Published in final edited form as:
Pharmacogenomics. 2013 September ; 14(12): 1383–1387. doi:10.2217/pgs.13.134.

University of Chicago Center for Personalized Therapeutics: research, education and implementation science

M Eileen Dolan[1,*], **Michael L Maitland**[1], **Peter H O'Donnell**[1], **Yusuke Nakamura**[1], **Nancy J Cox**[1], and **Mark J Ratain**[1]

[1]Committee on Clinical Pharmacology & Pharmacogenomics, 900 E 57th Street, KCBD 7100, University of Chicago, Chicago, IL 60637, USA

Abstract

Pharmacogenomics is aimed at advancing our knowledge of the genetic basis of variable drug response. The Center for Personalized Therapeutics within the University of Chicago comprises basic, translational and clinical research as well as education including undergraduate, graduate, medical students, clinical/postdoctoral fellows and faculty. The Committee on Clinical Pharmacology and Pharmacogenomics is the educational arm of the Center aimed at training clinical and postdoctoral fellows in translational pharmacology and pharmacogenomics. Research runs the gamut from basic discovery and functional studies to pharmacogenomic implementation studies to evaluate physician adoption of genetic medicine. The mission of the Center is to facilitate research, education and implementation of pharmacogenomics to realize the true potential of personalized medicine and improve the lives of patients.

Pharmacogenomics is a field that studies the role of genomic variation in drug response with the goal to personalize pharmacological treatment strategies that maximize the potential for therapeutic benefit, while minimizing the risk of toxicity. Studies range from discovery of genetic variants associated with drug response to clinical implementation of variants that impact patient care. The potential for cost savings through increased drug efficacy is great, particularly as we embark on changes in healthcare. Technological advances in DNA sequencing and polymorphism characterization have moved the field from a hypothesis-driven approach to a discovery-oriented, genome-wide approach with little bias regarding which variants are most relevant for outcome.

The University of Chicago (IL, USA), founded in 1891, was organized from the beginning around the principle that progress in solving the most challenging of problems could be achieved only through multidisciplinary approaches. The leadership, overall composition and strategic research plan around pharmacogenomics reflect this overarching principle. A

Tel.: +1 773 702 4441, Fax: +1 773 702 9268, edolan@medicine.bsd.uchicago.edu.

Financial & competing interests disclosure
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

major asset to coalesce pharmacogenomics research and education at the University of Chicago is the Center for Personalized Therapeutics (CPT).

Mission & scope of the Center for Personalized Therapeutics

The CPT is an integral and highly visible component of the University of Chicago that includes both academic (Biological Sciences Division [BSD]) and service (University of Chicago Medicine [UCMC]) units. Working directly with UCMC facilitates patient-oriented research activities and is important to eventually provide billable clinical services in personalized therapeutics. The CPT's service unit includes an outpatient clinic and an inpatient consultative service. Mark Ratain, the Director, reports to the Dean of the BSD and the President of UCMC. The CPT's academic unit spans the entire range of pharmacogenomic research, including pharmacology, genomics, informatics, clinical validation, clinical implementation, outcomes and public policy.

Although the University does not have a School of Pharmacy, strength in the genomics aspect of pharmacogenomics comes from the combination of well-respected geneticists within the Section of Genetic Medicine housed within the Department of Medicine and the Department of Human Genetics. Clinicians and scientists with expertise in pharmacology, clinical trial design and new drug development are appointed in multiple clinical Departments (e.g., Medicine and Pediatrics), as well as the Departments of Health Studies and Pathology. In addition to collaboration with departments, CPT interfaces and collaborates with the Committee on Clinical Pharmacology and Pharmacogenomics (CCPP); the Comprehensive Cancer Center; the Center for Health and the Social Sciences; the Center for Clinical Medical Ethics; and the Institute for Genomics and Systems Biology. CPT brings many of these experts together in efforts to advance basic, translational and clinical research. Furthermore, the future vitality of the CPT depends on the successful development of its junior faculty. One function of CPT is to train the next generation of investigators in a robust manner that will ensure their future success. Therefore, CPT works to assist junior faculty in obtaining independent funding.

Interaction with CCPP

The focus of the CCPP, chaired by Eileen Dolan, is training, primarily of post graduates, in clinical pharmacology and pharmacogenomics [101]. The trainees are supported by grants (including National Institute of General Medical Sciences [NIGMS] funding specifically for clinical pharmacology), an industry fellowship, or support from the BSD and Comprehensive Cancer Center. The fellows can receive accreditation by the American Board of Clinical Pharmacology. Clinical and basic laboratory mentors provide most of the training through fellows' conduct of postdoctoral projects in: pharmacogenomics, drug development, clinical pharmacology, genetics of drug abuse and clinical trial design. We complement the research training with a core didactic program supported by our faculty and the Institute for Translational Medicine/Clinical and Translational Science Awards Program. Some fellows also complete elective coursework related to their specific interests and Nancy Cox, Section Chief of Genetic Medicine teaches an ongoing course in 'Genetics and

Genomics in Grant Writing'. Most fellows are then prepared to begin a career in academics, industry or government with the vast majority in academic positions.

The CCPP draws faculty from diverse departments across the institution. This provides an environment for the exchange of ideas and sharing of resources across disciplines. Faculty interact through conferences and teaching activities of CCPP. The CCPP faculty has expertise in many areas of collaborative research. The establishment and expansion of these collaborations has been a wellspring for training fellows in the broad applications of clinical pharmacology and pharmacogenomics, and providing them with the independence to take promising projects with them into junior faculty positions.

The traditional fellowship is 2 years, during which trainees are exposed to leading edge genomic technology, research, innovative comprehensive didactics and teaching experience. In addition, fellows learn by performing service for the BSD institutional review board, the Hospital Pharmacy and Therapeutics Committee, and the inpatient Clinical Pharmacology consultation team. This clinical exposure has been especially appealing for nonphysicians seeking better understanding of opportunities and obstacles in translational and clinical research.

The CCPP has longstanding experience overlapping joint training with other medical subspecialty or residency programs. The Associate Director for our training grant, Michael Maitland, has coordinated with our Hematology–Oncology fellowship leaders to offer joint training for Clinical Therapeutics in Oncology. This track is a 4-year program combining comprehensive fellowship training in the Section of Hematology/Oncology, Department of Medicine and in Clinical Pharmacology and Pharmacogenomics. Fellows can be accredited in Hematology, Oncology and/or in Clinical Pharmacology. Trainees completing this program develop expertise in cancer pharmacology and pharmacogenomics. This track is intended for physicians seeking a career in the field of clinical pharmacology in oncology. Lastly, there is a 2-year Clinical Therapeutics in Industry Fellowship track that consolidates the didactic and service elements of the academic clinical pharmacology and pharmacogenomics training in the first year, so that the second year of training is primarily in an industry setting. Although the trainees are expected to become board-certified in Clinical Pharmacology, the focus of the program is to build a skill set suitable for a career in industry.

Didactic education within the CCPP

A popular course among fellows, but also open to graduate students and upper level undergraduates with completed coursework in genetics, is 'Pharmacogenomics'. The objectives of the course are to expose the students to the basic principles of pharmacology, genomics, statistics and pharmacogenomics. The ethics and economics of pharmacogenomics are also discussed. A workshop on performing genome-wide association studies as well as problem sets to test student's knowledge of performing these types of analysis is included. To stimulate the students' interest in the diversity of opinion in this field, they participate in a debate on different topics, such as gene patenting or direct to consumer genotyping. The students are required to write a grant proposal in the area of

pharmacogenomics providing them with practical experience along with an opportunity to present the proposal to the class and defend their approach. Instructors are involved in several iterations of the proposal to help students formulate testable hypotheses and consider alternative approaches and ultimately to write a grant proposal. The intention of the class is to teach the 'how to' as opposed to 'what is' pharmacogenomic research. Therefore, much of the class is dedicated to: where to get pharmacogenomic information; how to utilize pharmacogenomic information to answer important research questions; and to learn what level of evidence is reasonable for implementation of genetic markers.

The 'Genetic Basis of Personalized Medicine' course brings in leading investigators to present different aspects of disease-related genetics/genomics and translational medicine to fellows and junior faculty. The course emphasizes research methods, study designs and analytical methods, and relevant clinical examples from varied medical fields. The bread and butter course for the fellows is entitled 'Advanced Clinical Pharmacology' that includes fundamental principles of the practice of clinical pharmacology relevant to drug development and personalized therapeutics. Topics covered in the course include pharmacokinetics, drug metabolism, protein binding, absorption, renal and hepatic elimination, pharmacodynamics, pharmacokinetic modeling methods, evaluation of adverse events, and preclinical and clinical components of drug development.

To gain experience in education, fellows participate as teaching assistants in 'Advanced Clinical Pharmacology and Therapeutics' a course offered to fourth-year medical students following completion of their clerkships. The course introduces basic concepts of clinical pharmacology and therapeutics. The fellows direct the students on cases that will improve understanding and management of practical problems in medicine and therapeutics. Lastly, the fellows are required to attend a weekly seminar series to provide intellectual discourse with faculty across disciplines. Traditional journal club format discussions are intermixed with research-in-progress talks, guest lecturers from the faculty within and outside the University and case reports. Fellows have the option of various additional courses relevant to their career development such as 'Introductory Statistical Genetics', 'Human Variation and Disease', 'Genomics and Systems Biology', 'Biostatistical Methods' and 'Introduction to Clinical Trials'.

Research within the Center for Personalized Therapeutics

An important goal of the CPT is to foster interaction between basic and clinical investigators, with a focus on discovery of pharmacogenomics markers that are evaluated in the context of clinical trials at all phases of drug development. This includes work in Phase I and II oncology clinical trials, as well as trials within large cooperative groups such as Alliance (a major cooperative group funded by the National Cancer Institute, MD, USA). The ultimate goal is to develop innovative, personalized and effective therapies for cancer patients. An important component of research within the Center is the Pharmacogenomics of Anticancer Agents Research (PAAR) Group, a group that has been NIH funded since 2000. Mark Ratain, Nancy Cox and Eileen Dolan colead this effort bringing in diverse backgrounds to enhance their ability to build pharmacogenomics within the Center.

The goals of PAAR are to discover and validate functional germline polymorphisms relevant to the pharmacokinetics and/or pharmacodynamics of anticancer agents [102]. In addition, PAAR investigators develop new methodologies and tools that are broadly applicable to pharmacogenomic and genomic researchers. Research includes preclinical models such as lymphoblastoid cell lines, hepatic microsomes, human neurons and cancer cell lines. One area of great interest is the development of cell-based models for pharmacogenomic discovery and functional studies. The utilization of lymphoblastoid cell lines, and more recently human neurons, has allowed the group to study cytotoxicity of cancer chemotherapeutics. Genetic variants identified in the lymphoblastoid cell lines have been found to validate in clinical trials and lymphoblastoid cell lines are used to functionally validate clinical discoveries [1,2].

In addition, researchers within the Center for Personalized Therapeutics work in the area of new drug development by using genomic research findings to identify new targets, leading to the development of antibodies, peptide vaccines, and small molecular compounds. The discovery of important genes in development and progression of cancers using genome-wide approaches has been used to develop new anticancer agents.

The 1200 Patients Project: clinical implementation of routine pharmacogenomic testing

Peter O'Donnell serves as principal investigator of The 1200 Patients Project, a large clinical study exploring the feasibility and benefit of incorporating broad pharmacogenomic testing into routine clinical practice for patients with any type of disease. The study of pharmacogenomics is complicated by the fact that response and toxicity are multigenic traits and are often confounded by nongenetic factors. Implementation of pharmacogenomics has been hampered by poor physician knowledge about important drug–gene relationships, limited avenues for testing, delays in the receipt of pharmacogenomic results even when testing is pursued and lack of guidelines to assist with interpretation of results. Some projects are ongoing to address gaps in knowledge and interpretation [3].

Our Center has developed its own unique program aimed at overcoming all of the above barriers to more widespread implementation of pharmacogenomics in routine practice: entitled The 1200 Patients Project. This institutional-wide clinical program offers pre-emptive, broad pharmacogenomic testing free of charge to patients (with individual patient results delivered to each patient's provider) thereby simultaneously achieving routine clinical availability of pharmacogenomic testing with instantaneously and repeatedly accessible results available for all tested variants for the remainder of the patient' lifetime [4]. The patient-specific results are available through a custom-designed web-based interface, the genomic prescribing system, which provides relevant pharmacogenomic guidance and consultations to participating providers at any clinical moment. Finally, from an implementation science standpoint, encounter-level data are being collected for thousands of visits at which such information is available and/or utilized in order to better understand how future programs and iterations of pharmacogenomic results delivery systems could be improved and expanded.

Future perspective

We have an active, vibrant, state of the art pharmacogenomics program at the University of Chicago. From a clinical standpoint, expansion of the availability of pre-emptive pharmacogenomic clinical testing for use in additional patients and patient populations is ongoing. From a basic science standpoint, we plan to build unique resources to discover and functionally validate pharmacogenomic markers in relevant tissue types using differentiated cells from induced pluripotent stem cells. In addition, we are introducing a new area called 'immunopharmacogenomics' that links the relationship between immune responses in patients and efficacy/toxicity of drugs. We plan to continue to forge new ground in analytical approaches to evaluating different populations and next-generation sequencing, particularly focused on ways to integrate omics data to enhance prediction of adverse events and outcomes of therapy.

Acknowledgments

The authors are grateful to M Domecki (administrator of CCPP) and D Stoit (administrator of CPT) for their hard work and organizational skills.

This work is supported in part by NIH grants: Clinical Therapeutics training grant T32 GM007019 (MJ Ratain). Other sources of funding for fellowships within Committee on Clinical Pharmacology and Pharmacogenomics include University of Chicago Cancer Research Foundation Women's Board, Division of Biological Sciences; and infrastructure and research within CPT is supported by the Conquer Cancer Foundation, the Pharmacogenomics of Anticancer Research Grant: U01 GM061393 (MJ Ratain, ME Dolan and NJ Cox) and NIH K23 GM100288 (PH O'Donnell). The authors are employees of the University of Chicago.

References

1. Stark AL, Dolan ME. Lymphoblastoid cell lines in pharmacogenomics: how applicable are they to clinical outcomes? Pharmacogenomics. 2013; 14(5):447–450. [PubMed: 23556440]
2. Cox NJ, Gamazon ER, Wheeler HE, Dolan ME. Clinical translation of cell-based pharmacogenomic discovery. Clin. Pharmacol. Ther. 2012; 92(4):425–427. [PubMed: 22910437]
3. Relling MV, Klein TE. CPIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. Clin. Pharmacol. Ther. 2011; 89(3):464–467. [PubMed: 21270786]
4. O'Donnell PH, Bush A, Spitz J, et al. The 1200 patients project: creating a new medical model system for clinical implementation of pharmacogenomics. Clin. Pharmacol. Ther. 2012; 92(4):446–449. [PubMed: 22929923]

Websites

101. Committee on Clinical Pharmacology and Pharmacogenomics. http://ccpp.bsd.uchicago.edu
102. Pharmacogenomics of Anticancer Agents Research Group. http://paarpharmacogenomics.org

Highlights

- The University of Chicago supports basic, translational and clinical research as well as undergraduate, graduate, medical students, clinical/postdoctoral fellows and faculty education in the area of pharmacogenomics.
- The Center for Personalized Therapeutics provides infrastructure to bring together the academic and patient-oriented research activities in personalized medicine.
- The Committee on Clinical Pharmacology and Pharmacogenomics is the educational arm of the Center and serves to train clinical and postdoctoral fellows with a structured program with various options to combine with other subspecialties or with industry experience.
- Coursework in pharmacogenomics, genetics of medicine, advanced clinical pharmacology as well as teaching experience and journal club help round out the didactic education for trainees.
- Pharmacogenomics of Anticancer Agents Research encompasses a large research program that runs the gamut of discovery of genetic markers through preclinical and clinical studies, analytical method development and pharmacogenomic clinical studies.