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# Riding technology waves

Biological investigation has changed markedly over the past 200 years and much of that progress has been fueled by advances in technology. The most recent technological milestone reached is the draft human genome sequence, published in *Nature* and *Science* this past month. Investigators now have at their disposal one of the greatest data repositories ever assembled. The knowledge acquired by sifting through this marvelous compendium is already spawning new directions for inquiry into the basics of immune regulation and will eventually provide insights on how to manipulate the immune system to prevent and treat immune-based disorders such as autoimmune conditions, cancer or immunodeficiencies.

As with all progress, the more things change, the more they stay the same. Scientists still classify, but technical advances have shifted the focus from classification of species to categorizing protein families. The advent of the complete human genome sequence will not be "the end of genetics as we know it", as suggested by some, but merely switch emphasis from a concentration on single genes to the consideration of systems of genes.

Immunologists have a history of taking advantage of the latest technological developments. Microscopic and surgical techniques moved immunology from its roots in vaccine development and the chemistry of haptens to new areas, such as defining the role of lymphocytes and the thymus in immunity. Inbred animal strains that are resistant or susceptible to various pathogens helped focus attention on the genetic basis of the immune response. Transplantation studies also brought genetics to the fore, in an attempt to understand and overcome graft rejection. The demonstration that immune responses could be mapped to a major locus, and that this locus could be further mapped through judicious crossing of strains, pointed to the importance of the major histocompatibility complex of genes. Some of the best of mammalian genetics was achieved by immunologists struggling with questions of compatibility.

But the most significant recent advances have been realized with molecular tools. The realization of the utility of restriction enzymes coupled with the ability to deduce the sequence of genes presaged molecular biology's great contributions to the medical sciences: suddenly the keys were available to many a puzzle. One of the first great outstanding questions in all of biology to succumb to the new technology was the pioneering work by Tonegawa and Hozumi, in their *tour de force* demonstration of the existence of somatic recombination at the immunoglobulin locus. The study of gene rearrangement in lymphocytes coupled with the stunning elegance of flow cytofluorimetry (another technology that forever changed immunology) put lymphocytes on the cutting edge of studies in mammalian development and cell lineage commitment. Thus, harnessing new technological advances has served immunology well and provided closure to questions that were especially contentious and murky, such as definitively demonstrating the lack of an I-J locus in the murine immune response region (from which an antigen-specific suppressive factor was proposed to arise).

Accumulated data pertaining to the human genome greatly simplifies the quest for genetic answers, although the compendium remains imperfect. Because the genetic sequence is not 100% trustworthy and the search and motif tools are not yet error-free, mining the gems from this hoard of data is still not a trivial exercise. Nonetheless, we can expect much over the next few years. Combining expressed-sequence tag libraries with whole genome scans will undoubtedly uncover more members of immunological protein families. A better understanding of which newly discovered members are important to particular aspects of immune regulation will aid in development of therapeutics that more discreetly target tissues, stages of development or the most relevant processes. Complete knowledge of the genome also improves DNA microarray design by lessening the chance that commercial or lab-generated arrays fail to contain the appropriate sequences, leading to better identification of the key genes responsible for inflammatory, allergic and other immune responses.

One of the most intractable problems in modern medicine is the unraveling of the numerous genes involved in susceptibilities to various autoimmune pathologies, tumors and degenerative diseases. With different genetic analyses for these multigenic disorders pointing fingers at common culprits, at present it is not clear how to translate what has been learned into specific treatments. The "new genetics", with its basis in the work of the Human Genome Project, married to more traditional human genetic studies, massive mutated mouse screens and gene-display assays heralds faster progress than ever on this front. Thus, the sequencing of the human genome, while a milestone in and of itself, only proclaims the new era. New technologies will continue to create fresh avenues of inquiry and new therapeutics. Like all beginnings, this one comes wrapped with hopes and fraught with uncertainties. One thing that is certain, however, is that a new era of insight into the complexities of immune regulation and dysregulation is well underway.