Learning from Nature: From Natural Products to Designer Molecules

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IRCC Research Paper Award Lecture on August 11, 2010
Nature-Inspired Discoveries
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A Japanese bullet train with a kingfisher's nose
“…Where nature finishes producing its own species, man begins, using natural things and in harmony with this very nature, to create an infinity of species”

Leonardo da Vinci (1452 –1519)

“…It’s a case of learning from nature. We look at living things and ask ourselves how they do what they do. We try to extract basic principles from this, then use them to assemble structures…..”

George M. Whitesides
Role of Synthetic Chemistry

- Biology
- Materials
- Chemistry
- Medicine
Discovery of Taxotere

- Discovered by Pierre Potier at CNRS at Gif-sur-Yvette.
- Developed by Rhône-Poulenc Rorer (now Sanofi-Aventis).
- Docetaxel is currently protected by patents (U.S. patent 4814470, European patent no EP 253738, due to expire in 2010) which are owned by Sanofi-Aventis.
- Twice as active as Taxol.
Some Parts are Greater than the Whole

All parts of the molecule are not needed for the anticancer activity.

Deletion of unnecessary parts makes the molecule and its synthesis much simpler but with similar biological activity.

Wender P. A.; Miller, B. L. Nature 2009, 460, 197-201
Discovery of Clarithromycin and Azithromycin

- Clarithromycin invented by researchers at the Japanese drug company Taisho Pharmaceutical in the 1970s
- Erythromycin, because of poor acid stability in the digestive tract causes side effects, such as nausea and stomach ache
- Azithromycin shows improved acid stability, increased oral bioavailability, longer half-life, higher intracellular concentration, and broader antibacterial activity
- Binding to the growing peptide in the trough of the 50S subunit to inhibit the protein biosynthesis
Modification of Radicicol and Epothilone B

- Excision of epoxide oxygen and introduction of trifluoro methyl group and a double bond results in improved stability and cytotoxicity

Modification of Epothilone A to Ixabepilone

While natural epothilones A & B show potent antineoplastic activity in vitro, these effects were not seen in preclinical in vivo models due to their poor metabolic stability and unfavorable pharmacokinetics.

Ixabepilone demonstrated superior preclinical characteristics, including high metabolic stability, low plasma protein binding and low susceptibility to multidrug resistance protein-mediated efflux.

It also showed in vivo antitumor activity in a range of human tumor models.

Approved in October 2007 for breast cancer.

Discovery of Darunavir

Darunavir is a protease inhibitor

- Proteases are vital for both viral replication within the cell and release of mature viral particles from an infected cell
- Saquinavir-type inhibitors have severe side effects, are toxic, costly to manufacture, require high therapeutic dose and show a disturbing susceptibility to drug resistant mutations, and specifically show poor absorption properties
- Darunavir was designed to overcome these issues
- Approved by the FDA on June 23, 2006 as HIV protease inhibitor
- Marketed by Tibotec pharmaceutical company
Pemetrexed (ALIMTA, LY231514, MTA) is a novel antimetabolite that inhibits at least three enzymes (used in purine and pyrimidine synthesis) involved in the folate pathway.

These enzymes are thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase.

Clinically developed by Eli Lilly and Company in 2004.

Approved by the FDA in February 2004.

Designed to alleviate the severe side effects of Methotrexate.

To lower the side effects, patients are given folic acid (Vitamin B9) and Vitamin B12.
Objectives

- Total Synthesis of Natural Products
- Simplifying the Target Molecules (Natural Products)
- Designing New Molecular Scaffolds (Natural Product-like Molecules)
Isolated by B. J. Baker and co-workers from Antarctic Tunicate Synoicum Adareanum in 2006

It shows cytotoxic activity against melanoma, colon cancer cell line and one renal cancer cell line

Polyketide natural product belongs to the Leptomycin family

Isolated from marine sponge Callyspongia truncata in the Nagasaki Prefecture

It shows remarkable in vitro cytotoxicity ($IC_{50} = 0.01$ ng/mL) against KB cells

It binds covalently to the nuclear export protein CRM1

Kaliappan, K. P.; Gowrisankar, P. *Synlett* 2007, 1537-1540
Total Synthesis of Natural Products (Cladospolides)

- Isolated from different *Cladosporium* sp.
- Responsible for the plant’s growth regulation, which is believed to occur via the inhibition of gibberellin biosynthesis

Kaliappan, K. P.; Si, D. *Synlett* 2009, 2441-2444
Total Synthesis of Natural Products (Angucyclinones)

- Large group of naturally occurring quinones
- Isolation started from 1960s
- Isolated from *Streptomyces*
- Show antibacterial, antiviral, antitumor activity

Kaliappan, K. P.; Ravikumar, V. *Synlett* 2007, 977-979
Kaliappan, K. P.; Ravikumar, V. *J. Org. Chem.* 2007, 72, 6116-6226
Simplifying the Target Molecules (Eleutheroberin)

- Isolated from marine soft corals found in the Indian Ocean by Fenical in 1995
- As active as Taxol

Kaliappan, K. P.; Kumar, N. *Tetrahedron* 2005, 61, 7461
Simplifying the Target Molecules (Dysidiolide)

- Isolated in 1996 from the Marine Sponge Dysidea etherea
- First natural inhibitor of dual specificity phosphatase Cdc25 A
- Potential anticancer agent
- Unusual hydroxybutenolide side chain

Simplifying the Target Molecules (Thapsigargins)

Thapsigargin; $R^1=\text{octanoyl}, R^2=\text{butanoate}$
Tribolide; $R^1=H, R^2=(S)-2\text{-methyl butanoate}$
Nortrilobolide: $R^1=H, R^2=\text{butanoate}$
Thapsivillosin F: $R^1=H, R^2=\text{3,3-dimethylacrylate}$

Designing New Molecular Scaffolds

- Moderate activity – colon (IC$_{50}$ = 4.37 μM), breast (IC$_{50}$ = 4.38 μM), leukemia (IC$_{50}$ = 7.38 μM), and ovary (IC$_{50}$ = 8.63 μM) cancer cell lines

- Good activity – pancreas (IC$_{50}$ = 2.64 μM) and oral (IC$_{50}$ = 2.75 μM) cancer cell line

Designing New Molecular Scaffolds

Sugar-Triquinane Hybrids
Kaliappan, K. P.; Nandurdikar R. 
*Chem. Commun.* 2004, 2506

Taxol-Sugar Hybrids
Kaliappan, K. P.; Das, P.; Kumar, N. 
*Tetrahedron Lett.* 2005, 46, 3037
Designing New Molecular Scaffolds

Sugar-Endiyne Hybrid

C-aryl glycosides

Spiro-C-aryl glycosides

Sugar based B-lactams

Hyacynthacines

Sugar based triazoles
Designing New Molecular Scaffolds

An Expedient Enantioselective Strategy for the Oxatetracyclic Core of Platensimycin

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Received April 11, 2007

ABSTRACT

An enantioselective route for the synthesis of oxatetracyclic core of platensimycin is reported for the first time using a 5-exo-trig cyclization followed by intramolecular etherification as key reactions. The requisite dienynone for the radical cyclization is synthesized in eight steps from the Wieland–Miescher ketone employing a Claisen rearrangement.
History of Antibiotics

Although potent antibiotic compounds for treatment of human diseases caused by bacteria were not isolated and identified until the twentieth century, the first known use of antibiotics was by the ancient Chinese over 2,500 years ago.

Development of the narrow-spectrum antibiotic Salvarsan by Paul Ehrlich in 1909 in Germany, for the first time allowing an efficient treatment of the then-widespread problem of Syphilis.
Further developed in Britain following the re-discovery of Penicillin in 1928 by Alexander Fleming

More than ten years later, Ernst Chain and Howard Florey became interested in his work, and came up with the purified form of penicillin. The three shared the 1945 Nobel Prize in Medicine
Tuberculosis

Chest X-ray of a patient suffering from tuberculosis

Dr. Robert Koch discovered the tuberculosis bacilli 1905 Nobel Prize in medicine

Tubercular decay has been found in the spines of Egyptian mummies. Pictured: Egyptian mummy in the British Museum

Mantoux tuberculin skin test

Public health campaigns tried to halt the spread of TB

Scanning electron micrograph of Mycobacterium tuberculosis

PREVENT DISEASE

CARELESS SPITTING, COUGHING, SNEEZING, SPREAD INFLUENZA AND TUBERCULOSIS
A 24-year-old man infected with leprosy

Cutaneous leprosy lesions on a patient’s thigh

G. H. A. Hansen, discoverer of *Mycobacterium leprae*

*Mycobacterium leprae*, the causative agent of leprosy
Need for New Antibiotics

- Antibiotics available in the market were discovered in 1930’s and 40’s

- Some of the recent antibiotics are either derivatives or semisynthetic version of existing ones

- In the last 50 years only two new antibiotics of new chemical classes, linezolid and daptomycin have gone to clinicals

- It has become difficult to identify new classes of anti-biotics which could act on different targets which is the need of the hour
Platensimycin

- Isolation: It was isolated from *Streptomyces platensis* found in soil in South Africa.
- Platensimycin is the first antibiotic natural product with a new mechanism of action (inhibiting condensing enzyme FabF) discovered in over 40 years.
- Structure – 2D NMR, X-ray Crystallography

Methicillin resistant *Staphylococcus Aureus (MRSA)*
Vancomycin resistant *enterococci (VRE)*
Penicillin-resistant *Streptococcus pneumoniae (PRSP)*

Merck Research Laboratories in Rahway, New Jersey.

For reviews on platensimycin, see:
Mechanism of Action of Platensimycin

- **β-ketoacyl-ACP product**
  - $\text{R} \overset{\text{O}}{\overset{\text{S}}{\text{ACP}}} + \text{CO}_2$

- **malonyl-ACP substrate**
  - $\overset{\text{O}}{\overset{\text{S}}{\text{ACP}}} \text{HO-CH}_2\text{S-ACP}$

- **acyl-enzyme intermediate**
  - $\overset{\text{S}}{\text{R-ACP}} \overset{\text{O}}{\text{O}}$

- **fatty acid-ACP substrate**
  - $\overset{\text{O}}{\overset{\text{S}}{\text{ACP}}}$

- **HS-ACP**

- **platensimycin**

Diagram shows the interaction between these components in the mechanism of action.
Synthesis of Oxatetracyclic core of (-)-Platensimycin

1) NaBH₄, MeOH → TBSO⁻
2) TBSCI → TBSO⁻

1) DIBAL-H, DCM → TBSO⁻

NaH, cat. KH, THF, rt, 12 h, 89%

Decalin, 180 °C → TBSO⁻
5 d, 59%

1) TBAF, 89%
2) IBX, DMSO, 82%

K₂CO₃, MeOH, 73%
Synthesis of Oxatetracyclic core of (-)-Platensimycin

Our Proposed Diversity Route

- Different aryl groups
- Vary the length of the linker
- Different Alkyl Groups
- Different Alkyl Groups
Acknowledgements

Ph.D Students
1. Dr. Nirmal Kumar (Ranbaxy)
2. Dr. Rahul Nandurdikar (NCI-Bethesda)
3. Dr. V. Ravikumar (Advinit)
4. Dr. Samaresh Panda (Lupin)
5. Dr. A. Subrahmanyam (UMASS, Amherst)
6. Dr. P. Gowrisankar (Purdue University)
7. Dr. S. Narayanamurthy (UMASS, Amherst)
8. Dr. Prasanta Das (UTexas, Southwestern Medical Center, USA)

M. Sc. Students
1. Dr. Raghunath Roy (UMASS, Amherst)
2. Vikram Bhat (Univ. of Chicago)
3. Somnath Jana (Oregon State Univ.)
4. Dipankar Basak (UMASS, Amherst)
5. Shiven Kapur (Stanford University)
6. Venuka Durani (Ohio State Univ.)
7. Ankit Sharma (Univ. of Geneva)
8. Subham Mahapatra (Oregon State Univ.)
9. Sumit Kumar (Asset Link)
10. Anirudha Sasmal (University of Pittsburgh)
11. Animesh Verma (Lovely University)
12. Amit Kumar (University of Zurich)
13. Souvagya Biswas (Ohio State University)
14. G. Deepti (Cornell University)
15. Chintan Sumaria
16. Shravan Challa
17. Shyamal Chakraborty

Financial and Other Support
1. Swarnajayanti Fellowship, DST, New Delhi
2. Department of Science & Technology, New Delhi
3. CSIR, New Delhi
4. IIT Bombay
5. SAIF, IIT-Bombay