

## To the editor:

### B cells versus T cells as primary barrier to hematopoietic engraftment in allosensitized recipients

Two publications in *Blood*<sup>1,2</sup> questioned a primary role of cell-mediated immunity in marrow graft rejection among allosensitized hosts, and proposed instead that preformed antibody “was the major barrier to engraftment.”<sup>2(p1307)</sup> Both involved H-2 disparate mice. Antibody-mediated rejection was completed by 3 hours. Two earlier reports, published more than 45 years ago, showed engraftment could be prevented by serum antibodies when mice differed at H-2 but not when the mice were H-2-compatible.<sup>3,4</sup>

How have murine findings translated into the settings of randomly bred larger mammals, including humans?

Most transplantations for patients with aplastic anemia have involved human leukocyte antigen (HLA)-matched donors,<sup>5</sup> and many canine studies on transfusion-induced sensitization used dog leukocyte antigen (DLA)-identical littermates.<sup>6,7</sup> Antibodies to minor histocompatibility antigens have been the exception. Cross-matches between transfused HLA- or DLA-matched recipients and donors were negative. We reported strong correlations between in vitro host cell-mediated immunity against HLA-identical sibling cells and rejections in transfused aplastic anemia patients.<sup>5</sup> Weaker correlations with antibody-dependent cell-mediated cytotoxicity assays<sup>8</sup> were considered “red flags” signifying cellular immunity, since rejections did not occur outright as expected with antibodies but almost always after periods of initial graft function.<sup>5</sup> T lymphocytes from rejecting recipients were host, consistent with cellular mechanisms. Moreover, panel-reactive lymphocytotoxic antibodies in aplastic anemia patients did not predict graft outcomes.<sup>9</sup> Thus, humoral immunity as cause of rejection of major histocompatibility complex (MHC)-matched grafts seemed unlikely.

What about MHC-mismatched grafts, the setting in which murine data were especially persuasive? Human data were inconclusive. While positive B-cell cross-matches predicted rejection, it was less clear that rejections were caused by antibodies. Likely, antibodies were epiphenomena similar to those after cell-mediated rejection of MHC-mismatched skin grafts. Canine studies aimed at overcoming transfusion-induced cell-mediated graft rejections in DLA-mismatched recipients conditioned with 920 cGy total body irradiation (TBI) were more informative. Dogs received either 2 transfusions from marrow donors on days -20 and -13, or 6 weekly transfusions beginning day -50 before irradiation. The first study found that combining procarbazine and rabbit antithymocyte serum (ATS) beginning on day -8 significantly enhanced engraftment compared with controls ( $P < .01$ ) and with dogs given either agent alone.<sup>10</sup> Eight of 10 procarbazine/ATS dogs had anti-donor lymphocytotoxic antibodies and 2 did not. One of the latter

rejected the graft, while the other (and all 8 dogs with antibodies) had sustained engraftment. Overall, 16 of 17 rejecting dogs had antibodies as did 18 of 21 dogs with engraftment ( $P > .05$ ). Therefore, no correlation was found between humoral antidonor immunity and rejection in a setting where cellular immunity was blunted.

Results in the second study were similar.<sup>11</sup> Twelve of 15 procarbazine/ATS dogs engrafted compared with 4 of 15 controls ( $P < .01$ ). We tested for both antidonor antibodies, with findings similar to the first study, and platelet refractoriness on day -15 (Table 1). Among 15 dogs, 5 had reduced platelet recovery and shortened survival; all 5 engrafted. Ten dogs were platelet-refractory; 7 engrafted and 3 rejected.

Taken together, available data point toward cell-mediated immunity as a major barrier to hematopoietic grafts in transfused MHC-matched recipients. At least in randomly bred dogs, cellular immunity also appeared to trump antibodies as primary barrier to MHC-mismatched grafts. The reasons for the differences in results among mice and larger randomly bred mammals were not obvious but might include differences in TBI dosing (borderline TBI doses in some of the murine experiments) and numbers of transplanted hematopoietic cells.

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**Table 1. Marrow donor platelet survival (day -15) in 15 canine recipients**

No. of recipients	Platelet data		Marrow rejection
	Percentage recovery	Days survival	
5	12-75 (median 39)	0.9-3.9 (median 1.5)	No
7	Refractory*		No
3	Refractory*		Yes

In this study,<sup>11</sup> dogs were given 6 weekly preceding blood product transfusions from their donors (beginning on day -50), procarbazine/ATS (beginning on day -8) before 920 cGy total body irradiation (day 0), and hematopoietic grafts from DLA-mismatched unrelated donors.

\*Less than 5% recovery.