The Center's Stage

People, Money and Things Getting Done

An e-newsletter produced periodically by The University of Toledo College of Pharmacy's

Center for Drug Design and Development (CD3)

July 31, 2009 Edition

Editorial Note

Already operating for nearly fifteen years in such a capacity, we are pleased to say the CD3 has been well ahead of today's trend that is finally recognizing and beginning to respond to the critical need for effective follow-up medicinal chemistry which is savvy about ADMET issues subsequent to the identification of new 'hit compounds.' The flipside of being in this position, however, is that the CD3's last two years have been ENORMOUSLY busy - to the extent that we now find ourselves 'suddenly' well behind in the delivery of our newsletter. Thus, please bear with us as we try to catch-you-up just-a-bit by highlighting at least some of the most salient events which have occurred during this period.

People

Still running steady at about twenty 'core members' overall, there have been considerable changes among the makeup of the CD3 team, as well as among the numerous investigators who collaborate with the CD3 in an ad hoc manner across various programs. Beginning with our student participants, it is important to emphasize that in addition to presently funding the stipends and thesis research projects for nine [9] graduate students across four different departments, the CD3 continues to afford a unique environment for students at all levels to gain experience in practical research and development (R&D) activities associated with technologies that show promise for future deployment within the clinic. Working with the Director [1], the CD3's mix of graduate students, six [6] PhD Research Associates and two [2] Technicians, tackle R&D problems by a team approach that exemplifies the added value of such interdisciplinary efforts when focused upon a common goal. Specific kudos are in order for our matriculated students Drs. Jidong Liu and Ritesh Mittal who achieved their PhDs during this period from the Medicinal & Biological Chemistry (MBC) Department, and who are now permanently employed within the industry. Likewise, Mohammed El-Dakdouki (MED) and Mike Reese will be graduating next month with respective PhD and MS degrees from the MBC Department. A UT *Robert N. Whiteford Memorial Achievement Scholarship* contributed significantly to MED's efforts along with an *ACS Travel Stipend* which allowed him to present his thesis work at last year's prestigious National Medicinal Chemistry Symposium held in Pittsburgh. Among our Research Associates, we are equally pleased to convey that Dr. Mugunthu Dhananjeyan was able to parley the experience that he gained within the CD3 while devising and conducting validated, GLP-compliant analytical methods, so as to recently land a permanent job within the industry as a Group Leader in charge of exactly these types of critical activities for drug development.

People joining or passing through the CD3 across this period include: (i) Three [3] exceptionally qualified high school students who took advantage of the CD3's *'Research Shadow Program'* to assist in their career-path decisions; (ii) Three [3] undergraduate students for which

the first took advantage of the CD3's environment for her BSPS degree Practicum Experience, the second enhanced her credentials so as to recently become accepted to the Professional Pharmacy Program upon her second application, and the third is presently strengthening his credentials for an application to medical school; (iii) Four graduate students for which two have joined for the long-haul toward a PhD and an MD/PhD, respectively, and are thus included within the above nine-count of 'core participants,' another [1] worked in an ad hoc manner so as to take advantage of the intellectual property (IP) experiences uniquely afforded by the CD3's operations and from which he was then able to land a job within the scientific IP arena, and the last [1] as part of the College's Visiting Graduate Student Program with Szeged University in Hungary; (iv) One new postdoctoral associate [also already counted above], Dr. Rahul Khupse, who you may remember as a former PhD graduate from the CD3; and (v) One [1] sabbatical visitor, Dr. Janet Salzwedel, who has joined us for the remainder of this year from Adrian College in Michigan.

Taken together and also including the CD3's Secretary, that's twenty-eight [28] people who worked WITHIN the CD3's operation over just this report period. Several individual and groups of collaborators, which become too numerous to delineate in our highlighted report, have additionally worked WITH the CD3 during this period as well. **Without any doubt, it is the dynamic created by the CD3's core participants, ad hoc visitors and collaborative investigators directly engaged in ongoing research projects, that represents the true heartbeat of the CD3. And in this sense, the CD3 continues to grow stronger and stronger each year.**

Money

Reminding readers that the CD3 receives no dollars from UT, we previously have been quite pleased to report that for the last several years the CD3 has been operating with an annual budget of ca. $ 1 M, all of which was being procured from a variety of extramural sources via grants and Sponsored Research Agreements (SRAs). Unfortunately, for the more recent period pertaining to this update we must convey that the CD3's budget has slipped to the point where it is now running closer to ca. $ 750 K per year. This has resulted from two factors, namely the general fall in the overall economic climate and the specific loss of the CD3's large SRA with a big pharma partner caught-up in its own financial challenges. Responding to this slip, we have stepped-up our grant writing initiatives to a very demanding pace. For example, our present funding derives from four grants and one SRA that have been awarded from among nearly twenty-five of such submissions and wherein about ten are still pending. **For the sake of advancing the very promising research programs described below, the entire CD3 is firmly committed to keeping its high pace of grant/SRA procurement activities going into the future no matter what the state of the global economy.**

And Things Getting Done

Fourteen publications, two patents and thirty-four presentations that the CD3 team members were involved with during this period are listed in Appended Item 1. A quick scan of this list conveys both our high level and broad range of technical activities. In terms of R&D, the CD3 was very happy to see that one of our collaborator's compounds was entered into Phase I clinical testing for the potential treatment of Alzheimer's disease. The CD3 previously contributed significantly to the preclinical development of this compound by working with their initial UT spin-off company via SBIR relationships. In similar progressions of promising technologies, the CD3 is now poised to move into serious preclinical development stages for three compounds that derive from our own basic research programs. The first is directed toward

breast cancer and is part of a collaboration further highlighted immediately below. The second is directed toward prostate cancer and the third reflects a cardiovascular indication. Because both of the latter's rapid progressions are dependent upon procuring additional funding, however, no additional details will be conveyed at this juncture - please look forward to hearing about them in another (and not so distant) newsletter.

For some cancers, the field of oncology is approaching the point where cardiovascular medicine was nearly twenty years ago when early prognostic indicators coupled with preventative measures began to mitigate the occurrence of disease. As part of a collaboration involving the USDA Southern Regional Research Center and Tulane University, the CD3 has been assessing the health benefits of soy-related matrices after treatments that induce the formation of new natural product profiles. One compound derived from these collaborative studies has been shown to be particularly promising as a breast cancer preventative agent. It is called 'glyceollin I' (GLY I) but because it is produced in only very low quantities when seeds are stressed by a fungus, its further development has been limited by supply issues.

During the last eighteen months, the CD3 has made two important discoveries that may alleviate the critical supply issue for this precious compound. First, a synthetic chemistry method involving 13 steps was invented and subsequently optimized for scale-up such that it produced over two grams of material after a herculean effort was conducted by a closely-working, CD3 Synthesis Team across a nearly a six-month period. Second, we found that soybean plants infected by cyst root nematodes produce significant levels of GLY I. Thus, Ohio crops otherwise rendered less valuable due to these infections could instead become extremely valuable as a source of GLY I, or perhaps as a functional food capable of preventing certain cancers. Appended Item 2 provides a snapshot of many of the CD3 members as we gathered just before a field trip to harvest several different varieties of soybean plants infected by cyst root nematodes.

Other highlights include the Director's involvement in organizing and participating in the Medicinal Chemistry sections of the technical program associated with the IUPAC General Assembly and World Chemistry Congress held in Torino, Italy; and more recently the CD3's role in helping UT to host the Middle Atlantic Graduate Student Symposium for which the Director served as the Faculty Advisor and wherein Dr. Phil Portoghese delighted all of the attendees by delivering a Plenary Lecture.

All-in-all, the CD3 finished the last two years with a 'bang' followed by an even bigger 'bang,' respectively. And clearly, we are already proceeding to put our 'best feet forward' as we continue to roll into the future. From the Director: KUDOS TO ALL OF THE STAFF AND STUDENTS for continuing to make the CD3 such a vibrant operation within UT!

Appended Item 1. Publication, Patent and Presentation Activities

Publications

1. *Total Synthesis of Xanthohumol*. R. Khupse and P. Erhardt. J. Nat. Products, **70**, 1507-1509 (2007).

2. *Theoretical Investigation of Tautomeric Equilibria for Isonicotinic Acid, 4-Pyridone, and Acetylacetone In Vacuo and In Solution*. P. Nagy, G. Alagona and C. Ghio. J. Chem. Theory Comput., **3**, 1249-1254 (2007).

3. *Monte Carlo Structure Simulations for Aqueous 1,4-Dioxane Solutions*. P. Nagy, G. Volgyi and K. Takacs-Novak. J. Chem Phys. B, **112**, 2085-2090 (2008).

4. *Practical Synthesis of Lespedezol A_1*. R. Khupse and P. Erhardt. J. Nat. Products, **71**, 275-277 (2008). **Note that our paper was one of this journal's 'most-accessed' articles during 1st quarter of 2008 for which we received a very congratulatory communication from both the ACS and the senior editor of JNP.**

5. *Rapid and Sensitive HPLC Assay for Simultaneous Determination of Procaine and para-Aminobenzoic Acid from Human and Rat Liver Tissue Extracts*. M. Dhananjeyan, J. Trendel, C. Bykowski, J. Sarver, H. Ando, and P. Erhardt. J. Chrom. B, **867**, 247-252 (2008).

6. *Ab Initio Study of Hydrogen-Bond Formation Between Aliphatic and Phenolic Hydroxy Groups and Selected Amino Acid Side Chains.* P. Nagy and P. Erhardt. J. Physical Chem. A, **112**, 4342-4350 (2008).

7. *Catalytically Active Peptidylglycine α-Amidating Monooxygenase in the Media of Androgen Independent Prostate Cancer Cell Lines.* J. Trendel, N. Ellis, J. Sarver, W. Klis, M. Dhananjeyan, C. Bykowski, M. Reese and P. Erhardt. Journal Biomolecular Sciences, **13**, 804-809 (2008).

8. *Total Syntheses of Racemic, Natural (-) and Unnatural (+) Glyceollin I.* R. Khupse and P. Erhardt. Organic Letters, **10**, 5007-5010 (2008).

9. *Monte Carlo Structure Simulations for tertiary-Butyl Alcohol Solutions in Water/Acetonitrile Solvents*. P. Nagy, M. Dhananjeyan and P. Erhardt. J. Molecular Structure: THEOCHEM, **895**, 116-126 (2009).

10. *Drug Discovery.* Paul Erhardt in Advanced Pharmacology edited by K. Bachmann, M. Hacker and W. Messer. Elsevier, Oxford, United Kingdom. **In Press (**175 page chapter).

11. *Pharmacokinetic Modeling*. J.P. Byers and J.G. Sarver in Advanced Pharmacology edited by K. Bachmann, M. Hacker and W. Messer. Elsevier, Oxford, United Kingdom. **In Press** (164 page chapter).

12. *Prodrugs*: *Strategic Deployment, Metabolic Considerations and Chemical Design Principles.* P. Erhardt, R. Khupse, J. Sarver and J. Trendel. In Burger's Medicinal Chemistry, Drug Discovery and Development. Edited by D. Abraham. John Wiley & Sons, Inc. Hoboken, New Jersey, **In Press** (103 page chapter).

13. *Paclitaxel.* P. Erhardt and M. El-Dakdouki. In Analog-Based Drug Discovery Part II: Natural Products. Edited by J. Fischer and R. Ganellin. Wiley-VCH, Weinheim, Germany, **Accepted** (83 page chapter).

14. *Total Syntheses of Racemic and Natural Glycinol*. Amarjit Luniwal, Rahul S. Khupse, Michael Reese, Lei Fang and Paul W. Erhardt. J. Nat. Products, **Submitted**.

Patents

1. *Aralkyl Ester Soft Drugs (Broader Scope Elections after Phenytoin Indication).* P. Erhardt. U.S. Publication No. **US 2007/0135505 A1** (2007).

2. *Methods for Synthesizing Glycinols, Glyceollins I and II, Compositions of Selected Intermediates, and Uses Directed Toward Therapeutic Applications.* P. Erhardt, R. Khupse, J. Sarver, T. Cleveland, S. Boue, T. Wiese, M. Burow and J. McLachlan. Provisional Patent Application, **Filed** (2008); and Patent Application, **Filed** (2009).

Presentations (Presenter is underlined; All travel for P. Erhardt paid by extramural parties)

1. *Directing Drug Distribution (Avoiding Multidrug Resistance While Targeting Cancer Cells).* Paul Erhardt. Lecture at Research Triangle Institute, RTP, North Carolina (July, 2007).

2. *Directing Drug Distribution (Avoiding Multidrug Resistance While Targeting Cancer Cells).* Paul Erhardt. Presentation at the World Chemistry Congress, Torino, Italy (August, 2007). Note that P. Erhardt also served as the co-chair for the IUPAC 2007 General Assembly and World Chemistry Congress Session 2 *"Chemistry Protecting Health"* technical program that took place during this international assembly.

3. *PAM Inhibitors*. Paul Erhardt, Jeffrey Sarver and Wieslaw Klis. Poster at the Department of Defense IMPaCT Meeting, Atlanta, Georgia (September, 2007).

4. *Challenges Faced in the Less Industrialized Regions of the World*. Paul Erhardt. Lecture at the US EPA Human Biomonitoring Meeting, RTP, North Carolina (September, 2007).

5. *Directing Drug Distribution (Avoiding Multidrug Resistance While Targeting Cancer Cells).* Paul Erhardt. Departmental seminar for the UT Chemical Engineering Program (October, 2007).

6. *Soybean Natural Products*. Paul Erhardt, Mugunthu Dhananjeyan, Peter Nagy and Jeffrey Sarver. Overview for Marcy Kaptur's staff visiting UT (November, 2007).

7. *Molecular Cloning of PAM*. Nicole Ellis, Jeff Sarver, Jill Trendel, Wieslaw Klis and Paul Erhardt. Departmental seminar for the UT Biology Graduate Program (November, 2007).

8. *Using the Folate Transporter to Direct Drug Distribution.* Jidong Liu and Paul Erhardt. Departmental seminar for MBC (ca. November, 2007).

9. *Using the Ascorbate Transporter to Direct Drug Distribution*. Ritesh Mittal and Paul Erhardt. Departmental seminar for MBC (ca. December, 2007).

10. *Targeting Cancer Cells While Reducing MDR Liability*. Mohammad El-Dakdouki and Paul Erhardt. Departmental seminar for MBC (April, 2008).

11. *Avoiding Multidrug Resistance Using Paclitaxel as a Model Scaffold*. Mohammad El-Dakdouki, Jeffrey Sarver and Paul Erhardt. Poster at the UT Graduate Student Research Symposium (May, 2008).

12. *Preparation of (S)-Esmolol Employing Different Strategies*. Lei Fang (jointly), Michael Reese (jointly), Mugunthu Dhananjeyan, Jeffrey Sarver and Paul Erhardt. Poster at the UT Graduate Student Research Symposium (May, 2008).

13. *Mechanistic Studies for O-Debenzylation of Sulfur-Containing Substrates Having Therapeutic Importance by Using Pentamethylbenzene/TFA*. Amarjit Luniwal, Ritesh Mittal and Paul Erhardt. Poster at the UT Graduate Student Research Symposium (May, 2008).

14. *Directing Drug Distribution (Avoiding Multidrug Resistance While Targeting Cancer Cells).* Paul Erhardt. Lecture at the University of Oklahoma College of Pharmacy (May, 2008).

15. *Soybean Natural Product Total Syntheses*. Paul Erhardt and Rahul Khupse. Overview presented to project collaborators at Tulane University and the USDA ARRS, New Orleans, Louisiana (May, 2008).

16. *Soybean Natural Products*. Ed Cleveland, Paul Erhardt and John McLachlan. Presentation for Marcy Kaptur and several staff visiting UT (May, 2008).

17. *The CD3 and Drug Development Resources At The University of Toledo*. Paul Erhardt. Overview presented for the Global Cardiovascular Innovation Center at the Cleveland Clinic Foundation, Cleveland, Ohio (May, 2008).

18. *Ultrasound Imaging for Breast Cancer*. Jill Trendel, Mohammad El-Dakdouki, Nicole Ellis, Jeffrey Sarver and Paul Erhardt. Poster at the Department of Defense 'Era of Hope' Breast Cancer Meeting, Baltimore, Maryland (June, 2008).

19. *Monte Carlo Modeling of Solution Structures with Small Organic Solutes in Pure and Mixed Solvents*. Peter Nagy, Paul Erhardt, G. Volgyi and K. Takacs-Novak. Presentation at CERMACS (local ACS Section) Meeting, Columbus, Ohio (June, 2008).

20. *Avoiding Multidrug Resistance Using Paclitaxel as a Model Scaffold*. Mohammad El-Dakdouki, Jeffrey Sarver and Paul Erhardt. Poster at the National Medicinal Chemistry Symposium, Pittsburgh, Pennsylvania (June, 2008).

21. *Preparation of (S)-Esmolol Employing Different Strategies*. Lei Fang (jointly), Michael Reese (jointly), Mugunthu Dhananjeyan, Jeffrey Sarver and Paul Erhardt. Poster at the National Medicinal Chemistry Symposium, Pittsburgh, Pennsylvania (June, 2008).

22. *Mechanistic Studies for O-Debenzylation of Sulfur-Containing Substrates Having Therapeutic Importance by Using Pentamethylbenzene/TFA*. Amarjit Luniwal, Ritesh Mittal and Paul Erhardt. Poster at the National Medicinal Chemistry Symposium, Pittsburgh, Pennsylvania (June, 2008).

23. *Avoiding Multidrug Resistance Using Paclitaxel as a Model Scaffold*. Mohammad El-Dakdouki, Jeffrey Sarver and Paul Erhardt. Presentation for the MAGSS at Wayne State (July, 2008).

24. *Preparation of (S)-Esmolol Employing Different Strategies*. Lei Fang (jointly), Michael Reese (jointly), Mugunthu Dhananjeyan, Jeffrey Sarver and Paul Erhardt. Poster for the MAGSS at Wayne State (July, 2008).

25. *Mechanistic Studies for O-Debenzylation of Sulfur-Containing Substrates Having Therapeutic Importance by Using Pentamethylbenzene/TFA*. Amarjit Luniwal, Ritesh Mittal and Paul Erhardt. Poster for the MAGSS at Wayne State (July, 2008).

26. *Drug Discovery and Development*. Paul Erhardt. Presentation for the Translational Research Seminar Program on the UT HSC (September, 2008).

27. *Avoiding Multidrug Resistance Using Paclitaxel as a Model Scaffold*. Mohammad El-Dakdouki, Jeffrey Sarver and Paul Erhardt. Poster for the Annual BioOhio Conference at Columbus (October, 2008).

28. *Preparation of (S)-Esmolol Employing Different Strategies*. Lei Fang (jointly), Michael Reese (jointly), Mugunthu Dhananjeyan, Jeffrey Sarver and Paul Erhardt. Poster for the Annual BioOhio Conference at Columbus (October, 2008).

29. *Mechanistic Studies for O-Debenzylation of Sulfur-Containing Substrates Having Therapeutic Importance by Using Pentamethylbenzene/TFA*. Amarjit Luniwal, Ritesh Mittal and Paul Erhardt. Poster for the Annual BioOhio Conference at Columbus (October, 2008).

30. *Drug Discovery and Development*. Paul Erhardt. Two-part presentation for the Interdisciplinary Research, Technology Development and Business Incubation Special Graduate Program Invited Lecturer Series on the UT HSC (November, 2008).

31. *Soybean Natural Product Research*. Paul Erhardt, Mugunthu Dhananjeyan, Rahul Khupse, Peter Nagy, Jeff Sarver and Jill Trendel. Overview presented to project collaborators at Tulane University and the USDA ARRS, New Orleans, Louisiana (March, 2009).

32. *Ultrasound Imaging for Breast Cancer*. Mohammad El-Dakdouki, Jill Trendel, Jeff Sarver, Nicole Ellis and Paul Erhardt. Presentation for the 237th ACS National Meeting at Salt Lake City (March, 2009). Abstract # ORGN-266.

33. *Exploration of Solution Structure and Thermodynamic Parameters Upon Monte Carlo Simulations*. Peter Nagy, Mugunthu Dhananjeyan, Paul Erhardt, G. Volgyi, E. Baka and K. Takacs-Novak. Poster for the 41st Central Region ACS Meeting (CERMACS) at Cleveland (May, 2009).

34. *Total Synthesis of Natural (-)-Glycinol*. Amarjit Luniwal, Rahul Khupse, Michael Reese, Mohammad El-Dakdouki, Lei Fang, and Paul W. Erhardt. Presentation for the MAGSS at UT (June, 2009).

Appended Item 2. CD3 Soybean Harvest Team (Fall '08)

Back Row - Amarjit Luniwal, Michael Reese, Pat Hacker, Crystal Bykowski, Nicole Ellis, and Judy Erhardt.

Front Row - Dr. Mugunthu Dhananjeyan, Lei Fang, Dr. Peter Nagy, Mohammad El Dakdouki, Dr. Wayne Hoss (Executive Associate Dean of Pharmacy: Torn between shovel and suit, Dr. Hoss ultimately was not able to join us in the field), Dr. Paul Erhardt (CD3 Director), Dr. Jeff Sarver, Dr. Jill Trendel, and Dr. Rahul Khupse.

Not Depicted - Dr. Jim Bretz, Zhiyong Hu, and Khushboo Patel.

New CD3 Members in '09 - Chad Hicks, Neha Malik, Mike Robinson, Dr. Janet Salzwedel, and Attila Vanyolos.