

The Origin and Development of the NIH Pharmacogenetics Research Network (PGRN)

From a Gleam in the Eye to
Graduation



1998 - 2020



Ronald Krauss, UCSF
and the last Chair of the NIH PGRN

PGRN – Fertilization (Workshop, 1998)

Understanding Individual Variations in Drug Responses: From Phenotype to Genotype

Location: NIH Campus, Bethesda, MD

Start Date: 6/9/1998 8:00 AM

End Date: 6/10/1998 4:30 PM

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- [Background](#)
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Executive Summary

The working group recommended that NIGMS stimulate research in the area of pharmacogenetics/pharmacogenomics by: 1.) soliciting grant applications to examine the fundamental mechanisms underlying individual variations in drug responses, and 2.) establishing a resource database of polymorphic variants for proteins known to be essential in determining individual responses to drugs. The group emphasized the importance of relating a phenotype for a drug response to a genotype, in order to determine the functionally important sequence variants.

PGRN - Conception (RFA, 1999)

PHARMACOGENETIC RESEARCH NETWORK AND DATABASE

Release Date: December 22, 1998

RFA: GM-99-004

National Institute of General Medical Sciences
National Heart, Lung, and Blood Institute
National Human Genome Research Institute
National Institute of Environmental Health Sciences
National Institute of Mental Health
National Institute on Alcohol Abuse and Alcoholism

Public Briefing Date: March 19, 1999

Letter of Intent Receipt Date: April 30, 1999

Application Receipt Date: July 27, 1999

PURPOSE

The purpose of this request for applications (RFA) is to stimulate formation of a network of Research Groups of investigators and development of a public Pharmacogenetic Database, which will become available to the scientific community for use as a research tool. The study of pharmacogenetics and pharmacogenomics presents opportunities to researchers working at levels ranging from the most molecular to the most clinical, in the fields of pharmacology, physiology, genetics, genomics, medicine, epidemiology, statistics, bioinformatics, and computational biology. It would be desirable to bring investigators with these backgrounds together in a research framework, so that functional variation in proteins and genes that play essential roles in determining drug responses can be studied, interpreted, and related to clinical research situations in a rapid and efficient manner.

PGRN Birth Announcement

First Awards Made in NIH Effort to Understand How Genes Affect People's Responses to Medicines

Tuesday, April 4, 2000, 12:00 p.m. EDT

Diet, environment, and lifestyle can all influence how a person responds to medicines--but another key factor is genes. The National Institute of General Medical Sciences, the National Institute of Environmental Health Sciences and other components of the National Institutes of Health are sponsoring a nationwide research effort to understand how a person's genetic make-up determines the way a medicine works in his or her body, as well as what side effects the person might be prone to developing.



"The outcome of pharmacogenetics research has the potential to improve the health of all Americans, by making the medicines of today and tomorrow safer and more effective for everyone," said Dr. Rochelle Long, a pharmacologist at NIGMS who spearheaded the pharmacogenetics initiative.



PGRN-I Getting to know each other



Pharmacogenetics Research Network and Knowledge Base
Second Scientific Meeting

MARCH 12, 2002

SPEAKERS
Russ Altman
Patrick Brown
Rebecca Eisenberg
David Flockhart
Kathleen Giacomini
Ronald Krauss
Julio Licinio
Howard McLeod
Prakash Nadkarni
Daniel O'Connor
Mark Ratain
Dan Roden
Mark Rothstein
Richard Weinsztein
Scott Weiss

SESSIONS
Keynote: Microarrays in Pharmacogenomic Studies
Keynote: Pharmacogenetics and Intellectual Property
Pharmacogenetic Studies of Enzymes and Transporters
Cardiovascular and Pulmonary Pharmacogenetics
Pharmacogenetic Studies in Ethnic Populations
Pharmacogenetics Knowledge Base
Cancer Pharmacogenetics

RESEARCH SPONSORS
National Institute of General Medical Sciences
National Heart, Lung, and Blood Institute
National Cancer Institute
National Human Genome Research Institute
National Institute of Environmental Health Sciences
National Library of Medicine

**FAIRCHILD AUDITORIUM
STANFORD UNIVERSITY**

To register go to:
<http://www.pharmgkb.org/2002/meeting/>



2002



Pharmacogenetics Research Network (PGRN) and PharmGKB
Fourth Open Scientific Meeting

March 8, 2004

RESEARCH SPONSORS
National Institute of General Medical Sciences
National Cancer Institute
National Heart, Lung, and Blood Institute
National Human Genome Research Institute
National Institute of Environmental Health Sciences
National Library of Medicine

SESSIONS
Common Variants-Common Disease
Current Developments in Pharmacogenetics
Human Variation: Discovering the Cause
Genomics and Databases
Presentations from PGRN Members
Poster Session

SPEAKERS
Daniel O'Connor
Ronald Krauss
Julio Licinio
Urs Meyer
Neil Risch
Dan Roden
Richard Spielman
Kari Stefansson
Richard Weinsztein
Scott Weiss

Sunset Village Grand Horizon Room
Covel Commons
UCLA

MEETING SPONSORS
NHLBI
NCI
NIH
PGRN

URL TO REGISTER:
<http://www.pharmgkb.org/meetings/2004>



2004

PGRN-I First Report Card 2005

Project Period: April 2000 to August 2005

Funding: \$140 million (funded largely by the National Institute of General Medical Sciences and the National Heart, Lung, and Blood Institute, with additional support from the National Cancer Institute, the National Library of Medicine, the National Institute of Environmental Health Sciences, and the National Human Genome Research Institute).

Number of Centers: 12

Number of Individual Research Grants: 1

Publications in Scientific Journals: more than 380

Genetic Variations (Single Nucleotide Polymorphisms or SNPs) in Database: more than 1 million

PGRN-II 2005-2010: Growing up

SPONSORS:

**NIGMS
NHLBI
NHGRI
NCI
NIEHS
NLM**

Primary Sites:

**Brigham and
Women's Hosp.**

**Children's Hosp.
Oakland**

Indiana Univ.

Mayo Foundation

Stanford Univ.

**St. Jude
Children's Hosp.**

UCSF

Univ. of Chicago

Univ. of Florida

**Univ. of
Maryland**

Vanderbilt Univ.

**Washington
Univ.**

NIH Pharmacogenetics Research Network



www.nigms.nih.gov/pharmacogenetics
www.pharmgkb.org



2008

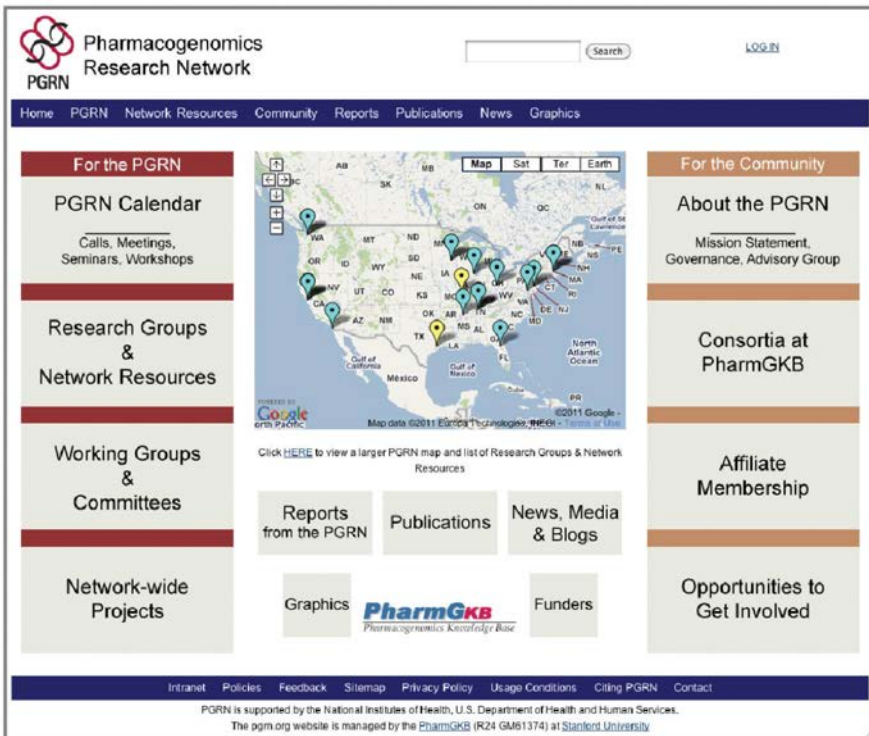


PharmGKB

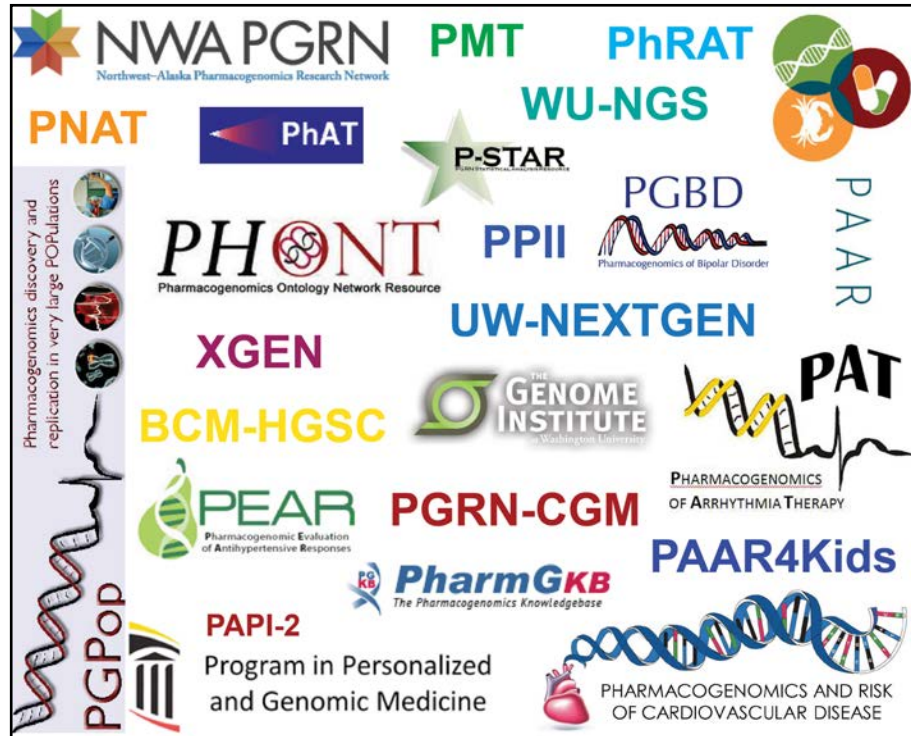
The Pharmacogenetics and Pharmacogenomics Knowledge Base



PGRN-III 2010-2015: Many new faces



The screenshot shows the PGRN website homepage. At the top is the PGRN logo and navigation links: Home, PGRN, Network Resources, Community, Reports, Publications, News, Graphics. The main content area is divided into three columns. The left column, 'For the PGRN', includes links to the PGRN Calendar, Research Groups & Network Resources, Working Groups & Committees, and Network-wide Projects. The middle column features a map of the United States with state abbreviations and a search bar. Below the map are links to Reports from the PGRN, Publications, News, Media & Blogs, Graphics, and Funders. The right column, 'For the Community', includes links to About the PGRN, Consortia at PharmGKB, Affiliate Membership, and Opportunities to Get Involved. The footer contains links to Intranet, Policies, Feedback, Sitemap, Privacy Policy, Usage Conditions, Citing PGRN, and Contact. A note at the bottom states: 'PGRN is supported by the National Institutes of Health, U.S. Department of Health and Human Services. The pgrn.org website is managed by the PharmGKB (R24 GM61374) at Stanford University.'



A collage of logos for various PGRN network members and resources. The logos include: NWA PGRN (Northwest-Alaska Pharmacogenomics Research Network), PMT, PhRAT, WU-NGS, PNAT, PhAT, P-STAR, PGBD (Pharmacogenomics of Bipolar Disorder), PAAR, PHONT (Pharmacogenomics Ontology Network Resource), PPII, UW-NEXTGEN, XGEN, BCM-HGSC, THE GENOME INSTITUTE (Washington University), PAT (Pharmacogenomics of Arrhythmia Therapy), PEAR (Pharmacogenomic Evaluation of Antihypertensive Responses), PGRN-CGM, PAAR4Kids, PAPI-2 (Program in Personalized and Genomic Medicine), and PharmGKB (The Pharmacogenomics Knowledgebase). A vertical banner on the left side of the collage reads: 'Pharmacogenomics discovery and replication in very large Populations'. At the bottom right, there is a logo for 'PHARMACOGENOMICS AND RISK OF CARDIOVASCULAR DISEASE' featuring a heart and DNA helix.

PGRN-III Launch: Retreat 2010



Class of PGRN-III



Complementary Unbiased Approaches in Zebrafish and in Human Populations to Dissect Genetic Determinants of the Human QT Interval

David J. Milan¹, Albert M. Kim¹, Ian L. Jones¹, Arne Pfeuffer^{2,3}, Adam H. Amsterdam⁴, Khaled M. Sabeh¹, John D. Mably⁵, David S. Rosenbaum⁶, Randall T. Peterson⁷, Stefan Käbb⁸, Dan M. Roden⁹, Calum A. MacRae¹ for the Pharmacogenomics of Arrhythmia Therapy Study Group

Abstract

GWAS are identifying candidate loci modulating common human heart disease risk factors, including establishing functional significance and dissecting modest effects. We describe a hybrid strategy combining functional genomics, zebrafish, with unbiased approaches to identify a novel gene, *NOS1AP*, involved in cardiac action potential regulation. The model was validated by demonstrating prolongation of zebrafish cardiac action potential duration (APD) during challenge with the APD-prolonging drug, sotalolol, and sea anemone toxin-II. The validation was then extended to GWAS modulation by *NOS1AP* and *KCNH2*. Genes previously identified by GWAS approaches as modifiers of the human QT interval. Next, a screen of *NOS1AP* variants in zebrafish embryos revealed that *NOS1AP* modulates APD. For altered drug sensitivity, identified 15 novel candidate QT-modifying polymorphisms in each of these were then tested for association with QT interval in subjects. This study was validated. The value of this systems approach was further supported using protein-protein interaction databases to reveal a new proposed complex pathway for QT interval control.

APD and arrhythmias with reduced zKCNH2, pharmacology of HERG, and the sodium channel inactivation inhibitor ATXII

(a) APD recordings from atrium and ventricle recorded at 0 days post-fertilization. (b) Sequential optical maps obtained during spontaneous cardiac depolarization. The impulse arises in the atrium and passes at the atrioventricular boundary (AVB), before emerging into the ventricle (V). A 4x atrial invasive catheter (AIC) placed in the AVB generates the atrioventricular boundary.

NOS1AP, identified as a regulator of human QT by GWAS, modulates zebrafish action potentials

(a) Action potential recordings from atrium and ventricle recorded at 0 days post-fertilization. (b) Sequential optical maps obtained during spontaneous cardiac depolarization. The impulse arises in the atrium and passes at the atrioventricular boundary (AVB), before emerging into the ventricle (V). A 4x atrial invasive catheter (AIC) placed in the AVB generates the atrioventricular boundary.

Exposing mutant fish embryos to an I_{Ca} blocker identifies lines with aberrant drug response

(a) Zebrafish embryos exposed to 1 μM flunarizine, an I_{Ca} blocker, show increased APD. (b) Zebrafish embryos exposed to 1 μM flunarizine, an I_{Ca} blocker, show increased APD. (c) Zebrafish embryos exposed to 1 μM flunarizine, an I_{Ca} blocker, show increased APD.

Further growth and development: moving to PGx Implementation



Pharmacogenomics
Research Network



The International Warfarin
Pharmacogenetics Consortium



Michael
Caldwell

Belted
Galloway



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 19, 2009 VOL. 360 NO. 8

Estimation of the Warfarin Dose with Clinical
and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*

The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Overcoming Challenges of Real-World Implementation

AR Shuldiner^{1,2}, MV Relling³, JF Peterson^{4,5}, JK Hicks³, RR Freimuth⁶, W Sadee⁷, NL Pereira⁸,
DM Roden^{4,9}, JA Johnson¹⁰ and TE Klein¹¹; for the Pharmacogenomics Research Network
Translational Pharmacogenetics Program Group

Pharmacogenetics — Tailoring Treatment for the Outliers

Janet Woodcock, M.D., and Lawrence J. Lesko, Ph.D., F.C.P.

PGRN-Riken Center for Genomic Medicine Leveraging the power of GWAS



Cruising with the PGRN



PGRN-IV 2015-2020: - Reaching Maturity:

- Supported research – NIGMS funded 3 P50 Centers, an R01, and a Hub
- Facilitated collaborations and interactions by establishing a **membership** program
- Provided **research resources** to the pharmacogenomics research community
- Held monthly web-based **Research In Progress Seminars**
- Established and maintained new **website**
- Organized biannual **scientific meetings** with ASHG and the American Society for Clinical Pharmacology & Therapeutics

PGRN Resources

PGRN RESOURCES

PGRN-RIKEN >

BioBank Japan

RPGEH

PGRN Hub

PharmGKB

Clinical Implementation

Pharmacogenomics IPSC
Library And Service

Functional
Pharmacogenes

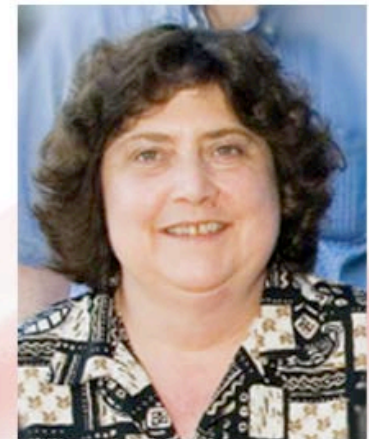
Research In Progress Seminars

2nd Friday of each month
<http://www.pgrn.org/rips.html>


October Featured Investigator

Debbie Nickerson, PhD

Professor of Genome Sciences
Adjunct Professor of Bioengineering



PGRN-IV Hub: the administrative home and transition to the future



The banner features a dark red background with a faint DNA helix and a white pill. The PGRN logo is in the top left. Navigation links are in the top right. The main text reads 'Welcome to the Hub' with a subtitle 'Your home for the Pharmacogenomics Research Network PGRN'. A 'Join the PGRN' button is at the bottom.

Pharmacogenomics Research Network

Home What is PGRN? Members Data & Tools PGRN Resources News Meetings

Welcome to the Hub

Your home for the
Pharmacogenomics Research Network
PGRN

[Join the PGRN](#)

The mission of the Pharmacogenomics Research Network (PGRN) is to catalyze and lead research in precision medicine for the discovery and translation of genomic variation influencing therapeutic and adverse drug effects.

All individuals interested in pharmacogenomics research may apply.



A profile card for Naohiro Terada, MD, PhD. It includes a photo, title, affiliation, research goal, and a 'Continue reading' button.

2018 May Featured Investigator
Naohiro Terada, MD, PhD
Professor and Director
Department of Pathology
Center for Cellular Reprogramming
University of Florida
Our research goal here is to provide a solution to fill the gap between the tremendous amount of gene linkage data obtained from pharmacogenomics studies and the unmet need to understand the biological importance of these data.
We are currently establishing a stem cell (PSC) bank and very practical methods to decode biological significance of genetic variations on differential drug responses...
[Continue reading](#)

Tweets by @pgrnhub



Live Now ! Big Data in Precision Medicine
[@StanfordMed bigdata.stanford.edu](#)



May 23, 2018

PGRN Retweeted



I'm excited about the progress the [@AllofUsResearch](#) Program is making around genomic data. We're also hard at work on plans for a pilot study to responsibly return genetic info to participants. More to come! [#JoinAllofUs](#)



May 23, 2018



The Hub of the Hub – Kathy G.



1st PGRN Symposium with ASHG 2016



2016 PGRN-ASHG SYMPOSIUM

THE EXPANDING UNIVERSE of Pharmacogenomics

Organized by the Pharmacogenomics Research Network (PGRN)

Monday, October 17, 2016
Tuesday, October 18, 2016
Vancouver, Canada

The agenda includes the following sessions:

- Session 1: Innovative Approaches for Pharmacogenomic Discovery
- Session 2: Pharmacogenomics in Drug Discovery
- Session 3: Technologies in Pharmacogenomic Studies
- Session 4: Panel Discussion: Issues for Clinical Implementation of Pharmacogenomics
- Session 5: Pharmacogenetics in a Human Evolution Context

The full agenda and registration information can be found at www.pgrn.org



Pharmacogenomics

Open Poster Session & Reception



October 19, 2017
Orlando, FL

- 39 posters displayed
- 175 attendees
- 4 trainee award winners

2nd PGRN Symposium with ASHG

The Pharmacogenomics Research Network (PGRN) presents:
2018 PGRN-ASHG Meeting

The Genomics of Drug Response *from Discovery to Implementation*

Monday, October 15, 2018, 1pm - 6:30pm

Tuesday, October 16, 2018, 8am - 4pm
(including a joint session with ASHG from 1pm - 4pm)

San Diego Convention Center
San Diego, California

Registration fee: \$25

Session 1: The Role of Human Genetics in Drug Development from Target Identification to Clinical Trials

Session 2: Challenges and Opportunities in Pharmacogenetic Implementation

Session 3: Dual Genomes in Pharmacogenomics

Session 4: Panel Discussion on Genomics and Precision Drug Therapy

Session 5: Pharmacogenomics: Rare Diseases and Rare Adverse Drug Reactions

Part 1: Drug Development for Rare Genetic Diseases

Part 2: Immunopharmacogenomics



More information and registration at pgrn.org/ashg-2018





2019 PGRN Poster Session @ ASHG Annual Meeting



Congratulations!

Trainee Award Winners



Honorable Mention



2020: Graduation from NIH

Class photos 1



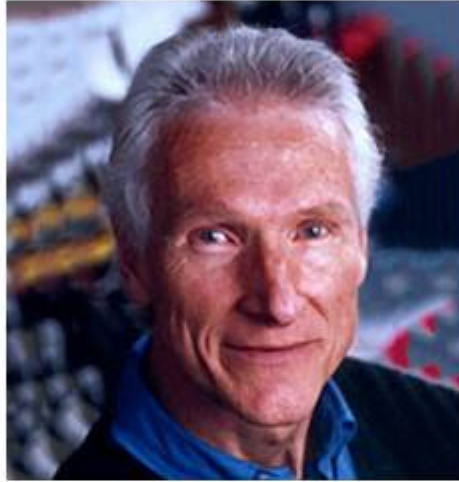
Class Photos 2



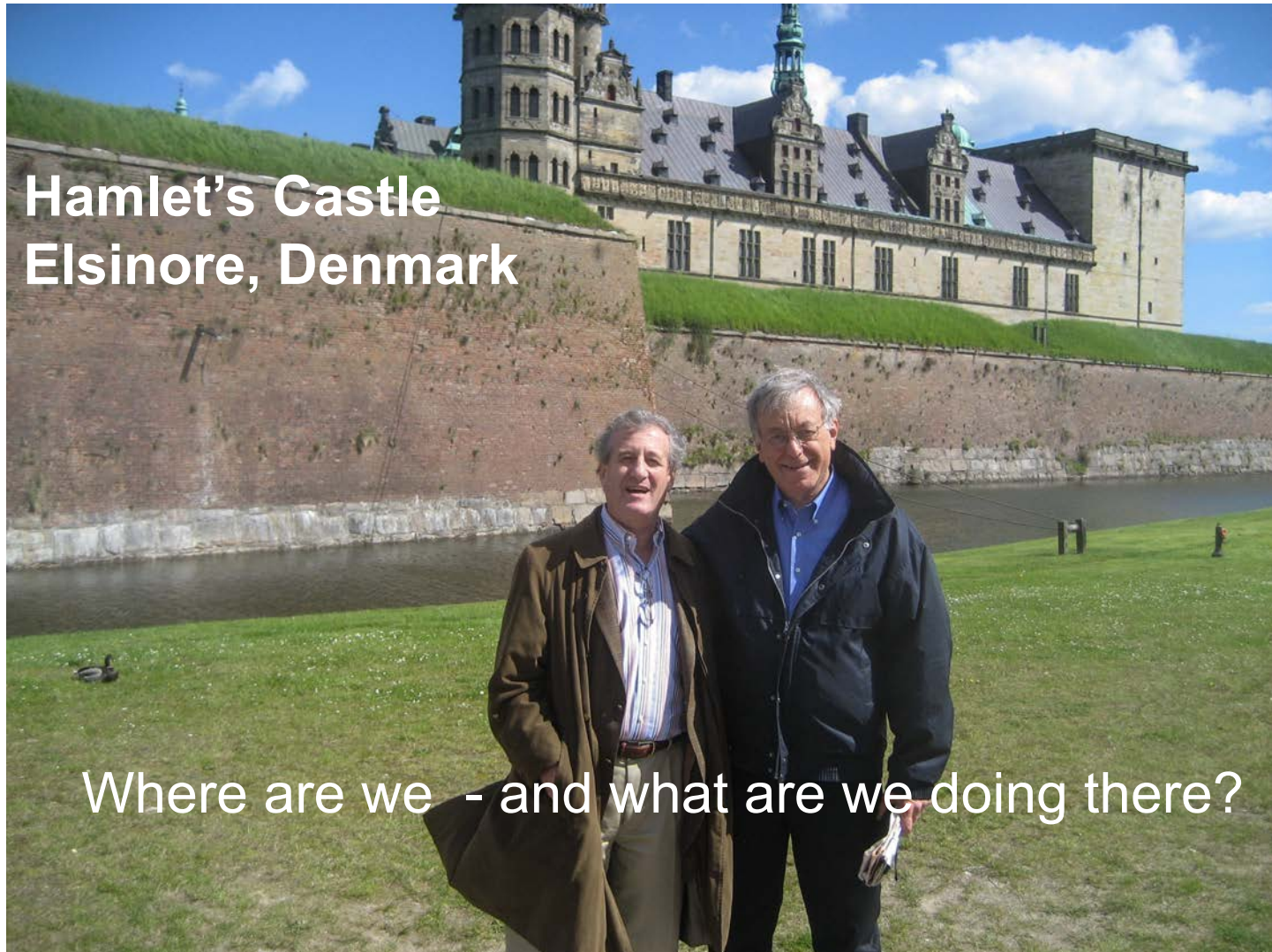
Class Photos 3



Class Photos 4



With thanks to Dan Roden for photos



Hamlet's Castle
Elsinore, Denmark

Where are we - and what are we doing there?