NATIONAL CANCER INSTITUTE IMMUNOTHERAPY AGENT WORKSHOP PROCEEDINGS

OPENING REMARKS

Martin A. "Mac" Cheever, M.D., and Stephen Creekmore, M.D., Ph.D., the workshop co-chairs, welcomed and thanked the participants, including several who participated via teleconference. The goal of the meeting is to develop a recommended prioritized list of agents that have the potential to become immunotherapeutic drugs[1] for treating cancer. The purpose of the list is to recommend certain agents that hold particular promise to the National Cancer Institute (NCI), nongovernmental funding agencies, industry, and individual investigators. Possible positive outcomes could include encouragement of (1) Rapid Access to Interventional Development (RAID) applications for the manufacture or (2) distribution of company-manufactured agents through RAID or the Cancer Therapy Evaluation Program (CTEP), (3) reinvigoration of their development by companies with such agents on the shelf or licensing them to other companies for development, or (4) investment by venture capitalists in new development. This rank-setting exercise could also serve as a report card: if a year or two goes by and the list remains substantially unchanged, it would be a signal that the current system for developing immunotherapeutic agents is not working optimally.

Dr. Creekmore emphasized the importance of the workshop's priority list to the RAID program, the Division of Cancer Treatment and Diagnosis (DCTD), and the National Cancer Advisory Board (NCAB), as well as to the Special Emphasis Panel that guides the progress of promising agents through RAID. He also speculated that some participants might wish to offer opinions or input after this workshop. Dr. Creekmore emphasized that the recommendations generated are not binding, although the outcome will be of great interest to NCI at multiple levels within the Clinical Center Research (CCR) group and the Developmental Therapeutics Program (DTP). The deliberations, opinions, and rankings will be taken very seriously.

Dr. Cheever highlighted the evolution of the prioritization process, which started with a Web site designed to elicit input from various parties about agents with known substantial immunologic or physiologic activity that have not been tested or have been inadequately tested in cancer patients. The Web site was broadly publicized by the NCI through e-mail contacts with intramural immunologists and immunotherapists, extramural holders of immunology and immunotherapy grants, and with past RAID investigators and reviewers, as well as notification via the *NCI Cancer Bulletin.* The Web site was also broadly publicized through journal ads and newsletter notices by the most relevant scientific societies including the AACR, AAI, ASCO, ASH, CVC, and iSBTc.

[1] "Immunotherapeutic drug," for the purpose of this workshop, was defined as an agent that requires participation of or modifies the host immune system for efficacy; for example, cells, antibodies or other specific cell-targeting agents, and vaccines, cytokines, and pathogen-associated molecular pattern (PAMP) agonists. Many are expected to work in synergy with or by an additive effect with other immunotherapeutic or small molecule drugs. Some are likely to be very effective in activating or otherwise substantially modifying immune responses with little expectation that they can be efficacious when used as monotherapy, that is, without other agents.

In all, 124 agents were suggested via the Web site. Respondents expressed particular interest in vaccine adjuvants; T-cell growth factors; agents to inhibit immune checkpoint blockade; functional antibodies, cytokines, ligands, and receptors; and agents "left on the shelf" by drug companies, as well as suggestions for specific antigens for vaccines and antigen-specific antibodies.

The organizing committee[2] winnowed the list of 124 agents down to 30. The committee's focus was on agents with the greatest potential for multiple uses by multiple investigators supporting the development of multiple types of regimens, thereby excluding specific antigens for vaccines and antigen-specific antibodies desired by individual groups, regardless of their attractiveness or potential utility.

The organizing committee established the following criteria for the workshop participants to use as they assigned priorities to the agents under consideration:

- Potential for use in cancer therapy.
- Perceived need by multiple, independent clinical investigators.
- Potential use in more than one clinical setting (i.e., against different tumor types or as part of multiple therapy regimens).
- Not broadly available for testing in patients.
- Not commercially available or likely to be approved for commercial use in the near future.

Criteria that *should not* be used for priority ranking included:

- Prior failed attempts to commercialize an agent and ownership of an agent.
- Intellectual property. Ownership status is subject to change.

For ease of discussion, the candidates were organized loosely into four groups:

(1) Adjuvants
(2) T-cell growth factors
(3) Anti-checkpoint blockade and varied agents
(4) Co-stimulatory and varied agents

Each one of the 30 agents was presented by a workshop participant as a primary reviewer, followed by comments by secondary and tertiary reviewers. In advance of the meeting, the primary presenters submitted PowerPoint slides based on a standard template (Appendix A). Although these slides were not projected during the meeting, they served as outlines for the presentations and were printed in a workshop book. The PowerPoint slides can be accessed and downloaded from: http://web.ncifcrf.gov/research/brb/site/home.asp.

[2] The organizing committee included members of the Joint American Association of Immunologists/American Association for Cancer Research Extramural Immunology Expert Steering Committee (James Allison, Mac Cheever, Olja Finn, Ira Mellman, Drew Pardoll, Ralph Steinman, and Louis Weiner) and NCI scientists from the Division of Cancer Biology (Kevin Howcroft, Susan McCarthy, and Alan Mufson) and the Division of Cancer Treatment and Diagnosis (Richard Camalier, Jerry Collins, Stephen Creekmore, Toby Hecht, Jill Johnson, Howard Streicher, and James Zwiebel).

At the end of each presentation, the participants conferred about the pros and cons of all agents presented to that point in the session and, by consensus, ranked them according to the established criteria. At the end of each of the four sessions, the participants ranked all agents in that category by consensus. After all the presentations, the participants generated a preliminary ranking of the top 20 agents across all four categories by verbal acclamation. The preliminary ranking was used as the basis for subsequent exchanges and balloting by e-mail. The final ranking was determined by e-mail ballots from the workshop participants (see Table 4 for a listing of votes).

The workshop participants were selected by the organizing committee from suggestions submitted by the AACR, AAI, ASCO, ASH, CVC, and iSBTc, as well as from the leadership of the NCI Center for Cancer Research, the Division of Cancer Biology, and the Division of Cancer Diagnosis and Therapy. Members of the RAID SEP, including academic and industry, representatives were also included. Representatives from industry and the FDA were invited to observe and comment during the proceedings.

The final ranking is presented in Table 1 above. Details of the proceedings follow. Each agent is presented in the order presented in the workshop.