International Clopidogrel Pharmacogenomics Consortium
(ICPC)
Memorandum of Understanding
March 7, 2012

Background

A number of pharmacogenomics research centers (the "consortium") are interested in discovering new genetic variants that are important for predicting response to clopidogrel using candidate gene, genome wide association studies (GWAS), and other methods. In addition, large sample sizes provide the opportunity for various subgroup analyses to define in a more granular way phenotype-genotype associations. Many members of the consortium have collected cohorts of patients with who have been treated with clopidogrel and obtained drug/metabolite levels, platelet function testing and/or cardiovascular outcomes and for whom genotype data and/or DNA is available, and are willing to share these data and DNA samples for a combined analysis. In particular, there is an interest among these groups in working together to perform a new GWAS and/or candidate gene study on a large cohort (target of at least 10,000) looking for variations associated with clopidogrel response. This creates an opportunity to perform genotyping on DNA samples and then to combine the resulting genotype and associated phenotype data and to link them effectively to each other. Alternatively, if genotype data already exist, it may be used in combined analysis. For the consortium effort, genotype data generated in individual laboratories may be subjected to quality assurance measures through genotyping of a subset of samples at a central laboratory.

PharmGKB scientists are trained to accept, integrate and curate the data into a form that is compatible with dissemination on PharmGKB and other public databases. PharmGKB is interested in data dissemination, and so embarks upon this collaboration in data aggregation with the assumption that the genotype data and/or metadata are destined to end up on public databases (dbGAP and PharmGKB) as primary places for distribution upon publication of the results. Submission of genotype and phenotype data to a public resource is a desirable outcome and for GWAS may be mandatory for some grantees (from NIH or Wellcome Trust). For others, we recognize that submission or sharing of data outside of the consortium may not be possible because of differences in international laws and practices.

Memorandum of Understanding

1. In order to be a participant in the consortium, a research group must agree to provide the "minimal data set" as described in Appendix A. This includes both specific phenotyping and genotype data and the ability to share DNA for new candidate gene and/or GWAS genotyping or for quality assurance measures. Participants must be able to provide the minimal data set as described below in order to participate. There are also secondary phenotypes of interest and these are specified as "additional data" in Appendix A. Participation in the ICPC does not require the availability of the additional data, only the minimal data set. For GWAS, the consortium participant understands that their data will ultimately be made available on a public

database (e.g. dbGAP or PharmGKB), per NIH requirements that were established as part of the agreement for the collaboration with RIKEN (http://bts.ucsf.edu/pgrn-cgm/).

2. PharmGKB will assist in the selection of samples for inclusion in the GWAS and/or candidate gene genotyping to be conducted by ICPC after tallying the sites willing to participate, and based on the sample selection approach agreed upon by the consortium.

3. For GWAS, we will require DNA for each phenotyped sample. For genotype data already available it will be desirable to have DNA on at least 10% of the samples for genotyping at a central laboratory for quality assurance measures. The amount of DNA required for participation is detailed in Appendix B. If the amount of DNA is the limiting factor for participation in the consortium, ICPC will offer Whole Genome Amplification (WGA). ICPC may not always use the entire DNA supply, and the extra DNA should be available for additional genotyping and/or deep sequencing of regions which appear especially promising. In addition, any extra DNA remaining can be returned to the original site. University of Maryland, Baltimore (UM) staff will coordinate sample collection with PharmGKB to assure that all samples and data are associated properly. It is agreed that the DNA will be held by UM until the consortium decides their effort is complete, at which time the sites can request remaining DNA to be returned to them.

Consortium members signing this document agree that the biospecimens were acquired under a protocol that underwent local ethics review and approval and that these samples were obtained from human subjects who gave informed consent to share these samples for future unspecified use including genetic testing.

4. PharmGKB will allocate personnel resources from its staff to work with each center to accept that center's relevant phenotype data, and curate the data using standards for phenotype files, as they are currently employed on PharmGKB (e.g. sample files at http://www.pharmgkb.org/search/browse.action?browseKey=phenotypeDatasets).

5. Consortium members will designate contact persons with whom PharmGKB staff can work for each individual data set. These contact persons should be very familiar with the details of the data sets, or have easy access to those who do.

6. PharmGKB staff will put the phenotype data into standard PharmGKB phenotype data templates, and will work with each center to carefully document the details and meaning of each measurement. This is a critical activity for resolving subtle differences in the data sets. The result will be a phenotype file suitable for submission to the PharmGKB. Curation of the data is an iterative process. Participating centers and the PharmGKB perform several iterations of curation as the scientific questions become refined and the request for specific data increases.

7. If relevant, PharmGKB staff will also work with UM and other sites with existing GWAS and/or candidate gene genotype data to prepare genotype submissions to PharmGKB based on the data in these datasets, and will prepare files suitable for submission to the PharmGKB and other databases.

8. The phenotype and genotype submissions will remain with PharmGKB while the consortium members work to understand it. The data is not open to the general public, and is password protected. Genotypes and phenotypes will be linked, and all display functionality of PharmGKB will be available for the data.

9. ICPC data analysis will be coordinated by the PGRN Statistical Analysis Resource (P-STAR, http://www.pgrn-star.org/) led by Marylyn Ritchie. Statisticians from each site are encouraged to join the analysis group and to participate in the analyses.

10. Investigators outside of the consortium who are interested in analyzing the data, but who have not contributed data can only enter the consortium as registered collaborators with one of the groups who have submitted data and are part of the consortium or PharmGKB. These collaborators must agree to the terms of this MOU and be considered a member of whichever consortium site sponsors them.

11. Consortium members are free to write papers based on their own samples and data before, during, and after the activities associated with this memorandum and consortium.

12. Consortium members may not write papers based on the data of others, except with explicit permission of those who collected the data. In general, consortium members will announce their intention to write a paper based upon some or all of the data, in order to maintain transparency and to allow other interested parties to potentially join these efforts.

13. Only consortium members who have submitted data will have access to the complete data set and agree to use these data only as a basis for conversation with the originators. Consortium members with access to the data agree that viewing these data is associated with responsibility for not publishing or disclosing it without approval of the ICPC members.

14. Access to the ICPC data sets and draft publications is limited to 1) consortium members that have contributed data and 2) the PharmGKB team (members of PharmGKB curation and science staff who also agree to the MOU, including Drs. Klein, Altman and perhaps others as necessary).

15. It is anticipated that there will be several publications that result from this consortium effort. For example the initial “alpha” study will likely evaluate candidate gene variants associated with a significant response to clopidogrel. This will be based on the “minimal data set” as described in Appendix A.

16. Co-authors of ICPC publications will include all data contributors, data analysts, data curators, and writing group who have participated in ICPC. The writing group will be comprised of leaders of the ICPC and others who make substantial contributions to actually creating the text and figures of the initial paper. The role of each author in the groups listed above will be specifically noted in a footnote in the paper. All authors will have an opportunity to read and comment on the paper before submission. There may be additional authorship rules of specific journals that the consortium will be required to adhere to.

17. Other analyses may include seeking variants involved in stratified analyses (e.g., indication, gender-specific effects), specific outcomes (e.g., stent thrombosis) or on side effects (e.g., bleeding). In these scenarios, those participants with major contributions to the respective cohorts will be expected to have lead roles in resulting manuscripts, and will have major roles in the analysis approach that is undertaken if they indicate a desire to do so.

18. For secondary papers, all consortium members will be listed in a footnote as described in 16, but the writing group will be formed based on interest and willingness to lead the secondary analysis. Secondary analyses will be initiated through submission of a manuscript proposal to the Steering Committee to insure that all members who wish to participate have the opportunity, to maintain transparency, and to prevent redundant analyses.

19. With publication and release of the data on the public site, PharmGKB and the consortium will engage in appropriate dissemination, announcements, and emphasis of the availability of this exciting data set to the community.

20. Data to be posted to public databases (e.g. dbGAP or PharmGKB) will require an investigator outside the ICPC to apply for access to the individual level data. The members of the consortium contributing samples will establish the rules for accessing the individual level ICPC GWAS and/or candidate gene data by an outside investigator. If other efforts arise from the consortium, the consortium members will similarly work to define the rules for access to those data. Those groups with existing genotype data may establish their own rules for accessing their raw data, or may utilize those agreed upon by the ICPC. These data will be made available to other investigators after the publication of the relevant data.

21. In order to join the ICPC, a participating investigator must (1) send an email to Dr. Teri Klein (teri.klein@stanford.edu) indicating acceptance of the terms of this MOU; (2) send in the ICPC information sheet indicating the basic parameters of their data and DNA.

APPENDIX A

MINIMAL DATA SET (REQUIRED FOR ALL PARTICIPANTS AS PART OF PRIMARY ANALYSIS)

Membership in ICPC requires the availability of the following phenotype data and DNA:

1. Assessment of clopidogrel response phenotypes, which may include active metabolite levels, ADP-stimulated platelet aggregation testing (e.g., aggregometry, VerifyNOW), or clinical outcomes (e.g., individual or composite CVD outcomes). The minimal length of treatment and period of follow-up for clinical outcomes must be >30 days. All phenotypes must have been obtained using well-validated protocols and methods.

2. For clinical outcomes endpoints, accurate and well-validated indications for clopidogrel treatment, e.g., CHD/PCI, stroke, PVD.

3. If there has been any genotyping of the patients, results of this should be provided.

4. If no genotyping has been performed, DNA must be available and the group must be willing to send DNA to a centralized laboratory for genotyping. If genotype data is available, DNA in at least 10% of the samples must be available for validation of genotyping at a central laboratory. Note: The ICPC will offer whole genome amplification to groups who can demonstrate that they cannot participate in the Consortium otherwise.

5. A minimum of 50 subjects fulfilling these criteria.

ADDITIONAL DATA SET (NOT REQUIRED BUT DESIRABLE FOR SECONDARY ANALYSES)

In addition to the minimal data set, we are interested in additional data for secondary analyses. NOTE: These are NOT required for participation but are optional for these additional analyses.

6. Availability of side effects such as bleeding.

7. Ethnic origin of patients.

8. Other potential covariates e.g., BMI, age, sex, medication usage (PPIs), serum lipids, bp/hypertension, diabetes status, smoking, renal function, ejection fraction.

9. Availability of platelet aggregation or clinical outcomes from the placebo arm of randomized controlled trials for analysis of effect modification.

APPENDIX B

For this study, UM requires 70 microliters of DNA at a concentration of 50 to 60 ng/microliter.

This means that each DNA sample will be approximately 3.5-4.2 micrograms (e.g. 70 microliters x 50 ng/microliter = 3500 ng = 3.5 micrograms).

These DNA need to be collected and extracted upon entry into the consortium, or quickly thereafter, because the genotyping will happen relatively quickly.

Commitment and Signatures

Study Name: _____

I agree to abide by the principals of this agreement.

Yes: ___ , No: ____

No intellectual property will be claimed by any of the investigators involved in discoveries made by the combined consortium using shared data.

Yes: ___ , No: ____

I agree that under no circumstance will results of analyses be presented prior to the final publication without the written consent of all groups who contributed data to the analyses.

Yes: ___ , No: ____

I agree not to share my group's GWAS data for public relations, or serve as a replication cohort with a competing group without prior notification of the consortium or until publication of this project.

Yes: ___ , No: ____

We will not conduct follow-up experiments based on ICPC results prior to publication of the data without the disclosure of this activity and agreement by the ICPC.

Yes: ___ , No: ____

Name in print : _____

City, Date : _____ , _____

Signature : _____

Please return signed copies by fax or email to:

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