino-benzamide derivatives. Structural and pharmacological (full) analogues.
Drug therapy of type 2 diabetes with GLP-1 agonist

1993  exenatide: pioneer GLP-1 agonist drug (natural product, sc injection)
1996  liraglutide: GLP-1 analogue (QD)
2005  semaglutide: GLP-1 analogue (Phase III) (SC, once per week)

Exenatide is a synthetic version of a hormone found in the saliva of the Gila monster.

GLP-1: glucagon-like peptide - 1, it regulates glucose metabolism and insulin secretion.
Liraglutide is a long-acting GLP-1 agonist with two structural modifications of human GLP-1: substitution of a Lys (lysine) to Arg (arginine) and attachment of a 16 C fatty acid side chain to a Lys via a glutamic acid (Glu) linker.
Similarity of hormone GLP-1 and liraglutide
JAK3 inhibitors for the treatment of rheumatic arthritis

(JAK 3 : Janus kinase 3)

1999 tofacitinib (first selective JAK3 inhibitor)

Tofacitinib (Pfizer, 1999)

FDA approved tofacitinib in 2012, a pyrrolo-pyrimidine derivative. According to a study in 2014 it may have potential applications in the treatment of obesity:
It coverts white fat tissues into more metabolically active brown fat.
Drug therapy of type 2 of diabetes with DPP-4 inhibitors

2001 sitagliptin: pioneer DPP-4 inhibitor (QD)
1998 vildagliptin: pioneer discovery
2008 omarigliptin: Phase III (once weekly)

Inhibition of dipeptidyl peptidase-4 (DPP-4) prevents rapid degradation of GLP-1.

Oral drugs for treatment of type 2 of diabetes.

Sitagliptin was approved by FDA in 2006. It is a pioneer DPP-4 inhibitor.

Its lead compound derives from HTS (high-throughput screening)
Dipeptidyl Peptidase IV Inhibitors

Mechanism of action

\[ \text{H}_3\text{N}^+ - \text{His} - \text{Ala} - \text{Glu} - \text{Gly} - \text{Thr} - \text{Phe} - \ldots \]

DPP-4 cleaves GLP-1 at the penultimate position from the N-terminus.
Research of substrate-based DPP-4 inhibitors resulted in vildagliptin, an adamantyl-glycyl-cyanopyrrolidine derivative.
SGLT2 inhibitors for the treatment of diabetes 2
(SGLT2 : sodium-glucose-transporter type 2)

2002  dapagliflozin: pioneer SGLT2 inhibitor
2003  canagliflozin
2004  empagliflozin

![Phlorizin](image)

Dapagliflozin and analogues inhibit sodium glucose transport proteins. Natural product phlorizin served as a lead compound, a non-selective SGLT ½ inhibitor, with poor bioavailability and side effect profile.
Structure of dapagliflozin, canagliflozin and empagliflozin

Dapagliflozin and analogues are C-aryl glucosides, selective SGLT 2 inhibitors
PDE4 inhibitor for the treatment of psoriatic arthritis

2004 apremilast
(PDE4 : phosphodiesterase 4)

Apremilast is an isoindole derivative.
It was approved by FDA in 2014, and by EC in 2015 for the treatment of both patients with psoriasis and psoriatic arthritis.
First all oral therapy for treatment of hepatitis C

2007 sofosbuvir : viral RNA polymerase inhibitor
(RNA : ribonucleic acid)

Sofosbuvir inhibits viral RNA polymerase.
It is a prodrug metabolized to the active triphosphate derivative in the human body.
It has been marketed in 2013.
Remarkable drug discoveries

1. Drospirenone
2. Escitalopram
3. Ezetimibe
4. Lamotrigine
5. Omeprazole

IMS (2013) : > 15 b $

In spite of their generic status these remarkable drugs represent a high market value.
Discovery of drospirenone

spironolactone: first successful aldosterone antagonist
side effects: low receptor selectivity

Clinical candidate: spirorenone
Five times higher anti-aldosterone activity
Hormonal side effects much lower
Serendipities in clinical studies of spirorenone

1. Low doses of spirorenone resulted in reduction of testosterone level in men
2. Metabolic transformation to 1,2-dihydrospirorenone (drospirenone)

Drospirenone: orally active progestin with anti-androgen properties. Successful contraceptive.
Discovery of escitalopram
Serendipitous formation of a phthalane derivative

![Chemical structures and reactions](image_url)
Serendipitous mechanism of action

melitracen : norepinephrine (NE) reuptake inhibitor unselective

talopram : selective and more potent NE reuptake inhibitor, halted in Phase II (psychomotor side effects)
Serotonin Reuptake Inhibitors

1971 New research program at Lundbeck initiated by Professor Arvid Carlsson selective serotonin (5-HT) reuptake inhibitors (SSRIs)

Lead compound: talopram

some talopram analogues were dual 5-HT/NE inhibitors

Optimization with help of substituents: citalopram
enantiomers of citalopram

Different activities of $S$- and $R$-citalopram

$S$-citalopram: primary inhibition (S1) at SERT protein (SERT: serotonin transporter) and secondary allosteric binding site (S2)

$R$-citalopram: counteracts with S1 and S2 sites

$S$ - citalopram

$R$ - citalopram
Serendipitous selection of citalopram

Structure-activity relationships of direct analogues of citalopram: highest activity of a synthesis byproduct at S1 site

Fortunately not this byproduct was selected. The very active synthesis byproduct has no allosteric activity.
Discovery of ezetimibe

Schering-Plough (now Merck) focused on inhibitors of the enzyme ACAT (acyl-Coenzyme A cholesterol acyltransferase). The esterification of cholesterol is mediated ACAT.

Lead molecules: SA 58035 (Sandoz) and CI 976 (Parke-Davis)
Ring-closure derivatives

2-azetidinone derivatives:

Poor correlation between *in vitro* and *in vivo* activity

*In vivo* results were followed to give SCH 48461 as clinical candidate
Potent metabolite of SCH 48461 and ezetimibe

Standalone drug whose mechanism of action was elucidated years after its introduction (Niemann-Pick C1-Like 1 protein)
Discovery of lamotrigine

Folic acid produces epileptogenic foci and some antiepileptic drugs have antifolate properties

\[ \text{Folic acid} \]

\[ \text{Phenobarbital} (1911, \text{Bayer}) \]

\[ \text{Phenytoin} (1946, \text{Parke Davis}) \]

\[ \text{Carbamazepine} (1957, \text{Geigy}) \]
Antifolate drug research at Burroughs Wellcome

Lead compound: pyrimethamine, antimalaria drug (1950) with some anticonvulsant and antifolate activity

![Pyrimethamine](image1)

**pyrimethamine (1951, Burroughs Wellcome)**

![BW 99U](image2)

**BW 99U**

![BW 288U](image3)

**BW 288U**

![Lamotrigine](image4)

**Lamotrigine (1979 Wellcome)**

BW 288U: good anticonvulsant and a mediocre antifolate
Lamotrigine: successful antiepileptic drug: blocker of voltage sensitive sodium ion channels
Discovery of omeprazole

Gastrin is a peptide hormone which stimulates the production of HCl in the parietal cells. Antigastrin research (in the 1960s)

Structure elucidation of gastrin (1964)

ICI synthesized a thousand substances similar to gastrin, but none could be developed.

Antigastrin compounds:

![CMN 131 (Servier)](image1)

![SC - 15396 (Serle)](image2)
Hässle research

Lead molecule: CMN 131
New derivatives to avoid the thioamide moiety
New animal model: conscious gastric fistula dog
Discovery of timoprazole

![Chemical structures of H 124/26 and timoprazole]

H 124/26
(Hungarian patent application)

Potent inhibitors of acid secretion
Adverse effect: enlargement of the thyroid gland
Mechanism and discovery of omeprazole

Discovery of proton pump
(Hässle, 1977)

Analogue optimization, discovery of omeprazole (1979)

omeprazole (1979 Hässle)
Omeprazole cycle

Prodrug or omeprazole cycle (1990)
Active metabolite of omeprazole: „sulfenamide“

OMEPRAZOLE

Proton

OMEPRAZOLE prodrug

SULFENAMIDE active metabolite
Drug's Therapeutic Efficacy vs. Therapeutic Satisfaction

Source: Japan Health Science Foundation "Prospects on Medical Needs in 2015"
Summary

1. Examples of successful target-based drug discoveries of last 50 years

2. In some cases the starting targets and the drug product have different mechanism of action:
   a.) drospirenone
   b.) escitalopram
   c.) ezetimibe
   d.) lamotrigine
   e.) omeprazole
Fischer János és Ganellin Robin
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I. General aspects

1. Serendipities in Target-based Drug Discoveries (S)(M)
   János Fischer (Richter) and David Rotella (Montclair Uni.)

2. Drug Discoveries & Mechanism of Action (S) (M)
   David Swinney (Inst. for Rare and Neglected Diseases, USA)

II. Drug Class Study

1. Insulin Analogues (S) (M)
   John M. Beals (Lilly, USA)
III. Case Histories

1. **Avanafil** Koichiro Yamada (Tanabe-Mitsubishi, Japan)
2. **Dapagliflozin** William Washburn (BMS, USA)
3. **Elvitegravir** Hisashi Shinkai (JT, Japan)
4. **Linagliptin** Matthias Eckhardt (Boehringer Ingelheim, G)
5. **Pemetrexed** Edward Taylor (Princeton University, USA)
6. **Perampanel** Shigeki Hibi (Eisai, Japan)
7. **Telaprevir** Govinda Rao (Vertex, USA)
8. **Trastuzumab emtansine** Sandhya Girish (USA)
Successful Drug Discoveries Vol. I.

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