FINAL RANKINGS

Following the workshop, the participants engaged in online discussions and balloting via e-mail, culminating in the final priority rankings for the agents of interest. The essence of the comments submitted via e-mail is reflected in the paragraphs below, and the results of the final voting are tabulated in a chart.

Dr. Cheever led off the e-mail discussion by listing several concerns he had with the preliminary ranking:

- *Anti–TGF-beta:* First, the high preliminary ranking was based on discussion at the end of the workshop. The PowerPoint presentation did not develop justification for the agent in cancer therapy. Therefore, a better justification would be required to support a final ranking of the agent in the top 10. Second, the presentation listed multiple anti–TGF-beta agents in development. Therefore, anti–TGF-beta might not ultimately meet the criterion of "Not broadly available for testing in patients."
- *Anti–IL-10 and anti–IL-10 receptor:* First, the PowerPoint presentation did not provide adequate justification for the agent's ranking. Therefore, a better justification would be required to support a final ranking of the agent in the top 10. Second, the workshop participants seemed much more enthusiastic about anti–IL-10 receptor; however, the receptor was not mentioned in the PowerPoint presentation. Therefore, some rationale would be needed to justify inclusion of the receptor among the highest-ranked agents. Third, Dr. Cheever was not aware of any IL-10 receptor agents approaching readiness for clinical development. Several lower-ranked agents (e.g., Flt3 ligand, poly I:C, MPL, and resiquimod) have proven efficacy in the clinic.
- There are hundreds of cancer vaccines in clinical trials, but a dearth of adjuvants. It seems that adjuvants with known efficacy should have a higher priority than agents with little data available such as anti-OX40 and anti–B7-H4.

Dr. Houghton agreed with Dr. Cheever's comments about the lack of justification for the high preliminary rankings of anti–TGF-beta and IL-10 receptor.

Dr. Weiner concurred with Dr. Cheever regarding the prioritization of adjuvants. Although MPL might not be as exciting and novel as some of the higher-rated compounds, it would be generally useful to the investigator community.

Dr. Weber posited that the anti–IL-10 and anti-TGF antibodies should be highly ranked on grounds of broad applicability and potential clinical utility. If cancer vaccines are not very immunogenic, then MPL would not make a difference, although an agent such as anti-OX40 or anti–TGF-beta might.

Dr. Jaffee generally agreed with Dr. Cheever's comments, but added that some good adjuvants are available and that checkpoint inhibitors are just as, if not more, difficult to obtain. She recommended highly ranking a checkpoint inhibitor as well as the best adjuvant. She agreed that not enough data are available on anti–B7-H4 to justify a very high ranking, although this would

be a good example of an agent for which we need a mechanism to have regular follow-up so that it can be assigned a higher priority should more positive data become available. It is a unique agent in the class of checkpoint inhibitors. She also recommended moving anti-GITR higher on the list because of the need to have a Treg inhibitor.

Dr. Berzofsky said he thought the ranking prepared at the end of the meeting was quite good, although many choices of exact position on the list were subjective. He opined that the rankings of a few agents should be rethought, and he emphasized the need for both adjuvants and checkpoint inhibitors. He thought that although anti–TGF-beta is very important and promising, it is already in active clinical development/trials by Genzyme. He said he has been very impressed by the mouse data on anti–IL-10 receptor from the laboratories of Anne O'Garra, Giorgio Trinchieri, and others. Additionally, a very effective anti–IL-10 receptor antibody was made a number of years ago by DNAX, but it has not been made available by Schering Plough, which purchased DNAX. He opined that some of the other adjuvants should be moved up in the rankings.

Dr. Mackall agreed with several others that anti–IL-10 receptor and MPL should be moved up in the rankings and anti–TGF-beta should be demoted. She reiterated Dr. Jaffee's desire to see some of the higher-risk agents receive some kind of real priority and suggested developing another category for considering non–GMP-grade production/acquisition to further preclinical work. This line of research would be distinct from the objective of producing clinical-grade material, but arguably would be equally important and potentially less costly.

Dr. Disis wrote that adjuvants that are more likely to elicit Th1 responses should receive higher priorities.

Dr. Margolin expressed her expectation that the priority ranking will reflect considerable expertise and judgment and hoped that it will be used wisely by the target audiences.

Dr. Prendergast agreed about assigning higher priorities to anti-GITR and MPL.

Dr. Whiteside noted that she also rearranged several agents on the priority list, pointing out that some of the antibodies (e.g., anti-GITR, anti–IL-10, and anti–IL-10 receptor) lack any record of effectiveness in human cancer, and it may be premature to put them in the top part of the list.

Dr. Ho opined agreed that because of the difficulty in ranking items with limited preclinical data on this list, a regular reassessment of the rankings, as several suggested, seemed to be a reasonable approach. He also seconded Dr. Mackall's idea of a separate list for non-GMP requests.

Dr. Urba observed that it may be difficult to arrive at a consensus on some of the details of the ranking. He posited that the preliminary ranking was adequate in that the important molecules were represented in a reasonable order. He acknowledged others' comments about the rankings of TGF-beta and anti–IL-10 receptor antibodies but did not agree with rating MPL higher, because it will likely become available to the clinical community because GSK is using it as an adjuvant. It might have to be purchased, but it would be available. He agreed with Dr. Jaffee that

checkpoint inhibitors are very important and recommended keeping their priority rankings as they were.

Dr. Calzone took a different approach. He placed the prioritized candidates into two groups on his ballot: "Deny" or "To Next Step." The main reason for placing an agent in the "Deny" group was that clinical development was in progress or very likely. He placed eight candidates in the "To Next Step" category and prioritized them. MPL was advanced to number one because it seemed as if it would enhance a wide range of tumor vaccine studies. The rest in the "To Next Step" category were cytokines whose adjuvant potential requires further clinical study. Dr. Calzone pointed out that he is employed by Amgen, which holds the intellectual property rights to the molecules IL-15 and Flt3 ligand. He wrote that he had learned that Amgen's discussions with NIH/NCI on Flt3 ligand for *in vivo* clinical trials have been long, complex, and frustrating on both sides. However, IL-15 is a different matter. He offered to arrange the proper discussion of IL-15 and Flt3 ligand with Amgen, depending on the ultimate RAID prioritization of these agents.

Dr. Palucka said that she approached this priority exercise by asking what would be needed to vaccinate today and what is available or could be available for clinical testing soon. On that basis, she assigned higher priorities to agents needed to mobilize APCs, serve as adjuvants, help T cells via cytokines and/or co-stimulation, and control regulatory/suppressor mechanisms.

Dr. Sondel said he would like to emphasize adjuvants and agents that might be applied broadly to a variety of diseases or combined with a variety of therapeutic strategies (e.g., Flt3 ligand, MPL, CD-40 ligand/anti-CD40).

Table 4. Final Rank with Preliminary Rank and Individual Ballots

Final Rank	Agent	Prelim Rank	Voter 1	2	3	4	5	6	7	8	9	10	11	12	13	14	14	MEDIAN	MEAN With Imputed Unr	MEAN without Imputed Unr
1	IL-15	1	1	1	5	2	1	1	1	1	1	1	1	2	1	1	2	1 (1-5)	1.47	1.47
2	Anti-PD1	2	3	4	3	No (9)	2	2	2	3	2	2	2	1	2	2	1	2 (1-9)	2.67	2.43
3	IL-12	3	2	3	2	3	3	3	3	2	3	3	3	4	3	3	5	3 (2-5)	3.00	3.00
4	Anti-CD40	4	5	2	6	No (9)	4	5	4	5	4	4	4	3	4	4	6	4 (2-9)	4.60	4.29
5	IL-7	5	8	5	11	5	5	4	5	6	5	5	5	6	5	5	13	5 (4-13)	6.20	6.20
6	CpG	6	9	6	Unr(16)	No(9)	6	6	6	4	6	6	6	7	6	6	4	6 (4-16)	6.86	5.99
7	1-MT	8	10	9	Unr(16)	No (9)	8	7	(8)	8	8	8	8	9	8	8	7	8 (8-16)	8.73	8.15
8	Anti-CD137	9	11	10	8	No(9)	9	8	10	9	9	9	9	10	9	9	3	9 (3-11)	8.80	8.79
9	Anti-TGF-b	7	4	14	Unr(16)	No (9)	7	12	12	10	10	11	7	8	7	7	11	9 (4-16)	9.67	9.23
10	Anti-IL10R	10	12	15	9	7	10	13	15	7	7	7	10	11	10	10	10	10 (7-15)	10.20	10.20
11	FLT3L	11	13	8	1	4	11	9	11	12	11	13	11	12	11	11	12	11 (1-13)	10.00	10.00
12	Anti-GITR	12	6	11	10	6	12	16	7	11	12	14	12	5	12	12	8	11 (5-16)	10.27	10.27
13	CCL21 Adv	13	14	12	15	No(9)	13	14	17	Unr(20)	16	15	13	13	13	13	Unr(21)	13 (9-21)	13.13	12.24
14	MPL	16	16	7	7	1	16	10	9	16	13	12	16	16	16	16	14	14 (1-16)	12.33	12.33
15	Poly I:C	14	15	13	4	No(9)	14	11	13	14	14	10	14	14	14	14	15	14 (4-15)	12.53	12.78
16	Anti-OX40	15	17	16	Unr(16)	8	15	15	14	15	15	19	15	15	15	15	9	15 (8-17)	14.60	14.50
17	Anti-B7-H4	17	18	17	12	No(9)	17	17	16	17	17	18	17	17	17	17	17	17(12-18)	16.2	16.71
18	Resiquimod	18	7	18	14	No(9)	18	18	18	13	18	17	18	18	18	18	16	18(7-18)	15.87	16.36
19	LIGHT	19	19	19	13	No(9)	19	19	19	18	19	20	19	19	19	19	19	19(13-20)	17.93	18.57
20	Anti-LAG3	20	20	20	Unr(16)	Unr(9)	20	20	20	19	20	16	20	20	20	20	18	20(18-20)	18.53	19.56
21	IL-21	21	Unr(21)	21	Unr(16)	Unr(9)	21	21	21	Unr(20)	21	21	21	21	21	21	20	21(20-21)	19.73	20.90
Unr	IL-4	Unr	Unr				Unr						Unr		Unr	Unr				Unr
Unr	sLAG3	Unr	Unr				Unr						Unr		Unr	Unr				Unr
Unr	TGF-beta R	Unr	Unr				Unr						Unr		Unr	Unr				Unr

Unr = Unranked; Rank was determined by median. If the medians were equal, the ranking of ties was determined by means. The means were calculated both including an imputed number for the unranked agents and with inclusion of an imputed number for the unranked agents. The imputed number used is included in the (parentheses). The last three rows contain agents the workshop decided to leave unranked. They were not used to determine median or mean calculations. Several participants chose not to vote. Mac Cheever and Steve Creekmore, as chairpersons, elected not to vote.