66th Meeting of the National Cancer Institute (NCI)
NCI Council of Research Advocates (NCRA)
National Institutes of Health (NIH)

Cancer Immunotherapies

Building 31C, 6th Floor, Conference Room 6
NIH Campus
Bethesda, Maryland
Tuesday, October 21, 2014

Members Present

Mr. Max Wallace, Chair
Mr. David Arons
Dr. Gregory J. Aune
Ms. Susan G. Braun
Ms. Andrea Stern Ferris
Ms. Joya Delgado Harris
Ms. Linda S. House
Mr. Jeffrey A. Kaufman
Ms. Shelley Fuld Nasso
Dr. Senaida Poole
Mr. Jon Retzlaff
Dr. Regina Vidaver

Speakers

Mr. Max Wallace, Chief Executive Officer, Accelerate Brain Cancer Cure; Chair, Informed Consent Working Group

Ms. Kelley Landy, Acting Director, Office of Advocacy Relations (OAR), Office of the Director (OD), NCI, NIH

Dr. Steven A. Rosenberg, Chief, Surgery Branch; Head, Tumor Immunology Section, Center for Cancer Research (CCR), NCI

Dr. Crystal Mackall, Chief, Pediatric Oncology Branch; Head, Immunology Section, CCR, NCI

Dr. Jeffrey Schlom, Chief, Laboratory of Tumor Immunology and Biology; Head, Immunotherapeutics Group, CCR, NCI

Dr. John T. Schiller, Deputy Chief, Laboratory of Cellular Oncology; Head, Neoplastic Disease Section, CCR, NCI

Dr. Harold E. Varmus, Director, NCI

Dr. Peter Bross, Medical Review Officer, Office of Cellular, Tissue, and Gene Therapies, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration (FDA)

Ms. Wendy K.D. Selig, President and Chief Executive Officer, Melanoma Research Alliance (MRA); Co-chair, Organizational Engagement Working Group

Ms. Joya Delgado Harris, Director, Office of Research Integration, American Cancer Society; Co-chair, Advocate Engagement Working Group

Mr. Jon Retzlaff, Managing Director, Science Policy and Government Affairs, American Association for Cancer Research (AACR); Co-chair, Organizational Engagement Working Group

Facilitator

Dr. Clifford Goodman, The Lewin Group

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Welcome and Opening Remarks
Mr. Max Wallace, Ms. Kelley Landy, and Dr. Clifford Goodman

- Ms. Landy and Mr. Wallace welcomed participants and discussed the meeting topic, cancer immunotherapies.

- The group, which was formerly known as the Director's Consumer Liaison Group (DCLG), now has a new name—the NCI Council of Research Advocates.

- Mr. Wallace introduced new NCRA members:
  - Dr. Poole is a program officer with the California Breast Cancer Research Program.
  - Ms. Nasso is chief executive officer of the National Coalition for Cancer Survivorship.
  - Dr. Aune, a pediatric oncologist, is an assistant professor of pediatrics at the University of Texas Health Science Center and a 23-year survivor of Hodgkin lymphoma.
  - Dr. Vidaver is a program manager for the Wisconsin Research and Education Network at the University of Wisconsin School of Medicine and Public Health.

- The February 2014 DCLG meeting focused on pediatric cancer, and it has led to further involvement of the NCRA with pediatric cancer advocates, including a White House discussion involving about 100 pediatric cancer advocates that was moderated by Mr. Wallace.

The Role of Adoptive T-Cell Therapy
Dr. Steven A. Rosenberg

- The three main approaches to cancer immunotherapy are nonspecific stimulation of immune reactions, active immunization to enhance anti-tumor reactions (cancer vaccines), and passive transfer of activated immune cells with anti-tumor activity or adoptive immunotherapy. Dr. Rosenberg focused on the third approach.

- Results of autologous tumor-infiltrating lymphocytes (TILs) to treat melanoma were first reported in 1988 and chimeric antigen receptors (CARs) for treating lymphoma in 2010.

- Cell transfer therapy offers the advantages of administering large numbers of highly selected cells with a high likelihood of tumor immune response and administering cells activated outside of the body to exhibit anti-tumor function.

- The TIL adoptive transfer technique begins with removing the tumor, followed by identifying the tiny proportion of lymphocytes that can recognize the tumor, expanding them, and re-infusing them into the same patient after first eliminating the body's own immune system.

- Among all cancers, melanoma appears to have a unique ability to produce an immune response. Studies have demonstrated that adoptive cell therapy can mediate complete, durable, and likely curative regressions of metastatic melanoma. The challenge is to increase the number of complete regressions.

- The hypothesis is that the ideal targets for cancer immunotherapy are the mutations in each cancer. Since each patient has unique mutations, this is the ultimate personalized therapy.

- Investigators are now trying to apply the process of adoptive T-cell therapy to common epithelial cancers.

- Identification and targeting of mutations unique to each cancer has the potential to improve therapy for melanoma and extend cell therapy to patients with common epithelial cancers.

- The search for drugs must be replaced by an effort to personalize treatment for each patient and to take advantage of a person with cancer's unique mutations.

- Cancer treatment today, categorized by organ of origin, is illogical. Mutations are not organ-specific. In the future, treatment will target metabolic pathways that straddle organ boundaries; in 10 years, treatments will be divided by approaches, not organs.

Immunotherapies in Childhood Cancer
Dr. Crystal Mackall

- Despite early successes, childhood cancer cure rates have plateaued, and toxicities from treatment are unacceptable. New approaches are needed.

- Unlike adult cancers, mutation rates are low in childhood cancers. Individualized therapy is not likely to be effective in childhood cancers.

- NCI is conducting a range of pediatric oncology trials that are studying consolidation immunotherapy, checkpoint inhibitors, adoptive therapy, and gene therapy. Progress is slow and incremental.

- A recent study of the treatment of childhood neuroblastoma with antibody-based immunotherapy documented an impressive survival advantage for children in the immunotherapy group.

- Researchers have been working for 30 years to optimize synthesized receptors to target cancer. The work on chimeric-type receptors has moved slowly, but incremental progress and understanding of T-cells have incentivized the work.

- Recently, investigators demonstrated that CD19-CAR T-cell therapy is feasible, safe, and mediates potent anti-leukemic activity in children and young adults with chemotherapy-resistant B-precursor acute lymphoblastic leukemia. Patients experienced a range of toxicities, but all toxicities were reversible.

- Novel toxicities have been observed. A child's immune system can become so supercharged through cytokine release syndrome (CRS) that it poses a threat to the child's life, with high fevers. This can be controlled with immunosuppression, and investigators are learning when and how to turn it off. Collaborators on the Pediatric Cancer Immunogenomics Dream Team have designed a grading system to diagnose and manage CRS with an algorithm for treatment.

- Researchers are seeking targets other than CD19. For example, CD22 is a promising target, with a trial scheduled to begin shortly. Other researchers are interested in using T-cell-expressing CARs in solid tumors. Another strategy is to mine the cell surface of pediatric solid tumors.

- This golden age for using immunotherapy to treat cancer is a payoff from more than 50 years of dedicated research into the inner workings of the human immune system and the relationship between the immune system and cancer. Success requires long-term commitment in basic science.

Therapeutic Cancer Vaccines
Dr. Jeffrey Schlom

- Vaccine therapy attempts to activate cytolytic T-cells in the body and does not require that the antigen be on the cell surface. A variety of platforms are being investigated in clinical trials.

- Unlike conventional cancer treatment, therapeutic vaccines induce a cellular memory response. With adequate immune system function, subsequent therapies can boost the treatment and extend overall survival.

- Therapeutic vaccines target the immune system, and their action is delayed. Antitumor effects occur within months or years, rather than weeks, and the initial response can be an increase in tumor size. Eventually, however, antitumor effects result in cytotoxic cell death and tumor shrinkage.

- The PROSTVAC vaccine against prostate cancer significantly extended overall survival in castrate-resistant metastatic prostate cancer patients.

- Earlier vaccination, when a patient has a smaller tumor burden, might have a greater impact on clinical outcomes.

- Multiple randomized multicenter trials have demonstrated that vaccine treatment induces no change in time to progression, but does lengthen survival.

- Vaccines to target brachyury and epithelial-mesenchymal transition, which can be implicated in cancer, are being designed.

- A phase I trial of a novel anti-programmed death ligand 1(PD-L1) checkpoint inhibitor has demonstrated tumor shrinkage or cessation of tumor growth in multiple types of cancer.

Cancer Immunoprevention Efforts
Dr. John T. Schiller

- Infection with the human papillomavirus (HPV) is common and associated with sexual activity. Lifetime incidence of genital HPV infection in the United States is greater than 80 percent. Most infections clear spontaneously, eliminating cancer risk for that infection.

- HPV causes 5 percent of all cancers worldwide, including cancers of the cervix, anus, vulva/vagina, penis, and oropharynx. In the United States, Pap screening has reduced the incidence of cervical cancer by approximately 80 percent, but the incidence of HPV-positive oropharynx cancer increased 225 percent between 1988 and 2004.

- Persistent infection with a high-risk strain of HPV, particularly HPV 16 or 18, is the single most important risk factor for progression to precancer and cancer. Current Pap screening is considered secondary prevention of cervical cancer. Prevention of HPV would be a primary prevention approach.

- Immunoprevention is based on antibody-mediated immunity and provides uncertain and delayed benefit to individuals. It can take decades for benefits to be realized.

- Two commercial vaccines against HPV are available: Gardasil from Merck and Cervarix from GlaxoSmithKline. The regimen for both vaccines is three intramuscular injections over 6 months. HPV vaccines have an excellent safety record.

- Despite the success of the HPV vaccine, uptake in the United States is only 33 percent for three doses. Countries that are doing well generally have school delivery rather than clinic delivery. Other reasons for poor uptake in the United States include lack of advocacy from primary care providers and mixed messaging and misinformation on safety and efficacy.

- The future of HPV vaccination could involve regimens that require less than three doses. In one large trial, a single dose was effective. This model could be an important advance in public health. A future vaccine also is likely to protect against infection by more types of HPV.

- Advocacy is needed to increase the uptake of current vaccines and to help plan a research agenda for future improvements.

NCI Director's Update
Dr. Harold Varmus

- The NIH budget has only gone down in recent years, Dr. Varmus said. NCI is protected for the next fiscal year, but 2016 could be worse, with the possibility of sequestration again looming.

- With the establishment of the National Clinical Trials Network, NCI has changed the structure of trials. With the new structure, trials will enroll fewer patients but will be conducted in a more efficient way, with incorporation of new technology and more trials that provide scientific value.

- NCI now has a dual presence in Frederick, Maryland, and will parallel research efforts of the Departments of Energy and Defense, with larger, more ambitious grants. One of the Frederick projects will focus on *RAS* genes. Another project will likely focus on imaging.

- NCI will also expand efforts in the area of global health.

- Retaining the vitality of the NIH Clinical Center is important for the intramural program but difficult in this time of flat budgets.

- Advocates' support of the NIH scholars program could help NCI retain senior investigators, who often leave the Institute because they can earn more at academic centers.

- As Dr. Varmus and colleagues described in a recent journal article[i], the hypercompetitive atmosphere that has resulted from flat budgets can deter young people from pursuing biomedical research careers.

- While funding is essential, the most treasured commodity in biomedical research is talent. It is important to attract the right people and the right ideas.

- Data about scientific communities are needed; for example, how many graduates move on to successful careers in science?

- Dr. Varmus would like to have 5-year plans that appropriators would consider when they make annual appropriations.

Regulatory Advances in Cancer Immunotherapies
Dr. Peter Bross

- Three FDA offices regulate oncology products, and the FDA is interested in working with the advocacy community.

- Personalized treatment approaches require specialized regulatory methods. For example, the purity of modified cellular products is a concern, animal models are often not relevant to assess toxicity and efficacy in humans, and assays that identify a specific population must be consistent in sensitivity and specificity.

- Using autologous products poses a unique set of regulatory challenges.

- To support licensure, endpoints for cancer immunotherapy must reflect clinical benefit. Overall survival is the preferred endpoint. Time to progression might not be sustained with cancer immunotherapies.

- FDA-expedited programs fall into four categories: fast track, accelerated approval, priority review, and breakthrough therapy.

- Another classification is expanded access. For expanded access, the potential benefits must justify potential risks and access should not interfere with clinical investigations to support marketing approval. Often manufacturers do not have the resources to support expanded access.

- Advocates must understand the complexities in regulating new and novel products.

Partnering With the Private Sector to Advance Cancer Immunotherapies
Ms. Wendy K.D. Selig

- The Melanoma Research Alliance (MRA) can provide a model for how advocates can be part of advancing cancer immunotherapies. MRA, along with a large number of partners, funds mainly translational research with a potential for near-term clinical impact. It facilitates collaboration and communication among academia, industry, and government and works to build relationships with key FDA leadership.

- Melanoma, an aggressive cancer with a poor prognosis in late stages, is an ideal case study for immunotherapy. It is at the crossroads of molecular biology and immunology.

- The past few years have marked a change for metastatic melanoma patients, with increasingly promising treatment possibilities. Findings in melanoma research are beginning to demonstrate that molecular targets and immunotherapy, which once seemed at odds, need to work together.

- The Immunology Dream Team, a 3-year project focused on the complex relationship between cancer and the immune system, is a collaboration among MRA, the Cancer Research Institute, and Stand Up To Cancer. Findings will lead to a better understanding of which patients will respond best to immunotherapy and how to use these techniques to treat melanoma.

- MRA works actively with the FDA to encourage access to therapies in late-stage development for more melanoma patients. MRA also frequently engages with pharmaceutical company leaders and the FDA to press for expanded access programs for anti-PD1 drugs and combination therapies based on promising data from clinical trials.

- The melanoma work raises the issue of targeting individual tumor types rather than having a site-specific focus. For example, the initial work on ipilimumab was in prostate cancer, and many melanoma patients are alive today because of that drug.

Discussion: How Advocates Can Advance Cancer Immunotherapy Research

- The themes that dominated the discussion were risk/benefit trade-offs, educating the public and primary care physicians, timing for treatment, need for culture change, support for alternative partnerships, legal ramifications, and identifying opportunities with other viruses.

- It takes time to see results, but the changes with immunotherapy are not marginal; people are being cured. Something that once seemed fringe is now very promising.

- There was a question about whether it might be possible to create a registry for bone marrow donation information that could be mined for use in personalized therapy.

- The role of health equity should be considered in the context of HPV vaccine uptake. It is important to address disparities and ensure access to treatment.

- More data about psychosocial support for cancer treatment would be useful.

- The NCRA should address the impact of early access to treatment and how early access can be handled responsibly.

- As suggested by Ms. Selig's presentation, the time has come for fearless creative convening. Alliances among nonprofits, industry, and regulators should be pursued.

- Advocates can educate, explain, and help the patient community understand the opportunities offered by immunotherapy—which might not be a cure, but which could turn cancer into a chronic manageable disease.

- There are good tools to educate patients about immunotherapy. Risks and benefits, which are changing as treatment advances, must be specified.

- Creative, early, and frequent engagement with the larger advocacy community could help with HPV vaccine uptake.

- Pediatric patients require special considerations, including access to technology in areas where children are not geographically close to academic centers and the problems related to developing treatments for a small number of patients.

- How is success in cancer research measured? What techniques are considered fringe today that could be accelerated so that it does not take 30 years to get results? How can advocates reinforce and incentivize the work? How can the field get the most out of each dollar that is spent?

- Young researchers are dropping out of science because of the competitive funding environment. What could be done to bring more talent to cancer research and support those thinking of leaving the field?

- Industry was mentioned in every presentation. Would it be in the purview of NCI to have top-echelon pharmaceutical personnel talk to the NCRA about business models?

- Industry focuses on making a profit, which is a challenge with individualized therapy. But companies are interested in furthering their work by engaging with advocate groups.

- It is important to educate the patient population about expectations regarding immunotherapy. Primary care providers, school nurses, and practitioners outside oncology specialties also require education. Questions about toxicities, patient selection, and adjuvant therapy remain.

- Both NCI and advocacy groups need to know about the long-term side effects of immunotherapy, as part of the risk/benefit package. It is important not to overpromise. A pre-step to educating the public might be a message to the research community to report out both the good news and the bad news.

- Culture change is necessary. One message is that immunotherapy works better when it is administered earlier. Just because it is a relatively new approach, it should not be reserved until late in the course of disease after other treatments have failed.

- The NCRA can formulate, structure, and make proposals around explorations of alternative partnerships between industry, NCI, and nonprofits.

- Moving into neoadjuvant or earlier settings could raise legal questions. Litigious situations caused by not following proper protocol should be avoided. How can advocates engage the legal community to make it easier for people to try innovative treatments earlier?

- Are there more aspects of vaccines that researchers should explore? For example, do the Centers for Disease Control and Prevention have data about viruses such as Epstein-Barr that are causative or related to development of certain cancers? Is there more vaccine development that could be stimulated?

Working Group Updates

Advocate Engagement

- The group will begin by considering and building on previous recommendations from the Advocates in Research Working Group. They are working with the NCI Office of Advocacy Relations to obtain further information on the current landscape of advocacy at NCI.

Organizational Engagement

- The group discussed a webinar to explore new ideas and a funders' meeting. It is considering new members to bring in and ways to educate the public and policymakers. The group will also provide a forum for the Institute to discuss promotion plans for the NCI Annual Plan and Budget (Professional Judgment or Bypass Budget), which will be presented on December 2, 2014, at a joint meeting of the National Cancer Advisory Board (NCAB) and the Board of Scientific Advisors (BSA).

Informed Consent

- The goal of this group is not to create a new template for informed consent but to consider new directions in research and how it can provide helpful information that can be included in existing informed consent documents. The group is beginning by digesting relevant information.

Open Discussion: Next Steps

- Upcoming meetings for the NCRA are scheduled for Thursday, February 5, 2015; Monday, June 22, 2015; and Monday, October 19, 2015.

- Suggestions for themes of upcoming meetings included the following:
  - NCI plans for umbrella trials
  - The bypass budget and the role for advocates
  - A module for distress screening

- Ms. Landy will work with NCRA members on ideas for upcoming meetings in an iterative process. She asked NCRA members to email any additional thoughts to her.

- Mr. Wallace asked members to think about whether they would prefer a single topic for a meeting or a series of modules, and to email him and Ms. Landy ideas for both, as well as suggestions for speakers.

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[i] Alberts, B., Kirschner, M. W., Tilghman, S., & Varmus, H. (2014b). Rescuing US biomedical research from its systemic flaws. *Proceedings of the National Academy of Sciences, 111*(16), 5773-5777. doi: 10.1073/pnas.1404402111