Applying molecular immunohematology discoveries to standards of practice in blood banks: now is the time

Gregory A. Denomme and Willy A. Flegel

Lessons from more than 100 years of immunohematology exemplify that many critical discoveries were made serendipitously and their more rapid implementation could have benefited transfusion recipients and pregnancies. Constituents of blood that are not essential for the attempted therapeutic benefit of a transfusion are largely removed from today’s blood products. We are now moving on to avoid unnecessary exposure to potentially harmful constituents of the therapeutically required cells, like blood group antigens that are foreign to the patient. Cost efficacy needs to be kept in mind but may eventually prove much better than anticipated, once hidden benefits are captured, as we show by examples from past immunohematologic developments. Here, we detail clinical applications for molecular immunohematology advances including “dry-matching” that will improve transfusion outcomes and argue for their widespread implementation by rapid timelines through standards of practice.

A
dvances in clinical immunohematology, like in many other fields of science, occur with staggered frequency. Each innovative application or development stems from a discovery followed by peer acceptance as a standard of practice. The lag phase from innovation to a standard of practice varies depending on a number of factors such as clinical urgency, limitations of the existing practice, and improvements in safety. The better use of resources, like the introduction of automation, may entail sometimes an obvious cost-to-benefit ratio.

It took several decades after the discovery of the ABO blood group system in 1901 and anticoagulated storage of blood in 1918 for international acceptance of lay blood donors as a standard of practice to support community transfusion needs. In the meantime, it seemed too cumbersome to coordinate A, B, and AB matching and precompatibility testing, despite the proof of principle in 1913. Many institutions simply used the “null” group O phenotype found among staff and faculty for transfusion purposes. Once the demand for blood increased and blood banks were established to prepare and store blood, it became practical to amass resources to test for the A and B antigens and to collect donations of all four prevalent ABO blood groups from the public.

In 1942 Rhesus (Rh) was recognized as the next most clinically important blood group system in pregnancy and transfusion. In 1945, the antiglobulin technique was described and within a mere 6 years the Lutheran, Kell, Lewis, Duffy, and Kidd blood group systems were identified. In fact, by the time the AABB was inaugurated in 1947, immunohematology had begun what could be considered its first golden era. A tally of the blood group antigens listed in the index of Peter D. Issitt’s Applied Blood Group Serology published in 1970 is a reminder of the impact that reagent red blood cell (RBC) screening and antibody identification had to immunohematology. During this era, the standards of practice were adapted

ABBREVIATIONS: AIHA = autoimmune hemolytic anemia; DVI = D category VI; HDFN = hemolytic disease of the fetus and newborn; RgG = Rh immune globulin.

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regularly as clinically significant blood group systems were identified and enhancement reagents were introduced, like albumin, low-ionic-strength saline (LSS), and hexadimethrine bromide (Polybrene, Sigma-Aldrich, St Louis, MO). The use of compounds to alter the RBC membrane, like enzymes and ZZAP, also became more common. At the close of the past century, solid-phase and column agglutination platforms became part of the standard of practice in immunohematology.

**MOLECULAR METHODS IN IMMUNOHEMATOLOGY**

The turn of the past century may be considered a watershed from the introduction of molecular methods into immunohematology. In 2006 and 2007, more than 82 reports on blood group antigens were published in *TRANSFUSION* alone. While serology is retaining its relevance, 15 of these 82 publications could be considered to be based on RBC antigen serology only. Approximately two-thirds of these publications, however, would outright qualify as “molecular.” Many molecular immunohematology publications addressed routine clinical applications and clinical consequences. A large number of publications on basic transfusion medicine research topics document the need to explore genetic features and to collate the allelic variety present within and among the various populations worldwide. A Workshop on Molecular Methods in Immunohematology was sponsored in September 2006 by Food and Drug Administration (FDA)/Center for Biologics Evaluation and Research, Department of Health and Human Services Office of the Secretary/Office of Public Health and Science, National Institutes of Health/National Heart, Lung, and Blood Institute. The report of the event is a testament to the relevance that active transfusion medicine research groups attribute to molecular immunohematology. It also shows a shift to clinical applications of molecular immunohematology methods that is in full swing.

**ADOPTING STANDARDS OF PRACTICE IN IMMUNOHEMATOLOGY: LESSONS FROM THE D CATEGORY VI STORY**

Progress from discovery to the implementation and then recognition as a standard of practice is often slow. The development of antisera over the second half of the 20th century is particularly insightful. The story of D category VI (DVI) is a good example how serendipitously a novel technology gets introduced into practice despite its immediate benefit for the transfusion recipients concurrent with cost efficacy. The solution to the DVI problem was not entirely obvious and would not have been possible without research in the application of monoclonal antibodies (MoAbs) as blood grouping reagents. DVI was discovered in 1962 and DVI transfusion recipients are long known to develop alloanti-D frequently, if transfused with D+ blood. Yet, it was not until 1996 that the first regulatory body mandated the immediate-spin (direct agglutinating) phase of anti-D testing not reactive with DVI RBCs. The solution to the problem was found inadvertently by an innovative application of MoAb technology. It was resolved by producing blended anti-D reagents that did not react with DVI in the immediate-spin phase (performed only on transfusion recipients and pregnant women) and were positive when tested using the indirect antiglobulin phase (donors and newborns). Research was not specifically channeled into the problem of distinguishing DVI RBCs, which was deemed to be of limited value because carriers of DVI are infrequent (<1 in 5000 in Central Europe) and to some extent restricted by ethnicity. Moreover, the DVI issue was mired in assigning a different D status to people who present as a recipient and later as a donor. Good clinical practice prevailed eventually and patients and pregnant women benefited from the advancement in MoAb production.

If we step back a little further, the landmark discovery on MoAb production in 1975 was adapted to manufacture blood group antisera after a lengthy controversy initially independent of the DVI issue. When the first murine monoclonal anti-A and anti-B were reported from research laboratories in 1980, followed by human monoclonal anti-D in 1987, they were greeted with statements like “at best of research interest only,” “may define the phenotype more precisely for basic research,” “of no possible clinical or routine value,” and “much too expensive for any foreseeable future.” However, at the Second International Workshop and Symposium on Monoclonal Antibodies against Human Red Blood Cells and Related Antigens in Lund 1990, the astounding benefits for clinical use were already apparent to immunohematologists with an interest in this field.

It was understandable that MoAbs had exceptionally robust and unique specificity. But it was quite unexpected that immunoglobulin M (IgM) anti-D would have innovative applications over the use of immunoglobulin G (IgG) anti-D. The immediate idea was that IgM monoclonal anti-D reagents could be used in automated phenotyping platforms and at high dilution, which of course made them extremely attractive from an economical standpoint by cutting the costs to less than 10 percent compared to polyclonal antisera. Moreover, MoAbs unexpectedly proved to be useful to distinguish DVI from normal D, a task previously insurmountable and therefore neglected when polyclonal anti-D was the standard of practice.

Research in what appeared to be an impractical and complicated technology, that is, the use of monoclonal anti-Ds and their reactivity with variant D RBCs, eventually came to fruition: a detailed understanding of the topology of partial D antigens was achieved, the way was
paved to monoclonal antisera as a standard of practice in immunohematology in the 1990s, the DVI issue was resolved, and the potential for their use as a replacement therapy of human-derived Rh immune globulin (RhIG) was opened up. All these innovations were accomplished for the benefit of the patient.

### TIMELINES FROM IMMUNOHEMATOLOGY DISCOVERIES TO THEIR APPLICATION

A specific application or benefit of a discovery may be obvious in the beginning but later the same innovation may prove instrumental in solving more than one problem. Some discoveries moved more rapidly based on urgency regardless of the complex nature of the solution to the problem. Anti-D prophylaxis was based on a seminal work in the early 1960s and was rapidly captured as the concept for the prevention of hemolytic disease of the fetus and newborn (HDFN). It took only 4 years from the first human experiments to implementation for the prevention of HDFN. Some 25 years later, anti-D was shown to be useful for the treatment of childhood acute immune thrombocytopenic purpura and then adult chronic immune thrombocytopenic purpura. Who would have been able to predict the chain of events in 1964 when the administration of passive anti-D was first proposed as a preventative treatment for HDFN?

There had been a debate about the need for anti-complement activity in antiglobulin serum and in particular what complement components should be detected. The requirement for anti-complement activity in antiglobulin serum for use with the direct antiglobulin test (DAT) was proposed as early as and into the mid-1970s when eventually anti-C3d was described. Later, the possible failure of monospecific anti-IgG to detect clinically significant anti-Kidd became a major concern. Some anti-Kidd were detected with antiglobulin serum only, and although they are rare, the work in the antiglobulin field demonstrated the need of RBC reagents with homozygous inheritance for Kk and Jk antigens.

It is worthwhile to recall a number of practical immunohematology discoveries and their application to a standard of practice (Table 1). We realize that there are often lengthy timelines from their discovery and application in innovative laboratories to their recognition as standards of practice.

### IMPACT OF KEY DEVELOPMENTS

There are many examples testifying how a “bench-to-bedside” approach has improved patient care in transfusion medicine (Table 2). Recombinant blood components have largely replaced pooled fractionation and for good reason. Leukoreduction is another example how an innovation that was initially designed to address one problem, like platelet (PLT) refractoriness due to HLA alloimmunization, may eventually prove to have benefits of larger relevance in other aspects of transfusion medicine, like reduction in postsurgical infection and length of hospital stay. Infectious disease detection by nucleic acid amplification testing (NAT) and HLA typing by high-resolution genotyping of HLA-A and -B are other innovations that have been or are currently being adopted into standards of practice.

**TABLE 1. Immunohematology discoveries and their practical application listed by approximate years**

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Year</th>
<th>Standards of practice in blood banks</th>
<th>Year</th>
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<tbody>
<tr>
<td>ABO blood group system</td>
<td>1901-1913</td>
<td>Blood banks established in North America</td>
<td>1935</td>
</tr>
<tr>
<td>Rh, Lutheran, Kell, Lewis, Duffy, and Kidd</td>
<td>1939-1951</td>
<td>US Public Health Services issue permits to manufacture blood</td>
<td>1946</td>
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<tr>
<td>AABB establishes and promotes Standards</td>
<td></td>
<td></td>
<td>1947</td>
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<tr>
<td>Anti-D immunosuppression</td>
<td>1962</td>
<td>RhIG prophylaxis</td>
<td>1965</td>
</tr>
<tr>
<td>Antiglobulin reagent</td>
<td>1945</td>
<td>Increased sensitivity for antibody detection</td>
<td>1945-1951</td>
</tr>
<tr>
<td>Enzyme-treated RBC</td>
<td>1947</td>
<td></td>
<td>1952</td>
</tr>
<tr>
<td>LISS</td>
<td>1964</td>
<td></td>
<td>1974</td>
</tr>
<tr>
<td>Polybrene</td>
<td>1977</td>
<td>Monoclonal anti-A/B approved for clinical use</td>
<td>1980</td>
</tr>
<tr>
<td>MoAb production</td>
<td>1975</td>
<td>First standard for monoclonal anti-D</td>
<td>1989</td>
</tr>
<tr>
<td>Clinical significance of DVI</td>
<td>1982-1983</td>
<td>Automated and semiautomated instruments</td>
<td>1992</td>
</tr>
<tr>
<td>Solid-phase testing</td>
<td>1984</td>
<td></td>
<td>1993-1999</td>
</tr>
<tr>
<td>Column agglutination</td>
<td>1990</td>
<td>DNA-based genotyping methods and kits</td>
<td>2000</td>
</tr>
<tr>
<td>Nucleic acid sequences of blood group genes</td>
<td>1987-1995</td>
<td>Molecular protocols when RBC phenotyping fails</td>
<td></td>
</tr>
<tr>
<td>GYP, ABO, RH, KEL, JK, FY</td>
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**MOLECULAR IMMUNOHEMATOLOGY STANDARDS OF PRACTICE**

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directly only within the past 5 years.\textsuperscript{126} The implementation of predonation sampling has reduced the incidence of bacterial contamination since then,\textsuperscript{127,128} and research in pathogen inactivation may soon be introduced into practice. Have we invested wisely in transfusion medicine when we are just beginning to address PLT bacterial contamination and posttransfusion alloimmunization, while on the other hand, we have repeatedly reduced the incidence of transfusion-associated viral transmission to the point where additional investments will be met with a small incremental benefit?

In comparison, little has changed in the majority of blood group laboratories as a result of molecular immunohematology discoveries since the early 1990s. Immune-mediated transfusion reactions have been well documented for more than 60 years\textsuperscript{8} with the risk of delayed hemolytic transfusion reactions still estimated to be 1 in 2000 per patient transfused, and the risk of a delayed serologic transfusion reaction remains at approximately 1 in 2500 per unit transfused.\textsuperscript{129-136} What is surprising is the paucity of studies designed to evaluate the impact that delayed transfusion reactions can have on transfusion recipients, in terms of hospital stay, comorbid implications, the effect on blood bank resources, and the overall effect on the health of the patient, especially those who have the highest risk like older intensive care patients with a history of transfusion and pregnancy. Yet, molecular innovations, which could lower the risk of severe adverse transfusion reactions, have not been adopted as a standard of practice.

Because the risk of viral transmission by blood products has nearly been resolved and bacterial contamination of PLTs is being addressed, the next most common risk in transfusion medicine are immunohematologic complications: the delayed transfusion reaction and its associated risks of morbidity and mortality should be the next issue to be addressed as other transfusion-associated risks become more and more remote. While transfusion-related acute lung injury (TRALI) is currently a major research focus, we cannot exclude the possibility that the morbidity and mortality associated with delayed serologic and hemolytic transfusion reactions may be equal to or larger than those associated with TRALI.

**DIVIDENDS PAID BY MOLECULAR IMMUNOHEMATOLOGY APPLICATIONS**

Innovations in immunohematology are widespread and their solutions to concrete problems in transfusion medicine are obvious. For several applications, the solutions are simple and affordable. Moreover, if these solutions are like in any other field of medicine, there will be dividends applicable to different areas of transfusion immunology and possibly biology. For instance, the additional advantages that MoAbs provided to applications in transfusion
Matching the genotype of donor and patient could have been anticipated by many of us, and how could they have been? The DVI story is a case in point, and several suppliers that failed to adopt MoAb technology or lagged behind in its implementation were forced out of the market. Such lessons from paradigm shifts in immunohematology should be heeded by suppliers as well as researchers in the field alike, unless we wish to forgo important quality benefits at a very reasonable incremental price tag or in some instances at a calculable cost saving in patient care.

PRESENT APPLICATIONS FOR MOLECULAR IMMUNOHEMATOLOGY DISCOVERIES

An impressive list of applications for molecular immunohematology discoveries exists today.

- Among the 302 acknowledged RBC antigens, the molecular basis is known for nearly all of the 262 antigens that are clustered in the 29 currently recognized blood group systems. Microarray-based platforms are set to perform mass donor blood group genotyping for several clinically important blood group genotypes. It has been predicted in editorials, reviews, and discussions that molecular blood group genotyping could replace serologic phenotyping of blood.

- In the clinical setting, a multitude of molecular biologic techniques performed by immunohematology laboratories have demonstrated a direct benefit to the patient. Soon after the RH D gene was identified, the genetic prediction of fetal risk for HDFN was devised. This innovation used amniotic fluid-derived DNA and obviated the need to obtain fetal blood for risk assessment and also became feasible for antigens other than D. The test is now standard of practice and the College of American Pathology provides survey samples to evaluate competency.

- The electronic crossmatch has been implemented in a minority of laboratories in the United States and the United Kingdom as an attempt to reduce blood bank activity that was considered unnecessary; many potential transfusion recipients are not alloimmunized and a full “wet” crossmatch was deemed a waste of valuable resources.

- Matching the genotype of donor and patient could also replace allo- and autoabsorptions. The current turnaround time may be 6 to 8 hours for a patient with autoimmune hemolytic anemia (AIHA) with positive DAT and after recent transfusions, which could be achieved faster by molecular techniques.

- The molecular bases were established for the Donbrowk major antigens in 2000 and for Scanni in 2003. The clinical relevance will be captured eventually since phenotyping for antigens of these blood group systems had hitherto been impracticable, simply because there is no supply for such routine antisera. In commercial reagent RBC panels, Do4/b or Sc4/b are infrequently designated, which alone would benefit patients by identifying these clinically significant alloantibodies during pretransfusion testing.

- Problems with availability of some antisera are paralleled by their skyrocketing costs. Molecular techniques are steadily improving and their costs are going down. We may soon experience a day when molecular technology will actually be cheaper than serology in addition to being better. For some practical applications, this day has already past.

- Some laboratories still use inappropriate Rh haplo-type frequency tables to determine paternal D antigen zygosity in light of the fact that Rhesus box analysis and RH D gene dosing provide much more reliable approaches. The discovery of Rhesus boxes and the confirmation of their clinical applicability made RH D zygosity determination a reality within a few years.

These are but a few examples of the several innovations in molecular immunohematology (Table 3). Many of them should become a standard of practice in immunohematology soon.

IMPEDEMENTS TO MOLECULAR IMMUNOHEMATOLOGY

Why has there not been a clear and more rapid progression from discovery and innovation in molecular immunohematology to a standard of practice? One reason may be that some innovations are alleged to lack a reasonable cost-to-benefit outcome. Indeed, there are regulatory and financial obstacles that prevent innovations from benefiting patient care. We propose that there are, among other possible avenues, regulatory ways to let these innovations become standard of practice.

For example, full submissions for FDA approval may come with a US $300,000 price tag. It is encouraging that the FDA provides avenues for review of in-house applications of innovations and is willing to provide feedback as to their suitability. Many molecular immunohematology innovations could become standards of practice because of their impact that serology cannot address. As a point in case, Do4/b designation on commercial reagent RBC panels could be recommended at a minimal incremental cost, since the major expense for reagent panel cells are the marketing and distribution costs. In the European Union, test kits delineating partial D from weak D types and to genotype for several clinically important
blood group antigens were licensed several years ago.\textsuperscript{113,117}

There is an immediate need to teach more blood bank technologists in molecular blood bank theory and techniques. While there will remain plenty of work for classical blood serologists for many years to come, innovative technologists have started to apply molecular testing for the benefit of their patients now. Small molecular research units are not going to be able to provide molecular testing on a 24/7 basis and as fast as clinically needed. Decisions are needed to remove impediments due to these required investments in personnel and infrastructure.

### TOWARD “DRY-MATCHING” RBC TRANSFUSIONS BY BLOOD GROUP GENOTYPES

The goal of immunohematology research is to improve the safety and efficacy of transfusions. Our immediate aim in immunohematology should be to implement current molecular innovations now. Future molecular research should be directed to reduce the risk of delayed immune transfusion reactions, which can be prevented most consistently by eliminating any potential RBC alloimmunization in the first place. The ultimate goal is to make it clinically feasible to antigen-match RBC units with recipients using blood group genotypes only, which we would like to term “dry-matching.” Similar terms had been proposed, like allelic matching (A-matching), extended antigen-matching (EA-matching), blood group antigen-matching (BGA-matching), genomatching, or in silico matching (IS-matching).

### THE FUTURE OF IMMUNOHEMATOLOGY

We pose four key questions, which future immunohematology research and development should address, and provide a detailed approach to their resolution (Table 4).\textsuperscript{172-180} Several of these innovations could be recommended and instituted immediately.

First, it should be noted that the alloimmunization rate of 1 in 2000 during pregnancy\textsuperscript{181-184} still represents a significant risk to the fetus and newborn. Implementing innovations that lower the rate of alloimmunization by transfusion would consequentially reduce this risk of secondary immunization by the fetus. The multiply transfused patient who becomes alloimmunized can benefit from molecular blood group genotyping where serology is unreliable due to recently transfused RBCs. The same argument applies in the setting of AIHA\textsuperscript{160} where protocols should be used to genotype patients as RBC phenotyping is unreliable.\textsuperscript{117} Both recombinant and soluble antigens should be developed as nonsubjective tools for the specific detection of clinically significant antibodies and the
TABLE 4. Key immunohematology questions and future approaches and applications

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<thead>
<tr>
<th>Question</th>
<th>Approaches to its resolution</th>
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<tr>
<td>How can improvements to pretransfusion and perinatal screening benefit patients?</td>
<td>Commercially available RBC reagent panels can be improved: Genotype designation like homozgyosity for RHD, FyA and FyB, or DoA and DoB should become a recommended standard of practice. Investments can be made in the use of recombinant blood group antigens and in proteomic and microfluidic devices to detect alloimmunization. Where recombinant antigens are not feasible, exalted antigen RBC antigen expression can be explored (e.g., D antigen). Mass blood group genotyping would identify rare antigen combinations including null RBC. Soluble recombinant reagents to detect/neutralize high frequency clinically insignificant antibodies can be made available for use in clinical diagnostics/antibody investigations. Molecular weak D testing to distinguish partial and weak D types would avoid use of D− blood where D alloimmunization is not a risk. RhiG prophylaxis would be avoided in pregnancy when weak D types are identified. Neonatal ABO genotyping opens up the use of ABO-matched neonatal transfusion in the absence of a reverse group. Anti-D alloimmunizations in pregnancy can be due to inadequate administration of RhiG, population variation in the immune response to the D antigen (mother-to-infant &quot;vertical&quot; alloimmunization) and the inadvertent previous transfusion of D+ blood (errors in weak D and DEL detection). There should be a focus on avoiding anti-D immunization and improving its detection, possibly T-cell responses. The &quot;most probable genotype&quot; method for paternal zygosity should be replaced by molecular assays to determine RHD zygosity. Detection of fetal RHD DNA in maternal plasma could be used to avoid exposure to human-derived RhiG. What can be done for donor testing to improve transfusion safety? Mass blood group genotyping can be developed to a standard of practice for extended donor database management. Donors can be screened for low copy number antigens (e.g., weak D or DEL). The benefits of patient-to-donor pretransfusion RBC genotype dry-matching can be realized. Nonhemolytic antibody induced loss of RBC antigens during transfusion of crossmatch-incompatible blood may hint to more general mechanisms in transplantation. Identification of immune response genes for a specific blood group antigen (e.g., D antigen) would be beneficial to transfusion medicine and apply to several fields outside immunohematology. The oral induction of D antigen tolerance can be explored because of its potential clinical application and general interest in immune regulation. The mechanism of RhiG prophylaxis can be researched. Studies on the regulation of blood group allo- vs. autoimmunizations and their dependence on minute differences in antigen structure may hint to an underlying mechanism of loss of self tolerance. Resolving the Rh crystal structure and the function of the Rh complex will be of significant general biologic interest.</td>
</tr>
<tr>
<td>Is the management of D− pregnancies both appropriate and optimal?</td>
<td>Anti-D alloimmunizations in pregnancy can be due to inadequate administration of RhiG, population variation in the immune response to the D antigen (mother-to-infant &quot;vertical&quot; alloimmunization) and the inadvertent previous transfusion of D+ blood (errors in weak D and DEL detection). There should be a focus on avoiding anti-D immunization and improving its detection, possibly T-cell responses. The &quot;most probable genotype&quot; method for paternal zygosity should be replaced by molecular assays to determine RHD zygosity. Detection of fetal RHD DNA in maternal plasma could be used to avoid exposure to human-derived RhiG.</td>
</tr>
<tr>
<td>What are future impacts inside and outside immunohematology?</td>
<td>The benefits of patient-to-donor pretransfusion RBC genotype dry-matching can be realized. Nonhemolytic antibody induced loss of RBC antigens during transfusion of crossmatch-incompatible blood may hint to more general mechanisms in transplantation. Identification of immune response genes for a specific blood group antigen (e.g., D antigen) would be beneficial to transfusion medicine and apply to several fields outside immunohematology. The oral induction of D antigen tolerance can be explored because of its potential clinical application and general interest in immune regulation. The mechanism of RhiG prophylaxis can be researched. Studies on the regulation of blood group allo- vs. autoimmunizations and their dependence on minute differences in antigen structure may hint to an underlying mechanism of loss of self tolerance. Resolving the Rh crystal structure and the function of the Rh complex will be of significant general biologic interest.</td>
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neutralization of insignificant antibodies. At the same time, we should consider carefully how to direct immunohematology resources to reduce alloimmunization further. We know that up to 80 percent of healthy D− persons transfused with D+ blood make anti-D, but 20 percent do not respond. In patient cohorts, the response rate is approximately 20 to 30 percent. Studies designed to develop markers that predict immune response to D (and other blood group antigens) would have direct application to the prevention of RBC alloimmunization and predictably have an impact in other areas of immunology. For example, follow-up of D− transfusion recipients who fail to make anti-D after D+ RBC transfusions may be enlightening through analyzing their immune response genes.

Second, the management of D− pregnant women should be improved, which may further reduce the incidence of anti-D and encourage the appropriate and often more limited use of RhiG. Fetal DNA detection in maternal plasma is an important discovery that would avoid application of a human plasma product and eliminate the need for obstetrical intervention and informed consent.

Third, donor testing can be improved to 1) type RBC antigens at an unprecedented high throughput and level of precision, 2) avoid anti-D alloimmunization (e.g., by weak D blood mislabeled as D−), 3) facilitate antigen matching of appropriate blood products for alloimmunized recipients, and 4) preferably prevent any chance of alloimmunization in the first place. This seemingly unrelated topic of blood group genotyping might be used to explore what motivates human recruitment and repeat donation. Many donors would be happy to learn that their blood is required for a special needy patient. An encouraging report demonstrated that simply hearing about a needy patient or knowing one’s blood type increased the likelihood of donating again.
Fourth, research in some key areas of immunohematology are likely to provide very valuable benefits to other areas of transfusion medicine, much like the Nobel prize-winning work done on the moiety expressing the Colton blood group antigens, which sprang from a curiosity-driven analysis of a “contaminant” during an attempt to purify the RBC membranes’ Rhesus proteins. Understanding the mechanism of antibody-induced loss of RBC antigens and the mechanism of RhIG prophylaxis and resolving the structure and function of Rh are but a few challenges that will likely contribute to basic knowledge outside the field of immunohematology.

Molecular immunohematology may assist with progress to understand the role of blood group antigens in diseases outside the scope of transfusion medicine, for example, the involvement of DARC (the Duffy antigen) in kidney disease, the innate resistance to malaria, or the induction of auto- rather than alloantibodies.

NOW IS THE TIME

We propose that now is the time to realize the benefits that donor-recipient blood group genotype dry-matching would have on reducing the incidence of delayed transfusion reactions and its associated comorbidities, which could be monitored using randomized double-blind controlled trials. Donor and recipient extended matching for Rh, Kel, Kidd, Duffy, and MNS would stop the induction of the majority of alloantibodies that are currently occurring in the more than 80 to 90 percent of the immunized patients. Also, genotyping of recipients would allocate the appropriate blood type for recipients with weakly expressed D and Fy^a^ antigens and for the Fy null phenotype. We could start with key blood group antigens and apply the knowledge to selected particularly vulnerable patient populations.

CONCLUSION

There is a long-lasting trend in the development of blood products and transfusion medicine, which may be captured by the note: “The purer, the better.” Cost-efficacy considerations often delayed the implementation of a purer product but did not prevent its eventual use in patient care. Since cells that are not essential for the attempted therapeutic benefit are largely removed from today’s blood products, we are moving forward to avoid the unnecessary exposure to potentially harmful constituents of the therapeutically required cells, like bioactive substances and antigens that are foreign to the patient. Molecular immunohematology is providing us with the opportunity to implement a novel tool set to personalize medicine and to adapt the blood products to the clinical needs of patients. The technical means are largely available today for this paradigm shift. Once we have started to apply these novel versatile molecular tools, their ensuing clinical benefits will be experienced more widely.

Implementation of molecular immunohematology poses difficulties and their solutions may appear impractical to many people for the moment. However, transfusion medicine specialists with the help of the AABB have formulated solutions that proved beneficial to many practices in immunohematology, and examples from past solutions proved that the introduction of a standard of practice directly benefits patients. Often, the new standard of practice may seem to be expensive and to result in a permanent cost increase. In fact, industrial partners may be reluctant to invest in innovations for exactly this perception. However, we detailed in this commentary several molecular immunohematology innovations that should be implemented now, because of their immediate impact on patient care. Other innovations are imminent to change immunohematology practice profoundly and may affect other fields of transfusion medicine as well.

It may be a sobering thought to note that eventually our current serology-based tool set will be considered primitive. Its improvement by innovative molecular and biologic tools may be disregarded for quite some time by skeptical people as much too complicated. Through standards of practice, the field of molecular immunohematology is still poised to apply innovations that will rapidly prove to be simple.

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