Objectives of NIPER, Raebareli

- Enhancement of creativity, motivation and inculcate professionalism.

- Bring synergy between academics, R&D organizations and industry through training and exposure to such environment.

- Facilitate collaborations between pharmacy, biotechnology, information technology and prepare for meeting global challenges.

- Prepare professionals to suit the needs of pharmaceutical industry.

- Expose the students and scholars to high-tech areas such as drug design and molecular modeling.

- Harness natural products, local skills and knowledge in health care.
MESSAGE

Due to exceptional growth of the pharma industry worldwide, there is tremendous demand for highly trained and talented human work force for research and development in this sector. To meet out needs of the pharmaceutical industry, Government of India established six new National Institutes of Pharmaceutical Education and Research (NIPERs), including NIPER, Raebareli under the aegis of Ministry of Chemical and Fertilizers, a step in the right direction.

It is matter of great satisfaction that the Director, CSIR-Central Drug Research Institute, Lucknow and his management team have gone beyond this normal call to duty with devotion and motivation to establish NIPER, Raebareli as a centre of excellence comparable to the best in the country.

I am also happy to note that NIPER, Raebareli has added M.S. (Pharm.) “Pharmacology and Toxicology” from this current academic year 2012-13 in addition to M.S. (Pharm.) Medicinal Chemistry and M.S. (Pharm.) Pharmaceutics already being offered from 2008-09 onwards.

The Government of Uttar Pradesh has identified approx. 50 acre land in Raebareli district for NIPER, Raebareli. I am sure that U.P. Government would quickly transfer the identified land to NIPER, Raebareli thus facilitating construction of full-fledged NIPER campus.

On the occasion of 4th Annual Day celebration of NIPER, Raebareli, I extend my felicitations and best wishes to all students, faculty, management and the Director and associated scientists of the mentor institute CSIR - Central Drug Research Institute, Lucknow.

I am confident that NIPER, Raebareli shall achieve greater heights in years to come.

(DILSHER SINGH KALHA)
19th October, 2012

MESSAGE

I am pleased to know that NIPER, Raebareli has successfully completed four years of functioning since its inception in 2008. Application of new approaches to drug design and discovery and all activities related to drug development requires excellent, well trained and dedicated human resources. The management and faculty members of NIPER, Raebareli are firmly progressing in their endeavor to achieve the goal.

The creation of a new professional institute is, beyond doubt, a difficult task requiring support at every execution level. Despite the challenges, the mentor Director, CSIR-Central Drug Research Institute, management team and faculty members of NIPER, Raebareli have been doing an excellent job in providing best facilities and infrastructure resources needed.

I am happy to know that M.S. (Pharm.) "Pharmacology & Toxicology " has been added from the current academic year 2012-13 in addition to M.S. (Pharma.) Medicinal Chemistry and M.S. (Pharm.) Pharmaceutics already being offered from 2008-09.

On the occasion of 4th Annual Day celebration of NIPER, Raebareli, I extend my felicitations and best wished to all students, staff, faculty and management.

I am confident that NIPER, Raebareli shall flourish as center of excellence imparting higher education, research and development in pharmaceutical sciences.

(Dr. Raja Sekhar Vundru)
It is a matter of great satisfaction that NIPER, Raebareli has completed 4\textsuperscript{th} year of functioning since its inception in 2008. The institute has been striving very hard to prove itself a centre of excellence in creation of trained human capital in the field of pharmaceutical education, research and development to cater to the need of pharma industry of the country. The faculty members of NIPER, Raebareli as well as the scientists of CSIR-Central Drug Research Institute, Lucknow have been putting their extra energy, devotion and motivation despite some logistic distances.

It is also a matter of satisfaction that one more stream in the field of Pharmacology and Toxicology has been added from current academic year in addition to two main streams in the field of M.S. (Pharm.) in Medicinal Chemistry, and Pharmaceutics being offered from 2008 onwards.

The infra structure facilities and resources created in record time at NIPER, Raebareli with the untiring efforts of the management team need special mention. I am sure these efforts will continue in future.

I congratulate all the students, faculty, management and other associated scientist of CSIR-CDRI on this auspicious occasion being an important milestone in the journey of NIPER, Raebareli. I am confident that this institute shall achieve greater heights in years to come.

\begin{flushright}
Dr. Tushar K. Chakraborty
Mentor & Director,
CSIR-CDRI, Lucknow
\end{flushright}
Professional education provides the students to unearth and polish their talents in a particular direction to not only make their career bright but also serve the society in excellent manner. Indian pharmaceutical industry is growing consistently and needs skilled and talented researchers. NIPER, Raebareli always gives emphasis on overall development of outstanding talents by providing students a wide exposure and opportunity of interaction through participation in various conferences, seminars and visits to industry.

Since its inception in 2008, the institute has been offering M.S. (Pharm.) degree in Medicinal Chemistry and Pharmaceutics. A 3rd discipline has been introduced in M.S. (Pharm.) in Pharmacology and Toxicology from the current academic session where a total of seven students have joined the course. NIPER, Raebareli is making sincere efforts to produce competent and talented human resource in the area of pharmaceutical education and research that would cater to the needs of our country. Three batches of students have passed out, the 4th batch students are carrying out their project work in CSIR-CDRI and the 5th batch of students has joined a couple of months back. This year also the faculty has been strengthened further and a new lab has been created to cater to the need of students.

I acknowledge with utmost appreciation the ongoing endeavors of our dedicated faculty. I am also thankful to the mentor, all associated scientists of CSIR-CDRI and staff members for their full support and cooperation.

Dr. P.K. Shukla
Project Director
The National Institute of Pharmaceutical Education and Research (NIPER), Raebareli, created on November 14, 2008 under the mentorship of CSIR-Central Drug Research Institute, Lucknow, is completing 4 years of its creation. Like previous years the fourth batch had two streams M.S. (Pharm.) Medicinal Chemistry and M.S. (Pharm.) Pharmaceutics and the students were provided with excellent teaching and laboratory exposure supported by the staff of NIPER, Raebareli, eminent scientists of CSIR-CDRI, CSIR-NBRI and other reputed educational institutions of Lucknow and New Delhi. During the current academic year 2012-2013, a new stream of M.S. (Pharm.) Pharmacology and Toxicology has been started where Dr. Neeraj Sinha and Dr. Kashif Hanif have been given the responsibility of course-coordinators. Before starting the new course, a new laboratory has been created. The total strength of student in I semester of the current academic year is 39 and III semester is 31. Till now a total of 88 students have passed out and 70 are continuing in the I and III semester.

The 5th batch students joined NIPER, Raebareli in the first week of August, 2012 through joint entrance examination conducted by NIPER, Mohali. There are 16 students in M.S. (Pharm.) Medicinal Chemistry, 16 in Pharmaceutics and 7 in Pharmacology and Toxicology. During the past one year, a new lab for M.S. (Pharm.) Pharmacology and Toxicology was created and a number of new equipments were ordered for purchase out of which few have already been installed and are being used to teach the students. The list of new equipments installed recently includes Audiogenic Chamber, Pole Climbing Apparatus, Histamine Chamber, Digital Swimming Test Chamber, Metellar balance, Electrophoresis unit etc. Now our labs are well equipped in both the disciplines. In addition one small lab space and an animal holding room have also been created. The 4th batch students have joined CSIR-CDRI under the able supervision of different scientists of CSIR-CDRI for the III and IV semester after completing I and II semester here in Raebareli.
Seated on the dais (l. to r.) are: Dr. D. K. Dikshit, Project Director, NIPER, Raebareli; Dr. V.P. Kamboj, Ex-Director, CSIR-CDRI and Dr. T. K. Chakraborty, Director, CSIR-CDRI during 3rd Annual Day Celebrations held on 14th November, 2011.

NIPER, Raebareli celebrated its 3rd Annual Day on 14th November, 2011. The Annual Day lecture “Art and Science of New Drug Development” was delivered by Dr. V.P. Kamboj, Ex-Director, CSIR-Central Drug Research Institute, Lucknow. Dr. T.K. Chakraborty, Director, CSIR-CDRI, Lucknow addressed the staff members and students of NIPER and the scientists of CDRI. The function was attended by eminent scientists, technologists and academia of Uttar Pradesh. Students were also given awards for their participation in various extracurricular activities during the year.

As in previous years, this year also a symposium “4th NIPER (RBL)-CDRI Symposium on Medicinal Chemistry and Pharmaceutical Sciences” was organized during February 23-25, 2012 at CSIR-CDRI, Lucknow to enable the students in updating their knowledge and awareness.
about recent scientific developments. This was the 4th symposium in the annual series with an aim to give an exposure to the students of NIPER, Raebareli and other pharmacy colleges of the country, to recent developments in the frontier areas of drug discovery, development and delivery systems as well as to interact with researchers working in pharmaceutical sciences. The inaugural address was delivered by Professor D.K. Gupta, Vice Chancellor, CSMMU, Lucknow and the key note lecture was delivered by Professor Prabhat Arya, Institute of Life Sciences,
Hyderabad on the topic 'Post genomics drug discovery: challenges and opportunities'. The inaugural function was presided over by Dr. V.P. Kamboj, Former Director, CSIR-CDRI, Lucknow. About 95 posters were presented and over 25 lectures on various research topics were delivered by eminent speakers from pharma industry and academia (notably Ranbaxy Laboratories, Zydus, Reddy's Laboratories, Hyderabad, BHU, CSIR-CDRI, Lucknow, CSIR-NCL, Pune, JNCASR, Bangalore, IIT, Bombay, IIGEB, New Delhi and Delhi University) during two days of scientific deliberations. Several current topics such as (i) Biochemical assay and
characterization of a protease inhibitor (ii) Inhibiting protein- Protein interactions in pathogens (iii) Targeting microtubules of *P. falciparum* (iv) Epigenetic modifications in transcription regulation: Implications in therapeutics (v) Nanoformulations: let us go green (vi) Green chemistry in pharmaceutical sciences (vii) Drug discovery for malaria: challenges and opportunities (viii) Repositioning of FDA approved drugs in cancer and osteoporosis and many others were presented and discussed. The poster session was spread over two days where in addition to the original research work based presentations, M.S.(Pharm.) students also displayed their project based presentations. The students had discussions with the speakers from the pharma-industry and eminent scientists about their prospects in research and pharma-industry. The best and the second best posters in above two distinct categories were recognized in the form of cash award. A cultural program on the evening of 24th February, 2012 was also arranged for the participants.

Teaching for II semester of 4th batch of M.S. (Pharm.) Medicinal Chemistry and M.S. (Pharm.) Pharmaceutics was completed in the first week of May, 2012 and final examinations were conducted from May 28-June 7, 2012. The II semester was competed on 20th June, 2012 after practical examination and seminar. The results of the II semester examination were declared on 10th July, 2012. Out of 33 students, 1 student secured A, 10 students secured A(-), 11 students secured B, 10 students secured B(-) and 1 student secured C grade. IV semester of 3rd batch of M.S. (Pharm.) Medicinal Chemistry, and Pharmaceutics was competed on 26th June, 2012 after final presentation of their thesis work. The results of the IV semester examination were declared on 27th June, 2012. Out of 30 students, 4 students secured A, 8 students secured A(-), 14 students secured B and and 4 students secured B(-) grade. All the above 33 students of 4th Batch reported at CSIR-CDRI, Lucknow for their III semester started from 1st July, 2012. Students from both the disciplines have been associated with scientists in the Divisions of Medicinal & Process Chemistry, Pharmaceutics, and Pharmacokinetics & Metabolism for their project work and the students are making good progress.

In the mean time, two new faculty members have joined NIPER, Raebareli (1 for Medicinal Chemistry and 1 for Pharmacology & Toxicology), and the total strength of staff is given at the end of this report. As a regular feature our library is regularly updating itself and presently...
more than 850 books on various related topics to the courses run are available for students. Few more books have recently been processed for procurement to update and cater the needs of students. Recently the library facilities have been made available to students from 9:00 AM to 1:00 PM on Saturdays to facilitate their development", delivered by Prof. J.K. Paliwal, Deptt. of Pharmaceuticals, NIPER, Mohali. It was really valuable for students as well as for faculty. Before these lectures, one science quiz was organized by Dr. Anuj Garg and Dr. Gulam Husain. The programme concluded with a short cultural presentation by 1st year students.
studies.

Various extracurricular activities including sports were organized under the supervision of Dr. Abha Sharma, Mr. Achint Jain, Mr. Anuj Garg, Mr. Manoj Mishra and Mr. Somit Kumar. The students participated with full enthusiasm in these activities and secured different positions. Institute congratulates those who won the prizes and wish good luck to all others for their future endeavours. Like previous years, Rx Pharmacy Day, 2012 was successfully organized at NIPER, Raebareli on 22nd September, 2012, with the support of Mr. Achint Jain and all the faculty and staff members. Scientific session included very informative lecture by Dr. D.K. Dikshit, Ex-Chief Scientist, CSIR-CDRI, Lucknow and Ex-project Director, NIPER, Raebareli has given comprehensive lecture on “Drug Research - A Historical Perspective”, in that he has told so many mile stones in the field of drug discovery, which were unexplored by the students. The second lecture was delivered by Dr. Ashok Kumar, President, IPCA Lab., Mumbai on the topic “Innovations”, which was lively, interactive and full of motivation for everyone while the third talk was on the topic “PK-PD in drug discovery& of the institute. Mr. Siddharth Singh and Ms. Vineeta Saran, 1st year students hosted the event and vote of thanks was delivered by Mr. Achint Jain, faculty member of institute.

The NIPER, Raebareli students working in CSIR-CDRI under the supervision of CSIR-CDRI Scientists were successful in getting a few publications in reputed journals and they deserve hearty congratulations. Few of the passout students of 3rd batch got admissions to Ph.D. courses in CSIR-CDRI and NIPER, Mohali. This year the placement brochure has been published and various pharmaceutical Industries and academic institutions are being contacted for suitable placement of our students.

The time ahead is full of new challenges and expectations. It is hoped that forthcoming year would unfold itself with unlimited achievements in every field. The management committee of NIPER, Raebareli is striving hard to meet out new challenges, creation of new disciplines, induction of fresh blood in teaching, development of infrastructure and facilities to make NIPER, Raebareli a centre of excellence in pharmaceutical education and research in the country.
Infrastructure and major facilities

Dissolution Apparatus (Pharmaceutics Lab)

Magnetic Stirrer (Pharmaceutics Lab)

HPLC (Pharmaceutics Lab)

pH Meter (Pharmaceutics Lab)

Medicinal Chemistry Lab

Medicinal Chemistry Lab
The students were inspired for scientific publication and presentation to bring NIPER, Raebareli on scientific research platform which led to publications in reputed journals with inputs from project work and presentation of papers in conferences.


**Papers Presented in Conferences by NIPER, Raebareli Students**

*4th NIPER (RBL)-CDRI Symposium on Medicinal Chemistry and Pharmaceutical Sciences (23-25 February, 2012)*

1. Rapid Assembly of Molecular Diversity via Exploitation of Isocyanide-Based Multi-Component Reactions - Ashish Sharma.
2. Anticancer Activity of Indigoide Drugs - Dyoti Sahu, Sonakshi Chauhan, Dr.Devesh Sawant.
3. Our DNA is Not Our Destiny - Mohan, M.
4. Palladium Catalysed C-C Bond Cross-Coupling Reaction and their Synthetic Applications in Drug Synthesis - Mrityunjay Singh.
5. Click Chemistry and its Applications - Prerna Ganwir, Archita Gupta.
7. Palladium Catalyze C-C Cross Coupling Heck Reaction and Their Synthetic Application in Drug Discovery - Shekh Sabir and Mrityunjay Singh.
11. Formulation and Evaluation of W/O/W Type Multiple Emulsion of Isoniazid - Ponnam Sairam, Chinnapatla Mahesh Reddy and Manoj Deevenapalli.


19. Development of Multifunctional Organocatalysts and Organocatalytic Cascade Reactions To Synthesize Complex Bioactive Natural Products - Shubhra Sharma, Piyush Kumar, Yashoda Krishna and Dipankar Koley.


23. Solid Phase Synthesis of Biologically Active Peptides (Temporins) - W.Haq and Renu Yadav.

24. determination of In Vitro Metabolic Stabilility of Lumefantrine and Investing Its CYP Inhibitory Potential Using Rat Liver Microsomes - Isha Taneja, Sumit Arora, KSR Raju, SP Singh, Wahajuddin and GK Jain.


28. Antiproliferative Lipid Coated Biodegradable Calcium Phosphate Nanoparticles for Si RNA Delivery - Deonarayan Singh, Dr. Surender Reddy Bathula.


30. Anticancer Activity of Indigoid Drugs - Dyoti Sahu, Sonakshi Chauhan and Dr. Devesh Sawant.

31. Chemistry for the Twenty First Century: Bringing the “Real World” Into the Lab - Manasa P.L.

32. Engineering of Indole-Based Tethered Biheterocyclic Alkaloid Meridianins into -Carboline Derived Tetracyclic Polyheterocycles via Amino Functionalization/6-Endo Cationic π-Cyclization - Meena Devi, D, Manisha Yadav, Sabyasachi Sanyal and Bijoy Kundu.

33. Solid Phase Synthesis of Biologically Active Peptides (Temporins) - W.Haq and Renu Yadav.
34. Development of Multifunctional Organocatalysts and Organocatalytic Cascade Reactions to Synthesize Complex Bioactive Natural Products - Shubhra Sharma, Piyush Kumar, Yashoda Krishna and Dipankar Koley


## Academic Calendar: 2012-13

### Semester (July to December)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation of Students</td>
<td>3rd August, 2012</td>
</tr>
<tr>
<td>Commencement of Semester</td>
<td>6th August, 2012</td>
</tr>
<tr>
<td>Departmental Introduction Session of Faculty, Staff and Students</td>
<td>6th August, 2012</td>
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<tr>
<td>1st Sessional Examination - (I Semester)</td>
<td>6th August, 2012</td>
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<tr>
<td>Submission of Semester Attendance of Students up to 27th September, 2012</td>
<td>10th-14th September, 2012</td>
</tr>
<tr>
<td>Mid-Term Examination - (I Semester)</td>
<td>28th September, 2012</td>
</tr>
<tr>
<td>Foundation Day</td>
<td>8th 12th October, 2012</td>
</tr>
<tr>
<td>2nd Sessional Examination - (I Semester)</td>
<td>14th November, 2012</td>
</tr>
<tr>
<td>Faculty Assessment by Students</td>
<td>21st-27th November, 2012</td>
</tr>
<tr>
<td>Submission of Semester Attendance of Students up to 6th December, 2012</td>
<td>26th-27th November, 2012</td>
</tr>
<tr>
<td>Submission of Mid-Term Report on Thesis Work - III Semester</td>
<td>7th December, 2012</td>
</tr>
<tr>
<td>End-Semester Examination - (I Semester)</td>
<td>6th-7th December, 2012</td>
</tr>
<tr>
<td>Mid-Term Presentation of Thesis Work - (III Semester)</td>
<td>10th 21st December, 2012</td>
</tr>
<tr>
<td>Provisional Registration for January to June 2013 Semester</td>
<td>10th-14th December, 2012</td>
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<tr>
<td>Submission of Marks by Examiners (I &amp; III Semester)</td>
<td>17th 21st December, 2012</td>
</tr>
<tr>
<td>Declaration of Result (I &amp; III Semester)</td>
<td>21st December, 2012 onwards with late fee</td>
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<tr>
<td></td>
<td>Up to End of 1st Week Jan 2013</td>
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<td>Up to 18th January, 2013</td>
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### Semester (January to June)

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<th>Activity</th>
<th>Dates</th>
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<tbody>
<tr>
<td>Commencement of Semester</td>
<td>7th January, 2013</td>
</tr>
<tr>
<td>Assignment of II Semester Masters Students to Advisors</td>
<td>2nd Week of January, 2013</td>
</tr>
<tr>
<td>1st Sessional Examination - (II Semester)</td>
<td>14th-18th February, 2013</td>
</tr>
<tr>
<td>Submission of Semester Attendance of Students</td>
<td>Up to 28th February, 2013</td>
</tr>
<tr>
<td>Mid-Term Examination - (II Semester)</td>
<td>11th 15th March, 2013</td>
</tr>
<tr>
<td>2nd Sessional Examination - (II Semester)</td>
<td>15th-19th April, 2013</td>
</tr>
<tr>
<td>Constitution of SRCs for II Semester Students</td>
<td>3rd Week of April, 2013</td>
</tr>
<tr>
<td>Presentation of Seminar (II Semester Students)</td>
<td>30th April 6th May, 2013</td>
</tr>
<tr>
<td>Faculty Assessment by the Students</td>
<td>2nd 3rd May, 2013</td>
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<tr>
<td>Provisional Registration July to December 2013 Semester</td>
<td>7th 15th May, 2013</td>
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15th May, 2013 onwards with late fee

<table>
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<tr>
<th>Event</th>
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<tbody>
<tr>
<td>Submission of Semester Attendance of Students</td>
<td>Up to 7th May, 2013</td>
</tr>
<tr>
<td>End-Semester Examination - (II Semester)</td>
<td>27th May 7th June, 2013</td>
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<tr>
<td>Submission of Marks by the Examiners (End Semester Exam)</td>
<td>Up to 14th June, 2013</td>
</tr>
<tr>
<td>Submission of Unbound Copy of Thesis - (IV Semester)</td>
<td>12th-13th June, 2013</td>
</tr>
<tr>
<td>Defence of Thesis* - (IV Semester)</td>
<td>27th-21st June, 2013</td>
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<tr>
<td>Declaration of Result (II &amp; IV Semester)</td>
<td>Up to 26th June, 2013</td>
</tr>
<tr>
<td>Last Date for Submission of Bound Copies of the Thesis** - (IV Semester)</td>
<td>28th June, 2013</td>
</tr>
<tr>
<td>Notification of Time Table for August-December, 2013</td>
<td>Semester 8th July, 2013</td>
</tr>
</tbody>
</table>

Note:
* Scholars will be required to submit their project work report 15 days before the scheduled dates for comprehensive examinations.
** Those students who leave the institute before 30th June shall get their fellowship till the day they were present in the institute.
Creative Section
"Click Chemistry" is a term that was introduced by K. B. Sharpless in 2001 to describe reactions that are high yielding, wide in scope, create only byproducts that can be removed without chromatography, are stereospecific, simple to perform and can be conducted in easily removable or benign solvents. This concept was developed in parallel with the interest within the pharmaceutical, materials, and other industries in capabilities for generating large libraries of compounds for screening in discovery research. Several types of reaction have been identified that fulfill these criteria, thermodynamically-favored reactions that lead specifically to one product, such as nucleophilic ring opening reactions of epoxides and aziridines, non-aldol type carbonyl reactions, such as formation of hydrazones and heterocycles, additions to carbon-carbon multiple bonds, such oxidative formation of epoxides and Michael Additions, and cycloaddition reactions.\(^1\)

1. **Azide-Alkyne Cycloaddition:**

   For example, an examination of the azide-alkyne cycloaddition shows that it fulfills many of the prerequisites. Many of the starting monosubstituted alkynes and organic azides are available commercially, many others can easily be synthesized with a wide range of functional groups, and their cycloaddition reaction selectively gives 1, 2, 3- triazole (scheme-1 and 2).

   **Azide-Alkyne Cycloaddition reaction:**

   \[
   R-N_3 + \overset{\text{Cu(II) (cat)}}{\text{H}_2\text{O}} \rightarrow R' \overset{\text{Scheme- 1}}{\text{N}} \]

   **Scheme-1**

   \[
   R-N_3 + \overset{\text{Cp^*RuCl(PPh_3) (cat.)}}{\text{dioxane, } \Delta} \rightarrow R' \overset{\text{Scheme- 2}}{\text{N}} \]

   **Scheme-2**

2. **Mechanism of the Huisgen Azide-Alkyne 1, 3-Dipolar Cycloaddition:**

   This reaction is highly exothermic, but the high activation barrier is responsible for a very low reaction rate, even at elevated temperature. Another drawback is the formation of regioisomers, as the two possible HOMO-LUMO interactions of the substrates are closely related in terms of energy. The thermal reaction therefore often gives approximately 1:1 mixtures of both the 1, 4-substituted and the 1, 5-substituted regioisomers.\(^{1b, 4}\)

   \[
   \overset{\text{PhO}}{\text{Scheme-3}} \]

   **Scheme-3**
3. **Mechanism of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC):**

As one of the best click reactions to date, the copper-catalyzed azide-alkyne \(^{6,7,8}\) cycloaddition features an enormous rate acceleration of \(10^7\) to \(10^8\) compared to the uncatalyzed 1, 3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization.

\[
R-N_2 + \equiv = R' \xrightarrow{\text{CuSO}_4 \cdot 5\text{H}_2\text{O}} 0.25 - 2 \text{ mol-% CuSO}_4 \cdot 5\text{H}_2\text{O} \\
5 - 10 \text{ mol-% sodium ascorbate} \\
\text{H}_2\text{O} / \text{tBuOH (1:1), r.t., 6 - 12 h}} \xrightarrow{R: \text{alkyl}, \text{CH}_2\text{OBn}} R': \text{Ph, CO}_2\text{H}
\]

**Scheme- 4**

The active Cu (I) catalyst can be generated from Cu (I) salts or Cu (II) salts using sodium ascorbate as the reducing agent. Addition of a slight excess of sodium ascorbate prevents the formation of oxidative homocoupling products. Disproportionation of a Cu (II) salt in presence of a Cu wire can also be used to form active Cu (I). DFT calculations have shown that coordination of Cu (I) to the alkyne is slightly endothermic in MeCN, but exothermic in water, which is in agreement with observed rate acceleration in water. However, coordination of Cu to the acetylene does not accelerate a 1, 3-dipolar cycloaddition. Such a process has been calculated to be even less favorable than the uncatalyzed 1, 3-dipolar Cycloaddition (see fig-1). Instead, a copper acetylide forms, after which the azide displaces another ligand and binds to the copper. Then, an unusual six-membered copper (III) metallacycle is formed. The barrier for this process has been calculated to be considerably lower than the one for the uncatalyzed reaction. The calculated rate at room temperature is \(1 \text{ s}^{-1}\), which is quite reasonable. Ring contraction to a triazolyl-copper derivative is followed by protonolysis that delivers the triazole (see scheme-4) product and closes the catalytic cycle.

![Fig 1: Mechanism of the Copper-Catalyzed Azide-Alkyne Cycloaddition.](image)

4. **Mechanism of the Ruthenium- Catalyzed Azide-Alkyne Cycloaddition (RuAAC):**

A search for catalysts revealed that pentamethycyclopentadienyl ruthenium chloride [\(\text{Cp}^*\text{RuCl}\)] complexes are able to catalyze the cycloaddition of azides to terminal alkynes regioselectively leading to 1, 5-disubstituted 1, 2, 3-triazoles. In addition, RuAAC can also be used with internal alkynes, providing fully substituted 1, 2, 3-triazoles (see scheme- 5 and 6) contrast with CuAAC\(^{8,9}\).

\[
R-N_3 + \equiv = R' \xrightarrow{\text{Cp}^*\text{RuCl(PPh}_3)_2} 2 \text{ mol-%} \\
\text{dioxane, 60 °C, 12 h}} \xrightarrow{R: \text{alkyl, Ar, EFL, allyl}} R': \text{alkyl, CH}_2\text{NR}_2\text{OH, CH}_2\text{NR}_2\text{OH}
\]

**Scheme-5**
The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) appears to proceed via oxidative coupling of the azide and the alkyne to give a six-membered ruthenacycle, in which the first new carbon-nitrogen bond is formed between the more electronegative carbon of the alkyne and the terminal, electrophilic nitrogen of the azide. This step is followed by reductive elimination, which forms the triazole product. DFT calculations support this mechanistic proposal and indicate that the reductive elimination step is rate-determining (see fig-2).

Fig 2: Mechanism of the Ruthenium-Catalyzed Azide-Alkyne Cycloaddition.

References:
2. Development and Applications of Click Chemistry Gregory C. Patton.
3. 1, 3-Dipolar Cycloaddition Chemistry, published by Wiley and updated in 2002.

K. Ankarao
M.S. (Pharm.) Medicinal Chemistry
Semester I
Higgs Boson - The Godly Particle...!! Is It or Isn't It?

On July 4, two experiments analyzing data from the Large Hadron Collider at the European Center for Nuclear Research (CERN) at the border of Switzerland and France announced that they had discovered a new particle, which looks similar to the long-sought Higgs boson. One of these two experiments is ATLAS, a collaboration of 163 institutions and nearly 3,000 physicists.

The discovery was made using the largest scientific instrument ever built: the Large Hadron Collider, or LHC. At this collider, protons get accelerated in a circular tunnel 100 yards below the Earth’s surface to 99.999999 percent of the speed of light. The tunnel has a circumference of 16.5 miles, and the protons take one full turn 11,254 times each second. Eventually, they collide with protons traveling in the opposite direction at points in the tunnel where the experiments are located.

When the protons collide, they interact with each other, and some process occurs. This can be the production of a Higgs boson, but much more often it is just the production of other particles, e.g. two quarks or a photon and a quark, etc. Since the first collisions in 2009, 800 trillion interactions have taken place, and only about 200 were identified to be due to this new Higgs-like particle. Finding those 200 events relies on a sophisticated system of detector technologies that are used to identify different particle species and to measure their energies and angles. This discovery made big news all over the world, and one might wonder why scientists are so excited about this. There are in fact several reasons for this excitement.

First of all, the known interactions of the elementary particles fail to account for one of their most crucial properties: mass. Without mass, nature would be very different. It was the quest for the origin of mass that was the biggest single motivation for building the LHC. The first theory for producing mass, the Higgs mechanism invented nearly in 1964 says that empty space was not really empty but was filled with a field that affected the propagation of particles, giving them mass. It is different from the more familiar electric, magnetic and gravitational fields. These fields result from symmetries and are only generated by sources. But there are some similarities. Oscillations of fields lead to quantum particles: the photon for electric and magnetic fields and the Higgs boson for the Higgs field.
Second, the Higgs boson is different, unlike any other known fundamental particle. All other particles are either matter particles or force carriers, and the Higgs boson is neither of those. For instance, the electrons and quarks are constituents of the atoms, while the photon is the force carrier of the electromagnetic force. The Higgs is not part of the building blocks of the atom, and it also does not mediate a conventional force. The Higgs, however, has a plethora of interactions with many parameters. Furthermore, it destroys some of the original symmetries, leading to the observed diversity of particle masses and to the complexity of the structures we see in nature.

Third, if this particle really is a Higgs boson, and it certainly looks like one so far, we are now confronted with the pressing question of the instability of the Higgs field. In the mid-1970s, a very puzzling aspect of the Higgs was discovered; the Higgs field that pervades all space has a tendency to grow in strength, increasing particle masses almost without limit. In other words, the Higgs seems to do its job too well! In some sense, discovering a Higgs boson is a huge relief, as the entire theory of how fundamental particles interact with each other needed a mass-generation mechanism. But in another sense it leads to a huge puzzle: Why aren’t the particles masses much larger?
SATYENDRA NATH BOSE

The sub-atomic particle “boson” is named after Bengali physicist Satyendra Nath Bose whose pioneering work in the field in the early 1920s changed the way particle physics has been studied. The work done by Bose and Albert Einstein laid the foundation for the discovery of the God particle. While paying tribute to Bose’s work, Paolo Giubellino, a CERN spokesperson, had said back in October last year that “India is like a historic father of the project”. Bose specialised in mathematical physics. A Fellow of the Royal Society, he was awarded the Padma Vibhushan in 1954. Bose was born in Calcutta, the eldest of seven children. His father, Bose, worked in the Engineering Department of the East Indian Railway Company. Bose never received a doctorate, nor was he awarded a Nobel Prize, though the Nobel committee recognised other scientists for research related to concepts he developed.

In the coming decade, the number of proton collisions at the LHC will increase by about two orders of magnitude. The particle just discovered will be subjected to precision tests to confirm its Higgs nature and quite possibly to see deviations from the simplest Higgs theory. The leading idea is super symmetry, which extends the symmetries of space and time. Super symmetry predicts lots of new particles, which are being eagerly sought at the LHC but have not shown up yet. Is this because they decay in unexpected ways to give signals in the detector that are hard to distinguish from the many other processes that occur? Or are the super particles heavier than expected, requiring an upgrade in the proton beam energy that is planned to come online in about two years? Another possibility, actively pursued is the multiverse. Maybe there are many universes, with most having very strong Higgs fields but no observers to make measurements.

Where will the Higgs lead — more symmetry, more universes … or something else entirely?

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Semester III
The Role of Medicinal Chemist In Drug Discovery:
Then and Now

Introduction
The role of the medicinal chemist has changed significantly in the past 25 years. In the early era (‘then’) of drug discovery (1950 to about 1980), medicinal chemists relied primarily on data from in vivo testing. In the more recent (‘now’) period (about 1980 to the present), the development of new technologies, such as high-throughput in vitro screening, large compound libraries, COMBINATORIAL TECHNOLOGY, defined molecular targets and structure based drug design, has changed that earlier and relatively simple landscape. Although these new technologies present many opportunities to the medicinal chemist, the multitude of new safety requirements that have arisen has also brought unanticipated hurdles for the task of translating in vitro activity to in vivo activity.

Simultaneously, the knowledge base that supports drug research has expanded considerably, increasing the challenge for chemists to understand their fields of expertise. The process of demonstration of adequate clinical safety and efficacy in humans has also become more complex, and ever-increasing amount of data is now required by regulatory agencies. In fact, despite the use of many new technologies, and the growing resources and funding for drug research, the number of launches of new medicines in the form of NEW MOLECULAR ENTITIES (NMEs) has been generally decreasing in the last decade. Clearly, the difficulty and complexity of drug research has increased in the past two decades. It is our aim with this article to discuss how these changes have influenced the role of medicinal chemists and to suggest ways to help them to contribute more effectively to the drug discovery process.

Stages in the drug discovery process
The drug discovery process begins with the identification of a medical need, including a judgment on the adequacy of existing therapies (if there are any). From this analysis, together with an appraisal of the current knowledge about the target disease, the hypotheses on how to possibly improve therapy will emerge i.e. what efficacy, safety or mechanistically novel improvements will advance the method of drug treatment for patients with the target disease? On the basis of these hypotheses, specific objectives will be set for the project. Then, testing selected chemicals in appropriate biological tests can begin. Key subsequent steps in the process include detecting relevant biological activity (a ‘hit’) for a structurally novel compound in vitro, then finding a related compound with in vivo activity in an appropriate animal model, followed by maximizing this activity through the preparation of analogous structures, and finally selecting one compound as the drug development candidate. This drug candidate then undergoes toxicological testing in animals, as required by law. If the compound passes all these tests, all the accumulated research data are assembled and submitted as an Investigational New Drug Application (IND) to the Food and Drug Administration (FDA) in the United States (or comparable agency in other countries) before clinical trials are initiated. In the clinic, there is sequential evaluation in normal human volunteers for toleration (Phase I), efficacy and dose range in patients (Phase II), followed by widespread trials in thousands of appropriate patients to develop a broad database of efficacy and safety. For the few (4–7%) drug candidates that survive this series of development trials, a New Drug Application (NDA) that contains all the accumulated research data is filed for thorough review by the experts at the FDA. Only with their approval can the new drug be offered to doctors and their patients to treat the disease for which it was designed.
The Medicinal Chemist-Then and Now

Then (1950s–1980s). About 25–45 years ago, a medicinal chemist’s tasks differed in some ways from those of a chemist today; an example of a successful project from this era (the development of the anti-inflammatory agent piroxicam. At that time, the medicinal chemist and a pharmacologist counterpart were the main drivers of the research programme: compounds were designed and individually synthesized by the chemist in gram quantities to accommodate the need for testing in whole animals by the pharmacologist. Given the limited synthetic methodology available, these syntheses were often time consuming and, even with one or two technical assistants working in the laboratory, the output from one chemistry laboratory was limited to an average of one to three compounds per week. Commercially available starting materials were often limited. The chemist had only a few tools (for example, infrared and ultraviolet spectroscopy, and column chromatography) to assist with compound characterization and purification. Outsourcing was rare; all tasks, including bulk syntheses, toxicological testing and analogue synthesis, were done in-house. The creativity and intuition of the medicinal chemist was pivotal to the success of the programme, although given the limited number of compounds produced, serendipity had a large role as well.

Projects generally used in vivo models for primary screening, as little was known about the detailed biological mechanisms involved in most diseases. In vitro testing against a key enzyme or specific receptor involved in the disease process was usually not possible; in vitro receptor-based pharmacology only became common in the 1980s and 1990s. In addition, compound collections for exploratory biological screening were limited. The data generated from the test models were compiled, analyzed and displayed by hand in the form of charts and graphs. Similarly, searching the literature for relevant information involved the handling of bound volumes taken individually from the library shelves. Small companies tend to rely on informal communication and timelines, and this was often the case in the smaller pharmaceutical industry ‘then’. For the medicinal chemist, the benefit of this informality was ready access to colleagues in other disciplines to evaluate a compound that the chemist was interested in. The disadvantage came once a chemist’s compound was selected for further development. The
chemist, who would probably have moved on to another project, usually heard little or nothing about the drug candidate until the (often) bad news came back that the candidate had failed some key test. Keeping abreast of the progress of the drug candidate required the same proactive, informal action that the chemist had used previously to periodically contact the appropriate scientists in other disciplines to get some news about the drug candidate. To address these issues, most organizations in the 1980s established interdisciplinary matrix teams for each drug candidate to facilitate information exchange and joint planning between departments, such as chemistry, biology, pharmaceutics, toxicology, pharmacokinetics, clinical medicine and regulatory affairs, all of which have important roles in drug development.

Overall, the process of drug discovery ‘then’ was slower and operated from a relatively smaller knowledge base. Several factors combined to slow the process: there was less known about diseases, there were fewer available compounds to screen, there were no computerized technologies for handling information and data, there was a need to manually search the literature, there was a need to individually prepare gram quantities of each new compound for testing, and chemists rarely received information from other disciplines about their development candidates. On the other hand, once a lead was identified in the primary in vivo test model, many of the pharmacokinetic (ADME) problems were mainly in hand or could be rapidly addressed, thereby expediting the selection of a drug candidate to study in the clinic.

Now (1980s–present)

Two powerful technologies have put numbers on the chemist’s side: combinatorial chemistry (combiChem) and high-throughput screening (HTS). CombiChem allows chemists to generate rational, focused libraries of compounds that define SARs in a fraction of the time that was required ‘then’. Depending on where they work, chemists can design, synthesize and purify libraries themselves, or hand over the final synthesis steps to a group of chemists designated for this purpose. This group might also make lead-compound libraries that target specific receptor or enzyme families to provide better quality leads that are suitable for library follow up. The development of HTS of large sample collections, including the designed libraries, has produced marked decreases in the personnel, time and money required to identify compounds that hit a specific biological target, although many companies are struggling to triage the large number of screening hits to viable lead compounds that can support a successful drug discovery project. In this struggle, costs can escalate significantly as the generation of large amounts of data is not the same as generating viable, quality leads. Finally, new graphics software, such as Excel and Spotfire2, can facilitate the retrieval and analysis of the mountain of data generated from screening compound libraries in a large panel of in vitro assays. The molecular genetics revolution has driven the development of another key ingredient in today’s drug discovery model: the use of molecularly defined biological targets, such as enzymes, receptors and transporters. One is the advantage of a known mechanism of action over a ‘black-box’ (that is, unknown) mechanism obtained from animal-model testing that could produce unanticipated toxicity during drug development. Another is the use of structure-based drug design, which allows the chemist to design new compounds by directly visualizing the interaction of a lead compound with the target protein through X-ray crystallographic analysis, but which is only possible with a molecularly defined target protein.

The changing landscape of the pharmaceutical industry

Some basic questions are being asked about the new technologies and procedures now used for drug research, compared with the dwindling supply of new drugs approved in recent year. For example, has
the introduction of major changes in the drug discovery process caused the obvious drop in new drug output? Is this drop temporary, to last only until the new technologies begin to yield some products? Have the changes produced a decrease in output by stifling the creativity of the scientists (including the medicinal chemists) involved in drug discovery? Has the role of serendipity, so important to drug discovery in the past, been supplanted by robots? What has happened to the role of the medicinal chemist’s intuition and creativity in producing quality drugs? How many of most successful drugs of today could have been made through the limited chemical pathways offered by combichem techniques? By their account, the role of the medicinal chemist has changed considerably from that of a highly autonomous, independent inventor ‘then’ to a significant player in a large team that is increasingly influenced by the business units ‘now’. In our opinion, whatever the merits of the business decisions that led to this change, the role of serendipity, chemical intuition and creativity in thoughtfully selecting a chemical target to synthesize in order to discover the best-quality drugs has not diminished. There must always be an opportunity in research for the useful chance observation by a prepared mind. There are many examples of ‘back burner’ (that is, unauthorized) projects that have yielded important new drugs. Although the new technologies that have accelerated the process of drug discovery provide some undoubted benefits, the human factor remains an integral part of success in this endeavour. It is our hope that the accounts of successful drug discoveries presented here will serve as a reminder of the chemists whose decisions actually led to these success stories.

Today, the rapidly expanding knowledge base concerning diseases, their causes, symptoms and their effects on the human body holds great promise for the discovery of important new medicines. Sequencing the human genome also offers the opportunity for finding many more novel and selective therapies. Such discoveries will probably come from teams of scientists, including medicinal chemists, whose careers are devoted to this one task. The enormous cost of this task will be borne mainly by those pharmaceutical companies that can successfully generate the required research funds from the sale of their existing drugs. Medicinal chemists today live in exciting times. They are key participants in the effort to produce more selective, more effective and safer medicines to treat the diseases of mankind.

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Semester I
Our DNA is Not Our Destiny

Epigenomics emerging as potential source for new therapies and drug design.

Introduction

Epigenetic conditions act as a mask over certain genes and those genes express themselves differently without the organism’s DNA being fundamentally altered.

DNA Packaging varies greatly with Cell Cycle. DNA is never completely naked. Genetic codes that are most needed by a cellular structure will be wrapped more loosely, thus allowing easier access to the information stored there. Epigenetic changes are of two types. The first one is methylation of cytosine residues in the DNA, and the second type of epigenetic changes pertains to Histones, the proteins around which DNA is wrapped. These changes ultimately result in repression or enhancement of expression of genes.

Epigenetic Abnormities are documented in:
- Coronary artery disease
- Cancer
- Diabetes mellitus (type i and type ii)
- COPD
- Asthma
- Schizophrenia
- Bipolar disorder
- Depression
- Addiction

These epigenomic profiles change throughout the course of the disease. Revealing the epigenomic landscape is not just essential for a more complete understanding of normal development, but is also necessary to gain insight into the etiology of complex diseases.

Epigenetics and Different Aspects of Life:
A lot of factors affect epigenomic changes in a life of an individual. Some of them are:
- Pathogenesis of diseases
- Development of multicellular organism (cellular differentiation) and stem cells
- Environment-organism interaction and
- Nutrition supplements and environmental toxins.
Complex Diseases and Current Epigenetic Therapeutics:

Epigenomics in Cancer:
Cancer cells are likely to contain localized regions of DNA hypermethylation
Currently available epigenetic drugs for cancer:

A) DNA demethylating agents:
- 5-azacytidine and decitabine (inhibit DNA methyltransferase enzymes, causing reduced overall levels of DNA methylation)

B) Histone deacetylase (HDAC) inhibitor:
- vorinostat and valproic acid (work by blocking HDACs, enzymes that remove acetyl groups from histone tails)

5-azacytidine’s efficacy in mds:
A large phase III clinical study showed that Vidaza almost doubles the 2-year survival rate of MDS patients compared with conventional care and many patients on Vidaza become transfusion independent.

Potential adverse effects:
DNA hypomethylation can promote tumor formation and treatment of tumor cells with a global DNA hypomethylation agent, 50-aza-20-deoxycytine, can promote aspects of tumor progression.

Epigenomics in COpd:
Patients with COPD have increased levels of histone acetylation in the histones nearby the promoter regions of genes involved in the inflammatory response.

Epigenomics in Depression:
The effect of imipramine appears to be mediated through its ability to inhibit HDACS in the hippocampus of a rodent model.

Epigenomics in Diabetes Mellitus:
The diabetes mellitus drugs glucagon-like peptide 1 (GLP-1) and glucose-dependent insulintropic-peptide 1 (GIP) can induce global changes in histone acetylation.

Some Epigenetic Mechanisms:
DNA association with histone proteins to form chromatin and chromatin remodeling.
Methylation.
RNA transcripts and their encoded proteins.
Other specific epigenetic processes include:
Prions, structural inheritance systems, paramutation, bookmarking, imprinting, gene silencing, x chromosome inactivation, position effect, reprogramming, transvection, maternal effects, the progress of carcinogenesis, many effects of teratogens, regulation of histone modifications and heterochromatin, and technical limitations affecting parthenogenesis and cloning.
New Avenues for Epigenomic Therapy:

Inhibition of Pad4:

A newly developed epigenetic therapy targets the protein arginine deiminase 4 (PAD4), a protein that is expressed in a variety of human tumors.

DNA Demethylases:

The recent discovery of enzymes with DNA demethylating activity has also opened the door to potential areas of epigenomic drug design.

Repetitive Elements:

Research on PAD4 and AID provided a greater understanding of specific aspects of epigenomics, but more research is needed to reveal the ability of cellular stresses and the microenvironment to promote significant changes throughout the epigenome.

Conclusion and Future Avenues:

The importance of epigenetic regulation is not limited to its function in embryogenesis and disease as discussed. Our knowledge of epigenomics is in its infancy, and a greater understanding of the causes and consequences of these changes will lead to the identification of new drug targets and therapies.

Epigenetic therapies are attractive options for treating many diseases. With all of these great developments, the future looks bright for epigenetic drugs. "The bottom line is that these drugs have finally given hope for discovering new drugs for old diseases,"

References:


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Semester III
Synriam - A New Breakthrough in Anti-Malarial Therapy

Opening a new history in research & development in India, the drug manufacturing company Ranbaxy Laboratories Limited launched a new anti-malarial drug, Synriam on the occasion of World Malaria Day on April 25 2012. Multi-center clinical trials were organised in India and Thailand in 2009 and in Bangladesh in 2010. Trials are on-going in several countries in sub-Saharan Africa like the Democratic Republic of Congo, Ivory Coast, Mali, Mozambique and Senegal for the evaluation of the new drug in uncomplicated Plasmodium falciparum malaria have suggested that the drug yields a cure rate of over 95 per cent. The drug, a combination of artemolane maleate 150 mg and piperaquine phosphate 750 mg, Arterolane is a short-acting anti-malarial molecule and piperaquine is a long-acting molecule. Salt structure of artemolane was changed to a tosylate salt to a maleate salt, increasing its solubility is now available in the market. An adult suffering from malaria will need only one tablet a day for three days. In case of other malaria medicines two to four tablets are required, twice daily for three or more days. The new drug regime will lead to better compliance, says Ranbaxy. The Company is working on dosage for children. A pack of three tablets will cost Rs 130. The drug is also independent of fatty foods or milk restrictions, unlike other anti-malarial therapies. The drug can be chemically synthesized.

Ranbaxy was earlier working on an anti-malarial drug in partnership with international non-profit Medicines for Malaria Venture (MMV). But the deal was called off in 2009. Synriam is a new molecule, confirms the company spokesperson. Malaria spreads through the bite of the infected female anopheles mosquito. There are four types of malarial parasites, of which Plasmodium falciparum and Plasmodium vivax are the most common. Plasmodium falciparum accounts for about 90 per cent of the deaths caused due to malaria. Traditional drugs are proving ineffective because the deadly malaria parasite has acquired resistance to available drugs. Availability of plant-based Artemesinin, a primary ingredient in established anti-malarial therapies is finite and unreliable. This leads to price fluctuations and supply constraints. There was a critical need for a new anti-malarial drug that would address these challenges, a note from Ranbaxy says.

India accounts for over 75 per cent of the 2.5 million reported cases of malaria in Southeast Asia. More than two-thirds of the population lives in the malaria-affected parts of the country. According to WHO, 15,000 people die annually due to malaria in India whereas medical journal Lancet says that 205,000 Indians die of malaria annually. Around 117 districts in India are chloroquine resistant. Due to chloroquine resistance in falciparum malaria, the national programme advised the treatment to be changed to Artemesinin-based combination therapy (ACT) since 2010. Currently, Odisha, Jharkhand, West Bengal, Northeastern states, Chhattisgarh and Madhya Pradesh contribute bulk of malaria cases in India. Urban areas also contribute to malaria cases due to poor civic cleanliness,

Ranbaxy took over eight years to develop Synriam. The drug has a cure rate of over 95 per cent. It has been approved by the Drugs Controller General of India (DCGI) after trials were conducted in partnerships with medical colleges and hospitals in Odisha, Karnataka and Jharkhand and the National Institute of Malaria Research of the Indian Council of Medical Research (ICMR). Trials were also conducted in Africa and Thailand. It also follows the WHO recommendations for using combination therapy in malaria. Ranbaxy got part of financial support from the Department of Science and Technology under the Union ministry of chemicals and fertilizers for the drug discovery.

References -

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Semester I
DNA beyond Genetics

DNA—it's not just for genetics anymore
DNA Origami for targeted delivery

Recently nano-particles have been used as drug delivery vehicles due to their high delivery efficiencies and the possibility to circumvent cellular drug resistance. Conventional delivery nano-particles such as liposomes and polymeric systems are heterogeneous in size, composition and surface chemistry, and this can lead to suboptimal performance, a lack of tissue specificity and potential toxicity remains an obstacle to their widespread use. Here is a novel drug carrier system based on "self-assembled, spatially addressable DNA origami" nano-structures that confronts those limitations. DNA origami is construction of 3-D shapes from short segments of DNA by fusing six strands of DNA to create a tetrahedron (a six-edged, four-faced pyramid).

The researchers have shown that they can assemble the DNA cages around protein molecules, and then open when they encounter "trigger" molecules once they’re inside cells. What’s new here is they introduced fluorescently labelled DNA tetrahedrons into human kidney cells grown in the lab. The DNA cages survived for at least 48 hours, despite an attack by cellular enzymes. The experiment means that the cages are capable of surviving a sometimes-harsh cellular environment.

A DNA tile based self-assembly provides an attractive route to create nano-architectures of programmable patterns. It also offers excellent scaffolds for directed self-assembly of nano-meter-scale materials, ranging from nano-particles to proteins, with potential applications in constructing nano-electronic/nano-photic devices and protein/ligand nano arrays

Although a multitude of promising anti-cancer drugs have been developed over the past 50 years, effective delivery of the drugs to diseased cells remains a challenge. Some cancers are resistant to chemotherapy, we can attack them successfully by hiding drugs inside folded-up DNA (DNA origami). To target the particles to tumor cells, the researchers attached three folate molecules to each tetrahedron. Short protein fragments could also be used to target the particles to a variety of tumors. The folded DNA might also alter the pH inside the cells, increasing the drug’s activity.

Short Interacting RNA (siRNAs) by Origami

Short interfering RNA (siRNAs) a therapeutic agent that suppresses the expression of targeted genes.

RNA interference (RNAi), is a natural phenomenon that cells use to control their gene expression. Genetic information is normally carried from DNA in the nucleus to ribosomes, cellular structures where proteins are made. Short interfering RNA (siRNA) disrupts this process by binding to the messenger RNA molecules that carry DNA’s instructions, destroying them before they reach the ribosome. They have shown some success in turning off cancer genes in animal studies, and clinical trials are now underway in patients with liver cancer. Nano-particles tend to accumulate in the liver, spleen and lungs, so liver cancer is a natural target but it has been difficult to target such particles to tumors in other organs.

If a short interfering RNA (siRNAs) is injected as such into the bloodstream, it’s $t_{1/2} = 6$ min minutes. If we make a bigger nano-particle of a (siRNAs) using origami methods, the DNA tetrahedron protect the RNA from rapid absorption by the kidneys and excretion, which usually happens with RNA administered on its own. The nucleic acid nano-particles circulated in the bloodstream with a $t_{1/2} = 24$ min. long enough to reach their targets. DNA origami can deliver snippets of (siRNAs) directly to tumors only when,
1) There are at least three folate molecules per nano-particle.
2) The ligands are in the appropriate spatial orientation.

**DNA Origami as a Carrier for Circumvention of Drug Resistance**

The cancer cells may not recognise the DNA origami as a threat in the way that frees doxorubicin is recognised.

Baoquan Ding at the National Center for Nanoscience and Technology in Beijing, China, and colleagues loaded a tubular piece of folded DNA with doxorubicin, a chemotherapy drug. The DNA Trojan horse (Origami) delivered a dose of the drug that proved lethal to human breast-cancer cells, even though they had developed resistance to doxorubicin.

Doxorubicin, a well-known anti-cancer drug, was non-covalently attached to DNA origami nano-structures through intercalation. A high level of drug loading efficiency was achieved, and the complex exhibited prominent cytotoxicity not only to regular human breast adenocarcinoma cancer cells (MCF-7), but more importantly to doxorubicin-resistant cancer cells, inducing a remarkable reversal of phenotype resistance. With the DNA origami drug delivery vehicles, the cellular internalization of doxorubicin was increased, which contributed to the significant enhancement of cell-killing activity to doxorubicin-resistant MCF-7 cells. Presumably, the activity of doxorubicin-loaded DNA origami inhibits lysosomal acidification, resulting in cellular redistribution of the drug to action sites. Results suggest that DNA origami has immense potential as an efficient, biocompatible drug carrier and delivery vehicle in the treatment of cancer.

![Fig. 1. Origami preparation for doxorubicin](image)

**DNA 'organises itself' on silicon**

Shapes of DNA have been used to enhance the production of circuits for next-generation computer chips making chips with components closer together leads to smaller devices and faster computers.

The origami can be designed to serve as a scaffold for electronic components just six billionths of a meter apart.

Several research groups have shown that DNA itself can be used to store or manipulate data, and the juggling of DNA in a test tube or within bacteria has been shown to solve simple computational tasks.

**How does Origami release the inner components?**

DNA origami could allow for 'autonomous' delivery. DNA aptamers, which can be configured to identify and seek certain proteins, allowing them to be programmed to find diseased tissue. Once the origami nano-bots get there, the aptamers recognize the infected cells and break apart, swinging open the tube and releasing the treatment therein. In essence, the scientists have created a lock-and-key system.
Preparation of DNA Origami

A simple method for folding long, single-stranded DNA molecules into arbitrary two-dimensional shapes. The design for a desired shape is made by raster-filling the shape with a 7-kilobase single-stranded scaffold, and by choosing over 200 short oligonucleotide 'staple strands' to hold the scaffold in place. Once synthesized and mixed, the staple and scaffold strands self-assemble in a single step. The resulting DNA structures are roughly 100 nm in diameter and approximate desired shapes such as squares, disks and five-pointed stars with a spatial resolution of 6 nm. Because each oligonucleotide can serve as a 6-nm pixel, the structures can be programmed to bear complex patterns such as words and images on their surfaces. Finally, individual DNA structures can be programmed to form larger assemblies, including extended periodic lattices and a hexamer of triangles (which constitutes a 30-megadalton molecular complex).

Fig : 2  A Hexagonal Origami

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Semester I
Acridine as an Anti-Cancer Agent

Acridine Derivatives as Chemotherapeutic Agents
Acridine derivatives are one of the oldest classes of bioactives, widely used as antibacterial and antiprotozoal agents. Some work in these areas continues, but recent research has focused mainly on their use as anticancer drugs, because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase enzymes.

Mechanisms of Action of DNA Intercalating Acridine-based Drugs: How Important are Contributions from Electron Transfer and Oxidative Stress
Reactive oxygen species (ROS) are produced continuously in living cells as a by-product of respiration and other metabolic activity. Some ROS may react with DNA, and in some cases may abstract an electron from the double helix, leading to long range electron transfer (ET) reactions. Thus, the DNA of living cells may be in a continuous state of ET. We consider here whether acridine-based anticancer or antimicrobial drugs, which bind to DNA by intercalation, might either donate electrons to, or accept electrons from, the double helix, thus actively participating in ET reactions. We focus in particular on two acridine-based drugs that have been tested against human cancer in the clinic. Amsacrine is a 9-aminacridine derivative that appears to act as an electron donor in ET reactions on DNA, while N-[2-(dimethylamino) ethyl] acridine-4-carboxamide (DACA) may act as an electron acceptor. Such reactions may make important contributions to the antitumor activity of these drugs.

Acridine-Based Agents with Topoisomerase II Activity Inhibit Pancreatic Cancer Cell Proliferation and Induce Apoptosis

A series of substituted 9-aminoacridines is evaluated for antiproliferative activity toward pancreatic cancer cells. The results indicate that the compounds inhibit cell proliferation by inducing a G1-S phase arrest. A model is also developed that explains the molecular basis to inhibition through a DNA “threading” mechanism. We conclude that the drugDNA complex formed blocks topoisomerase II binding and activity leading to catalytic inhibition of the enzyme and the induction of apoptosis and programmed cell death.

Pyrazolacridine as an Anticancer Agent
Pyrazoloacridine (PZA) is the first of a new class of rationally synthesized acridine derivatives to undergo clinical testing as an anticancer agent. Recent studies suggest that PZA might be a dual inhibitor of DNA topoisomerase I and DNA topoisomerase II that exerts its effects by diminishing the formation of topoisomerase-DNA adducts. Consistent with this unique mechanism of action, PZA exhibits broad spectrum antitumor activity in preclinical models in vivo. In addition, this agent displays several unique properties including solid tumor selectivity, activity against hypoxic cells, and cytotoxicity in noncycling cells. PZA also retains full activity against cells that are resistant to other
agents on the basis of overexpression of P-glycoprotein or the multidrug resistance-associated protein (MRP). PZA has been studied in phase I trials in adults and children, and is currently undergoing broad phase II trials in a number of tumor types. No significant anti-tumor activity has been seen in gastrointestinal malignancies and prostate cancer. Results from ongoing or recently completed trials are awaited before the utility of this agent in our current armamentarium can be defined. Because of its unique properties, combination studies with other antineoplastic agents are warranted.

**Acridine Orange could be an Innovative Anticancer Agent under Photon Energy**

Acridine orange (AO) was extracted as a dye from coal tar over a hundred years ago. It has various unique biological activities and has been shown to be a useful fluorescent dye specific for DNA and RNA, a pH indicator, photosensitizer, antitumor and antimalarial drug, and detector of bacteria and parasites. It has recently been found that AO accumulates in musculoskeletal sarcomas and that after illumination of the tumors with visible light or irradiation with low-dose X-rays, the dye rapidly exerts selective cytoidal effect against the sarcoma cells. Therefore, surgery combined with photo-(PDT) or radiodynamic therapy (RDT) with AO (AO-PDT and -RDT) has been applied to human musculoskeletal sarcomas. The results of a clinical study on the outcome of this therapeutic strategy revealed that it yielded better local control and remarkably better limb function than wide resectional surgery. Based on our experimental studies, it was clarified that AO accumulates in acidic organelles or structures, especially lysosomes, depending on the acidity. An enormous number of protons are produced in cancer from lactate or CO₂ under hypoxic conditions, which are moved into the extracellular fluid or lysosomes to maintain the intracellular fluid pH. Therefore, AO shows marked accumulation in the acidic lysosomes of cancer cells. Photon energy from visible light or X-rays excites the AO accumulated in lysosomes; the excited AO emits fluorescence and forms activated oxygen from intra-cytoplasmic oxygen. The activated oxygen destroys lysosomes, with the released lysosomal enzymes causing rapid death of the cancer cells. On the other hand, normal cells can exclude AO quickly because they are not acidic. Thus, AO-PDT and AO-RDT exhibit strong and selective cytoidal effect against malignant tumors. In conclusion, we believe that AO-PDT and AO-RDT exhibit selective anticancer cell activity and that AO excited by photon energy has excellent potential as an anticancer agent.

**Acridine and Acridone Derivatives, Anticancer Properties and Synthetic Methods**

Acridine derivatives are interesting chemotherapeutic agents that were first used as antibacterial and antiparasite agents. In this review we wish to concentrate our attention on the anticancer properties of acridines used in clinics since the 1970's. Based on recent results, an outlook on antitumour acridine chemotherapy will be proposed. The biological activity of acridines is mainly attributed to the planarity of these aromatic structures, which can intercalate within the double-stranded DNA structure, thus interfering with the cellular machinery. Recent understanding of the mode of action of acridines leads to continuous and exciting research in this heterocyclic family. Indeed, biological targets such as topoisomerases I and II, telomerase/telomere and protein kinases emerge and allow the design of novel acridine-based patterns. This review further pinpoints the latest progress in the development of anticancer agents based on naturally occurring and synthetic acridines (e.g. acridones, pyridoacridines); for this matter in vitro/in vivo studies and clinical trial results will be discussed. The DNA-affinic property of acridine is also useful to vectorise drugs into cell nuclei and some applications in hypoxia-selective treatment, platinum or N-mustard derived conjugates will be reported. Some other properties including inhibition of multidrug resistance or potential impact on Alzheimer disease will be treated. It is noteworthy that the position and the nature of the substituent on the heterocyclic core are determinants for the biological property and
selectivity observed. So, we wish also to disclose a summary of recent synthetic methodologies developed for acridine synthesis.

References


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Semester I
GEORG WITTIG (1897-1987)

Synthesis of alkenes from aldehydes and ketones using compounds called phosphonium ylides in the Wittig reaction. He shared the Nobel Prize in Chemistry with Herbert C. Brown in 1979.

Wittig was born in Berlin, Germany and shortly after his birth moved with his family to Kassel, where his father was professor at the applied arts high school. He attended school in Kassel and started studying chemistry at the University of Tübingen in 1915. He was drafted and became a lieutenant in the cavalry of Hesse-Kassel (or Hesse-Cassel). After being an English prisoner of war from 1918 till 1919, Wittig found it hard to restart his chemistry studies owing to overcrowding at the universities. By a direct plea to Karl von Auwers, who was professor for organic chemistry at the University of Marburg at the time, he was able to resume university study and after 3 years was awarded the Ph.D. in organic chemistry.

Wittig's contributions also include the preparation of phenyllithium and the discovery of the 1, 2-Wittig rearrangement and the 2, 3-Wittig rearrangement.

Wittig was well known in the chemistry community for being a consummate experimenter and observer of chemical transformations, while caring very little for the theoretical and mechanistic underpinnings of the work he produced.

Wittig reaction

The Wittig reaction or Wittig Olefination is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide (often called a Wittig reagent) to give an alkene and triphenylphosphine oxide.

The Wittig reaction was discovered in 1954 by George Wittig, for which he was awarded the Nobel Prize in Chemistry in 1979. It is widely used in organic synthesis for the preparation of alkenes. It should not be confused with the Wittig rearrangement.

Wittig reactions are most commonly used to couple aldehydes and ketones to singly substituted phosphine ylides. With simple ylides this results in almost exclusively the Z-alkene product. In order to obtain the E-alkene, the Schlosser modification of the Wittig reaction can be performed.

Classical Mechanism

The steric bulk of the ylide 1 influences the stereochemical outcome of nucleophilic addition to give a predominance of the betaine 3 (c.f. Bürgi-Dunitz angle). Note that for betaine 3 both R, and R, as well as PPh3+ and O- are positioned anti (trans-diastereal) to one another.
Carbon-carbon bond rotation gives the betaine 4, which then forms the oxaphosphetane 5. Elimination gives the desired Z-alkene 7 and triphenylphosphine oxide 6. With simple Wittig reagents, the first step occurs easily with both aldehydes and ketones, and the decomposition of the betaine (to form 5) is the rate-determining step. However, with stabilised ylides (where R stabilises the negative charge) the first step is the slowest step, so the overall rate of alkene formation decreases and a bigger proportion of the alkene product is the E-isomer. This also explains why stabilised reagents fail to react well with sterically hindered ketones.

\[
\begin{align*}
\text{Ph} \quad &\text{Ph} \quad \text{Ph} \quad \text{Ph} \\
\text{P} &\text{P} \quad \text{P} \quad \text{P} \\
\text{O} &\text{O} \quad \text{O} \quad \text{O} \\
\text{R} \quad &\text{R} \\
\end{align*}
\]

**Wittig reagents**

**Preparation of phosphorus ylides**

The Wittig reagent is usually prepared from a phosphonium salt, which is in turn made by the reaction of triphenylphosphine with an alkyl halide. To form the Wittig reagent (ylide), the phosphonium salt is suspended in a solvent such as diethyl ether or THF and treated with a strong base such as phenyllithium or n-butyllithium:

\[
\text{Ph}_3\text{P} \cdot \text{CH}_2\text{R} \cdot \text{X} + \text{C}_8\text{H}_{15}\text{Li} \rightarrow \text{Ph}_3\text{P} \cdot \text{CH} - \text{R} + \text{LiX} + \text{C}_8\text{H}_{15} \quad \text{Ph}
\]

The simplest ylide used is methylenetriphenylphosphorane (Ph\textsubscript{3}P=CH\textsubscript{2}). It is also a precursor to more elaborated Wittig reagents. Alkylation of Ph\textsubscript{3}P=CH\textsubscript{2} with a primary alkyl halide R-CH\textsubscript{2}-X, produces substituted phosphonium salts:

\[
\text{Ph}_3\text{P} \cdot \text{CH} + \text{RCH}_2\text{X} \rightarrow \text{Ph}_3\text{P} \cdot \text{CH}_2\text{CH}_2\text{R} \cdot \text{X}
\]

These salts can be deprotonated in the usual way to give Ph\textsubscript{3}P=CH-CH\textsubscript{2}R.

**Structure of the Ylide**

The Wittig reagent may be written in the **phosphorane** form (the more familiar representation) or the **ylide** form:

\[
\begin{align*}
\text{Ph} &\text{Ph} \\
\text{P} &\text{P} \\
\text{C} &\text{C} \\
\text{R} &\text{R} \\
\end{align*}
\]

**phosphorane form**

\[
\begin{align*}
\text{Ph} &\text{Ph} \\
\text{P} &\text{P} \\
\text{I} &\text{I} \\
\text{C} &\text{C} \\
\text{R} &\text{R} \\
\end{align*}
\]

**ylide form**
The ylide form is a significant contributor, and the carbon is quite nucleophilic.

**Scope and Limitation**

Simple phosphoranes are very reactive and are unstable in the presence of moisture and oxygen in the air. They are therefore prepared in a super dry solvent (usually THF) under nitrogen or argon and the carbonyl compound is added as soon as the phosphorane has been formed.

More stable phosphoranes are obtained when the ylide contains a group that can stabilize the negative charge from the carbanion. For example: Ph₃P=CHCO₂R and Ph₃P=CHPh.

![Chemical structure of ylides](image)

From the phosphonium salts, these reagents are formed more readily, requiring only with NaOH, and they are usually more air-stable. These are less reactive than simple ylides, and so they usually fail to react with ketones, necessitating the use of the Horner–Wadsworth–Emmons reactions an alternative. They usually give rise to an E-alkene product when they react, rather than the more usual Z-alkene.

**References**

Ulcer Caused by Helico Bacter Pylori

In the year 2005 Nobel Prize in Physiology or Medicine was awarded to Barry Marshall and Robin Warren, who with tenacity and a prepared mind challenged a prevailing dogma. By using technologies generally available (fibre endoscopy, silver staining of histological sections and culture techniques for microaerophilic bacteria), they made an irrefutable case that the bacterium *Helicobacter pylori* is causing disease. By culturing the bacteria they made them amenable to scientific study. These Two Australian scientists have been awarded the Nobel Prize for medicine for their discovery that stomach ulcers can be caused by a bacterial infection. Robin Helicobacter pylori play a key role in the development intestinal ulcers of both stomach Warren and Barry Marshall showed the bacterium and intestinal ulcer. They can now be cured with a short-term course of drugs and antibiotics. In 1982, when *H. pylori* was discovered by Dr Marshall and Dr Warren, stress and lifestyle were considered the major causes of stomach and intestinal ulcers. It is now firmly established that the bacterium causes more than 90% of duodenal (intestinal) ulcers and up to 80% of gastric (stomach) ulcers.

Dr Warren, a pathologist from Perth, paved the way for the breakthrough when he discovered that small curved bacteria colonised the lower part of the stomach in about 50% of patients from which biopsies had been taken.

**Helicobactor Pylori**

*H. pylori* are found in the stomach of about 50% of all humans. In the developing country almost everyone is infected. Infection is typically contracted in early childhood and the bacteria may remain in the stomach for life. In most people there are no symptoms however it can trigger ulcer in 10-15% of those infected.

**Key Observations**

He also made the crucial observation that signs of inflammation were always present in the stomach lining close to where the bacteria were seen. Dr Marshall became interested in the findings and together they initiated a study of biopsies from 100 patients. After several attempts, Dr Marshall succeeded in cultivating a hitherto unknown bacterial species - *H. pylori* - from several of these biopsies. Together they found that the organism was present in almost all patients with gastric inflammation, duodenal ulcer or gastric ulcer. Even though stomach ulcers could be healed by inhibiting gastric acid production, they frequently relapsed, since bacteria and chronic inflammation of the stomach remained. Dr Marshall and Dr Warren showed patients could only be properly cured when *H. pylori* was eradicated from the stomach.

Dr Marshall proved that *H. pylori* caused gastric inflammation by deliberately infecting himself with the bacterium. The Nobel citation praises the doctors for their tenacity, and willingness to challenge prevailing dogmas. By using technologies generally available they made an irrefutable case that the bacterium *H. pylori* are causing disease. By culturing the bacteria they made them amenable to scientific study. It is thought that *H. pylori* infection can trigger an ulcer by stimulating increased acid production in the stomach, leading to damage to the stomach or intestinal lining.

That year’s Nobel Laureates in Physiology or Medicine made the remarkable and unexpected discovery that inflammation in the stomach (gastritis) as well as ulceration of the stomach or duodenum (peptic ulcer disease) is the result of an infection of the stomach caused by the bacterium *Helicobacter pylori*. Their results led to the recognition that gastric disorders are infectious diseases, and overturned the previous view that they were physiological illnesses.
Summary

This year’s Nobel Laureates in Physiology or Medicine made the remarkable and unexpected discovery that inflammation in the stomach (gastritis) as well as ulceration of the stomach or duodenum (peptic ulcer disease) is the result of an infection of the stomach caused by the bacterium *Helicobacter pylori*.

Robin Warren (born 1937), a pathologist from Perth, Australia, observed small curved bacteria colonizing the lower part of the stomach (antrum) in about 50% of patients from which biopsies had been taken. He made the crucial observation that signs of inflammation were always present in the gastric mucosa close to where the bacteria were seen.

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Semester I
Microwave Irradiation as a New Convenient Synthetic Procedure in Drug Discovery

Microwave (MW) assisted organic synthesis has emerged as a new “lead” in organic synthesis. The technique offers simple, clean, fast, efficient, and economic method for the synthesis of a large number of organic molecules. In the recent years microwave assisted organic reaction has emerged as a new tool in organic synthesis. The advantages of this enabling technology have, more recently, also been exploited in the context of multistep total synthesis and medicinal chemistry/drug discovery, and have additionally penetrated related fields such as polymer synthesis, material sciences, nanotechnology and biochemical processes. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents and reagents lead to environmental pollution. The growth of microwave assisted organic synthesis holds a significant potential for a reduction of the by product, reduction in waste production and lowering of the energy costs. Microwave synthesis has since been shown to be an invaluable tool for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds.

Presently, thermally driven organic transformations take place by either of two ways: conventional heating or microwave accelerated heating. In the first way, reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and reactants. In the second way, microwaves couple directly with the molecules of the entire reaction mixture, leading to a rapid rise in temperature. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses. Microwave irradiation will directly activate most molecules that possess a dipole or are ionic. Since energy transfer occurs in less than a nanosecond, the molecules are unable to completely relax or reach equilibrium. This creates a state of nonequilibrium that results in a high instantaneous temperature (Ti) of the molecules and is a function of microwave power input. These instantaneous temperatures are very consistent with the temperatures that would be expected in a microwave system and are directly responsible for the enhancements in reaction rates and yields. Microwave assisted organic synthesis is mainly based on the efficient heating of materials by ‘microwave dielectric heating’ effects.

Microwave irradiation triggers heating by two main mechanisms:

- dipolar polarization and
- ionic conduction.

Application

There occurs a significant decrease in reaction time for organic reaction carried out with microwave irradiation. Microwave reactions are now being used for the enhancement of rate of many of the reactions like Biginelli reaction, Heck and Suzuki coupling reaction, Negishi reaction, Sonogashira reaction. One of the m is explained below:

Biginelli Reaction

Direct method for the synthesis of DHMP involves the one-pot condensation of an aldehyde, β-ketoester and urea under strong acidic conditions. However, the yields of the products were very low (20-25%). Conducting the reaction in a solvent under microwave irradiation ensured complete homogeneity and effective microwave heating of the reaction mixture under solvent-free conditions.
Figure 2. Synthesis of dihydropyrimidinones (4a-i) using acetic acid as a solvent and MW as a heating technique

**Microwave in Drug Discovery**

Nowadays, Microwave assisted organic synthesis is gaining widespread acceptance in drug discovery laboratories. The rapid acceptance of this technology parallels the rising cost of R&D and decrease in the number of FDA approvals, which have led to what is termed as a productivity crisis. Reducing the cost of failure, either by failing candidates sooner or by improving the overall probability of success, is the most powerful solution to improving R&D productivity. Microwave technology, by accelerating chemical reactions from hours or days to minutes, provides quick results.

**Conclusion**

Microwave technology is emerging as an alternative energy source powerful enough to accomplish chemical transformations in minutes, instead of hours or even days. For this reason, microwave irradiation is presently seeing an exponential increase in acceptance as a technique for enhancing chemical synthesis. Enhanced Microwave Synthesis (EMS) provides the ability to cool a reaction vessel externally while simultaneously administering microwave irradiation, allowing more energy to be directly applied to a chemical reaction. Reactions with large activation energies will benefit greatly from this new technology. In addition, a whole new arena of biochemical applications can now be explored. Clearly, microwave irradiation has emerged as a powerful tool for organic synthesis. In concert with a rapidly expanding applications base, microwave synthesis can be effectively applied to any type of chemistry, resulting in faster reaction times and improved product yields. Additionally, microwave synthesis creates new possibilities in performing chemical reactions. Because microwaves can transfer energy directly to the reactive species, they can promote transformations that are currently not possible using conventional heat, creating a new realm in synthetic organic chemistry.

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Semester III
Gliadel Implants

Chemical Name

The chemical name of Gliadel (carmustine) is 1, 3-bis (2-chloroethyl)-1-nitrosourea (or BCNU).

Chemical Structure

\[
\text{\includegraphics[width=0.3\textwidth]{carmustine_structure.png}}
\]

Description

GLIADEL Implants are sterile, off-white to pale yellow implants approximately 1.45 cm in diameter and 1 mm thick. Each implant contains 7.7 mg of carmustine and 192.3 mg of a biodegradable polyanhydride copolymer (Poliferprosan 20). Poliferprosan 20 consists of poly [bis (p-carboxyphenoxy) propane: sebacic acid] in a 20:80 molar ratio and is used to control the local delivery of carmustine. Carmustine is homogeneously distributed in the copolymer matrix.

Mode of Action

GLIADEL is designed to deliver carmustine directly into the surgical cavity created after tumour resection. Exposure to the aqueous environment of the cavity, the anhydride bonds in the copolymer are hydrolysed, releasing carmustine, carboxyphenoxypropane, and sebacic acid. The carmustine released from GLIADEL diffuses into the surrounding brain tissue and produces an antineoplastic effect by alkylating DNA and RNA.

Carmustine has been shown to degrade both spontaneously and metabolically. The production of an alkylating moiety, hypothesised to be chloroethyl carbonium ion, leads to the formation of DNA cross-links. The tumouricidal activity of GLIADEL is dependent on release of carmustine to the tumour cavity in concentrations sufficient for effective cytotoxicity. More than 70% of the copolymer degrades by three weeks. The metabolic disposition and excretion of the monomers differ. Carboxyphenoxypropane is predominantly eliminated by the kidney and sebacic acid (an endogenous fatty acid) is metabolised by the liver and expired as CO2 in animals.

Pharmacokinetics

Animal studies suggest that nearly all the carmustine in the implants is released within 7 days of implantation. GLIADEL implants are biodegradable in the human brain when placed into the cavity after tumour resection. The rate of biodegradation is variable from patient to patient. During the biodegradation process, an implant remnant may be observed on brain imaging scans or at reoperation. Even though extensive degradation of all components has occurred. Data obtained from review of CT scans obtained 49 days after implantation of GLIADEL demonstrated that images consistent with implants were visible to varying degrees in the scans of 11 of 18 patients. Data obtained at re-operation and autopsies have demonstrated implant remnants up to 232 days after GLIADEL implantation. Implant remnants removed at re-operation from two patients with recurrent malignant glioma, one at 64 days and the second at 92 days after implantation, were analysed for content. The following table presents the results of analyses completed on these remnants.
Indications

GLIADER is indicated in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. GLIADER is also indicated for use as adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiform (GBM) for whom surgical resection is indicated.

Contraindications

GLIADER is contraindicated in patients with a history of hypersensitivity to carmustine or any of the components of GLIADER. GLIADER is also contraindicated in breast-feeding mothers.

Precautions

Surgery

Patients undergoing craniotomy for malignant glioma and implantation of GLIADER should be monitored closely for known complications of craniotomy which include seizures/convulsions intra-cranial infections, abnormal wound healing, and brain oedema (see “Adverse Events”). Cases of Intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with GLIADER, including one case leading to brain herniation. Communication between the surgical resection cavity and the ventricular system should be avoided to prevent the implants from migrating into the ventricular system and causing obstructive hydrocephalus. If a communication larger than the diameter of a wafer exists, it should be closed at operation prior to implantation.

Imaging Studies

Computed tomography (CT) and magnetic resonance imaging (MRI) of the head may demonstrate enhancement in the brain tissue surrounding the resection cavity after placement of GLIADER implants. This enhancement may represent oedema and inflammation caused by GLIADER or tumour progression.

Use in Pregnancy

There are no studies in either pregnant women or laboratory animals on GLIADER, but the active component, carmustine, when administered systemically, can cause foetal harm when administered to a pregnant woman and has been shown to be embryotoxic in rats and rabbits and teratogenic in rats.

Use in Lactation

It is not known if carmustine, carboxyhexoxypropane or sebacic acid is excreted in human milk. Since some drugs are excreted in human milk and because of the potential for serious adverse reactions from carmustine in nursing infants, women being treated with GLIADER should not breast-feed their infants. For women who wish to breast-feed their infants, GLIADER is contraindicated.

Dosage and Administration

Each GLIADER implant contains 7.7 mg of carmustine, resulting in a dose of 61.6 mg when eight implants are placed in the tumour resection cavity. It is recommended that a maximum of eight implants be placed if the size and shape of the resection cavity allows it. Otherwise, use the maximum number of implants possible. No more than eight implants should be used per surgical procedure, as there is no clinical experience with this dose.

Instructions for Opening Pouch Containing GLIADER Implant

**Figure 1:** To remove the sterile inner pouch from the outer pouch, locate the folded corner and slowly pull in an outward motion.
Figure 2: Do NOT pull in a downward motion rolling knuckles over the pouch. This may exert pressure on the implant and cause it to break.

Figure 3: Remove the inner pouch by grabbing hold of the crimped edge and pulling upward.

Figure 4: To open the inner pouch, gently hold the crimped edge and cut in an arc-like fashion around the implant.

Figure 5: To remove the GLIADEL implant, gently grasp the implant with the aid of forceps and place it onto a designated sterile field.

Once the tumour is resected, tumour pathology is confirmed, and haemostasis is obtained, up to eight GLIADEL Implants may be placed to cover as much of the resection cavity as possible. Slight overlapping of the implants is acceptable. Implants broken in half may be used, but implants broken in more than two pieces should be discarded in a biohazard container. Oxidised regenerated cellulose (Surgicel®) may be placed over the implants to secure them against the cavity surface. After placement of the implants, the resection cavity should be irrigated and the dura closed in a water tight fashion.

Storage
GLIADEL must be stored at or below -20°C (Deep Freeze). GLIADEL implants have been demonstrated to be stable at either -18°C or -20°C. Unopened outer sachets may be kept at a temperature of not more than 22°C for a maximum of six hours. Refreezing of sachets is allowed if they have not been opened and have been kept for a maximum of 6 hours at a temperature of not more than 22°C. GLIADEL Implants should be used within 30 days when refrozen.

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Semester I
SB-728 - A Virus-Free Gene Therapy for HIV Shows Promise

HIV infection results in the death of immune system cells, particularly CD4+ T-cells leading to AIDS, a condition in which the body's immune system is depleted to such a degree that the patient is unable to fight off common infections. Ultimately, these patients succumb to opportunistic infections or cancers. According to UNAIDS/WHO, over 2.7 million people were newly infected with HIV in 2007 with an estimated 2.0 million people dying of AIDS in the same year. There are now over 33 million people living with HIV and AIDS worldwide. The CDC estimates that, in the United States alone, there were 1.2 million people living with HIV/AIDS, approximately 54,000 new infections and 23,000 deaths in 2007.

Current Treatments and Unmet Medical Need

Current standard of care for HIV infection relies on a maintenance strategy of daily antiretroviral drugs designed to reduce viral replication and keep the infection in check. There are approximately 30 antiretroviral drugs approved by the FDA and almost all are designed to inhibit some stage of the pathway of viral replication. As HIV reproduces, variants of the virus emerge, including some that are resistant to antiretroviral drugs. Therefore, people infected with HIV take a combination of antiretroviral drugs known as highly active antiretroviral therapy (HAART). Currently available drugs do not cure HIV infection or AIDS. They can suppress the virus, even to undetectable levels, but they cannot eliminate HIV from the body. Hence, people with HIV need to take antiretroviral drugs on a daily basis which can have significant undesirable side effects. There is no therapeutic approach available which protects CD4+ T-cells, reduces viral load and does not require continuous daily dosing.

Sangamo's Therapeutic Approach

The therapeutic approach aims to use ZFN (Zinc finger nuclease)-mediated gene editing technology to replicate a naturally occurring human mutation which renders individuals largely resistant to infection with the most common strain of HIV. CCR5 is a co-receptor for HIV entry into T-cells and, if CCR5 is not expressed on their surface, HIV infects them with lower efficiency.

How do ZFNs work?

First, After HIV binds to the CD4 protein on CD4 cells, the virus must then latch onto another receptor on the cell's surface either CCR5 or CXCR4. Usually, when people contract HIV, their virus starts off using the CCR5 receptor. Later on, as HIV disease progresses, the virus can switch to the CXCR4 receptor this occurs in about 50 percent of treatment-experienced patients.

Selzentry (maraviroc), an antiretroviral approved by the U.S. Food and Drug Administration, works by blocking the interaction between CCR5 and HIV, ultimately retarding the virus's ability to infect CD4 cells. ZFNs like SB-728 can go one step further—they can block the gene responsible for making CCR5, mimicking a naturally occurring human mutation that renders individuals largely resistant to the virus. This mutation, dubbed CCR5 delta-32, appears to have no harmful effect in the human body. There's also the case of an HIV-positive leukemia patient who was cured of both diseases when he received a bone marrow transplant from a "matched" donor who had inherited this delta-32 CCR5
mutation from both parents. (When the mutation is inherited from one parent, CCR5 is produced, but it’s at low quantities and is associated with slower HIV disease progression. When the mutation is inherited from both parents, which is very rare, little or no CCR5 is expressed on CD4 cells, rendering the cells impervious to forms of HIV that use the CCR5 receptor to enter cells.)

ZFNs have both therapeutic and curative potential. At present, the most widely known research involves Sangamo’s therapeutic-focused CCR5-knockout ZFN, which is dubbed SB-728-T. Therapy involves removing CD4 cells from patients’ blood, treating the cells with SB-728-T to knock out the CCR5 gene, multiplying the cells in the lab, then transplanting the HIV-resistant genetically modified cells back into the body.

The latest breakthrough involves the actual cell treatment process. Scientists had assumed that ZFN proteins cannot cross cell membranes, so the standard ZFN delivery method has been a gene-therapy technique in which a relatively harmless virus is used to carry a designer ZFN gene into cells. Once inside, the ZFN gene starts producing ZFN proteins, which seek and destroy their target gene within the cellular DNA.

One potential risk of this approach is that viral DNA even if the virus is not a retrovirus may end up being incorporated randomly into cellular DNA, disrupting a valuable gene such as a tumor-suppressor gene. Another risk with this delivery method is that ZFN genes will end up producing too many ZFN proteins, resulting in a high number of “off-target” DNA cuts. Finally, gene therapies that employ viral DNA may not be effective or may need to be delayed in people with antibodies to the virus being used, because high levels of virus-specific antibodies that may attack the ZFNs.

After several applications of ZFNs, aided by a special cooling method that improves the ability of the proteins to get across cell membranes, the scientists were able to inactivate CCR5 genes with an efficiency similar to that of the gene therapy-based approach. A DNA-based method and the viral-based methods ended up producing ZFNs for up to several days, causing a significant amount of off-target DNA damage. But the directly delivered ZFN proteins remained intact within cells for only a few hours, causing minimal off-target damage.

**SB-728:**

SB-728 is a ZFN-based approach for modification of the gene encoding CCR5, the major co-receptor used by HIV to infect cells of the immune system. Our first application is an autologous ZFN-CCR5-modified T-cell product (SB-728-T) which are evaluating in an ongoing Phase 2, two Phase 1/2 and two Phase 1 trials in subjects with Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS).

A population individual that is immune to HIV infection, despite multiple exposures to the virus, has been identified and studied extensively. The majority of these individuals have a natural mutation, CCR5delta32, resulting in the expression of a shortened, or truncated, and non-functional CCR5 protein. This mutation appears to have no observable deleterious effect. In addition, a study published in Blood in December 2010 reported an effective cure when an AIDS patient with leukemia received a bone
marrow transplant from a “matched” donor with this delta-32 CCR5 mutation. This approach transferred the hematopoietic stem cells (HSCs) residing in the bone marrow from the delta-32 donor, and provided a self-renewable and potentially lifelong source of HIV-resistant immune cells. After transplantation, the patient was able to discontinue all anti-HIV drug treatments, CD4 counts increased, and viral load dropped to an undetectable level, demonstrating effective transplantation of protection from HIV infection. In addition, individuals that have only one of the two copies of their CCR5 gene mutated are known as “elite controllers” and, while they may become infected with the virus, they are able to keep their HIV infection in check without drugs.

Using, ZFN-mediated gene disruption technology we may disrupt the CCR5 gene in cells of a patient’s immune system to make these cells permanently resistant to HIV infection. The aim is to provide a population of HIV-resistant cells that can fight HIV and opportunistic infections thereby mimicking the characteristics of individuals that carry the natural mutation.

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Semester I
This receptor has been proposed as a target for treating sleep disorders. The receptor has also been proposed as a target for treating neuropathic pain. Because of its ability to modulate other neurotransmitters, H₃ receptor ligands are being investigated for the treatment of numerous neurological conditions, including obesity (because of the histamine /orexinergic system interaction), movement disorders (because of H₃ receptor modulation of dopamine and GABA in the basal ganglia), schizophrenia and ADHD (again because of dopamine modulation) and research is underway to determine whether H₃ receptor ligands could be useful in modulating wakefulness (because of effects on noradrenalin, glutamate and histamine).

H₃ Receptor

Histamine H₃ receptors are expressed in the central nervous system and to a lesser extent the peripheral nervous system, where they act as auto receptors presynaptic histaminergic neurons, and also control histamine turnover by feedback inhibition of histamine synthesis and release. The H₃ receptor has also been shown to presynaptically inhibit the release of a number of other neurotransmitters (i.e. it acts as an inhibitory heteroreceptor) including, but probably not limited to dopamine, GABA, acetylcholine, noradrenaline, and serotonin.

Distribution in the Body

- Central nervous system
- Peripheral nervous system
- Heart
- Lungs
- Gastrointestinal tract
- Endothelial cells

Functioning

Histamine H₃ receptor pharmacology, functions and biochemistry are far from being fully understood; however, progress is being made. Activation of this Gq/Go-protein-coupled receptor affects cognition, the sleep-wake cycle, obesity and epilepsy, which are physiological and pathological conditions that are the main focus of research into the therapeutic potential of selective H₃ receptor ligands. This heterogeneity of targets can be reconciled partially by the fact that the histamine system constitutes one of the most important brain-activating systems and that H₃ receptors regulate the activity of histamine and other neurotransmitter systems. Furthermore, the H₃ receptor shows functional constitutive activity, polymorphisms in humans and rodents with a differential distribution of splice variants in the CNS, and potential coupling to different intracellular signal transduction mechanisms. In light of the genetic, pharmacological and functional complexity of the H₃ receptor, the importance of the histamine system as a therapeutic target to control the sleep-wake cycle.

Conclusions

Sleep-wake disorders constitute a major challenge of public health due to their high prevalence (19-37%) in the general population. Somnolence is associated with various pathological conditions including sleep apnea, excessive daytime sleepiness due to nocturnal insomnia, Parkinson’s disease and narcolepsy or circumstances related to lifestyle, including daytime sleepiness due to voluntary sleep restriction or sleep deprivation resulting from night shift work, overwork or jet-lag. Novel, safe,
Efficacious and more specific therapeutic approaches are, therefore, in great demand in sleep medicine. The present study has distinguished two classes of wake-promoting agents: those involving histamine and those that appear histamine-independent and supports the role of the brain H3-receptors as potentially novel therapeutic targets for vigilance and sleep-wake disorders. Compared to current wake promoting medications, H3R-antagonists appear to possess several advantageous characteristics that might favor their development as novel therapeutics for the treatment of sleep-wake disorders especially somnolence. A well-defined mechanism of action that is based on a clearly defined molecular target and the well established.

Subhadra Thakur
M.S.(Pharm) Medicinal Chemistry
Semester I
A generic drug (generic drugs, short: generics) is a drug defined as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use. It has also been defined as a term referring to any drug marketed under its chemical name without advertising.

A generic drug must contain the same active ingredients as the original formulation. According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamic properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use. The FDA's use of the word "identical" is very much a legal interpretation, and is not literal. In most cases, generic products are available once the patent protections afforded to the original developer have expired. When generic products become available, the market competition often leads to substantially lower prices for both the original brand name product and the generic forms. The time it takes a generic drug to appear on the market varies. In the US, drug patents give 20 years of protection, but they are applied for before clinical trials begin, so the "effective" life of a drug patent tends to be between seven and 12 years.

Economics

Generic drugs are usually sold for significantly lower prices than their branded equivalents. One reason for the relatively low price of generic medicines is that competition increases among producers when drugs no longer are protected by patents. Companies incur fewer costs in creating generic drugs (only the cost to manufacture, rather than the entire cost of development and testing) and are therefore able to maintain profitability at a lower price. The prices are low enough for users in many less-prosperous countries to afford them. For example, Thailand has imported millions of doses of a generic version of the blood-thinning drug Plavix (used to help prevent heart attacks), at a cost of 3 US cents per dose, from India, the leading manufacturer of generic drugs.

Generic manufacturers do not incur the cost of drug discovery. Sometimes, reverse-engineering is used to develop bioequivalent versions to existing drugs. Generic manufacturers also do not bear the burden of proving the safety and efficacy of the drugs through clinical trials, since these trials have already been conducted by the brand name company. (See the Approval and regulation section, below, for more information about the approval process.) The average cost to brand-name drug companies of discovering and testing a new innovative drug (with a new chemical entity) has been estimated to be as much as $800 million.

Generic drug companies may also receive the benefit of the previous marketing efforts of the brand-name drug company, including media advertising, presentations by drug representatives, and distribution of free samples. Many drugs introduced by generic manufacturers have already been on the market for a decade or more, and may already be well known to patients and providers (although often under their branded name).

For as long as a drug patent lasts, a brand name company enjoys a period of "market exclusivity" or monopoly, in which the company is able to set the price of the drug at a level which maximizes profitability. The profit often greatly exceeds the development and production costs of the drug. (This is partially offset by research and development of other drugs which do not make a profit.) The advantage of generic drugs to consumers comes in the introduction of competition, which prevents
any single company from dictating the overall market price of the drug. Competition is also seen between generic and name-brand drugs with similar therapeutic uses when physicians or health plans adopt policies of preferentially prescribing generic drugs as in step therapy. With multiple firms producing the generic version of a drug, the profit-maximizing price generally falls to the ongoing cost of producing the drug, which is usually much lower than the monopoly price.

**Patent issues**

**When a generic drug can be produced**

When a pharmaceutical company first markets a drug, it is usually under a patent that, until it expires, allows only the pharmaceutical company that developed the drug (or its licensees) to sell it. Generic drugs can be produced without patent infringement for drugs where: 1) the patent has expired, 2) the generic company certifies the brand company's patents are either invalid, unenforceable or will not be infringed, 3) for drugs which have never held patents, or 4) in countries where the drug does not have current patent protection. Patent lifetime differs from country to country; typically an expired patent cannot be renewed. In the U.S., patent extensions may be granted if changes are made; some pharmaceutical companies have sought extensions on things as minor as changes to the shape and color of the pill; generic makers are excluded while the adjudication of the extension is considered. A new version of the drug with significant changes to the compound could be patented, but this requires new clinical trials. In addition, a patent on a changed compound does not prevent sales of the generic versions of the original drug unless regulators take the original drug off the market, as happened in the case of terfenadine.

**Challenging patents**

Brand-name drug companies have used a number of strategies to extend the period of market exclusivity on their drugs, and prevent generic competition. This may involve aggressive litigation to preserve or extend patent protection on their medicines, a process referred to by critics as “evergreening”. Patents are typically issued on novel pharmacological compounds quite early in the drug development process, at which time the 'clock' to patent expiration begins ticking. Later in the process, drug companies may seek new patents on the production of specific forms of these compounds, such as single enantiomers of drugs which can exist in both "left-handed" and "right-handed" forms, different inactive components in a drug salt, or a specific hydrate form of the drug salt. If granted, these patents 'reset the clock' on patent expiration.

**Approval and Regulation**

**U.S. generics approval process**

Enacted in 1984, the U.S. Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act, standardized U.S. procedures for recognition of generic drugs. An applicant files an Abbreviated New Drug Application (ANDA) with the Food and Drug Administration (FDA), and seeks to demonstrate therapeutic equivalence to a specified, previously approved “reference listed drug”. When an ANDA is approved, the FDA adds the drug to its Approved Drug Products list, also known as the Orange Book, and annotates the list to show equivalence between the references listed drug and the approved generic. The FDA also recognizes drugs using the same ingredients with different bioavailability, and divides them into therapeutic equivalence groups. For example, as of 2006, diltiazem hydrochloride had four equivalence groups, all using the same active ingredient, but considered equivalent only within a group.
On October 4, 2007, FDA launched the Generic Initiative for Value and Efficiency, or GiVE. GiVE will use existing resources to help FDA modernize and streamline the generic drug approval process. It also aims to increase the number and variety of generic drug products available. Having more generic-drug options means more cost-savings to consumers, as generic drugs cost about 30 percent to 80 percent less than brand name drugs.

In the United States, generic drug substances are named through review and recommendation of the United States Adopted Names.

Shweta Anand, Bharti Saini
M.S. (Pharm) Medicinal Chemistry
Semester III
Cloud Computing in Pharmaceutical Sector: The Need of the Future

Cloud computing means that instead of all the computer hardware and software for the companies & their networks, it's provided for you as a service by another company and accessed over the Internet, usually in a completely seamless way. Cloud computing is a natural evolution of the widespread adoption of virtualization, service-oriented architecture, autonomic and utility computing. Details are abstracted from end-users, who no longer have need for expertise in, or control over, the technology infrastructure "in the cloud" that supports them, freeing the Pharmaceutical companies from the need to pay for costly service contracts with outsourcers, nor do Pharmaceutical companies have to dedicate rooms full of servers, thus reducing maintenance, power & other upkeep costs.

The impact of cloud computing is just beginning to be felt in the areas of research, development and healthcare information exchange. The explosion of data from next generation sequencing, growing importance of biologics in the research process, and importance of publicprivate partnerships (PPPs) to come up with new discoveries is making cloud based computing an increasingly important aspect of R&D. Cloud computing encompasses any subscription-based or pay-per-use service. It has been a rage where multinational pharmaceutical firms started the new trend of cloud computing, for the betterment of their services, trials & reduction in cost.

We are already seeing complex genetic sequences and biomarker data being hosted in the cloud by open source bodies, which are then accessed in a secure fashion by individual companies for their research needs. However, there is still a need for more integrated data sharing across research, development, manufacturing, and sales functions to improve trials, increase time to market for drugs, and utilize feedback faster, especially in the Indian scenario. The impact to pharmaceutical companies of increased usage of cloud computing is a reduced dependence on their own IT infrastructure. This will provide the ability to move away from capital expenditure intensive deployments to a pay-as-you-require business model.

The main business advantage of cloud computing is the standardization and streamlining of operations, higher reusability, better integration, and stronger collaboration with external entities and the health care ecosystem. However, as the uptake of cloud increases, we can also expect greater focus on aspects related to security, privacy, data protection and IP management when reliance on the cloud grows.

Some pharmaceutical and biotechnology companies have adopted cloud computing for some computer-intensive research tasks such as bioinformatics, molecular modeling, and proteomics. These applications often follow narrower flavors referred to as infrastructure as a service (IaaS) which means having near immediate access to processing and storage services on demand, or platform as a service (PaaS), which provides a hosted environment for developing custom applications. These types of uses are likely to be particularly attractive to start-ups, since they can avoid capital-intensive investments on computing infrastructure and just rent what they need in the early stages of product development. Cloud computing also reduces the start up times to mere 12 months. This is equally important to a large pharmacy company, which can be subject to bureaucratic obstacles and interminable delays when trying to add a server through internal IT organizations, & reducing the expenditure many fold.

Cloud computing has also found considerable uses in effective ADR (Adverse Drug Events) reporting. India can really profit from such a technology in the NPP (National Pharmacovigilance Programme),
by reducing the time of the ADR reporting to minutes, which can reach the medical staff, also provides a secure method of monitoring clinical status of patients & investigations at the hospital or state level.

Adverse Drug Reactions are fourth to sixth leading cause of death among hospitalized patients and it occurs in 0.3 per cent to 7 per cent of all hospital admissions in India & the incidence of serious ADRs is 6.7 percent. There is a rapid increase in the number of new drugs entering the market from last few decades, India being the second most populated country has over one billion potential drug consumers, and number of pre-clinical and clinical data become a necessity to conclude the complete safety of a drug, therefore, it becomes necessary to report any untoward reaction of any pharmaceutical product to assess its safety and efficacy to ensure maximum patient health. In today's world of speedier, reliable and efficient technology, one cannot turn a blind eye to the support technology can give, not only in improving reporting frequency and ease, but also reducing the cost of doing so. For this we can use the concurrently E-records and cloud computing systems. e-Healthcare records are not a new thought, but coupling it with cloud computing can really help improve the process. The evolving of the Internet in terms of capability, speed and security, now means that data can be safely stored and beckoned for when needed. Cloud computing gives us precisely the same, as service providers now offer new services without large upfront investments. They provide services as Software-as-a-service, Platform-as-a-service or infrastructure-as-a-service. This thus helps hospital's have access to infinite data storage and processing as a service which can be combined with a suitable e-healthcare records software, to ease the medical staff in clearly reporting & acknowledging patient data. The medical staff can easily track a new medication without any extra cost of infrastructure, servers, power, maintenance and training costs. This data can further be used by Institutions conducting Trials. This also helps the pharmaceuticals manufacturers to making patient safe drugs and gathering data, which formerly was collected by them at an additional cost. Manufacturers will now be able to measure the effectiveness & risks of their drugs in the market. It will introduce new opportunities to minimize damage by providing information not only to the medical community, but also to patients and to develop specific solutions to specific problems, leading to timely and speedier actions. This will also help improving communication between the medical staff, a healthy record keeping process, better communication of the pharmacist between the physicians & the patients( Helping impart awareness to the patient regarding the medications and lastly it will remove the two major problems which are underreporting and misinterpretations by the medical staff. So, it will give better reach to useful data and help in speeding up information transfer from the laboratory, to the physicians and pharmacists to the patients, reducing the cost of healthcare and the damage to the lives of patients who show ADR’s to new medications.

Cloud computing is a novel upcoming technology which has a promising future in bringing appreciable improvements to the field of Pharmacy.

Proportion of Life Sciences R&D Informatics Budget Devoted to Cloud Computing in Three Years, Commercial Sector

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</tr>
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Source: Insight Pharma Reports
References:

Vinita Saran
M.S. (Pharm) Medicinal Chemistry
Semester I
Mera Lab... Meri Zubaani...

CDRI me project ke 1 saal ki meri kahani,
I would like to tell you all about mera lab... meri zubaani...
Nawabon ki is purani haweli me hua karta th badshahon ka basera,
Par pichle kuch saalon se rehta hai yahan bas scientists aur organic chemists ka dera...
Chalti rehti hain yahan din raat bas organic reactions,
Toh apne project ke liye main bhi yaha aa gayi hu samajhne kuch ke mechanisms...
Bade- bade complicated structures aur electrons ka yaha-waha jana,
Hausla deti hu apne mann ko, inhe dekh tu mat ghabrana...
Naye- naye instruments, na dekha jinhe na pehle kabhi sune jinke naam,
Ab to har roz bas karna hota hai din bhar unhi ke saath kaam...
Roz nayi schemes khojna, aur jo theek ho to nayi reactions lagana,
Compound ban jaye to NMR, IR, Mass data nikalwane ke liye lambi- lambi quataron ke peecho bhaagna...
Electrons ki bhasha bolein, na jene nucleophiles electrophiles karte hain kya guftagu,
Mere dimag me hain jo sawal, kabhi samajh me aao mujhe, mere neurons se bhi ho rubaru...
Sochti hu oil bath me reflux pe lage RBF me karte hain ye chemicals apas me kya baat,
To solve this query karti hu Clayden, Carey jaisi moti- moti books se har din mulakat...
Koi nayi drug ban jaye is koshish me kar raha har scientist in chemicals se chedkhani,
Par koi bhi na samajh pata, ye chemicals to reaction mixture me karte bas apni manmani...
I guess by the end of this year ho jayenge organic chemistry ke mere saare concepts clear,
I would be able to successfully put my own reactions without any fear...
Aage chal ke kya pata bana lu main bhi kisi disease ke treatment ke liye koi drug,
But karte rehna hoga us din tak pahuchne ke liye mujhe bahut hard work...
Sapna hai, karun main bhi in bade-bade scientists ki list me apna naam shumaar,
Pukareenge Jab log mujhe scientist Priyanka Swami to kitna proud feel karega mera parivar... :-)

Priyanka Swami
M.S. (Pharm) Medicinal Chemistry
Semester III
A Journey So Far: Synthesis and Development of Organofluorine Containing Blockbuster Drugs

Abstract

Approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine including drugs such as Lipitor, Lexapro and Prozac. Recent advances in catalysis have made the incorporation of fluorine into complex organic molecules easier than ever before, but selective, general and practical fluorination reactions remain sought after. Fluorination of molecules often imparts desirable properties, such as metabolic and thermal stability, and fluorinated molecules are therefore frequently used as pharmaceuticals or materials. But the formation of carbon-fluorine bonds in complex molecules is a significant challenge. Here we discuss reactions to make organofluorides that have emerged within the past few years and which exemplify how to overcome some of the intricate challenges associated with fluorination.

Introduction

Carbon-fluorine bonds have an integral role in pharmaceuticals, agrochemicals materials and tracers for positron emission tomography. Fluorine uniquely affects the properties of organic molecules through strong polar interactions due to the atom's high electronegativity and small size. For example, the introduction of fluorine into pharmaceuticals can make them more bioavailable, lipophilic and metabolically stable, and can increase the strength of a compound's interactions with a target protein. During the past five years, chemists have developed new methods to incorporate fluorine into organic molecules by making carbon-fluorine (CF) and carbon-trifluoromethyl (CF3) bonds on both aromatic rings and a lipphatic chains. These new bond forming reactions can be efficient means to access desired organic molecules that are not readily synthesized using traditional fluorination chemistries. In particular, the development of suitable catalysts for these reactions has significantly influenced the progress of modern fluorination. In this review, I present fundamental challenges of organofluorine chemistry and novel transition -metal-catalysed and organocatalysed CF and CF3 bond-forming reactions.

Challenges associated with CF bond formation

Difficulties in CF bond formation arise from the facts that fluorine is the most oxidizing and most electronegative element and that fluoride has a small ionic radius. Owing to its electronegativity and anionic radius, fluoride, the most abundant form of the element on Earth, can form strong hydrogen bonds with, for example, water, alcohols, amines and amides and therefore is typically only weakly nucleophilic in the presence of hydrogen-bond donors. Weakly nucleophilic fluoride limits access to CF bonds via nucleophilic substitution reactions, which are a conventional and still common way to make CF bond. When hydrogen-bond donors are meticulously excluded, fluoride is a better nucleophile, but also basic, which can lead to undesired side reactions.

Metal-catalyzed cross-coupling reactions

Metal-catalyzed cross-coupling reactions are reactions that join two molecular fragments using a metal as catalyst. The 2010 Nobel Prize in Chemistry was awarded to pioneers of palladium-catalyzed carbon-carbon cross-coupling reactions first disclosed over 40 years ago. Since then, cross-coupling reactions have become a staple of modern organic synthesis and have been developed for virtually every element in the first and second row of the p-block of the periodic table. Common examples of transition metals used in cross-coupling catalysis include palladium, copper, nickel and iron. In general, when cross-coupling reactions unite two fragments, one fragment serves as the electrophile and the other fragment serves as the nucleophile. As shown in panel a of the Box Figure below, the elementary organometallic chemistry steps of a catalysis cycle are: (1) Oxidative
addition. A metal inserts into as-bond of the electrophile. This step increases the formal oxidation state of the metal and increases the number of ligands bound to the metal. (2) Transmetallation. The nucl eophile replaces a ligand on the metal. After trans-metallation, both molecular fragments to be coupled are bound to the metal. Reductive elimination, the actual bond-forming event that makes the organic product extrudes the new organic molecule with both molecular fragments united by a new s-bond, leaving the metal in its original oxidation state and ready to start the catalysis cycle again.

Catalysed spF and spCF3 bond formation

Metal-catalysed Aromatic CF3 bond formation
Advantages of fluorine in drug development

The importance of fluorine in medicinal chemistry is well recognized. Indeed, an increasing number of drugs on the market contain fluorine, the presence of which often is of major importance to activity. The role of fluorine in medicinal chemistry is put in to further, more detailed perspective in the introductory sections of the two reviews cited above. These reviews have dealt with major areas such as anticancer drugs and associated anti-inflammatory drugs, antiviral drugs, and others. There are of course, an enormous number of topics that remain to be considered, encompassing the entire range of disease targets contained in the domain of medicinal chemistry. Herein there will be focus on topics that include fluorinated drugs for treatment of diseases of the central nervous system, various cardiovascular diseases and obesity, antibacterial agents, and antifungal therapy. These topics were chosen because fluorine substitution has played and continue to play an important role in the development of more active and more selective agents. Certain of these are well known, such as the fluoroquinolone antibacterial agents and fluoroazole antifungal agents. Others are just now emerging, such as the highly fluorinated cholesterol ester transfer protein inhibitor s. Discussions of the processes of discovery and lead development where appropriate will include the rationale for fluorine substitution. Even in cases where the choice of specific fluorine substitution results from empirical structure-activity relationship (SAR) data, the beneficial effects of fluorine often can be determined through subsequent analysis. In the design of analogues of biologically important compounds, replacement of a C=H bond or C=O bond with fluorine has special advantages.

Conclusion

The reactions presented in this abstract have begun to address some of the unmet needs in organofluorine chemistry. In medicinal chemistry, milligram to gram quantities of functionalized fluorinated molecules are more readily accessible now than before. On the other hand, current methods still lack practicality and cost efficiency for general use in large-scale manufacturing. And although fluorination to prepare tracer mol-ecules for positron emission tomography (PET) with the isotope 18 F only requires small amounts of material, the recent advances in fluorination technology have not given access to general 18 F-tracer synthesis, because the stringent reaction requirements for practical and general 18 F-fluorination are not met. Future research in fluorination chemistry will need to focus on the development of more general and practical fluorination reactions.

Ashish Sharma
M.S. (Pharm) Medicinal Chemistry
Semester III
New Trends in Cancer Treatment by Using si-RNA and sh-RNA

Cancer is a disease of genes, whether based on aberrant changes in sequence or expression (epigenomics). The constellation of genetic and epigenetic abnormalities characterizing cancer cells present new and more specific targets for cancer treatment and, hopefully, prevention. Indeed, in 1997, antibody-based Herceptin (trastuzumab) became the first targeted therapy for breast cancer, specifically for HER2-positive metastatic breast cancer. In 2001, the small molecule Gleevec (imatinib mesylate), became the first approved kinase inhibitor for cancer targeting bcr-abl in chronic myeloid leukemia (CML), and it has since been approved for the treatment of gastrointestinal stromal tumors (GIST) targeting c-kit.

The recent discovery of RNA interference (RNAi), a natural process through which the expression of a targeted gene can be knocked down with high specificity and selectivity, presents an invaluable tool for personalized cancer therapy. Target specific RNAi agents have the potential to selectively knockdown key abnormally over- or constitutively expressed molecular targets that are essential for the survival of each patient’s tumor for effective personalized cancer treatment.

Small interfering RNA (siRNA) and short hairpin RNA (shRNA):

The applications of RNAi can be mediated through two types of molecules; the chemically synthesized double-stranded small interfering RNA (siRNA) or vector based short hairpin RNA (shRNA). Effective RNAi was initially demonstrated by the application of synthetic siRNA later, siRNA produced in vitro by T7 RNA polymerase was found to be active and it was soon demonstrated that active siRNA consists of a hairpin structure can be transcribed in cells from an RNA polymerase III promoter on a plasmid construct.

Although siRNA and shRNA can be applied to achieve similar functional outcomes, siRNA and shRNA are intrinsically different molecules. Therefore, the molecular mechanisms of action, the RNA interference pathways, the off-target effects and the applications can also be different.

Schematic representation of (a) siRNA (b) shRNA mediated RNA interference pathway

Conclusion:

Despite limitations in developing effective delivery vehicles and concerns regarding potential off-target activity, clinical development has been initiated. As the science of this fledgling technology advances, it is evident that issues such as target selection, effector potency, and delivery vehicle design, and off-target effects will continue to be addressed and resolved. Bi-functional RNAi products are evolving components in this transition to clinically effective and safer therapeutics.

Chaitanya Krishna
M.S. (Pharm) Medicinal Chemistry
Semester III
Acquired Immunodeficiency Syndrome (AIDS)

HIV is the Human Immunodeficiency Virus. It is the virus that can lead to acquired immune deficiency (1, 2).

**Symptoms**
- Chills
- Fever
- Rash
- Sweats (particularly at night)
- Swollen lymph glands
- Weakness
- Weight loss

**Routes of Transmission of HIV, India, 2011-12 (till January 2012)**
- Heterosexual, 88.2%
- Parent to child, 5.0%
- Not Specified, 2.7%
- Homosexual, 1.5%
- Infected Syringe and Needles, 1.7%
- Blood and Blood Products, 1.0%

**Treatment**
There is no cure for AIDS at this time. Antiretroviral therapy suppresses the replication of the HIV virus in the body. A combination of several antiretroviral drugs, called highly active antiretroviral therapy (HAART), has been very effective in reducing the number of HIV particles in the bloodstream. This is measured by the viral load (how much free virus is found in the blood). Preventing the virus from replicating can improve T-cell counts and help the immune system recover from the HIV infection (3).

HAART is not a cure for HIV, but it has been very effective for the past 12 years. People on HAART with suppressed levels of HIV can still transmit the virus to others through sex or by sharing needles. There is good evidence that if the levels of HIV remain suppressed and the CD4 count remains high (above 200 cells/mm³), life can be significantly prolonged and improved.

However, HIV may become resistant to one combination of HAART, especially in patients who do not take their medications on schedule every day. Genetic tests are now available to determine whether an HIV strain is resistant to a particular drug. This information may be useful in determining the best drug combination for each person, and adjusting the drug regimen if it starts to fail. These tests should be performed any time a treatment strategy begins to fail, and before starting therapy.

There are a variety of new drugs on the market for treating drug-resistant HIV.

Treatment with HAART has complications. HAART is a collection of different medications, each with its own side effects. Some common side effects are:

- Collection of fat on the back ("buffalo hump") and abdomen
- Diarrhea
- General sick feeling (malaise)
- Headache
When used for a long time, these medications increase the risk of heart attack, perhaps by increasing the levels of cholesterol and glucose (sugar) in the blood.

Physician prescribing HAART should carefully watch the patient for possible side effects. In addition, blood tests measuring CD4 counts and HIV viral load should be taken every 3 months. The goal is to get the CD4 count as close to normal as possible, and to suppress the amount of HIV virus in the blood to a level where it cannot be detected.

Other antiviral medications are being investigated. In addition, growth factors that stimulate cell growth, such as erythropoetin (EpoGen, Procrit, and Remorum) and filgrastim (G-CSF or Neupogen) are sometimes used to treat AIDS-associated anemia and low white blood cell counts.

Medications are also used to prevent opportunistic infections (such as Pneumocystis jiroveci pneumonia) if the CD4 count is low enough. This keeps AIDS patients healthier for longer periods of time. Opportunistic infections are treated when they happen.

Prevention strategies

Prevention is the mainstay of the strategic response to HIV/AIDS in India as 99 percent population of the country is uninfected. The HIV prevalence pattern in the remaining one percent population largely determines the prevention and control strategy for the epidemic in the country (3).

Who is at risk?

The HIV prevalence trend in the country shows disproportionately higher incidence of the infection among certain population groups. An analysis of Annual Sentinel Surveillance data (2003-2005) shows that female sex workers (FSWs), men-who- have-sex-with-men (MSM) and injecting drug users (IDUs) have disproportionately higher incidence of HIV infection. Whereas HIV prevalence in the general population is 0.88 percent, its prevalence among FSWs is 8.44%, IDUs 10.16%, MSM 8.74% and among the attendees of STD clinics it is 5.66% (see the table below). To gain control over HIV/AIDS spread in the country therefore effective interventions are needed for HRGs (3).

### HIV Prevalence among High Risk Groups

<table>
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<th>percent +ve 2004</th>
<th>percent +ve 2005</th>
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<tbody>
<tr>
<td>Female Sex Workers</td>
<td>32 - 83</td>
<td>10.30</td>
<td>9.43</td>
<td>8.44</td>
</tr>
<tr>
<td>Injecting Drug Users</td>
<td>18 – 30</td>
<td>13.30</td>
<td>11.20</td>
<td>10.16</td>
</tr>
<tr>
<td>Men having Sex with Men</td>
<td>9 – 18</td>
<td>12.10</td>
<td>7.50</td>
<td>8.74</td>
</tr>
<tr>
<td>ANC population</td>
<td>266 - 267</td>
<td>0.87</td>
<td>0.89</td>
<td>0.88</td>
</tr>
<tr>
<td>STD population</td>
<td>163-175</td>
<td>5.61</td>
<td>5.55</td>
<td>5.66</td>
</tr>
</tbody>
</table>

Evidence also suggests that India’s HIV/AIDS epidemic is largely due to unsafe sex worker-client interactions. About 86 percent HIV incidence in the country is from unprotected sex. Perinatal transmission of the infection is 2.72 percent, whereas 2.57 percent HIV infection is due to transfusion of infected blood or blood products. Though HIV transmission through injecting needles is only 1.97 percent of overall prevalence, it is the major route of the infection transmission in the north-east region.
Epidemic in General Population

Through MSM and sex worker-client interactions the infection spreads to general population. As a majority of men with MSM behaviour are married and a majority of sex worker clients are migrant labours and truck drivers, they pose the risk of infecting their spouses and unborn children.

Targeted Interventions for Prevention, Care and Treatment

For the overall reduction in the epidemic, targeted interventions (TIs) are aimed to effect behaviour change through awareness rising among the high risk groups and clients of sex workers or bridge populations. These interventions are aimed to saturate three high risk groups with information on prevention; address clients of sex workers with safe sex interventions, and build awareness among the spouses of truckers and migrant workers, women aged 15 to 49 and children affected by HIV or vulnerable population groups. Apart from prevention of HIV infection, TIs facilitate prevention and treatment of sexually transmitted diseases as they increase the risk of HIV infection, and are linked to care, support and treatment services for HIV infection (3).

![Map of India](http://www.maps evaluatesindia.com)

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M.S. Pharmacology & Toxicology
Semester I
Alzheimer's Disease (Pharmacological Management)

Alzheimer's disease (AD) mainly occurs during the old age of human beings. It is frequently addressed as the disease of forgetfulness. It generally derived from the low cholinergic activity. The first step toward the best possible long-term management is early diagnosis of Alzheimer's disease, thereby facilitating early initiation of cholinesterase inhibitor treatment, which may stabilize/reduce the rate of symptomatic cognitive and functional decline. Cholinesterase inhibitor therapy with rivastigmine, donepezil, or galantamine is endorsed as standard first-line therapy in patients with mild-to-moderate Alzheimer's disease.

Symptoms
1. **Memory loss**: Forgetting recently learned information is one of the most common early signs of dementia. A person begins to forget more often and is unable to recall the information later.
2. **Difficulty performing familiar tasks**: People with dementia often find it hard to plan or complete everyday tasks. Individuals may lose track of the steps involved in preparing a meal, placing a telephone call or playing a game.
3. **Problems with language**: People with Alzheimer's disease often forget simple words or substitute unusual words, making their speech or writing hard to understand. They may be unable to find the toothbrush, for example, and instead ask for "the thing for my mouth."
4. **Disorientation to time and place**: Peoples with Alzheimer's disease might lose in their own neighborhood, forget where they are and how they got there, and not know how to get home.
5. **Poor or decreased judgment**: Those with Alzheimer's may dress inappropriately, wearing several layers on a warm day or little clothing in the cold. They may show poor judgment, like giving away large sums of money to telemarketers.
6. **Problems with abstract thinking**: Someone with Alzheimer's disease may have unusual difficulty in performing complex mental tasks, like forgetting what numbers are for and how they should be used.
7. **Misplacing things**: A person with Alzheimer's disease may put things in unusual places: an iron in the freezer a wristwatch in the sugar bowl.
8. **Change in mood or behavior**: Patient suffering with Alzheimer's disease may show rapid mood swings—from calm to tears to anger, for no apparent reason.
9. **Changes in personality**: The personalities of people with dementia can change dramatically. They may become extremely confused, suspicious, fearful or dependent on a family member.
10. **Loss of initiative**: A person with Alzheimer's disease may become very passive, sitting in front of the TV for hours, sleeping more than usual or not wanting to do usual activities.

**Pharmacological Management** for AD can be divided into three major areas:
- Preventative treatment.
- Primary anti-dementia therapy for management of cognitive symptoms.
- Secondary treatment for management of behavioural and psychological symptoms of dementia.
Management of Cognitive Symptoms

The Cholinergic Hypothesis

There is a relationship between the cholinergic neurotransmitter system and memory and cognitive performance. Impaired cholinergic neurotransmission contribute to the cognitive symptomatology of AD:

- Progressive loss of cholinergic neurones in the basal forebrain nuclei.
- Depletion of the enzyme choline acetyltransferase, which catalyses the synthesis of acetylcholine.
- Reduction in levels of brain acetylcholine.

Cholinergic pharmacology is characterized by the failure of acetylcholine precursors (e.g. choline, lecithin), releasing agents, and selective muscarinic agonists.

Cholinesterase Inhibitors

The acetylcholinesterase inhibitors (AChEIs) are the only licensed agents for primary treatment of AD. There are three AChEIs marketed—i.e., donepezil, rivastigmine and galantamine. The first AChEi developed (tacrine) is no longer available due to hepatic adverse effects. Following are common adverse events associated with cholinesterase inhibitors:

1. Donepezil (Aricept) - nausea, vomiting, diarrhoea, anorexia, insomnia, and muscle cramps fatigue, syncope.
2. Rivastigmine (Exelon) - nausea, vomiting, anorexia, weight loss, dyspepsia, asthenia, dizziness, fatigue, diarrhoea.
3. Galantamine (Razadyne, Razadyne ER) - nausea, vomiting, anorexia, weight loss, syncope, fatigue, dizziness, dyspepsia, diarrhoea.

Other Putative Cognitive Enhancers

Vitamin E (1000 units twice daily) or selegiline (5 mg twice daily) both delayed the time to functional worsening of AD symptoms. Ginkgo biloba, derived from the Chinese maidenhair tree, is a putative cognitive enhancer with reported anti-inflammatory and antioxidant properties. Although generally safe, ginkgo may cause bleeding and should be used with caution in patients receiving aspirin.

Partial Glutamate Antagonists

Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, improved cognition and global functioning in groups of patients with moderate to severe dementia. Glutamate is the major excitatory neurotransmitter in the brain. Memantine (Namenda) works by partially decreasing the effect of glutamate to activate nerve cells. It has not been proven that memantine slows down the rate of progression of Alzheimer's disease.

Management of Behavioural and Psychological Symptoms of Dementia

Changes in personality and behaviour are commonly associated with AD, often becoming significant in the moderate and severe stages of dementia. These changes may be extremely disruptive to patients and caregivers in both home and residential care settings, resulting in reduced quality of life and increased costs of care. Behavioural and psychological symptoms associated with dementia (BPSD) have a multifactorial aetiology, including neurobiological, psychological and social contributors.

Conventional Antipsychotics

Antipsychotics are the most commonly used class of drugs in the treatment of BPSD—for the treatment of agitation and psychotic symptoms. Side effects of this class of drugs are common amongst older patients and include extrapyramidal movement disorder; sedation; and tardive dyskinesia, which develop in one-third of patients at twelve months.
**Atypical Antipsychotics**

Atypical antipsychotics have superiority over conventional agents in terms of side-effect profile, and possibly, efficacy. However, the newer drugs (e.g., risperidone, olanzapine, quetiapine, ziprazadone) are more costly than conventional agents, and have the potential to cause weight gain (e.g., olanzapine) and derangement of glucose metabolism. Risperidone has demonstrated efficacy for both psychotic symptoms and more general BPSD and has shown significant efficacy for aggression and psychotic symptoms compared to both placebo and haloperidol.

**Anxiolytics**

Benzodiazepines are commonly used in the treatment of BPSD, and are used primarily for anxiety, agitation and sleep disturbance. Non-benzodiazepine sedative, zolpidem, may be useful in restoring normal sleep. The side-effect profile of benzodiazepines includes sedation, motor (ataxia) and cognitive impairment (amnesia and confusion) and potential withdrawal syndrome. An increase in falls can occur. Sleep architecture may also be altered, with inhibition of rapid eye movement and delta wave sleep. Therefore, benzodiazepines are poor choices for regular use in dementia, but can have a role for short-term management of anxiety or sleep disturbance. Preferred agents are those with short action and no active metabolite, including oxazepam and lorazepam.

**Antidepressants**

It is important to treat depression in dementia, and a low threshold should exist for initiating treatment. Selective serotonin reuptake inhibitors (SSRIs) are the first-line antidepressants. SSRIs (e.g., citalopram and sertraline) in dementia have shown a significant effect on both psychosis and depression, suggesting that these agents could have antipsychotic potential in dementia patients.

**Scales and Evaluation Instruments Used to Monitor Response to Pharmacological Therapy in Clinical Practice**

**Mini-Mental State Examination**

- Measure cognition
- Assesses orientation, registration, recall, language, and attention
- Uses a 30 point scale
- Requires approximately 5 to 10 minutes to complete

**Clinician’s Interview Based Impression of Change plus Caregiver Input**

- Global assessment of functioning
- Overall assessment of behaviour, general psychopathology, cognition, activities of daily living
- Overall scale of 1 (marked improvement) to 7 (marked deterioration)
- Based on simple interview with patient and caregiver

**Function Activities Questionnaire**

- Intended to quantify level of disability
- Scores functional capacity on a scale of 1 (normal) to 7 (severely incapacitated)
- Requires 5 to 10 minutes to complete
- Filled out by caregiver

**Physical Self-Maintenance Scale and Instrumental Activities of Daily Living**

- Evaluates patient’s ability to perform basic and instrumental tasks
- Assesses 8 areas of higher function on a scale of 1 to 5, and 6 basic tasks that are fundamental to daily function
- Requires about 10 minutes to complete scale
• Very useful in clinical practice
• Minimal training required to administer

Neuropsychiatric Inventory-Questionnaire
• Measures disturbed behaviours
• Assesses frequency and severity of 12 symptoms (agitation, irritability, depression, etc)
• Can be completed by the interviewer in 10 to 15 minutes

Conclusion

Alzheimer’s disease is a progressive neurodegenerative disease affecting significant number of older people. The availability of acetylcholinesterase inhibitors to stabilise the core cognitive symptoms of mild to moderate Alzheimer’s disease for up to twelve months has heralded a noticeable shift to a more positive attitude to the assessment and management of patients. Donepezil, rivastigmine, and galantamine are currently prescribed. Important advances have also been made in the pharmacological management of behavioural and psychological symptoms of Alzheimer’s disease, improving the quality of life for both patients and caregivers. The continuing endeavour to elucidate preventative treatment is important if our approach to Alzheimer’s disease is to shift from palliative care.

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Semester I
Carcinogenicity Testing

Introduction

This chapter presents an historical overview of cancer, carcinogenicity testing, and human cancer causes. Cancer has been known for a very long time but the awareness of human chemical carcinogenicity increased in the 20th century. This in turn has produced legislation that prohibits the use of carcinogens in the food chain and has provided guidelines for carcinogenicity testing in animals. Lifetime studies (18–24 months) in two main rodent species (rat and mouse), also known as the “Standard Chronic Bioassay,” have been conducted since 1960.

Meanwhile, various deficiencies have been detected in the Chronic Bioassay; over-sensitivity being the major one. Hundreds of compounds have been tested with the Chronic Bioassay method, and about 50% have yielded (false) positive results. Lack of relevance to man has often been demonstrated by additional mechanistic studies. Additionally, more mechanistic and molecular knowledge has been gained in regards to the human carcinogenicity concept, including genotoxic versus epigenetic carcinogens, the multi-stage cancer theory, and human life style factors involved in carcinogenesis.

The above evolutions have opened new opportunities for carcinogenicity testing, including short-term alternative carcinogenicity models. In addition, carcinogenicity testing is evolving from a standard chronic bioassay to a weight-of-evidence approach, where the mechanisms involved in rodent and human carcinogenesis are considered, and where communication between industry and regulatory authorities is encouraged.

Carcinogenicity Testing Guidelines

In the 1970s and 1980s, the US, European, and Japanese Registration Authorities established guidelines for carcinogenicity testing in animals for the various chemicals characterized by possible long-term intake by man. These chemicals included food and color additives, agrochemicals, industrial chemicals, solvents, human pharmaceuticals, and veterinary products. The guidelines were based upon the Chronic Bioassay of the National Toxicological Programme (NTP) and gave indications for route and frequency of dosing, dose levels, group sizes, duration of the study, and observations during the study. A summary of the various guidelines is provided in Table 1.

Table 1: Establishment of guidelines for carcinogenicity testing in animals-

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<tr>
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<td>Pharmaceuticals</td>
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Current Carcinogenicity Testing

A description of the standard approaches in carcinogenicity testing for the safety of chemicals is provided.

Standard Rodent Chronic Bioassay

Species and strains

According to the previously described guidelines, carcinogenicity studies have to be performed in two rodent species, usually the rat and the mouse. Ideally, the strains should have a low spontaneous incidence of cancer, but they should also be sensitive to induction of cancer by human carcinogens. Commonly used species are the Sprague Dawley, Fisher F344, or Wistar strains in rats, and the CD-1 or C57BL-based strains in mice. At least 50 animals are included per sex in each dose group. Today, at least three dose groups are used as well as at least one negative control group, which results in minimally 200 males and 200 females for one study.

Doses and Route of Administration

The animals are exposed daily to the test compound from the age of 6 weeks onward. The administration procedure should simulate human exposure as closely as possible; oral intake is the most common route. In the past, the test item was often mixed in the drinking water or the feed, either in a fixed concentration in the feed during the entire study or with regular adaptations to maintain a steady ratio of mg/kg of body weight intake during the entire life expectancy. Nowadays, oral gavage administration in the stomach is used, except for agrochemicals and food additives, where feed administration is still applicable. Oral gavage administration provides more certainty of test item intake, but also leads to another pattern of test item exposure in the body (peak concentrations after dosing). Dose-selection for the various dose groups has been based mainly upon a MTD, which is defined to elicit slight target organ toxicity but will not shorten the treated animals' survivability from any toxic effects other than the induction of neoplasms. For the most part, a body weight gain loss of 10% is considered acceptable as evidence of minimal toxicity. The medium dose may elicit minimal toxicity; however, the low dose should be free of any toxicity.

Duration

The studies are designed to last for at least 24 months and survival should be at least 25 animals per sex in the control and low dose groups, both in males and females. In the past, the studies were often extended beyond 24 months because survival (especially in the control and low dose group) was still above 25 animals/group/sex, and because of concern that the carcinogenic effect might become visible only at a later end point. Currently, most of the studies are not extended since geriatric pathology increases, which can complicate and obscure the assessment of carcinogenicity.

Experimental Condition

Experimental conditions are of utmost importance because they can influence the results of the study. Factors such as hygiene, temperature, relative humidity, number of air replacements, and light have to
be maintained and monitored consistently during the study. Now carcinogenicity studies are performed under Specific Pathogen Free (SPF) conditions. This means that SPF animals are obtained from commercial breeders and are placed in SPF rooms after arrival in the experimental unit. Other factors taken into account are quarantine, health monitoring, and hygienic measures during handling, such as sterile gloves and mouth masks. Good Laboratory Practice (GLP) has also contributed to improved test conditions. GLP not only applies to the way animals are handled, but also to appropriate documentation and recording of all actions during a study. This leads to better traceability, reconstruction, and interpretation of study data and results. All the improvements in experimental conditions have led to increased survival in the animals. In the past, various deaths occurred due to respiratory or other infectious diseases; these are almost totally excluded within the current improved health condition of the animals.

Parameters Examined in the Study

During the 24-month study, various study parameters are examined. The daily follow-up is of utmost importance in order to pick up unexpected findings. If problems arise, the study director’s, veterinarian’s, or pathologist’s attention is drawn, and immediate and appropriate actions are requested. After necropsy during or at the end of the study, a mean list of 30 tissues is sampled and examined macroscopically. This may lead to a total number of 12,000 or more tissue samples for a single carcinogenicity study. All tissues are fixed and processed for further microscopic examination for neoplastic and non-neoplastic changes. These examinations are done by pathologists specialized in rodent pathology. The final aim is to detect the number of animals with tumors, but also multiplicity of tumors and whether the tumors caused death of the animal.

Histopathological examination is performed on all animals to detect “non-neoplastic” and especially “neoplastic” changes induced by the test compound. Non-neoplastic changes may include inflammatory, degenerative, or other changes in various tissues, either caused by the test item or by geriatric pathology. Neoplastic changes, or tumors, can be divided into “benign” and “malignant” neoplasms. Benign neoplasms are well defined, often encapsulated, noninvasive, and well differentiated. They grow relatively slowly, display relative few mitoses, and are not metastatic. Malignant tumors are less well defined and usually not well encapsulated. They are invasive and relatively undifferentiated; they grow rapidly, display abundant mitosis, and finally undergo metastasis.

Historical Control Data

Historical control data can be used to interpret the changes seen in carcinogenicity data. These control data can apply to the various parameters studied, such as hematology, biochemistry, and the incidences of tumors. They may be used when differences are seen between the incidences of tumors in the dosed groups and spontaneous incidences in concurrent control animals, where coincidence is suspected, or for tumors with very sporadic incidences. Spontaneous incidences in tumors are commonly seen in untreated rats and mice, and vary from strain to strain. Examples include pituitary and mammary tumors in rats, and liver and lung tumors in mice. The incidences of tumors can vary, and even today, there is no clear understanding of their etiology, except for ad-libitum feeding. On the other hand, caloric restriction could retard aging (associated with a reduction in the rate of cell replication), and reduce the incidence of degenerative diseases and tumor incidences.

Statistical Analysis

Statistical analysis is performed on all parameters in the study. Its most fundamental objective is to
determine whether administration of the test agent results in an increase in tumor incidence rates as compared to those in unexposed controls. Various statistical methods can be used. Tests for increased tumor occurrence rates between dosages may be based on “pair-wise comparisons,” such as the Chi-square test, the Fisher’s exact test, or the Cochran–Armitage test. These tests are most appropriate when survival rates do not differ appreciably in the various dose groups.

If the treatment results in reduced survival, early mortality in the high-dose groups may preclude the development of tumors and other statistical methods are required. Peto proposed a test for differences in tumor occurrence rates due to treatment, taking into account differences in survival and the times at which tumors were observed. This procedure requires information on the cause of death of each animal, and is based on a time-stratified contingency table analysis of the prevalence of incidental tumors that did not kill their host and a similar analysis of fatal tumors that resulted in death prior to the study. These two analyses are then combined to arrive at an overall test for increase in trend in tumor occurrence rates allowing for differential survival rates among the treatment group.

Cancer Risk Assessment

Once carcinogenicity testing has been performed, carcinogenicity risk assessment must be performed. Regulatory agencies have the responsibility to identify and assess compounds that are administered in food, provided as pharmaceuticals, or have the potential to be released in the environment at levels that warrant concern. Various topics have to be addressed when characterizing the carcinogenic risk. These include hazard identification (i.e., the likelihood to be a human carcinogen), dose-response, and extent of human exposure. Each of these assessments involves the use of many assumptions and estimations, the magnitude of which may be decreased by the incorporation of more information (e.g., mechanistic studies, pharmacokinetic data, and improved low dose extrapolation models). In addition, the International Agency for Cancer Research (IARC) has evaluated and published carcinogenic risk to humans for hundreds of chemicals in both systems. Chemicals, including pharmaceuticals, are assigned to five groups: 1) carcinogenic to humans; 2) probably carcinogenic to humans; 3) possibly carcinogenic to humans; 4) not classifiable for human carcinogenicity; and 5) probably not carcinogenic to humans. Assignment to one of these groups is based on scientific judgment of data derived from studies in humans and animals as well as supporting data. Data are estimated providing sufficient, limited, or inadequate evidence for carcinogenicity in humans and rodents.

Future Opportunities

Data from short to medium-term toxicity studies that precede carcinogenicity studies reveal that most of the nongenotoxic agents which induce tumors in rodents also produce other pathological changes in the tissues in which the tumors develop and at dose levels at which tumors are observed. These early changes range from altered hormone levels, impaired ion balance, and organ enlargement to specific and marked histopathological changes. These findings may be used for early detection of nongenotoxic carcinogens, and may also be extremely valuable for designing protocols for long-term bioassays. Furthermore, a thorough understanding of such early indicators will lead to the elucidation of specific mechanisms involved in carcinogenesis. Together with examination of possible thresholds for underlying toxic events, this confirms the basis for assessment of carcinogenic risk and for the regulation of human exposure. Based upon the above rationale, a “tier approach in carcinogenicity testing and assessment” of pharmaceuticals can be followed, possibly with refinement, reduction or replacement of test methodologies in carcinogenicity testing. A first approach, according to the ICH S1A guideline scenario on the need for carcinogenicity testing, prescribes long-term carcinogenicity testing.
(in one or two species) for compounds with continuous or intermittent exposure to humans and compounds with cause for concern. If there is no long-term exposure to the compound, and if there is no cause for concern, no further action is recommended, whereas short- or long-term studies may be warranted for suspicious findings. A second approach postulates that much of the information necessary to assess the carcinogenic potential of a new drug without a bioassay is usually available by the end of the first clinical studies in patients. (Suspicious findings from in vivo genotoxicity studies and 3-6 month toxicology studies aimed at assessing risk factors associated with carcinogenicity in humans include: genotoxicity, immune suppression, hormonal activity, and chronic irritation/mitogenic activity). Evaluation of this package will, therefore, identify the presence or absence of the known causes of cancer from pharmaceuticals in humans, under conditions relevant to the use of the drug in question. If cause for concern remains at this stage, useful information on long-term adverse effects that might represent a carcinogenic hazard to humans may be obtained (e.g., from a 12-month study, usually in rats, conducted at clinically relevant dose levels). Finally, a third approach has been proposed with five stages that focus on the chemical structure, DNA reactivity, epigenetic effects, limited bioassays, and finally, the application of “accelerated bioassays.” These accelerated bioassays require 40 weeks and apply to the use of sensitive markers for induction of neoplasia in comparison to positive control compounds for important organs in human carcinogenesis. It enables data acquisition of the entire carcinogenesis process directed toward developing mechanistic information. This system would have the potential to replace the chronic bioassay in rodents in some circumstances and could serve an alternative to a chronic bioassay in a second species.

Conclusion

In the 20th century, the concept of carcinogenesis and carcinogenicity testing has evolved enormously, although the standard Chronic Bioassay still contains many of deficiencies. New carcinogenicity testing strategies, however, are to be expected. Also, validation results with regards to the alternative carcinogenicity models will become available and lead into new insights in the most appropriate short-term carcinogenicity studies.

References


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Semester I
Emergence of Antimicrobial Resistance in Microorganisms-
An Irrational Use of Antimicrobials

Emergence of antimicrobial resistance in microorganisms is a global problem and really a concerned for the developing countries like India where antibiotics constitutes the major portion of the expenditure on medicines due to high burden of infectious diseases. Therefore, antimicrobials play a critical role in limiting morbidity and mortality in India. Antimicrobial resistance increases the cost of treatment as cheap old conventional antimicrobial agents should be replaced by new expensive antimicrobials for effective treatment of resistant microorganisms. The economic constraints prevent the use of expensive new antimicrobials to treat infectious diseases which occurred due to resistant microorganisms. This increases the risk of spreading the diseases as well as resistance in the microorganisms.

Development of drug resistance in microorganism is a natural biological phenomenon but the factors that influence the spread of resistance are ecological, epidemiological, cultural, social and economic. Every time an antimicrobial is used whether appropriately or not, in human beings or in animals, the probability to develop antimicrobial resistance in microorganisms is increased. Irrational uses of antimicrobials are very high due to prevalence of self-medication in India. This self-medication is mainly takes place in small towns and rural area where there are lacks of health facilities and many people do not have financial ability to bear the expenses.

The other possible reasons for irrational use of drugs particularly antimicrobials include the following:

(i) Doctors prescribe antimicrobials to any patients with fever, taking it as a sign of bacterial infection, especially when they are concerned that patient will not return for follow up.
(ii) Lack of microbiological facilities or unwillingness of patients to undergo tests.
(iii) The patient’s expectation of being given an antibiotic over the counter or in a prescription at clinic.
(iv) Incentives for pharmacists to sell more antimicrobial drugs.
(v) The lack of knowledge in public about the rational and appropriate use of antimicrobials.

The awareness programme among the health professionals and patients could curtail the use of antimicrobials without harming health outcomes and reduce the risk of developing antimicrobial resistance in microorganisms.

Ministry of Health and Family Welfare, Govt. of India task force announced a new antimicrobial policy for containment of antimicrobial resistance in 2011. The policy recommended the monitoring antimicrobial resistance, regulations for use and misuse of antimicrobials in the country, creation of national surveillance system for antimicrobial resistance, mechanism of monitoring prescription audits, regulatory provision for monitoring use of antibiotics in human, veterinary & industrial sectors and identification of specific intervention measures for rational use of antimicrobials. In order to monitor and check unauthorized sale of antibiotics, a separate schedule as Schedule H1 under the Drugs and Cosmetics Rule was proposed in the policy. As part of provisions under this new schedule, a system of colour coding of third generation antibiotics and all newer molecules like carbapenems (Erta penem, Imipenem, Meropenem), Tigecycline, Daptomycin may be put in place restricting their access to only tertiary hospitals, the ministry has proposed. Appropriate regulations should also be formulated for not selling antibiotics without prescription.
The following three strategies should be followed to improve drug use:

- **Educational Strategy**: Training, printing materials, media based approach discourage self medication by the general public.
- **Managerial Strategy**: Monitoring and supervision, generic substitution, patient cost sharing (economic incentives) etc.
- **Regulatory strategy**: enforcement, sanction, drug withdrawal, market control.

Antimicrobial resistance diverts the financial resources that could otherwise be used for improving health and threatens the success of global efforts to combat the major infectious diseases of poverty. In this scenario, implementation of proposed containment of antimicrobial policy can be considered appropriate risk management to protect health care initiatives and the availability of treatment for future generations. In addition to prevent the irrational use of antimicrobials, prevention of microbial infections, their spread and discovery of newer antimicrobials are essential in the containment of antimicrobial resistance.

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Nanomedicines: Emergence of a New Era in Biomedical Sciences

Introduction:

The prefix "nano-" comes from the Greek root nanos, or dwarf and means one-billionth $10^{-9}$. Though this discipline is in its infancy but it has potential to change biomedical science in the future. Due to the advances in the field of nanotechnology, nanodevice manufacturing has been growing gradually. Some medical nanodevices may have mobility - the ability to swim through the blood, or crawl through body tissue or along the walls of arteries. Others could have different shapes, colours, and surface textures, depending on the functions they would be intended to perform. They would have different types of robotic manipulators, different sensor arrays. Each medical nanodevice could be designed to do a particular job extremely well, and would have a unique shape and behaviour. The most elementary nanomedical devices are used to diagnose illness and to repair damages and infections. Nanomedicine is useful in monitoring, control, construction, repair, defence, and improvement of all human biological systems. Nanomedicine includes the following technologies which work at the molecular level and useful in engineered nanodevices and nanostructures (Table-1).

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<th>Nanorobotic devices</th>
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<td>DNA-based devices and nanorobots, Diamond-based nanorobots, Cell repair devices</td>
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Nanomaterials:

Nanoparticles

Nanoparticles can be engineered to target cancer cells for using in the molecular imaging of a malignant lesion. Large numbers of nanoparticles are safely entered into the body and they preferentially bind to the cancer cell, finding the anatomical counter of the lesion and making it visible. These nanoparticles give the ability to see cells and molecules that otherwise cannot detect by conventional imaging. Tagged nanoparticles are particles which can track biological events by simultaneously tagging each biological component and become a new class of bioorobes for many biological applications.

Nanostructured materials:

Quantum dots (QDs)

A Quantum dot is a semiconductor nanostructure that confines the motion of conduction band electrons, valence band holes, or excitons (bound pairs of conduction band electrons and valence band holes) in all three spatial directions. A Quantum dots contains a small finite number of elementary electric charges (of the order of 1-100). Small Quantum dots, such as colloidal semiconductor nanocrystals, can be as small as 2 to 10 nanometers, corresponding to 10 to 50 atoms in diameter and a total of 100 to 100,000 atoms within the quantum dot volume. These nanocrystal fluorophores have several potential medical applications including diagnostics, imaging, targeted drug delivery, and
photodynamic therapy. The diverse potential applications of Quantum dots are attributed to their unique optical properties including broad-range excitation, size-tunable narrow emission spectra, and high photostability. It has been employed for imaging of pre-labelled cells. They have ability to image single cell migration in real time so it is expected to be important in study of embryogenesis, cancer metastasis, stem cell therapeutics and lymphocyte immunology.

**Dendrimers**

Dendrimers are highly branched, star-shaped macromolecules with nanometer-scale dimensions. They have mainly three components: (1) Central core, (2) Interior dendritic structure (the branches) and (3) Exterior surface with functional surface groups. The various combinations of these components yields products of different shapes and sizes with shielded interior cores that are ideal candidates for applications in both biological and materials sciences. While the attached surface groups affect the solubility and chelation ability. The different cores impart unique properties to the cavity size, absorption capacity, and capture-release characteristics. Applications of dendrimers include drug delivery, gene transfection, catalysis, energy harvesting, photo activity, molecular weight and size determination, rheology modification, and in nanoscale science and technology as antiviral drugs/vaccines (prion clearing agents, multivalent binding inhibitors), tissue repair scaffold, targeted carriers of chemotherapeutics and bioimaging (optical oxygen sensors).

**Nanoshells**

Metal nanoshells are a novel type of composite spherical nanoparticle consisting of a dielectric core covered by a thin metallic shell which is typically gold. Nanoshells possess highly favorable optical and chemical properties for biomedical imaging and therapeutic applications. By varying the relative dimensions of the core and the shell, the optical resonance of these nanoparticles can be precisely and systematically varied over a broad region ranging from the near-UV to the mid-infrared. This range includes the near-infrared (NIR) wavelength region where tissue transmissivity peaks. In addition to spectral tunability, nanoshells offer other advantages over conventional organic dyes including improved optical properties and reduced susceptibility to chemical/thermal denaturation. Furthermore, the same conjugation protocols used to bind biomolecules to gold colloid are easily modified for nanoshells.
Fullerene-based nanomedicines

Fullerenes have attracted considerable attention in different fields of science since their discovery in 1985. Investigations of physical, chemical and biological properties of fullerenes have yielded promising information. It is inferred that size, hydrophobicity, three dimensionality and electronic configurations make them an appealing subject in medicinal chemistry. Their unique carbon cage structure coupled with immense scope for derivatization make them a potential therapeutic agent. The study of biological applications has attracted increasing attention despite the low solubility of carbon spheres in physiological media. The fullerene family, and especially C60, has appealing photo, electrochemical and physical properties, which can be exploited in various medical fields. Fullerene is able to fit inside the hydrophobic cavity of HIV proteases, inhibiting the access of substrates to the catalytic site of enzyme so produce antiviral activity. It can be also used as radical scavenger and antioxidant. At the same time, if exposed to light, fullerene can produce singlet oxygen in high quantum yields. This action, together with direct electron transfer from excited state of fullerene and DNA bases, can be used to cleave DNA. In addition, fullerenes have been used as a carrier for gene and drug delivery systems. Also they are used for serum protein profiling as material enhanced laser desorption ionisation (MELDI) for biomarker discovery.

Nanotube-Nanotweezers

Nanotweezers are nanoscale electromechanical systems which works based on carbon nanotubes. It has been developed for manipulation and interrogation of nanostructures. Electrically conducting and mechanically robust carbon nanotubes were attached to independent electrodes fabricated on pulled glass micropipettes. Voltages applied to the electrodes closed and opened the free ends of the nanotubes, and this electromechanical response was simulated quantitatively using known nanotweezer structure and nanotube properties. The mechanical capabilities of the nanotweezers were demonstrated by grabbing and manipulating submicron clusters and nanowires. The conducting nanotube arms of the tweezers were also used for measuring the electrical properties of silicon carbide nanoclusters and gallium arsenide nanowires.

Nanorobotic Devices:

Nanomedicine offers the prospect of powerful new tools for the treatment of human diseases and the augmentation of human biological systems. These tools are called nanomedical devices. Nanodevices are somewhere from 100 to 10,000 times smaller than human cells. They are similar in size to large biological molecules such as enzymes and receptors. So this offers an extraordinary and paradigm, changing opportunity to study and interact with normal as well as cancer cell at the molecular and cellular scales and during the earliest stage of cancer process. Due to the small size, nanoscale devices can readily interact with biomolecules on both the surface of cells and inside of cells. The design of the size of nanomedical robots have to include the limit of the capillaries sizes which are located in the capillary beds where in turn the arteries and veins in the body meet. These capillaries have a maximum diameter of 20 microns but an average diameter of 8 microns and the design of nanomedical robots have to be below those sizes because blood cells must flow through those areas as well.

Medical Nanorobotics of Tomorrow

In the longer term, perhaps 10 to 20 years from today, the earliest molecular machine systems and nanorobots may join the medical armamentarium. It is finally giving physicians the most potent imaginable tools to get the better of human disease, ill health and aging. Organic building materials
(e.g. proteins, polynucleotides) are very good at self-assembly but the most reliable and high-performance molecular machines may be constructed out of diamondoid materials, the strongest substances known. Many technical challenges must be overcome before medical nanorobots can become a reality.

**Nanoscale Robotic Actuator**

Micro- and nano-scale robotics has become a new emerging area of systems and controls area recently. These miniature robots have unique advantages such as accessing to unprecedented and small areas, increased flexibility, functionality and robustness, and being low cost, many (swarms), adaptive and distributed. The locomotion and manipulation dynamics of these robots are dominated by micro/nano-scale forces and the scaling effects. The long term target is the miniaturization of these robots down to micrometers size. However, currently, these robots have sizes from tens of centimeters down to millimeters due to limited miniaturization and integration capabilities of available power sources, communication, control and computation schemes and tools, and coarse to fine motion mechanisms, sensors, manipulators, and actuators.

**Nanosensors and Nanoprobes**

The nanosensor equipped with antibody-based bioprobe capable of monitoring biochemicals of single cells was developed by T. Vo-Dinh et al. from *Oak Ridge National Laboratory* and published in 1998. The preparation of this kind of nanosensor was based on BTP- benzo [a] pyrene tetrol, a biomarker of DNA damage. Interrogation of single cells for the presence of BPT was carried out using antibody nanoprobes. These antibody nanoprobes were prepared from quartz optical fibres which were pulled in a fibre puller to extremely small dimensions (10-100 nm range). Antibodies to BPT were attached to the tips of the fibres. The fibres were then coated with silver, so as to prevent light from emerging anywhere along the length of the fibre except the tip, where the antibodies are located.

**Clottocytes**

The clottocyte is an artificial, mechanical platelet which designed by Robert A. Freitas Jr. The response time of a clottocyte would be on the order of 100-1000 times quicker than natural platelets, achieving complete haemostasis in as short as one second. Clottocytes would have several distinct advantages over their natural counterparts. For instance platelet function can be adversely affected by drugs such as aspirin.

Clottocytes would be immune to the effects of drugs, and could functions optimally without any chemical fluctuations in the bloodstream. Clottocytes represent an example of a unique nanotechnological benefit which could not even achieved by biotechnology. Clottocytes are 10,000 times more effective to achieving clotting, by its volume, compare to natural platelets, therefore it is required at only “0.01% of the concentration of platelets in the bloodstream.”

![Image of clottocytes](TheNanoAge.com)
Clottocytes would be approximately 2 micron diameter spherical nanorobots, powered by serum oxyglucose, and controlled by an onboard nanocomputer. They would contain a compactly folded fiber mesh which could be unfurled in the immediate vicinity of a damaged blood vessel. The overlapping nettings deployed by activated clottocytes would trap blood cells and halt bleeding almost instantaneously.

**Microbivore**

Nanorobotic phagocytes (artificial white cells) called microbivores could patrol the bloodstream, seeking out and digesting unwanted pathogens including bacteria, viruses, or fungi. During each cycle of nanorobot operation, a target bacterium becomes bound to the surface of the blood borne. Microbivore like a fly on flypaper, via species-specific reversible binding sites. Hence microbivores, each 2-3 microns in size, would be up to~1000 times faster-acting than either unaided natural or antibiotic-assisted biological phagocytic defences.

**Respirocytes**

The respirocyte is a bloodborne 1-micron-diameter spherical nanomedical device designed by Robert A. Freitas Jr. The device acts as an artificial mechanical red blood cell. It is designed as a diamondoid structure, in 1000-atmosphere pressure vessel with active pumping and powered by endogenous serum glucose, and can deliver 236 times more oxygen to the tissues per unit volume than natural red cells while simultaneously managing carbonic acidity. An individual respirocyte consists of 18 billion precisely arranged structural atoms plus 9 billion temporarily resident molecules when fully loaded. An on board nanocomputer and numerous chemical and pressure sensors allow the device to exhibit behaviors of modest complexity, remotely reprogrammable by the physician via externally applied acoustic signals.

**Reference**

6. Patel GM, A new era on medicine are expected to happen in the coming years, 5(4) (2007)

**Kalpesh M. Vaghasiya**  
M.S. (Pharm.) Pharmacy  
Semester 1
Drug Delivery System through Nail

Anatomy and physiology of nail:
The nails are composed of flat, hornyscales which form protective cover for the distal of the finger & toes. Each nail consist of following parts
1) A body, the attached uncovering of the nail
2) A free edge, the anterior unattached extension of the body
3) The nail root, the posterior or proximal part of the nail, which lies beneath a fold of the skin.

Nail plate is the most visible part of the nail apparatus.
The human nail plate consists of three layers; (1) The dorsal (2) intermediate layer derived from the matrix& (3) the ventral layer from nail bed. The intermediate layer is three - quarter of the whole nail thickness & consists of the soft keratin. The upper layer, dorsal, is only a few cell layers thick but consist of hard keratin, with a relatively high sulphur content, mainly in the form of amino acids cysteine, which constitutes 94 % by weight of nail. The upper layer of the nail mainly diffuses into & through the nail plate. The ventral layer consists of soft hyponychial in which many pathological changes occur. Thus, in the treatment of these nail diseases; an effective drug concentration in the ventral nail plate would be of great importance.

Diseases of nail:
The nail plate may appear abnormal as result of, a congenital defect, disease of skin with involvement of the nail bed, systematic disease, reduction of blood supply, local trauma, tumors of the nail fold or nail bed, infection of the nail fold, infection of the nail plate.

Table 1 : Characteristics of nail diseases
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name of Disease</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Leuconychia</td>
<td>White spots or lines appears on one or more nails &amp; grow out spontaneously.</td>
</tr>
<tr>
<td>2</td>
<td>Onychomycosis</td>
<td>Yellow-brown patches near the lateral border of the nail.</td>
</tr>
<tr>
<td>3</td>
<td>Tinea Unguis</td>
<td>Ringworm of the nails, is characterized by nail thickening, deformity, and eventually results in nail plate loss.</td>
</tr>
<tr>
<td>4</td>
<td>Onychatrophia</td>
<td>Is an atrophy or wasting away of the nail plate which causes it to lose its luster, become smaller and sometimes shed entirely.</td>
</tr>
<tr>
<td>5</td>
<td>Onychogryposis</td>
<td>Are claw-type nails are characterized by a thickened nail plate and are often the result of trauma.</td>
</tr>
<tr>
<td>6</td>
<td>Onychorrhexis</td>
<td>Are brittle nails which often split vertically, peel and/or have vertical ridges.</td>
</tr>
<tr>
<td>7</td>
<td>Leuconychia</td>
<td>Is evident as white lines or spot in the nail plate and may be caused by tiny bubbles of air that are trapped in the nail plate layers due to trauma.</td>
</tr>
<tr>
<td>8</td>
<td>Koilonychia</td>
<td>Is usually caused through iron deficiency anemia. These nails show raised ridges and are thin and concave.</td>
</tr>
</tbody>
</table>
Psoriasis

The nail is characterized by raw, scaly skin and is sometimes confused with eczema.

Melanonychia

Are vertical pigmented bands, often described as nail ‘moles’, which usually form in the nail matrix?

Scope for the treatment of nail disorders

- **Surgical extraction:** extremely traumatic and has largely been consigned to history.
- **Chemical removal:** Cosmetically unappealing. There are chances of relapse once new nail regenerates.
- **Oral Systemic antifungal therapy:**
  - limited by its toxicity
  - drug interaction
  - contraindication
  - increase microbes resistance
  - relapse is very common
- **Topical therapy:** Avoid problems associated with systemic treatment.

Drug delivery system through nail:

Current topical treatments have limited therapeutic effectiveness possibly because they cannot sufficiently penetrate in the nail plate to transport a therapeutically sufficient quantity of antifungal drug to the target sites to eradicate the protection. Also the analysis of the drug’s penetration is a difficult task. Here in the present article a method to analyze the drug permeated across nail barrier is suggested.

Advantages of drug delivery system through nail

- This applies both for the effect of drugs acting locally as well as the effect of drugs which are absorbed into the blood, lymphatic and tissue fluids, and transferred systemically for an action at sites distant from the point of application.
- In some instances there may be a need to overcome first pass metabolic degradation of drug in the liver, or variation in drug handling, consequent on concentration, or dose-related kinetics. Again, to achieve an optimal effect, there may be a need to keep the dosage constant, as well as a necessity to avoid the peaks of blood concentration of drug.
- Advantages of the patch system is based upon a surprising discovery that finger nails and toe nails provide an effective route of systemic administration for a wide range of therapeutically active substances by simple local application. Nails also have the advantage that drug delivery through them is not complicated by the presence of hair follicles and sweat glands, as in skin, nor the very wide variation in permeability of the stratum corneum at different body sites and in different individuals.
- Advantage of the invention is that a large range of carrier bases can be used and selected so that the effect of the nail itself could be optimised to act both as a reservoir and rate limiting delivery system for the applied drug, by using partitioning between the vehicle and nail and subsequent systemic absorption from the nail.
- Particular advantage of the invention that the range of therapeutically active substances which can be administered is not limited in the same way as the stratum corneum to particularly critical lipid/water solubility partition characteristics.
- The active substances can be administered in a wide range of dosage amounts.
Major challenges

- The nail plate is much thicker creating a much longer diffusional pathway for drug delivery.
- Stable disulphide bonds, responsible for the hardness of the nail, are believed to restrict drug penetration.
- The chemical and physical differences between the nail plate and the Stratum corneum may thus explain the long treatment times and lack of efficacy of currently available topical formulations.
- Therefore, when designing topical formulations for nail drug absorption it is essential to consider the physicochemical properties of the drug molecule (e.g. size, shape, charge log P etc), the formulation characteristics (e.g. vehicle, pH drug concentration), possible interactions between the drug and keratin and possible penetration enhancers.

Approaches of nail drug delivery

a) Topical application: Topical delivery is the most desired therapy due to relatively less severe side effects and better patient compliance particularly in case of pediatric patients. Two factors that could limit the accumulation and activity of drugs in the nail on topical application.
   1) The physicochemical properties of the drug need to be favorable for absorption through nail matrix.
   2) The nail matrix is reported to be relatively more permeable to polar compounds than nonpolar compounds. Second, binding of the drug to keratin reduces the availability of the free drug. Antifungal drugs are reported to possess high binding affinity to keratin.

b) Chemical penetration enhancement: The common approach for enhancing nail drug delivery has been to use keratolytic and thiolytic agents. These agents are known to increase the permeability of nail matrix by chemical modification of keratin.

Formulation:

The most convenient topical preparations are the nail lacquers (nail varnish) containing antifungal agents.

Nail lacquers (varnish, enamel) are made up of:
- Solvent usually organic to solubilise all the components
- Film forming polymers e.g. nitro cellulose
- Plasticizer: Which contribute to the flexibility and durability of the film?
- Resin which increase the adhesion of the film to the nail plate.
- Suspending agents: Which increase the viscosity of the enamel?
- Colouring agents (optional)
- Penetration enhancers

Selection of potential nail penetration enhancers:

The utility of compounds possessing sulfhydryl (-SH) groups (mercaptan compounds) to enhance nail penetration has been reported. The primary mechanism for enhancement of nail penetration as thought to be by reduction of disulphide linkages in the nail keratin matrix. Keratolytic agents such as salicylic acid, urea and papain have been investigated as

Potential I nails penetration enhancers.
Table 2: Penetration enhancing agents.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Penetration enhancing agent of different functional group</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amino acid derivatives</td>
<td>to reduce keratin in human hair via a sequence of two reversible, nucleophilic displacements.</td>
</tr>
<tr>
<td>2</td>
<td>Pyrithione and its derivative</td>
<td>Pyrithion (2-mercaptopyridine-1-oxide) is a fungicidal and bactericidal agent. Compounds containing a -SH group are themselves oxidized while reducing disulphide linkages in nail keratin.</td>
</tr>
<tr>
<td>3</td>
<td>Sulfites and Bisulphites</td>
<td>Sulphites and bisulphites are known to be reducers of disulphide linkages in keratin, and thus are popularly used for permeation waving of hair.</td>
</tr>
<tr>
<td>4</td>
<td>Keratolytic Agents</td>
<td>Salicylic acid, urea and guanidine hydrochloride are investigated as keratolytic agents. These substances are thought to tertiary structure and possibly secondary linkages (such as hydrogen bonds) in keratin. Thus promoting penetration through the nail.</td>
</tr>
<tr>
<td>5</td>
<td>Amphiprotic solvent</td>
<td>Dimethyl Sulphoxide (DMSO): Increasing permeability by disordering the lipid structure of Stratum corneum and interact with keratin in corneosite in con. Dependent manner.</td>
</tr>
<tr>
<td>6</td>
<td>Hydrophobins</td>
<td>Decreases surface tension and adhere to hydrophobic and hydrophilic surfaces.</td>
</tr>
</tbody>
</table>

Ideal characteristics:
- Formulation must be chemically & physically stable.
- Viscosity of the lacquers.
- Quick drying.
- Even film, good adherent.
- Colorless and non-glossy.
- Well tolerated locally.

Mechanism:
- The lacquer is applied with a brush.
- Solvent evaporates leaving a water insoluble film adhered to the nail plate.
- It assumed that dispersed drug will dissolve in the polymer film before it is released.
- Drug release from the film will be governed by Fick’s law of diffusion.
- Partitioning of drug molecules from the film into the nail.
- Diffusion across nail plate towards nail bed.

Table 3: Developed formulations for nail disorders.31.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name of Product</th>
<th>Name of drug</th>
<th>Uses/Indications</th>
<th>Name of Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eco-Nail nail lacquer</td>
<td>5% econazole +18% SEPA nail</td>
<td>Promotes the release of econazole from dried lacquer film, creating a large chemical</td>
<td>MacroChem Corporation</td>
</tr>
<tr>
<td></td>
<td>lacquer</td>
<td>gradient at the lacquernailinterface, todrive econazole into the deepnail plate.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Loceryl nail film</td>
<td>antifungal drug, amorolfine</td>
<td>Non-water-soluble film of amorolfineformed on the nail plate, and this filmremains in place for 1 week.</td>
<td>Galderma Australia Pty Ltd</td>
</tr>
<tr>
<td>3</td>
<td>Umecta nail film</td>
<td>Urea 40%</td>
<td>Psoriatic nails, brittle and thick nails, andcalluses.</td>
<td>JSJ Pharmaceuticals</td>
</tr>
<tr>
<td>4</td>
<td>Tazorac 0.1% Gel</td>
<td>Tazarotene</td>
<td>Used in the Treatment of Fingernail, Psoriasis.</td>
<td>Allergan Inc</td>
</tr>
<tr>
<td>5</td>
<td>Zalain nail patch</td>
<td>Sertaconazol nitrate</td>
<td>Once-a-week nail patch for treatment ofonychomycosis &amp; onychodystrophy</td>
<td>Labtec</td>
</tr>
<tr>
<td>6</td>
<td>Penlac nail lacquer</td>
<td>Ciclopirox Topical solution</td>
<td>A broad-spectrum antifungal medicationthat also has antibacterial and anti-inflammatory properties.</td>
<td>Dermik Laboratoires Inc.</td>
</tr>
</tbody>
</table>

Recent advances in nail delivery:<ref>
Apart from the traditional formulationslike nail lacquers, nail varnish, and nail patches recent technologies are introduced in the development of more efficient drug delivery. Here some of the recent technologies are listed which open the new horizons for drug delivery to the human nail.

a) Electrochemotherapy for Nail disorders.
Recently the iontophoretictrans-nail delivery method studied.Iontophoresis was found to enhance the transport of drugs across the nail platesignificantly. Similar to transdermal iontophoresis, the predominant mechanisms contributing to enhanced transport of drugs in the case of transnail iontophoresis are electrophoresis and electroosmosis. Iontophoretic permeselectility of the human nail plate and its applicability on the trans-nail delivery of drugs are also under investigation.

b) Mesoscissioning technology
Mesoscissioning technology creates a micro-conduit through the skin or nailwithin aspecified depth range. Fullyopen pathways can be painlessly seizes(cut) through the stratum corneum ofthe skin or through the nail. Microconduits, 300-500 microns in Diameter, are produced within seconds and without sensation.

c) NanoPatch Nail Fungus
NanoPatch Fungus uses AC/DC electrochemistry and targeted drug delivery to actively push antifungal drugs right through the nail cuticle to the actual location of the fungus growth.

Ultra-Sound Technique for Nail Drug Delivery System
A novel ultrasound-mediated drug delivery system has been developed for treatment of a nail fungal disorder (onychomycosis) by improving delivery to the nail bed using ultrasound to increase the permeability of the nail. The slip-in device consists of ultrasound transducers and drug delivery compartments above each toenail. The device is connected to a computer, where a software interface allows users to select their preferred course of treatment. In vitro testing, canine nails are exposed to 3 energy levels (acoustic power of 1.2 W and exposure durations of 30, 60, and 120 seconds). A stereo -
microscope is used to determine how much of a drug-mimicking compound is delivered through the nail layers by measuring brightness on the cross section of each nail tested at each condition, where brightness level decreases coincide with increases in permeability. Current treatments for onychomycosis include systemic, topical, and surgical. Even when used all together, these treatments typically take a long time to result in nail healing, thus making this ultrasound-mediated device a promising alternative.

**Assay of nail’s inner drug content by unique method:**
- Collection of nail samples: Human nail samples are collected.
- Evaluated by Raman spectroscopy for formalin content.
- Permination study: Specially modified franz diffusion cells with a diffusion area of 0.785 cm².
- Miling test: Detect the amount of drug remain in the cell.
- Surface tension and contact angle measurements: By withenny plate method.

**Conclusion:**
- Found limited success till now. Oral therapy is still the first choice despite its obvious short comings.
- Mode of treatment is cost effective.
- Efficacy has established in clinical trials.
- Effect needs to be put into finding suitable permeation enhancer which can guide drug through highly keratinized nail membrane.

**References:**

Dave Kandarp M.
M.S. (Pharm.) Pharmaceutics
Semester I
Magnetic Microspheres in Targeted Drug Delivery System

Introduction

Targeted drug delivery system is a method for delivering a drug to a specific site in the body. Magnetic microspheres are prepared by encapsulating the paramagnetic particles along with the drug/diagnostic agent in polymeric matrix or conjugated on the surface of the microsphere (1-100μm). Microspheres are made of biodegradable materials like albumin or gelatin which can reside in the body without negative effect. Magnetic microspheres upon administration are attracted to applied magnetic field at target site like tumour. In practice, the magnetic field is usually generated by placing a magnet on the surface of the patient as close to the target site and then the magnets attract the microspheres to the immediate area of the wound site and stop them there. The spheres gradually break down and release the drug (Fig. 1)

![Fig-1 Magnetic drug targeting to the target area](image)

Magnetic radioactive microspheres are applied in method similar to non-radioactive microspheres. The loaded microspheres are introduced into blood vessel, and in as little as half an hour, they are gathered at the target site to emit radiation that kills surrounding cancer cells.

Principle of targeting to magnetic microsphere by magnet

Magnetic microsphere targeting technique is based on the fact that when the magnetic carrier is intravenously administered, the accumulation takes place within area to which the magnetic field is applied and often augmented by magnetic agglomeration. The accumulation of the carriers at the target site allows them to deliver the drug locally. Efficiency of accumulation of magnetic carrier on physiological carrier depends on physiological parameters e.g. Particle size, surface characteristic, field strength and blood flow rate etc. Very high concentration of chemotherapeutic agents can be achieved near the target site without any toxic effect to normal surrounding tissue or to whole body.

Paramagnetic microspheres have been made to size range from 1 micron to greater than 100 microns. To control the motion of such microspheres within the body, a magnetic force due to an externally applied magnetic field and a hemodynamic drag force due to blood flow combine to create a total vector force on the spheres. In order to effectively overcome the influence of blood flow, and in order to achieve desired external magnetic field-controlled guidance, the magnetic force due to the external field must be larger than the drag force, the magnetic force on the microsphere is governed by

\[ F = \nabla (m \times B_0) \] [Newton]

Where \( F \) is the magnetic force, \( m \) is the total magnetic moment of the material in the microsphere, \( \nabla \) is the magnetic field gradient, it is sum of three rectangular coordinates\( (x, y, z) \) assumed in our modeling to be derived from characteristics of the \( B \) field alone, and \( B \) is the magnetic flux density, also...
known simply as the B field. Each of these quantities thus influences the degree to which an external magnetic field may be used to guide internal microspheres.

The force that counteracts the magnetic force on the particle in the bloodstream is due to blood flow. Stokes Law governs the hemodynamic forces on a particle in a flowing liquid.

\[ F = 6 \pi \eta v r, \]

Where \( F \) is the drag force, \( \eta \) is the viscosity of the fluid, \( v \) is the relative velocity of a spherical particle, and \( r \) is the radius.

It is apparent from the equation that increased magnetic moments offer forces sufficient for the extra vascular migration at proportionately lower field gradients. Satisfactory targeting of microspheres (with 20% magnetite) could be achieved using magnets of 0.55 to 0.80 Tesla field strength, 0.01 Tesla /mm field gradient and 0.4 to 0.8 cm (diameter).

Benefits of magnetic microspheres

1. The magnetic localization of a therapeutic agent results in the concentration of the therapy at the target site consequently reducing or eliminating the systemic drug side effects and problem of their rapid clearance by RES is also minimized.
2. Linear blood velocity in capillaries is 300 times less as compared to arteries, so much smaller magnetic field is sufficient to retain them in the capillary network of the target area.
3. Avoidance of acute toxicity directed against endothelium and normal parenchyma cell, controlled release within target tissue for intervals of 30 minutes to 30 hrs. As desired, adaptable to any part of body.
4. In case of tumour targeting, microsphere can internalize by tumour cells due to its much increased phagocytic activity as compared to normal cells.

Drawbacks of magnetic microspheres

1. By the use of magnetic microspheres in the delivery system, the drug cannot be targeted to deep seated organs in the body.
2. Magnetic targeting is a costlier technical approach and requires specialized manufacturer and quality controlled system.
3. It needs specialized magnet for targeting, advanced technique for monitoring, and trained personnel to perform the procedure.

Applications

1) Magnetic microsphere carriers have received considerable attention, because of their wide applications in the fields of biomedicine and bioengineering, biological and biomedical developments and trends such as enzyme immobilization, cell isolation, protein purification, and target drugs.
2) Drug discovery, molecular targeting, DNA analysis, proteomics, and understanding the pathways of cell cycle regulation.
3) Gene therapy with DNA plasmids and also delivery of insulin. Vaccine delivery for treatment of diseases like hepatitis, influenza, pertussis, ricin toxoid.
4) Radioactive microsphere's application can be used for radioembolisation of liver and spleen tumours. Used for radiosynovectomy of arthritis joint, local radiotherapy.
5) Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial/intravenous application. Tumour targeting with doxorubicin and also treatments of leishmaniasis.

6) Magnetic microspheres can be used for stem cell extraction and bone marrow purging.

7) In 2011 BioPAL has developed Micro TRACK™ (Iron-Labelled Microspheres for cell tracking) to locate and track implanted cells in in-vivo systems using MRI technology.

8) Micro TRACK™ are also available with amine groups for attaching proteins and ligands or with rhodamine B for fluorescent imaging.

9) Now a day magnetic microspheres are used in effective contraceptives in which drug delivery is designed responsive to change in steroid excretion during menstrual cycle.

Conclusion

Targeted drug delivery is an effective method to assist the drug molecule to reach preferably to the desired site. Magnetic microsphere delivery platforms have the ability to deliver simultaneous medical applications of gene therapy, destroy built up plaque in arteries, image and extract foreign metallic and ferric objects from the body and affect cancer therapies of in-vitro vesicular blockage, targeted radiation therapy and hyperthermia. Magnetic targeted chemotherapy has better tumour targeting, therapeutic efficacy and lower toxicity.

Future Perspective

The use of strong magnetic fields of the ferrofluid (colloidal iron oxide solutions) is an important factor associated with its limited implementation. Development of stable magnetic microspheres is challenging task and also their fate in biological system are not explored as yet. Future research should explore the issues related to their toxic effects in humans. The stability and safety studies will ensure their use in human and can be utilized as an effective tool for targeted drug delivery systems.

References:


Sudhir Shahi,
M.S. (Pharm.) Pharmaceutics
Semester I
# Status of Marketing Authorization of Vaccine from 2009 to August 2012

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name of the firm</th>
<th>Name of the molecule approved</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/s Biomed (P) Ltd., C-96, Site No 1, Bulandsahar Road, Industrial Area, Ghaziabad, U.P.</td>
<td>Meningococcal polysaccharide vaccine (Group A &amp; C)</td>
<td>For active immunization against Neisseria meningitidis Group A &amp; C</td>
</tr>
<tr>
<td>2</td>
<td>M/s Serum Institute of India Ltd., 212/2, Hadapsar, Pune-411 028, India.</td>
<td>Diphtheria, Tetanus, Pertussis, Hepatitis-B and Haemophilus influenzae Type b Conjugate Vaccine Adsorbed, liquid</td>
<td>For active immunization against Diphtheria, Tetanus, Pertussis, Hepatitis-B and Haemophilus influenzae Type b in infants</td>
</tr>
<tr>
<td>3</td>
<td>M/s Panacea Biotec Ltd., B-1 Extn. A/27, M/CIE, Mathura Road, New Delhi</td>
<td>Oral Poliomyelitis Vaccine (Type 1, 2, &amp; 3)</td>
<td>Active Immunization agent against infection caused by type 1, 2 &amp; 3 Polioviruses</td>
</tr>
<tr>
<td>4</td>
<td>M/s Shantha Biotech, Survey No: 272, Athwadi Village, Medchal, Mandal, Ranga Reddy District - 501 401, Hyderabad</td>
<td>Killed Bivalent (O1 &amp; O139) oral cholera vaccine</td>
<td>For active immunization against Vibrio Cholera</td>
</tr>
<tr>
<td>5</td>
<td>M/s Panacea Biotec Ltd., B-1 Ext., A-27, M/CIE, Mathura Road, New Delhi - 110 044</td>
<td>Diphtheria, Tetanus and whole cell pertussis (DTP) vaccine</td>
<td>For the primary immunization of infants, at or above the age of 6 weeks, and of children through six years of age against Diphtheria, Tetanus and whooping cough</td>
</tr>
<tr>
<td>6</td>
<td>M/s Human Biologicals Ltd., (A Division of Indian Immunological Ltd.), Rkshapuram, Gachibowli, Hyderabad (AP)</td>
<td>Rabies Vaccine (Vero Cell cultured, Freeze Dried)</td>
<td>For active immunization against Rabies, both as prophylaxis and post bite cases.</td>
</tr>
<tr>
<td>7</td>
<td>M/s Biovel Life Science, Sy No 16, Ekarajapura, Hasagala Post, 8th Km, Siddagatta Road, Hosakote, Bangalore-562 114</td>
<td>Haemophilus Influenza type b (Hib) conjugate vaccine</td>
<td>For active immunization against Haemophilus influenzae Type b infection in children of the age group of 6 weeks to 5 years</td>
</tr>
<tr>
<td>8</td>
<td>M/s Biovel Life Science (P) Ltd., Sy. NO 16, Ekarajapura, Hasagala Post, 8th Km, Siddagatta Road, Hosakote, Bangalore-562 114</td>
<td>VI Capsular Polysaccharide Typhoid vaccine</td>
<td>For active immunization against typhoid fever for adults and children older than two years of age</td>
</tr>
<tr>
<td>9</td>
<td>M/s Biol.E.Ltd., 18/1 and 83, Azamabad, Hyderabad-500 020</td>
<td>Reconstituted pentavalent vaccine (diphtheria, tetanus, Pertussis [whole cell], Hepatitis b [r DNA] and hib conjugate vaccine</td>
<td>For active immunization against Diphtheria, Pertussis, Tetanus, Hepatitis B, Haemophilus influenzae Type b infections</td>
</tr>
<tr>
<td></td>
<td>Company Details</td>
<td>Vaccine Type</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10</td>
<td>M/s Panacea Biotec Ltd, B-1 Ext., A-27, Mohan Co-op. Indusrial estate Mathura Road New Delhi-110 044</td>
<td>Bivalent Polio Type 1 &amp; Type 3 vaccine, Live Oral</td>
<td>For active Immunization against Type 1 &amp; Type 3 Poliomyelitis infection in Children from 0 to 5 years of age</td>
</tr>
<tr>
<td>11</td>
<td>M/s Haffkine Bio-Pharma Co. Ltd., AcharyaDondeMarg, Parel, Mumbai-400 012, India</td>
<td>Bivalent Polio Ty 1 &amp; Type 3 vaccine, Live Oral</td>
<td>For active Immunization against Type 1 &amp; Type 3 Poliomyelitis infection in Children from 0 to 5 years of age.</td>
</tr>
<tr>
<td>12</td>
<td>M/s. Bharat Biotech International Ltd., Genome Valley, Shameerpet (Mandal), Reddy (Dist), hyderabad</td>
<td>Bivalent Polio Type 1 &amp; Type 3 vaccine, Live Oral</td>
<td>For active Immunization against Type 1 &amp; Type 3 Poliomyelitis infection in Children from 0 to 5 years of age.</td>
</tr>
<tr>
<td>13</td>
<td>M/s Cadilla Healthcare Ltd., Sarkhej-Bavla, N.H. No. 8A, Moraiya, Tal, Sanand, Dist. Ahmedabad – 382 210, india.</td>
<td>Inactivated Influenza vaccine (Whole virion)</td>
<td>For active Immunization against influenza disease caused by pandemic (H1N1) 2009 virus in the age group of 18 years and above.</td>
</tr>
<tr>
<td>14</td>
<td>M/s Serum Institute of India Ltd., 212/2, Hadapsar, Pune-411 028, India.</td>
<td>Influenza Vaccine (Live Attenuated freeze dried) for Intranasal.</td>
<td>For active immunization against influenza disease caused by pandemic (H1N1) 2009 virus in the age group of 03 years and above.</td>
</tr>
<tr>
<td>15</td>
<td>M/s Biol.E.Ltd.,18/1 and 3, Azamabad, Hyderabad-500 020</td>
<td>Liquid pentavalent vaccine</td>
<td>Active immunization of Against Diphtheria, pertussis, tetanus, Hepatitis b, Hlb type b infection</td>
</tr>
</tbody>
</table>

Ponnam Sairam  
M.S. (Pharm.) Pharmaceutics  
Semester III
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Drugs Name</th>
<th>Notification No. &amp; Date</th>
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<tbody>
<tr>
<td>1</td>
<td>Fixed dose combinations of crude ergot preparations except those containing Ergotamine, Caffeine, analgesics, antihistamines for the treatment of migraine, headaches.</td>
<td>Substituted vide GSR NO. 304(E) Dated 07.06.1991</td>
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<tr>
<td>2</td>
<td>Fixed dose combination of Rifampicin, Isoniazid and Pyrazinamide, except those which provide daily adult dose given below:</td>
<td>Substituted vide GSR NO. 100(E) Dated 11.02.2003</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>Minimum</td>
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<tr>
<td></td>
<td>Rifampicin</td>
<td>450 mg</td>
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<td></td>
<td>Isoniazid</td>
<td>300 mg</td>
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<td></td>
<td>Pyrazinamide</td>
<td>1000 mg</td>
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<tr>
<td>3</td>
<td>Fixed dose combination of Salbutamol or any other bronchodilator with centrally acting anti-tussive and/or antihistamine.</td>
<td>Substituted vide GSR NO. 290(E) Dated 16.04.2008</td>
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<tr>
<td>4</td>
<td>Fixed dose combination of Metoclopramide with systemically absorbed drugs except fixed dose combination of metoclopramide with aspirin/ paracetamol</td>
<td>Substituted vide GSR NO. 603(E) Dated 24.08.2001</td>
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<td>5</td>
<td>Letrozole for induction of ovulation in anovulatory infertility.</td>
<td>GSR NO. 752(E) Dated 12.10.2011</td>
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<td>6</td>
<td>Gatifloxacin formulation for systemic use in human by any route including oral and injectable.</td>
<td>GSR NO. 218(E) Dated 16.03.2011</td>
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<td>7</td>
<td>Human Placental Extract and its formulations for human use except its 1. Topical application for wound healing, and 2. Injection for pelvic inflammatory disease.</td>
<td>Substituted vide GSR NO. 418(E) Dated 30.05.2011</td>
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<td>9</td>
<td>Nimesulide formulations for human use in children below 12 years of age.</td>
<td>GSR NO. 82(E) Dated 10.02.2011</td>
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<td>10</td>
<td>Fixed dose combination of Cyproheptadine with Lysine or Peptone.</td>
<td>GSR NO. 170(E) Dated 12.03.2001</td>
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<tr>
<td>11</td>
<td>Fixed dose combination of Loperamide Hydrochloride with Furazolidone.</td>
<td>GSR NO. 170(E) Dated 12.03.2001</td>
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<tr>
<td>12</td>
<td>Fixed dose combination of Nalidixic Acid with any anti-amoebic including Metronidazole.</td>
<td>GSR NO. 170(E) Dated 12.03.2001</td>
</tr>
</tbody>
</table>

Bikkasani Anilkumar  
M.S. (Pharm) Pharmaceutics  
Semester III
- Budget,
- Committees,
- Faculty and Staff
## Budget 2011-12 (Actual Expenditure)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Heads</th>
<th>Amount (₹)</th>
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<tbody>
<tr>
<td>A</td>
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<td>Salary</td>
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<td>Honorarium</td>
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<td>Stipend</td>
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<td>TA/DA</td>
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<td>Housekeeping, maintenance &amp; Security</td>
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<td>Printing /Advt/Stationary</td>
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<td>Convocation &amp; Examination</td>
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<td>Campus Rent / Hostel</td>
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<td>Electricity, Telephone &amp; Water</td>
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<td></td>
<td>Contingency / Misc.</td>
<td>2308268</td>
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<td><strong>Sub Total</strong></td>
<td><strong>27192878</strong></td>
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<td></td>
<td>10 % Institutional overhead (FY 2011 - 12) at last year's recurring expenditure</td>
<td>2500000</td>
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<td><strong>Total expenditure including overhead - A</strong></td>
<td><strong>29692878</strong></td>
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<tr>
<td>B</td>
<td>Non Recurring</td>
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<td>AC/Computer/Xerox</td>
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<td>Furniture/ Fixtures</td>
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<td>Books &amp; Journals</td>
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<td>Equipments</td>
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<td></td>
<td><strong>Total - B</strong></td>
<td><strong>6289179</strong></td>
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<td></td>
<td><strong>GRAND TOTAL (A+B)</strong></td>
<td><strong>35982057</strong></td>
</tr>
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(Rupees Three Crore Fifty nine Lakh Eighty Two Thousand Fifty Seven Only)
### Management Committee

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dr. T. K. Chakraborty</td>
<td>Chairperson</td>
</tr>
<tr>
<td></td>
<td>Mentor and Director</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSIR-CDRI, Lucknow</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Dr. P. K. Shukla</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Project Director</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Dr. B. Kundu</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Dean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
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</tr>
<tr>
<td>5.</td>
<td>Dr. S. K. Puri</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Registrar</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Dr. R.P. Tripathi</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Course Co-ordinator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Dr. Atul Kumar</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Course Co-ordinator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Dr. P.R. Mishra</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Course Co-ordinator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
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<tr>
<td>9.</td>
<td>Mr. Wahajuddin</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Course Co-ordinator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
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</tr>
<tr>
<td>10.</td>
<td>Dr. Neeraj Sinha</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Course Co-ordinator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NIPER, Raebareli</td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>Dr. Kasif Hanif</td>
<td>Member</td>
</tr>
<tr>
<td></td>
<td>Course Co-ordinator</td>
<td></td>
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<tr>
<td></td>
<td>NIPER, Raebareli</td>
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<tr>
<td>12.</td>
<td>Controller of Administration</td>
<td>Member</td>
</tr>
<tr>
<td>13.</td>
<td>Controller of Finance &amp; Accounts</td>
<td>Member</td>
</tr>
<tr>
<td>14.</td>
<td>Stores &amp; Purchase Officer</td>
<td>Member</td>
</tr>
</tbody>
</table>
Departmental Academic Advisory Committee

M.S. (Pharm.) Medicinal Chemistry

Dr. B. Kundu
Dr. Atul Kumar
Dr. Ashish Arora
Dr. Anand Tiwari (Ranbaxy)

Chairperson
Dean’s nominee
Member (Academic)
Member (Industry)

M.S. (Pharm.) Pharmaceutics

Dr. C. Nath
Dr. P.R. Mishra
Dr. S. K. Singh
Dr. S. P. D. Dwivedi (Zydus Cadila)

Chairperson
Dean’s nominee
Member (Academic)
Member (Industry)

M.S. (Pharm.) Pharmacology & Toxicology

Dr. Madhu Dikshit
Dr. Neeraj Sinha
Dr. S. K. Rath
Dr. R.K. Khar

Chairperson
Dean’s nominee
Member (Academic)
Member (Industry)

Board of Studies and Research (BSR)

Dr. B. Kundu
Dr. R. P. Tripathi
Dr. P. R. Mishra
Dr. Neeraj Sinha
Dr. Sudha Jain
Dr. Raghvendra Pal
Dr. S.K. Rath

Dean
Course Coordinator (Medicinal Chemistry)
Course Coordinator (Pharmaceutics)
Course Coordinator (Pharmacology & Toxicology)
Lucknow University
Ex-Scientist, CSIR - CDRI, Lucknow
Scientist, CSIR - CDRI, Lucknow

Chairperson
Departmental Member
Departmental Member
Departmental Member
Expert Member
Expert Member
Expert Member
Student Research Committee

M.S. (Pharm.) Medicinal Chemistry

Dr. R.P. Tripathi
Advisor of the respective student
Dr. Atul Kumar
Dr. Ashish Arora
Department Head (Course Co-ordinator)
Chairperson
Expert Member
Dean’s Nominee

M.S. (Pharm.) Pharmaceutics

Dr. P.R. Mishra
Advisor of the respective student
Dr. R.S. Bhatta
Dr. Amir Nazir
Department Head (Course Co-ordinator)
Chairperson
Expert Member
Dean’s Nominee

M.S. (Pharm.) Pharmacology & Toxicology

Dr. Neeraj Sinha
Advisor of the respective student
Dr. Kasif Hanif
Dr. Sharad Sharma
Department Head (Course Co-ordinator)
Chairperson
Expert Member
Dean’s Nominee

Grievance Committee

Dr. Kanchan Hajela
Dr. S. Batra
Dr. P.R. Mishra
Chairperson
Member
Convenor

Committee for the Sexual Harassment at Workplaces

Dr. Shailja Bhattacharya (CSIR - CDRI, Lucknow)
Dr. Madhu Dikshit (CSIR - CDRI, Lucknow)
Dr. Abha Sharma (NIPER, Raebareli)
Dr. Sanjay Batra (CSIR - CDRI, Lucknow)
Administrative Officer (CSIR - CDRI, Lucknow)
Dr. Sudha Jain (Lucknow University)
Chairperson
Member
Member
Member
External Member
# State Level Co-ordination Committee

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Designation and Details</th>
</tr>
</thead>
</table>
| 1. | Principal Secretary | Chairperson  
Department of Industries  
Govt. of Uttar Pradesh |
| 2. | Secretary (Technical Education) | Member  
Govt. of Uttar Pradesh |
| 3. | Dr. T. K. Chakraborty | Member  
Director  
CSIR - CDRI, Lucknow |
| 4. | Shri S. C. Sharma | Member  
Director & Incharge of NIPERs  
Department of Pharmaceuticals  
Ministry of Chemicals & Fertilizers,  
Govt. of India |
| 5. | Two Representatives from Industries  
(To be nominated) | Member |
| 6. | Prof. P. P. Singh | Member  
Nodal Officer  
NIPER, SAS Nagar, Mohali |
| 7. | Dr. P.K. Shukla | Member Secretary  
Project Director  
CSIR-CDRI, Lucknow |
# Steering Committee

<table>
<thead>
<tr>
<th>No.</th>
<th>Position</th>
<th>Name</th>
<th>Institution</th>
<th>Title</th>
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<tbody>
<tr>
<td>1.</td>
<td>Secretary</td>
<td>Department of Pharmaceuticals</td>
<td>Chairperson</td>
<td>Ministry of Chemicals &amp; Fertilizers, Govt. of India</td>
</tr>
<tr>
<td>2.</td>
<td>Additional Secretary &amp; Financial Adviser</td>
<td>Department of Pharmaceuticals</td>
<td>Member</td>
<td>Ministry of Chemicals &amp; Fertilizers, Govt. of India</td>
</tr>
<tr>
<td>3.</td>
<td>Joint Secretary Incharge of NIPERs</td>
<td>Department of Pharmaceuticals</td>
<td>Member</td>
<td>Ministry of Chemicals &amp; Fertilizers, Govt. of India</td>
</tr>
<tr>
<td>4.</td>
<td>Director</td>
<td>NIPER, SAS Nagar, Mohali</td>
<td>Member</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Principal Secretary/ Secretary (Industries)</td>
<td>Govt. of Uttar Pradesh</td>
<td>Member</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Director (Mentor Institute)/ Project Director of each new NIPER (at Ahmedabad, Hajipur, Hyderabad, Kolkata, Guwahati &amp; Raebareli)</td>
<td></td>
<td>Member</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Director/ Deputy Secretary Incharge of NIPERs</td>
<td>Department of Pharmaceuticals</td>
<td>Convenor</td>
<td>Ministry of Chemicals &amp; Fertilizers, Govt. of India</td>
</tr>
</tbody>
</table>
Faculty

Medicinal Chemistry
Dr. Devesh Sawant
Dr. Abha Sharma
Dr. K.N. Tiwari

Pharmaceutics
Mr. Anuj Garg
Mr. Achint Jain

Pharmacology & Toxicology
Dr. Gulam Mohammed Husain

GUEST FACULTY
CSIR-Central Drug Research Institute, Lucknow

Division of Medicinal & Process Chemistry
Dr. A. K. Saxena
Dr. B. Kundu
Dr. Ram Pratap
Dr. K. Awasthi
Dr. S.N. Suryawanshi
Dr. R. P. Tripathi
Dr. Kanchan Hajela
Dr. P.M.S. Chauhan
Dr. Y.S. Prabhakar
Dr. Arun K. Shaw
Dr. W. Haq
Dr. V.L. Sharma
Dr. Atul Kumar
Dr. Atul Goel
Dr. Gautam Panda
Dr. K.V. Sashidhara
Dr. Dipankak Koley
Dr. P.P. Yadav
Dr. M.S. Reddy
Dr. Namrata Rastogi

Division of Sophisticated Analytical Instrument Facility
Dr. Brijesh Kumar
Dr. Sanjeev Kumar Shukla
Dr. Ravi Shankar Ampopathi
Division of Parasitology
Dr. S. K. Puri
Dr. Shailja Bhattacharya
Dr. Anuradha Dube

Division of Pharmacokinetics & Metabolism
Dr. S.K. Singh
Dr. Jawahar Lal
Dr. R.S. Bhatta
Dr. J.R. Gayen
Mr. Wahajuddin

Division of Pharmaceutics
Dr. Amit Misra
Dr. P.R. Mishra
Dr. Surendra Bathula Reddy
Dr. Manish Kumar Chourasia

Division of Pharmacology
Dr. Rakesh Shukla
Dr. P.N. Yadav

Division of Biochemistry
Dr. Arvind Kumar Srivastava
Dr. Neena Goyal

Division of Toxicology
Dr. Sharad Sharma
Dr. C. Nath
Dr. Sarika Singh

Division of Endocrinology
Dr. Ritu Trivedi

Division of Biometry & Statistics
Dr. Mukesh Srivastava

Division of Laboratory Animals
Dr. Himanshu K Bora

Division of Molecular & Structural Biology
Dr. Ashish Arora
Dr. Tejender Thakur
Dr. Amogh A Sahasrabuddhe
Staff

Administration
Mr. U.S. Rawat *(Consultant)*
Ms. Deepa Bakshi *(Asstt. Academic Affairs)*
Ms. Harsha Chaudhary *(Asstt.)*
Ms. Asiya Praveen *(Asstt.)*
Mr. Kamal Singh *(Asstt.)*
Mr. Neeraj Kumar *(Asstt.)*
Mr. Amar Mishra *(Liaison Officer cum Receptionist)*

Placement Cell
Dr. Monika Sachdev *(Professional Advancement & Placement Officer)*

IT Resource Manager
Mr. Manoj Kumar Mishra

Stores & Purchase
Mr. Ravindra K Shukla *(Asstt.)*
Ms. Richa Nigam *(Asstt.)*
Ms. Swati Mourya *(Asstt.)*

Accounts
Ms. Mona Jain *(Asstt.)*

Library
Mr. Somit Kumar *(Asstt. Librarian)*

Lab Assistants
Mr. Nityanand Rai
Ms. Namita Dube
Ms. Shweta Rai
Ms. Lubna Azmi
Mr. Sushil Kumar Singh

Electrician
Ramchandra