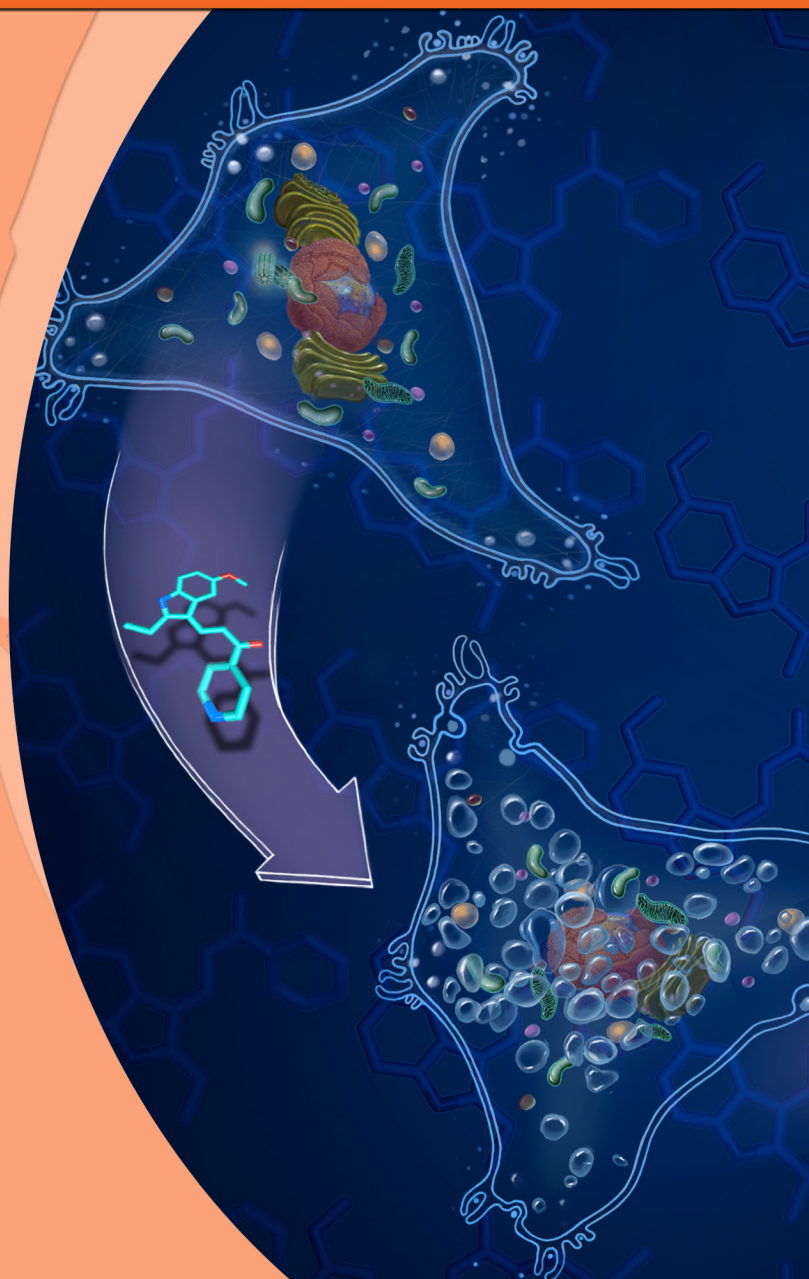
The University of Toledo College of Pharmacy and Pharmaceutical Sciences welcomes you to the celebration of Distinguished University Professor Paul Erhardt's 20th anniversary of leadership of the Center for Drug Design and Development (CD3).

Research Symposium

Center for Drug Design and Development

June 22, 2014



COLLEGE OF PHARMACY AND PHARMACEUTICAL SCIENCES
THE UNIVERSITY OF TOLEDO

Dear Colleagues, friends, and supporters of the CD3:

I am writing to note with pleasure the 20th anniversary celebration of the Center for Drug Design and Development (CD3) under the leadership of Dr. Paul W. Erhardt. He is the Director of CD3, professor of medicinal and biological chemistry, and a joint professor of biochemistry and cancer biology. This is a momentous milestone for a most important component of the College of Pharmacy and Pharmaceutical Sciences, significant because of the splendid history of the CD3 under the leadership of Dr. Erhardt.

It is a history that includes the training of learners: from high school students seeking direction in selecting a course of study to bachelor's, master's and PhD students enjoying the breadth of degree offerings of the magnificent University of Toledo (UT) and conducting research. Dr. Erhardt has mentored more than 40 undergraduate and graduate students as well as 14 postdoctoral fellows and six sabbatical visitors.

This marvelous history includes discoveries that have enthralled researchers, attracted extramural funding and shown to all the leadership and research direction skills of Dr. Paul Erhardt. This legacy of achievement was recognized in 2012 when he was named a Distinguished University Professor. The path to this status was laid through his many accomplishments. He received the Outstanding Research Faculty Award in 2004 and 2006, the Excellence Award for Research in 2009 and 2010, and the Outstanding Faculty Teaching Award in 1995. In addition to being a contributing member of UT service activities, Dr. Erhardt travels the world for lectures, presentations and conferences.

Just one example of the impact of his research is a patent issued for a compound that he synthesized. It is marketed as Brevibloc® (USAN: Esmolol Hydrochloride), the injection form of which is indicated for the rapid control of ventricular rate in perioperative and postoperative patients with atrial fibrillation or atrial flutter.

When one considers the impact of Dr. Paul W. Erhardt, it moves one to ask what manner of man could be so impactful in so many ways for such a long time. Who could touch so many learners in his laboratory? Who could improve the human condition through compounds synthesized in his laboratory? The University of Toledo and mankind are significantly advantaged by the ongoing work and career of Dr. Erhardt.

In awe of this giant in the world of research, I remain.

Very truly yours,

Johnnie L. Early, II, PhD, RPh
Dean and Professor

College of Pharmacy and Pharmaceutical Sciences
Office of the Dean • Mail Stop 1013 • 3000 Arlington Ave. • Toledo, OH 43614
Phone: 419.383.1997 • Fax: 419.383.1907 • www.utoledo.edu/pharmacy

Donors

The organizers of this symposium, along with the Center for Drug Design and Development, the Department of Medicinal and Biological Chemistry and The University of Toledo College of Pharmacy and Pharmaceutical Sciences, express our sincere gratitude to our sponsors for their generous donations to this celebration of excellence.

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Welcome

Welcome to The University of Toledo and a celebration of the 20th anniversary of Dr. Paul Erhardt's directorship of the Center for Drug Design and Development or, as we say in the college, CD3. During Dr. Erhardt's tenure as Director of CD3, there have been many noteworthy accomplishments. Dr. Erhardt has extended the avenues of research beyond traditional resources, such as the National Institute of Health, to include the U.S. Department of Defense, the U.S. Department of Agriculture, and the pharmaceutical industry.

Dr. Erhardt was the first faculty member in the College of Pharmacy and Pharmaceutical Sciences to obtain a Susan B. Komen award for cancer research. He has honored this commitment from the Komen Foundation by faithfully leading teams of walkers in the annual walk to defeat breast cancer. The team he assembled last year earned an award for the largest team to participate in the walk. Dr. Erhardt's graduate students, all of whom worked in the CD3 on their research projects, now occupy positions in industry or academia.

A number of undergraduate and graduate students and postdoctoral fellows who were involved in CD3 research, as well as visiting faculty members, submitted highly complimentary letters supporting his nomination for Distinguished University Professor status. He was named a Distinguished Professor of Medical Chemistry in 2012. These letters of support attest to the impact of his guidance and support in the direction of their professional careers. Please join me in this celebration of Dr. Erhardt's career achievements at The University of Toledo.

Marcia F. McInerney, Ph.D.
Distinguished University Professor of Medicinal and Biological Chemistry
Associate Dean for Research and Graduate Studies
College of Pharmacy and Pharmaceutical Sciences
The University of Toledo

As Chair of the Department of Medicinal and Biological Chemistry, I would like to extend a sincere welcome to all of you who are helping us celebrate the 20th anniversary of Paul Erhardt and the UT Center for Drug Design and Development (CD3). Back in 1994, the Center occupied a small lab in University Hall, the oldest building on Main Campus, built in 1931. After Dr. Erhardt took over as director, the Center gradually expanded, first moving to Wolfe Hall on the Main Campus and then expanding to occupy space in both Wolfe Hall and the Wolfe Center on the Health Science Campus. During that time, Paul has mentored a large number of undergraduate research students, graduate students, and postdoctoral researchers, as well as sabbatical faculty, visiting summer students, and high school students. He has also trained graduate students throughout the Department and University in industry standards, intellectual property, and good laboratory practices. The Department is grateful for his many contributions. I am happy that many of these CD3 alumni and friends are able to join us for this celebration.

We are honored to have a highly distinguished panel of speakers who will enlighten us further regarding the advances and opportunities in Medicinal Chemistry happening today. I hope that many of you will be able to stay for the 47th Annual Mid-Atlantic Graduate Student Symposium (MAGSS) in Medicinal Chemistry, which will follow this Symposium. Again, welcome to The University of Toledo, and enjoy the celebration.

Katherine Wall, Ph.D.
Professor and Chair
Medicinal and Biological Chemistry
College of Pharmacy and Pharmaceutical Sciences
The University of Toledo

CD3's Anniversary Celebration

Reflections from Dr. Paul W. Erhardt

Because I've served as Director of the Center for Drug Design and Development (CD3) over the last twenty years, I was asked to provide a few words of personal reflection for this very special occasion. Wondering *"has it really been that long?"* the first thing that came to mind and still maintains the most prominent image is the adage *"time flies when you're having fun."* For really not being a morning person any more than the average of us, what else could routinely pop me out of bed at 4 a.m. other than a true desire to charge into a new day when the prior one had seemingly just left off? Certainly contributing to this feeling has been my own all-encompassing fascination for the science of medicinal chemistry, a science where the intriguing relationships between its beautiful chemical structures and their biological properties are oftentimes applicable toward potentially alleviating some health issue being experienced by people less fortunate than I. Even more than that, however, has been my very privileged exposure to a constant flow of wonderful collaborators and highly talented students across all of these years. In particular, the students' eagerness to tackle this same discipline has always been refreshing and, in turn, has served to continually inspire me.

The CD3 itself constitutes the stew pot in which all of these ingredients come together to create a dish that is far greater than just the sum. Addressing technical problems in teamwork fashion, the CD3's constituencies have always been supportive and have rallied to get the job done. Our numbers of patents, papers and graduate thesis documents provide solid testimonials to that, and we can all be very proud for such accomplishments. Furthermore, the camaraderie established when tackling this complex field has brought us together like a close-knit family, vibrant with each generation of new student members arriving as our matured graduates depart. Thus, in the end, it has been and will always be the CD3's people that make the CD3 so very special in its productivity and fun.

In retrospect, we have worked hard together and we have played hard together, both ultimately being driven by a desire to do something positive by deploying medicinal chemistry for the sake of the common good. Since *"a picture is* [often] *worth a thousand words",* I offer the two below as a cap to my reflections. The first shows the CD3's 'Soybean Harvest Team' gearing up to work in the field to collect infected plants as a source for a unique family of natural product compounds having potential to treat breast and prostate cancers. The second reflects 'Team CD3' playfully gearing up for the annual Susan G. Komen 'Race for the [breast cancer] Cure' held in Toledo, where in that particular year our 'family' ultimately went-on to win two types of team participant awards.

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Dr. Paul W. Erhardt

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100 Glendale Avenue, Toledo, OH 43614 | 419-381-6800

8:30-9:00 am	Continental Breakfast
9:00 am -9:30 am	Opening Ceremony Johnnie Early, PhD Dean, UT College of Pharmacy and Pharmaceutical Sciences Wayne Hoss, PhD Professor Emeritus of Pharmacology and Former Executive Associate Dean of the UT College of Pharmacy and Pharmaceutical Sciences Katherine Wall, PhD Professor and Chair, Department of Medicinal and Biological Chemistry, UT College of Pharmacy and Pharmaceutical Sciences Marcia McInerney, PhD Associate Dean for Research and Graduate Programs Distinguished University Professor of Medicinal Chemistry, UT College of Pharmacy and Pharmaceutical Sciences
Session 1	Current Research at the CD3 Session Chair: Marcia McInerney, PhD
9:30 am – 10:10 am	William Anthony Maltese, PhD Professor and Chairman The University of Toledo, Department of Biochemistry and Cancer Biology *"Methuosis: A Novel Form of Death Induced in Brain Cancer Cells by Indole-Based Chalcones"*
10:10 am – 10:50 am	Christopher Trabbic, PhD Postdoctoral Fellow The University of Toledo, Center for Drug Design and Development *"Subtle Chemical Substitutions on Indolyl-pyridinylpropenones Reveal Diverse Mechanisms of Cytotoxicity in Glioblastoma Cells"*
10:50 am – 11:05 am	Coffee Break

11:05 am – 11:45 am	Jeffrey Sarver, PhD Research Associate Professor The University of Toledo, Center for Drug Design and Development *"In Vitro and In Vivo Metabolism of Selected Indole-Based Chalcone Structures"*
11:45 am – 12:05 pm	Brian Kress, BSPS Graduate Student The University of Toledo, Center for Drug Design and Development "*Selective N-acylation of Glucosamine"*
12:05 pm – 12:30 pm	Duane Mancini, BSPS Graduate Student The University of Toledo, Center for Drug Design and Development *"Kilogram Scale Synthesis of Amphiphiles"*
12:30 pm – 1:30 pm	Lunch
Session 2	Where are they now? Session Chair: Viranga Tillekeratne, PhD The University of Toledo, Professor of Medicinal and Biological Chemistry Department of Medicinal and Biological Chemistry
1:30pm – 2:00 pm	Yasser Heakal, PhD, MBA, RPh Assistant Professor of Pharmacology Department of Pharmaceutical Sciences D'Youville School of Pharmacy *"Toll-like Receptor 2 in Breast Cancer: Friend or Foe?"*
2:00 pm – 2:30 pm	Rahul Khupse, PhD Assistant Professor The University of Findlay Department of Pharmaceutical Sciences *"Diverse Uses of Glucosamine Analogues and New Anticancer Chalcones "*
2:30 pm – 2:45 pm	Coffee Break
Session 3	Plenary Lectures Session Chair: Christopher Trabbic, PhD

2:45 pm – 3:45 pm	Gunda Georg, PhD Professor and Head, Medicinal Chemistry Robert Vince Endowed Chair McKnight Presidential Chair in Medicinal Chemistry Director - Institute for Therapeutics Discovery & Development *"Drug Discovery in Academia: Minnelide for Pancreatic Cancer and Gamendazole for Male Contraception"*
3:45 pm – 4:45 pm	Christopher A Lipinski, Ph.D Consultant Scientific Advisor, Melior Discovery *"Thoughts on Drug Discovery"*
4:45 pm	Closing Remarks
3:00 pm - 5:30 pm	Registration: Mid-Atlantic Graduate Student Symposium (MAGSS)
6:30 pm	CD3-MAGSS Gala Dinner Master of Ceremonies: Kenneth Bachmann, PhD Co-Founder and Vice President for Pharmacoinformatics CeutiCare, LLC The University of Toledo, Distinguished University Professor of Pharmacology Mistress of Ceremonies: Amanda Bryant-Friedrich, PhD The University of Toledo, Associate Professor of Medicinal and Biological Chemistry Department of Medicinal and Biological Chemistry Remarks Norm Billups, PhD Dean Emeritus, UT College of Pharmacy and Pharmaceutical Sciences Gala Speaker: Mukund Chorghade, PhD Chief Scientific Officer, THINQ Pharma *"Fascinating Excursions into Chiral Chemistry: An Insider's Perspective"*

Speakers

Mukund S. Chorghade, Ph.D.

Dr. Mukund Chorghade is President of Chorghade Enterprises and Chief Scientific Officer, THINQ Pharma / THINQ Discovery, AGN Biofuels and Empiriko. He is also an adjunct research professor at Northeastern University and has appointments at Harvard and MIT. He provides synthetic chemistry and development expertise to pharmaceutical and biopharmaceutical companies. He also provides consultations on collaborations with academic, government and industrial laboratories. He advises technology based companies on process re-engineering and project management of technology transfer; establishes strategic partnerships and conducts cGLP/cGMP compliance training and implementation in chemical laboratories. He oversees projects in medicinal chemistry, chemical route selection, manufacturing and formulation of bulk actives to finished dosage forms.

Dr. Chorghade earned his B. Sc. and M. Sc. degrees from the University of Poona, and a Ph. D. in organic chemistry at Georgetown University. He completed postdoctoral appointments at the University of Virginia and Harvard University, visiting scientist appointments at University of British Columbia, College de France / Universite' Louis Pasteur, Cambridge and Caltech and directed research groups at Dow Chemicals, Abbott Laboratories, CytoMed and Genzyme. A recipient of three "Scientist of the Year Awards", he is an elected Fellow of the ACS, AAAS and RSC and has been a featured speaker in several national and international symposia. He is active in ACS, AAAS, RSC, was NESACS and Brazosport Section Chair and serves on numerous professional Scientific Advisory Boards and Committees.

Gunda I. Georg, Ph.D.

Dr. Georg is Professor and Head of the Department of Medicinal Chemistry and the founding Director of the Institute for Therapeutics Discovery and Development (ITDD) at the University of Minnesota College of Pharmacy. She holds the Robert Vince Endowed Chair and the McKnight Presidential Chair in Medicinal Chemistry. She is the Co-Editor-in-Chief for the Journal of Medicinal Chemistry, the most cited journal in the field. She is an AAAS Fellow, a Fellow of the American

Chemical Society, and has received the Ernest H. Volwiler Research Achievement Award of the American Association of Colleges of Pharmacy, the Sato Memorial International Award of the Pharmaceutical Society of Japan, the University of Minnesota Academy for Excellence in Health Research, and others.

Dr. Georg received a BS in pharmacy (1975) and a PhD degree in medicinal chemistry (1980) from Philipps University in Marburg, Germany. She was a postdoctoral fellow in the Department of Chemistry at the University of Ottawa in Canada. After 22 years as a faculty member at the University of Kansas she joined the University of Minnesota in 2007. Her research focuses on the design, synthesis, and evaluation of biologically active agents. Current major therapeutic areas are focused on cancer and male contraception. These projects require the development of synthetic methods, semi-synthesis and total synthesis of natural products, and structure-activity studies aimed at improving the therapeutic efficacy of lead compounds, including natural products, and hits from high throughput screening. She has published more than 195 papers and book chapters on various aspects of synthetic medicinal chemistry. She is a co-inventor of the drug, Lusedra@, a water-soluble analogue of the anesthetic propofol, that was marketed by Esai Pharmaceuticals in 2009. She is also the co-inventor of Minnelide an anticancer agent that has been licensed to a company and that is in phase I clinical trial (since 2013). Gamendazole, a male contraceptive agent, discovered by Dr. Georg and collaborators, is in preclinical development and expected to enter clinical trial in 2014. Dr. Georg's research has been funded mainly by the National Institutes of Health. She is the leader of a group of Minnesota faculty that was selected for a leading role in the National Cancer Institute's Chemical Biology Consortium, a collaborative drug discovery partnership focused on discovering and developing new drugs to fight cancer. She also leads a NIH-supported UO1 research program (2012-2017) and a major NIH Research contract (2013-2018) to discover non-hormonal contraceptive agents. This project involves the collaboration with 9 research groups from the University of Kansas, the Moffitt Cancer Center, Columbia University, Harvard Medical School, Baylor, and others. At the University of Kansas she was the PI of a state-wide NIH-funded Center for Cancer Experimental Therapeutics (Center of Biomedical Research Excellence = COBRE).

Dr. Georg has trained more than 100 PhD and post-doctoral students, most of whom have pursued careers in the pharmaceutical industry. She is actively involved in professional organizations including the American Chemical Society. She has served for many years as grant

reviewer on NIH study sections, for the NSF, AAAS, foundations and universities. She is a member of advisory boards for several scientific journals.

Christopher Lipinski, Ph.D.

Dr. Christopher Lipinski enjoyed a thirty-two year career at Pfizer in Groton, CT from which he retired in 2002 at the most senior scientific position. He is currently a Scientific Advisor to Melior Discovery, a drug repurposing startup located in Exton, PA and carries out his medicinal chemistry consulting through Christopher A. Lipinski, Ph.D., LLC located in Waterford, CT. Dr. Lipinski served on the scientific advisory board for academic drug discovery at the Center for Drug Discovery and Development at The University of Leuven, Belgium. He has been a conference committee member for the annual MipTec, The Leading European Event for Drug Discovery held in Basel, Switzerland. He is a member of the American Chemical Society (ACS) and the American Association of Pharmaceutical Sciences (AAPS). He is the author of the "rule of five" a widely used filter to select for acceptable drug oral absorption and now with over 6,000 citations is the most highly cited paper in medicinal chemistry drug discovery.

Chris is a member of the ACS "Medicinal Chemistry Hall of Fame". In 2006 he received an honorary law degree from the University of Dundee and won the Society of Biomolecular Sciences Achievement Award. In 2005 he won the ACS E. B. Hershberg Award for Important Discoveries in Medicinally Active Substances and in 2004 won the ACS Division of Medicinal Chemistry Award. An adjunct faculty member in Biochemistry at the University of Massachusetts Amherst, Chris has over 285 publications and invited presentations and 19 issued US patents. He can be contacted at clipinski@meliordiscovery.com.

OncoRx Pharmaceuticals, Inc.

Thioridazine (Mellaril®) is a highly potent dopamine receptor D_2 antagonist having a phenothiazine chemical structure. Thioridazine, a commonly prescribed antipsychotic drug for controlling the symptoms of schizophrenia for over 40 years, was withdrawn from the worldwide market due its serious risk of cardiotoxicity. In addition to its effectiveness as an antipsychotic, thioridazine has demonstrated extraordinary *in vitro* efficacy in the control of drug-resistant tumors, their cancer stem cell subpopulations, and the inhibition of the P-glycoprotein drug transporter that is responsible for the efflux of drugs from tumor cells. Unlike most chemotherapeutic drugs and targeted kinase inhibitors that are regularly used in cancer therapy, phenothiazines such as thioridazine distribute equally to brain tissue and plasma after administration. This provides a considerable advantage over the new generation of targeted therapeutics whose anticancer potential is limited to drug-sensitive tumors that reside outside of the brain. Unfortunately, thioridazine (Mellaril®) was withdrawn because it produces abnormal ventricular repolarization in patients and increases the risk of *torsade de pointes* and cardiac sudden death at clinically relevant plasma concentrations.

In July, 2000, the FDA issued a black box warning to inform physicians that thioridazine (Mellaril®) was shown to prolong the QT interval during repolarization of the heart in a dose related manner. In 2001, it was reported that the typical phenothiazine antipsychotic drugs such as thioridazine cause sudden cardiac death in a dose related manner. In June, 2004 the FDA announced that there is a qualitative relationship between QT prolongation and the risk of *torsade de pointes*. In 2005, thioridazine (Mellaril®) was withdrawn from the worldwide market due to concerns that thioridazine causes increased risk of *torsade de pointes*-type cardiac arrhythmias and sudden cardiac death.

Responding to the need for a safer noncardiotoxic version of thioridazine, we initiated development of our proprietary analog of thioridazine (BG-7862) in May of 2012 for the treatment and control of resistant tumors in metastatic and triple-negative breast cancers, metastatic melanoma, glioblastoma and pancreatic cancer. Our initial research studies have been performed in collaboration with Dr. Paul Erhardt, Distinguished Professor and Director of the Center for Drug Design and Development (CD3) at the University of Toledo, and Dr. Max S. Wicha, Distinguished Professor of Oncology and Director, University of Michigan Comprehensive Cancer Center.

Our preclinical research studies have demonstrated that our proprietary analog of thioridazine (BG-7862) is as effective as thioridazine in controlling the growth of inflammatory and triple-negative breast tumors, metastatic melanoma tumors and the cancer stem populations of each type of tumor. We have completed a number of *in vitro* cytotoxicity studies, a pharmacokinetic study in mice, a hERG binding cardiotoxicity study and a number of studies in our metastatic tumor model which examines the morphological and compositional changes that occur after inducing the epithelial-to-mesenchymal transition. Our hERG studies have demonstrated that BG-7862 has a low risk of causing QT interval prolongation during repolarization of the heart; an important advantage over the use of thioridazine. Currently we are conducting xenograft studies in mice using triple-negative breast and metastatic melanoma tumors carrying the $BRAF^{V600E}$ mutation to evaluate our drug's ability to reduce the subpopulation of self-renewing cancer cells in these tumors.

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Dinner Program

Welcome Remarks

Master of Ceremonies: Kenneth Bachmann, PhD
Co-Founder and Vice President for Pharmacoinformatics, CeutiCare, LLC
The University of Toledo, Distinguished University Professor Emeritus of Pharmacology

Mistress of Ceremonies: Amanda Bryant-Friedrich, PhD
The University of Toledo, Associate Professor of Medicinal and Biological Chemistry
Department of Medicinal and Biological Chemistry

Remarks

Norm Billups, PhD
Dean Emeritus, The University of Toledo College of Pharmacy and Pharmaceutical Sciences

Toast

Kenneth Bachmann, PhD

Interdenominational Blessing

Dr. Channing Hinman
Professor Emeritus of The Department of Medicinal and Biological Chemistry

Dinner

Introduction of the Speaker

Amanda Bryant-Friedrich

Gala Speaker: Mukund Chorghade, PhD
Chief Scientific Officer, THINQ Pharma

"Fascinating Excursions into Chiral Chemistry: An Insider's Perspective"

Dessert

Presentations and Remarks

Paul Erhardt, PhD
Distinguished University Professor of Medicinal and Biological Chemistry and Director of The University of Toledo Center for Drug Design and Development

Announcements

Acknowledgments

As the organizers of the 20th Anniversary Celebration for the Center of Drug Design and Development under the direction of Distinguished University Professor Paul Erhardt, we thank you for joining us in this celebration of excellence. It has been our pleasure to get to know those who have worked with, trained through or supported the Center over the years.

We would like to acknowledge the support of the wonderful staff members of the College of Pharmacy and Pharmaceutical Sciences at The University of Toledo in making this event a success. Without Charisse Montgomery, Donna Haar, Cynthia Soncrant, Linda McPherson, Holly Helminski and Kwabena Kankam, many things would have been left unattended. We also wish to acknowledge those who financially sponsored this event. Your support was vital. We hope that you will never be strangers to the CD3, and we hope to see you on campus again in the near future.

Sincerely,

Amanda Bryant-Friedrich and Viranga Tillekeratne
Co-organizers