initial induction chemotherapy, MRD was detected in one-third of patients without morphologic evidence of disease, which in turn was highly correlated with relapse and an independent predictor of outcome.[6] In adult AML, prospective studies are about to be published. However, based on the existent data, many AML trial groups are in the process of implementation MRD monitoring (flow cytometry and molecular) in new clinical trials.

Fine-tuning of techniques and merging of flow and molecular genetic assays may ultimately bring us closer to the final goal of real individualized risk assessment and therapy in patients with AML.

MRD is at the edge to offer a new definition for CR and is possibly useful as a surrogate end point for outcome of studies investigating new drugs in AML.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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● ● ● GENE THERAPY

Comment on Martino et al, page 2224

Stealth gene therapy

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In this issue of *Blood*, Martino et al[1] report on a novel adeno-associated viral (AAV) vector, which overcomes one of the last remaining impediments for liver gene therapy, the anticapsid immune response.

Just over 7 years ago, the first successful gene therapy for hemophilia appeared to be at hand, until an unexpected immune response against the vector capsid led to clearance of corrected liver cells and a loss of the replacement factor IX gene.[2] Since that trial, much has been learned, and in 2011, it was reported that intravenous injection of an AAV8 vector encoding factor IX was able to achieve sustained factor IX expression in 6 individuals with hemophilia B.[3] This stunning achievement, long-lasting correction of a genetic disease from a single drug injection, is nearly unprecedented in medicine and will likely change the course of hemophilia therapy.[4] However, although the trial was largely successful, the anticapsid immune response did occur at the most corrective vector dose, and transient immunosuppression with prednisolone was used to prevent the immune system from eliminating hepatocytes harboring the replacement factor IX gene. Thus, improved strategies are still needed to circumvent the anticapsid immune response before AAV can become an off-the-shelf drug for hemophilia B. In Martino et al, High, Herzog, Mingozzi, and colleagues, who pioneered the use of AAV for hemophilia gene therapy,[2,5,6] describe an innovative modification to the AAV capsid that demonstrates the potential to avoid immune-mediated clearance.

One of the challenges of studying the anti-AAV capsid response has been the lack of experimental systems that model the outcome in humans. More than a decade of AAV research in rodents and dogs failed to elicit the anticapsid response that was ultimately observed in humans. Thus, before testing whether they could generate an AAV that would evade the anticapsid response, Martino et al developed a model that would mimic the response in humans. To do this, they immunized mice with a known immune epitope from the AAV2 capsid, isolated CD8+ T cells, and expanded them ex vivo by repeat stimulation with the antigen. This established a pool of CD8+ T cells with specificity against the AAV capsid. When these anticapsid T cells were transferred into mice that were injected 24 hours prior with an AAV2 vector expressing factor IX, they killed the hepatocytes harboring the vector, and this resulted in diminished factor IX expression and an elevation in transaminases in the serum. This was similar to the outcome observed in the earlier human trial of AAV2 and in 1 of the patients in the recent AAV8 trial.[2,3]

With a suitable model established for studying the anticapsid response, the authors evaluated the immune evasive potential of a novel AAV2 vector variant they previously generated,[7] which harbors mutations in 3 different tyrosine residues that are normally exposed on the vector's surface. In contrast to what was observed with the wild-type AAV2 vector, when they transferred anticapsid CD8+ T cells into mice injected with the AAV2 variant vector, there was no transaminitis, and factor IX expression was similar to the levels in mice that did not receive the anticapsid T cells. This is a promising achievement because it was performed in a system that models some of the hallmarks of the patients' response to therapy. It is important to note that the anticapsid response that occurred in patients was subdued by transient immunosuppression.[3] A therapy that does not require any immune modulation would obviously be preferable, but clinical adoption of their AAV2 variant will initially be warranted mostly in patients where immunosuppression is contraindicated. It also remains to be determined whether the tyrosine mutations can be introduced into the capsids of other AAV vector serotypes and improve immune evasion without impacting the efficiency of gene transfer.

The success of Nathwani et al in using gene therapy to establish long-term expression of factor IX in patients with hemophilia B is among a string of recent successes in human gene therapy, which have restored vision to the sightless and released immunodeficient patients from isolation.[8-10] There are still obstacles for gene therapy before it will become a routine treatment, but studies such as that by Martino et al are an excellent example of how bench to bedside and back to bench can help to overcome these obstacles.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● LYMPHOID NEOPLASIA

Comment on Vegliante et al, page 2175

SOX11 is a mantle cell lymphoma oncogene

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In this issue of *Blood*, Vegliante et al establish for the first time the oncogenic role and mechanisms of SOX11 in mantle cell lymphoma.[1]

Mantle cell lymphomas (MCL) are CD5-positive mature B-cell lymphoid tumors derived from antigen-naive pregerminal center B cells located in the mantle zone surrounding normal germinal center follicles.[2,3] The t(11;14)(q13;q32), a chromosomal rearrangement driving overexpression of the cyclin D1 gene, is a hallmark of this disease.[2] Still, the full spectrum of genetic lesions involved in the pathogenesis of MCL remains to be established. MCLs are typically aggressive tumors associated with poor prognosis. However, recent studies have identified a distinct clinical group of t(11;14)(q13;q32)-positive MCL cases that show an indolent clinical course and prolonged survival.[4-6] Notably, smoldering MCLs show hypermutated immunoglobulin genes indicating that they originate from postgerminal center B cells. In addition, they characteristically lack expression of *SOX11*, a transcription factor aberrantly and universally expressed at high levels in aggressive classic MCL cells. Most notably, and in contrast with its high levels of expression in classic MCL, *SOX11* is not expressed in lymphoid progenitors and mature B-cell populations.

Based on these observations, Vegliante and coworkers proposed that aberrant expression of *SOX11* could play an oncogenic role in the pathogenesis of classic MCL. The underlying hypothesis is that SOX11 could sit atop of an oncogenic transcriptional network controlling critical effector target genes and pathways responsible for B-cell transformation and the aggressive clinical course typically associated with SOX11-high MCLs. Should this premise hold true, deciphering the structure of the SOX11-controlled oncogenic network in MCL could identify new therapeutic targets for the treatment of this disease.

Toward this goal, these investigators first addressed the identification of SOX11 direct target genes via chromatin immunoprecipitation microarray analyses using a promoter array platform. These experiments uncovered over 1000 promoter sequences occupied by SOX11 in MCL cells. In addition, and to establish the specific role of SOX11 in the control of gene expression in MCL, they analyzed the gene expression changes associated with *SOX11* small hairpin RNA knockdown. Despite the complexity of the data and the large number of genes controlled by SOX11 identified, 2 major findings stood out from these analyses. First, *SOX11* knockdown in MCL cells results in upregulation of gene expression signatures associated with plasma cell differentiation while suppressing the genetic programs characteristic of B cells. In addition, *PAX5*, a key transcription factor strictly required for the establishment of B-cell identity[7] and a major negative regulator of plasma cell differentiation,[8] stood out as one of the most significant direct target genes upregulated by SOX11 in MCL cells.

Consistently, *SOX11* knockdown cells showed transcriptional and immunophenotypic changes consistent with repression of the B-cell program and upregulated *PRDM1/BLIMP1*, a transcription factor tumor suppressor gene involved in the termination of the B-cell program during plasma cell differentiation.[9] Notably, *PRDM1/BLIMP1* is a known direct target gene repressed by PAX5.[8] Moreover, xenograft studies demonstrated a marked loss of tumorigenic potential in *SOX11* knockdown cells.

The relevance of these findings was then elegantly highlighted by integrative analyses of *SOX11* small hairpin RNA knockdown induced signatures with those derived from a panel of well-characterized MCL clinical samples. These studies showed significant