Annual (& 10 Year Anniversary) Report
July 2003 – June 2004 (& 1994 – 2004)

A Synopsis of Activities Pertaining To The Center For Drug Design & Development (CD3)

Submitted by
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In recognition of the CD3's ten-year anniversary, this year's annual report also conveys some of the trends that have occurred since the CD3's re-establishment in 1994. Using a new format, three aspects of the Center's overall operation are emphasized beginning with the CD3's most important resource, its people. This topic is followed by a brief accounting of finances and, finally, by an appended listing of the Center's numerous activities from which just two items have been selected for discussion within the report's text. For each topic, updates pertaining to the last year serve as lead-ins for a broader purview relative to the last ten years. Graphs providing annual totals for several parameters across this entire period have been placed in the appendix.

People

To accommodate the significant growth in funded projects, three scientists joined the CD3's staff during the last year on a full-time basis: Nicole Ellis (B.A. in biology), Peter Nagy (Ph.D. in computational chemistry) and Mugunthu Dhananjeyan (Ph.D. in chemistry). In addition, Matt O'Kane (B.A. in chemistry) also worked with the CD3 on a periodic basis to address a special, collaborative project with the Medical College of Ohio. Money is available to hire one more technician and this process is just being initiated.

Thus, over the course of ten years, the CD3 has grown from an initial size of 2 people (namely myself as the newly arrived Director plus Pam Hennen for whom 50 % of her job description is associated with her role as the CD3's Secretary) to its present level of ten staff members (the remaining four individuals being Wieslaw Klis and Jeff Sarver who have been conducting research in a steadfast manner within the CD3 for several years, Susanne Nonekowski who joined more recently to serve as a part-time teaching faculty within the MBC Department, and one new-hire technician who is yet to be identified). An organizational chart for the CD3 is provided as appended Item 1. The chart also conveys the breadth of expertise afforded from this broad, interdisciplinary mix of scientists by indicating the functional titles for their various areas of primary responsibility.

The CD3's involvement with students has also steadily increased over the years. In terms of graduate students who received their stipends from external sources via the CD3's grants during the last year, one student (Mohammad Noshi) completed an M.S. degree in Medicinal Chemistry, seven individuals are continuing their studies as a result of this funding mechanism, and an eighth will likely be added during the Spring semester.

Five of these students are working toward a Ph.D. degree from the MBC Department, one toward an M.S. degree from the Pharmacology Department, and the last (Nicole Ellis) is pursuing an M.S. degree from the Biology Department on a part-time basis while retaining her job as a full-time technician. The new student intends to pursue a degree in medicinal chemistry (MBC Dept.). All of these graduate students' research projects are derived from grants awarded to the CD3. One graduate student studying Plant Science and two undergraduate students also took advantage of the CD3's programs during the course of the last year to broaden their overall educational experience by assisting in the conduct of lab-based, experimental procedures. Appended Item 2 lists the name, degree level being sought, year of study and area of interest for all of the aforementioned students.

Appended Item 3 provides a graph that depicts the CD3's number of staff and students over the course of the last ten years. When the most recent students are combined with the present staff, the total number of people who were actively associated with the CD3 during just the last year becomes nineteen (not counting the new position that is soon to be filled or the new student that will soon be grant-funded). All of these individuals' salaries are being paid for by the CD3's grants except for the Director who is paid as a tenured faculty member, one graduate student who was funded by the Plant Science operation, and the two undergraduate students who were non-salaried.

Money

The CD3's annual operating budget for the last year was about $ 971 K, all of which was obtained through extramural sources plus UT's contribution derived from such funding. When future years are also considered, the Center's operating budget surpasses $ 1.5 M in presently approved funding. Appended Item 4 provides a listing of the CD3's active grants while Item 5 provides a listing of the grant/contract applications that are pending. As shown graphically in appended Item 6, the present year's level of nearly $ 1 M in financing reflects a steady increase in extramural funding from the CD3's initial level of zero about ten years ago. A shift away from University-related grants can also be noted across this period.

And Things Getting Done

Five papers, two patents and seven presentations were produced by the CD3 during the last year. These items are recorded in appended Item 7. In addition: (i) Four major reports were submitted to external funding agencies in order to update them about the status of the respective grant-sponsored research projects that the CD3 has been conducting; and, (ii) One major report was submitted to the International Union of Pure and Applied Chemistry (IUPAC) as part of the CD3 Director's new role within that organization (next paragraph). The full versions of the four proprietary research documents are appended as Item 8 which is attached only to the hardcopy of the CD3's Annual Report that is being submitted to UT's Office of Research. Non-proprietary summaries for these projects are provided at the end of this section. Individuals

interested in reviewing any of these documents in full must first contact Paul Erhardt. Alternatively, the annual report that was submitted to the IUPAC is provided in its entirety as appended Item 9.

Numerous efforts toward furthering the CD3's network and overall research and teaching enterprise are listed in appended Item 10. Only two, major events from this area are highlighted herein. First: After serving one-year as President-elect, Paul Erhardt officially assumed the Presidency of the IUPAC Chemistry and Human Health Division (Div. VII) in January for a term of three years. Distributing about $ 40 K each year, most of the Div. VII-sponsored projects seek to bring cutting-edge medicinal chemistry to less developed nations in a way that can upgrade their standard of living or allow them to become more competitive in the global marketplace. Second, and closely related to the former: Because of such networking activities within these types of voluntary organizations, as well as within the private and academic sectors, the CD3 was able to procure approximately **$ 600 K** of expensive paclitaxel-related chemicals for its anticancer research program at an extraordinarily reduced, total cost of less than $ 3 K.

Appended Item 11 provides an accounting of the CD3's papers, patents and presentations produced over the course of the last ten years. It may be interesting to note that the 97-98 dip in such activities corresponds to the Director's agreement to serve as a one-year, Interim Assistant Dean for the College during the latter's move to Wolfe Hall and wherein a critical stage was also set for the College of Pharmacy's subsequently successful accreditation by the ACPE.

Research Report Excerpts: Non-Proprietary Summaries

(1) Susan G. Komen breast cancer funding final report for the *MDR SAR* research program.

In general, anticancer agents have little selectivity for killing cancer cells compared to other healthy cells in the body which are normally undergoing rapid growth and division. This less than ideal situation becomes particularly problematic during chemotherapy when cancer cells develop resistance to the anticancer agent, generally in the form of a multiple drug resistance or MDR syndrome. The purpose of our research is to discover chemical components that can be incorporated into an anticancer drug molecule so as to completely avoid, or at least significantly lesson, the initial drug's liability toward prompting MDR.

Toward this end, we have begun to define certain chemical features that are unacceptable to one of the principal biochemical factors that contribute to MDR, namely a drug efflux transporter called 'Pgp.' For example, specific incorporation of these features into the molecular framework of paclitaxel reduces this anticancer agent's susceptibility to MDR by a factor of nearly ten-fold. We are presently fine-tuning our initial assessment of such features and, in addition, exploring the possibility that they might be further coupled with another type of molecular system that is able to cause drugs to preferentially hone toward cancer cells compared to healthy cells.

Thus, should our next phase of explorations also prove successful, the future prospects of our research could provide for the incorporation of well-defined chemical functionalities onto anticancer agent molecules wherein the added groups would lesson

the parent drug's liability for MDR upon continued dosing while simultaneously improving the initial preference for cancer cells relative to healthy cells at the onset of therapy.

(2) US Army prostate cancer funding second annual report for the *Pam Inhibitors* research program.

Male hormones typically stimulate tumor growth during the initial stages of cancer of the prostate (**CaP**). Because of this, drugs that can block the effects of these hormones generally represent an effective early therapy. However, as disease progresses, tumors often develop the ability to grow even in the presence of these types of drugs. One way that this appears to occur is through the overpopulation of the tumor with specialized cells that can produce their own hormones and growth factors. Preliminary evidence suggests that some of these specialized cells over-express and then rely upon a secondary processing enzyme complex called *Peptidylglycine á-Amidating Monooxygenase* (**PAM**) to convert certain peptides into active growth factors. Thus, inhibiting PAM within these specialized cells may provide a means of treating advanced stages of prostate cancer. Furthermore, co-treatment with hormone blocking drugs and PAM inhibitors during the early stages of disease may circumvent the progression to hormone-independent cancer.

At this point our accumulating results continue to suggest that selected compounds operating mechanistically as PAM inhibitors, may be able to attenuate the rapid growth of human prostate cancer cultures that have become hormone independent and show high PAM expression levels. If these results are able to be confirmed by the *in vivo* studies that are planned during the next year, this will provide preliminary target validation of this pathway as a new mechanistic avenue toward the potential treatment of hormone-independent prostate cancer. The pursuit of analogues tailored for their use within humans by injection or by the oral route, as well as for their potency and selectivity toward human prostate cancer cells versus healthy cells, would thus merit very serious further study. It is the intention of our research program to either negate or to firmly establish manipulation of the PAM pathway as a viable therapeutic direction. Furthermore, if it is the latter, then it also becomes our intention to be well on the way toward grooming a compound that might be able to be used clinically, if not by itself representing the optimal structural prototype, then by the accumulation of key SAR data that could be useful toward the further design of such a prototype.

(3) ICSU/IUPHAR/IUPAC fourth annual report for the *Human Drug Metabolism Database* (hDMdb) informatics program.

The hDMdb project intends to establish a database of metabolic biotransformations that are done by humans to xenobiotic compounds. Three fields of data will be interfaced within the database: (i) Chemical name, property and structure-related information pertaining to each xenobiotic and its metabolites; (ii) Metabolic biotransformation-related information pertaining to various biological parameters of the study or exposure, along with analytical and statistical details associated with the assays or assessments that were involved; and, (iii) Genetic- or phenotype-related information

relative to the observed patterns of metabolism for each case. The database will be housed by the University of Toledo CD3 and made available on the Internet via a non-profit format. Investigators will be able to turn to the database as a collection of standard data that will allow: (i) Explicit structure searching to validate new drug metabolism research assays in terms of their ability to predict clinical outcomes; (ii) Two-dimensional (2D) and 3D substructure searching to identify analogous metabolic occurrences relative to novel compounds undergoing development as new drugs; and, (iii) Statistically derived probability rankings to be made about competing metabolic possibilities for any given compound. The global pharmaceutical research enterprise, regulatory bodies, and practicing clinicians all represent an audience anxious to utilize such a database.

(4) USDA first annual reports for the *Enhancing Soy Natural Products* program.

Hormonal changes in post-menopausal women can increase the risk of developing breast cancer, bone loss, and reduced cardiovascular health. Populations consuming a diet high in soybean phytoestrogens (that mimic human estrogen) have lower incidences of several diseases, including breast and prostate cancer. Recently, research has shown that isoflavones, a group of phytoestrogens found in soybean derived foods, are compounds that reduce the risk of certain potential health problems when consumed in the diet. Identifying the phytoestrogenic activity of soybean isoflavones would benefit the nutritional health of the population in general, particularly women. The probability that an American woman will develop breast cancer is currently estimated to be one in nine. Evidence suggests that natural steroidal estrogens (xenoestrogens) or compounds that mimic the biological activities of natural steroidal estrogens, are encountered in industrial environments where incidence of breast cancer has been on the rise. The occurrence of breast cancer is lower, by comparison, in Asian women who consume much greater quantities of legume products, including soybeans that contain isoflavonoids. The research project relates to National Program 108, Food Safety Animal and Plant Products. Techniques are being determined by Agricultural Research Service (ARS) scientists to manipulate phytoestrogen levels in soybean seed and soy-based products to maximize health benefits by their consumption. Research to manipulate and produce optimal levels of beneficial “nutraceutical” (medicines from plants) compounds (such as phytoestrogens) in soybean in the field and in resultant soy-based products will: 1) add value to soy-based products thus benefiting the agricultural economy in the U.S., and 2) increase the health of females consuming soy-based products, thus helping to decrease health problems and costs due to pre- and post-menopausal hormone changes.

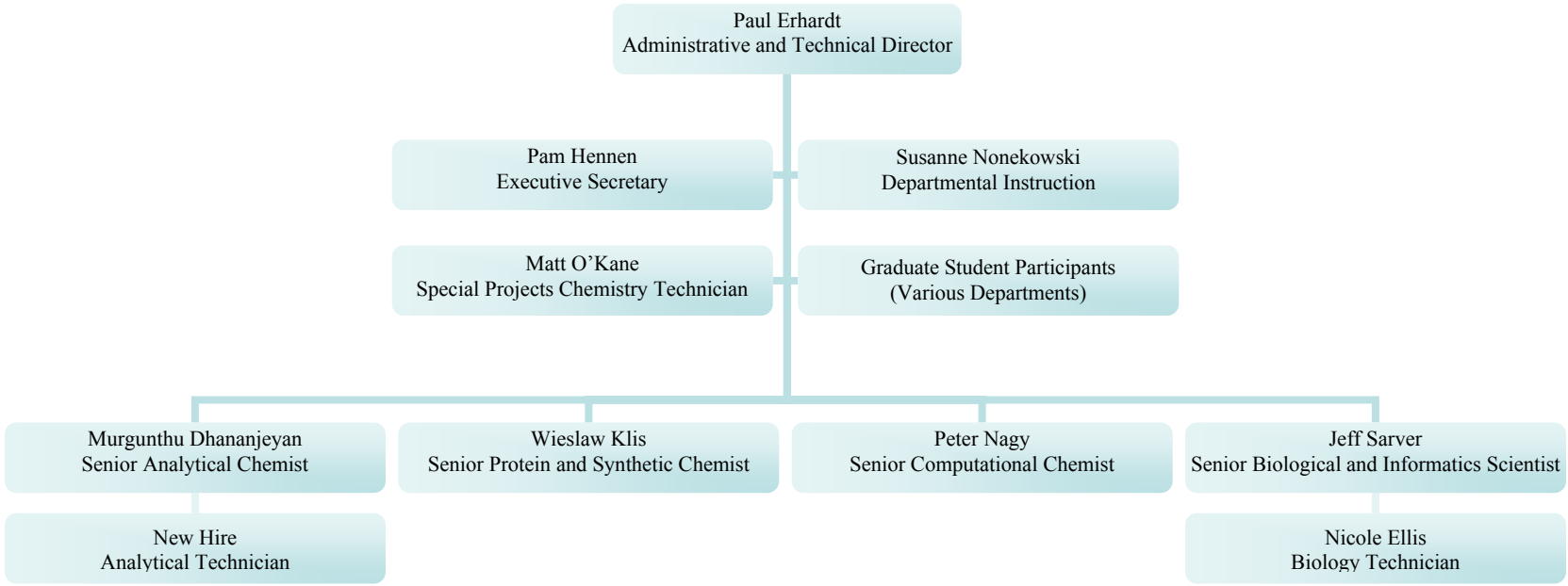
The CD3 is presently working closely with the CBR and the ARS SRRC to assess several soy-related dietary supplements available within the Toledo and New Orleans areas. Assessment involves fingerprinting the natural product chemical components by using HPLC, and characterizing the biological properties in terms of phytoestrogen, anti-oxidant, immuno-stimulatory, anticancer and cancer preventative activities, by using biochemical, cell-based and rodent model assays. Computational studies will be additionally undertaken to model the interaction of selected components with the two types of estrogen receptors. Having this information as a backdrop, the CD3 will further

delineate stress factors and modified feedstocks that influence the biochemical production of soy phytochemicals. As part of the latter, the CD3 has also initiated the total synthesis of some constituents that have already become of interest but are present as a mixture in only very trace amounts when soybeans are subjected to one type of stress condition during growth. Ultimately, it is hoped that procedures can be characterized that will enhance the levels of natural products having desirable selective estrogenic, anticancer, or cancer preventative activities. Depending upon the chemical nature of the enhanced materials, the complexity of their potentially synergistic mixtures, and the optimal manner for their ingestion by humans, finalization of the procedures could take different forms of deployment, i.e. ranging from a field-, greenhouse- or hydroponic-crop derived added value food, dietary supplement or nutraceutical, to an ethical pharmaceutical agent or set mix of agents initially obtained by field- or greenhouse crop-harvest, hydroponics, plant cell culture, or even total chemical synthesis. Overall, it is envisioned that this basic research and practical development program will take ten years to complete.

Appendix Items

1. CD3 Organizational Chart.
2. Students who worked with the CD3 during 2003-2004.
3. CD3 staff and student numbers over the last 10 years.
4. Active grants (2004).
5. Pending grants and contracts (2004).
6. CD3 funding over the last 10 years.
7. Papers, patents and presentations produced during 2003-2004.
8. Proprietary Research Reports.
9. Annual Report to the IUPAC.
10. Miscellaneous activities undertaken during 2003-2004.
11. Papers patents and presentations produced over the last 10 years.

Item 1. CD3 organizational chart.



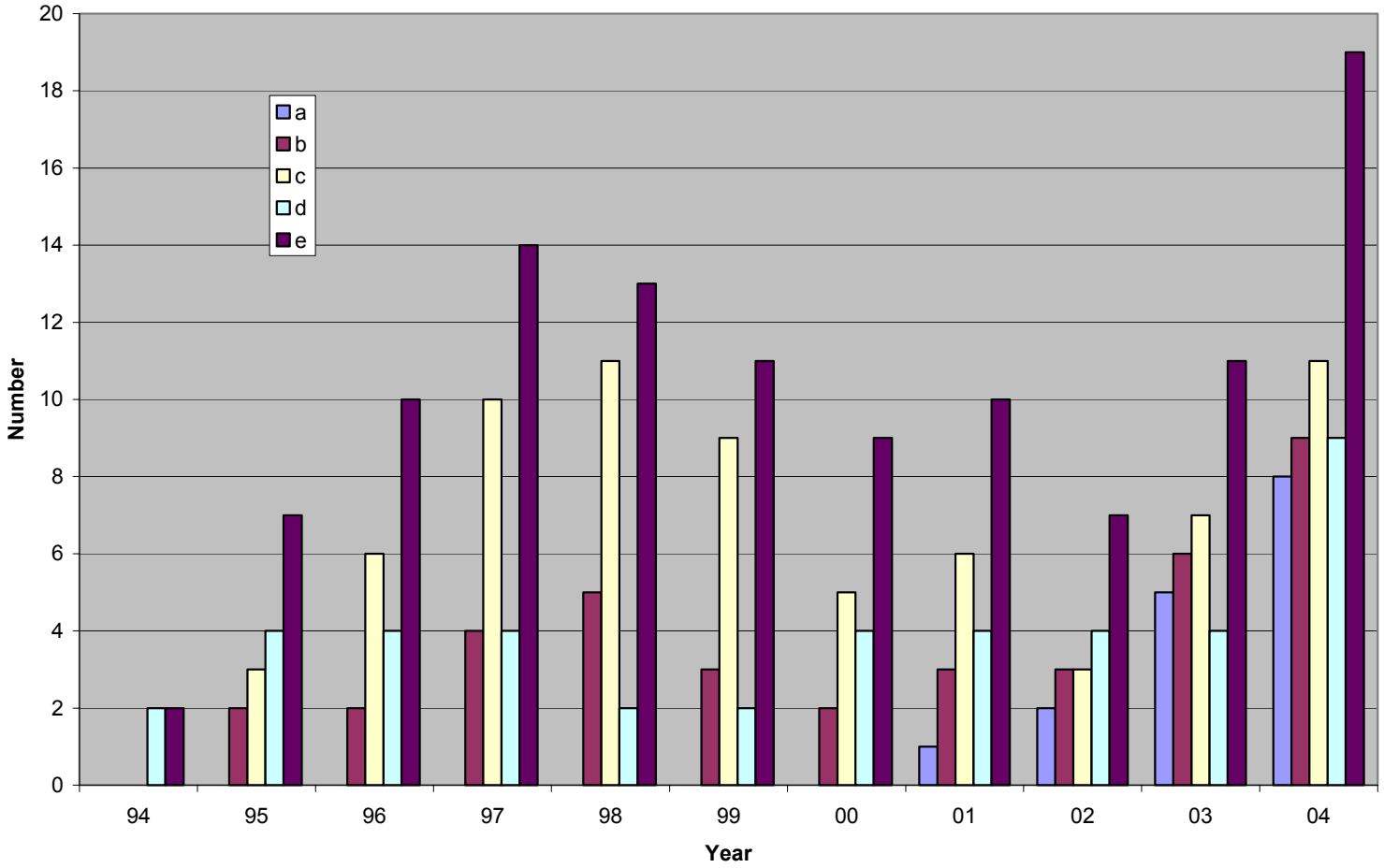
Item 2. Students who worked with the CD3 during 2003-2004.

Name	Degree Pursued	Year	Area
Wissam Abou-Alaiwi*	Ph.D.	3	Plant Science
Timour Bascan*	B.S.	4	Bioengineering
Mohammad El Dakdouki *	Ph.D.	1	Medicinal Chemistry
Nicole Ellis	M.S.	1	Biology
Jessica Fox*	Pharm.D.	5	Pharmacy
Yasser Heakal	Ph.D.	2	Medicinal Chemistry
Zhiyong Hu	Ph.D.	#	Medicinal Chemistry
Rahul Khupse	Ph.D.	3	Medicinal Chemistry
Jidong Liu	Ph.D.	2	Medicinal Chemistry
Ritesh Mittal	Ph.D.	2	Medicinal Chemistry
Mohammad Noshi	M.S.	Completed	Medicinal Chemistry
Yanmin Zhang	M.S.	1	Pharmacology

*All students are funded from external grants obtained by the CD3 except for those marked with an asterisk. It is anticipated that MED will also soon be able to be funded by the CD3.

#Long-distance thesis work being pursued by student part-time while working full-time for Johnson & Johnson (New Jersey).

Item 3. CD3 staff and student numbers over the last 10 years.



a = CD3-funded graduate students.
b = Graduate students.
c = Graduate and undergraduate students.
d = Staff.
e = Staff and students (d & c).

NOTE: 2004 'e' statistic does not add to 20 because one of the CD3's staff is also a grad student.

Item 4. Active grants (2004).

PI: P. Erhardt 3/1/2000-Open
International Committee Scientific Unions (ICSU) $70K
Enhancing Global Input Into A Human Drug Metabolism Database
The overall goal of this project is to construct a non-profit, www-based database pertaining to human drug metabolism.[a]

PI: P. Erhardt 4/1/2002-3/31/2005
US Army Prostate Cancer Res. $550K
PAM Inhibitors
This study will examine the PAM pathway as a possible therapeutic target in hormone independent prostate cancer.

PI: P. Erhardt 7/1/04 – Annual Renewal
USDA Grant Year 2[b] $440 K/yr (CD3 portion)
Phytoestrogens in Development of Natural Products
This project seeks to study and enhance soy matrices.

Corp. PI: W. Hoss et al./UT PI: P. Erhardt 7/1/04-7/1/06
NIH SBIR Phase II Grant (Resubmission) $134 K
Development of CDD-0102
This SBIR project provides assistance to Cognitive Pharmaceuticals, Ltd. development of an M-1 agonist to treat Alzheimer's disease.

[a]This funding has already been used to establish a core Bioinformatics Resource within the Coll. of Pharmacy that can interact with the www via a double server system maintained by UT's Information Science group coupled to three local workstations.

[b]Funding for 7/1/05-6/31/06 (Year 3) has already been "voted-in" at $500 K. It is anticipated that this level of annual funding will now run for another 6 to 8 years.

Note: Because of the Director's networking activities within several voluntary organizations, as well as within the private sector, he was able to procure ca. **$600,000.00** of expensive paclitaxel-related chemicals for the CD3's research at a total cost of less that $3,000.00.

Item 5. Pending grants and contracts (2004).

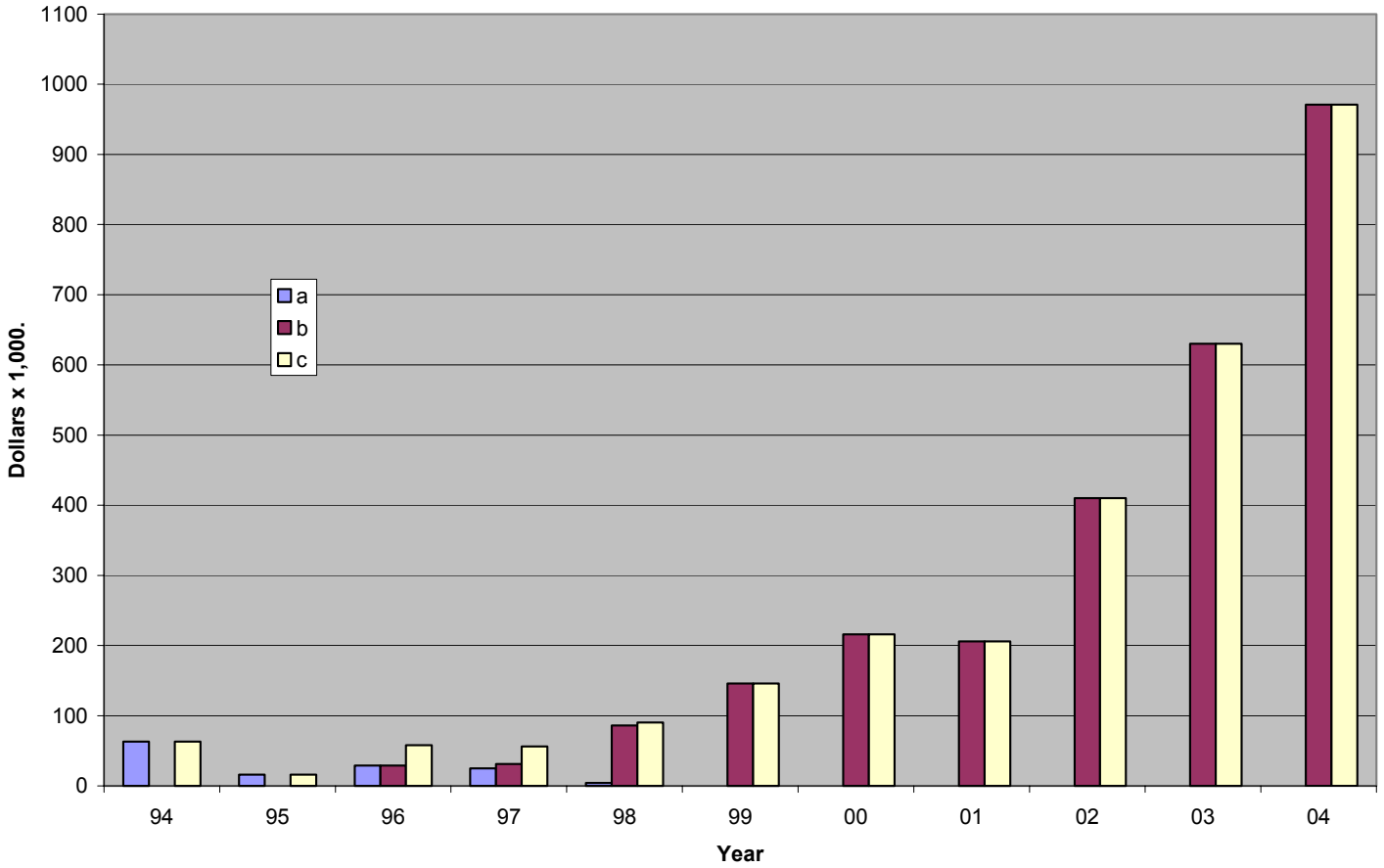
PI: P. Erhardt — 9/15/04 – 9/14/05 (plus renewals)
US Dept. of Agriculture — $167 K/yr
A Partnership for Pharmaceutical and Economic Development of Wild Lebanese Plants
This project intends to enhance Lebanon's ability to compete in the global agricultural community.

PI: P. Nagy (Co-PI: P. Erhardt) — 7/1/04 – 6/31/05
Ohio Supercomputer Center — 2,000 RUS Computer Time
Theoretical Studies for Paclitaxel and for Ligands of Estrogen Receptors
These studies will examine the molecular details associated with epimerization of paclitaxel and the interaction of phytoestrogens with estrogen receptors.

PI: P. Erhardt — 3 Years (plus renewals)
ARYx Sponsored Res. Agree. — $550 K
This project will further evolve UT soft drug technology licensed to ARYx.

PI: P. Erhardt — 2 Years (plus renewals)
Pfizer Grant — $400 K (plus an LC-MS at $300 K)
This project will involve collaborative prodrugs research.

Item 6. CD3 funding over the last 10 years.



a = UT-related (e.g. '94 Start-up; deARCE, etc.).
b = Extramural.
c = Total.
NOTE: Not shown above for 2004 is an additional $600 K worth of chemicals procured via the CD3's network.

Item 7. Papers, patents and presentations produced during 2003-2004.

Items marked with an asterisk indicate activities conducted in response to personal invitations.

Publications

1. *A Human Drug Metabolism Database: Potential Roles in the Quantitative Predictions of Drug Metabolism and Metabolism-Related Drug-Drug Interactions*. P.W. Erhardt. Current Drug Metabolism, **4**, 411-422 (2003)**.***
2. *Medicinal Chemistry In The New Millennium. A Serious Look At Drug Metabolism.*(Revised/Updated/Revised) K. Bachmann, K. Brouwer, C. Crespi, P. Erhardt, F. Guengerich and R. Lowery. Pure and Applied Chem., **Accepted**.*
3. *Using Drug Metabolism Databases During Drug Design and Development.* Chapter completed for a book to be titled Drug Design and Development, Edited by Mukund Chorghade, **Accepted**. *
4. *Application of Simple Mathematical Expressions to Relate the Half-lives of Xenobiotics in Rats Versus Humans*. K. Ward, P. Erhardt and K. Bachmann. J. Pharmacology and Toxicology Methods, **Accepted**.
5. *Using a Hard Nucleophile on a Soft Drug: Production of Esmolol's Metabolite via Hydrolysis After Treatment with Bis(tributyltin) Oxide.* C. Zhang and P. Erhardt. Org. Lett., **Submitted**.

Patents[a]

1. *Aralkyl Ester Soft Drugs.* P.W. Erhardt. US Patent Number 6,750,238 B1, June 15, 2004.
2. *Aralkyl Ester Soft Drugs (Cont. in Part): Method and Compositions for Treating Persistent Pulmonary Hypertension.* P.W. Erhardt and M.M. Aouthmany. US Patent Number 6,756,047 B2, June 29, 2004.

[a]P. Erhardt spent a significant amount of time assisting in UT's prosecution of these and several related patent applications by virtue of his technical expertise as the principal inventor and by his qualifications as a U.S. P.T.O. Certified Patent Agent.

Presentations (Underline denotes presenter)

1. *Considering Drug Metabolism During Drug Design and Development*. P.W. Erhardt. Industry Lecture Series, PPD Discovery, Chapel Hill, NC (July 2003).*
2. *Drug Metabolism Terms* and *Human Drug Metabolism Database* oral reports delivered by Paul Erhardt to IUPAC Div. VII at International meeting in Ottawa, Canada (Aug., 2003).
3. *Chemical Fingerprinting of Natural Matrices Having Anticancer Properties*. P.W. Erhardt. Univ. Minnesota Coll. Pharmacy Seminar Program, Minneapolis, MN (Sept., 2003). *
4. *HTS* oral report delivered by Paul Erhardt to SBS Academic Outreach Committee at International Meeting in Portland, OR (Sept., 2003).
5. *Chemical Fingerprinting of Natural Matrices* and *MBC Graduate Student Recruitment* seminar. P.W. Erhardt. Oakland University Seminar Program, Oakland, MI (Nov., 2003).*
6. *Phase 0: Not At All Nothing During Clinical Drug Metabolism.* Paul Erhardt. IBC Preclinical Forum, Boston, MA (Feb., 2004).*
7. *Drug Metabolism Terms* and *Human Drug Metabolism Database* and *Present Trends in Patenting Drugs* oral reports delivered by Paul Erhardt to IUPAC Div. VII Med. Chem. subcom. at International ACS meeting in Anaheim, CA (March, 2004).

Item 8. Proprietary Research Reports

The full versions of the following documents have been attached only to the hardcopy of the CD3's Annual Report that is being submitted to UT's Office of Research.

1) Susan G. Komen breast cancer funding final report for the *MDR SAR* research program (13 pages).

2) US Army prostate cancer funding second annual report for the *PAM Inhibitors* research program (42 pages).

3) ICSU/IUPHAR/IUPAC fourth annual report for the *Human Drug Metabolism Database* informatics program (27 pages).

4) USDA first annual reports for the *Enhancing Soy Natural Products* program:
    a. Senator Mike DeWine's Questionnaire (5 pages).
    b. Marcy Kaptur's (Roger Szemraj) Questionnaire (3 pages).
    c. USDA CRIS Report, CD3-related portion (8 pages).

Item 9. IUPAC report.

IUPAC Division VII. Chemistry and Human Health

Bureau Report: January – September, 2004

Paul Erhardt, President

I. Executive Summary

The merger of the former Medicinal Chemistry and Clinical Chemistry/Toxicology Sections into the Division of Chemistry and Human Health (VII) has proven to be an effective way for the IUPAC to oversee and allocate funding to all of these areas while using a condensed administrative infrastructure. To promote the core of expertise required to support the technical diversity afforded by these areas, Division VII, in turn, maintains three, standing Subcommittees led by appointed Chairpersons who are recognized internationally within each of their fields. These Subcommittees are Clinical Chemistry, Medicinal Chemistry, and Toxicology. An ad hoc Subcommittee, also led by an appointed Chairperson, has additionally been organized to deal with the IUPAC nomination and election processes for the Division. While a few members of each Subcommittee also sit on the Division Committee, the majority of the technical Subcommittee members are drawn as volunteers from each of these fields, respectively. The Election Committee has representation from all three areas.

The Subcommittees hold independent meetings on a regular basis and each Chairperson provides an update about their activities by either personally attending or forwarding a written report to the Division meetings which are held about twice a year. This focus of expertise coupled with the broader perspectives afforded during the Division meetings, has proven to be an effective way to encourage and initiate the evaluation of new IUPAC Project submissions, as well as to provide for assessments of ongoing projects and their subsequent impact. Final approval of new projects and additional tracking of ongoing projects, occur at the Divisional level wherein an equitable balance across all activities and the Division VII's IUPAC-allocated funds is sought among all three Subcommittees. Presently, Division VII is carrying 24 projects for which 2 are interdivisional, contributes to 2 additional interdivisional projects, and has 3 projects undergoing review for which 2 are interdivisional.

II. Activities Organized by the Six Goals of the IUPAC Strategic Plan

1. Provide leadership as a worldwide scientific organization that objectively addresses global issues involving the chemical sciences.

Division VII's organization into three subcommittees allows this, as well as all of the other, strategic objectives to be focused within the contexts of Clinical Chemistry, Medicinal Chemistry and Toxicological Chemistry. Each subcommittee brings together a group of experts from around the globe to discuss items relevant to their area. For example, through such discussions, the Medicinal Chemistry group has determined that the global harmonization of

patent laws impacting upon the pharmaceutical industry would benefit from a broad consideration of several issues. Toward that end, a project proposal is presently being drafted to objectively address these issues by starting with a general survey that will be administered globally to a variety of scientists, practitioners and administrators for whom patents are an important aspect of their work.

2. Facilitate the advancement of research in the chemical sciences through the tools that it provides for international standardization and scientific discussion.

All three of Division VII's Subcommittees remain extremely active in producing glossaries and recommendations for standardization of terms within their respective areas. A quick scan down the list of completed, ongoing and proposed projects indicates our numerous activities in this area (see Section IV. Tabular Material).

Another type of tool that Division VII is constructing in conjunction with the IUPHAR and the latter's initial funding supplied by the ICSU, is an Internet database that will contain human drug metabolism data and will, in turn, be made available to users across the globe via a non-profit basis. With an emphasis on the chemical structures for both the parent drug or xenobiotic and the various metabolic biotransformation products, the Human Drug Metabolism Database (hDMdb) database will be extremely useful to both the medicinal and toxicological chemistry arenas. It is interesting to note that while Division VII has already been working on this project for four years, the importance of such projects within the chemical community is only just now beginning to be fully appreciated. For example, statements quoted in the recent C&E News (June 28, 2004 pages 37-41) article that highlighted an international conference dedicated to 'Charting Chemical Space: Finding New Tools To Explore Biology" indicate that one of the 'grand challenges' elaborated by Stuart Schreiber and several other well-recognized scientists was an outright appeal for the production of open databases having chemical structures connected to biological properties.

3. Assist the chemistry-related industry in its contribution to sustainable development, wealth creation, and improvement in the quality of life.

Moving forward from one of its earlier publications ('Medicinal Chemistry in the Development of Societies: Biodiversity and Natural Products,' Eur. J. Med. Chem., **32**, 2000, pages 1121-1125) which specifically addresses the critical role that the pharmaceutical industry can play in developing nations, Division VII is now undertaking follow-up projects that intend to bring workshops on this topic to such countries. Our initial program will target the pharmaceutical industry in India which has heretofore been able to establish strengths in process (scale-up) chemistry but not in the earlier stages of drug discovery and invention, despite their long history with natural product-based remedies and herbal medicines. This undertaking may also be applicable to China and many other Eastern countries. Even less developed nations are being targeted in a somewhat different manner (see Strategic Goal 4.)

4. Foster communication among individual chemists and scientific organizations, with special emphasis on the needs of chemists in developing countries.

The aforementioned hDMdb project is also applicable to this goal. For example, during a poster presentation about this project at the recent International Society for the Study of Xenobiotics (ISSX) meeting (Vancouver, September, 2004), its 'free-access-for-all' principle was applauded by several scientists from less developed nations who happened to have become engaged in a broader discourse with scientists from some advanced countries who wanted to know if the database might be able to be commercialized so as to generate funding that could move its development along at a faster pace (but with the inherent principle then falling into place that the db would thus be made available only to those who could afford to purchase it).

Continuing from Strategic Goal 3, we have determined that the best follow-up to our earlier publications for countries which are in the very early stages of development in that they completely lack any type of sophisticated chemical industry infrastructure, needs to be approached at a more fundamental level, i.e. by educational programs directed through their budding academic institutions rather than at the industrial level. Division VII's ongoing projects on basic clinical/medicinal/toxicological chemistry education within the Latin America region represents an initiative along these lines.

I assume similar to all of the other Divisions, Division VII repeatedly votes in favor of IUPAC sponsorship of meetings and conferences applicable to our area whenever they are to be organized or hosted by less developed nations and wherein the caliber of the related chemical technologies is to be held in the highest regard. During the last year, Division VII has favorably reacted to about two of such requests each quarter.

5. Utilize the IUPAC's global perspective and network to contribute to the enhancement of chemistry education, the career development of young chemical scientists, and the public appreciation of chemistry.

Ongoing chemical education initiatives pertinent to human health have been described above for audiences in industry (Strategic Goal 3) and academia (Strategic Goal 4). For the public at large, two additional initiatives deserve mention. First, as a follow-up to our prior, somewhat technical article ('Natural and Non-natural Substances Related to Human Health,' PAC, **74**, 2002, pages 1957-1985) Division VII produced a summary version which compares the attributes of synthesized drug versus natural sources for chemical compounds in laypersons terms. Subsequent to publication of the latter in CI, this has now been picked-up within the lay press with translations being effected by other countries as evidenced by the entries noted on the Web-based, Eureka Alert Service.

The second initiative to be mentioned in this regard is a project submission that is under review entitled 'Molecular Gastronomy.' The end-product form this project will be a short monograph wherein the point will be made clear that when a person undertakes everyday cooking, they are indeed practicing chemistry and that in the process of trying to improve palatability, various procedures can also either enhance or diminish the overall nutritional and/or medicinal value of a given food item or dietary supplement.

6. Broaden national membership base and seek the maximum feasible diversity in membership of IUPAC bodies in terms of geography, gender and age.

One of the new project criteria that Division VII has laid in place from the onset during the Subcommittee meetings and then further reinforces at the Divisional level, is that the proposed project participants list reflects the exact spirit conveyed by this final IUPAC strategic goal. That these participants might then become future members in various IUPAC bodies provides a grass-roots technical approach toward accomplishing this end. Exemplifying this scenario is the fact that the current President of Division VII first became involved with the IUPAC via an invitation to participate on a project about eight years ago and has gradually become more and more active. The same philosophy has been applied to the Subcommittee charged with the Division VII-related nomination and election processes, although in this case there is the possibility that a new member might become immediately involved at a higher administrative level within the IUPAC infrastructure.

In terms of seeking younger members (also applicable to Strategic Goal 5.), Division VII had the pleasant experience of hosting a 'Young Observer' during the Ottawa meeting. To further support this program, Division VII subsequently encouraged this individual to seek IUPAC sponsorship for a symposium that he was trying to set-up in his country. This has all occurred favorably and a full set of proceeding papers covering the symposium's cutting-edge chemistry in the area of nuclear delivery and functional modification by small molecules will soon be published in PAC. It is hoped that through such mentoring, this young and rising investigator will gradually become more and more active within the IUPAC as well.

III. Challenges, Problems and Solutions

Within this topic, Division VII would like to suggest one item for potential discussion, namely 'additional financing mechanisms for the Divisions.' The problem that Division VII has is that its IUPAC budget gets spread very thin based just upon its technical projects load which, in turn, makes it difficult for the Division to optimize certain administrative activities or to embark upon new recruitment initiatives (the latter presumably being an ongoing challenge for everyone within IUPAC in terms of either getting new members or new projects or both). A brief summary (proposal or potential solution) follows.

We propose that in addition to the current, projects-based funding mechanism (with the presently recommended bump-up percentage allocated for administration), Divisions be allowed to also obtain additional funds via two new mechanisms: (1) Recouping a share of any royalties on published books, monographs etc. for which they were responsible for generating, e.g. a 75/25 split with the IUPAC first receiving all of such funds and then, after deducting any cost outlays that they may have incurred including that of the initial money the IUPAC allocated via the Division to the relevant project at its outset, distributing 75 % of such remaining monies to the appropriate Division; and, (2) Receiving a share of any monies obtained by their own efforts toward fund raising, e.g. again a 75/25 split with the money initially to be received by the IUPAC but then immediately divided such that 75 % goes directly to the Division since the IUPAC will have had no overhead for any of such initiative that would need to be first accounted for.

These monies should be for unrestricted use by each Division with the only provisos being that the money must in some way be directed toward the IUPAC Strategic Goals and, obviously, can not be used for any person's or entity's profit. For example, in the case of Division VII, we would like to use such funds to be able to pay for the expenses for additional people to attend our Subcommittee and Divisional meetings, which, as alluded to in the Executive Summary, become the drivers for all of our efforts in general and, as clearly indicated in Section II, Goals 4, 5 and 6 represent a very specific, grass-roots approach toward engaging our relevant chemical communities and recruiting new participants. Such funding could be particularly valuable for the latter when further directed toward recruitment of scientists from less developed nations and of young (not yet well-established) scientists, both of whom are likely to have financial difficulties of their own.

One of the benefits of undertaking fund-raising at the Divisional level is that it can be pursued from one technical expert to another identical technical expert (IUPAC Division person to industry person) with the reasons for encouraging an interaction then being able to be built-up from a very common base. One of the challenges will be to coordinate such activities with the IUPAC National Adhering Organizations who may also be attempting to conduct such fund-raising. In the States, the NAO has such a program but it is administrator to administrator and it appears to be having little success. I plan to attend their next meeting (November) to see how we might either work together or move independently in this regard. However, since the same issue could arise in other countries as well, an over-riding policy/directive from the IUPAC itself becomes a more efficient and uniform way to address this aspect of the proposal.

IV. Tabular Material

Projects Completed 2003-2004

720/4/93	Exposure Assessment and Decision Rules in Compliance Testing for Implementation of Exposure Limits. Published.
700/2/98	Natural and Unnatural Substances Related to Human Health. Published in PAC with follow-up summary in CI which then prompted several lay press publications.
2000-034-2-700	Glossary for Toxicokinetics of Chemicals. Undergoing publication.
2000-059-1-700	Properties and Units for Transfusion Medicine and Immunohaematology. Published.
2001-077-2-700	Best Practices for Workplace Exposure Assessment: A Critical Review of Methodology. **Abandoned.**

Current Projects (all end in -700)

1999-047-1-	Immunochemistry of Metal Sensitization.

2000-009-1- Drug Metabolism Terms.

2000-010-1- Human Drug Metabolism Database.

2000-014-1- Recommendations for the Use of Nanotechnology in Clinical Laboratories.

2001-048-2- Research and Training in Medicinal Chemistry in India, Pakistan and Sri Lanka.

2001-049-2- Glossary of Terms Used in Process Chemistry/Manufacturing of Active Pharmaceutical Ingredients, and Pharmaceutics.

2001-050-2- Chemical, Pharmacological Aspects of Natural Products with Medicinal and Nutritive Value.

2001-053-2- Fundamental Toxicology for Chemists.*

2001-058-1- Concepts and Structure for Requests in Clinical Laboratories.

2001-066-1- Global Use of the C-NPU Concept System for Properties in Toxicology.

2001-067-1- Properties and Units for Function Examinations.

2001-068-1- Properties and Units in Medical Molecular Biology.

2001-070-1- Properties and Units for Urinary Calculi.

2001-001-1- Compendium of Terms Associated With Drug Discovery and Development.

2002-051-1- Analogue-Based Drug Discovery.

2003-001-2- Explanatory Dictionary of Concepts in Toxicokinetics.

2003-028-1- Glossary for Chemists of Terms Used in Toxicology: Revision and Updating.

2003-044-1- Glossary of Terms Used in Combinatorial Chemistry.

2003-059-1- Quantifying the Effects of Compound Combinations.

2004-019-3- Glossary of Terms Used in Biomolecular Screening.

2004-023-1- Internationally Agreed Terminology for Observations in Scientific Communication.*

2004-025-1- Compendium of Targets of the Top 100 Commercially Important Drugs.

2004-028-1- Practical Studies for Medicinal Chemistry: An Integrating Approach for Developing Countries.

* Denotes Interdivisional Project. In this regard, Division VII also participates on projects 2001-005-1-300 (Post-genomic Chemistry) and 2001-020-1-300 (Glossary of Terms and Basic Protocols Used in Photodynamic Therapy).

Projects Undergoing Review

2001-069-1- C-NPU Concepts and Traceability of Measurements.

2003-016-1- Integrating Environmental Exposure Pathways for Medicinal Products.*

2004-020-1- Molecular Gastronomy.*

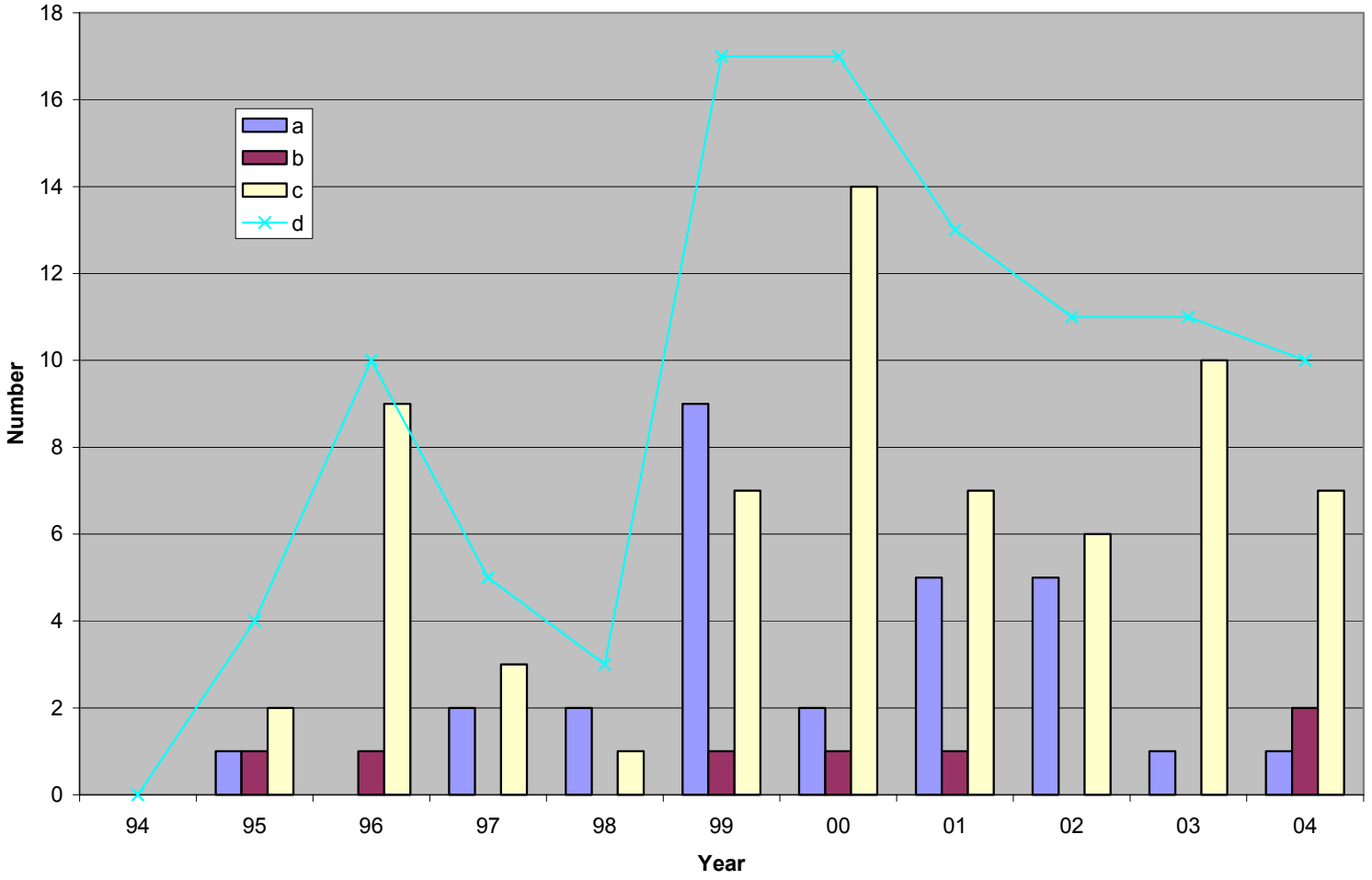
*Denotes potential Interdivisional Project.

-end of report to the IUPAC-

Item 10. Miscellaneous activities undertaken by the CD3 during 2003-2004.

- NIH Grants Study Section Member: *SBIR Program Drug Design & Development*. Meetings are scheduled twice per year, generally in the Washington, D.C. area (my own schedule typically limits my attendance to one meeting per year – participated in the November meeting again during this report period).
- U.S. Army Research Grants Review Panel Member: *Prostate Cancer Research*. Attended session in April (Washington, D.C. area).
- Chair of two IUPAC Working Parties for the Medicinal Chemistry Sub-section: *Metabolism Terms*; and, *Human Drug Metabolism Database*. Meetings are scheduled twice per year, generally in conjunction with an international scientific meeting (my own schedule typically limits my attendance to one meeting per year but this time I was able to participate in the Ottawa and Anaheim meetings during this report period).
- Assumed Presidency of the IUPAC's Chemistry and Human Health Division (#VII) at the December Division meeting in London.
- Participated on the AACP's Committee to select the next winner of the Paul Dawson Biotechnology Award.
- *Academic Outreach Committee* member for the Society of Biomolecular Screening (SBS). In addition to numerous conference calls, meetings are once per year in conjunction with their annual international conference.
- Provide manuscript reviews for a variety of journals at an average rate of two per quarter; Book reviews at rate of one per year.
- Continued orchestration of the CD3's operating plan throughout UT and the Northwest Ohio Community by numerous informal meetings. Expansion of the CD3's network to the international level is also effected via chairmanship of two IUPAC International Working Parties (see above) and presentation of National-level invited lectures. For the latter, expenses were reimbursed by third parties.
- Continued the *Centers' Stage* newsletter which is published jointly with the Center for Applied Pharmacology (**CAP**) in order to promote the operation of both Centers and UT research in general.
- Continued to develop and implement the Biopharmaceutical Analysis Research Laboratory (**BARL**) as a core resource on behalf of the entire College.
- Continued to develop and implement a Biological Testing core Resource (**BTR**) in the area of oncology research on behalf of the entire University. Several faculty from the UT Chemistry Dept. and from the Bowling Green Biology Dept. as well as from our own College, have already begun to refer to this resource within their grant submissions.
- Continued to develop and implement a Bioinformatics Resource (**BR**) for the entire College.
- Provided chemical synthesis and analytical support to move promising Coll. Pharmacy technology forward, e.g. potential Alzheimer treatment being developed by W. Messer et al.
- Provided chemical synthesis and analytical support to move promising UT/MCO technology forward via contract.
- Continue to develop and implement a core resource in peptide and peptidomimetic chemistry (**PMC**).
- Assisted the UT Office of Research in its prosecution of patent applications derived from studies conducted by the CD3.
- Note that because of the CD3's networking activities within these types of voluntary organizations as well as within the private sector, the Director was able to procure approximately $600,000.00 of expensive paclitaxel-related chemicals for our research at a total cost of less that $3,000.00.

Item 11. Papers, patents and presentations produced over the last 10 years.



a = Papers.
b = Patents.
c = Presentations.

- Blue line = Total (a + b + c).
- 95 'a' and 'b', and 96 'b' reflect work conducted prior to arrival at UT.