The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research

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Abstract The purpose of the National Cancer Institute pilot project to prioritize cancer antigens was to develop a well-vetted, priority-ranked list of cancer vaccine target antigens based on predefined and preweighted objective criteria. An additional aim was for the National Cancer Institute to test a new approach for prioritizing translational research opportunities based on an analytic hierarchy process for dealing with complex decisions. Antigen prioritization involved developing a list of "ideal" cancer antigen criteria/characteristics, assigning relative weights to those criteria using pairwise comparisons, selecting 75 representative antigens for comparison and ranking, assembling information on the predefined criteria for the selected antigens, and ranking the antigens based on the predefined, preweighted criteria. Using the pairwise approach, the result of criteria weighting, in descending order, was as follows: (*a*) therapeutic function, (*b*) immunogenicity, (*c*) role of the antigen in oncogenicity, (*d*) specificity, (*e*) expression level and percent of antigen-positive cells, (*f*) stem cell expression, (*g*) number of patients with antigen-positive cancers, (*h*) number of antigenic epitopes, and (*i*) cellular location of antigen expression. None of the 75 antigens had all of the characteristics of the ideal cancer antigen. However, 46 were immunogenic in clinical trials and 20 of them had suggestive clinical efficacy in the "therapeutic function" category. These findings reflect the current status of the cancer vaccine field, highlight the possibility that additional organized efforts and funding would accelerate the development of therapeutically effective cancer vaccines, and accentuate the need for prioritization. (Clin Cancer Res 2009;15(17):5323–37)

Virtually any mutant, overexpressed or abnormally expressed protein in cancer cells, can serve as a target for cancer vaccines and/or T-cell therapy (1–75). Scores of cancer vaccines are immunogenic in clinical trials, and many of them have shown efficacy in at least small numbers of patients. No cancer vaccine has yet been approved by the Food and Drug Administration despite extensive developmental efforts by academia and industry. Nevertheless, there is consensus that optimally designed cancer vaccine trials combining the best antigens with the most effective immunotherapy agents might yield positive clinical results.

Cancer vaccine development is limited by several factors, including funding constraints. Limited resources mandate transparent methods to prioritize developmental opportunities with the least possible bias. A National Cancer Institute (NCI) immunotherapy agent workshop was held in July 2007 to rank agents with high potential to serve as immunotherapeutic drugs.[9] The ranking was based on the likelihood for efficacy in cancer therapy and was exceedingly well vetted, with broad and substantial input from academia, industry, and the government. Many of the ranked immunotherapeutic agents are effective as components of cancer vaccine regimens in preclinical models, but this abundance of promising opportunities raises immediate questions as to which antigen or sets of antigens are most appropriate for codevelopment. Our current effort to prioritize cancer antigens represents the logical next step in

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[9] http://dcb.nci.nih.gov/ImmunAgentWork

Translational Relevance

We report on the development of a prioritized list of cancer vaccine target antigens using well-vetted criteria generated by expert panels. The elucidation and weighting of criteria to assess cancer antigens will assist investigators in the immunotherapy field in determining the characteristics and the experimental data required to select the most promising antigens for further development and testing in clinical trials.

attempting to focus translational efforts on cancer vaccine regimens with the highest potential for success.

The task of ranking cancer antigens is immense, and the number of potential cancer antigens is almost limitless. At present, investigator-initiated funding of science dictates innovation (i.e., that each investigator discovers and develops his/her own antigens). This leads to an ever-increasing number of potential vaccine targets as well as validation of those targets through preclinical and early clinical cancer vaccine development. Few investigators have both the financial and organizational resources to advance their vaccines past early developmental stages.

The NCI, recognizing the untapped potential of therapeutic cancer vaccines as well as many other novel therapies, embarked on a new approach to the identification, prioritization, and funding of translational cancer research based on recommendations of the Translational Research Working Group (TRWG).[10] The primary objective is to identify specific translational cancer research projects that warrant a dedicated effort to accelerate progress through focused collaborations. This process requires a mechanism for identifying high-priority translational research projects based on scientific validity, clinical need, and technical feasibility. The initial endeavor of NCI to implement the TRWG recommendation for prioritization of translational opportunities has focused on evaluation of a method to select cancer antigens for subsequent development through the Immune Response Modifier Pathway, one of the six TRWG pathways leading from fundamental laboratory discoveries to definitive testing in clinical trials (76, 77).

The Immune Response Modifier Pathway was selected as the pilot effort for several reasons. It is the most complex of the TRWG pathways, and successful application of a prioritization process in this context is expected to be generalizable to other TRWG pathways. In addition, the immunology community had already prioritized immunotherapy agents at the NCI Immunotherapy Agent Workshop,[9] an experience that greatly facilitated implementation of this pilot project.

The methodology for prioritization of cancer antigens was based on the analytic hierarchy process (AHP), a structured technique and mathematical model for dealing with complex decisions. AHP has been refined since its initial description by Thomas L. Saaty in the 1970s (78) and has been used throughout the world in a wide variety of decision settings spanning government, business, industry, health care, and education. AHP is considered most useful to teams contending with complex problems that involve human perception and judgment (79). The process breaks down a complex problem into a hierarchy of subproblems that can be compared with each other on a pairwise basis. It has unique advantages where major decision elements are difficult to quantify or compare or where communication among team members is impeded by their different specializations, terminologies, or perspectives. For the current project, criteria for cancer vaccines were determined. The criteria were then broken down into subcriteria for greater granularity within each higher level criterion. A panel of cancer vaccine experts used pairwise comparisons to weight first the criteria and then the subcriteria within the criteria. The AHP converted the weighted criteria into numerical values that could be analyzed and compared for the ranking of antigens and to permit the comparison of rankings based on hypothetical alternative weightings.

The AHP generated primary and alternative priority rankings of 75 cancer antigens based on criteria preidentified and weighted by a broadly constituted panel of cancer vaccine experts. These rankings are dynamic, given that priorities change as knowledge accrues from new studies. The associated lists of weighted criteria inform investigators as to what experimental evidence is required to advance antigens to higher priority levels. Above all, the rankings provide a basis for deciding which antigens are most likely to pay off on investments to generate cancer vaccines for testing in later-stage clinical trials.

Materials and Methods

Decision Lens, Inc., provided the AHP methodology as a Web-based tool with four modules.[11] The first phase of the process focused on identifying the participants, criteria, and alternatives to be prioritized. In the second phase, criteria essential to the decision were identified, grouped, compared, and weighted using the Build Model and Compare Criteria modules. The third phase focused on the Evaluate Alternatives module, wherein alternatives (antigens) were compared with each of the weighted criteria to determine their benefit or value using customized rating scales. The Reporting module provided a flexible tool for the analysis of information to facilitate informed decision making.

Phase I: decision preparation. The key objective of the decision preparation phase was to gather the critical data needed to make the decision and to define expectations for key participants about the decision process. There were three distinct steps to the process.

The first step was to determine who would be participating in the prioritization process. The NCI selected investigators who participated in the Immunotherapy Agent Workshop. The Workshop participants had been selected based on recommendations from the AACR, American Association of Immunologists, American Society of Clinical Oncology, American Society of Hematology, Cancer Vaccine Consortium, International Society for Biological Therapy of Cancer, and NCI intramural and extramural program staff. Experts from this group were used to contribute to the criteria determination, weighting, and evaluation steps of the process (list of participants available as Supplementary Data A, B, and C).

[10] http://www.cancer.gov/TRWG

[11] http://www.decisionlens.com

Table 1. Cancer antigen pilot prioritization: criteria and subcriteria, definitions, and weightings

Subcriteria	Definition	Weight of subcriteria
Therapeutic function (weight of criteria, 0.32)		
Controlled vaccine trial suggestive (data ranked as being superb, very strong, adequate, or fair)	Clinical trial data showing that a vaccine induced clinical responses in at least a small number of patients or provided suggestive evidence of benefit vs controls	
Superb data controlled vaccine trial suggestive		100.0% (1.0)
Very strong data controlled vaccine trial suggestive		93.0% (0.93)
Adequate data controlled vaccine trial suggestive		85.0% (0.85)
Fair data controlled vaccine trial suggestive		75.0% (0.75)
Responses in T-cell therapy		65.0% (0.65)
Preexistent immunity/survival correlation		15.0% (0.15)
Positive appropriate animal models		10.0% (0.1)
Not applicable		0.0% (0.0)
Immunogenicity (weight of criteria, 0.17)		
Immunogenic in clinical trials	T-cell and/or antibody responses elicited in clinical trials	100.0% (1.0)
T-cell immunity observed	Spontaneous T-cell responses observed in some patients	39.0% (0.39)
Immunogenic in appropriate animal models	Immunogenic in animal models with natural levels of antigen expression similar to humans	11.0% (0.11)
Antibody immunity observed	Spontaneous antibody observed in some patients	10.0% (0.1)
Not applicable		0.0% (0.0)
Oncogenicity (weight of criteria, 0.15)		
Oncogenic "self" protein	Associated with oncogenic process (i.e., oncogenic "self" protein)	100.0% (1.0)
Persistent viral antigen	Persistently expressed viral antigen	34.0% (0.34)
Function uncertain, correlated to decreased survival	Uncertain function, but increased expression correlated with decreased survival and/or more aggressive or advanced disease	25.0% (0.25)
Tissue differentiation, not oncogenic	Associated with tissue differentiation, but not oncogenic	12.0% (0.12)
Tumor-related stroma	Expression on tumor-related stroma, but not on malignant cells	12.0% (0.12)
Not applicable		0.0% (0.0)
Specificity (weight of criteria, 0.15)		
Absolute specificity	Absolutely specific (e.g., mutated oncogene, idiotype protein, or viral protein)	100.0% (1.0)
Oncofetal antigen	Antigens expressed in fetus with no or little expression in adult tissue (includes cancer testis antigens)	54.0% (0.54)
Overexpressed in cancer	Overexpressed in cancer, but expressed in some normal adult tissues	35.0% (0.35)
Abnormal posttranslational modification	Core protein expressed in normal tissue, but expressed in cancer with unique posttranslational changes (e.g., glycosylation or phosphorylation)	23.0% (0.23)
Tissue specific (expendable tissue)	Tissue-specific expression in normal adult tissue relatively expendable for survival (e.g., prostate and melanocytes)	21.0% (0.21)
Unique random mutations	Unique random mutations specific to each patient	10.0% (0.1)
Tumor stroma antigen	Normal antigen expressed on tumor stroma	10.0% (0.1)
Not applicable		0.0% (0.0)
Expression level and % positive cells (weight of criteria, 0.07)		
High level, all cancer cells	Highly expressed on all cancer cells in patients designated for treatment	100.0% (1.0)
High level, most cancer cells	Highly expressed on most cancer cells in patients designated for treatment	37.0% (0.37)
Lower level, all cancer cells	Lower level of expression on all cancer cells in patients designated for treatment	23.0% (0.23)
Lower level, most cancer cells	Lower level of expression on most cancer cells in patients designated for treatment	8.0% (0.08)
Not applicable		0.0% (0.0)
Stem cell expression (weight of criteria, 0.05)		
Stem cell expression, presumptive	Evidence for expression on putative cancer stem cells	100.0% (1.0)

(*Continued on the following page*)

Table 1. Cancer antigen pilot prioritization: criteria and subcriteria, definitions, and weightings (Cont'd)

Subcriteria	Definition	Weight of subcriteria
No info about stem cells, but on all stages from premalignant to metastatic	Present at all stages of tumor development, from premalignant to metastatic cancer cells, but without information about putative stem cells	66.0% (0.66)
No info about stem cells, but on most cancer cells	Expression on all or most cancer cells, but without information about putative stem cells	20.0% (0.2)
Not applicable		0.0% (0.0)
No. patients with antigen-positive cancers (weight of criteria, 0.04)		
Many patients, high level	High level of expression in many patients with a particular tumor type	100.0% (1.0)
Many patients, lower level	Low level of expression in many patients with a particular tumor type	16.0% (0.16)
All patients/unique antigens	Unique antigens from random mutations presumed to be present in all patients	14.0% (0.14)
Few patients, high level	High level of expression in a small subset of patients with a particular tumor type	11.0% (0.11)
Not applicable		0.0% (0.0)
No. epitopes (weight of criteria, 0.04)		
Longer antigen	Longer antigen with multiple epitopes and the potential to bind to most MHC molecules	100.0% (1.0)
Short antigenic segment	Short antigenic segment with one or few epitopes and the potential to bind to only selected MHC molecules	13.0% (0.13)
Cellular location of expression (weight of criteria, 0.02)		
Cell surface expression, no or little circulating antigen	Normally expressed on the cell surface with no or little circulating antigen	100.0% (1.0)
Internal with MHC presentation	Internal only with MHC presentation	95.0% (0.95)
Cell surface expression, and circulating antigen	Normally expressed on the cell surface with substantial circulating antigen	25.0% (0.25)
Not applicable		0.0% (0.0)

The 19 investigators listed in Supplementary Data A provided the criteria used to evaluate cancer antigens. Top-down and bottom-up approaches were used. For the top-down approach, approximately half of the experts were asked to submit via e-mail what they regarded to be characteristics of an "ideal" cancer antigen. For the bottom-up approach, the remaining experts were asked which characteristics made the following antigens good or poor candidates for therapeutic development: (*a*) mutated segment of p53, (*b*) MUC1, (*c*) MAGE-A3, (*d*) HER-2/neu, (*e*) gp100, and (*f*) mutated proteins unique to each patient. The two lists were vetted, combined, and structured into a list of criteria and subcriteria. Using the same information source, definitions for each criterion and subcriterion were developed. The final criteria and definitions are shown in Table 1.

The cancer antigens to be prioritized were determined through a search of the PubMed database over the last 5 y using the terms "cancer vaccine target." One hundred of the most frequently mentioned antigens were selected and submitted to the participating experts for categorization according to the predefined criteria and subcriteria. Eighty investigators (listed in Supplementary Data B) with expertise in one or several of the cancer antigens were asked to categorize the one or

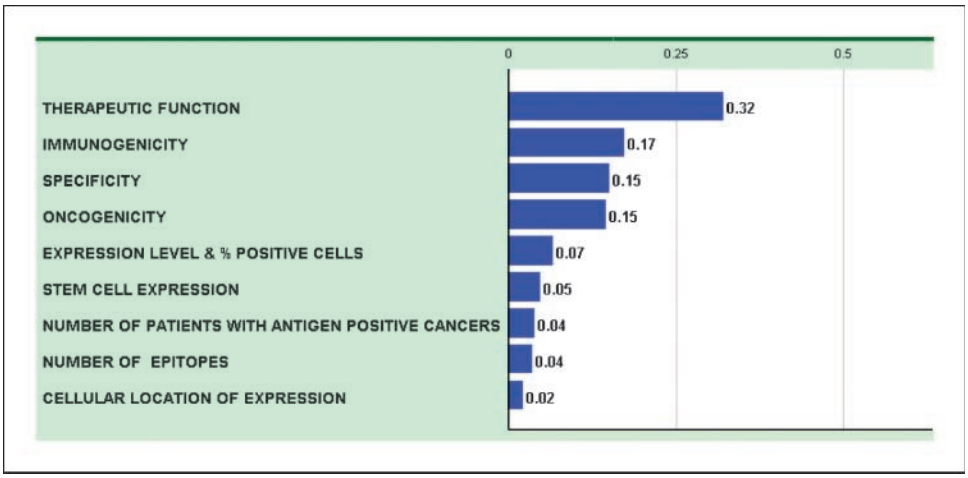

Fig. 1. Criteria for an ideal cancer antigen were weighted by pairwise comparison and the resulting relative weights are indicated. Therapeutic function was considered the most important criteria and was more than twice (0.32/0.15) as important as specificity or oncogenicity.

Table 2. Characteristics of an ideal cancer antigen

Criteria	Top subcriteria
Therapeutic function	Superb data controlled vaccine trial suggestive
Immunogenicity	T-cell and/or antibody responses elicited in clinical trials
Oncogenicity	Associated with oncogenic process (i.e., oncogenic "self" protein)
Specificity	Absolutely specific (e.g., mutated oncogene, idiotype protein, or viral protein)
Expression level and % positive cells	Highly expressed on all cancer cells in patients designated for treatment
Stem cell expression	Evidence for expression on putative cancer stem cells
No. patients with antigen-positive cancers	High level of expression in many patients with a particular tumor type
No. epitopes	Longer antigen with multiple epitopes and the potential to bind to most MHC molecules
Cellular location of expression	Normally expressed on the cell surface with no or little circulating antigen

several antigens according to the criteria and subcriteria. These experts were typically corresponding authors on published articles about the specific antigens. In certain cases, when necessary and where appropriate, experts not directly involved with the particular antigen were asked to categorize select antigens based on the predefined criteria. For some antigens, several experts were asked to categorize the antigen. A few experts did not respond and certain antigens were no longer under development. In the final analysis, 75 antigens were scored according to the predefined criteria. Differences in scoring were debated and voted on at the face-to-face "assessment of alternatives" meeting described below. An example of the antigen information form sent to the antigen experts is provided in Supplementary Data D.

Phase II: criteria refinement and weighting. The criteria and subcriteria were used as the basis for discussion during a Web-facilitated remote meeting using the Decision Lens model. They were discussed and definitions were refined based on the combined expertise of the 19 expert participants (Supplementary Data A). The criteria were then compared in a pairwise fashion to determine the experts' cumulative judgment of their relative importance to each other. The relative importance of each criterion to each of the other criterion was voted on by each expert, and the relative importance of each was given a numerical rating on a scale from -9 to +9. The subcriteria within each criterion were then compared in a similar pairwise fashion by the same process.

Each expert participant had a single vote of equal weight. Participants who were unable to complete their pairwise comparisons during the facilitated meeting were able to complete the process online at a later date. Thirty-six pairwise comparisons were used to assess the relative priority of the nine criteria. Similar pairwise comparisons of subcriterion within each criterion were determined to generate the relative weight of each subcriterion to other subcriterion. Subcriteria were compared only to subcriteria within their parent criteria. The cumulative results of the ratings of all of the experts were converted to a set of priority ratios for the criteria and subcriteria. The results were nonlinear in their value differences.

Phase III: assessment of alternatives. The weighted criteria and subcriteria, which were used as rating scales, were used to assess the relative priority of each of the 75 cancer antigens at a face-to-face meeting of 16 participants that was hosted by the NCI (Supplementary Data C). The information provided by up to three experts (Supplementary Data B) per antigen on the antigen information sheet (Supplementary Data D) was entered in the Decision Lens software tool. The subcriteria/rating scales were ordered from highest to lowest weight, but information on the relative weights of each criterion and subcriterion was shared with participants only after the evaluation was completed. Each antigen was assigned to a meeting participant who acted as a reviewer and led the discussion of that antigen.

Each antigen was categorized according to the criteria and subcriteria. If an antigen fulfilled more than one subcriterion within a criteria, the subcriteria with the highest value was selected. If a difference of opinion among participants was noted, it was discussed and then voted on. Often, consensus was not reached. When consensus was not reached, the votes ended up with a value between the two subcriteria. The value scores were calculated by taking the average of the ratings and then multiplying it by the weight of the criterion to cumulate to an aggregate score. The participants voted using a radiofrequency keypad and each vote had equal weight. Participants who were unable to complete antigen prioritization during the facilitated meeting were able to complete the process online at a later date.

Results

Weighting of criteria. The AHP pairwise comparison process resulted in a weighted model where the criteria relative weights reflect the derived priorities of the group of participants (Table 1; Fig. 1). The numerical values reflect the relative priorities of each criterion. As an example, pairwise comparisons of criteria determined that therapeutic function represented 32% of the weight and immunogenicity represented 17% of the weight, whereas cellular location of expression represented only 2% of the weight. Thus, therapeutic function was deemed to be approximately twice as important as immunogenicity and ~16 times more important than the cellular location of expression.

In some cases, there was considerable variation in response during the pairwise comparison process. The participants were asked to explain their positions so that their implicit knowledge could become explicit and possibly result in readjustment of votes. However, the final weighting did not require and often did not achieve consensus.

Weighting of subcriteria/rating scales. The subcriteria were similarly weighted by pairwise comparisons. Weighting is presented in Table 1. The subcriteria, which served as the rating scales for each criterion, are also nonlinear. The top subcriterion for each antigen received full value for the criterion. Other subcriteria received less value for the criteria with the level dependent on the predetermined weighting. For example, for the criterion specificity, an antigen deemed to have absolutely specificity received 100% of the value for that criterion, whereas an antigen that was overexpressed in cancer as the highest ranking within this category only received 35% of that value. The experts agreed that top subcriterion for each criterion approximately portrayed an "ideal cancer antigen" (Table 2).

The criterion therapeutic function carried the most weight in the prioritization process. This category also generated substantial debate about the assessment of available information. The basis of the criterion was defined as clinical trial data showing that a vaccine induced clinical responses in at least a small number of patients, or provided suggestive evidence of benefit versus

Table 3. Cancer antigen pilot prioritization: ranking based on predefined and preweighted criteria

Antigens (rank/reference number and name)	Criteria				
	Cumulative score	Therapeutic function (0.32)	Immunogenicity (0.17)	Oncogenicity (0.15)	Specificity (0.15)
1. WT1	0.81	0.75 (fair)	1.0 (trials)	1.0 (oncogenic)	0.54 (oncofetal)
2. MUC1	0.79	0.75 (fair)	1.0 (trials)	1.0 (oncogenic)	0.23 (post-translational)
3. LMP2	0.78	0.75 (fair)	1.0 (trials)	0.34 (viral)	1.0 (absolute)
4. HPV E6 E7	0.77	0.89 (mixed)	1.0 (trials)	0.34 (viral)	1.0 (absolute)
5. EGFRvIII	0.76	0.76 (mixed)	1.0 (trials)	0.62 (mixed)	1.0 (absolute)
6. HER-2/neu	0.75	0.85 (adequate)	1.0 (trials)	1.0 (oncogenic)	0.35 (overexpressed)
7. Idiotype	0.75	0.76 (mixed)	1.0 (trials)	0.12 (differentation)	1.0 (absolute)
8. MAGE A3	0.71	0.79 (mixed)	1.0 (trials)	0.25 (mixed)	0.54 (oncofetal)
9. p53 nonmutant	0.67	0.42 (mixed)	1.0 (trials)	1.0 (oncogenic)	0.35 (overexpressed)
10. NY-ESO-1	0.66	0.75 (fair)	1.0 (trials)	0.25 (prognosis)	0.54 (oncofetal)
11. PSMA	0.65	0.75 (fair)	1.0 (trials)	0.25 (prognosis)	0.21 (tissue specific)
12. GD2	0.65	0.75 (fair)	1.0 (trials)	0.12 (differentation)	0.35 (overexpressed)
13. CEA	0.62	0.75 (fair)	1.0 (trials)	0.12 (differentation)	0.35 (overexpressed)
14. MelanA/ MART1	0.60	0.77 (mixed)	1.0 (trials)	0.12 (differentation)	0.21 (tissue specific)
15. Ras mutant	0.60	0.1 (animal)	1.0 (trials)	1.0 (oncogenic)	1.0 (absolute)
16. gp100	0.59	0.75 (fair)	1.0 (trials)	0.12 (differentation)	0.21 (tissue specific)
17. p53 mutant	0.58	0.35 (mixed)	1.0 (trials)	1.0 (oncogenic)	0.1 (unique)
18. Proteinase3 (PR1)	0.57	0.7 (mixed)	1.0 (trials)	0.12 (differentation)	0.35 (overexpressed)
19. bcr-abl	0.56	0.00	1.0 (trials)	1.0 (oncogenic)	1.0 (absolute)
20. Tyrosinase	0.56	0.65 (T cell Tx)	1.0 (trials)	0.12 (differentation)	0.21 (tissue specific)
21. Survivin	0.55	0.1 (animal)	1.0 (trials)	1.0 (oncogenic)	0.35 (overexpressed)
22. PSA	0.55	0.75 (fair)	1.0 (trials)	0.12 (differentation)	0.21 (tissue specific)
23. hTERT	0.54	0.15 (preexistent)	1.0 (trials)	1.0 (oncogenic)	0.35 (overexpressed)
24. Sarcoma translocation breakpoints	0.54	0.00	0.39 (T cell)	1.0 (oncogenic)	1.0 (absolute)
25. EphA2	0.53	0.1 (animal)	1.0 (trials)	1.0 (oncogenic)	0.35 (overexpressed)
26. PAP	0.52	0.69 (mixed)	1.0 (trials)	0.12 (differentation)	0.21 (tissue specific)
27. ML-IAP	0.50	0.00	1.0 (trials)	1.0 (oncogenic)	0.35 (overexpressed)
28. AFP	0.49	0.15 (preexistent)	1.0 (trials)	0.24 (mixed)	0.54 (oncofetal)
29. EpCAM	0.48	0.1 (animal)	1.0 (trials)	0.12 (differentiation)	0.35 (overexpressed)
30. ERG (TMPRSS2 ETS fusion gene)	0.48	0.00	0.39 (T cell)	1.0 (oncogenic)	1.0 (absolute)
31. NA17	0.48	0.59 (mixed)	1.0 (trials)	0.00	0.35 (overexpressed)
32. PAX3	0.47	0.00	1.0 (trials)	1.0 (oncogenic)	0.54 (oncofetal)
33. ALK	0.46	0.00	0.39 (T cell)	1.0 (oncogenic)	0.42 (mixed)
34. Androgen receptor	0.45	0.1 (animal)	0.39 (T cell)	1.0 (oncogenic)	0.35 (overexpressed)
35. Cyclin B1	0.44	0.1 (animal)	0.39 (T cell)	1.0 (oncogenic)	0.35 (overexpressed)
36. Polysialic acid	0.44	0.00	1.0 (trials)	0.12 (differentiation)	0.54 (oncofetal)
37. MYCN	0.42	0.00	0.39 (T cell)	1.0 (oncogenic)	0.54 (oncofetal)
38. RhoC	0.42	0.00	0.39 (T cell)	1.0 (oncogenic)	0.35 (overexpressed)
39. TRP-2	0.42	0.1 (animal)	1.0 (trials)	0.12 (differentiation)	0.21 (tissue specific)
40. GD3	0.41	0.00	1.0 (trials)	0.12 (differentiation)	0.35 (overexpressed)
41. Fucosyl GM1	0.41	0.00	1.0 (trials)	0.12 (differentiation)	0.35 (overexpressed)
42. Mesothelin	0.41	0.00	1.0 (trials)	0.25 (prognosis)	0.35 (overexpressed)
43. PSCA	0.41	0.75 (fair)	0.11 (animal)	0.12 (differentiation)	0.21 (tissue specific)
44. MAGE A1	0.40	0.00	1.0 (trials)	0.25 (prognosis)	0.54 (oncofetal)
45. sLe(animal)	0.40	0.00	1.0 (trials)	0.12 (differentiation)	0.35 (overexpressed)
46. CYP1B1	0.40	0.00	1.0 (trials)	0.00	0.35 (overexpressed)
47. PLAC1	0.39	0.00	0.39 (T cell)	1.0 (oncogenic)	0.54 (oncofetal)
48. GM3	0.38	0.1 (animal)	1.0 (trials)	0.12 (stroma)	0.35 (overexpressed)
49. BORIS	0.38	0.1 (animal)	0.11 (animal)	1.0 (oncogenic)	0.54 (oncofetal)
50. Tn	0.37	0.00	1.0 (trials)	0.25 (prognosis)	0.23 (post-translational)

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Table 3. Cancer antigen pilot prioritization: ranking based on predefined and preweighted criteria (Cont'd)

Antigens (rank/reference number and name)	Criteria				
	Expression level and % positive cells (0.07)	Stem cell expression (0.05)	No. patients with antigen-positive cancers (0.04)	No. epitopes (0.04)	Cellular location of expression (0.02)
1. WT1	0.37 (high most)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
2. MUC1	1.0 (high all)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
3. LMP2	0.37 (high most)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
4. HPV E6 E7	0.23 (low all)	0.73 (mixed)	0.16 (many pts lo level)	1.0 (multiple)	0.95 (internal)
5. EGFRvIII	0.37 (high most)	1.0 (stem cells)	0.11 (sm subset hi level)	0.13 (single)	1.0 (surface)
6. HER-2/neu	0.37 (high most)	0.66 (all stages)	0.11 (sm subset hi level)	1.0 (multiple)	0.25 (circulating)
7. Idiotype	1.0 (high all)	0.66 (all stages)	0.14 (unique)	1.0 (multiple)	1.0 (surface)
8. MAGE A3	0.37 (high most)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
9. p53 nonmutant	0.37 (high most)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
10. NY-ESO-1	0.37 (high most)	1.0 (stem cells)	0.11 (sm subset hi level)	1.0 (multiple)	0.95 (internal)
11. PSMA	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
12. GD2	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.62 (mixed)
13. CEA	0.37 (high most)	0.66 (all stages)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
14. MelanA/ MART1	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
15. Ras mutant	0.23 (low all)	1.0 (stem cells)	0.16 (many pts lo level)	0.13 (single)	0.95 (internal)
16. gp100	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
17. p53 mutant	1.0 (high all)	0.77 (mixed)	0.14 (unique)	0.13 (single)	0.95 (internal)
18. Proteinase3 (PR1)	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	0.13 (single)	0.95 (internal)
19. bcr-abl	0.23 (low all)	1.0 (stem cells)	0.16 (many pts lo level)	0.13 (single)	0.95 (internal)
20. Tyrosinase	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
21. Survivin	0.37 (high most)	0.66 (all stages)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
22. PSA	0.08 (low most)	0.66 (all stages)	0.16 (many pts lo level)	1.0 (multiple)	0.25 (circulating)
23. hTERT	0.23 (low all)	1.0 (stem cells)	0.16 (many pts lo level)	1.0 (multiple)	0.95 (internal)
24. Sarcoma translocation breakpoints	1.0 (high all)	1.0 (stem cells)	1.0 (many pts hi level)	0.13 (single)	0.95 (internal)
25. EphA2	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
26. PAP	0.23 (low all)	0.2 (most)	0.16 (many pts lo level)	1.0 (multiple)	0.25 (circulating)
27. ML-IAP	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
28. AFP	0.37 (high most)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
29. EpCAM	1.0 (high all)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
30. ERG (TMPRSS2 ETS fusion gene)	0.37 (high most)	0.66 (all stages)	1.0 (many pts hi level)	0.13 (single)	0.95 (internal)
31. NA17	0.00	0.00	1.0 (many pts hi level)	0.13 (single)	0.95 (internal)
32. PAX3	0.08 (low most)	0.2 (most)	0.00	1.0 (multiple)	0.95 (internal)
33. ALK	1.0 (high all)	1.0 (stem cells)	1.0 (many pts hi level)	0.27 (mixed)	0.95 (internal)
34. Androgen receptor	0.37 (high most)	0.66 (all stages)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
35. Cyclin B1	0.32 (mixed)	0.66 (all stages)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
36. Polysialic acid	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
37. MYCN	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
38. RhoC	0.37 (high most)	0.66 (all stages)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
39. TRP-2	0.37 (high most)	1.0 (stem cells)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
40. GD3	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
41. Fucosyl GM1	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
42. Mesothelin	0.37 (high most)	0.66 (all stages)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
43. PSCA	0.37 (high most)	0.2 (most)	0.16 (many pts lo level)	1.0 (multiple)	1.0 (surface)
44. MAGE A1	0.00	1.0 (stem cells)	0.16 (many pts lo level)	1.0 (multiple)	0.95 (internal)
45. sLe(a)	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
46. CYP1B1	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
47. PLAC1	0.37 (high most)	0.2 (most)	0.11 (sm subset hi level)	1.0 (multiple)	1.0 (surface)
48. GM3	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
49. BORIS	0.08 (low most)	0.66 (all stages)	0.16 (many pts lo level)	1.0 (multiple)	0.95 (internal)
50. Tn	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)

(*Continued on the following page*)

Table 3. Cancer antigen pilot prioritization: ranking based on predefined and preweighted criteria (Cont'd)

Antigens (rank/reference number and name)	Criteria				
	Cumulative score	Therapeutic function (0.32)	Immunogenicity (0.17)	Oncogenicity (0.15)	Specificity (0.15)
51. GloboH	0.37	0.00	1.0 (trials)	0.12 (differentiation)	0.35 (overexpressed)
52. ETV6-AML	0.37	0.00	0.00	1.0 (oncogenic)	1.0 (absolute)
53. NY-BR-1	0.36	0.00	0.39 (T cell)	0.12 (differentiation)	1.0 (absolute)
54. RGS5	0.35	0.00	1.0 (trials)	0.00	0.35 (overexpressed)
55. SART3	0.35	0.00	1.0 (trials)	0.00	0.35 (overexpressed)
56. STn	0.34	0.00	1.0 (trials)	0.25 (prognosis)	0.23 (post-translational)
57. Carbonic anhydrase IX	0.34	0.00	1.0 (trials)	0.00	0.35 (overexpressed)
58. PAX5	0.33	0.00	0.39 (T cell)	1.0 (oncogenic)	0.21 (tissue specific)
59. OY-TES1	0.32	0.00	0.1 (antibody observed)	1.0 (oncogenic)	0.54 (oncofetal)
60. Sperm protein 17	0.30	0.1 (animal)	0.11 (animal)	0.25 (prognosis)	0.54 (oncofetal)
61. LCK	0.28	0.00	1.0 (trials)	0.00	0.35 (overexpressed)
62. HMWMAA	0.27	0.1 (animal)	0.11 (animal)	0.00	0.35 (overexpressed)
63. AKAP-4	0.26	0.1 (animal)	0.11 (animal)	0.12 (differentiation)	0.54 (oncofetal)
64. SSX2	0.26	0.00	0.39 (T cell)	0.25 (prognosis)	0.54 (oncofetal)
65. XAGE 1	0.23	0.00	0.1 (antibody observed)	0.00	0.54 (oncofetal)
66. B7H3	0.22	0.00	0.00	0.25 (prognosis)	0.35 (overexpressed)
67. Legumain	0.19	0.1 (animal)	0.11 (animal)	0.00	0.35 (overexpressed)
68. Tie 2	0.18	0.1 (animal)	0.11 (animal)	0.00	0.23 (post-translational)
69. Page4	0.17	0.00	0.00	0.12 (differentiation)	0.21 (tissue specific)
70. VEGFR2	0.16	0.1 (animal)	0.11 (animal)	0.12 (stroma)	0.1 (stromal)
71. MAD-CT-1	0.15	0.00	0.1 (antibody observed)	0.00	0.54 (oncofetal)
72. FAP	0.14	0.1 (animal)	0.00	0.00	0.1 (stromal)
73. PDGFR-β	0.14	0.00	0.11 (animal)	0.12 (stroma)	0.1 (stromal)
74. MAD-CT-2	0.14	0.00	0.1 (antibody observed)	0.00	0.54 (oncofetal)
75. Fos-related antigen 1	0.13	0.1 (animal)	0.11 (animal)	0.00	0.1 (stromal)

controls. The quality of published or publicly reported data was often disputed by the panel members. In anticipation of this discussion, the subcategory controlled vaccine trials suggestive was subdivided before the meeting into the following subcriteria: (*a*) superb data suggesting therapeutic benefit in a controlled vaccine trial, (*b*) very strong data suggesting therapeutic benefit in a controlled vaccine trial, (*c*) adequate data suggesting therapeutic benefit in a controlled vaccine trial, and (*d*) fair data suggesting therapeutic benefit in a controlled vaccine trial.

Although subjective, these four subcriteria parallel the evaluation process commonly used to assess NIH grant applications and emphasized the need for expert evaluation at all stages of the process. The other subcriteria within the criterion of therapeutic function were as follows: (*e*) responses in T-cell therapy trial, (*f*) preexistent immunity/survival correlation, and (*g*) positive data in appropriate animal models.

The results of the evaluation and weighting of the 75 cancer antigens are presented in Table 3 (see supplemental information). The results presented in Fig. 2 show the cumulative score for each antigen. The color-coded bars indicate the relative contribution of each criterion.

No antigen exhibited all of the top subcriteria (Table 2). By this assessment, no antigen, among those selected, satisfied the criteria for an ideal cancer antigen. The dominant criterion was therapeutic function, and the top 14 antigens all have significant contributions from that criterion (i.e., fair to very strong data controlled vaccine trial). Altogether, 20 antigens were deemed to have at least fair data controlled vaccine trial suggestive. None were deemed to have superb data by any of the experts.

The second dominant criterion was immunogenicity. All 46 of the 75 antigens, including the top 14, had documented immunogenicity in human clinical trials. The total weight of therapeutic function plus immunogenicity was 0.49. The dominance of therapeutic function and immunogenicity biased the ratings toward antigens already in analyzable clinical trials (i.e., antigens further along in the developmental process).

To assess priorities without bias toward already having been in clinical trials, the antigens were reranked, excluding therapeutic function and immunogenicity (Fig. 3). After excluding these top two criteria, the antigen ranking was dominated by the criteria of "oncogenicity," specificity, and "stem cell expression." In this alternative model, the breakpoint region of translocated fusion genes (Ewing's sarcoma and alveolar rhabdomyosarcoma; ALK, bcr-abl, and ETV6-AML) and mutant oncogenes (ras) rose to the top. The method of reporting data in Table 3 allows reprioritization of the antigens and development of alternative rankings based on alternative assessment or weighting of criteria and subcriteria of interest.

Table 3. Cancer antigen pilot prioritization: ranking based on predefined and preweighted criteria (Cont'd)

Antigens (rank/reference number and name)	Criteria				
	Expression level and % positive cells (0.07)	Stem cell expression (0.05)	No. patients with antigen-positive cancers (0.04)	No. epitopes (0.04)	Cellular location of expression (0.02)
51. GloboH	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
52. ETV6-AML	0.23 (low all)	0.66 (all stages)	0.11 (sm subset hi level)	0.13 (single)	0.95 (internal)
53. NY-BR-1	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
54. RGS5	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
55. SART3	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
56. STn	0.37 (high most)	0.2 (most)	0.16 (many pts lo level)	1.0 (multiple)	1.0 (surface)
57. Carbonic anhydrase IX	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
58. PAX5	0.23 (low all)	0.2 (most)	0.16 (many pts lo level)	1.0 (multiple)	0.95 (internal)
59. OY-TES1	0.08 (low most)	0.2 (most)	0.16 (many pts lo level)	1.0 (multiple)	0.95 (internal)
60. Sperm protein 17	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
61. LCK	0.00	0.00	0.00	1.0 (multiple)	0.95 (internal)
62. HMWMAA	1.0 (high all)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
63. AKAP-4	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
64. SSX2	0.08 (low most)	0.2 (most)	0.11 (sm subset hi level)	1.0 (multiple)	0.95 (internal)
65. XAGE 1	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
66. B7H3	0.37 (high most)	0.2 (most)	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
67. Legumain	0.37 (high most)	0.2 (most)	0.00	1.0 (multiple)	1.0 (surface)
68. Tie 2	0.00	0.00	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
69. Page4	0.37 (high most)	0.00	1.0 (many pts hi level)	1.0 (multiple)	0.95 (internal)
70. VEGFR2	0.00	0.00	1.0 (many pts hi level)	1.0 (multiple)	0.25 (circulating)
71. MAD-CT-1	0.00	0.00	0.00	1.0 (multiple)	0.95 (internal)
72. FAP	0.00	0.00	1.0 (many pts hi level)	1.0 (multiple)	1.0 (surface)
73. PDGFR-β	0.00	0.66 (all stages)	0.00	1.0 (multiple)	1.0 (surface)
74. MAD-CT-2	0.00	0.00	0.16 (many pts lo level)	1.0 (multiple)	0.00
75. Fos-related antigen 1	0.00	0.00	0.11 (sm subset hi level)	1.0 (multiple)	1.0 (surface)

NOTE: Row 1: criteria are listed in descending order of weighting. The numbers refer to relative weighting of each criterion. The cumulative numbers total 1. Column 1: antigens are listed in descending order of ranking. The numbers refer to the ranking as well as to a literature reference for each antigen. Column 2: cumulative scores are listed in descending order of ranking. The cumulative score for each antigen is the sum product of predetermined weights for the nine criteria. Cumulative score for each antigen is the sum product of the weight of each criteria multiplied by the score of the subcriteria. Total score = (weight of criteria 1) × (score of subcriteria for criteria 1) + (weight of criteria 2) × (score of subcriteria for criteria 2) + (weight of criteria 3) × (score of subcriteria for criteria 3) + etc. Columns 3 to 11: numbers represent the weight of the top subcriteria appropriate for that antigen within the criteria denoted in the column. The words are abbreviations for the subcriteria as indicated in Table 1. The full names and weighted scores for each subcriterion are presented in Table 1.
Abbreviations: Column 3 (THERAPEUTIC FUNCTION): Fair, fair data; Mixed, the panel members disagreed on what should be the top subcategory (See Supplementary data for exact votes); Adequate, adequate data; Animal, animal data; T cell Tx, T-cell therapy data; Preexistent, preexistent immunity. Column 4 (IMMUNOGENICITY): Trial, immunogenic in clinical trials; T cell, T-cell immunity observed; Animal, immune in animal models; Ab, antibody immunity observed. Column 5 (ONCOGENICITY): Oncogenic, oncogenic "self" protein; Viral, persistent viral antigen; Differentiation, differentiation antigen; Prognosis, correlated with decreased survival; Stroma, tumor related stroma. Column 6 (SPECIFICITY): Oncofetal, oncofetal antigen; Post-translational, abnormal post-translational modification; Absolute, absolute specificity; Overexpressed, overexpressed in cancer; Tissue specific, normal tissue antigen; Unique, unique random mutation. Stromal, tumor stroma antigen. Column 7 (EXPRESSION LEVEL & % POSITIVE CELLS): High most, high level, most cancer cells; High all, high level all cancer cells; Low all, low level, all cancer cells; Low most, low level, most cancer cells. Column 8 (STEM CELL EXPRESSION): Stem cells, on stem cells; All stages, no info about stem cells, on all stages; Most, no info about stem cells, on most cancer cells. Column 9 (No. PATIENTS WITH ANTIGEN-POSITIVE CANCERS): Many pts hi level, many patients, high level; Sm subset hi level, few patients, high level; Unique, all patients, unique antigens; Many pts lo level, many patient, low level. Column 10 (No. EPITOPES): Multiple, multiple epitopes in longer antigen; Single, single epitope, short antigen. Column 11 (CELLULAR LOCATION OF EXPRESSION): Internal, internal antigen with MHC expression; Surface, cell surface expression with little circulating antigen; Circulating, cell surface expression with circulating antigen.

Discussion

This study developed a well-vetted, priority-ranked list of cancer vaccine target antigens based on predefined and preweighted objective criteria developed by a panel of content experts. The AHP method and Decision Lens platform provided the framework to catalogue and weight vaccine development decision criteria and to rank 75 selected antigens. This process was done in three stages by three panels of cancer vaccine experts with overlapping members. The first panel defined the criteria to be ranked for priority. The second panel weighted the criteria. The third panel ranked the 75 antigens according to the predefined

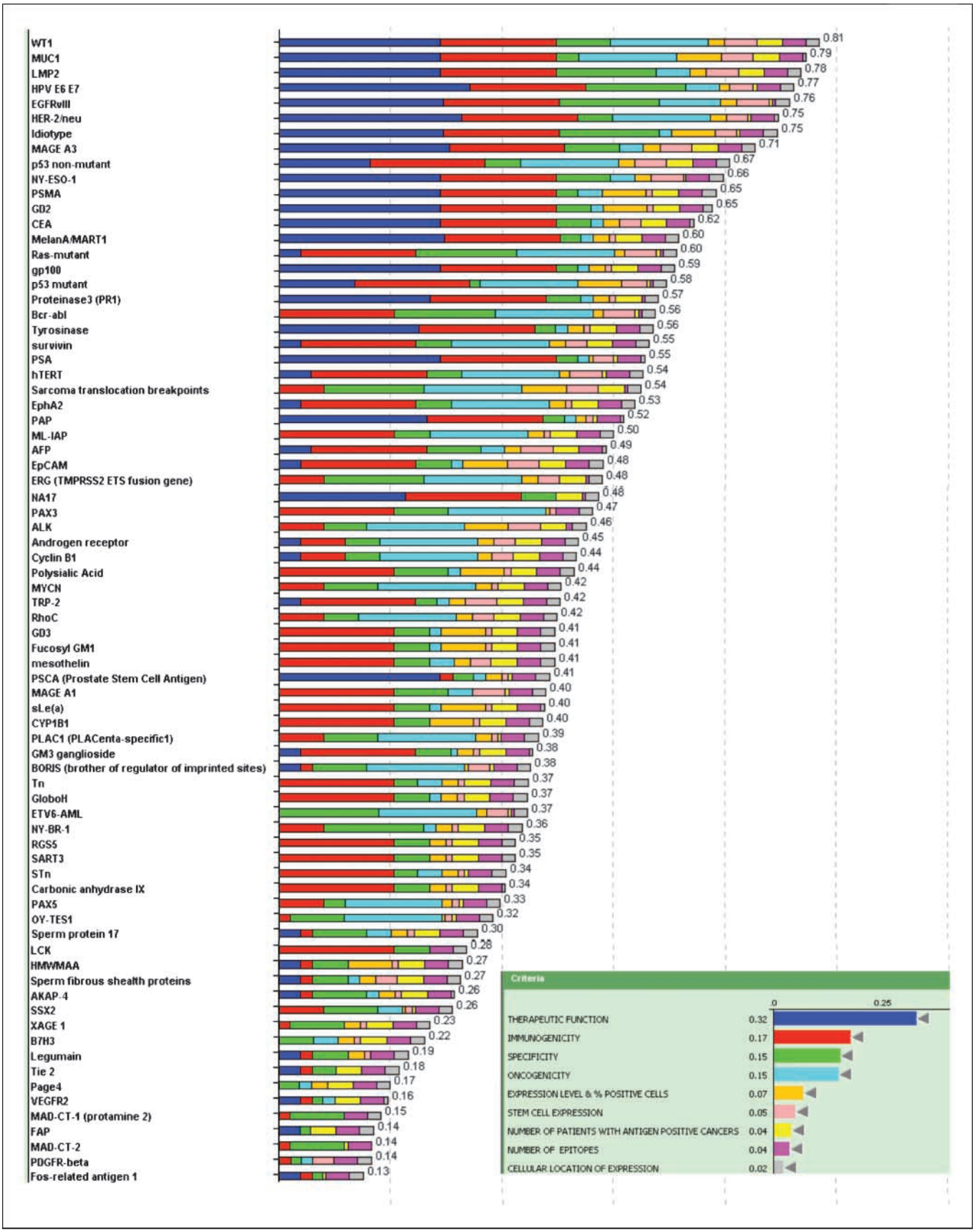

Fig. 2. Cancer antigen pilot prioritization: representation of ranking based on predefined and preweighted criteria and subcriteria. Inset, the color used to designate each criterion and its relative weight. Number at the end of each bar, relative rank of that antigen.

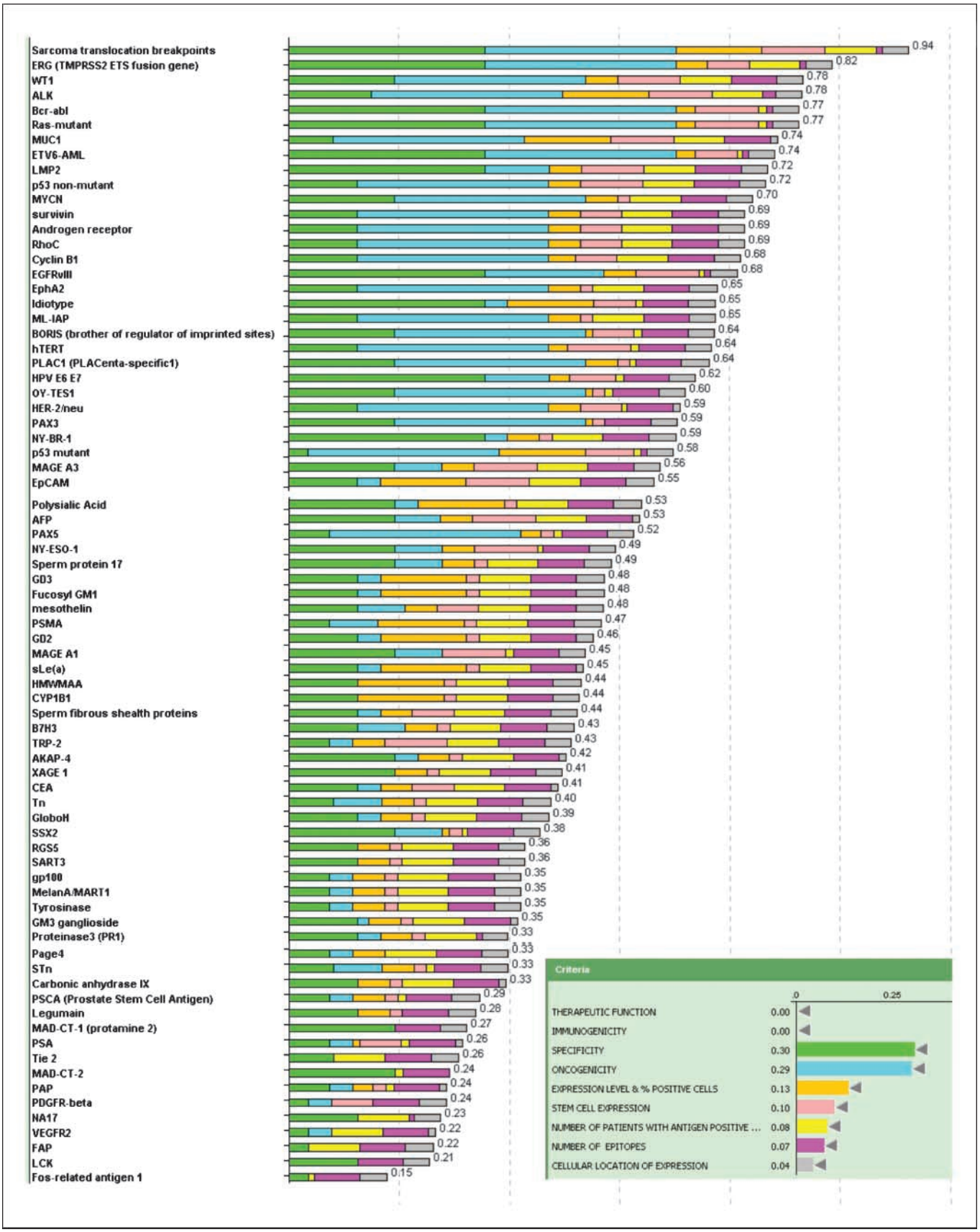

Fig. 3. Representation of ranking following exclusion of therapeutic efficacy and immunogenicity. Inset, the color used to designate each criterion and its relative weight. Number at the end of each bar, relative rank of that antigen.

preweighted criteria based on information on the antigens provided by researchers familiar with the individual antigens. The broad nature of the input underpinning the list of criteria should facilitate subsequent NCI or other funding agency discussions as to which antigens to test in subsequent focused translational/clinical studies.

This study is termed a "pilot prioritization project" with the emphasis on "pilot." One of the goals was to determine whether the methods used could be used to rank priorities for subsequent efforts to accelerate translational research. The finding that 20 of the 75 evaluated antigens had some clinical efficacy and that 46 of them had validated immunogenicity in human clinical trials not only documents the extent and vigor of the cancer vaccine field but also accentuates the need for prioritization. Notably, there are cancer antigens under development that were not included in this prioritization effort, again accentuating the breadth of the opportunities in the field.

Of the 46 antigens with validated immunogenicity and 20 with suggestive clinical data, none are Food and Drug Administration approved for general use. It is generally assumed that development of any of the top antigens will require concerted collaboration on the part of experts in cancer vaccine development. We anticipate that the prioritization of immunotherapy agents with high potential for cancer therapy[9] and the current ranking of cancer antigens will jointly lay the foundation for such focused collaborations.

The final scoring and ranking was necessarily done with incomplete knowledge. Much more was known about some antigens than others. Antigens that had undergone the most prior research had a marked advantage in the ranking. The experts ranked therapeutic efficacy and immunogenicity as the top criteria. Within these categories, there were many types of trials with different end points and different patient selection criteria. Thus, it was necessary to further divide the criteria according to the level of the data. The subcategorization was not precise and was subjective along the scale of fair to superb data. The experts had varying opinions about the quality of the data, and the panel had no opportunity to examine raw data from any trials. An in-depth analysis of primary clinical data for the antigens would be required to substantiate the results before any definitive action could be taken. Furthermore, the ranking at best represents the current state of our knowledge and will change as new information becomes available.

The order changed appreciably when reanalyzed without the top criteria therapeutic efficacy and immunogenicity. The leading criteria then became oncogenicity, specificity, and stem cell expression, and the priorities of the breakpoint region of translocated fusion genes (Ewing's sarcoma and alveolar rhabdomyosarcoma; ALK, bcr-abl, and ETV6-AML) and mutant oncogenes (ras) rose to the top. Arguably, it will be harder for them to achieve therapeutic efficacy, as these antigens require selective MHC presentation of a small and single epitope. Thus, there may be some underlying biological justification for their lower ranking.

Knowledge within other categories was often also incomplete or inadequate. For example:

1. Stem cell expression was deemed to be important, but the group recognized that the field of stem cell identification is rapidly evolving. Future thoughts and assessments about cancer stem cells could be markedly different.
2. The criterion of oncogenicity was important. However, many antigens not considered to be oncogenic are associated with a poor prognosis and are clearly involved in helping to sustain the malignant phenotype. Thus, the definition of oncogenic may be too restrictive. The outcome of immunologic pressure is often the evolution of antigen-negative variants. It would seem beneficial to target antigens, which, if lost, resulted in diminished ability of the cancer cells to survive or thrive. Necessity for maintaining a malignant phenotype is a broader definition than oncogenic per se and might be more relevant.
3. It was felt by the experts that antigens with no or little circulating antigen were substantially preferable to antigens with circulating antigen. However, the group did not have access to actual side-by-side data quantifying circulating antigen and did not define a threshold value discriminating between the two. Moreover, in certain cases, the amount of circulating antigen was not well characterized in the literature.

No antigen exhibited all of the top subcriteria. By this assessment, no antigen, among those selected, satisfied the criteria for an ideal cancer antigen. Some of the deficiencies, such as stem cell expression, are biological and cannot be changed. Others, such as immunogenicity and level of therapeutic efficacy, can potentially be changed with additional experiments and more data and, most compellingly, by the use of more effective vaccine formulations and schedules of administration. For antigens too early in development to have garnered evidence of clinical efficacy or immunogenicity, the dominance of those criteria in the experts' ratings provides a road map for investigators by emphasizing that high-quality data about these criteria are critical for prioritization of antigens for focused subsequent development.

Another question is whether there are ideal cancer antigens left to be discovered. It can be assumed that the first antigens discovered would be among the most abundant and the most immunogenic. Abundance and immunogenicity are both major criteria. By extrapolation, it can be argued that many of the antigens left to be discovered would be less abundant and less immunogenic molecules.

Of the 75 antigens evaluated, 46 were immunogenic in clinical trials and 20 of them had suggestive clinical efficacy in the therapeutic function category with documented vaccine-induced clinical responses in at least a small number of patients or suggestive evidence of benefit versus controls. However, none were deemed to have superb data in the category of therapeutic function. The lack of superb data could be multifactorial, including inadequate trial design or patient selection and inadequate vaccine formulation or regimens. These deficiencies can be overcome by more intelligent trial design based on assessment of past "productive failures."

Two profound biological issues limiting the efficacy of cancer vaccines are the strength of immunologic tolerance and the intrinsic limitations on the ability of T cells to expand in number in response to antigenic stimulation. There are normally exceedingly strict biological limits imposed on the immune system to prevent excessive T-cell activation and expansion. The same biological restrictions limit cancer vaccines. Immunotherapeutic agents that can circumvent many of the biological restrictions have been invented and formulated and proven to

be biologically active, including dendritic cell activators and growth factors, vaccine adjuvants, T-cell stimulators and growth factors, genetically modified T cells, immune checkpoint inhibitors, and agents to neutralize or inhibit suppressive cells, cytokines, and enzymes. Unfortunately, few of these agents are broadly available for the development of effective multiple component cancer vaccine regimens. The tools needed to raise T-cell levels to extraordinary levels *in vivo* and to maintain T-cell number for prolonged periods of time are at hand. A major problem facing immunotherapy today is a lack of broad availability of agents already in existence that could be effective in multiple component regimens and the administrative difficulties of funding and carrying out such multiple component regimens. It is highly likely that therapeutic regimens composed of optimal vaccine formulations with combinations of already invented immunotherapy agents in the above categories would lift the level of data into the superb data subcategory for many of the 20 antigens as well as others less studied. The current prioritization process, by validating that at least 20 antigens have suggestive clinical efficacy, highlights the need for an administrative and funding structure capable of translating these scientific discoveries into effective cancer therapies.

The AHP approach has several advantages over more standard evaluation and prioritization approaches. The AHP framework requires detailed discussion of the specific criteria in advance of the prioritization, permitting a comparison of individual perceptions and forcing the group to reach consensus on interpretations and definitions. This is presumed to improve the consistency of responses and has the effect of generating confidence in the results and "buy-in" among stakeholders. AHP allows the information to be evaluated quantitatively and qualitatively using both subjective and objective ranking scales. The ability to apply nonlinear weights to criteria and ranking scales was viewed as a distinct advantage over a system that simply averages the results. The Decision Lens platform provided an organized and consistent way to organize and view data, thereby facilitating evaluation. The transparency of the process was a benefit in that disagreements were quickly recognized and could be discussed. Finally, the Web-based asynchronous approach was viewed as an efficient use of experts' time.

The flexibility of the AHP/Decision Lens approach in permitting "what if" scenarios was exceptionally valuable in understanding how changing the weight of the criteria and subcriteria would affect the outcome and helped to provide a comfort level with the generated priority list. The approach accommodates viewing the data with selected criteria given any proportion of the weighing, including zero. The flexibility of the system has the advantage of simplifying reevaluation of alternatives when additional information becomes available, and allows for modification of criteria as more experience with generating cancer vaccines is gained. As one example, the flexibility will allow for alternative assessments of prioritization for the same antigen in different tumor types in circumstances where the antigen has markedly different expression patterns.

It must be noted that the AHP does not make decisions; rather, it provides a way to analyze and prioritize alternatives. One of the limitations of AHP is that it only ranks degrees of positivity. In some cases, there can be "deal-breaking" negative information that needs to be assessed outside of the AHP. A list of ranked alternatives provides a rational basis for decisions at the executive level. This pilot prioritization study produced a ranked list of cancer antigens that can be used by the broad immunotherapy community when considering further investment in experimental research for individual antigens as they move toward the goal of translating the most promising cancer antigens into vaccines for cancer treatment or prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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