"Novel Multifunctional Cyclodextrin-based Nanocarriers for Drug Encapsulation and Delivery as a Strategy to Overcome Current Therapeutic Drawbacks"

Newsletter 01/10/2009 - 30/09/2013
Summary of CYCLON lifecycle

CYCLON, a 4-year Marie Curie Initial Training Network (ITN) and 100% EU funded project, came to an end on September 30th, 2013. CYCLON, through training of young researchers within a highly competent and multi-disciplinary network, aimed at developing a new generation of multifunctional drug nanocarriers based mainly on a family of water soluble and biocompatible oligosaccharides, the cyclodextrins. CYCLON research belongs to the strongly inter- and multi-disciplinary area of Nanoscience by applying nano-bio-technological methods to design, develop and investigate pharmaceutical nanocarriers for drug delivery. These nano-platforms with multimodal capacities, i.e. combining drug transport and release with smart functionalizations for targeting, high drug payload, controlled triggering of Reactive Oxygen and Nitrogen Species (ROS and NOS) release, ability for imaging, and even ability to circumvent drug resistance, can help in significantly enhancing the in vivo efficiency of many known drugs with poor bioavailability characteristics. The research expanded in many dimensions and numerous cyclodextrin and Metal Organic Framework-based nanoplatforms emerged, that combined multifunctionality, drug delivery, imaging capacity, and biodegradability. Complemented by fundamental studies, the research has highlighted the potential of the nanoplatform approach to achieve important milestones. Proof of concept was given with cell line studies and skin tests. Within these research activities, the network has offered nine Early Stage Researchers (ESRs, PhD students) and four Experienced Researchers (ERs, post-doctorals) the opportunity to acquire a wide scientific background based on both fundamental and applied research training and complementary skills, taking advantage of the large span of scientific experience of the network groups through secondments and close interactions. All ESRs have now embarked on new research positions, while many of the ESRs have already obtained their PhD degree, the rest expected to graduate in 2014.

CYCLON to CycloN-Hit

The future is bright! The CYCLON consortium is proud to announce that the collaboration of the current partners will continue for four more years within the recently approved ITN Network CycloN-Hit, “Nanocarriers for the Delivery of Antimicrobial Agents to fight Resistance Mechanisms”.

The new project is an FP7-PEOPLE-2013-ITN (Grant Agreement N°:608407), it involves three more full partners and six associated partners (mainly SME companies), and is coordinated by Dr. Ruxandra Gref (CNRS-Paris), a very dynamic CYCLON partner.

The project will commence in March, 2014. Eleven Early Stage (PhD) and Five Experienced (Post-Doc) positions will open in the months to come. Just monitor www.itn-cyclon.eu!
CYCLON Consortium & MC Fellows

National Center for Scientific Research “Demokritos” (NCSR)
(Athens, GREECE), Institute of Advanced Materials, Physicochemical Processes, Nanotechnology & Microsystems
Dr. K. Yannakopoulou, Coordinator
ER: Dr. Linda Piras - ESR: Mr. A. Ricardo Gonçalves
University of Castilla-La Mancha (UCLM)
(Toledo, SPAIN), Faculty of Environmental Sciences
Prof. A. Douhal
ER: Dr. Maria-Bosarà di Nunzio - ESR: Mr. Yilun Wang
CNR/University South Paris (CNRS-PSUD)
(Paris, FRANCE), Faculty of Pharmacy
Dr. B. Gref
ER: Dr. Violeta Rodriguez Ruiz - ESR: Mrs. Valentina Agostoni
University of Iceland (UoI)
(Reykjavik, ICELAND), Department of Pharmacy
Prof. Th. Loftsson
ESR: Mr. Zoltan Fülöp
University of Catania (UNICT)
(Catania, ITALY), Department of Drug Sciences
Prof. S. Sortino
ER: Dr. Aurore Fraix - ESR: Mr. Noufal Kandoth
CNR-ISOF
(ITALY), Faculty of Pharmacy
Dr. Sandra Monti
ESR: Mrs Resmi Anand
University of Gothenburg (UGOT)
(Gothenburg, SWEDEN), Department of Physics & SkinResQU
Prof. Marica B. Ericson
ESR: Mr. Vladimir Kirejev
University of Almeria, (UAL)
(Almeria, SPAIN), Experimental Science College
Prof. A. Vargas-Berenguel
ESR: Mr. Ahmet Akyüç
CycloLab S.A.
(Budapest, HUNGARY)
Dr. E. Fenyvesi
ESR: Mr. Milo Malanga

MC Fellows Progress & Career

The CYCLON project is proud to report that all Post-doctoral fellows (Experienced Researchers) continue their careers in research within EU:
Dr. Aurore Fraix, is currently a Research Associate at the University of Catania, (with Prof. S. Sortino).
Dr. Violeta Rodriguez Ruiz, is now a Research Associate at the Department of Molecular Catalysis (LCM), Molecular and Materials Chemistry Institute of Orsay (ICMMO), University of Paris South, (with Dr. Richard Gil).
Dr. Maria Bosarà di Nunzio, has held a Research Associate position at the University of Toledo since 2011 (with Prof. A. Douhal).
Dr. Linda Piras, Research Associate, is now with Consiglio Nazionale delle Ricerche (CNR), Institute of Crystallography, Bari, Italy.
Mr. M. Malanga has been employed by CycloLab as a research chemist.

The CYCLON Early Stage Researchers, PhD recipients, are:
Noufal Kandoth, PhD, University of Catania, February 2013: Design, Synthesis and Characterization of Photactivatable Cyclodextrin-Based Nanoparticles for Multimodal Anticancer Therapy. Supervisor: Prof. S. Sortino
Resmi Anand, PhD, University of Bologna, April 2013: Spectroscopic Studies on Cyclodextrin and Metal Organic Framework based Potential Nanovectors for Delivery of Anticancer and Antiviral Drugs. Supervisor: Dr. S. Monti, CNRS/ISOF Bologna
Valentina Agostoni, PhD, University of South Paris, Faculty of Pharmacy, April 2013: Cyclodextrin-modified Metal Organic Frameworks. Nanoparticles for the Efficient Delivery of Hydrophobic Antiviral and Anticancer Drugs. Supervisor: Dr. R. Gref, CNRS Paris
Yilun Wang, PhD, University of Castilla-La Mancha, June 2013: Photodynamical Studies of Several Drug Molecules in Chemical and Biological Cavities. Supervisor: Prof. A. Douhal.
A.R. Gonçalves, V. Kirejev, M. Malanga, A. Akyüç and Z. Fülöp are into their final year towards the PhD degree.

During the project, senior scientists with a breadth of expertise and vast research experience have mentored students and post-docs. They have contributed with their discussions during the meetings in focusing the research by raising important questions. The CYCLON consortium is grateful for their involvement.

Dominique Duchêne, a professor of Pharmaceutical Technology since 1971, is a world-class scientist in the field of nanoparticles, drug delivery and cyclodextrin technology. Prof. Duchêne as an active network member mentored younger scientists and students whereas as Editor-in-Chief of the Journal of Drug Delivery Science and Technology (JDDST) invited the consortium to present the project’s activities in the journal. A CYCLON dedicated issue of JDDST was published in May-June 2012.

Dr. Irene M. Mavridis, Senior Researcher and crystallographer in NCSR “Demokritos”, Dr. Liliżo Jicsinszky, CycloLab Scientific Advisor and organic chemist and Prof. Boiko Cohen, UCLM, have participated in CYCLON events with active support, contributions to scientific discussions and mentoring of MC fellows.
The scientific achievements of CYCLON are many and diverge. The development of new cyclodextrin-based as well as Metal-Organic-Framework (MOF)-based nanoplatforms constitute novel multimodal systems for the delivery of therapeutic substances, as has been demonstrated by various approaches. The novelty lies on the combination of actions, such as release of a drug payload, thermally generated or photo-triggered in situ release of Reactive Oxygen Species (ROS) and Reactive Nitric Oxide Species (RNOS), simultaneous fluorescence imaging capacity as well as bio-compatibility/biodegradability of the nanoparticle/nanoplatform. In parallel, basic synthetic-structural-physicochemical and pharmacokinetic studies have been carried out to elucidate mechanisms and optimize properties. A total of 50 articles have already been published and more manuscripts are in the preparation stage. Therefore the results of CYCLON will continue to appear in the coming months. Moreover, in the duration of the project, more than 49 International and 14 National Conference poster and oral contributions were presented by CYCLON partners and fellows. Selected scientific results are highlighted next.

### A. Nanoplatforms—nanoparticles

**An engineered nanoplatform for bimodal anticancer phototherapu


**Impact of phosphorylation on the encapsulation of nucleoside analogues within porous iron(III) metal–organic framework MIL-100(Fe) nanoparticles**


**A multifunctional bichromophoric nanoaggregate for fluorescence imaging and simultaneous photogeneration of RNOS and ROS**


**Towards an improved anti-HIV activity of NRTI via metal–organic frameworks nanoparticles**


**Photoinduced fluorescence activation and nitric oxide release with biocompatible polymer nanoparticles**


---

**Research Highlights**

**A. Nanoplatforms-nanoparticles**

An engineered nanoplatform for bimodal anticancer phototherapu


Impact of phosphorylation on the encapsulation of nucleoside analogues within porous iron(III) metal–organic framework MIL-100(Fe) nanoparticles


A multifunctional bichromophoric nanoaggregate for fluorescence imaging and simultaneous photogeneration of RNOS and ROS


Towards an improved anti-HIV activity of NRTI via metal–organic frameworks nanoparticles


Photoinduced fluorescence activation and nitric oxide release with biocompatible polymer nanoparticles

Citric acid-γ-cyclodextrin crosslinked oligomers as carriers for doxorubicin delivery

β-Cyclodextrin polymer nanoparticles as carriers for doxorubicin and artemisinin: a spectroscopic and photophysical study

Self-assembly of cyclodextrins: formation of cyclodextrin polymer based nanoparticles

A spectroscopic investigation on β-cyclodextrin-meso-tetra(m-hydroxyphenyl)porphyrin conjugate focusing on topical delivery

Combination of spectroscopic and computational methods to get an understanding of supramolecular chemistry of drugs: from simple host systems to biomolecules

Selection of β-Cyclodextrin bearing Gold Glycaminoparticles towards GaL-3 overexpressing A431 cells in vitro
V. Kirejev, A. Aykaç, A. Vargas-Berenguel, M. B. Ericson, In manuscript.

β-Nitroso-β-cyclodextrins as novel bimodal carriers: preparation, detailed characterization, nitric oxide release and molecular encapsulation

Femto- to micro-second photobehavior of a photosensitizer drug trapped within a cyclodextrin dimer
Secondary face-to-face 2–2’ β-cyclodextrin dimers linked with fluorescent rigid spacer arms: a cyclodextrin-based ratiometric sensor for bile salts


Multiphoton microscopy – a powerful tool in skin research and topical drug delivery science


Binding ability properties of β-cyclodextrin dimers linked through their secondary faces towards cancer chemotherapeutic agent methotrexate


A permeation method for detection of self-aggregation of doxorubicin in aqueous environment


Femtosecond to second studies of a water-soluble porphyrin derivative in chemical and biological nanocavities


Spectroscopy and dynamics of topotecan anti-cancer drug comprised within cyclodextrins


A host-guest supramolecular complex with photoregulated delivery of nitric oxide and fluorescence imaging capacity in cancer cells

Fluorescent cyclodextrins developed during CYCLON are now commercial products available from CycloLab, www.cyclolab.hu/product1_1.html.

Commercial Products

Fluorescent cyclodextrins

CYCLON website

The continuously updated site www.itn-cyclon.eu has become the forum for announcements, activities, jobs, exchange of information and data among the partners and a reporting post for EU monitoring. The visibility of the site has increased steadily over the years receiving more than 1000 visits per month from all over the world. The website will continue to be updated keeping track of the latest news on cyclodextrins and MC fellows, and relaying information on CycloN-Hit.

Patents

Joint Patent Application (CNRS/CycloLab) Solide hybride organique inorganique amélioré à surface externe modifiée

Priority Date May 31st, 2012, French

http://dx.doi.org/10.1021/jp303826c
Reproduced with permission from the PCCP Owner Societies.

http://dx.doi.org/10.1039/C2CP44056C
Reproduced with permission from JDDST, Éditions de Santé.
Workshops

1. 2010: Advances in cyclodextrin chemistry and current applications
   UNICT, Catania, Italy, May 13.
   Current aspects of Cyclodextrin chemistry, structure, synthesis of multifunctional derivatives, properties and applications were discussed, in view of literature precedents and current commercial products of cyclodextrins. Prof. S. Sortino and A. Mazzaglia organised a very bright and stimulating event.

2. 2011: Photochemistry in Confined Media
   UCLM, Toledo, Spain, March 24.
   Drugs encapsulated within Cyclodextrin or Protein cavities can be studied photochemically as regards to species generated and their dynamics (singlet/triplet states, lifetimes, equilibria) require fast and ultra-fast spectroscopic methods for the analysis. The workshop was combined with a visit to Prof. A. Douhal’s state-of-the-art instrumentation for ultra-fast photochemical reaction dynamics studies.

3. 2012: Cyclodextrins and Cyclodextrin Derivatives as Pharmaceutical Excipients: Toxicological and Regulatory Issues
   UoI, Reykjavik, Iceland June 2.
   The focus was the various aspects related to excipients including pharmacokinetics, toxicology and methods of drug formulation using cyclodextrins in accordance to the guidelines set by the European Medicines Agency (EMA).
   The workshop was a pre-conference event of the Nordic Chapter Controlled Release Society International Conference: Drug Delivery & Targeting, that drew many academic participants and professionals from Northern Europe and elsewhere. Prof. T. Loftsson, a world-class expert on pharmaceutical technology and cyclodextrins, gathered an impressive number of participants, outside CYCLON for the 4-day combined events.

4. 2013: From Laboratory to the market. An industrial view
   CycloLab, Semmelweis University, Budapest, Hungary, January 17.
   The challenges and pitfalls of the cyclodextrin industrial manufacturers to comply with quality controls and regulations, were discussed. The starting, growing and maintaining a specialised company: from laboratory innovation to production, was the key lecture of the day by Dr. L. Szent, CSO of CycloLab. A tour guided by Dr. E. Fenyvesi in the facilities of CycloLab, both the R&D laboratories and the manufacturing plant for pharmaceutical grade cyclodextrin derivatives complemented the industrial/market dimension of the whole event.

Summer Schools

1. Methods in Micro-Nanotechnology and Nanobiotechnology
   NCSR, Athens, Greece September 13-17, 2010.
   The school, organized each summer since 2004 jointly by NCSR ‘Demokritos’ and the Bioacademy of Athens, focused on bridging the bio-world with principles, methodology, instrumentation and techniques of nanotechnology towards integrated systems and lab on chip devices. Lectures were combined with hands-on experience and demonstrations in the various laboratories. Drs. K. Yannakopoulou and I. Mavridis as well as the other members of the organising committee made this week-long school a memorable experience for the participants.

2. Photochemistry and Applications in Photoactivable Anticancer Drugs
   CNR-ISOF, Bologna, Italy September 26-28, 2011.
   The school drew a collection of photochemistry, specialists, covering the full breadth of basic concepts, mechanisms and theory to photochemistry (excited state properties, deactivation, photo-triggered reactions and energy transfer) and its applications to photodynamic (PDT) therapy using suitable sensitizer molecules. Dr. S. Monti, a prominent photochemist, succeeded in attracting many external participants from around the world.

3. Application of Nanodrugs in Photodynamic Therapy
   UGOT, Gothenburg, Sweden April 9-10, 2013.
   Principles and applications of photodynamic therapy (PDT) and short exposure into experiences from a dermatology clinic were the focus of this fourth and final CYCLON school. UGOT in collaboration with Chalmers University and the Center for Skin Research (SkinRes@U), coordinated by Prof. M. R. Ericson, is a pioneer in clinical PDT.
   The school was followed by a synonymous International Conference: Nanodrugs in Photodynamic Therapy. The training event was thus enriched with the latest advances on PDT applications from experts in the field.

   The conference, although a first in its kind, has been a great success. Many pioneer scientists and medical professionals lectured on the latest on PDT both in basic science and clinical practice. Almost all CYCLON partners participated with oral and poster presentations on collaborative work.
3. Nitric oxide photo-releasing nanoconstructs with multiple photo-functionalities
A. Fraix, N. Kandoth, S. Sortino
4. “Green” fluorescent mesoporous iron(III) trimate nano-particles for drug delivery
V. Agostoni, P. Horcajada, V. Rodriguez-Ruiz, H. Willaime, P. Couvreur, C. Serre, R. Gref
5. Impact of phosphorylation on the encapsulation of nucleoside analogues within pores iron(III) metal–organic framework MIL-100(Fe) nanoparticles
L. Piras, T. A. Theodossiou, M. D. Manouilidou, Y. G. Lazaro, S. Sortino, K. Yannakopoulou
Chem. Asian J., 2013, 8(11), 2768-2778.
7. Aspects of determining the molecular weight of cyclodextrins polymers and oligomers by static light scattering
I. Puskás, A. Szemjován, É. Fenyesvi, M. Malanga, L. Szente
8. Citric acid γ-cyclodextrin crosslinked oligomers as carriers for doxorubicin delivery
C. Aggelidou, T. A. Theodossiou, K. Yannakopoulou
10. A permeation method for detection of self-assembly of doxor-ubicin in aqueous environment
Z. Fülöp, R. Gref, T. Loftsson
Int. J. Pharm., 2013, 454(1), 559-561.
11. Spectroscopy and dynamics of topotecan anticancer drug comprised within cyclodextrins
M. R. di Nunzio, Y. Wang, A. Douhal
12. A multifunctional lichenomorph nanoscaffold for fluorescence imaging and simultaneous photogeneration of ROS and ROS
A. Fraix, A. R. L. Gonçalves, V. Cardile, A. C. E. Graziano, T. A. Theodossiou, K. Yannakopoulou, S. Sortino
Chem. Asian J., 2013, 8(11), 2634-2641.
13. A NO photo-releasing supramolecular hydrogel with bacterialidal action
N. Kandoth, J. Mosinger, R. Gref, S. Sortino
14. Dextran-based cyclodextrin polymers - their solubilizing effect and self-assembly
Z. Fülöp, T. T. Nielsen, R. L. Larsen, T. Loftsson
15. Towards an improved anti-HIV activity of NRTI via metal organic framework nanoparticles
16. An engineered nanoplatform for biomodal anticancer phototherapy with dual-color fluorescence detection of sensitizers
A. Fraix, N. Kandoth, I. Manet, V. Cardile, A. C. E. Graziano, R. Gref, S. Sortino
17. Unravelling molecular mechanisms in the fluorescence spectra of doxorubicin in aqueous solution by femtosecond fluorescence spectroscopy
P. Changenet-Barret, T. Gustavsson, D. Markovitsi, I. Manet, S. Monti
18. Photoinduced fluorescence activation and nitric oxide release with biocompatible polymer nanoparticles
E. Deriz, N. Kandoth, A. Fraix, V. Cardile, A. C. E. Graziano, D. Lo Faraco, R. Gref, F. M. Raymo, S. Sortino
19. Characterization and control of the aggregation behavior of cyclodextrins
I. Puskás, M. Schrott, M. Malanga, L. Szente
20. A host-guest supramolecular complex with photoregulated delivery of nitric oxide and fluorescence imaging capacity in cancer cells
21. Structural photodynamic behavior of topotecan, a potent anticancer drug, in aqueous solutions at different pHs
M. R. di Nunzio, Y. Wang, A. Douhal
22. Structural spectroscopy and dynamics of inter- and intra-molecular H-bonding interactions of topotecan, a potent anticancer drug, in organic solvents and in aqueous solution
M. R. di Nunzio, Y. Wang, A. Douhal
23. Self-assembly of cyclodextrin: formation of cyclodextrin polymer-based nanoparticles
Z. Fülöp, S. V. Kurkov, T. T. Nielsen, K. L. Larsen, T. Loftsson
24. Cyclodextrins as “smart” components of polymer nanoparticles
R. Gref, D. Duchêne
25. Cyclodextrin-based nanoconstructs for phototherapeutic therapies
A. Mazzaglia, M. T. Sciortino, N. Kandoth, S. Sortino
26. Cationic cyclodextrins: cell penetrating agents and other diverse applications
K. Yannakopoulou
27. Multiphoton microscopy – a powerful tool in skin research and topical drug delivery science
V. Kirejev, S. Gulbrandsen, J. Borgan, C. Simonsson, M.B. Ericson

28. Rhodamine-labeled cyclodextrin derivatives
M. Malanga, L. Jicsinszky, É. Fenyvesi

29. Photocontrolled binding of artemisinin to a bis(β-cyclodextrin) bearing azobenzene on the primary face

30. Binding ability properties of β-cyclodextrin dimers linked through their secondary faces towards cancer chemotherapeutic agent methotrexate
R. Anand, F. Manoli, A. Vargas-Berenguel, S. Monti

31. Secondary face-to-face 2-2’ β-cyclodextrin dimers linked with fluorescent rigid spacer arms: a cyclodextrin-based ratiometric sensor for lile salts
M. C. Martos-Maldonado, I. Quesada-Soriano, J. M. Casas-Solvas, L. García-Fuentes, A. Vargas-Berengue

32. Excited state intramolecular proton and energy transfer of t-l-hydroxypyrene interacting with the human serum albumin protein
M. Gil, Y. Wang, A. Douhal

33. Beta-cyclodextrin polymer nanoparticles as carriers for doxorubicin and artemisinin: a spectroscopic and photophysical study

34. Proton-transfer reaction dynamics within the human serum albumin protein
B. Cohen, C. M. Álvarez, N. A. Carmona, J. A. Organero, A. Douhal

35. Secondary face-to-face studies of a water soluble porphyrin derivative in chemical and biological nanocavities
Y. Wang, B. Cohen, L. Jicsinszky, and A. Douhal

36. Ultrafast dynamics of lumichrome in solution and in chemical and biological caging media
M. Gil, Y. Wang, A. Douhal

37. Stability and photodynamics of lumichrome structures in water at different pHs and in chemical and biological caging media
M. Marchena, M. Gil, C. Martin, J. Angel Organero, F. Sanchez, A. Douhal

38. Self-assembly of cyclodextrins: the effect of the guest molecule on the stability and photodynamics of lumichrome structures in water
M. Marchena, M. Gil, C. Martin, J. Angel Organero, F. Sanchez, A. Douhal

39. A cyclodextrin-based nanaassembly with bimodal photodynamic action
N. Kandoth, E. Vittorino, M. T. Scortinno, T. Parisi, I. Colao, A. Mazzaglia, S. Sortino

40. Photoactivated nanomaterials for biomedical release applications
S. Sortino

41. Proton-transfer reaction dynamics within the human serum albumin protein
B. Cohen, C. M. Álvarez, N. A. Carmona, J. A. Organero, A. Douhal

42. Structural photodynamics of camptothecin, an anticancer drug in aqueous solutions
M. R. di Nunzio, B. Cohen, A. Douhal

43. Stability and photodynamics of lumichrome structures in water at different pHs and in chemical and biological caging media
M. Marchena, M. Gil, C. Martin, J. Angel Organero, F. Sanchez, A. Douhal

44. Fluorescent cyclodextrin derivatives: major recent advances
M. Malanga

45. Gold nanoparticles decorated with a phot activable nitro-oxide donor/cyclodextrin host/guest complex
N. Kandoth, E. Vittorino, S. Sortino

46. Self-assembly of cyclodextrins: the effect of the guest molecule
M. Messner, S. V. Kuzirov, R. Flavia-Piera, M. E. Brewster, T. Lofferson

47. Stereoselective interaction of ketoprofen enantiomers with β-cyclodextrin: ground state binding and photochemistry
G. Marconi, E. Mezzina, I. Manet, F. Manoli, B. Zambelli, S. Monti,

48. Synthesis and characterisation of novel glyoclusters based on cell penetrating heptakis(6-aminoethylamino-6-deoxy)-β-cyclodextrin
L. Lampropoulou, K. Yannakopoulou

49. Combination of spectroscopic and computational methods to get an understanding of supramolecular chemistry of drugs: from simple host systems to biomolecules
S. Monti, I. Manet, G. Marconi

50. Exploring the ground and excited states structural diversity of lessimendan, a cardiovasculat calcium sensitizer
B. Cohen, J. A. Organero, L. Santos, L. R. Fidal, A. Douhal
MEMBERS & EVENTS

Supervisors, Mentors & Management Support

ESRs, ERs & Events
CYCLON has enabled

- The development of exciting new drug nanocarriers
- The proof of principle on multifunctionality of delivery
- The training of 13 young researchers
- The publication of over 50 journal articles
- The establishment of strong collaborations
- The commencement of CycloN-Hit with high initial velocity
"Novel Multifunctional Cyclodextrin-based Nanocarriers for Drug Encapsulation and Delivery as a Strategy to Overcome Current Therapeutic Drawbacks"

Newsletter 01/10/2009 - 30/09/2013