Interleukin 18 Gene Transfer Expands the Repertoire of Antitumor Th1-type Immunity Elicited by Dendritic Cell-based Vaccines in Association with Enhanced Therapeutic Efficacy

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ABSTRACT

Dendritic cells (DCs) are potent antigen-presenting cells that can prime and boost systemic antitumor immunity. Here, we have evaluated the ability of DCs transfected to secrete the potent Th1-biasing cytokine interleukin (IL-18) to promote enhanced antitumor immunity in a mouse sarcoma model. DCs infected with a recombinant adenovirus encoding IL-18 (AdIL.18DC) expressed higher levels of MHC and costimulatory molecules and were better stimulators than control DCs in mixed leukocyte reactions in vitro. Immunization of BALB/c mice bearing established day 7 CMS4 tumors with tumor peptide-pulsed control AdG5-transfected DCs or nontransduced DCs significantly inhibited the growth of established tumors but did not lead to complete regression of established tumors. Importantly, immunization with antigen-loaded AdIL.18DC resulted in tumor rejection or further suppression of tumor growth when compared with controls. The repertoire of naturally presented tumor peptides recognized by splenocytes (as deduced in IFN-γ ELISA assays) from AdIL.18DC-treated animals was far more diverse and of greater magnitude than that of all other groups, in association with improved therapeutic outcome. These results support the ability of IL-18 gene transfer to enhance the capacity of DCs to drive broadly reactive Th1-type therapeutic immunity prompted by single peptide epitope-based vaccines (i.e., epitope spreading).

INTRODUCTION

DCs[3] elicit primary and boost secondary CD4+ and CD8+ T-cell responses to specific antigens and are attractive candidates for inclusion in vaccines designed to treat cancer (1, 2). In particular, DCs pulsed with tumor-associated antigens in various forms, including whole cell lysate (3, 4), peptides (5, 6), proteins (7), RNA (8), or DNA (9, 10), have proven effective in promoting protective and therapeutic antitumor immunity in murine models. The results of several DC-based vaccine trials have also been recently reported in the setting of B-cell lymphoma, melanoma, prostate cancer, and renal cell carcinoma, among others (11–14). Although antitumor T-cell responses have been frequently stimulated by such vaccinations, objective clinical responses have only been observed in a minority of treated individuals. We hypothesized that these modest clinical successes associated with DC-based cancer vaccines might be improved if these therapies were modified in a manner that further supports Th1-type antitumor immunity.

IL-18 was originally identified as a monokine with important immunoregulatory functions, including the ability to induce high levels of IFN-γ secretion from both NK and T cells (i.e., IFN-γ-inducing factor; Ref. 15). IL-18 is a M, 18,300 member of the IL-1 family of proinflammatory cytokines, produced by activated macrophages and DCs, that appears to play an important role in driving Th1-dominated immune responses (16, 17).

Recently, the role of IL-18 as a biological “adjuvant” has been evaluated in murine tumor models. Systemic administration of rIL-18 induces significant antitumor effects in multiple murine tumor models (18, 19). However, rIL-18 administration has prompted severe “septic shock-like” toxicities, particularly when combined with rIL-12, that may ultimately prevent the widespread clinical application of this recombinant protein (20). To overcome such systemic toxicities, we examined the effectiveness of therapeutic immunization with genetically transduced DCs to provide paracrine secretion of IL-18 in the microenvironment of evolving antitumor T-cell activation. We demonstrate the novel finding that IL-18 gene-modified DCs not only potentiate the antitumor effects of single synthetic peptide-based immunizations in tumor-bearing mice, but they also prompt the evolution of a larger and more diverse “therapeutic” repertoire of specific antitumor CTLs in situ.

MATERIALS AND METHODS

Mice. Female BALB/c mice were purchased from The Jackson Laboratory (Bar Harbor, ME), used at 6–8 weeks of age, and maintained in microisolator cages. They were handled under aseptic conditions per an Institutional Animal Care and Use Committee-approved protocol and in accordance with recommendations for the proper care and use of laboratory animals. Cell Lines and Culture. CMS4 sarcomas (H-2d) express mutated p53 and present the wild-type p53232-240 epitope recognized by H-2Kd-restricted CTLs (21, 22). YAC-1, a NK cell-sensitive cell line, was a generous gift of Dr. William H. Chambers (University of Pittsburgh). These cell lines were maintained in complete media, as described previously (22).

Generation of DCs in Vitro from Bone Marrow. DCs were generated from BALB/c bone marrow in 7-day cultures as described previously (23) and isolated at the interface of 14.5% (w/v) metrizamide (Sigma, St. Louis, MO) in CM discontinuous gradients by centrifugation. DCs expressed CD11b, CD11c, CD40, CD54, CD80, and MHC class I and class II antigens (data not shown).

Viral Vectors. The mock adenoviral vector AdG5 was used as a control virus, as described previously (24). The adenovirus encoding mouse IL-18 gene under a cytomegalovirus promoter (AdmGM/IL18) and E1- and E3-deleted adenoviral vectors were constructed through Cre-lox recombination with reagents generously provided by Dr. Stephen Hardy (Somatix, Alameda, CA; Ref. 25). The cDNA encoding the mature mouse IL-18 fused with a mouse GM-CSF leader sequence (40 bp) and was inserted into the adenoviral vector pAdLOX21 as previously described (26). The cDNA encoding the mature mouse IL-18 fused with a mouse GM-CSF leader sequence was obtained by PCR amplification using a 60-bp 5’ primer corresponding to mouse GM-CSF leader sequence (40 bp) and 20 bp of annealing to the mature mouse IL-18 coding region. The digested PCR fragment containing the mouse granulocyte/macrophage/IL-18 cDNA was subsequently inserted into shuttle vector pAdlox and sequenced. Recombinant adenovirus was generated by cotransfection of SfiI-digested pAdlox-mGM/IL18 and helper virus DNA into the adenoviral packaging cell line CRE8 that expresses Cre recombinase. Recombinant adenoviruses were amplified in CRE8 cells, purified by CsCl density gradient centrifugation, and...
then dialyzed. Titters of viral particles were determined by optical densitome-
try, and viral particles were then stored at −80°C until use.

**Mouse IL-18 and IL-12 Production from Adenoviral-transduced DCs.** Five million DCs were transfected with recombinant adenoviral vector encoding mouse IL-18 (AdIL18) or mock vector (AdΔ5), as reported previously (24). After 48 h, adenoviral transected DCs were harvested and analyzed. Culture supernatants were also collected for measurement of mouse IL-18 and mouse IL-12 ELISA kits (BD Pharmingen, San Diego, CA), with lower levels of detection of 31.3 and 62.5 pg/ml, respectively.

**MLR.** Adenoviral transfectants and nontransduced DCs were irradiated (30 Gy) using a 40Co gamma irradiator (Nordion International Inc., Ontario, Canada), washed with RPMI 1640 (Life Technologies, Inc.), and seeded in triplicate cells/well in round-bottomed 96-well plates for use as stimulator cells. Allogeneic (C57/BL6) splenic responder CD3+ T cells (2 × 10^5) were added to DCs (at the indicated T:DC ratio) in a total volume of 200 μl of CM and cultured for 96 h. The wells were then pulsed with 1 μCi of [1H]thymidine (New England Nuclear, Boston, MA) for the last 18 h of incubation, and cells were harvested onto glass fiber filters (Wallac, Gaithersburg, MD). [1H]Thymidine incorporation was quantified using a beta plate liquid scintillation counter (Wallac), with results expressed as the mean cpm ± SE (SD) of three independent experiments.

**Flow Cytometry.** For phenotypic analysis of adenoviral transfected DCs, phycoerythrin- or FITC-conjugated monoclonal antibodies against mouse class surface molecules (CD11b, CD11c, CD40, CD54, CD80, CD86, H-2Kd, and I-A^d^ (all from BD Pharningen)) and appropriate isotype controls were used, and analysis was performed using a FACscan (Becton Dickinson, San Jose, CA) flow cytometer.

**Animal Experiments.** BALB/c mice were injected s.c. with 3 × 10^5 CMS4 cells in the right flank on day 0. On day 7, when tumor size reached approximately 20–30 mm^2^, BALB/c mice were treated s.c. (on the same flank of tumor) with immunization with 1 × 10^6 nontransduced or adenoviral transduced DCs prepulsed with the mouse p53_232-240 peptide in a total volume of 100 μl of PBS as described previously (21), and 1 week later, 1 × 10^6 nontransduced or adenoviral transduced DCs were injected intratumorally in a total volume of 100 μl of PBS. Tumor size was assessed every 3 or 4 days and recorded in mm^2^ by determining the product of the largest perpendicular diameters measured by vernier calipers. Data are reported as the average tumor area ± SD. To assess the impact of systemic immunity from vaccination, we examined the growth of contralateral untreated tumors. For the latter models, BALB/c mice were injected s.c. with 3 × 10^5 CMS4 cells in both flanks on day 0. On day 7, BALB/c mice were treated with vaccines as noted above. After 7 additional days, 1 × 10^6 adenoviral transduced DCs were injected in the tumor on the right flank, and both tumors were measured every 3 or 4 days.

**Cytolytic Assay and IFN-γ ELISA.** Splenocytes were harvested from 2 mice/group 7 days after intratumoral injection with adenoviral transduced DCs (i.e., day 21 after tumor inoculation). Responder cells (3 × 10^6 cells/well) were restimulated in vitro with 3 × 10^5 irradiated (10,000 rads) CMS4 cells in the presence of 30 IU/ml recombinant human IL-2 (Chiron Corp., Emeryville, CA) for 5 days in 24-well culture plates. The supernatants were collected and assessed in an ELISA for mouse IFN-γ production (BD Pharmingen). Lymphocytes were harvested after 5 days of in vitro restimulation and subjected to 5-h 51Cr release assays against the CMS4 and YAC-1 targets, as described previously (26). Assays were performed in triplicate wells, with spontaneous release of all assays never exceeding 25% of the maximum release.

**CD8+ T-Cell Response against Euluted Naturally Processed Peptides**

**Derived from CMS4 Cells.** Peptides were extracted from CMS4 cells as described previously (27) and separated on reverse-phase HPLC. Individual HPLC fractions were lyophilized to remove organic solvent and then reconstituted in 200 μl of PBS and stored at −20°C until use. CD8 + T cells were isolated from the spleen cells of immunized mice by using magnetic beads (MACS; Miltenyi Biotec, Auburn, CA) and then cocultured (1 × 10^5 cells/well) with syngeneic DCs and 96-well tissue culture plates. After 48-h incubations, culture supernatants were collected and analyzed for IFN-γ release using a cytokine-specific ELISA kit (BD Pharmingen).

**Statistical Analysis.** Statistical significance of differences between the groups was determined by applying Student’s t test or two-sample t test with Welch correction after each group had been tested for equal variance and Fisher’s exact probability test. Statistical significance of the differences in more than three groups was determined by applying one-way ANOVA. We defined statistical significance as P < 0.05.

**RESULTS**

**Cytokine Production, Phenotype, and MLR Stimulatory Capacity of Adenoviral mIL-18-transduced DCs.** To overcome the poor expression of mouse IL-18 from the previously reported adenoviral vector Ad-PTHmIL18 (24), we generated a new construct that incorporates the murine GM-CSF leader sequence fused with the mature mouse IL-18 cDNA. The novel cDNA, once cloned into adenovector AdmGM/IIL18, induces much higher transgene expression in the infected cells, when compared with the previously generated Ad-PTHmIL18 (data not shown). Forty-eight h after in vitro adenoviral transduction, bone marrow-derived DCs were subjected to phenotypic and functional analyses. Adenoviral mIL-18-transduced DCs (AdIL18DC) produced significant quantities of murine IL-18 (568.5 ± 206 pg/5 × 10^5 cells/48 h). In contrast, the culture medium of both adenovirus Ψ5-transduced DCs (AdΨ5DC) and nontransduced DCs (DCs) did not secrete detectable levels of mIL-18 (i.e., <31.3 pg/5 × 10^6 cells/48 h). Using flow cytometric methods, we determined that expression of MHC class I, MHC class II, CD80, CD86, and CD40 molecules on AdIL18DC was significantly elevated when compared with either AdΨ5 control virus-infected DCs and nontransduced DCs (Table 1, with these controls yielding indistinguishable results. When used as stimulators in MLRs, IL-18-transduced DCs exhibited significantly higher T-cell proliferation than AdΨ5-infected DCs or nontransduced DCs (Fig. 1). Because rIL-18 and recombinant IFN-γ stimulus increased IL-12p70 production from DCs, which is critical to the induction of Th1-type immunity, the supernatants of transduced DCs were also tested for production of IL-12 heterodimers. IL-12p70 production from IL-18-transduced DCs was significantly higher than that from either AdΨ5-infected DCs or nontransduced DCs (127 pg/5 × 10^6 cells/48 h versus <62.5 pg/5 × 10^5 cells/48 h for either control).

**CMS4 Tumor Growth Is Significantly Inhibited by Immunization with mIL-18-transduced DCs.** Next, we examined whether mIL-18 gene transfer enhances the therapeutic potential of DC-based vaccines in the CMS4 tumor model, where the p53_232-240 peptide serves as a H-2Kd presented “regressor” epitope. BALB/c mice were injected s.c. with 3 × 10^5 CMS4 cells. On day 7, these tumors exhibited a mean tumor area of 20–30 mm^2^ Tumor-bearing mice were then immunized with 1 × 10^6 nontransduced or adenoviral transduced (Ψ5- or mIL-18-transduced) DCs pulsed with the p53_232-240 peptide. In some groups, after an additional 7 days, tumors were injected with 1 × 10^6 nontransduced or adenoviral transduced DCs or PBS to direct primed immune effectors into the tumor to theoretically promote cross-presentation and “epitope-spreading.” As shown in Fig. 2A, tumor rejection was observed in three of six mice treated with AdIL18DC, and the growth of CMS4 tumors in the remaining three mice was significantly inhibited compared with that seen in mice treated with the other protocols (P < 0.05 at 14, 17, 21,

Table 1 Phenotypic characteristics of IL-18-transduced DCs

<table>
<thead>
<tr>
<th>DCs</th>
<th>MHC class I</th>
<th>MHC class II</th>
<th>CD80</th>
<th>CD86</th>
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<td>1388b</td>
<td>1547</td>
<td>1980b</td>
<td>1102b</td>
<td>218b</td>
</tr>
<tr>
<td>AdΨ5DC</td>
<td>510</td>
<td>1188</td>
<td>588</td>
<td>502</td>
<td>102</td>
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<tr>
<td>DC</td>
<td>604</td>
<td>1232</td>
<td>479</td>
<td>402</td>
<td>97</td>
</tr>
</tbody>
</table>

*Nontransduced and transduced DCs were harvested 7 days after initiation of the culture and stained with the antibodies listed here.

b P < 0.05 compared with those of nontransduced or mock DCs.
The data are shown as the mean ± SD. Similar results were obtained in three independent experiments. *P < 0.05 versus Ad5DC and DC.

We further examined the importance of IL-18 in the immunization component of our combination therapy. BALB/c mice bearing CMS4 tumor were immunized with p53 peptide-pulsed or nonpulsed AdIL18DC or p53 peptide-pulsed Ad5DC-infected DCs or PBS. After 7 days, all mice were treated with intratumoral injection of DC-AdmIL18. As shown in Fig. 2C, the tumor growth in mice treated with p53 peptide-pulsed AdIL18DC was significantly inhibited compared with that seen in mice treated with any other combined therapy (P < 0.05 at 14, 17, 21, 24, and 28 days). These results demonstrate that IL-18 gene transfer enhances the therapeutic effects of DC-based immunization (provided 1 week earlier) against established CMS4 tumors or, alternatively, that prevaccination with a single tumor epitope enhanced the efficacy of intratumoral IL-18 gene therapy.

We next examined whether transfection of DCs enhances their ability to elicit specific anti-CMS4 CTL generation after combinational therapy (as evaluated in Fig. 2). Spleen cells were obtained from mice 14 days after intratumoral injections and cocultured with irradiated CMS4 cells for 5 days. As shown in Fig. 3A, splenocytes from mice treated with the Ad5-infected DC regimen (i.e., p53 peptide-pulsed Ad5DC vaccine + Ad5DC intratumoral injection) or the nontransduced DC regimen displayed low-level cytolytic activity against CMS4 cells, whereas CTLs from mice treated with PBS were nonreactive. Importantly, splenocytes from mice treated with the AdIL18DC regimen displayed significantly stronger cytolytic activity versus either the Ad5DC or nontransduced DC regimens. As shown in Fig. 3B, no cytolytic activity was observed against the NK/LAK target YAC-1. These results demonstrate that the combined AdIL18DC vaccination/intratumoral injection therapy was superior in its ability to stimulate systemic CTL activity against a resident tumor in situ. Splenocytes obtained from mice treated with the AdIL18DC regimen also produced substantially elevated amounts of the Th1-associated cytokine IFN-γ (>10,000 pg/ml) as compared with effector cells obtained from mice treated with other DC regimens (Ad5DC = 2,980 pg/ml, DC = 1,189 pg/ml), which in turn exceeded production from mice injected with PBS only (68 pg/ml; Fig. 3C).
Irradiated CMS4 cells for 5 days before being applied as effector cells in 51 Cr release intratumoral injections (28 days after tumor inoculation) and then cocultured with /H9023 or the Ad5DC regimen. Similar results were obtained in three experiments.

CD8+ T cells from animals treated with therapies (based on a single synthetic epitope) can induce spreading in IFN-γ production from responder mice. CD8+ T cells from PBS-treated mice did not produce detectable levels of IFN-γ against any peptides. These results demonstrate that the DC-based combined therapies (based on a single synthetic epitope) can induce spreading in the CD8+ T-cell responses to CMS4-derived peptides, with the greatest degree of “epitope spreading” noted for therapies using DC-IL18. Notably, these expanded CTL repertoires were associated with increased therapeutic benefit.

DISCUSSION

Adenoviral mIL-18 gene-transduced DCs expressed elevated levels of both MHC class I and class II and costimulatory molecules related to the immunostimulatory capacity of DCs. It has been reported that activation of IL-18 receptor by IL-18 induces intranuclear translocation of nuclear factor-κB via recruitment of MyD88 (28), which regulates the expression of these (MHC and costimulatory) molecules. Thus, IL-18-induced phenotypic changes could be due to the direct effects of IL-18 and/or indirect effects, such as those promoted via IFN-γ production from IL-18-activated T cells or NK cells, that represent minor contaminants (<10%) in our DC preparations. MLR results demonstrate that the allostimulatory capacity of IL-18-transduced DCs was significantly greater than that of control DCs, consistent with the observed changes in DC costimulatory and MHC marker phenotype and the enhanced therapeutic efficacy that we observed in the CMS4 model.

In the current study, mice bearing established CMS4 tumors were treated with combination immunotherapy incorporating p53232–240 peptide-pulsed DC vaccines 7 days after tumor inoculation, followed by intratumor injection of (non-antigen-loaded) DCs 1 week later. We theorized that the first vaccination of tumor-bearing mice results in increased frequencies of p53 peptide-specific CTLs that circulate and,
after infiltrating tumors, result in lesional destruction and tumor antigen acquisition by infiltrating (or injected) DCs in situ, thereby promoting subsequent “cross-priming” of tumor-reactive T cells in the tumor-draining lymph nodes. These cross-primed T cells would exhibit an expanded repertoire of antitumor specificities capable of mediating more effective tumor clearance and greater immune protection against tumor cells expressing heterogeneous levels of individual antigens. Such cross-priming would be theoretically enhanced by intratumor injection of DCs (serving as cross-presenters), particularly if these cells were engineered to express a proinflammatory cytokine (such as IL-18) to recruit immune cells and promote Th1-type immunity.

Our results demonstrate that established tumor growth in mice immunized with peptide-pulsed DCs was significantly inhibited compared with that of tumors in mice immunized with non-peptide-pulsed DCs or PBS (in groups receiving a common intratumoral treatment), suggesting that the immunization phase of the combinatorial therapy plays an essential role in “priming” for subsequently broadened antitumor immune responses. Because tumor growth in mice subsequently treated with intratumoral injections of AdIL18DC on day 14 was further inhibited compared with controls, it is likely that intratumoral injection of AdIL18DC boosts antitumor immunity (which was promoted initially by the primary p53 peptide-pulsed DC immunizations) most effectively. Taken together, these observations suggest that both the initial immunization and the subsequent intratumoral injection of DCs play important roles in the induction and direction of therapeutic antitumor immunity in tumor-bearing mice, with intratumoral IL-18-transduced DCs optimally enhancing these effects in the current study. Major issues that have not been addressed by this study, but which we are currently evaluating, include the requirement for IL-18 gene therapy delivery via adenovirus-infected DCs (versus infected fibroblasts or direct injection of AdIL18 virus ± control DCs) for therapeutic efficacy and the IL-18 dose dependency of therapeutic efficacy.

Importantly, combinational vaccination using IL-18-transduced DCs also exhibited therapeutic effects against nontreated contralateral tumors, supporting the ability of this vaccination protocol to induce systemic antitumor immunity. These results suggest that immunization of cancer-bearing animals with IL-18 gene-transduced DCs may represent a promising approach to suppress tumor growth and ultimately regress disseminated lesions in cancer patients.

We have shown that immunization of tumor-bearing mice with p53 peptide-pulsed DCs promotes CM54-specific CTL cytolytic activity and IFN-γ production in the spleens of treated animals, particularly if IL-18-transduced DCs were applied in situ. Zitvogel et al. (29) reported that the antitumor effects of DC-based vaccination were dependent on production of Th1-associated cytokines such as IFN-γ, tumor necrosis factor α, and IL-12. Therefore, enhanced IFN-γ production resulting from IL-18 paracrine delivery via engineered DCs (promoted by either IL-18 or up-regulated IL-12) may also play an important role in the increased antitumor activity in vivo.

Previous reports have demonstrated that both CTLs and NK cells play important roles in the antitumor effects induced by systemic administration of IL-18 in murine tumor models (18, 19). Osaki et al. (24) reported that direct injection of an IL-18 adenovirus into tumor combined with systemic administration of IL-12 exerted antitumor effects mediated mainly by NK cells and partially by both CD8+ and CD4+ lymphocytes. We initially expected that the Th1 cytokine IL-18 produced by transduced DCs might also enhance the antitumor activities of both CTLs and NK cells induced by the vaccine. Our results indicate that specific CTL, but not NK cell, activity is associated with the improved efficacy associated with our IL-18-based combinational therapy in the CM54 model. This finding is consistent with our in vitro data supporting IL-18-mediated changes in DC phenotype and function relevant for T-cell activation. These results do not discount the potential important role that NK cells may play in licensing Th1-type immunity (30) but suggest that their direct antitumor effects in this model may be limited.

A number of recent examples suggest that the induction of (at least) limited autoimmunity and “epitope spreading” may drive the most effective therapeutic immune responses to cancer (31, 32). Indeed, in the therapy of established mice and human melanoma, the development of autoimmune vitiligo (destruction of normal melanocytes in the skin) is associated with better objective clinical responses (32, 33). Our results demonstrate that epitope spreading can also be best observed in mice that have been effectively treated with combinational therapy consisting of specific vaccination and subsequent intratumoral delivery of IL-18-transduced DCs. It will clearly be of great interest to prospectively evaluate the comparative effects of IL-18-transduced DCs loaded with diverse forms of tumor antigens (apoptotic bodies, lysate, conjugates, and peptides) to stimulate the greatest diversity in tumor-specific T-cell reactivity and discern the coordinate therapeutic benefits of these approaches.

Despite recent progress and early success reported for DC-based cancer immunotherapies, there is significant room for improvement in these regimens. To that end, we have demonstrated several novel findings in the current report, namely that (a) IL-18 transfection of DCs enhances their immunostimulatory phenotype/function, (b) IL-18 gene therapy (using DCs) provides superior efficacy when applied in combinational approaches as compared with vaccines only or intra-
tumoral delivery applications only, and (c) the therapeutic efficacy of these combinational therapies is associated with epitope spreading in the antitumor CD8+ T-cell repertoire that can be effectively primed using single peptide-based vaccines. Given current Food and Drug Administration concerns regarding the direct injection of recombinant adenooviruses into patients and the limited efficacy observed for single peptide-based cancer vaccines (34), these findings may provide the basis for safer, more effective cancer therapies.

ACKNOWLEDGMENTS

We thank Dr. Walter Olson and William Knapp for excellent technical support.

REFERENCES


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Announcements

MEETING OF THE RADIATION RESEARCH SOCIETY

The annual meeting of the Radiation Research Society will be held at the State University of Iowa, Iowa City, on June 22–24, 1953. The Society will be the guest of the University, and all meetings will be held on the campus. The program will consist of: (1) Two symposia, one on "The Effects of Radiation on Aqueous Solutions," which includes the following speakers: E. S. G. Barron, Edwin J. Hart, Warren Garrison, J. L. Magee, and A. O. Allen. The second is "Physical Measurements for Radiobiology" and companion talks by Ugo Fano, Burton J. Moyer, G. Failla, L. D. Marinelli, and Payne S. Harris. (2) On Monday night, June 22, a lecture by Dr. L. W. Alvarez on meson physics has been tentatively scheduled. On Tuesday night, June 23, Dr. L. H. Gray of the Hammersmith Hospital, London, will speak on a topic to be announced. Dr. Gray’s lecture is sponsored by the Iowa Branch of the American Cancer Society. Those desiring to report original research in radiation effects, or interested in attending or desiring additional information, please contact the Secretary of the Society, Dr. A. Edelmann, Biology Department, Brookhaven National Laboratory, Upton, L.I., New York.

ERRATUM

The following correction should be made in the article by Beck and Valentine, "The Aerobic Carbohydrate Metabolism of Leukocytes in Health and Leukemia. I. Glycolysis and Respiration," November, 1952, page 891; substitute for the last paragraph:

The data in Table 3 permit several interesting calculations. If one compares the amount of glucose actually disappearing with the sum of the amount equivalent to lactic acid produced plus that equivalent to O₂ consumption, it is seen that the amount of glucose "cleavage products" exceeds the amount of glucose utilized by 12 per cent in N and 27 per cent in CML and is exceeded by the glucose utilized by 16 per cent in CLL. If the assumption is made that, in this respect, the myeloid and lymphoid cells of leukemia are similar to those of normal blood, it may be that the computed normal figure represents a summation of the myeloid (M) and lymphoid (L) cells that make up the normal leukocyte population. Thus, if M = +0.27 and L = −0.16 and the normal differential is 65 per cent M and 35 per cent L, then

0.65 (+0.27) + 0.35 (−0.16) = +0.12

a figure identical to the observed +0.12 for normal leukocytes.
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