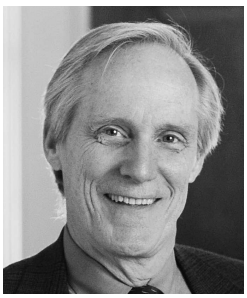
Editorial

Prospecting for Precision: Promises for Personalized Medicine



In this issue of *The Journal*, co–first authors Kim, Bang, and colleagues present provocative data suggesting an association with the clinical response to cyclophosphamide (CYC) therapy in patients with active lupus nephritis: whether administered according to the US National Institutes of Health (NIH) regimen of monthly intravenous doses or according to the Euro-Lupus biweekly schedule, response to CYC is associated with single-nucleotide polymorphism (SNP) in the telomeric end of the *FCGR* gene cluster adjacent to *FCGR2B* on chromosome 1q23[1]. The *FCGR2B* gene encodes the cell surface receptor, FcγRIIb (CD32B), which is the only Fcγ receptor with a tyrosine-based inhibitory motif in the human genome. The prospect of genetically based personalized, precision medicine coming to rheumatologic conditions apart from certain autoinflammatory and rare disease states[2] and specific considerations in pharmacogenomics[3] is very appealing and holds high promise for the future. The reasonable question is whether we have arrived or have more to do.

The study by Kim and Bang's group defines complete, partial, and non-responsiveness to CYC and relates these clinical categories to nearly 500,000 SNP in germline DNA obtained in a genome-wide association study. The technology is powerful and continues to advance with more densely featured SNP genotyping arrays and even with whole-genome sequencing, which is now both technically and financially within reach. Thus, the study design often determines the power of any given project, and Kim and Bang's group points out that their study population is relatively small and that there is no replication to confirm findings. Fine mapping, in large part through imputation, suggests local support for the association of clinical non-responsiveness with an SNP at the 3' end of *FCGR2B* (rs6697139), but the availability of other directly genotyped markers in the region is limited. This is not a surprise because the human FCGR locus is characterized by a distant duplication event, compounded by both additional deletions and duplications within human populations[4,5].

Nonetheless, the finding of an association of an SNP just 3' of the *FCGR2B* coding region is intriguing. Fc receptors encoded in this region of the genome bind IgG antibodies and are integral to the handling of immune complexes, whether for disposal or for cell signaling with activation of cell programs in myeloid cells, platelets, B lymphocytes, natural killer cells, and even some T lymphocytes[6]. In addition to pathways activated through Fc receptors *per se*, the cell signaling pathways initiated in response to nucleic acid-containing immune complexes may result from cooperative signals between Toll-like receptors and Fc receptors. Such cooperative signaling may also engage complement receptors after fixation of complement by the immune complexes; and based on the antigen in the immune complexes, it is likely that other receptor systems can be engaged both on the surface and in the cytoplasm of the cell.

Predicting the effect of an SNP such as rs6697139 can be challenging. The effect of a nonsynonymous coding SNP, which changes the protein sequence, can be approached with various bioinformatics algorithms[7]. Such protein coding variants have been identified and studied among members of the human low affinity Fc receptor cluster; and variants affecting ligand binding affinity[8], glycosylation sites[9], lateral mobility in the plane of the cell membrane[10], and signaling potential[11] have been identified. Variants affecting expression include not only regulatory SNP but also stop codons in coding sequences that affect expression by causing premature termination[12]. Studies of putative regulatory SNP are most straightforward when they are in the proximal promoter[13], and more difficult when they are in more distal sites. It is possible that CYC is affecting *FCGR2B* expression through an effect mediated by the rs6697139 major allele; but the work of Palmero, *et al*[14], referred to by the Kim and Bang group, suggests augmentation of receptor binding and with increased functional activity with CYC administration rather than the inhibition of function one might anticipate with increased expression (and binding function) of the inhibitory FcγRIIb. Despite this ambiguity, regulatory SNP are likely to play an important role in the genetic architecture of autoimmune phenotypes[15]; and the understanding of how they contribute to disease risk and inform precision medicine is an exciting challenge for future investigation.

The goal of precision medicine is often phrased as the

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right treatment for the right patient at the right time. It has been embraced by many research initiatives and agencies including the European Union's Innovative Medicine Initiative 2 (www.euresearch.ch/en/european-programmes/further-programmes/jtis/innovative-medicines-initiative/), the Canadian Institutes of Health Research Signature Initiative (www.cihr-irsc.gc.ca/e/43627.html), and the NIH's Precision Medicine Initiative program (www.nih.gov/precision-medicine-initiative-cohort-program), and holds the promise of more effective healthcare and better health. It also anticipates a deeper understanding of both individual and population-based differences in disease manifestations and disease management, based on genetic background, environment, and lifestyle. Might there be some such clues about lupus nephritis in this work by Kim and Bang's group?

It is interesting to note that rs1050501, a nonsynonymous SNP at position 161643798 in the genomic region encoding the transmembrane segment of FcγRIIb (Ile232Thr), is a strong risk factor for systemic lupus in multiple East Asian populations, but not in white populations[16,17]. It lies between rs1771568 and rs10917686 (see Table 2[1], Kim and Bang) and might be involved in the proposed association of rs6697139 with therapeutic response. Such an involvement could reflect rs6697139 serving as a surrogate marker for rs1050501 through linkage disequilibrium. Alternatively, both SNP might influence distinct and synergistic biological properties, or there may be some other epistatic relationship reflecting ancestral background. The insight, and perhaps the caution, could be that the proposed association of rs6697139 with the clinical response of lupus nephritis to CYC therapy may be reproducible in East Asians but not in other ancestry groups, just as the rs1050501 association with lupus risk is most strongly found in East Asian groups but only weakly in other population groups.

Thus, the answer to the question initially posed is that we have not yet arrived and we have more to do. The concept of personalized, precision medicine has generated a great deal of interest since genomic technology matured to the point of making genetic contributions to the matrix of precision achievable. Nonetheless, the prospect generates controversy[18], and we can anticipate that the pages of *The Journal* and other forums will serve as sounding boards for new applications and approaches to "big data," and potentially for our approaches to clinical trials[19] as we develop a deeper understanding of both individual and population-based differences in disease manifestations and disease management.

ROBERT P. KIMBERLY, MD;
Howard L. Holley Professor of Medicine,
Director, University of Alabama at Birmingham Center for Clinical and Translational Science,
University of Alabama at Birmingham,
Division of Immunology and Rheumatology,
1530 3rd Avenue South,
Birmingham, Alabama 35294-2182, USA.
Address correspondence to Dr. R.P. Kimberly; E-mail: rpk@uab.edu

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