REPORT of the IMMUNE RESPONSE MODIFIER PATHWAY PRIORITIZATION WORKING GROUP (IRMP WG)

A Working Group of the Clinical Trials and Translational Research Advisory Committee (CTAC)
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I. SUMMARY:

The NCI Translational Research Working Group identified modulation of the immune response as an important approach to cancer treatment and prevention, and developed the Immune Response Modifier (IRM) Developmental Pathway to a Clinical Goal. Immune response modifiers are unique because their primary mode of action is to modulate host responses; the host response in turn mediates cancer therapy and prevention. Host immune responses can be exquisitely targeted and can last long-term, well past the time of therapeutic administration. A hallmark of the Immune Response Modifier Developmental Pathway is the need for coordinated development of multiple components. Many existing agents,have substantial efficacy in activating and sustaining highly targeted immune responses. The selection of targets is virtually unlimited. Any mutant, overexpressed or abnormally expressed protein in or on cancer cells can serve as a target for cancer vaccine and/or T-cell therapy mediated immunotherapy. The immune system is highly complex and self-regulating. Agents that stimulate, direct, and control the immune response as well as those that overcome the self-regulation have been identified. A major challenge in the development of effective immunotherapy or immunopreventive agents is the recognized requirement for the simultaneous co-development of multiple agents. The multiplicity of translational options for the IRM Pathway mandate development of transparent methods to prioritize, with the least possible bias, translational opportunities to allow the development of rational, synergistic combinations of immune modulators.

The IRM Prioritization Working Group (IRMP WG), a working group of the NCI's Clinical Trials and Translational Research Advisory Committee (CTAC), was charged with prioritizing translational research opportunities in the IRM Pathway and recommending several high priority regimens for funding through the NCI Special Translational Research Acceleration Project (STRAP) program.

The IRM Pathway opportunities were prioritized through a series of workshops with broad representation from the scientific community involving well over 100 experts. Essential to the outcome were two NCI-sponsored workshops: the Division of Cancer Biology-sponsored Immunotherapy Agents Workshop held in the summer of 2007, and the Coordinating Center for Clinical Trials-sponsored Cancer Antigen Pilot Prioritization Project held in 2008. These efforts set the groundwork for prioritizing entire regimens, i.e., combinations of antigen targeted therapies and immune modifier agents. The IRM Subgroup of the Process to Accelerate Translational Science (PATS) Working Group of CTAC was charged with developing the criteria to rate translational research opportunities that encompass the entire IRM Pathway. Criteria and rating scales for scientific validity and feasibility for each major component of the IRM Pathway were identified and weighted, and the results of the IRM Pathway Criteria Development process were approved by CTAC on July 13, 2009.

The IRM Pathway Pilot Prioritization Project involved three steps: generating a list of IRM Pathway translational research opportunities, prioritizing the list to identify the opportunities that are "ripe" for acceleration, and providing recommendations to the NCI for the inaugural IRM Pathway STRAP(s). An IRM translational research opportunity is a complete multi-component regimen involving all aspects of the IRM Pathway. The IRM Prioritization WG prioritized IRM pathway components and regimens based on the approved predefined and preweighted criteria through a series of meetings and webinars in the fall of 2009.

The IRMP WG considered a total of 113 Translational Research Opportunities submitted in response to RFI NOT-CA-09-031 or as abstracts to the 2008 or 2009 NCI Translational Science Meetings. In addition, the top 20 Immune Modifying Agents (IMAs, identified by the 2007 NCI Immunotherapy Agent workshop) and top 15 cancer antigens (identified by the 2008 NCI Cancer Antigen Pilot Prioritization Project) were included. In total, 174 key component candidates were evaluated.

The IRMP WG judged that robust IRM Pathway regimens could be best generated by examining individual pathway components and assembling them in rational and synergistic ways. The key components were Targets and IMAs, and the construction of the best possible regimens could be accomplished by rationally combining top Targets with Top IMAs.

The four broad types of regimens were: (1) Cancer vaccines, (2) Adoptive therapy with effector cells, (3) Antibody therapy regimens, and (4) Combinations of IMAs to induce or augment immune response to autochthonous antigens.

The IRMP WG identified three distinct subtypes of Targets and five distinct subtypes of IMAs. Candidates within each subgroup were rated using the predetermined criteria and additional inclusion and exclusion criteria considered pertinent for recommendations for the STRAP program. The Target and IMA subgroups, and the top ranking candidates in each subgroup, are listed:

- Target A: Vaccine Targets
  - HPV E6/7, HER2, MAGE A3, MUC1, WT1, NY-ESO-1, PSA
- Target B: T-Cell Therapy Targets:
  - HPV E6/7, HER2, MAGE A3, MUC1, WT1, NY-ESO-1, PSA
- Target C: Antibody & T Body Targets
  - HER2, EGFR, CD20, CD19
- IMA D: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or dendritic cell growth factors.
  - CpG, FLT3L, Anti-CD40, IL12, CCL21
- IMA E: T cell stimulators or T cell growth factors
  - IL7, IL21, IL15, Anti-4-1BB
- IMA F: Inhibitors of T cell checkpoint blockade
  - Anti-CTLA-4, Anti-PD1
- IMA G: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, Anti-IL10
- IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)
  - IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)

The IRMP WG recommends that an Adoptive Therapy STRAP and two Cancer Vaccine STRAPS, one with a viral antigen and one with a “self” cancer antigen, be considered. It suggests that a high priority T cell stimulator or T cell growth factor (IL7, IL21, IL15, or Anti-4-1-BB) and/or a high priority Inhibitor of T cell checkpoint blockade (Anti-CTLA-4, Anti-PD1) be provided by the NCI as the IMA component to each STRAP regimen. A call for applications can be used to solicit the Target component of each regimen. The priority Targets listed above would receive the highest consideration. Proposals should not be restricted to these candidates Targets, but evidence must be provided for equivalency to these high-priority candidates. Cancer vaccines require appropriate adjuvants. Adjuvants for vaccine STRAPs should be provided by the NCI based on the recommendations of the previous NCI Immunotherapy Agent workshop.

In addition, it is recognized that several of the high-priority IMAs and Adjuvants recommended to the NCI are also Agents to increase antibody dependent cellular cytotoxicity (ADCC). Of the Targets, antibodies are the only approved approaches that are part of the current Standard of Care, and from a drug development perspective the Antibody scaffold has the lowest feasibility and regulatory hurdles. In the event that an IMA or adjuvant provided by the NCI for the STRAP program also augments ADCC, an additional STRAP encompassing the Antibody Therapy scaffold is highly recommended to maximize the NCI’s investment and impact.

Proposals submitted in response to the call for applications should be judged based on the CTAC-approved criteria for components of the IRM Pathway including: scientific validity and feasibility of the Target, Formulation, Combination regimen, Immune response assay, Patient selection assay, and Availability of patients for clinical trials. Additional criteria for consideration include clinical need, e.g. rare diseases and immunoprevention, and appropriateness for NCI investment.

It is recommended that a call for applications for an IRM STRAP is initiated, reviewed, and funded in FY2010.

II. BACKGROUND AND PURPOSE:

A. The Translational Research Acceleration Initiative

The prioritization of Immune Response Modifier Pathway Translational Research Opportunities is a project of the Translational Research Working Group (TRWG) implementation team. The TRWG was an NCI-sponsored working group charged with evaluating the status of the NCI's investment in translational research and envisioning its future in an inclusive, representative, and transparent manner. In 2007, the NCI accepted the 15 TRWG recommendations to accelerate translational cancer research as outlined in the report entitled *"Transforming Translation: Harnessing Discovery for Patient and Public Benefit"* (http://www.cancer.gov/trwg). Implementation of these recommendations is the responsibility of the TRWG Implementation Team, Coordinating Center for Clinical Trials, Office of the Director, NCI.

Key among the TRWG recommendations was the establishment of a yearly process to identify a small number of projects that are "ripe" for translation and provide the financial resources and the project management required to expedite moving those projects to the point of early stage clinical trials. This process, referred to as the Translational Research Acceleration Initiative, is being implemented and includes a) collecting information on the breadth of cancer translational research opportunities, b) prioritizing opportunities based on scientific validity, feasibility, and clinical need, and c) accelerating the advancement of a small number of high priority opportunities along the appropriate TRWG Pathway to Clinical Goals in a coordinated and highly-facilitated fashion.

The TRWG Pathways to Clinical Goals are process diagrams that outline the steps required to advance a basic science discovery through early phase clinical trials (Clinical Cancer Research 14: 5663-5699, 2008). The Pathways are expected to serve as useful tools for the research community, allowing individual investigators/programs focused on one aspect of a translational research question to consider their work within a broader developmental context and prompting them to develop the collaborations necessary to move their research forward. Two of the TRWG Pathways focus on the development of assessment tools and four focus on the development of interventions for cancer treatment or prevention, including the Immune Response Modifier Pathway (Clinical Cancer Research 14: 5664-5671,2008).The IRM Pathway was conceived as a tool to track the movement of candidate immune response modulators through the translational process to the point where they can be handed off for definitive clinical testing, and is anticipated to facilitate and accelerate that process.

B. The Immune Response Modifier Pathway Pilot Prioritization Project

Immune T cells can kill cancer cells. Cancer vaccines, T cell therapy and many combinations of immune modifying agents (IMAs) function by increasing the number of immune T cells capable of killing cancer cells. There are exceedingly strict biologic limits imposed on the immune system to prevent excessive T-cell activation and expansion during the normal immune responses to invading pathogens. The same biological restrictions limit the therapeutic expansion of T cells in response to cancer vaccines, T cell therapy regimens and combinations of IMAs. Immunotherapeutic agents that circumvent the biological restrictions have been invented and formulated, including (i) dendritic cell activators and growth factors, (ii) vaccine adjuvants, (iii) T-cell stimulators and growth factors, (iv) immune checkpoint inhibitors, and (v) agents to neutralize or inhibit suppressive cells, cytokines, and enzymes.

The TRWG conceptualized the Immune Response Modifier Developmental Pathway to assist the translational development of immune response modifiers for the treatment and prevention of cancer. The agents are unique because their primary mode of action is to modulate host responses which in turn mediate cancer therapy. In many instances, the agents do not directly contact or directly affect the tumor. The agents can be exquisitely targeted to particular components of the immune system and the subsequent immune response can mediate specifically targeted killing of cancer cells. A major confounding issue for the translational development of immune response modifier agents is the biological requirement for regimens containing multiple agents. It is extraordinarily difficult to develop multiple,

novel agents in parallel. It is expected that the development of multiple novel agents in parallel will require multiple reiterative steps with different regimens at the phase I/II clinical trial level to optimize the effect on modulating host responses.

There are hundreds of proposed cancer target antigens and immune modifying agents. A widely held view is that much suffering and death from cancer could be avoided if the cancer therapy establishment had the reagents, funding, and organization to learn how to use the agents already invented. Limited resources mandate transparent methods to prioritize translational research involving combinations of cancer targets and IMAs with the least possible bias. The development of an inclusive and transparent process for prioritizing combinations of cancer targets and IMAs, and the generation of specific recommendations for the first Special Translational Research Project in the IRM Pathway, is the goal of the IRM Pathway Pilot Prioritization Project.

The Translational Research Acceleration Initiative was piloted by focusing on a single TRWG Pathway, and the Immune Response Modifier (IRM) Pathway was selected for this purpose (**Figure 1**). The IRM pathway is the most complicated of the six TRWG pathways, suggesting that if a process for information collection, prioritization, and funding was established for Translational Research Opportunities (TRO) within this pathway, it could be applied to the remaining five pathways. In addition, the cancer immunotherapy community had previously initiated the prioritization of immune modifying agents (IMAs) with the support of the NCI Division of Cancer Biology, and a group of committed immunologists/immunotherapists could be identified.

In order to identify and rank a small number of projects in the IRM Pathway, the IRMP Working Group utilized the results of the NCI Immunotherapy Agent Workshop, the NCI Cancer Antigen Pilot Prioritization Workshop, as well as the criteria developed in the IRM Pathway Criteria Development Subgroup. The results of each of these workshops are detailed below.

C. The NCI Translational Science Meetings

The NCI Translational Science meetings were integral to the IRM Pathway Pilot Prioritization Project and Translational Research Acceleration Initiative. The first NCI Translational Science Meeting, held November 7-9, 2008 (http://ncitranslates.nci.nih.gov/Past_Meetings.htm), introduced the translational cancer research community to the TRWG Pathways to Clinical Goals. Meeting attendees are selected by NCI Program staff based on NCI-funded translational research grants with the purpose of accelerating early translational research by enhancing scientific collaborations and interactions among all the investigators NCI supports through its translational research funding. Submitted abstracts are identified by the TRWG pathway they represent, and organized into poster discussion sessions to enhance pathway-specific interactions and exchange of information and capabilities. Poster discussion co-chairs were encouraged to identify posters within their session that could be used to generate Translational Research Opportunities that completed a TRWG Pathway to Clinical Goal. Abstracts submitted to the second NCI Translational Science Meeting, scheduled for November 5-7, 2009 (http://ncitranslates.nci.nih.gov), were available for the IRM Pathway Pilot Prioritization Project. Abstracts submitted to both NCI translational science meetings provided a representative sampling of NCI-funded translational research that was used to help identify components of IRM Pathway Translational Research Opportunities.

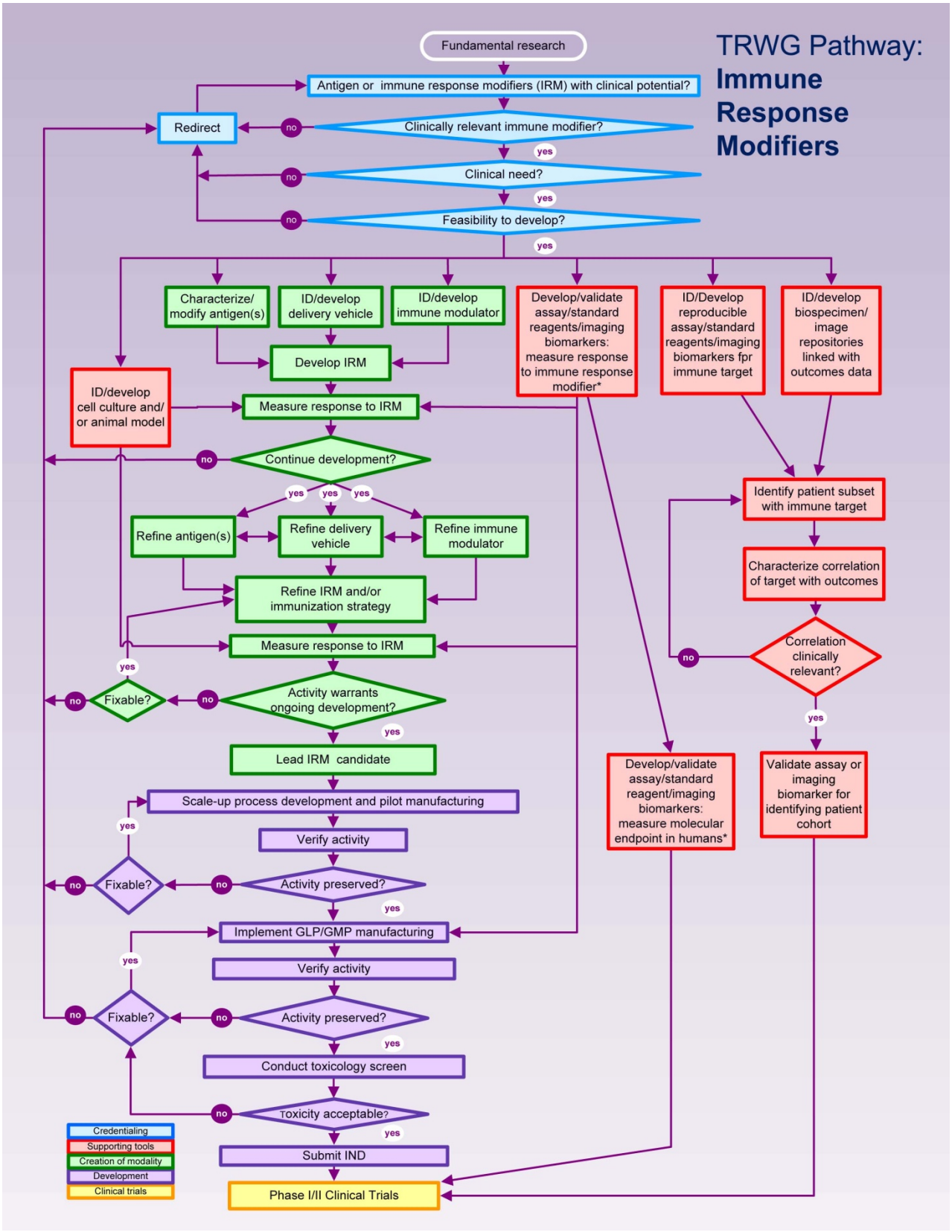

Figure 1: The Immune Response Modifier Developmental Pathway to a Clinical Goal

III. SUPPORTING WORKSHOPS and PROJECTS

A. NCI Immunotherapy Agent Workshop

The NCI Immunotherapy Agent Workshop, sponsored by the Division of Cancer Biology, was held on July 12, 2007. This group was charged with prioritizing immune modulating agents with "High Potential for Cancer Therapy". A full report of the results of this workshop is found at http://dcb.nci.nih.gov/ImmunAgentWork. A list of the participants is found in **Appendix A**.

The Immunotherapy Agent Workshop identified 20 high priority Immune Modifier Agents (IMAs) from a list of 124 agents suggested to an NCI Web site asking for suggestions and advice 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 publicized widely by the NCI with requests for advice sent to grantees with immunology or immunotherapy grants and to prior recipients of RAID awards, as well as to intramural scientists involved in immunology or immunotherapy. The Web site was further publicized to the membership of the major scientific societies involved in immunology, immunotherapy and cancer research, namely the American Association for Cancer Research (AACR), American Association of Immunologists (AAI), American Society of Oncology (ASCO), American Society of Hematology (ASH), the Cancer Vaccine Consortium (CVC), and the International Society of Biological Therapy of Cancer (iSBTc).

Criteria for inclusion on the ranked list included:

- 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

The categories and highest ranked agents are shown in **Figure 2.**

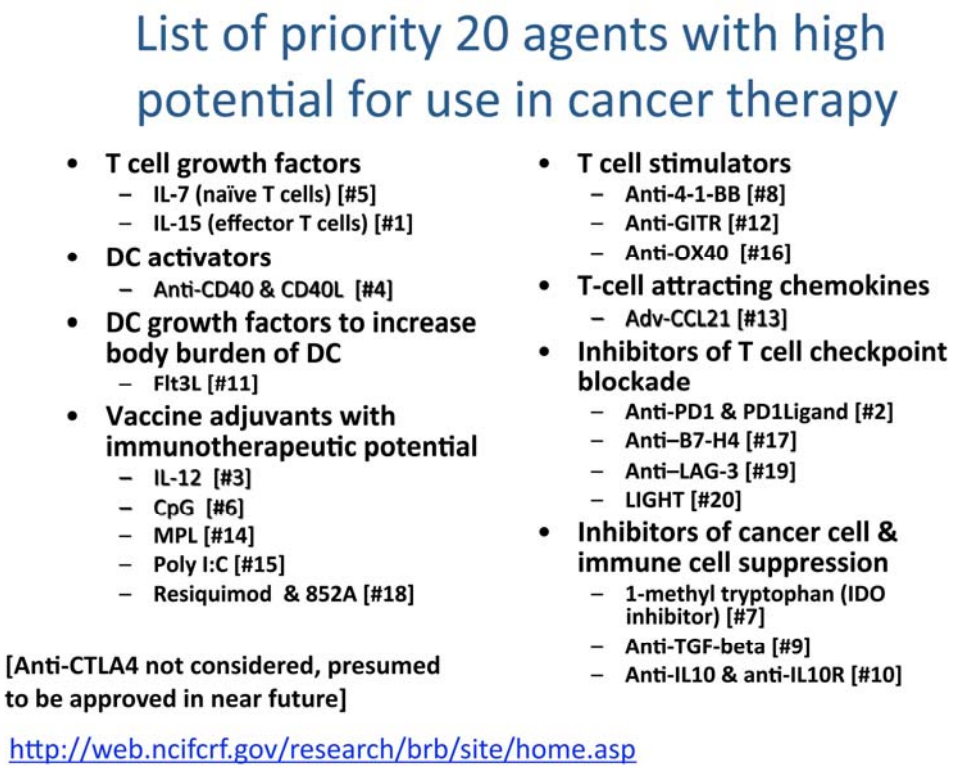

Figure 2. Priority ranking of Immune Modifying Agents (IMAs) as determined by the Immunotherapy Agents Workshop, 2007 [Numbers represent ranking].

CONCLUSIONS: The workshop developed a ranked list of agents with high potential for use in treating cancer. The ranking by workshop participants was based on the likelihood for efficacy in cancer therapy and was exceedingly well-vetted, with broad and substantial input. Despite substantial demonstrated immunological efficacy, these agents are not broadly available for testing in patients with cancer. Many had been tested in clinical trials in patients with cancer. They have proven substantial effects in activating, augmenting or sustaining human immune responses, but cancer was not eliminated when tested as monotherapy. Several additional IMAs, such as GM-CSF, IL2 and anti-CTLA4, have similar profound effects on the immune system, but were more broadly available and thus not included in the priority list. All have been manufactured or could readily be manufactured. All have great potential for benefiting cancer patients **if** they were available for testing and **if** funding were available for clinical trials to learn how to use them.

RELEVANCE TO IRMP WG PROCESS: The categories of ranked agents assisted in the development of components for the stratification of IMA translational research opportunity candidates. The top 20 prioritized IMAs were included as IMA Components in the 2009 IRMP WG prioritization process (designated M001 to M020). The IMAs were re-assessed by the IRMP WG Process using the criteria established by the IRM Pathway Criteria Development project. Of note, the top Agents from the July 2007 Workshop remained at the top of the prioritized list of IMA component candidates.

B. NCI Cancer Antigen Pilot Prioritization Project

The purpose of the NCI Cancer Antigen pilot project was to prioritize cancer antigens utilizing a well-vetted list of cancer vaccine target antigens based on well defined and weighted objective criteria. Antigen prioritization involved developing a list of "ideal" cancer antigen criteria/ characteristics and rating scales for each criterion, assigning relative weights to the criteria and the rating scales, selecting 75 representative antigens for comparison and ranking, and ranking the antigens based on the predefined, preweighted criteria. The Analytical Hierarchy Process (AHP) was used for the prioritization project. The AHP process is a structured technique for complex decision making based on mathematics and human psychology, and provides a comprehensive framework to structure the problem, to represent and quantify key elements, to relate those elements to overall goals, and to evaluate alternative solutions. A report of the process and results of the Antigen Prioritization Pilot Project is found in the publication entitled "The Prioritization of Cancer Antigens: A National Cancer Institute Pilot Project for the Acceleration of Translational Research", Cheever et al, *Clinical Cancer Research, 15: 5323, 2009*. Lists of approximately 100 expert scientists involved in the Cancer Antigen Prioritization Pilot Project are included in **Appendix A**.

CONCLUSIONS: The result of criteria weighting, in descending order, was as follows:

- Therapeutic function
- Immunogenicity
- Oncogenicity
- Specificity
- Expression level and % positive cells
- Stem cell expression
- Number of patients with antigen-positive cancers
- Number of epitopes
- Cellular location of expression

None of the 75 antigens had all of the characteristics of the "ideal" cancer antigen. However, 46 demonstrated immunogenicity 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.

RELEVANCE TO IRMP WG PROCESS: Final scores and ranking from the Cancer Antigen Pilot Prioritization Project were not used directly by the IRMP WG. Rather, the rating scale scores for the criteria of "Immunogenicity" and "Therapeutic function" scores, which carried the most weight in the Cancer Antigen prioritization process, were used for the assessment of cancer targets in the IRMP WG prioritization process. Cancer antigens with Therapeutic function scores $\geq$ .75 and Immunogenicity scores of 1.0 were added to the candidate Translational Research Opportunities (designated A001 – A015). As a result of experience gained with the Cancer Antigen Prioritization Process, the AHP was deemed a suitable approach for identifying and weighing criteria, and for prioritizing candidates within individual components of a TRWG Pathway.

C. Immune Response Modifier Pathway Criteria Development Project

The goal of the Immune Response Modifier Pathway Criteria Development project was to determine and weigh the criteria and rating scales to be used to prioritize Translational Research Opportunities encompassing the entire IRM Pathway. The IRM Subgroup of the Process to Accelerate Translational Science (PATS) Working Group, a working group of CTAC, was charged with this responsibility (members listed in **Appendix A**). A face-to-face meeting was held in Denver on April 19, 2009 using the AHP method of weighing criteria. Several facilitated and asynchronous web-based sessions completed the process. The Criteria for evaluation of IRM translational research opportunities developed by the IRM Subgroup was approved by the PATS WG and presented and approved by CTAC in July, 2009. These criteria, presented in the format used in the subsequent Immune Response Modifier Pilot Prioritization Project, are found in **Appendix B**.

RESULTS: The IRM Pathway was identified as having seven components for which an assessment of scientific validity and feasibility would be useful in identifying translational research opportunities that are "ripe" for acceleration. The components of the Immune Response Modifier Pathway regimens are:

COMPONENT	Pathway Nomenclature
• Target (antigen/antibody/T-cell)	(creation of modality domain)
• Formulation (cell preparation, delivery vehicle, adjuvant, etc)	(creation of modality domain)
• Immune Modifier Agent (cytokines, etc)	(creation of modality domain)
• Combination regimen	(creation of modality domain)
• Assay for immune response	(supporting tools domain)
• Assay to select patient population	(supporting tools domain)
• Availability of patients for trials	(clinical trials domain)

These components constitute criterion for assessment of an IRM translational research opportunity. Each component has a series of Subcriteria and Rating Scales, which stratify the level of evidence provided for each subcriterion. The Subcriteria for "Target" were "Immunogenicity and "Therapeutic Function", as identified previously by the Cancer Antigen Pilot Prioritization Project. The Subcriteria for the remainder of the Components, in general, were "Scientific Validity" and "Feasibility". The Rating Scales provide the level of evidence for Scientific Validity (e.g. experimental evidence obtained in humans, animals, or in vitro, in descending order) or Feasibility (e.g. commercially available vs piloted vs laboratory-grade reagent, in descending order). The Criteria, Subcriteria, and Rating Scales for IRM Pathway translational research opportunities are presented in **Appendix B**.

CONCLUSION: The most important (highest weight) components of the IRM Pathway in descending order are:

- Combination regimen
- Immune Modifying Agent
- Target
- Formulation
- Assay to select patient population

- Assay for immune response
- Availability of patients for trials

RELEVANCE TO IRMP WG PROCESS: The criteria, subcriteria, rating scales, and weights developed by the IRM Pathway Criteria Development project were used as the starting point to prioritize IRM translational research opportunities.

IV. THE IMMUNE RESPONSE MODIFIER PATHWAY PILOT PRIORITIZATION PROJECT

The Immune Response Modifier Prioritization Working Group (IRMP WG), a working group of the NCI's Clinical Trials and Translational Research Advisory Committee (CTAC), was charged with prioritizing translational research opportunities within the IRM Pathway as the IRM Pathway Pilot Prioritization Project. Committee members are listed in **Appendix A**. The IRM Pathway Pilot Prioritization Project involves 1) gathering comprehensive information on the breadth of IRM Pathway translational research opportunities within the scientific community, 2) prioritizing those opportunities to identify those most "ripe" for acceleration, and 3) providing the NCI with recommendations on specific projects to be considered for the Special Translational Research Acceleration Project (STRAP) Program. Each of these steps is presented below.

A. Collection of Immune Response Modifier Translational Research Opportunities

A Request for Information RFI NOT-CA-09-031 for Translational Research Opportunities in the IRM Pathway was open between July 20th – August 24th 2009 (http://grants.nih.gov/grants/guide/notice-files/NOT-CA-09-031.html). A specific format for submissions was requested to facilitate the evaluation of translational research opportunities by the pre-determined criteria and rating scales (http://patsinitiative.nci.nih.gov.**)**.The RFI resulted in 40 submissions, identified as R001 to R040 in the spreadsheet included in **Appendix C**. Of the 40 submissions, 32 contained information that could be evaluated using the IRM pathway criteria and rating scales, although few of them contained all of the components.

Many of the antigens that were identified as being of high priority in the Cancer Antigens pilot prioritization project and many of the IMAs identified in the Immunotherapy Agents Workshop were not included in the responses to the RFI. Thus, it was felt that the RFI produced only a subset of all potential IRM translational research opportunities that should be considered, and additional approaches were taken to develop as complete a collection of suitable IRM translational research opportunities as possible. The abstracts submitted to the NCI Translational Science Meetings (TSM) were identified as another source of information that described translational research opportunities within the IRM Pathway. These abstracts represent translational research supported by the NCI by virtue of the "by invitation only" protocol used to invite meeting attendees. Twenty-three (23) abstracts submitted to the 2008 TSM (T1-###) and 20 abstracts submitted to the 2009 TSM (T2-###) were coded to the IRM Pathway and contained information suitable for consideration as translational research as defined by the IRM Pathway. Although again there were few cases where all of the IRM pathway components were represented in a single abstract/translational research opportunity, the information within these abstracts could be deconstructed into the various essential components of the IRM Pathway,

Antigens and IMAs were identified by the previous workshop and were thus included in the IRMP WG assessment. The top 20 IMAs from the Immunotherapy Agents workshop were considered as candidates in the IMA component (M001-M020). Cancer antigens with Therapeutic function scores $\geq$ 0.75 and Immunogenicity scores of 1.0 were added as translational research opportunity candidates to be considered in the Target component (A001-A015).

RESULTS: A total of 110 translational research opportunities were collected and were parsed into different components of the IRM Pathway. It was rare to identify a translational research opportunity that contained all the components identified as being important for completing the IRM Pathway to the clinical goal of a cancer immunotherapy/immunoprevention regimen that could be advanced to late stage clinical trials.

CONCLUSION: The observation that few of the translational research opportunities contained all the components of the IRM Pathway support the view that the structure of research support in the United States accentuates the focused study of individual components of the IRM Pathway, but rarely supports the breadth of research required to complete the TRWG Pathway to early stage clinical trials. Facilitation

of activities that promote the linking of individual research groups with complementary expertise could assist in overcoming this barrier to translational research.

B. Prioritization of Immune Response Modifier Pathway Translational Research Opportunities

The collected IRM Pathway translational research opportunities were deconstructed into IRM pathway components by the IRMP WG Chair and CCCT staff. The Level of Evidence/Rating scale for the Subcriteria within each component/criteria was initially assessed by the Committee Chair and CCCT staff based on the submitted information and general knowledge of the field. The consensus evaluation was indicated on a customized Assessment Form for that translational research opportunity. In cases where more than one agent within a component was pertinent to a translational research opportunity, the one with the highest score was entered as part of the primary opportunity and the secondary component was entered as a separate opportunity.

IRMP WG members were assigned to evaluate the level of evidence/rating scale designation of specific translational research opportunities based on their area of expertise. The translational research opportunity, in the form of a response to the RFI or a NCI Translational Science meeting abstract, and the corresponding Assessment Form were made available to the IRM Pathway Prioritization Working Group members by emailing password-protected documents and/or through a password-protected website. The translational research opportunity assessments were evaluated by an IRM Prioritization WG member, who provided comments if they disagreed with the initial assessment. These differences in assessments were discussed at a face-to-face meeting of the IRMP WG in Bethesda on October 2, 2009, and resolved by consensus.

The Target component required a modification of the approach as the wording of the level of evidence/rating scales appeared to specifically refer to antigens for vaccine therapy and not necessarily T-cell targets or antibody targets. Three different Target component assessment forms were generated, retaining the original weights for the criteria, subcriteria, and rating scales, but altering the wording so it was pertinent to the target being assessed (i.e., T cell target and Antibody target) yet represented the same level of evidence.

The three Target categories are:

- Antigens (vaccine targets)
- T-cell therapy targets
- Antibody and T body targets

The IRM translational research opportunity assessment forms for each of the IRM Pathway components is found in **Appendix B**.

The agreed-upon rating for each translational research opportunity component was entered into a database designed to facilitate the AHP in 4 separate modules:

- Vaccine therapies (103 opportunities)
- Adoptive therapies (11 opportunities)
- Antibody therapies (16 opportunities)
- IMAs from the Immunotherapy Agent Workshop (20 opportunities)

Using the AHP approach, a cumulative score was generated for each translational research opportunity based on the information entered for each component in the IRM Pathway. An ordered list of the translational research opportunities in the Vaccine therapies module was viewed from the highest to the lowest ranking at the Oct 2ndface-to-face meeting.

The “Combination regimen” component of the IRM Pathway, composed of combinations of Targets and IMAs, received the highest weighting in the Immune Response Modifier Pathway Criteria Development Project. Presumably, the best IRM Pathway translational research opportunities would contain

combinations of the top Targets and the top IMAs. However, few of the responses to the RFI or the Translational Science meeting abstracts suggested combinations of the top Targets as determined by the Cancer Antigen Prioritization Project combined with Top IMAs, as identified by the Immunotherapy Agents Workshop. There are several presumed reasons for this. It was noted that many of the top IMAs identified by the Immunotherapy Agents workshop are not generally available. In addition, individual research groups tended to utilize and/or suggest the targets and agents with which they have the most experience. The IRMP WG felt is was mandatory to consider combinations of the top Targets and top IMAs. Accordingly, the IRMP WG favored considering individual components from the collection of IRM translational research opportunities exercise independently from the entire translational research opportunity as it was submitted in response to the RFI or as a NCI Translational Science meeting abstract. It was recognized that high priority IRM Pathway translational research opportunities that combine, test, and develop the most appropriate and appealing combinations of the top prioritized agents with the top prioritized antigens could best be assembled from individual prioritized components. Accordingly, the IRMP WG favored considering individual components from the collection of IRM translational research opportunities exercise independently from the entire translational research opportunity as it was submitted in response to the RFI or as a NCI Translational Science meeting abstract. It was recognized that high priority IRM Pathway translational research opportunities that combine, test, and develop the most appropriate and appealing combinations of the top prioritized agents with the top prioritized antigens could best be assembled from individual prioritized components.

As a result of the discussion at the Oct 2nd meeting that the best combinations might be derived by combining separate components from different proposed regimens, the components of the translational research opportunities were deconstructed and considered separately. The AHP software facilitated deconstruction and viewing of individual components in isolation or in small clusters. Each component was grouped with like components to generate lists for 3 types of targets and 5 types of IMAs. The following groups were identified:

TARGETS

- Targets A: Vaccine antigens
- Targets B: T-cell therapy antigens
- Targets C: Antibody and T-body antigens

IMAs

- IMA D: Adjuvants (vaccine adjuvants, dendritic cell activators or growth factors, T cell attracting chemokines)
- IMA E: T-cell factors (T cell stimulators or T cell growth factors)
- IMA F: Checkpoint inhibitors (Inhibitors of T cell checkpoint blockade)
- IMA G: Suppressive agents (agents to inhibit suppressive cells, cytokines, and enzymes)
- IMA H: ADCC agents (agents to increase antibody dependent cellular cytotoxicity)

The groups of Targets and IMAs could be assembled according to the four different regimens for cancer immunotherapy or immunoprevention in the following combinations.

REGIMEN	**TARGET**	**IMA** *(one or more of the following)*
Cancer Vaccines	A: Vaccine antigens	D: Adjuvants (required) E: T-cell factors, and/or F: Checkpoint inhibitors, and/or G: suppressive agents
Adoptive Therapy	B: T-cell therapy antigens	E: T-cell factors and/or F: Checkpoint inhibitors
Antibody Therapy	C: Antibody & T-body antigens	H: ADCC agents
IMA Combinations		Combinations of the above

The 4 types of immunotherapy/immunoprevention regimens considered in the IRM Pathway were conceptually viewed as “scaffolds” containing the indicated combinations of “buckets” of like targets or agents. Scaffolds also contain the additional components of the IRM Pathway, e.g. the target Formulation component, the Assay for Immune Response, the Assay to Select Patients, and the Patients for clinical trials component. The arrangement of buckets on the scaffolds is depicted in **Figure 3**.

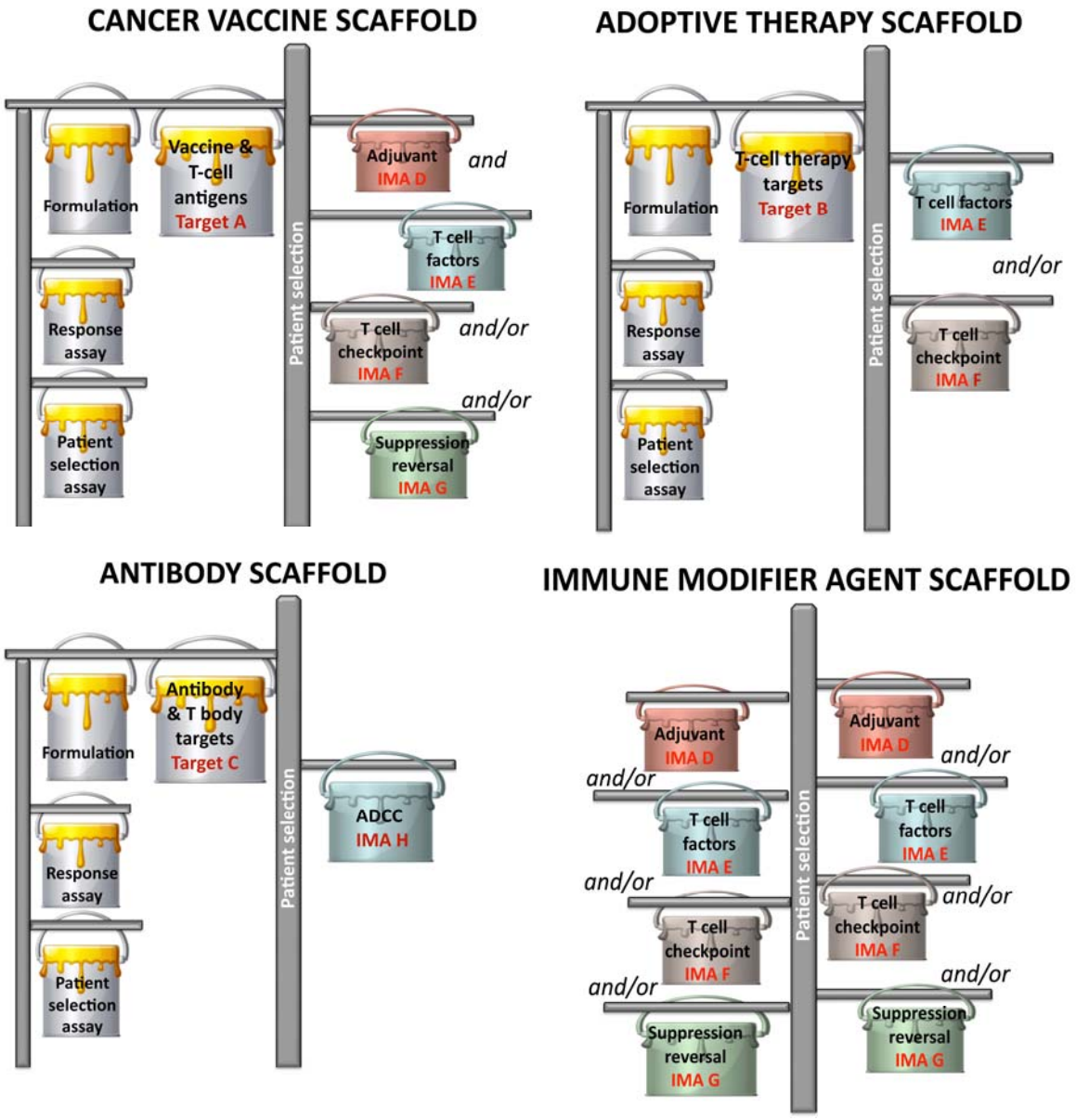

Figure 3. Assembly of IRM Pathway Buckets on Scaffold Regimens

The scores given candidate Targets and IMAs were examined by IRMP WG Members according to their assigned "bucket", facilitating the prioritization of candidates with similar activity or function. The candidates in buckets B, D, E, F, and G were examined by IRMP WG members during the webinar of October 7th, and those in buckets C and H and those remaining in bucket A were examined on October 9th. IRMP WG members unable to attend the Oct 2th meeting were expected to attend a webinar session, others were invited to participate.

The individual candidates within each bucket were listed in descending order from highest to lowest priority using the weighted Criteria, Subcriteria, and Rating Scales determined by the IRM Pathway Criteria Development Project (**Appendix B**) and the Level of Evidence for each Criterion as judged by the IRMP WG. Candidates receiving the top scores for Scientific Validity and Feasibility received an overall rating of 1.00 (100%) for that criterion.

The IRMP WG developed a set of exclusion criteria to address IRMs that would be unsuitable for STRAP consideration at this time. Note that these principles are intended to be flexible and are assumed to require modification with time.

- The target must be defined.
    - Autologous tumor will not be included. Autologous tumor can be highly immunogenic. However, given that the most highly immunogenic antigens are unique to each individual, it is difficult to compare level and character of immune responses from patient to patient. Evaluating the effect of IRM combinations on level and character of immune responses should be an essential aspect of the initial STRAP-funded translational research opportunities.
    - Allogeneic tumor will not be included. Allogeneic tumor can contain multiple important target antigens. Allogeneic tumors contain hundreds of irrelevant molecules that can act as decoys for the desired antigens. The important antigens are unlikely to be present in optimal concentrations. Immune responses to individual antigens are often difficult to measure. Multiplicities of different types of immune responses are elicited in response to a multiplicity of different antigens and types of antigens. Thus, it is difficult to know why therapy is effective when it's effective and why it fails when it fails.

- A vaccine construct must be appropriate for injecting multiple times.
    - Multiple vaccinations are necessary for eliciting immunity to many foreign antigens. Multiple vaccinations with cancer vaccines will be necessary to achieve maximal immune responses. Constructs, such as adenovirus, that induce neutralizing antibodies are not appropriate for multiple vaccinations. However, they might be used for prime-boost regimens as long as one component can be administered multiple times.

- The approach must be transportable and able to be performed in multiple laboratories.
    - Dendritic cell vaccines will not be used. Dendritic cell-based vaccines have proven to induce immune responses. The initial STRAP-funded translational research opportunity will focus on testing regimens that can be applied to many vaccines. DC regimens vary from laboratory to laboratory and might be difficult to precisely reproduce with essential quality control. There is scant evidence that DC vaccines are more effective than non-DC formulations using optimal IMAs as adjuvants. A more ideal focus of a STRAP-funded translational research opportunity would be on developing regimens that target and activate in situ DC, rather than in vitro processed DC.
    - Procedures that require bone marrow transplantation will not be used. It would be difficult to reproduce data from institution to institution.

- The agent should not be "over ripe". Agents that are readily available and can be tested through a variety of other funding mechanisms or commercial interests are less well suited for the inaugural STRAP than agents that have extraordinary promise but require effort to obtain and use in biologically driven rational combinations.

- A target should be expressed in a reasonable number of patients to allow iterative testing in a short period of time.

To achieve a short list of candidates in each bucket, the top ranking candidates were discussed to determine if they should be included or excluded using the principles above, continuing until approximately 3-5 promising candidates were identified. Lower priority candidates were examined to determine if any of them should remain in the bucket. Reasons for retaining a lower-scoring candidate include:

- A unique niche filled by that candidate
- Priority in the IMA Workshop or Antigen Prioritization Workshop

It was recognized that several desirable candidates were missing from the translational research opportunity database, and the IRMP WG recommended they be added (W-001 to W-003). With this addition, the total number of translational research opportunities considered was 113.

RESULTS: The candidates derived from the translational research opportunities are listed in the spreadsheet in **Appendix C**. The candidates that are recommended for consideration are highlighted. The spreadsheet columns include:

1. The source of the translational research opportunity (e.g. an RFI response, etc. See Collection of IRM Translational Research Opportunities section)
2. The Candidate Target or IMA considered in that bucket
3. The bucket designation
4. The priority ranking as recommended by the IRMP WG using predetermined, preweighted criteria (**Appendix B**)
5. Comments. The line in the Comments section denotes the separation between “high priority” and “lower priority” candidates. Reasons for excluding high priority candidates, or including lower priority candidates, in the final recommendations are indicated.

CONCLUSIONS: A subset analysis of translational research opportunity components and candidates allows comparison of Targets or IMAs with similar functions and purposes. A “scaffold and bucket” approach was suggested by IRMP WG members to assist in the construction of high-priority IRM Pathway translational research opportunities. Exclusion criteria were developed to address considerations that would make a component inappropriate for inclusion in a STRAP at this time. It should be noted that Targets, IMAs and Formulations excluded at this point, such as use of autologous tumor, will none-the-less benefit from knowledge gained and extrapolated by the focused recommendations of the IRMP WG.

V. RECOMMENDATIONS FOR THE INAUGURAL IRM PATHWAY SPECIAL TRANSLATIONAL RESEARCH ACCELERATION PROJECT (STRAP).

The first IRM STRAP(s) should be designed as IRM regimens with top Targets and top IMAs. The regimens (i.e., scaffolds) of choice are (1) Cancer vaccines, (2) Adoptive Therapy, (3) Antibody Therapy, and (4) IMA Combinations. Regimen scaffolds are composed of components from the appropriate target, formulation and IMA "buckets". The regimens should use components deemed to be of the highest priority by the IRMP WG to develop Translational Research Opportunity(s) that focuses on high priority areas of investigation and have the potential to significantly impact cancer treatment or prevention in the foreseeable future.

The following represent the recommended high-priority candidates within each bucket (See **Appendix C**):

WORKING GROUP PRIORITZED TARGETS AND ANTIGENS

- Target A: Vaccine Targets
  - HPV E6/7, HER2, MAGE A3, MUC1, WT1, NY-ESO-1, PSA
- Target B: T-Cell Therapy Targets:
  - HPV E6/7, HER2, MAGE A3, MUC1, WT1, NY-ESO-1, PSA
- Target C: Antibody & T Body Targets
  - HER2, EGFR, CD20, CD19
- IMA D: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or dendritic cell growth factors.
  - CpG, FLT3L, Anti-CD40, IL12, CCL21
- IMA E: T cell stimulators or T cell growth factors
  - IL7, IL21, IL15, Anti-4-1BB
- IMA F: Inhibitors of T cell checkpoint blockade
  - Anti-CTLA-4, Anti-PD1
- IMA G: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
  - Anti-TGF beta, IDO inhibitors, Anti-IL10
- IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)
  - IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)

The IRMP WG recommends that the Vaccine and Adoptive Therapy scaffolds be given highest priority for the inaugural STRAP. Thus, the T-cell factors and the T cell checkpoint agents buckets should be considered first as they are pertinent to both Scaffolds.

Based on the assessment that the addition of IMAs to established vaccine or adoptive therapy protocols is likely to result in additional clinical benefit, and that the availability of IMAs for clinical testing is a major barrier to further progress, it is recommended that the IMAs in the T-cell factor and T cell checkpoint buckets serve to "anchor" the inaugural STRAP and reduce the number of possibilities. Designated IMA(s) should be combined with high priority Targets for effective Cancer Vaccines or Adoptive Therapy approaches as depicted in **Figure 4**.

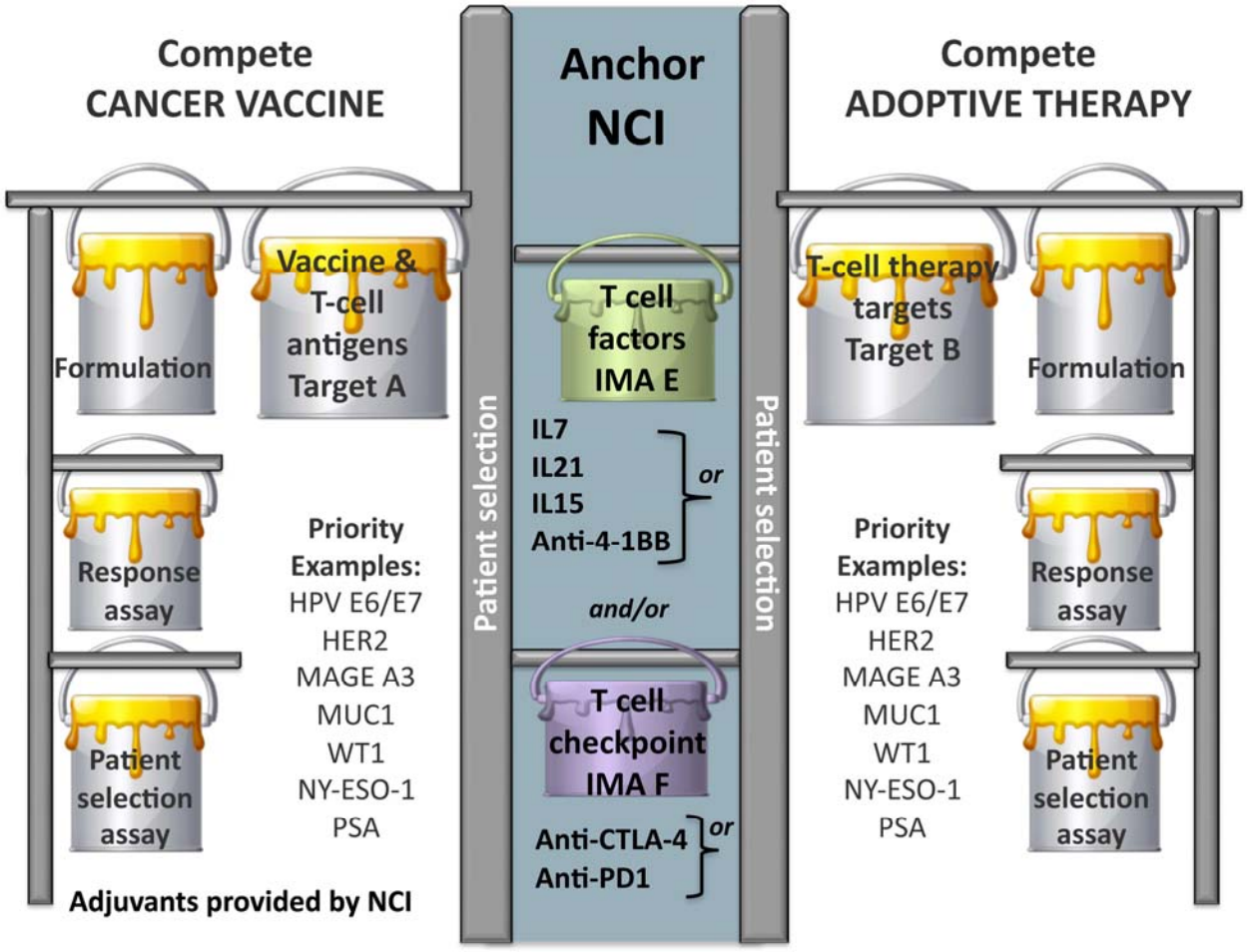

Figure 4. Illustration of the IRMP WG recommendations

The NCI should continue developing effective vaccine adjuvants as recommended by the Immunotherapy Agents Working Group, e.g., Anti-CD40, Flt3L, IL-12, CpG, MPL, Poly I:C, and resiquimod. These agents should be made available for use in vaccine formulations for STRAP-funded research.

The NCI should evaluate the high priority candidates within the T-cell factor and T cell checkpoint buckets for logistical feasibility and devise a strategy for providing one agent/bucket. This strategy could include synthesis of the GMP-grade IMA at the NCI, or procuring it through a contract with industry.

It is recommended that there be a call for applications for 4 STRAPs to test, in combination with the designated IMA(s): (1) a vaccine regimen against a viral antigen, (2) a vaccine regimen against a cellular antigen, (3) an adoptive therapy approach against a high-priority target, and (4) an antibody regimen with an agent to increase antibody-dependent cellular cytotoxicity. Response to the request must follow the IRM Pathway and include all pathway components.

The Target bucket priority candidates will be listed as high-priority examples in the STRAP announcement. Applicants are not required to use targets within this bucket, but an equivalent level of evidence for immunogenicity and therapeutic function must be demonstrated. The proposal must contain information on the formulation of the target antigen, the theoretical or experimental evidence for synergy with the designated IMA, details on the assay to be used to measure immune response and to identify patients that are likely to respond to the regimen, and information on the population of individuals to be

tested in early phase clinical trials. The proposal should demonstrate that the results are likely to benefit patients in the foreseeable future.

In addition, it is recognized that several of the high-priority IMAs and Adjuvants recommended to the NCI are also Agents to increase antibody dependent cellular cytotoxicity (ADCC). Of the Targets, antibodies are the only approved approaches that are part of the current Standard of Care, and from a drug development perspective the Antibody scaffold has the lowest feasibility and regulatory hurdles. In the event that an IMA or adjuvant provided by the NCI for the STRAP program also augments ADCC, an additional STRAP encompassing the Antibody Therapy scaffold is highly recommended to maximize the NCI's investment and impact.

IRM STRAP proposals should be evaluated based on the criteria established by the IRM Subgroup for the Target, Formulation, Combination Regimen, Immune response assay, Patient selection assay, and Availability of patients for clinical trials. Clinical need, including rare cancers and immunoprevention, should be taken into consideration, as should appropriateness for NCI investment. Trials should be designed to establish principles that can be extrapolated to other IRM regimens, or if the trials fail they will be "productive" failures that will lead the way to better alternatives.

It is important to note that although antigens, formulations, adjuvants and other IMAs are represented as independent elements, creation of an IRM regimen will requires successful integration of these components, which in turn may require substantial iterative testing in early phase clinical trials. Where an initial approach to integration fails, substitution of alternative components may be required. Coordination of component development to achieve timely and successful integration is a key scientific and management challenge for the STRAPs.

It is recommended that a call for applications for an IRM STRAP is initiated, reviewed, and funded in FY2010.

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APPENDIX A2

NCI Cancer Antigen Pilot Prioritization Project

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APPENDIX A3

NCI Cancer Antigen Pilot Prioritization Project

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NCI Cancer Antigen Pilot Prioritization Project

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as of 042009

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APPENDIX A6

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APPENDIX B1

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

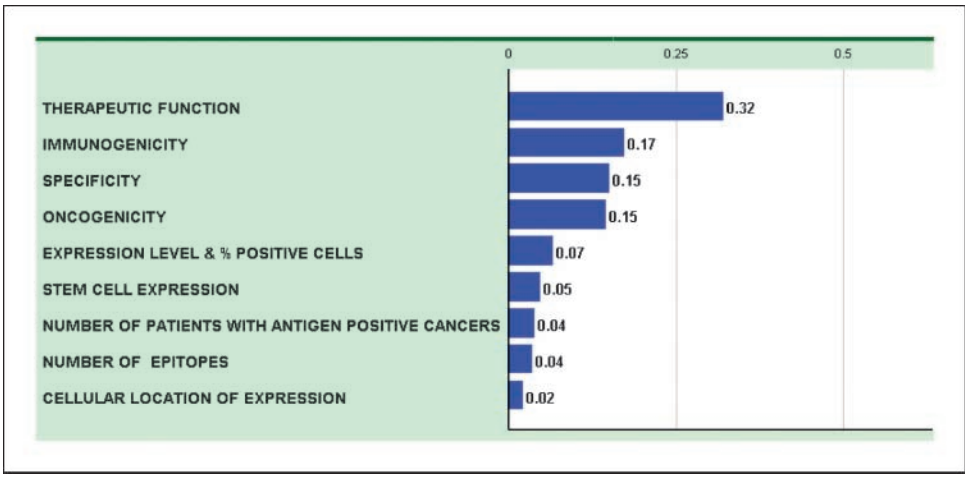

Fig. 1. Criteria for an ideal cancer antigen were weighted by pairwise comparison and the resulting relative weights are indicated. Therapeutic function was considered the most important criteria and was more than twice (0.32/0.15) as important as specificity or oncogenicity.

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

APPENDIX B1

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)

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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				
	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

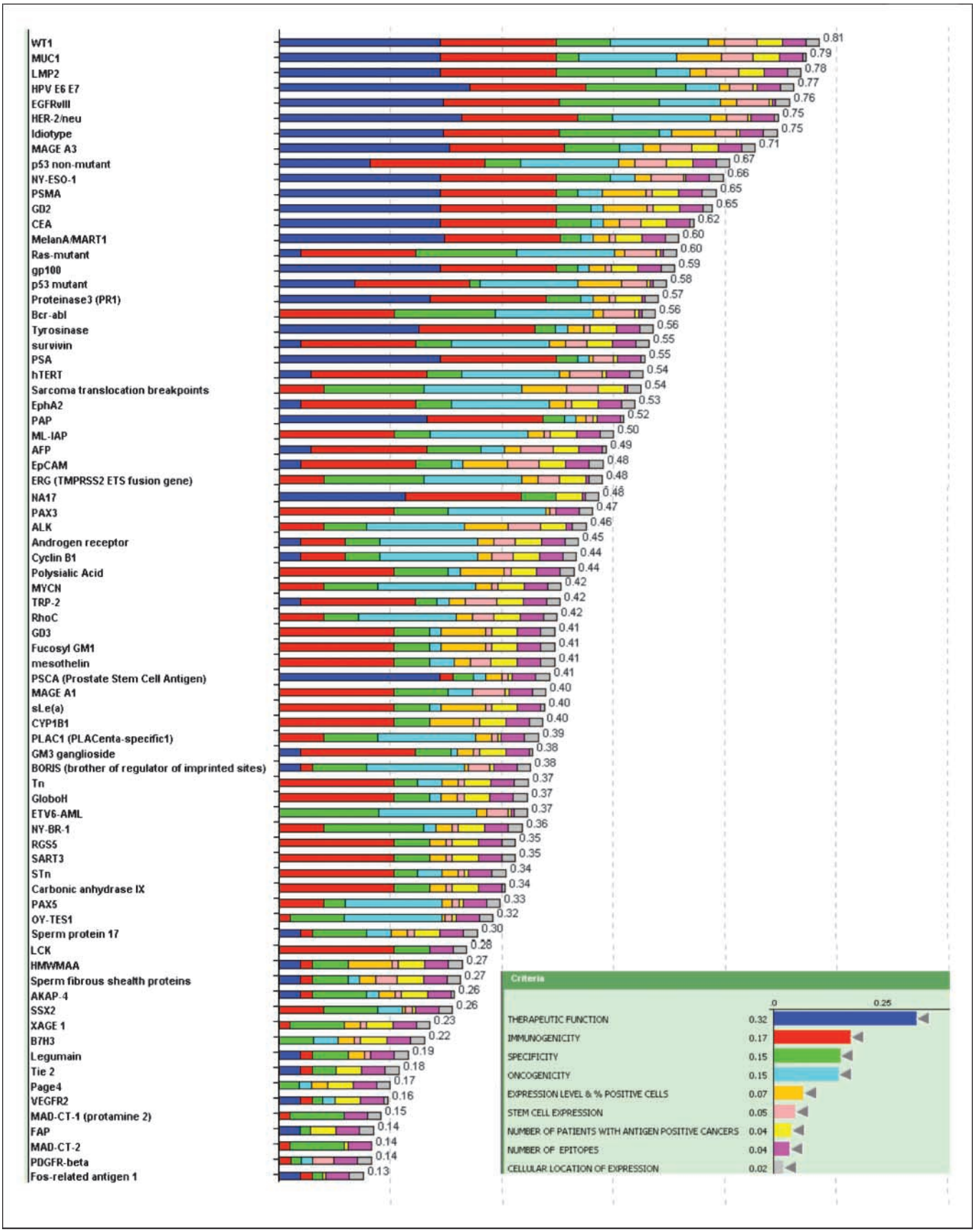

Fig. 2. Cancer antigen pilot prioritization: representation of ranking based on predefined and preweighted criteria and subcriteria. Inset, the color used to designate each criterion and its relative weight. Number at the end of each bar, relative rank of that antigen.

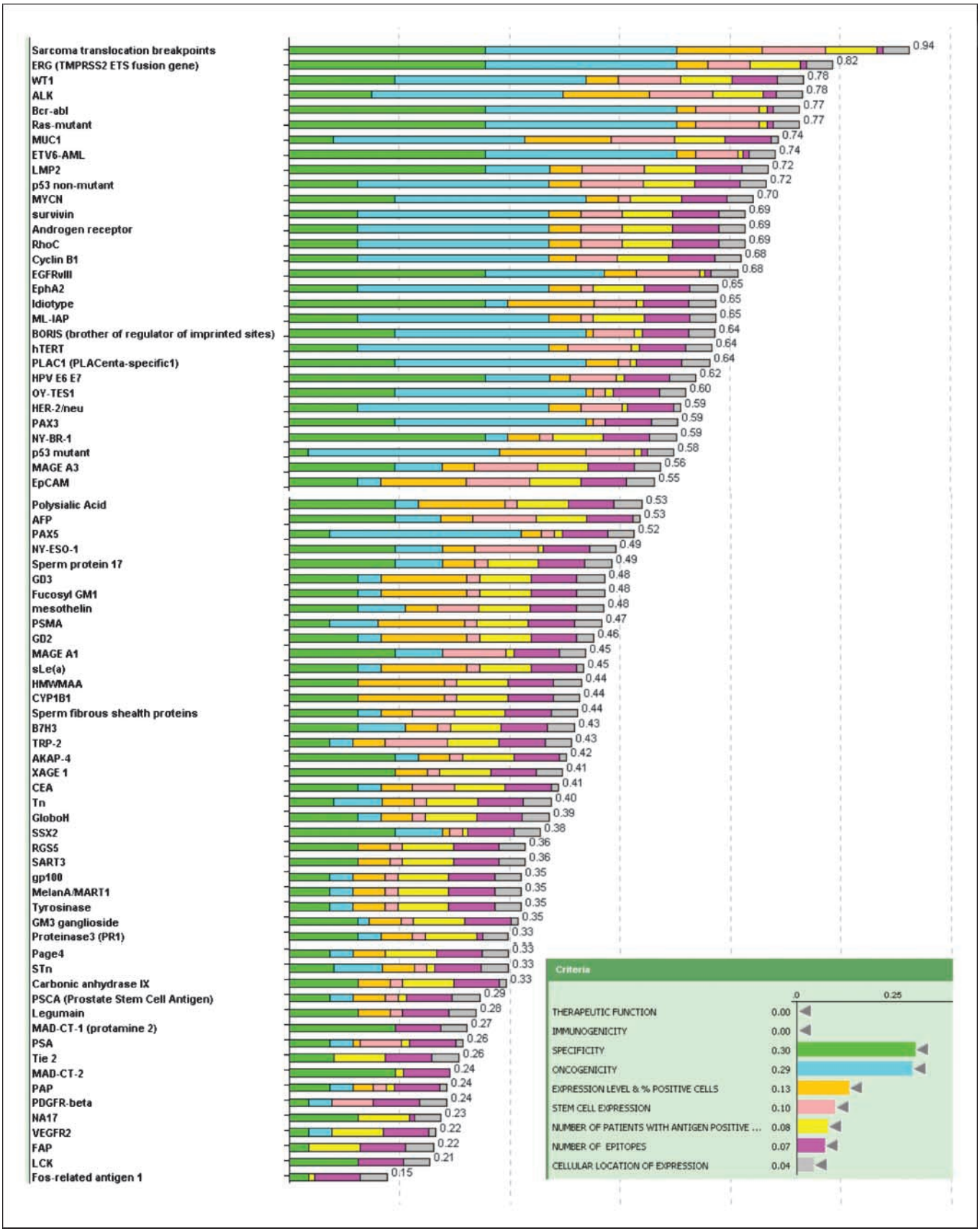

Fig. 3. Representation of ranking following exclusion of therapeutic efficacy and immunogenicity. Inset, the color used to designate each criterion and its relative weight. Number at the end of each bar, relative rank of that antigen.

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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.

Acknowledgments

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References

1. Oka Y, Tsuboi A, Oji Y, Kawase I, Sugiyama H. WT1 peptide vaccine for the treatment of cancer. Curr Opin Immunol 2008;20:211–20.
2. Lepisto AJ, Moser AJ, Zeh H, et al. A phase I/II study of a MUC1 peptide pulsed autologous dendritic cell vaccine as adjuvant therapy in patients with resected pancreatic and biliary tumors. Cancer Ther 2008;6:955–64.
3. Khanna R, Moss D, Gandhi M. Technology insight: Applications of emerging immunotherapeutic strategies for Epstein-Barr virus-associated malignancies. Nat Clin Pract Oncol 2005;2:138–49.
4. Trimble CL, Peng S, Kos F, et al. A phase I trial of a human papillomavirus DNA vaccine for HPV16+ cervical intraepithelial neoplasia 2/3. Clin Cancer Res 2009;15:361–7.
5. Sampson JH, Archer GE, Mitchell DA, Heimberger AB, Bigner DD. Tumor-specific immunotherapy targeting the EGFRvIII mutation in patients with malignant glioma. Semin Immunol 2008;20:267–75.
6. Weng WK, Czerwinski D, Timmerman J, Hsu FJ, Levy R. Clinical outcome of lymphoma patients after idiotype vaccination is correlated with humoral immune response and immunoglobulin G Fc receptor genotype. J Clin Oncol 2004;22:4717–24.
7. Mittendorf EA, Holmes JP, Ponniah S, Peoples GE. The E75 HER2/neu peptide vaccine. Cancer Immunol Immunother 2008;57:1511–21.
8. Brichard VG, Lejeune D. GSK's antigen-specific cancer immunotherapy programme: pilot results leading to phase III clinical development. Vaccine 2007;25 Suppl 2:B61–71.
9. Antonia SJ, Mirza N, Fricke I, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res 2006;12:878–87.
10. Old LJ. Cancer vaccines: an overview. Cancer Immun 2008;8 Suppl 1:1.
11. Olson WC, Heston WD, Rajasekaran AK. Clinical trials of cancer therapies targeting prostate-specific membrane antigen. Rev Recent Clin Trials 2007;2:182–90.
12. Wondimu A, Zhang T, Kieber-Emmons T, et al. Peptides mimicking GD2 ganglioside elicit cellular, humoral and tumor-protective immune responses in mice. Cancer Immunol Immunother 2008;57:1079–89.
13. Gulley JL, Arlen PM, Tsang KY, et al. Pilot study of vaccination with recombinant CEA-MUC-1-TRICOM poxviral-based vaccines in patients with metastatic carcinoma. Clin Cancer Res 2008;14:3060–9.
14. Yee C, Thompson JA, Byrd D, et al. Adoptive T cell therapy using antigen-specific CD8+ T cell clones for the treatment of patients with metastatic melanoma: *in vivo* persistence, migration, and antitumor effect of transferred T cells. Proc Natl Acad Sci U S A 2002;99:16168–73.
15. Toubaji A, Achtar M, Provenzano M, et al. Pilot study of mutant ras peptide-based vaccine as an adjuvant treatment in pancreatic and colorectal

cancers. Cancer Immunol Immunother 2008;57:1413–20.

16. Smith FO, Downey SG, Klapper JA, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res 2008;14:5610–8.

17. Carbone DP, Ciernik IF, Kelley MJ, et al. Immunization with mutant p53- and K-ras-derived peptides in cancer patients: immune response and clinical outcome. J Clin Oncol 2005;23:5099–107.

18. Rezvani K. PR1 vaccination in myeloid malignancies. Expert Rev Vaccines 2008;7:867–75.

19. Bergman PJ, McKnight J, Novosad A, et al. Long-term survival of dogs with advanced malignant melanoma after DNA vaccination with xenogeneic human tyrosinase: a phase I trial. Clin Cancer Res 2003;9:1284–90.

20. Maslak PG, Dao T, Gomez M, et al. A pilot vaccination trial of synthetic analog peptides derived from the BCR-ABL breakpoints in CML patients with minimal disease. Leukemia 2008;22:1613–6.

21. Xiang R, Mizutani N, Luo Y, et al. A DNA vaccine targeting survivin combines apoptosis with suppression of angiogenesis in lung tumor eradication. Cancer Res 2005;65:553–61.

22. Madan RA, Gulley JL, Schlom J, et al. Analysis of overall survival in patients with nonmetastatic castration-resistant prostate cancer treated with vaccine, nilutamide, and combination therapy. Clin Cancer Res 2008;14:4526–31.

23. Domchek SM, Recio A, Mick R, et al. Telomerase-specific T-cell immunity in breast cancer: effect of vaccination on tumor immunosurveillance. Cancer Res 2007;67:10546–55.

24. Mackall CL, Rhee EH, Read EJ, et al. A pilot study of consolidative immunotherapy in patients with high-risk pediatric sarcomas. Clin Cancer Res 2008;14:4850–8.

25. Yamaguchi S, Tatsumi T, Takehara T, et al. Immunotherapy of murine colon cancer using receptor tyrosine kinase EphA2-derived peptide-pulsed dendritic cell vaccines. Cancer 2007;110:1469–77.

26. Small EJ, Schellhammer PF, Higano CS, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006;24:3089–94.

27. Schmollinger JC, Vonderheide RH, Hoar KM, et al. Melanoma inhibitor of apoptosis protein (ML-IAP) is a target for immune-mediated tumor destruction. Proc Natl Acad Sci U S A 2003;100:3398–403.

28. Butterfield LH, Ribas A, Dissette VB, et al. A phase I/II trial testing immunization of hepatocellular carcinoma patients with dendritic cells pulsed with four α-fetoprotein peptides. Clin Cancer Res 2006;12:2817–25.

29. Birebent B, Mitchell E, Akis N, et al. Monoclonal anti-idiotypic antibody mimicking the gastrointestinal carcinoma-associated epitope CO17-1A elicits antigen-specific humoral and cellular immune responses in colorectal cancer patients. Vaccine 2003;21:1601–12.

30. Tomlins SA, Laxman B, Varambally S, et al. Role of the TMPRSS2-ERG gene fusion in prostate cancer. Neoplasia 2008;10:177–88.

31. Trakatelli M, Toungouz M, Blocklet D, et al. A new dendritic cell vaccine generated with interleukin-3 and interferon-β induces CD8+ T cell responses against NA17-A2 tumor peptide in melanoma patients. Cancer Immunol Immunother 2006;55:469–74.

32. Himoudi N, Nabarro S, Yan M, Gilmour K, Thrasher AJ, Anderson J. Development of anti-PAX3 immune responses; a target for cancer immunotherapy. Cancer Immunol Immunother 2007;56:1381–95.

33. Passoni L, Gallo B, Biganzoli E, et al. *In vivo* T-cell immune response against anaplastic lymphoma kinase in patients with anaplastic large cell lymphomas. Haematologica 2006;91:48–55.

34. Olson BM, McNeel DG. Antibody and T-cell responses specific for the androgen receptor in patients with prostate cancer. Prostate 2007;67:1729–39.

35. Krug LM, Ragupathi G, Ng KK, et al. Vaccination of small cell lung cancer patients with polysialic acid or N-propionylated polysialic acid conjugated to keyhole limpet hemocyanin. Clin Cancer Res 2004;10:916–23.

36. Kao H, Marto JA, Hoffmann TK, et al. Identification of cyclin B1 as a shared human epithelial tumor-associated antigen recognized by T cells. J Exp Med 2001;194:1313–23.

37. Wolchok JD, Yuan J, Houghton AN, et al. Safety and immunogenicity of tyrosinase DNA vaccines in patients with melanoma. Mol Ther 2007;15:2044–50.

38. Wenandy L, Sorensen RB, Svane IM, Thor Straten P, Andersen MH. RhoC a new target for therapeutic vaccination against metastatic cancer. Cancer Immunol Immunother 2008;57:1871–8.

39. Himoudi N, Yan M, Papanastasiou A, Anderson J. MYCN as a target for cancer immunotherapy. Cancer Immunol Immunother 2008;57:693–700.

40. Ragupathi G, Meyers M, Adluri S, Howard L, Musselli C, Livingston PO. Induction of antibodies against GD3 ganglioside in melanoma patients by vaccination with GD3-lactone-KLH conjugate plus immunological adjuvant QS-21. Int J Cancer 2000;85:659–66.

41. Dickler MN, Ragupathi G, Liu NX, et al. Immunogenicity of a fucosyl-GM1-keyhole limpet hemocyanin conjugate vaccine in patients with small cell lung cancer. Clin Cancer Res 1999;5:2773–9.

42. Laheru D, Lutz E, Burke J, et al. Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation. Clin Cancer Res 2008;14:1455–63.

43. Garcia-Hernandez Mde L, Gray A, Hubby B, Klinger OJ, Kast WM. Prostate stem cell antigen vaccination induces a long-term protective immune response against prostate cancer in the absence of autoimmunity. Cancer Res 2008;68:861–9.

44. Gribben JG, Ryan DP, Boyajian R, et al. Unexpected association between induction of immunity to the universal tumor antigen CYP1B1 and response to next therapy. Clin Cancer Res 2005;11:4430–6.

45. van Baren N, Bonnet MC, Dreno B, et al. Tumoral and immunologic response after vaccination of melanoma patients with an ALVAC virus encoding MAGE antigens recognized by T cells. J Clin Oncol 2005;23:9008–21.

46. Livingston PO, Hood C, Krug LM, et al. Selection of GM2, fucosyl GM1, globo H and polysialic acid as targets on small cell lung cancers for antibody mediated immunotherapy. Cancer Immunol Immunother 2005;54:1018–25.

47. Silva WA, Jr., Gnjatic S, Ritter E, et al. PLAC1, a trophoblast-specific cell surface protein, is expressed in a range of human tumors and elicits spontaneous antibody responses. Cancer Immun 2007;7:18.

48. Mkrtichyan M, Ghochikyan A, Loukinov D, et al. DNA, but not protein vaccine based on mutated BORIS antigen significantly inhibits tumor growth and prolongs the survival of mice. Gene Ther 2008;15:61–4.

49. Mazorra Z, Mesa C, Fernandez A, Fernandez LE. Immunization with a GM3 ganglioside nanoparticulated vaccine confers an effector CD8(+) T cells-mediated protection against melanoma B16 challenge. Cancer Immunol Immunother 2008;57:1771–80.

50. Gilewski T, Ragupathi G, Bhuta S, et al. Immunization of metastatic breast cancer patients with a fully synthetic globo H conjugate: a phase I trial. Proc Natl Acad Sci U S A 2001;98:3270–5.

51. Sabbatini PJ, Ragupathi G, Hood C, et al. Pilot study of a heptavalent vaccine-keyhole limpet hemocyanin conjugate plus QS21 in patients with epithelial ovarian, fallopian tube, or peritoneal cancer. Clin Cancer Res 2007;13:4170–7.

52. Yotnda P, Garcia F, Peuchmaur M, et al. Cytotoxic T cell response against the chimeric ETV6-AML1 protein in childhood acute lymphoblastic leukemia. J Clin Invest 1998;102:455–62.

53. Theurillat JP, Zurrer-Hardi U, Varga Z, et al. NY-BR-1 protein expression in breast carcinoma: a mammary gland differentiation antigen as target for cancer immunotherapy. Cancer Immunol Immunother 2007;56:1723–31.

54. Boss CN, Grunebach F, Brauer K, et al. Identification and characterization of T-cell epitopes deduced from RGS5, a novel broadly expressed tumor antigen. Clin Cancer Res 2007;13:3347–55.

55. Yajima N, Yamanaka R, Mine T, et al. Immunologic evaluation of personalized peptide vaccination for patients with advanced malignant glioma. Clin Cancer Res 2005;11:5900–11.

56. Tarp MA, Clausen H. Mucin-type O-glycosylation and its potential use in drug and vaccine development. Biochim Biophys Acta 2008;1780:546–63.

57. Lucas S, Coulie PG. About human tumor antigens to be used in immunotherapy. Semin Immunol 2008;20:301–7.

58. Yan M, Himoudi N, Pule M, et al. Development of cellular immune responses against PAX5, a novel target for cancer immunotherapy. Cancer Res 2008;68:8058–65.

59. Tammela J, Uenaka A, Ono T, et al. OY-TES-1 expression and serum immunoreactivity in epithelial ovarian cancer. Int J Oncol 2006;29:903–10.

60. Chiriva-Internati M, Cobos E, Da Silva DM, Kast WM. Sperm fibrous sheath proteins: a potential new class of target antigens for use in human therapeutic cancer vaccines. Cancer Immun 2008;8:8.

61. Harashima N, Tanaka K, Sasatomi T, et al. Recognition of the Lck tyrosine kinase as a tumor antigen by cytotoxic T lymphocytes of cancer patients with distant metastases. Eur J Immunol 2001;31:323–32.

62. Maciag PC, Seavey MM, Pan ZK, Ferrone S, Paterson Y. Cancer immunotherapy targeting the high molecular weight melanoma-associated antigen protein results in a broad antitumor response and reduction of pericytes in the tumor vasculature. Cancer Res 2008;68:8066–75.

63. Dubovsky JA, Albertini MR, McNeel DG. MAD-CT-2 identified as a novel melanoma cancer-testis antigen using phage immunoblot analysis. J Immunother 2007;30:675–83.

64. Chiriva-Internati M, Ferrari R, Yu Y, et al. AKAP-4: a novel cancer testis antigen for multiple myeloma. Br J Haematol 2008;140:465–8.

65. Zhou Q, Guo AL, Xu CR, et al. A dendritic cell-based tumour vaccine for lung cancer: full-length XAGE-1b protein-pulsed dendritic cells induce specific cytotoxic T lymphocytes *in vitro*. Clin Exp Immunol 2008;153:392–400.

66. Chen YW, Tekle C, Fodstad O. The immunoregulatory protein human B7H3 is a tumor-associated antigen that regulates tumor cell migration and invasion. Curr Cancer Drug Targets 2008;8:404–13.

67. Lewen S, Zhou H, Hu HD, et al. A Legumain-based minigene vaccine targets the tumor stroma and suppresses breast cancer growth and angiogenesis. Cancer Immunol Immunother 2008;57:507–15.

68. Luo Y, Wen YJ, Ding ZY, et al. Immunotherapy of tumors with protein vaccine based on chicken homologous Tie-2. Clin Cancer Res 2006;12:1813–9.

69. Yokokawa J, Bera TK, Palena C, et al. Identification of cytotoxic T-lymphocyte epitope(s) and its agonist epitope(s) of a novel target for vaccine therapy (PAGE4). Int J Cancer 2007;121:595–605.

70. Niethammer AG, Xiang R, Becker JC, et al. A DNA vaccine against VEGF receptor 2 prevents effective angiogenesis and inhibits tumor growth. Nat Med 2002;8:1369–75.

71. Hoeppner LH, Dubovsky JA, Dunphy EJ, McNeel DG. Humoral immune responses to testis antigens in sera from patients with prostate cancer. Cancer Immun 2006;6:1.

72. Lee J, Fassnacht M, Nair S, Boczkowski D, Gilboa E. Tumor immunotherapy targeting fibroblast activation protein, a product expressed in tumor-associated fibroblasts. Cancer Res 2005;65:11156–63.

73. Kaplan CD, Kruger JA, Zhou H, Luo Y, Xiang R, Reisfeld RA. A novel DNA vaccine encoding PDGFRβ suppresses growth and dissemination of murine colon, lung and breast carcinoma. Vaccine 2006;24:6994–7002.

74. Dubovsky JA, McNeel DG. Inducible expression of a prostate cancer-testis antigen, SSX-2, following treatment with a DNA methylation inhibitor. Prostate 2007;67:1781–90.

75. Luo Y, Zhou H, Mizutani M, et al. A DNA vaccine targeting Fos-related antigen 1 enhanced by IL-18 induces long-lived T-cell memory against tumor recurrence. Cancer Res 2005;65:3419–27.

76. Hawk ET, Matrisian LM, Nelson WG, et al. Translational Research Working Group. The Translational Research Working Group developmental pathways: introduction and overview. Clin Cancer Res 2008;14:5664–71.

77. heever MA, Schlom J, Weiner LM, et al. Translational Research Working Group. Translational Research Working Group developmental pathway for immune response modifiers. Clin Cancer Res 2008;14:5692–9.

78. Saaty TL. The analytic hierarchy process: planning, priority setting, resource allocation. New York: McGraw-Hill; 1980.

79. Bhushan N, Rai K. Strategic decision making: applying the analytic hierarchy process. London: Springer-Verlag; 2004.

APPENDIX B2

CRITERIA for IMMUNE RESPONSE MODIFIER PATHWAY PRIORITIZATION

The following has been recommended as criteria to assess Translational Research Opportunities in the Immune Response Modifier Pathway.

The criteria categories are indicated in the colored bars, and correspond to domains within the TRWG Immune Response Modifier Pathway (Clinical Cancer Research 14: 5692-5699, 2008) (http://clincancerres.aacrjournals.org/content/vol14/issue18/#CCR_SPECIAL_FOCUS). Subcriteria are indicated for each criteria, and correspond to information available on the scientific validity and feasibility of accelerating the development of the Opportunity to the point of early stage clinical trials. Rating scales and corresponding definitions indicate the level of evidence available for each subcriteria in descending order of robustness.

Opportunities demonstrating a high level of scientific validity and feasibility using these criteria will be further assessed by the NCI for clinical need and appropriateness for NCI investment. The resulting information will used in a variety of ways by the NCI, including but not limited to: 1) to inform the development of RFPs, RFAs, PAs, CRADAs, and/or Cooperative Agreements, including a limited number of Special Translational Research Acceleration Projects (STRAPs) through the NCI's Process to Accelerate Translational Science Initiative, 2) to inform the development, formulation, production and implementation of products/devices/processes through internal NCI mechanisms, or 3) no action taken. The information is designed to assist the NCI in facilitating the advancement of promising translational research Opportunities through the developmental process as rapidly, effectively, and efficiently as possible.

Creation of Modality and Development Domains of the Immune Response Modifier Pathway

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
ANTIGEN		
Immunogenicity	T cell and/or antibody responses elicited to antigen in clinical trials	Data supports this antigen as being immunogenic in clinical trials
	Spontaneous T cell responses to antigen observed in some patients	Data supports T cell immunity observed in some patients
	Immunogenic in animal models with natural levels of antigen expression similar to humans	Data supports this antigen as being immunogenic in appropriate animal models
	Spontaneous antibodies to antigen observed in some patients	Antibodies to this antigen are observed in some patients
	No data available	No data available

Therapeutic function	Efficacy in a controlled vaccine clinical trial	Data that antigen elicits a therapeutic response in a controlled vaccine trial is extremely convincing as judged by an informed expert
		Data that antigen elicits a therapeutic response in a controlled vaccine trial is adequate and moderately convincing
	Responses in T cell therapy	Evidence exists for the antigen as target of therapeutic response in T cell therapy
	Pre existent immunity correlates with survival	Pre existent B cell or T cell-mediated immunity to this antigen has shown a positive correlation with survival
	Efficacy in appropriate animal models	The antigen has shown efficacy in appropriate animal models
	No data available	No data available

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
FORMULATION (cell preparation, delivery vehicle, adjuvant, etc.)		
Scientific validity	Activity of the proposed formulation with this antigen demonstrated in clinical trials	Data for immunogenicity of specific formulation in human trials is superb as judged by an informed expert
		Data for immunogenicity of specific formulation in human trials is adequate
	Activity of the formulation class with this antigen demonstrated in clinical trials	Data for immunogenicity of the formulation class in human trials is superb as judged by an informed expert
		Data for immunogenicity of the formulation class in human trials is adequate
	Activity of the proposed formulation with this antigen demonstrated in animal models	Data in animal models for anti-tumor response of the specific formulation is superb as judged by an informed expert, spectacular potential for major effect in humans
		Data in animal models for immunogenicity or anti-tumor response of specific formulation is adequate
	Activity of the formulation class with this antigen demonstrated in animal models	Adequate data in animal models for the immunogenicity or anti-tumor efficacy of the formulation class
	No data available	No data available
Feasibility	Manufacturing of clinical grade formulation	GMP/clinical grade manufacturing of formulation at scale is reproducible and reliable
		Scalable clinical grade manufacturing process for the formulation has been piloted
	Manufacturing of clinical grade formulation for class-related agents	Scalable clinical grade manufacturing for the formulation class demonstrated
	Available as a laboratory formulation only	Laboratory formulation only
	Not formulated	Formulation not completely developed

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CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
IMMUNE MODIFIER AGENT (cytokines, etc.)		
Scientific validity	Augments specific immunity in human trials	Data for augmenting specific immunity in human trials is superb as judged by an informed expert
		Data for augmenting specific immunity in human trials is adequate
	Augments specific immunity in animals	Data for augmenting specific immunity in animals is superb as judged by an informed expert
		Data for augmenting specific immunity in animals is adequate
	Augments specific immune response in vitro	Adequate data for augmenting specific immunity in human cells in vitro
	No in vitro or in vivo data available	No in vitro or in vivo data available
Feasibility	Manufacturing of clinical grade agent	GMP/clinical grade manufacturing of the agent at scale is reproducible and reliable
		Scalable clinical grade manufacturing process for the agent has been piloted
	Manufacturing of clinical grade class-related modifier	Scalable clinical grade manufacturing process for the agent class has been demonstrated
	Available as a laboratory grade product	Laboratory product only
	Not developed	Not completely developed

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
COMBINATION REGIMEN		
Scientific validity	Activity of the specific combination demonstrated in human trials	Data available on immunogenicity of the specific combination in human trials
	Activity of combination of class-related molecules demonstrated in human trials	Data available on immunogenicity of combination for class-related molecules in human trials
	Activity of specific combination demonstrated in animal studies	Data available on anti-tumor response of specific combination in animal studies
	Activity of combination of class-related molecules demonstrated in animal studies	Data available on anti-tumor response of combination of class-related molecules in animal studies
	Theoretical basis exists for presumed efficacy of combination	Outstanding theory for efficacy of combination
		Adequate theory for efficacy of combination
		Weak rationale or rationale not adequately developed for combination

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Feasibility	All products available for human use	All products are available for human use
	All products but one available for human use	All products are available except for one which can be manufactured for human use within the foreseeable future
	Products can be available for human use	More than one product is not available, but all can be manufactured for human use within the foreseeable future
	Products are laboratory formulations	Some products are available as laboratory formulations only
	Products are not available	No products likely to be available within foreseeable future (i.e., 2 years)

Supporting Tools Domain of the Immune Response Modifier Pathway

For additional information on biospecimen-based assays, please see the Biospecimen-Based Assessment Modalities Pathway (Clin Cancer Res 2008 14: 5672-5677).

For additional information on imaging-based assays, please see the Imaging-Based Assessment Modalities Pathway (Clin Cancer Res 2008 14: 5678-5684).

http://clincancerres.aacrjournals.org/content/vol14/issue18/#CCR_SPECIAL_FOCUS

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
ASSAY FOR IMMUNE RESPONSE		
Validity & Feasibility	Clinically validated assay to quantify immune response	Assay has been clinically validated (i.e., demonstrated to measure a clinically meaningful response)
	Assay to quantify immune response developed and standardized	Assay has been analytically validated (i.e., meets standards of accuracy and reproducibility)
	Assay to quantify immune response in development	Assay is developed but not standardized or validated
	Assay to quantify immune response not available	A suitable assay to quantify immune response needs to be developed
ASSAY TO SELECT PATIENT POPULATION		
Validity & Feasibility	Assay to select patient population validated in a prospective clinical study	Assay has been shown to successfully identify target patient population in a prospective clinical trial
	Assay to select patient population validated in a retrospective or integrated correlative study	Assay shows promise in identifying target patient population using large numbers of samples from an appropriate patient cohort or an integrated correlative study
	Assay to select patient population in development	Assay to select patient population has been developed and analytically validated/standardized
		Assay to select patient population has been developed but not standardized or validated
	Assay to select patient population not available	Assay to select patient population needs to be developed

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Clinical Trials Domain of the Immune Response Modifier Pathway

CRITERIA Subcriteria	RATING SCALE	LEVEL OF EVIDENCE in descending order
AVAILABILITY OF PATIENTS FOR TRIALS		
Scientific Validity	Cancer type and stage of disease for clinical testing identified	Excellent data to support choice of population or patient subset for initial clinical trials with efficacy endpoints as judged by an informed expert
		Reasonable basis for choice of population or patient subset for initial clinical trials with efficacy endpoints
	Population not specified	Population is not specified
Feasibility	Availability of patients/individuals with required characteristics for clinical trials	Patients with appropriate stage of disease commonly are available and standard therapy is unlikely to preclude proposed experimental therapy
		Patients with appropriate stage of disease are not commonly available due to rarity of the stage or disease state, or competing protocols or confounding commonly used treatment regimens

APPENDIX C1

Request for Information (RFI): Immune Response Modifiers Pathway Translational Research Opportunities

Notice Number: NOT-CA-09-031

Key Dates

Release Date: July 20, 2009

Response Date: Responses must be received by August 24, 2009

Issued by

National Cancer Institute (NCI), (http://www.cancer.gov)

This is a Request for Information (RFI). It is to obtain knowledge and information for project planning purposes only and should not be construed as a solicitation for grants, contracts, etc.

Purpose and Objectives

This RFI is to gather information from the scientific community regarding opportunities in cancer immunotherapy and immunoprevention that would benefit from accelerated development through focused funding and coordinated management. This request is part of the NCI's new Process to Accelerate Translational Science as recommended by the Translational Research Working Group (TRWG). At the discretion of the NCI, the information gathered in response to this RFI may be used in a variety of ways by the NCI, including but not limited to: 1) assist NCI in the development of Requests for Proposals (RFP), Requests for Applications (RFA), Program Announcements (PA), Cooperative Research and Development Agreements (CRADA), Cooperative Agreements and/or other mechanisms/agreements; 2) assist in developing formulations, production and implementation of products/devices/processes using existing internal NCI mechanisms, to include but not limited to in-house staff, contracts, grants, cooperative agreements, etc.; or 3) no action taken.

Background

The TRWG was an NCI-sponsored working group charged with evaluating the status of the NCI's investment in translational research and envisioning its future in an inclusive, representative, and transparent manner. In 2007, the NCI accepted the 15 TRWG recommendations to accelerate translational cancer research as outlined in the report entitled *"Transforming Translation: Harnessing Discovery for Patient and Public Benefit,"* (http://www.cancer.gov/trwg).

One of the TRWG recommendations was the establishment of a yearly process to identify a small number of opportunities for specific cancer treatment, prevention or assessment modalities that are "ripe" for further development, and then to provide the funding or resources as well as the project management required to advance these opportunities as rapidly as possible to early stage clinical trials. This recommendation is being implemented and includes a prioritization process to identify and rank individual translational research opportunities, the provision of dedicated project management resources for the resulting prioritized projects, and the development of project specific funding approaches for these new, prioritized Special Translational Research Acceleration Projects (STRAPs).

The Process to Accelerate Translational Science was initiated with the first NCI Translational Science Meeting, held November 7-9, 2008 (http://ncitranslates.nci.nih.gov). This meeting educated the translational cancer research community about the TRWG Pathways to Clinical Goals (Clinical Cancer Research 14: 5663-5714, 2008, http://clincancerres.aacrjournals.org/content/vol14/issue18/#CCR_SPECIAL_FOCUS) and demonstrated that there are compelling translational research opportunities that warrant acceleration. The Pathways to Clinical Goals describe the steps required to create a treatment, prevention or assessment modality based on advances in scientific knowledge, and develop that modality to the point of early phase clinical trials. The term "Translational Research Opportunity" refers to a developmental project that follows one of these six TRWG Pathways (Agent, Immune Response Modifier, Interventive Device, or Lifestyle Alteration intervention, or Biospecimen-Based or Imaging-Based Assessment tool), and identifies the population/cancer type in which it is to be tested.

Information Requested

This RFI invites input from the scientific community on Translational Research Opportunities that follow the Immune Response Modifiers Pathway to testing in Phase I/II clinical trials (Clinical Cancer Research 14: 5692-5699, 2008, http://clincancerres.aacrjournals.org/cgi/reprint/14/18/5692.pdf). Information is sought from members of the scientific community at large, academic and non-academic translational cancer researchers, clinical oncologists, and investigators from the pharmaceutical/biotechnology industry. The opportunities can relate to a range of specific therapeutic regimens and target populations. Any information that can be shared regarding the immunogenicity and therapeutic function of an antigen, the scientific validity and feasibility of the formulation for that antigen, and/or the scientific validity and feasibility of combinations with immune modifier agents is requested. In addition, information on assays of

immune response, assays for patient selection, and the availability of patients for clinical trials, is requested. The Translational Research Opportunity Template (see below) provides the preferred submission format. Use of this format is requested; however, respondents are not required to use this format for their submission.

This RFI is for planning purposes and should not be construed as a solicitation for applications or as an obligation on the part of the Government to provide support for any opportunities identified in response to it. Please note that the United States Government will not pay for the preparation of any information submitted or for its use of that information.

Information Submission Instructions

1. Respondents are encouraged to utilize the Translational Research Opportunity Template to organize their responses. The template can be found at http://patsinitiative.nci.nih.gov.
2. Responses should be limited to twenty (20) pages in length. Brief and/or bullet information are encouraged wherever applicable in order to minimize overall response length and aid in the data processing.
3. It is preferred that responses be submitted in MS Word or PDF format via e-mail to NCI-RFI-IRMPathway@mail.nih.gov marked with the above RFI identifier (Notice Number) noted in the subject line. Respondents will receive an email confirmation acknowledging receipt of their response, but will not receive individualized feedback.
4. Responses will only be accepted through August 24, 2009.

Confidentiality

Responses to this RFI are voluntary and may be anonymous. Any identifiers (e.g. names, institutions, e-mail addresses, etc.) will be removed when responses are compiled. Anonymized results may be shared with scientific advisors convened by the NCI under confidentiality and conflict of interest agreements. No proprietary, classified, confidential, or sensitive information should be included in your response. The Government reserves the right to use any non-proprietary technical information in any resultant solicitation(s). As previously indicated, NCI can use the information gathered to develop grant, contract, or other funding initiatives.

Inquiries

Inquiries regarding this Notice may be directed to:

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NCI-RFI-IRMPathway@mail.nih.gov

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Office of Extramural Research (OER)
National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892
Department of Health and Human Services (HHS)
USA.gov Government Made Easy

APPENDIX C1

Immune Response Modifier Pathway
Translational Research Opportunity Template

It is requested that responses to RFI NOT-CA-09-031 utilize this Translational Research Opportunity Template to organize the submitted information. Responses should be limited to twenty (20) pages in length. Brief and/or bullet information are encouraged wherever applicable in order to minimize overall response length and aid in the data processing.

It is preferred that responses be submitted in MS Word or PDF format via e-mail to NCI-RFI-IRMPathway@mail.nih.gov marked with the above RFI identifier (Notice Number) noted in the subject line. Respondents will receive an email confirmation acknowledging receipt of their response, but will not receive individualized feedback. Responses will be accepted through August 24, 2009.

Submitted by: *(Submitter information is optional.)*

Name and title:
Affiliation:
e-mail:

Purpose

This template provides a structured format to describe opportunities in cancer immunotherapy and immunoprevention that would benefit from acceleration through focused funding and dedicated project management. The Translational Research Working Group Immune Response Modifier Pathway to Clinical Goals (Clinical Cancer Research 14: 5692-5699, 2008) should be used as the framework for the information provided.

Please note: Translational Research Opportunities address specific clinical or product development goals. This RFI is not intended to provide information on opportunities for discovery research, methodology development, or infrastructure development unless they are tightly linked to specific and concrete clinical or product development objectives.

Title

Please provide a descriptive title that summarizes the modality (e.g., vaccine, immune response modifier, cell-based therapy, etc) and the primary clinical target for the Translational Research Opportunity for which you are providing information.

Examples of Translational Research Opportunity titles:
"CLL therapy with anti-CD20 (Rituximab) plus IL21 and GM-CSF to enhance ADCC"

"T-cell checkpoint blockade inhibitor anti-CTLA4 plus T-cell growth factor IL7 in the treatment of melanoma"

"Therapy of relapsed leukemia using autologous T cells expressing chimeric T-cell receptors followed by T-cell growth factor IL15"

“Recombinant protein-based vaccine targeting dendritic cells utilizing IL-12 and CpG as adjuvants to prevent lung cancer in high risk populations”

APPENDIX C1

Concise summary of recommended opportunity

Please briefly summarize the essence and rationale of the proposed Translational Research Opportunity for which you are providing information, identifying:

- The primary clinical objective
- The key unresolved scientific issues or unfinished developmental tasks that must be addressed in order to test this modality in a clinical trial
- Up to 3 reasons (clinical and/or scientific) that demonstrate why your suggestion should be considered a high priority opportunity

APPENDIX C1

Scientific Validity and Feasibility of Opportunity Components

To assist in identifying Opportunities you feel NCI should pursue, consideration should be given to using the following templates. Note that the template and the color-coding correspond to the Translational Research Working Group Pathway for Immune Response Modifiers (Clinical Cancer Research 14: 5692-5699, 2008).

In using this template, please provide the information available on the following components of your Translational Research Opportunity. Each major component (indicated by a colored bar) has one or two subcomponents for which information is requested. Select the expandable box within each subcomponent that corresponds to the highest level of evidence available, and concisely summarize the information that is known. Provide literature references, non-proprietary data, or other information that address each listed characteristic of the component. Information can be provided on additional lower levels of evidence within a subcategory. Note that not all major components will be relevant to every proposed Opportunity and the entire component can be indicated as being *not applicable* at the top. Major components can be duplicated and used more than once as necessary for opportunities involving more than one antigen, formulation, immune response modifier, etc.

		COMMENTS / LITERATURE
COMPONENT: ANTIGEN		
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Immunogenicity	T cell and/or antibody responses elicited to this antigen in clinical trials	
	Spontaneous T cell responses to this antigen observed in some patients	
	Antigen is immunogenic in animal models with natural levels of antigen expression similar to humans	
	Spontaneous antibodies to this antigen are observed in some patients	
Therapeutic function	This antigen has shown efficacy in a controlled vaccine clinical trial	
	This antigen has shown responses in T cell therapy	
	Pre existent immunity to this antigen has shown a correlation with survival	
	This antigen has shown efficacy in appropriate animal models	

APPENDIX C1

		COMMENTS / LITERATURE
COMPONENT: FORMULATION (cell preparation, vehicle, adjuvant, etc.)		
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Scientific validity	Activity of the proposed formulation with this antigen demonstrated in clinical trials	
	Activity of the formulation class with this antigen demonstrated in clinical trials	
	Activity of the proposed formulation with this antigen demonstrated in animal models	
	Activity of the formulation class with this antigen demonstrated in animal models	
Feasibility	Manufacturing of clinical grade formulation (include information on stage of development, scale, reproducibility, etc.)	
	Manufacturing of clinical grade formulations for class-related agents (include information on stage of development, scale, reproducibility, etc.)	
	Available as a laboratory formulation	

APPENDIX C1

		COMMENTS / LITERATURE
COMPONENT: IMMUNE MODIFIER AGENT (cytokines, etc.)		
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Scientific validity	Augments specific immunity in human trials	
	Augments specific immunity in animals	
	Augments specific immunity in vitro	
Feasibility	Manufacturing of clinical grade agent (include information on stage of development, scale, reproducibility, etc)	
	Manufacturing of clinical grade class-related modifier (include information on stage of development, scale, reproducibility, etc)	
	Available as a laboratory grade product	

APPENDIX C1

		COMMENTS / LITERATURE
COMPONENT: COMBINATION REGIMEN		
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Scientific validity	Activity of the specific combination has been demonstrated in human trials	
	Activity of combination of class-related molecules has been demonstrated in human trials	
	Activity of specific combination has been demonstrated in animal studies	
	Activity of combination of class-related molecules has been demonstrated in animal studies	
	Theoretical basis exists for presumed efficacy of combination	

APPENDIX C1

		COMMENTS / LITERATURE
COMPONENT: ASSAY FOR IMMUNE RESPONSE		
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Validity & Feasibility	Assay to quantify immune response has been clinically validated	
	Assay to quantify immune response has been developed and standardized	
	Assay to quantify immune response is in development	

APPENDIX C1

		COMMENTS / LITERATURE
COMPONENT: ASSAY TO SELECT PATIENT POPULATION		
If entire component is not applicable to this Opportunity, enter "not applicable" in the adjacent comment box. If component is relevant but there is no data available, enter "no data available" in the adjacent comment box.		
Validity & Feasibility	Assay to select patient population has been validated in a prospective clinical study	
	Assay to select patient population has been validated in a retrospective or integrated correlative study	
	Assay to select patient population is in development	

APPENDIX C1

		COMMENTS / LITERATURE
COMPONENT: AVAILABILITY OF PATIENTS FOR TRIALS		
Scientific validity	Data supporting choice of cancer type and stage of disease for clinical testing	
Feasibility	Availability of patients/individuals with the required characteristics for clinical trials (include information on disease prevalence, competing protocols and status of standard therapy)	

APPENDIX C2

Immune Response Modifier Pathway Translational Research Opportunity

Scientific Evaluation Form

Opportunity identifier:

Opportunity Title:

Overall assessment of potential impact of this Translational Research Opportunity:

Directions:

Each Translational Research Opportunity has multiple Components. The components are indicated by a colored bar and correspond to the TRWG Immune Response Modifier Pathway*. Each Component has several Criteria to evaluate scientific validity and feasibility. Each Criterion is rated according to a predefined rating scale described in the table below. Indicate the **one** Rating Scale/definition within each Criterion that most accurately reflects the status of the Translational Research Opportunity component being considered. The rating scales are presented in the table in descending rank order of priority weight, i.e., the uppermost-row has the most weight. Mark the **uppermost row** for which there is supportive information by checking the box at the end of the row. If you disagree with the assessment made by the submitter, please mark the row that in your opinion most accurately represents the data available. Comments are optional, but you are encouraged to provide a brief rationale if you indicate a ranking on the rating scale other than that provided by the submitter.

*(CCR 14: 5692-5699, 2008, http://clincancerres.aacrjournals.org/cgi/reprint/14/18/5692.pdf.)

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ANTIGEN		Rating Scale/definition	Descriptor	Comments (optional)	✓
Name of Antigen (or NA if Not Applicable) ***NOTE: If there are two or more antigens, use a separate form for each antigen.*** ***For autologous tumor, use "autologous tumor - unique antigens" as the name of the antigen and rate Immunogenicity as "Human Immunogenic" and Therapeutic function as "Human Fair".*** ***For allogeneic tumor use "allogeneic tumor, shared antigens" as the name of the antigen. Rate Immunogenicity as "Human immunogenic" and Therapeutic function as "Human Fair"***					
CRITERIA Immunogenicity	T cell and/or antibody responses elicited to this antigen in clinical trials	Data supports this antigen as being immunogenic in clinical trials	Human immunogenic		
NOTE: Rating for immunogenicity of antigens is the same as Table 3, Column 4, in CCR 15: 5323, 2009 unless change is dictated by more recent data.	Spontaneous T cell responses to this antigen observed in some patients	Data supports T cell immunity observed in some patients	T cell immunity		
	Antigen is immunogenic in animal models with natural levels of antigen expression similar to humans	Data supports this antigen as being immunogenic in <u>appropriate</u> animal models	Animal immunogenic		
	Spontaneous antibodies to this antigen are observed in some patients	Antibodies to this antigen are observed in some patients	Antibodies		
		No data available	No data		
CRITERIA Therapeutic function	This antigen has shown efficacy in a controlled vaccine clinical trial	Data that antigen elicits a therapeutic response in a controlled vaccine trial is extremely convincing as judged by an informed expert dictated by more recent data)	Human adequate to superb		
		Data that antigen elicits a therapeutic response in a controlled vaccine trial is fair and moderately convincing	Human fair		
NOTE: Ratings for Therapeutic Function of Antigens is the same as Table 3, Column 3, of CCR 15: 5323, 2009 unless change is dictated by more recent data.	This antigen has shown responses in T cell therapy	Evidence exists for the antigen as a target of therapeutic response in T cell therapy	T cell response		
	Pre existent immunity to this antigen has shown a correlation with survival	Pre-existent B cell or T cell-mediated immunity to this antigen has shown a positive correlation with survival	Pre-existent immunity		
	This antigen has shown efficacy in appropriate animal models	Data supports a therapeutic response to the antigen in <u>appropriate</u> animal models	Animal		
		No data available	No data		

APPENDIX C2

T CELL THERAPY TARGET		Rating Scale/definition	Descriptor	Comments (optional)	✓
Name of Target (or NA if Not Applicable) **NOTE: If there are two or more targets, use a separate form for each.**					
CRITERIA Function of Target	Target is necessary for cancer cell survival and highly selective	Target is necessary for cancer cell survival and is highly selectively expressed by cancer cells or cancer stroma	Critical selective		
	Target is necessary for cancer cell survival, but not highly selective	Target is necessary for cancer cell survival and is highly selectively expressed by cancer cells or cancer stroma	Critical not selective		
	Target is not necessary for cancer cell survival, but highly selectively expressed	Target is not necessary for cancer cell survival, but is highly selectively expressed by cancer cells or cancer stroma	Not critical selective		
	Target is not necessary for cancer survival, is selectively expressed, but is expressed on normal tissues	Target is not necessary for cancer cell survival, and is highly expressed by cancer cells or cancer stroma, but is expressed by many normal tissues and/or circulates in substantial concentrations	Not critical overexpressed		
	Target is not critical and not highly selective	Target is not critical, is not selectively expressed by cancer cells and/or is circulates in substantial concentrations	Not critical not selective		
CRITERIA Therapeutic function	A T cell specific for this target has shown efficacy in a clinical trial.	Data that a T cell infusion specific for the target is effective in a controlled therapy trial is extremely convincing as judged by an informed expert	Human superb		
		Data that a T cell infusion specific for the target is effective in a controlled clinical trial is adequate and moderately convincing	Human adequate		
	This target antigen has shown efficacy in a controlled vaccine clinical trial	Data that antigen elicits a therapeutic response in a vaccine trial is at least moderately convincing	Vaccine efficacy		
	Pre existent immunity to this target has shown a correlation with survival	Pre-existent B-cell or T cell immunity to this target has shown a positive correlation with survival	Pre-existent Ab immunity		
	T cells specific for this target has shown to be effective in appropriate animal models	Data supports that a T cell specific for the target is effective in an <u>appropriate</u> animal models	Animal		
		No data available	No data		

APPENDIX C2

ANTIBODY & T BODY TARGET		Rating Scale/definition	Descriptor	Comments (optional)	✓
Name of Target (or NA if Not Applicable) ***Note: if there are two or more targets, use a separate form for each***					
CRITERIA Function of Target	Target is functional and highly selective	Target is functional, can be perturbated by antibodies and is highly selectively expressed by cancer cells or cancer stroma	Functional selective		
	Target is functional, but not highly selective	Target is functional, can be perturbated by antibodies but is expressed by many normal tissues in addition to cancer cells and/or circulates in substantial concentrations	Functional not selective		
	Target is non-functional, but highly selectively expressed	Target is non-functional, but is highly selectively expressed by cancer cells or cancer stroma	Non-functional, selective		
	Target is non-functional, is selectively expressed, but is expressed on normal tissues	Target is non-functional, and is highly expressed by cancer cells or cancer stroma, but is expressed by many normal tissues and/or circulates in substantial concentrations	Non-functional overexpressed		
	Target is non-functional and not highly selective	Target is non-functional, is not selectively expressed by cancer cells and/or is circulates in substantial concentrations	Non-functional target, not selectively expressed		
CRITERIA Therapeutic function	An antibody specific for this target has shown efficacy in a clinical trial	Data that an antibody specific for the target is effective in a controlled therapy trial is extremely convincing as judged by an informed expert	Human superb		
		Data that an antibody specific for the target is effective in a controlled clinical trial is adequate and moderately convincing	Human adequate		
	An MHC restricted T cell specific for this target has shown efficacy in a clinical trial	Data that an MHC restricted T cell specific for the target is effective in a controlled clinical trial is convincing.	T cell therapy		
	Pre existent immunity to this target has shown a correlation with survival	Pre-existent B-cell immunity to this target has shown a positive correlation with survival	Pre-existent Ab immunity		
	Antibody to this target has shown to be effective in appropriate animal models	Data supports that an antibody specific for the target is effective in an appropriate animal models	Animal		
		No data available	No data		

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FORMULATION (cell preparation, vehicle, adjuvant, etc.) T CELL CONSTRUCT ANTIBODY/ T-BODY CONSTRUCT		Rating scale/definition	Descriptor	Comments (optional)	✓
Name of Formulation, e.g., DNA, peptide, recombinant adenovirus, protein, fusion proteins, etc (or NA if Not Applicable) ***NOTE:* Structural components of vaccine such as lipids, liposomes and alum are entered as part of "Formulation"** *IRMs used as vaccine adjuvants and injected concurrently and contiguous with antigen injection, such as MPL, CpG, GM-CSF are entered as part of "Formulation".* *Dendritic cells are considered as "Formulation"* *IRMs used as adjuvants plus another immune function such as T cell growth factors or anti-check point inhibitor antibodies are entered as IRM Components in the next table.*					
CRITERIA Scientific validity	Activity of the proposed formulation with this antigen demonstrated in clinical trials	Data for immunogenicity of specific formulation in human trials is superb as judged by an informed expert. Defined as substantial and outstanding immunogenicity that is greater than possible with peptide or protein used alone.	Human superb		
		Data for immunogenicity of specific formulation in human trials is adequate. Defined as equivalent to most vaccine trials.	Human adequate		
	Activity of the formulation class with this antigen demonstrated in clinical trials	Data for immunogenicity of the formulation class in human trials is superb as judged by an informed expert	Class human superb		
		Data for immunogenicity of the formulation class in human trials is adequate	Class human adequate		
	Activity of the proposed formulation with this antigen demonstrated in animal models	Data in animal models for anti-tumor response of the specific formulation is superb as judged by an informed expert, spectacular potential for major effect in humans	Animal superb		
		Data in animal models for immunogenicity or anti-tumor response of specific formulation is adequate	Animal adequate		
	Activity of the formulation class with this antigen demonstrated in animal models	Adequate data in animal models for the immunogenicity or anti-tumor efficacy of the formulation class	Class animal		
		No data available	No data		

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CRITERIA Feasibility	Manufacturing of clinical grade formulation	GMP/clinical grade manufacturing of formulation at scale is reproducible and reliable. Defined as manufactured and distributed by a company or RAID or equivalent experienced organization.	Manufactured		
		Scalable clinical grade manufacturing process for the formulation has been piloted. Defined as manufactured by an academic institution use in local patients. Not scaled up for use at multiple institutions. ***NOTE: Dendritic cells in clinical trials at one institution are generally in this category***	Piloted		
	Manufacturing of clinical grade formulations for class-related agents	Scalable clinical grade manufacturing process for the formulation class demonstrated	Class manufactured		
	Available as a laboratory formulation	Laboratory formulation only	Laboratory		
	Not formulated	Formulation not completely developed	Undeveloped		

APPENDIX C2

IMMUNE MODIFIER AGENT (cytokines, etc)		Rating scale/definition	Descriptor	Comments (optional)	✓
Name of Agent (or NA if Not Applicable)					
CRITERIA Scientific validity	Augments specific immunity in human trials	Data for augmenting specific immunity in human trials is superb as judged by an informed expert. Defined as substantial and outstanding augmentation of immunogenicity that is greater than possible with a vaccine used alone.	Human superb		
		Data for augmenting specific immunity in human trials is adequate. Defined as demonstrated augmentation of immunogenicity that is less than outstanding.	Human adequate		
	Augments specific immunity in animals	Data for augmentation of specific immunity in animals is superb as judged by an informed expert	Animal superb		
		Data for augmenting specific immunity in animals is adequate	Animal adequate		
	Augments specific immunity in vitro	Adequate data for augmenting specific immunity in human cells in vitro	In vitro		
		No in vitro or in vivo data available	No data		
CRITERIA Feasibility	Manufacturing of clinical grade agent	GMP/clinical grade manufacturing of agent at scale is reproducible and reliable. Defined as manufactured and distributed by a company or RAID or equivalent experienced organization.	Manufactured		
		Scalable clinical grade manufacturing process for the agent has been piloted. Defined as manufactured by an academic institution use in local patients. Not scaled up for use at multiple institutions.	Piloted		
	Manufacturing of clinical grade class-related modifier	Scalable clinical grade manufacturing process for the agent class demonstrated	Class manufactured		
	Available as a laboratory grade product	Laboratory product only	Laboratory		
	Not developed	Not completely developed	Undeveloped		

APPENDIX C2

COMBINATION REGIMEN		Rating scale/definition	Descriptor	Comments (optional)	✓
Name of Each Agent in the Combination (or NA if Not Applicable)					
CRITERIA Scientific validity	Activity of the specific combination has been demonstrated in human trials	Data available on immunogenicity of the specific combination in human trials	Human specific		
	Activity of combination of class-related molecules has been demonstrated in human trials	Data available on immunogenicity of combination for class-related molecules in human trials	Human class		
	Activity of specific combination has been demonstrated in animal studies	Data available on anti-tumor response of specific combination in animal studies	Animal specific		
	Activity of combination of class-related molecules has been demonstrated in animal studies	Data available on anti-tumor response of combination of class-related molecules in animal studies	Animal class		
	Theoretical basis exists for presumed efficacy of combination	Outstanding theory for efficacy of combination	Theory superb		
		Adequate theory for efficacy of combination	Theory adequate		
		Weak rationale or rationale not adequately developed for combination	Weak rationale		
CRITERIA Feasibility	All products available for human use	All products available for human use	All		
	All products but one available for human use	All products available except for one which can be manufactured for human use within foreseeable future	All but one		
	Products can be available for human use	More than one product not available but can be manufactured for human use within foreseeable future	Some		
	Products are laboratory formulations	Some products are available as laboratory formulations only	Laboratory		
	Products are not available	No products likely to be available within the foreseeable future (i.e. 2 years)	None		

APPENDIX C2

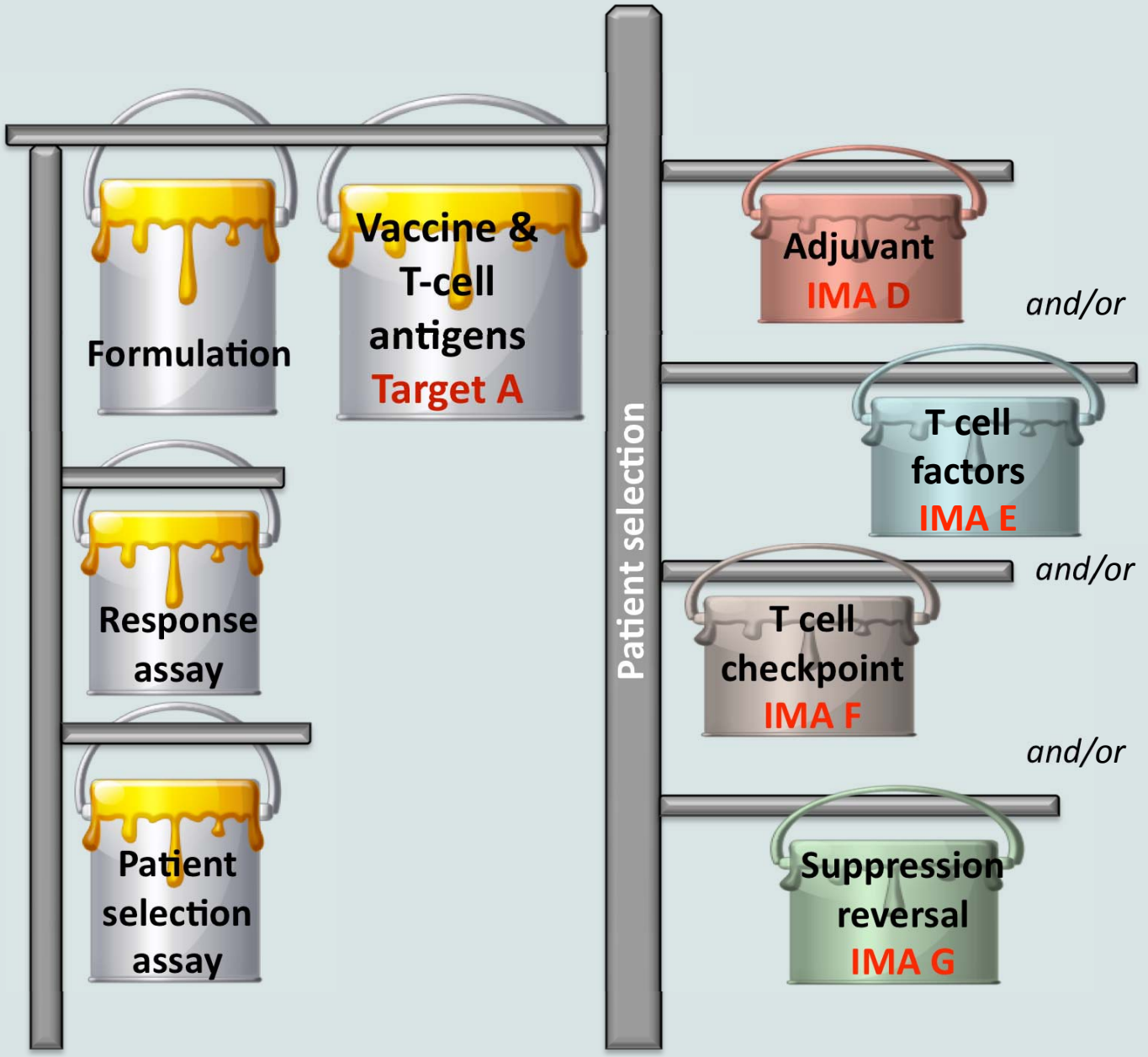
ASSAY FOR IMMUNE RESPONSE	Rating scale/definition	Descriptor	Comments (optional)	✓
Name of the Immune Response being assayed, e.g., T cell response, T cell number, antibody titer, IFN level, etc (or NA if Not Applicable)				
CRITERIA Validity & Feasibility	Assay to quantify immune response has been clinically validated	Assay has been clinically validated (i.e., demonstrated to measure a clinically meaningful immune response)	Validated	
	Assay to quantify immune response has been developed and standardized	Assay has been analytically validated (i.e., meets standards of accuracy and reproducibility)	Standardized	
	Assay to quantify immune response is in development	Assay is developed but not standardized or validated	In development	
	Assay to quantify immune response not available	A suitable assay to quantify immune response needs to be developed	Not available	

ASSAY TO SELECT RESPONSIVE PATIENT POPULATION	Rating scale/definition	Descriptor	Comments (optional)	✓
Name of Assay to be used, e.g., IHC for specific protein expression, PCR for presence of specific transcript, etc (or NA if Not Applicable) ***NOTE: Intended for antigen or target assays, e.g. FISH for HER2/neu expressing tumors or PCR for ras mutations. Assays to identify a tumor type, e.g. H &E morphology or expression of non-target antigens by IHC, are not applicable.***				
CRITERIA Validity & Feasibility	Assay to select patient population has been validated in a prospective clinical study	Assay has been shown to successfully identify target patient population in a prospective clinical trial	Prospective	
	Assay to select patient population has been validated in a retrospective or integrated correlative study	Assay shows promise in identifying target patient population using large numbers of samples from an appropriate patient cohort or an integrated correlative study	Retrospective	
	Assay to select patient population is in development	Assay to select patient population has been developed and analytically validated/standardized	Standardized	
		Assay to select patient population developed but not standardized or validated	In development	
	Assay to select patient population not available	Assay to select patient population needs to be developed	Not available	

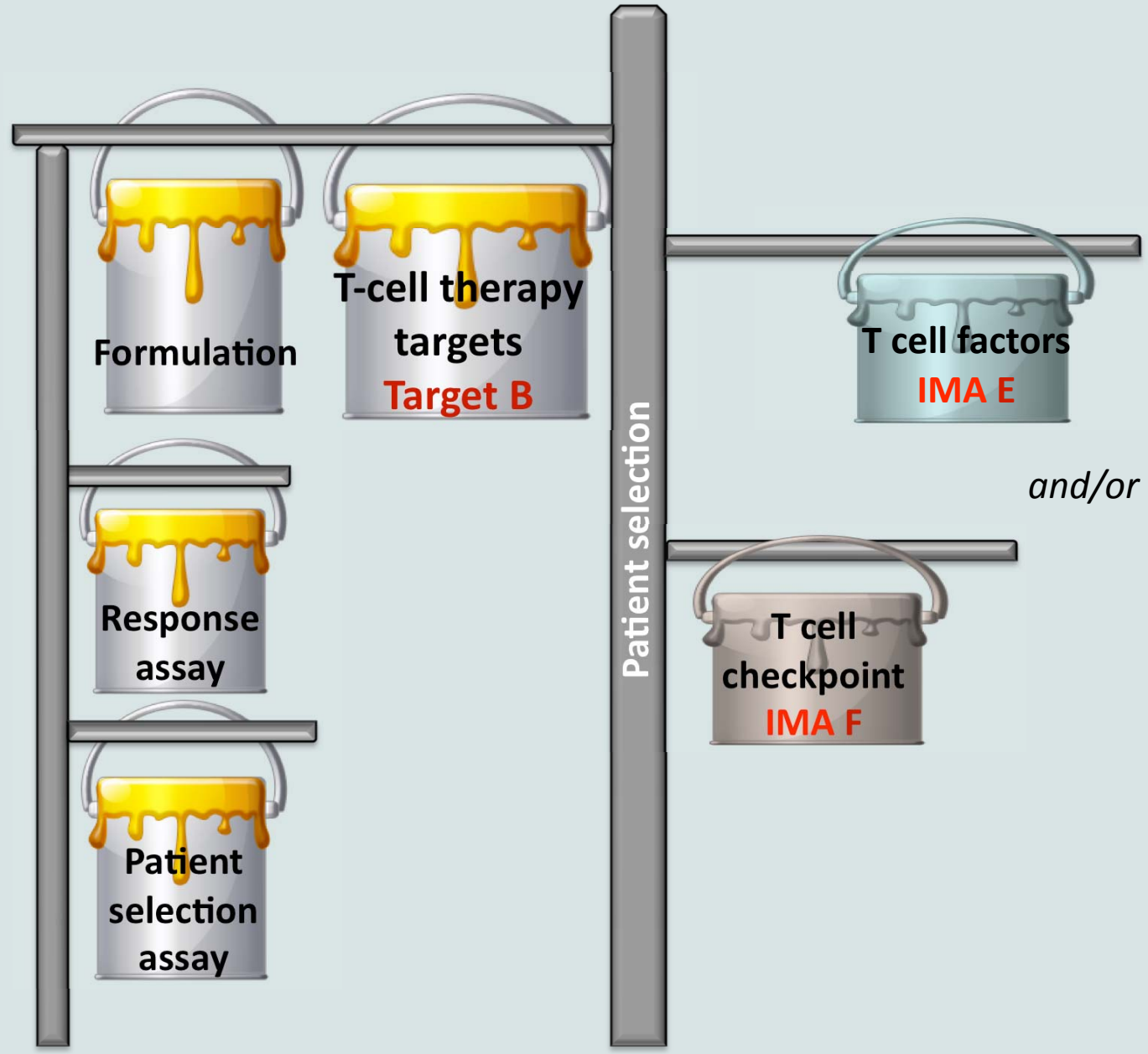
APPENDIX C2

AVAILABILITY OF PATIENTS FOR TRIALS	Rating scale/definition		Descriptor	Comments (optional)	✓
Name of population or patient subset for clinical trials					
CRITERIA Scientific validity	Data supporting choice of cancer type and stage of disease for clinical testing	Excellent data to support choice of population or patient subset for initial clinical trials with efficacy endpoints	Excellent		
		Reasonable basis for choice of population or patient subset for initial clinical trials with efficacy endpoints	Reasonable		
	Population not specified	Population is not specified	Not specified		
CRITERIA Feasibility	Availability of patients//individuals with the required characteristics for clinical trials	Patients with appropriate stage of disease are commonly available and standard therapy is unlikely to preclude proposed experimental therapy	Available		
		Patients with appropriate stage of disease are not commonly available due to rarity of the stage or disease state, or competing protocols or confounding commonly used treatment regimens	Not available		

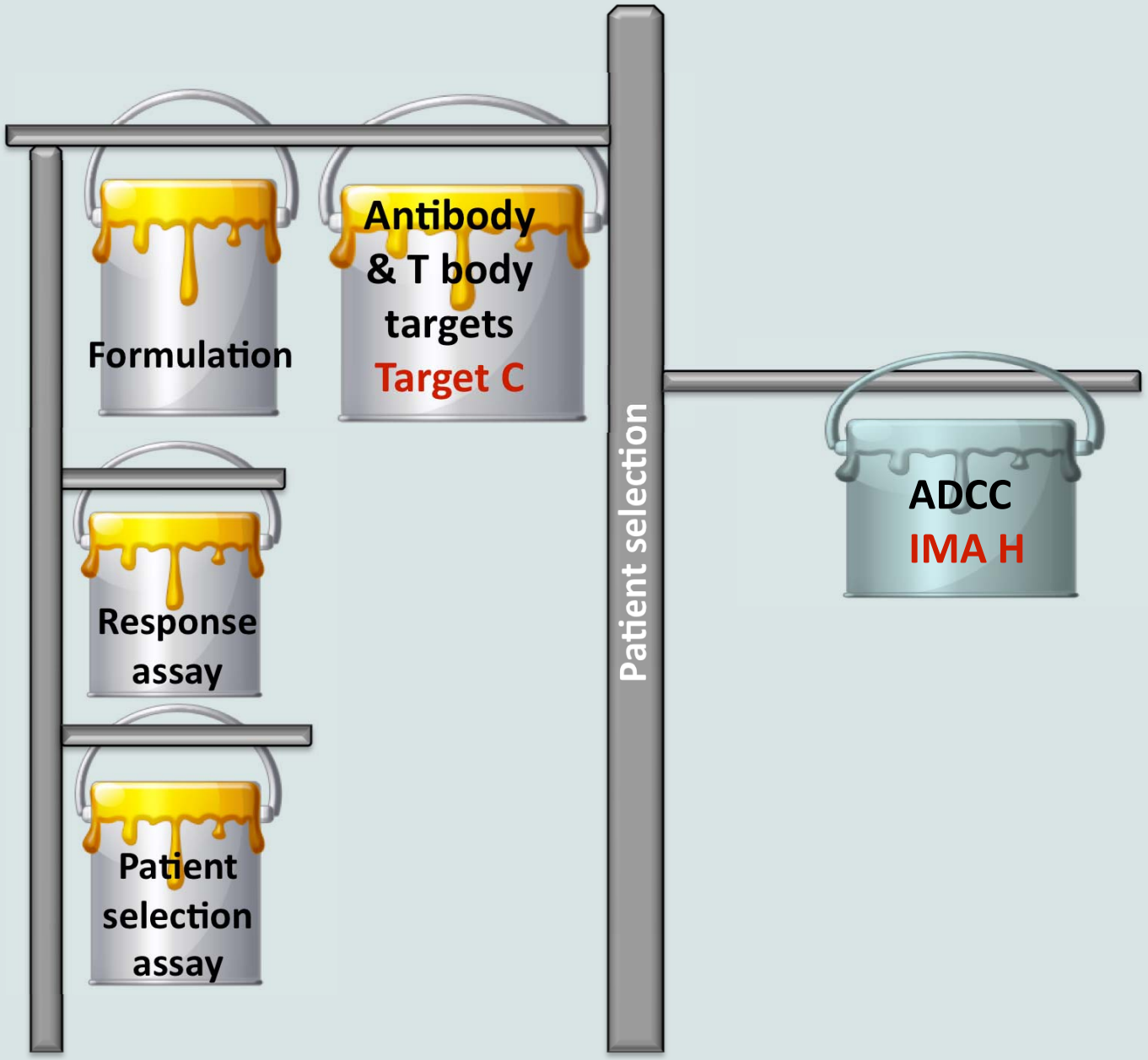
CANCER VACCINE SCAFFOLD



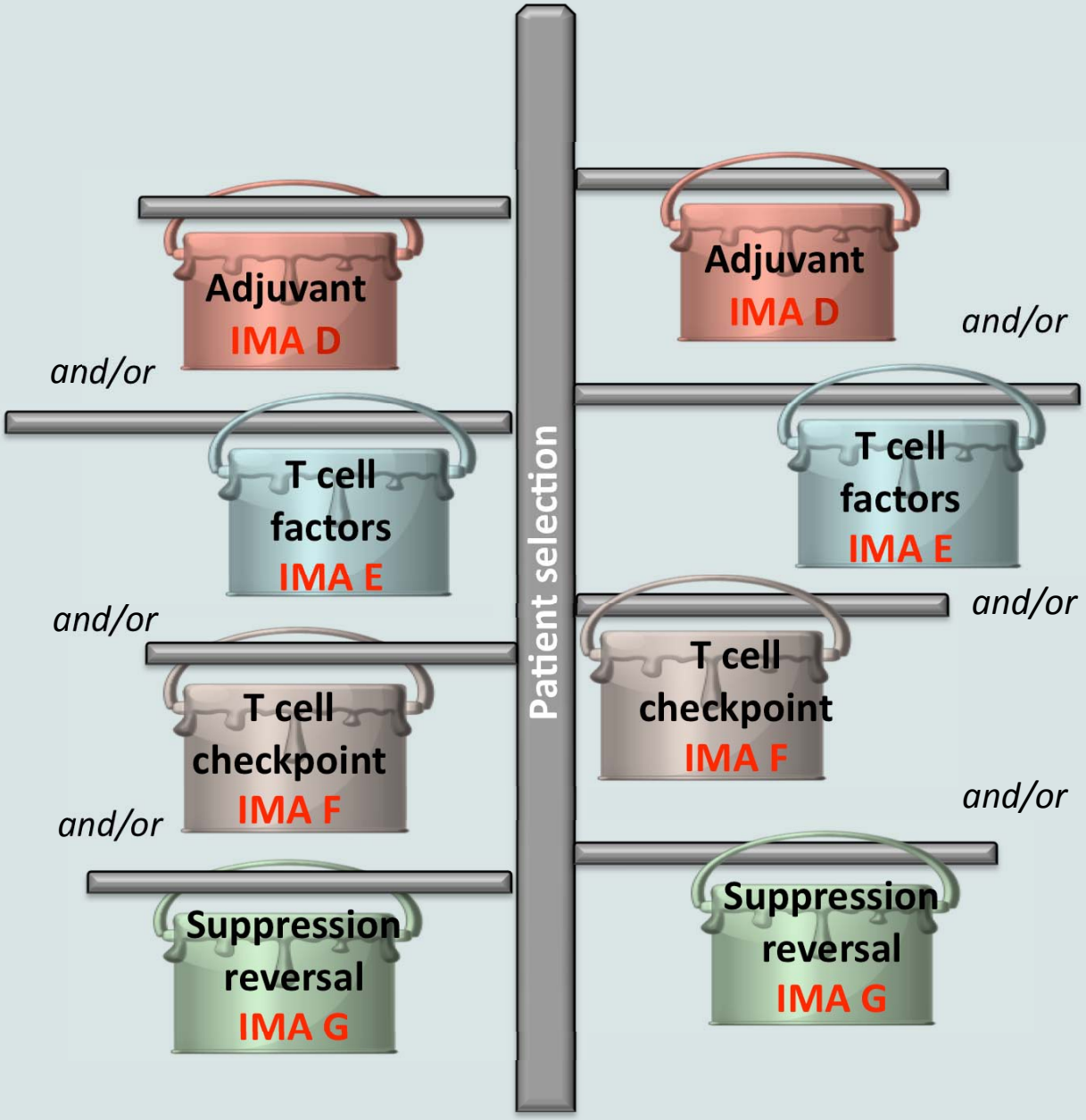
ADOPTIVE THERAPY SCAFFOLD



ANTIBODY SCAFFOLD



IMMUNE MODIFIER AGENT SCAFFOLD



APPENDIX D2

IMMUNE RESPONSE MODIFIER PRIORITIZATION WORKING GROUP

Version 10-21-09

Highlight=candidates recommended for 2009 Prioritization Process. In Comment column, dark line = separation of high and low priority candidates. Comments include rationale for exclusion of high priority candidates and inclusion of lower priority candidates. Notes are in parentheses.

Target A: Vaccine and T-cell antigens

Project	Candidate	Bucket	Rank	Comment
R028 CpG-MCL vaccine/ATC therapy (lymphoma)	CpG-activated, autologous whole-cell MCL	A	1.00	antigens not defined, patient specific
R016 Shed BrCa Ag, IL2 GM liposomes	Shed BrCa Ag	A	1.00	antigens not defined
R006 Auto tumor transfected w IGFR antisense (Astrocytoma)	Auto tumor/IGF-1R/AS ODN	A	1.00	patient specific
T1-334 MinorHA alloTcells CD3/CD28/IL2 expand (lymphoma)	MinorHA allo	A	1.00	antigens not defined
T1-343 MinorHA alloTh2 HSCT	Allogeneic hematologic malignanc shared antigens	A	1.00	antigens not defined
T1-342 Unique/shared autoTIL Lymph/deplet IL2 melanoma	Autologous tumor shared antigens	A	1.00	antigens not defined, patient specific
T2-302 Auto tumor + proteasome inhibitor (NSCLC)	Auto tumor	A	1.00	antigens not defined, patient specific
T1-522 HPV DNA by electroporation	HPV E6/7	A	0.93	(#4 on antigen list)
T1-542 HPV E6/7 DNA + vaccinia (higrade CIN2/3)	HPV E6/7	A	0.93	
A001 HPV E6/E7	HPV E6/E7	A,B	0.93	
R004 Anti-HER2 fused to LIGHT protein	HER2	A	0.90	(#6 on antigen list)
T2-030 Allo tumor/GM + Cy + Doxorubicin (BrCa)	HER2	A	0.90	
T1-546 HER2 Adv (EC +TM domain) + DC for BrCa	HER2	A	0.90	
T2-154 HER2 heterologous DNA	HER2 heterologous DNA	A	0.90	
A002 HER-2/neu	HER2	A,B	0.90	
A003 MAGE A3	MAGE A3	A	0.86	(#8 on antigen list)
T2-112 MelanA/MART1 recombTCR + PET reporter	MelanA/MART1	A	0.85	
A004 MelanA/MART1	MelanA/MART1	A,B	0.85	
A014 gp100	gp100	A,B	0.84	
R034 gp100/OX40mAB/HD IL-2 (melanoma)	gp100+Trp2	A	0.84	
R039 gp100/Trp2 + Hsp110 complex (melanoma)	gp100+Trp2	A	0.84	
T1-545 Heterol gp100/TYRP2/GM-CSF DNA particle	Heterol gp100/TYRP2	A	0.84	
R025 Melanoma peptide-pulsed IL-15DC for melanoma/IL7	(MART-1+ gp100+ MAGE-A3+ tyrosinase)	A	0.84	
T2-226 Adv Tyrosinase/MART1/MAGE-A6 + DC	Adv Tyrosinase+MART1+MAGE-A6	A	0.84	
A008 MUC1	MUC1	A,B	0.84	Include, #2 in antigen list
T1-530 MUC1 peptides w Tn carbohydrate (BrCa)	MUC1	A	0.84	
T1-538 EGFRvIII peptide vac + temozolomide (GBM)	EGFRvIII	A	0.84	#5 on antigen list, not included because small subset of patients
A005 EGFRvIII protein	EGFRvIII	A	0.84	
T2-083 Ad-shA20-FL (Inh A20 & activ TLR5)/EBV-sp T cell	EBV undefined antigens, possibly LMP	A	0.84	#3 on antigen list, not included because small subset of patients, not
T2-204 EBV LMP autoTcell	EBV LMP	A	0.84	top viral antigen
T1-335 EBV LMP autoT cell + chemotherapy	EBV LMP1 & LMP2	A	0.84	
A009 LMP2	LMP2	A,B	0.84	
T1-541-2 WT1 T cell Tx (ovarian)	WT1	A	0.84	Include, #1 on antigen list
R001 WT1peptide in Montanide (AML)	WT1	A	0.84	
A007 WT1	WT1	A,B	0.84	
R029 NY-ESO-1 + Anti-CTLA-4	NY-ESO-1	A	0.84	Include, #10 on antigen list, related to oncogenicity, note restricted
A010 NY-ESO-1	NY-ESO-1	A,B	0.84	distribution
R013 Trivalent Ganglioside/KLH/Saponin (Sarcoma)	GD2+GD3+GM2	A	0.84	
A012 GD2	GD2	A,B	0.84	

T2-313 CMV autoTcell transCXCR2 (GBM)	CMV	A	0.84	
T2-314 CMV TC Tx Glioblastoma	CMV pp65	A	0.84	
T1-518 PSMA-VRP vaccine (prostate)	PSMA	A	0.84	
A011 PSMA	PSMA	A,B	0.84	
A013 CEA	CEA	A	0.84	
A015 PSA	PSA	A	0.84	Include, top tissue specific antigen, note limited distribution (#22 on Ag list)
R026 ID-vaccine + anti OX40 (lymphoma/leukemia)	Lymphoma idiotype (ID)	A	0.84	(#7 on antigen list, patient specific, antigens not defined)
A006 Idiotype	Idiotype	A,B	0.84	
T1-519 Adv-p53 + DC +paclitaxel (small cell lung)	p53	A	0.62	(#9 on antigen list, low therapeutic function score)
R003 gp96 Ig + HLA-A1 allo tumor (NSCLC)	Allo tumor antigen+gp96-Ig	A	0.55	
T1-534 HSPPC-96 vaccine (GBM)	HSPPC-96 (glioma)	A	0.55	
T2-100 Aldehyde dehydrogenase 1 Family member	Aldehyde dehydrogenase A1	A	0.53	
R027-1 Sox2 peptide in Montainide/Anti-CTLA-4	Sox2	A	0.52	
T1-520 ERG & SIM2 peptides + anti-Tim-1 (prostate)	Prostate Antigens (ERG & SIM2 peptides)	A	0.49	
T1-523 AFP DNA + Adv AFP (HCC)electroporation	AFP	A	0.45	
R011 Anti protein milk fat globule EGF-8	EGF-8	A	0.42	
R033 Survivin Adv + DC (NSCLC)	Survivin	A	0.42	
T1-533 Adv-Carbonic Anhydrase 9/GM-CSF + DC	Carbonic Anhydrase 9	A	0.35	
T1-541-1 MUC6/CA125 autoTcell (ovarian)	MUC16/CA125	A	0.14	
R036 BORIS DNA + IL21 (BrCa)	BORIS	A	0.10	
T1-336 Endothelin B Receptor inhibitor (ovarian)	Endothelin B Receptor inhibitor	A	0.06	

Target B: T Cell Therapy

Project	Candidate	Bucket	Rank	Comments
T1-334 MinorHA alloTcells CD3/CD28/IL2 expand (lymphoma)	MinorHA allo	B	1.00	Not comparable between institutions, requires HSCTransplant
T1-342 Unique/shared autoTIL Lymph/deplet IL2 melanoma	Autologous tumor shared antigens	B	1.00	Target is not defined
T1-343 MinorHA alloTh2 HSCT	Allogeneic hematologic malignanc shared antigens	B	1.00	Not comparable between institutions, requires HSCTransplant
A001 HPV E6/E7	HPV E6/E7	A,B	0.93	
A002 HER-2/neu	HER2	A,B	0.90	
A003 MAGE A3	MAGE A3	A	0.86	(#8 on antigen list)
T2-112 MelanA/MART1 recombTCR + PET reporter	MelanA/MART1	A,B	0.85	
A004 MelanA/MART1	MelanA/MART1	A,B	0.85	
T1-541-2 WT1 T cell Tx (ovarian)	WT1	A,B	0.84	Include, #1 on antigen list
A007 WT1	WT1	A,B	0.84	
T2-204 EBV LMP autoTcell	EBV LMP	B	0.84	#3 on antigen list, not included because small subset of patients, not top viral antigen
T1-335 EBV LMP autoT cell + chemotherapy	EBV LMP1 & LMP2	B	0.84	
A009 LMP2	LMP2	A,B	0.84	
A005 EGFRvIII protein	EGFRvIII protein	A,B	0.84	#5 on antigen list, but small subset of patients
T2-313 CMV autoTcell transCXCR2 (GBM)	CMV	B	0.84	
A006 Idiotype	Idiotype	A,B	0.84	
A008 MUC1	MUC1	A,B	0.84	Include, #2 on antigen list
A010 NY-ESO-1	NY-ESO-1	A,B	0.84	Include, #10 on antigen list, note restricted distribution
A011 PSMA	PSMA	A,B	0.84	
A012 GD2	GD2	A,B	0.84	
A013 CEA	CEA	A	0.84	
A014 gp100	gp100	A,B	0.84	
A015 PSA	PSA	A	0.84	Include, top tissue specific antigen, note limited distribution (#22 on Ag list)
T1-541-1 MUC6/CA125 autoTcell (ovarian)	MUC16/CA125	B	0.10	

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Target C: Antibody and T Body antigens

Project	Candidate	Bucket	Rank	Comments
T1-345-1 HER2 CAR (nasopharyn ca)	HER2	C	0.90	
T2-122 HER2 CD3xHER2 bispecific	HER2	C	0.90	
W-003 EGFR inhibitor (monoclonal Ab)	EGFR	C	0.84	
T1-345-2 EGFRvIII CAR (nasopharyn ca)	EGFRvIII	C	0.84	Small subset of patients
R019 GD2 Ab/IL2 fusion neuroblastoma	GD2	C	0.84	Too few patients for iterative testing of different concepts
T1-352-2 GD2 Ab + alloNK	GD2	C	0.84	
T1-340 GD2 CAR neuroblastoma	GD2	C	0.84	
R014 IL-7 & Treg depletion ACT	GD2	C	0.84	
T2-163 CEA Ab/IL2 fusion (+RIT)	CEA	C	0.84	Present in too many normal tissues
R012 CD20 IgE	CD20	C	0.77	
R031 CD20 Ab/IL2 (NHL)	CD20	C	0.77	
R023 CD19 CAR membraneIL7	CD19	C	0.77	
T2- 329 CD19 CAR transCD28 (lymphoma)	CD19	C	0.77	
R002 urokinPlasminogen actR	UrokinPlasminogen activation R	C	0.68	
R020 Radiation induced Ag MoAb	Radiation induced antigens	C	0.42	
T2_200 PAM4 triFAB/hapten pre_targeting	PAM4	C	0.23	
R022 LewisY CAR	LewisY	C	0.09	

IMA D: Adjuvants (vaccine adjuvants, dendritic cell activators or growth factors, T cell attracting chemokines)

Project	Candidate	Bucket	Rank	Comments
R015 GM-CSF optimal dose - DC levels (melanoma)	GM-CSF	D	1.00	Ready for randomized Phase III trial, include as formulation
M006	CpG	D, H	1.00	Include as Formulation (#6 on IRM priority list)
M015	Poly I:C	D	1.00	Include as Formulation (#15 on IRM priority list)
R035 HPV + topic TLR3/TLR8 agonists (polyI:C)	poly I:C	D	1.00	
M011	FLT3L	D	1.00	# 11 on IRM priority list
M014	MPL	D	1.00	Include as Formulation (#14 on IRM priority list)
M004 Anti-CD40	CD40	D, E, H	0.51	(#4 on IRM priority list)
T2-009 IL2 + antiCD40 (renal ca)	CD40	D, E, H	0.51	
T2-346 Plasmid DNA (IL12 or 15) electropor (melan)	IL12	D, H	0.51	(#3 on IRM priority list)
M003	IL12	D, H	0.51	
M013	CCL21 Adv	D	0.51	(#13 on IRM priority list, only T cell attracting cytokine)
M018	Resiquimod	D	0.51	#18 on IRM priority list
T2-282 Adv IFN-Beta (mesothelioma)	IFNb Adv	D	0.40	
T1-353-1 IFN-beta intra tumor-pleural (mesothelioma)	INFb	D	0.40	
M001	IL15	D, E, H	0.30	
R018 TLR8 agonist VTX-2337 subcut (BRCA)	TLR8 agonist	D	0.10	
T2-034 Anti-MARCO treated DC	Anti-MARCO	D	0.06	

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IMA E: T cell factors (T cell stimulators or T cell growth factors)

Project	Candidate	Bucket	Rank	Comments
R040 IL2 High-Dose - tumor markers (melanoma)	IL2	E	1.00	Broadly available, not appropriate for this application
R016 Shed BrCa Ag, IL2 GM liposomes	IL2	E	1.00	
T1-342 Unique/shared autoTIL Lymph/deplet IL2 melanoma	IL2	E	1.00	
R025 Melanoma peptide-pulsed IL-15DC for melanoma/IL7	IL7	E, H	1.00	(#4 on IRM priority list) (T-cell growth factor)
M005	IL7	E, H	1.00	
R036 BORIS DNA + IL21 (BrCa)	IL21	E	1.00	(T-cell growth factor)
M008	Anti-4-1BB (anti-CD137)	E, H	0.30	(#8 on IRM priority list) (T-cell stimulator)
T2-346 Plasmid DNA (IL12 or 15) electropor (melan)	IL15	D, E, H	0.30	(#1 on IRM priority list) (T-cell growth factor)
M001	IL15	D, E, H	0.30	
M012	Anti-GITR	E	0.19	(#12 on priority list)
R026 ID-vaccine + anti OX40 (lymphoma/leukemia)	OX40mAb	E	0.14	(#16 on priority list)
R034 gp100/OX40mAB/HD IL-2 (melanoma)	OX40mAb	E	0.14	
R030 OX40 Ab	OX40mAb	E	0.14	
M016	OX40mAb	E	0.14	

IMA F: Checkpoint inhibitors (Inhibitors of T cell checkpoint blockade)

Project	Candidate	Bucket	Rank	Comments
R029 NY-ESO-1 + Anti-CTLA-4	Anti-CTLA-4	F	1.00	
R027-1 Sox2 peptide in Montainide/Anti-CTLA-4	Anti-CTLA-4	F	1.00	
M002	Anti-PD1	F	0.51	(#2 on IRM priority list)
M017	Anti-B7-H4	F	0.19	#17 on priority list
R004 Anti-HER2 fused to LIGHT protein	LIGHT fusion	F	0.19	#19 on priority list
M019	LIGHT	F	0.19	
M020	Anti-LAG3	F	0.05	#20 on priority list

IMA G: Suppressive agents (Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes)

Project	Candidate	Bucket	Rank	Comments
T1-335 EBV LMP autoT cell + chemotherapy	Chemotherapy	G	1.00	Not recommended for initial TRO, but major question
T2-030 Allo tumor/GM + Cy + Doxorubicin (BrCa)	Chemotherapy (Cy and Dox)	G	1.00	Not recommended for initial TRO, but major question
R005 HDAC Inhibitors (cutaneous Tcell lympoma)	HDAC Inhibitors	G	0.51	Limited to lymphoma
T1-343 MinorHA alloTh2 HSCT	Cyclosporine	G	0.51	limited to Th2 type responses
R024 Anti-TGFb mAb (melanoma)	Anti-TGFb	G	0.30	Include, #9 on IRM priority list
M009	Anti-TGFb	G	0.30	
R017 INCB024360 to inhibit IDO1	IDO1 inhibitor	G	0.30	Include, category #7 on IRM priority list
M007 IDO inhibitor (1MT)	1MT	G	0.30	Include, #7 on IRM priority list
M010	Anti-IL10 Receptor	G	0.30	Include, #10 on IRM priority list
T2-008 WP1066 (STAT3 inhibitor)	STAT3 inhibitor	G	0.19	
T2-169 Mannose receptor scFv prvnt macropolariza	Mannose receptor scFv	G	0.04	

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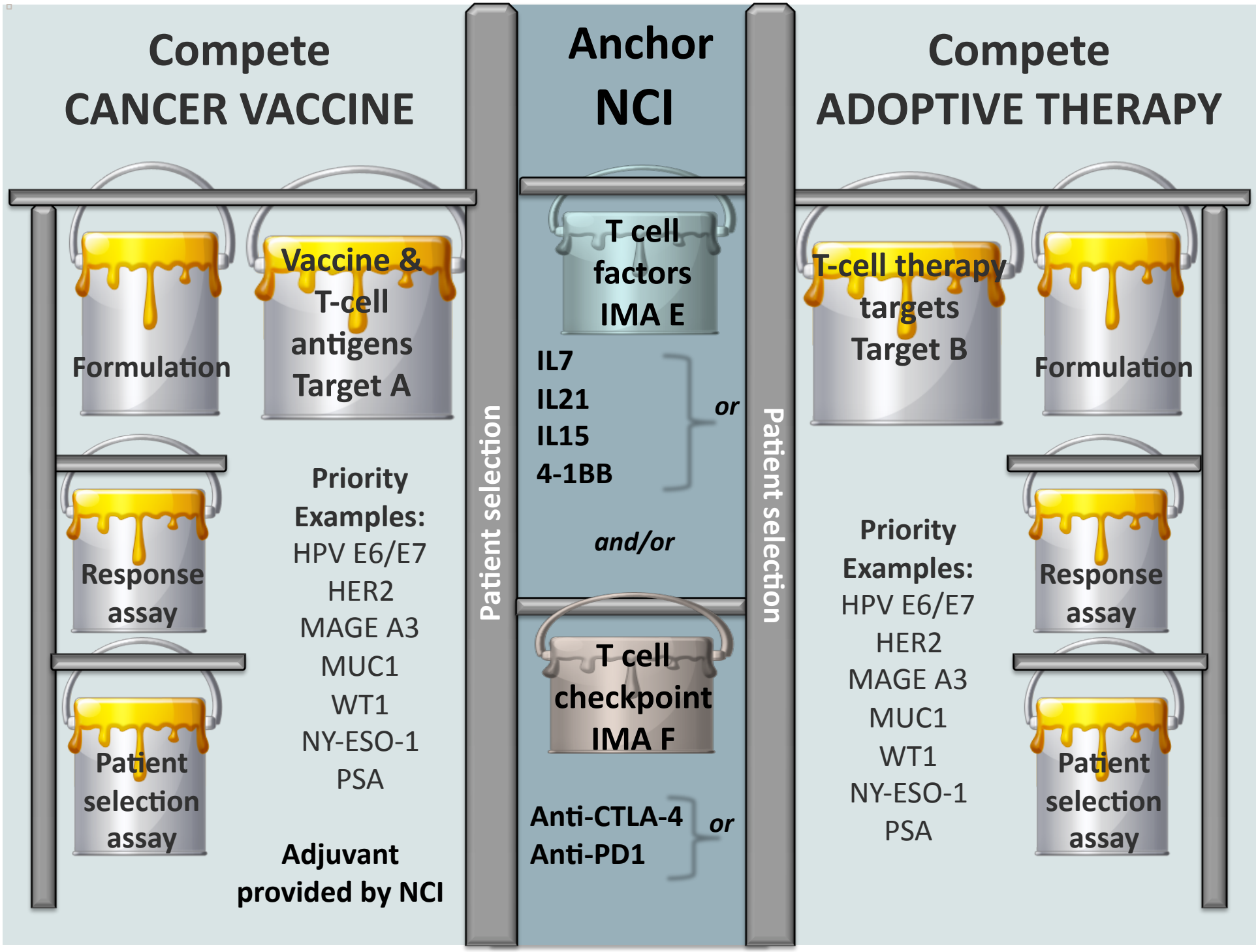
IMA H: ADCC (Agents to increase antibody dependent cellular cytotoxicity)

Project	Candidate	Bucket	Rank	
T2-122 HER2 CD3xHER2 bispecific	Bispecific Ab	H	1.00	Considered construct, not IRM
T1-345-1 HER2 CAR (nasopharyn ca)	Chimeric Antibody Receptor (CAR)	H	1.00	(CAR includes a prioritized ab to a prioritized ag)
M005	IL7	E, H	1.00	(#5 on IRM priority list)
M006	CpG	D, H	1.00	(#6 on IRM priority list)
R012 CD20 IgE	IgE antibody	H	0.80	Considered construct, not IRM
R031 CD20 Ab/IL2 (NHL)	Ab-IL2 fusion protein	H	0.80	Considered construct, not IRM
R023 CD19 CAR membraneIL7	CAR	H	0.68	(CAR includes a prioritized target and prioritized IMA)
T2- 329 CD19 CAR transCD28 (lymphoma)	CAR	H	0.65	(CAR includes a prioritized target)
R019 GD2 Ab/IL2 fusion neuroblastoma	Ab-IL2 fusion protein	H	0.55	Considered construct, not IRM
T1-352-2 GD2 Ab + alloNK	Ab + NK cells	H	0.55	patient specific
T1-340 GD2 CAR neuroblastoma	CAR	H	0.55	(CAR to antigen restricted to important pediatric disease)
R014 IL7 & Treg depletion ACT	CAR	H	0.55	CAR does not include a high priority ag or ab target
M004	Anti-CD40	D, E, H	0.51	(#4 on priority list)
M003	IL12	D, H	0.51	(#3 on priority list)
R002 urokinPlasminogen actR	Antigen specific Ab	H	0.42	(considered construct, not IRM)
R020 Radiation induced Ag MoAb	Antigen specific Ab	H	0.42	(Considered construct, not IRM)
W001 alpha-GalCer	alpha-GalCer	H	0.4	(suggested by WG)
M008	Anti-4-1BB (anti-CD137)	E, H	0.30	Include, #8 on IRM priority list
M001	IL15	D, E, H	0.3	
T2-200 PAM4 triFAB/hapten pre-targeting	Antigen specific Ab	H	0.23	(Considered construct, not IRM)
T2-163 CEA Ab/IL2 fusion (+RIT)	Ab-IL2 fusion protein	H	0.23	(Considered construct, not IRM)
T1-345-2 EGFRvIII CAR (nasopharyn ca)	CAR	H	0.23	(CAR does not include a high priority ag or ab target)
R022 LewisY CAR	CAR	H	0.09	(CAR does not include a high priority ag or ab target)
W002 beta-Glucan	beta-Glucan	H	0.08	(Suggested by Working Group - increases NK ADCC)


Compete
CANCER VACCINE
Formulation
Vaccine & T-cell antigens Target A
Response assay
Patient selection assay
Priority Examples:
HPV E6/E7
HER2
MAGE A3
MUC1
WT1
NY-ESO-1
PSA
Adjuvant provided by NCI
Patient selection
Anchor
NCI
T cell factors IMA E
IL7
IL21
IL15
4-1BB
or
and/or
T cell checkpoint IMA F
Anti-CTLA-4
Anti-PD1
or
Patient selection
Compete
ADOPTIVE THERAPY
T-cell therapy targets Target B
Formulation
Response assay
Patient selection assay
Priority Examples:
HPV E6/E7
HER2
MAGE A3
MUC1
WT1
NY-ESO-1
PSA