II-B. MEDICINAL CHEMISTRY

Drug Discovery Checkpoints

Target Identification
1 ggctgtggag gacgccaccg accggagacc atttggggcc tggagatgcc atcggagggc
61 aggagctcat cctggagagg ccaccgtaag gcctgacctg ggcctgggga gcttggcttg
121 aggaagctnt gggccgacca aggccgccag gagatgggt

Lead Definition

Target Characterization

Clinical Testing

7 y

Drug Formulation

Candidate Evaluation

2-6 y

Lead Optimization

Lead Definition
Stages in the Drug Discovery Process


10 Year Trends in Biomedical Research

50% Decline in new product submissions

250% increase in R & D expenditures

NME = New molecular entities
BLA = Biologics

FDA Report March 2004: Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products
Drug Potencies & Rate of Target Innovation

- High Target Innovation
- Re-Use of Established Mechanisms

• Ca. 130 “privileged druggable domains” cover all current drug targets (vs. total number of protein families (16,000) and folds (10,000).
• Of ca. 1,620 distinct human protein sequences are linked to a genetic disease, only 105 are actual drug targets.
• Target innovation is slow - The average rate over the past 20 years has been quite constant at 5 new “drugged” targets per year.
• The first approved indications for drugs acting on new targets are usually orphan diseases.

The State-of-the-Art in Drug Discovery:

Small, incremental advances in fundamental biology, chemistry, and clinical sciences

“The Most Fruitful Basis for the Discovery of a New Drug is to Start with an Old Drug”

James Black - 1988 Nobel Prize in Physiology and Medicine
Current Drug Discovery Challenges

In Search of New Leads.....
Medicinal Chemistry

The science that deals with the discovery or design of new therapeutic agents and their development into useful medicines.

It involves:

• Organic Synthesis
• Biological Target Identification & Assay Development
• Structure-Activity Relationships (SAR)
• Absorption, distribution, metabolism, and excretion (ADME)

Why Is Structural Diversity An Issue?
‘Drug-like’ & ‘Lead-like’ Properties

‘Drug-like’ & ‘Lead-like’ Properties
‘Drug-like’ & ‘Lead-like’ Properties

- Reactive functionalities should be filtered:

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Where Did (Do) Our Drugs Come From?
Screening of natural product extracts

High-Pressure Accelerated Solvent Extractor System

DCM & MeOH Extracts

Parallel HPLC

HT Solvent Concentrator

Multiwell Plates For HTS

Examples of Natural Products as Leads & Drugs

Cardiac glycosides, morphine, quinine, salicylic acid, taxol, camptothecin, penicillin, cyclosporin A, warfarin, artemisine….

Morphine

Codeine (pain killer)

17-ethynylestradiol (the "Pill" contraceptive)

Norethindrone (an "IB" contraceptive)

Ampicillin (antibiotic)

Clarithromycin (antibacterial)

Augmentin (antibiotic)

Cyclosporine A
Drug Discovery
One way to “discover” drugs

‘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.

Serendipitous Drug Discovery
Serendipitous Discovery of Librium without a Lead

In 1955 Roche set out to prepare a series of benzheptoxadiazines as potential new tranquilizer drugs, but the actual structure was found to be that of a quinazoline 3-oxide.

In 1957, during a lab cleanup, a vial containing what was thought to be the latter compound (X = 7-Cl, R¹ = CH₂NHCH₃, R² = C₆H₅) was sent for testing, and it was highly active.

Further analysis showed that the actual structure of the compound was the benzodiazepine 4-oxide, *Librium*, presumably produced in an unexpected reaction of the corresponding chloromethyl quinazoline 3-oxide with methylamine.
“Me Too” Compounds

Copying existing drugs with only minor chemical variations is usually referred to as “me too” research. Interestingly, sometimes these close analogs demonstrate major (usually unexpected) advantages, like the bioavailable, broad-spectrum lactamase-resistant penicillins, polar H1 antihistamines without sedative side effects, statins, or PDE5 inhibitors.


May & Baker Ltd. (1972)

Pfizer (1999)

Pfizer (1992)

Rational Drug Discovery
Structure-Activity Relationships (SARs)

Structurally specific drugs (most drugs):
Act at specific sites (receptor or enzyme)
Activity/potency susceptible to small changes in structure

Structurally nonspecific drugs:
No specific site of action
Similar activities with varied structures (various gaseous anesthetics, sedatives, antiseptics)
Example of SAR

Sulfadruugs

Lead: sulfanilamide (R = H)

Thousands of analogs synthesized

From clinical trials, various analogs were found to possess several different activities:

- Antimicrobial
- Antidiabetic
- Diuretic
- Antihypertensive

Sulfadruugs SAR

Sulfanilamides as Therapeutics

1936
- Sulfadiazine
- Sulfathiazole
- Sulfamerazine
- Sulfadolone
- Sulfapyridine
- Sulfacetamide

1942
- IPDT (Experimental Drug)

1955
- Cefuroxime
- Tobramycin

1948
- Acenocoumarin
- Carbenicillin
- Dihydrostreptomycin

1957
- Chlorothiazide

Other Sulfonamides
- Other Sulfonamides
- (Piroxicam)

**Rational Drug Discovery - Piroxicam**

- It took Pfizer ~18 years to develop the anti-inflammatory drug piroxicam, which was launched in 1980 during the “golden age of rational drug discovery”.

- The starting point for the development was chemistry-driven, i.e. to identify acidic, but not carboxylic acid-containing (salicylic acid) structurally novel compounds.

- Measurement of a physical property (pKa) as well as serum half-life in dogs was the guide for the synthesis program.

- Several generations of leads were refined and ultimately led to a successful structure with an acceptable safety and activity profile:

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**Bioisosterism**

**Bioisosteres** - substituents or groups with chemical or physical similarities that produce similar biological properties. Can attenuate toxicity, modify activity of lead, and/or alter pharmacokinetics of lead.
Isosteres

Classical Isosteres

1. Univalent atoms and groups
   a. CH₃, NH₂, OH, F, Cl
   b. Cl, PH₂, SH
   c. Br, iPr
   d. tBu

2. Bivalent atoms and groups
   a. CH₂ = NH = O = S = Se
   b. COCH₂R, CONH₂R, CO₂R, COSR

3. Trivalent atoms and groups
   a. C==N
   b. P==As

4. Tetravalent atoms
   a. \(\begin{array}{c}
   \text{C} \\
   \text{O}
\end{array}\)
   b. \(\begin{array}{c}
   \text{S} \\
   \text{Se}
\end{array}\)

5. Ring equivalents
   a. CH=CH = S (e.g., benzene, thiophene)
   b. CH = N (e.g., benzene, pyridine)
   c. O = S = CH₂ = NH (e.g., tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)

Non-Classical Isosteres

Do not have the same number of atoms and do not fit steric and electronic rules of classical isosteres, but have similar biological activity.
4. Ester group

5. Hydroxyl group

6. Catechol

7. Halogen

8. Thioether

9. Thiourea

10. Azomethine

11. Pyridine

12. Benzene

13. Ring equivalents

14. Spacer group

15. Hydrogen
Examples of Bioisosteric Analogues

**Anthistamines**

\[ R-X-(CH_2)_n-Y \]

\[ X = \text{NH, O, CH}_2 \]

\[ Y = \text{N(CH}_3)_2 \quad (n = 2) \]

\[ \text{(n = 1, 2)} \]

Diphenhydramine  
(\text{Benadryl})

Fexofenadine  
(\text{Allegra})

Rational Drug Discovery - From Hit to Lead

Case Study: Use of a combined rational design - combinatorial chemistry strategy


The interaction of LFA-1 with the ICAM proteins 1, 2, and 3 is critical to the adhesion, migration, and proliferation of lymphocytes.

A disruption of these protein-protein interactions could lead to agents for the treatment of psoriasis and transplant rejection.
An epitope comprising residues E34, K39, M64, Y66, N68, and Q73 within ICAM-1’s first domain was identified as essential for its interaction with LFA-1. The function of this epitope is embedded in the **carboxylic acid, amine, sulfide, phenol, and carboxamide** chemical functionalities of the amino acid side chains of these six residues and their display in three dimensions along one face of the protein.

Molecules which mimic this epitope could capture the LFA-1 binding specificity and safety inherent in ICAM-1’s function as a regulator of the immune system.
More or less serendipitously, compound 1 was found to be an inhibitor of LFA-1.
Comparison of the inhibition of ICAM-1/LFA-1 binding and the inhibition of mixed lymphocyte reaction (MLR). IC₅₀ values were determined from a 4P fit of data from titrations over concentrations of 10⁻³ to 10⁻¹⁰ M. Values reported are the mean±standard deviation for n>2 of experiments run in triplicate. ND, not determined. NA, not applicable.

<table>
<thead>
<tr>
<th>Substance</th>
<th>LFA-1 ELISA IC₅₀ (µM)</th>
<th>MLR IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kistrin</td>
<td>0.70 ± 0.21</td>
<td>40*</td>
</tr>
<tr>
<td>H₂N-CRGDMPC-COOH</td>
<td>207 ± 69</td>
<td>ND</td>
</tr>
<tr>
<td>H₂N-CGFDMPC-COOH</td>
<td>13 ± 3.2</td>
<td>ND</td>
</tr>
<tr>
<td>H₂N-CGY(D)/DMPC-COOH†</td>
<td>1.6 ± 0.1</td>
<td>ND</td>
</tr>
<tr>
<td>Compound 1</td>
<td>1.4 ± 0.7</td>
<td>ND</td>
</tr>
<tr>
<td>Compound 2</td>
<td>0.047 ± 0.014</td>
<td>10.3 ± 6.3</td>
</tr>
<tr>
<td>Compound 3</td>
<td>0.0037 ± 0.0015</td>
<td>1.33 ± 1.1</td>
</tr>
<tr>
<td>Compound 4</td>
<td>0.0014 ± 0.00014</td>
<td>0.003 ± 0.002</td>
</tr>
<tr>
<td>Cyclosporine A</td>
<td>NA†</td>
<td>0.061 ± 0.034</td>
</tr>
<tr>
<td>MHM 24 Fab§</td>
<td>0.0023 ± 0.0001</td>
<td>0.020 ± 0.008</td>
</tr>
</tbody>
</table>

*Incomplete titration, value estimated at 50% inhibition. †Y(D) = meta-tyrosine. ††The immunosuppressive activity of cyclosporine does not involve its direct binding to LFA-1 or ICAM-1. §MHM 24 Fab is the Fab fragment of the murine anti-human antibody recognizing LFA-1's CD11a subunit (7).

Two orthogonal views of the superimposition of compound 4 on the crystal structure of the first domain of ICAM-1 indicating that compound 4 mimics the ICAM-1 epitope. Residues highlighted in blue contribute significantly to LFA-1 binding. The E34 side chain of ICAM-1 has been rotated to a low-energy conformation to enhance the overlay with compound 4.
Conclusions:

Compounds 2 through 4 appear to be mimics of ICAM-1 resulting from the transfer of the ICAM epitope to a small molecule.
Compound 4 is a potent LFA-1 antagonist, which binds LFA-1, blocks the binding of ICAM-1, and inhibits LFA-1 mediated lymphocyte proliferation and adhesion in vitro.

This work represents the first reduction of a nonlinear, discontinuous but contiguous protein epitope (encompassing five residues spanning three different b-strands across the face of a protein surface) from a protein to a small molecule.

Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

The pharmacological hypothesis:

Ding et al. JACS 2005, 127, 10130.
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

Structure-Based Design:

- Phe19
- Trp23
- Leu26
- MDM2
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

Structure-Based Strategy:

(A)

(B) Trp23, Leu28, Phe19

p53 peptide
Structure-Based Design of Potent Non-Peptide MDM2 inhibitors

Gene-Family Distribution of Current Drugs

There currently are >21,000 drug products available. If you remove duplicate active ingredients, salt forms, supplements, vitamins, imaging agents, this number is reduced to 1,357 unique drugs of which 1,204 are "small molecule drugs" and 166 are "biological" drugs.

Further reading: