



## Pharmacogenomics education and research at the Department of Pharmacy, University of Patras, Greece

The Pharmacogenomics and Personalized Medicine group belongs to the Laboratory of Molecular Biology and Immunology, Department of Pharmacy and is active since 2009 mainly in the field of pharmacogenomics and personalized medicine. Herein, we describe the research interests, collaborations and accomplishments of the Pharmacogenomics and Personalized Medicine group together with the teaching activities of the group that greatly enhance the pharmacogenomics knowledge of graduate/postgraduate students and healthcare professionals.

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The Department of Pharmacy was originally founded in 1977 and received its first students in 1978 as a constituent department of the School of Physical-Mathematical Sciences, whereas since 1983, together with the Department of Medicine, they form the School of Health Sciences. The curriculum of the Department of Pharmacy has a length of 5 years, receiving over 180 undergraduate and over 40 graduate and doctoral students per year, who are conducting their graduate thesis mostly within the department's premises. The Laboratory of Molecular Biology and Immunology, consisting of the Immunology and Pharmacogenomics and Personalized Medicine groups (led by K Poulas and GP Patrinos, respectively) was founded in 2003. The latter group is active since January 2009, setting the milestone of pharmacogenomics (PGx) research in the department and the University of Patras as a whole.

### Pharmacogenomics research projects

Over the last 8 years, the Pharmacogenomics and Personalized Medicine group has built an international reputation of being one of

the very few research groups worldwide that approach PGx and Precision Medicine from wet-lab, dry-lab and public health perspectives (Figure 1), all of which yielded tangible deliverables, such as competitive funding from international funding bodies and generated high-profile publications related to PGx, showing a linear increase on an annual basis (Figure 2). Research interests include discovery work in the field of PGx, focusing mainly on  $\beta$ -type hemoglobinopathies and psychiatric disorders, while the group is also active in research projects involving next-generation sequencing, pharmacometabolomics and pharmacometagenomics, as ancillary disciplines for PGx as well as population PGx, related to the prevalence of PGx biomarkers in various European populations. The group's dry-lab activities focus on the design of genomic databases, translational tools and web services for documenting and translating PGx information into a clinically meaningful manner and last research into various disciplines of Public Health related with PGx, such as exploring stakeholder's views, opinions and knowledge related to PGx, ethics

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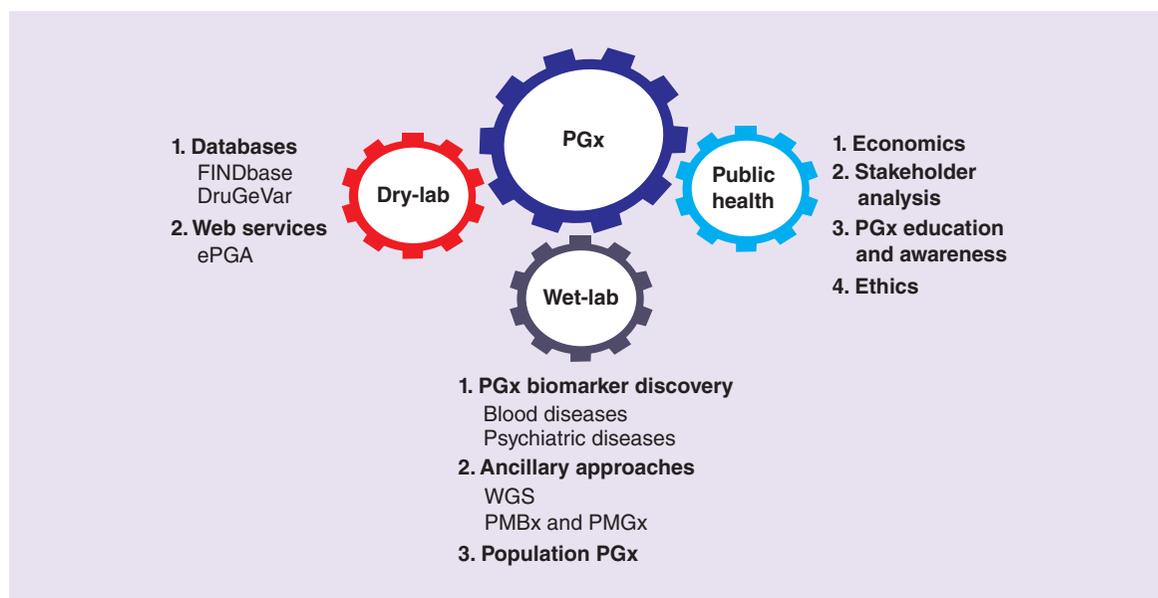
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**Figure 1. Outline of the various pharmacogenomics research and educational activities of the Pharmacogenomics and Personalized Medicine group at the Department of Pharmacy, University of Patras, Greece (January 2009 until August 2016).**

PGx: Pharmacogenomics; PMBx: Pharmacometabolomics; PMGx: Pharmacometagenomics; WGS: Whole-genome sequencing.

and economics of PGx, and assessing the PGx educational environment and increasing the general public's PGx awareness. These were all possible due to a large network of collaborating laboratories and research groups worldwide.

#### Discovery of novel genomic biomarkers for PGx

Our discovery expedition focuses mainly on drug treatment modalities of blood disorders, such as  $\beta$ -type hemoglobinopathies and acute lymphoblastic leukemia, and psychiatric disorders, namely schizophrenia and bipolar disorder.

We are interested in the understanding of the various molecular mechanisms that govern the transcriptional regulation of the human fetal globin genes in an effort to reactivate human fetal hemoglobin (HbF) transcription as a means to treat  $\beta$ -type hemoglobinopathies patients. Our long-term goal is to identify the genes involved in differentially increasing HbF levels, upon hydroxyurea (HU) treatment in groups of  $\beta$ -thalassemia patients, categorized based on the levels of HbF levels induction upon HU treatment in order to gain insights as to which genes and regulatory pathways are involved in the differentially elevated HbF levels in the two groups of patients, namely responders (higher HbF levels) and nonresponders (lower HbF levels). Our genome discovery work includes a combined array-based whole-transcriptome analysis of human erythroid progenitor cells and genomic biomarker screening in two independent cohorts

of  $\beta$ -type hemoglobinopathies patients, namely  $\beta$ -thalassemia homozygous and compound sickle cell disease/ $\beta$ -thalassemia patients of Cypriot and Greek descent, in collaboration with the Cyprus Institute of Neurology and Genetics (Nicosia, Cyprus), the University of Malta (Msida, Malta) and the Erasmus University Medical Center (Rotterdam, The Netherlands). Our study revealed a number of genomic loci involved in potentiating HbF levels in these patients, such as *KLF10* [1], *MAP3K5*, *PDE7B* [2], *FLT1* [3], *ASS1* [4] and *SIN3A* [5]. These genes exert their effect as modifier loci, through various pathways related to HbF production, such as nitric oxide biosynthesis and signaling pathway, or regulating genes previously implicated in fetal globin production, such as *KLF1* [6]. Our ongoing work has identified additional genomic loci involved in the modulation of HbF levels upon HU treatment that are currently being validated in larger patient cohorts.

Also, using a variety of genomic and *in vitro* functional assays, we have demonstrated, in collaboration with the Institute of Molecular Genetics and Genetic Engineering (Belgrade, Serbia) the role of promoter variants in the *TPMT* gene locus in the response to 6-mercaptopurine treatment, as a result of differential *TPMT* gene expression [7–9].

We also have a keen interest in the PGx of psychiatric disorders, particularly treatment-resistant schizophrenia and bipolar disease. In the latter case, using a combined genome-wide association study and a follow-up genotyping approach, we have shown, in collabo-

ration with the University of Cagliari (Cagliari, Italy) that variants in the *ACCNI* gene are associated with lithium response in bipolar disease patients [10].

#### Applying ancillary laboratory disciplines for PGx

Our group has successfully applied whole-genome sequencing to demonstrate its usefulness in determining personalized PGx profiles, something which can be particularly valuable for pre-emptive PGx testing. By applying highly accurate next-generation sequencing in a large cohort of Caucasian individuals, jointly with Complete Genomics, Inc. (CA, USA), we identified a large number of rare and even unique genomic variants in 231 pharmacogenes, some of which have a deleterious effect in drug metabolizing enzymes and transporters of some of the most commonly prescribed drugs, such as *CYP2D6*, *TPMT*, *UGT1A1*, among others, deduced from *in silico* analysis [11]. Currently, we are applying targeted next-generation sequencing focusing on genes encoding for enzymes implicated in drug treatment modalities in cardiology and oncology in the Emirati population, in close collaboration with the United Arab Emirates University (Al-Ain, UAE).

Furthermore, we are testing the principle of pharmacometabolomics and pharmacometagenomics, as ancillary disciplines to PGx, which, coupled with machine learning and information technologies (see below) could provide further insights into the tailoring of drug treatment modalities [12].

#### Population PGx

Since mid 2010, we have engaged into a multinational effort, led by the Golden Helix Foundation [13] in

Europe, to determine the prevalence of a large number of pharmacogenomic biomarkers in 231 pharmacogenes in several European countries. This pilot project suggests that several clinically actionable pharmacogenomic biomarkers have varying frequencies in several European populations [14], with direct implications in pre-emptive PGx testing, which could, hence, encourage large replication studies in these populations, especially those with emerging economies in an effort to provide better, cost effective and more targeted treatment options. This would allow establishing country-specific guidelines for population PGx and drug prioritization in these countries [15], which could also have a significant impact in the overall healthcare budget in these countries.

#### Databases & web services in translational PGx

In an effort to provide a comprehensive, well curated and continuously updated data repository on the prevalence of PGx biomarkers, we have developed a separate module in FINDbase worldwide database of clinically relevant genomic variation allele frequency [16], where the prevalence of PGx biomarkers is documented [17,18]. At present, FINDbase PGx biomarker module has 2337 records of PGx biomarkers in over 90 ethnic groups and/or populations (last assessed in August 2016). Also, we have developed DruGeVar [19], a separate database that triangulates between drugs, pharmacogenes and clinically actionable PGx variants [20,21], aiming to provide the missing link as to which pharmacovariants are related with variable metabolism of those drugs that bear PGx information in their labels, approved by regulatory agencies, such as the US FDA [22] and/or the EMA [23].

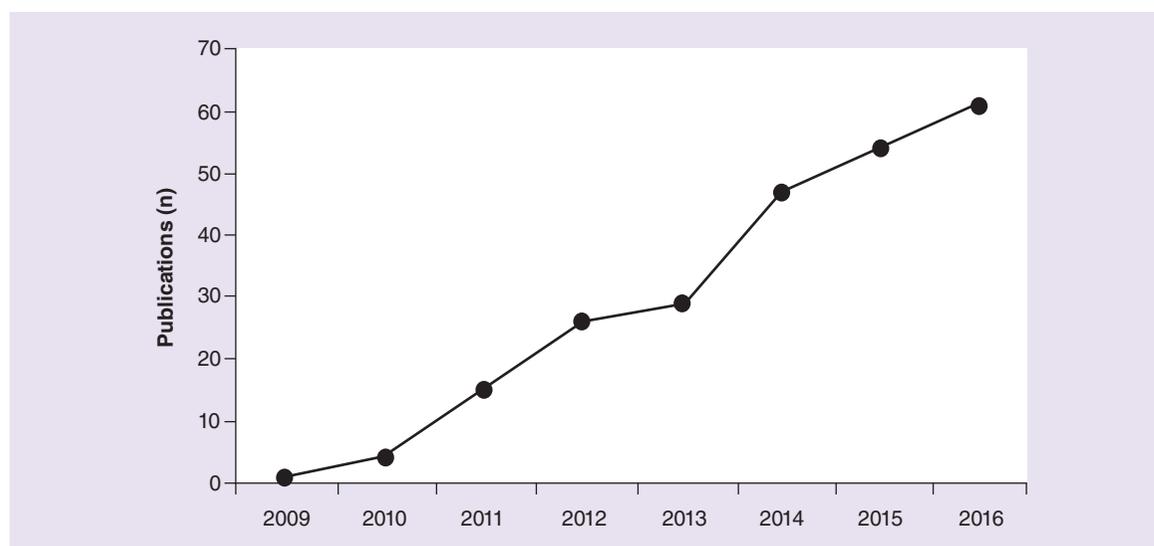


Figure 2. Graph depicting the number of scientific publications in international peer-reviewed journals produced from the Pharmacogenomics and Personalized Medicine group (textbook chapters are excluded).

Last, we have built the electronic PGx assistant [24], in collaboration with the Institute of Molecular Biology and Biotechnology (Heraklion, Greece), a state-of-the-art and unique web service aiming to translate PGx information into a clinically meaningful format [25], in conjunction to the PharmGKB knowledgebase. This service is already part of the RD-Connect data platform [26].

### Public Health PGx

The field of Public Health Genomics includes disciplines that are fundamental in catalyzing the adoption of genomics into medicine. To this end, there are often significant barriers that hamper the smooth incorporation of PGx research findings in the daily medical practice, which have to do more with disciplines related to Public Health Genomics rather than PGx research itself.

In our group, we have pursued a variety of approaches to critically appraise the impact of PGx to society [27], the level of awareness over PGx and personalized medicine in the general public and various healthcare professionals (physicians, pharmacists, genetic laboratories) [28–30], and ascertained the opinions of the various stakeholders that are potentially involved in the adoption of personalized medical interventions [31], also touching upon the ethics of the provision of genetics services [32] and proposed solutions to resolve practical ethical problems encountered when working in the field of genetics, including but not limited to direct-to-consumer genetic testing. In addition, we have performed, jointly with the University of Cagliari a comprehensive mapping of the various under- and postgraduate academic curricula in 11 countries of southeastern Europe, where we identified a vast heterogeneity in the provision of PGx education, contrary to the current situation in north-western Europe [33]. The latter dictates a harmonization of PGx education in these countries so that the future healthcare professionals are better educated to deliver comprehensive PGx services.

Also, in collaboration with the Golden Helix Foundation (London, UK), the University of Florida (FL, USA) and the Erasmus University Medical Center, we have engaged in economic evaluation projects to provide insights as to whether certain medical interventions in cardiology are cost effective in patient cohorts from developing economies, such as Serbia [34] and Croatia [35]; and development of economic models that could be potentially used in Genomic Medicine [36 FRAGOULAKIS V, MITROPOULOU C, VAN SCHAİK RH, MANIADAKIS N, PATRINOS GP. AN ALTERNATIVE ECONOMIC MODEL FOR RESOURCE ALLOCATION AND DECISION MAKING IN GENOMIC MEDICINE. *OMICS* (2016) MANUSCRIPT IN PREPARATION].

### Participation in international collaborative PGx research projects

The Pharmacogenomics and Personalized Medicine group participates in the H2020-funded Ubiquitous PGx [37] project, as one of the seven implementation sites. The main aim of this project is to promote PGx implementation by demonstrating that pre-emptive genotyping of an entire panel of clinically relevant PGx biomarkers can be used in clinical practice, is cost effective, and results in a better outcome for the patients. With pre-emptive PGx, data on multiple important pharmacogenes are collected prospectively and embedded into the patients' electronic record such that data are available at the time of decision making for a wide variety of common drugs, hence optimizing the use of PGx data together with the individual patient phenotype in clinical therapeutics.

Also, senior members of the group participate in other international collaborative efforts, such as the PGx Working Groups of the US-led Global Genomic Medicine Collaborative [38,39] and the Genomic Medicine Alliance [40,41]. Last, GP Patrinos is a member of the Committee for Human Medicinal Products (CHMP) Pharmacogenomics Working Party of the European Medicines Agency (EMA) [42].

### Pharmacogenomics education PGx in graduate & undergraduate courses at the Department of Pharmacy

PGx is included in the undergraduate curriculum of the course 'Molecular Biology and Genetics' in the Department of Pharmacy. Also, a dedicated module on PGx is available at the graduate program of the Department of Pharmacy. Most importantly, every year a large number of undergraduate and postgraduate students are participating in research projects in PGx and personalized medicine as part of their diploma thesis and their research project, respectively. Furthermore, doctoral students are undertaking their research projects in these topics (Figure 3), while several students from other institutes from abroad, namely Europe, Middle East and Asia are engaged in these projects as part of their short-term training internships.

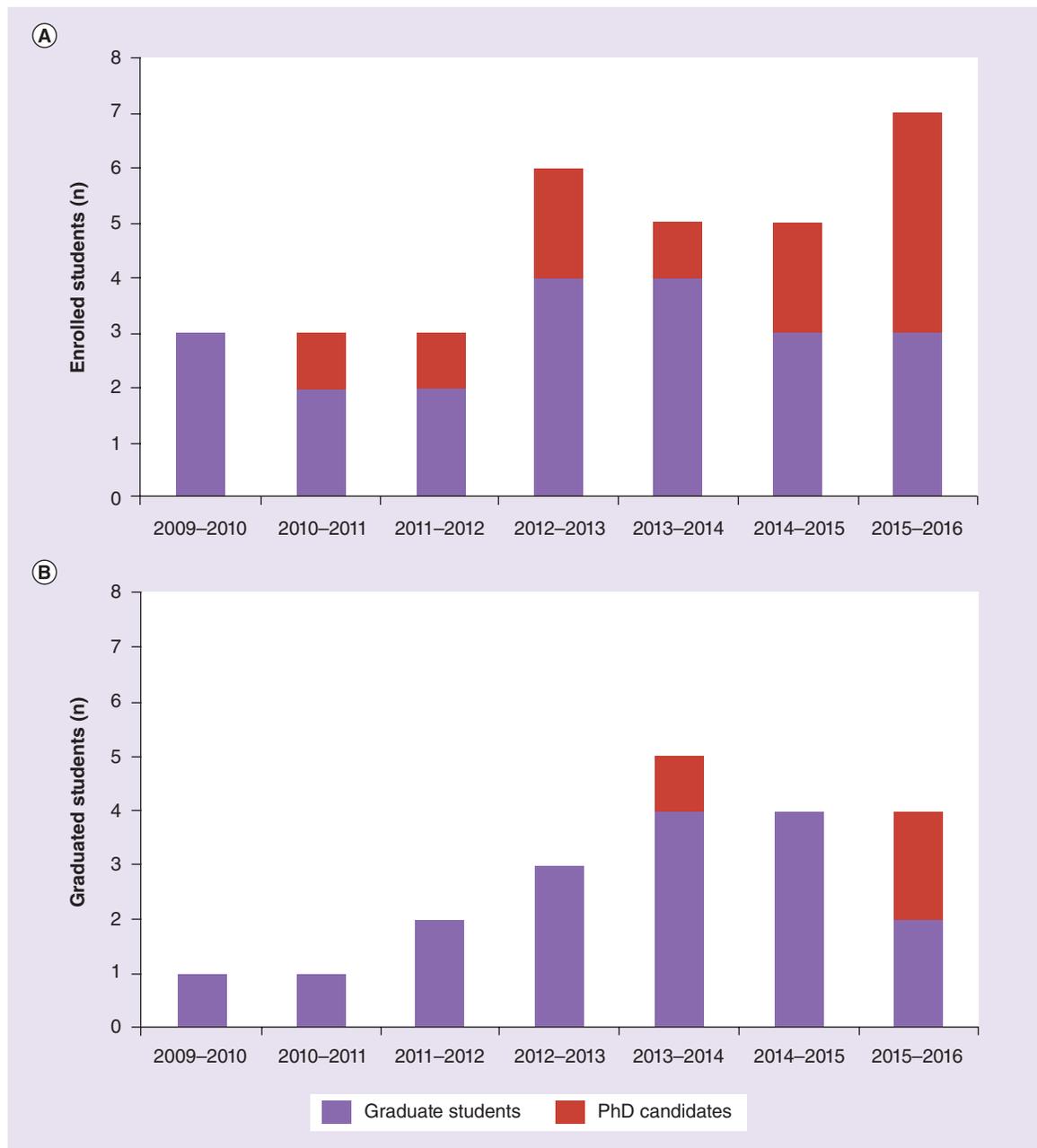
### Organization of international scientific events on PGx

The 7th Golden Helix Pharmacogenomics Day was organized in the Conference and Convention Center of the University of Patras on 20 October 2012. This international meeting was held as a satellite event to the 8th National Conference of Biosciences and has attracted >130 registered participants, mainly biomedical scientists and students. This free educational

event, belonging to an international conference series, organized since 2009 in 18 cities in Europe and the USA, aimed to provide timely updates on the field of PGx and personalized medicine to the local biomedical scientific community and to bring together faculty members from universities and research institutes from the local scientific arena working in the field of PGx to initiate collaborative projects.

### Conclusion

The Pharmacogenomics and Personalized Medicine group has been active in the research and educational activities in the field of PGx and obtained uninterrupted funding from national and international funding bodies for PGx research projects since 2009. The research projects described herein are diverse, spanning in wet-lab, dry-lab and public health genomics



**Figure 3. Overview of the graduate students and PhD candidates (depicted in blue and red, respectively), enrolled in and graduated from the University of Patras, Department of Pharmacy who have worked on pharmacogenomics projects at the Pharmacogenomics and Personalized Medicine group (January 2009 until August 2016). Students enrolled in interdepartmental graduate programs who worked on pharmacogenomics projects at the Pharmacogenomics and Personalized Medicine group are excluded.**

disciplines (Figure 1), but revolve around PGx, share common elements and involve collaborations across national and international groups.

In these projects, we employ state-of-the-art high-throughput technologies, such as whole-genome sequencing, whole transcriptome analysis, genome-wide association studies, accompanied by comprehensive *in silico* analysis, conventional follow-up genotyping and functional assays, where needed. Provision of training to young biomedical scientists remains top of our priorities, not only for students of the University of Patras but also from other institutes abroad. To achieve these, we collaborate extensively with several groups at the national and international level in Europe, Middle East, Asia and the USA, and its senior members actively participate and lead PGx projects in multinational PGx research consortia.

As far as PGx education is concerned, we will continue to enrich and upgrade the PGx education provided at both the undergraduate and postgraduate levels, keeping pace with the continuing expanding knowledge of genotype-guided treatment and drug-response phenotypes. The examples used in teaching not only focus on research but also on various aspects that involve the application of PGx in the clinic, such as ethics, regulation, economics, policy making, reimbursement and pricing, and so on. Teaching PGx to healthcare professionals alone will not overcome the barriers presently facing its clinical implementation, but without such comprehensive education the vision of personalized medicine will not be realized in the coming years.

PGx are expected to be fundamental in patient stratification and improved therapeutic strategies [43], ensuring better treatments at a lower cost for public health systems. Hence, it becomes apparent that translation of PGx research findings and their implementation in the

clinic is of paramount importance. As such, we actively participate in these challenges, not only by our own research findings but also through our participation in the Ubiquitous PGx project, aiming to provide the rationale for pre-emptive PGx testing in Europe [44]. It is likely that in the very near future whole-genome sequencing will be key to comprehensively determine one's PGx profile. As genomics knowledge will continue to get enriched, we will continue to understand the basic mechanisms that underlie PGx observations, which would help interpreting variable drug response in patients. Also, there is an urgent need to critically appraise the impact of PGx and personalized medicine to society as well as the level of awareness of PGx and personalized medicine of various stakeholders, in which our group will remain fully committed.

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