Editorial

Future directions in asthma pharmacogenomics

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One of the significant challenges in pharmacogenomics is that, for the most part, drug trials have small sample size. For example, in asthma, 90% of all drug trials enroll under 200 subjects thus making conventional genome wide association studies (GWAS) difficult. Sample size is further limited in that usually you are using only one arm of the clinical trial; the active drug treatment arm, to assess gene drug interaction. Interaction poses an addition burden on study power in pharmacogenomic studies. Although aggregation across multiple trials using meta-analysis techniques, as done by Li *et al.* in the current issue of *Annals of Translational Medicine* (1), is one traditional way to address this small sample size issue it has its limitations as entry criteria, and dosing differences vary across trials, often giving substantial heterogeneity that can compromise the ability to successfully perform meta-analysis. Since the trend in genetic association is to have larger and larger numbers of subjects to allow for assessment of rare variants this design approach is not optimal. Are there alternative approaches that might work?

One novel approach, again suggested by Li *et al.*, would be to add other omics to GWAS to enhance the ability to detect genes and pathways of relevance to drug treatment response (1). While there may be merit to this approach, it has at least one potential Achilles heel in that one is still comparing across individuals in a relatively small treatment arm and the between individual variability can be so great that the gene-drug effect is not detectable due to low power.

What is needed is a sensitive but specific omics strategy that can be adapted to the small sample size seen in asthma trials. There is an approach that is beginning to show promise. This approach is to use the individuals in the active treatment arm of a trial as their own control and perform RNAseq prior to drug administration and after drug administration to determine the within individual variability in change in drug response as reflected by change in gene expression due to drug. This approach has proven to be very sensitive and specific for drug treatment response and has already identified novel pathways of how asthma drugs actually work (2,3). This approach has formed the basis for a newly funded R01 for treatment response to asthma biologics R01 HL161362. The approach does require intentionality, at least to the extent that RNA is collected both before, and after, drug administration but also, by focusing on within person drug response, and ignoring the between person drug response, there is much greater likelihood of finding relevant novel genes and pathways influencing drug response with a small sample size. Obviously, one can add additional omics to the pre-post RNAseq, one addition of great interest and effect would be miRNA that can be assayed on the same RNA sample taken before and after drug administration. This would allow for the construction of mRNA-miRNA networks and creates an obvious approach to network validation by manipulation of miRNA-mRNA response. Other omics such as metabolomics, DNA sequencing and proteomics could be added as well. Another potential addition to such an approach would be the creation of lymphoblastoid cell lines from the responders and non-responders in such a pharmacogenomic study design. This would provide for the ability to perform *in-vitro* experiments directly referable to clinical responders and non-responders.

The last 25 years of asthma pharmacogenomics have identified many novel genes for treatment response

primarily using genetic association studies but the next 25 should be even more productive using these new novel study design approaches and multiple omics.

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