Final Meeting Summary of the 8th Cell Therapy/FDA Liaison Meeting
October 17, 2008
Bethesda, MD

Host organization

Participating organizations: AABB, AdvaMed, ASBMT, BIO, CAP, FACT, FDA, ISBTC, ISCT, PACT

Attendees were welcomed by the Co-chairs, Drs. Kurt Gunter and Lazlo Radvanyi; the meeting was called to order at 1:10pm.

COST RECOVERY

Presentation by Stephen Gottschalk

Stephen Gottschalk M.D., Baylor College of Medicine, presented his group's work on Epstein Barr Virus (EBV). Their main focus is on EBV-specific cytotoxic T Cells (EBV-CTLs). Data on EBV-CTL preparation and infusion were presented in the context of post-transplant lymphoproliferative disease (PTLD). The discussion included outcomes in 11/13 patients with active disease. Case studies, additional treatment outcomes, and genetic modification of CTLs (LMP-CTLs) were discussed. The facility requirements and costs of supplies, reagents and technical time related to the adoptive transfer of EBV- and LMP-specific CTLs were presented for discussion. Dr. Gottschalk concluded by sharing the funding sources for this phase I trial and said phase II studies are cost prohibitive unless the T cell production costs can be recovered. (See presentation 1). His group's manufacturing costs generally run $8-10,000 per patient, which only includes goods and services and is not fully burdened labor costs.

In the discussion the Stakeholders pointed out that advanced clinical studies were generally prohibitive for academic facilities and that the funding avenues available for larger pharmaceuticals studies are not available for cellular therapy products. Participants discussed CTEP and that the FDA Office of Orphan Products has a granting mechanism for drug development. NIAID might also present an option. http://www3.niaid.nih.gov/about/organization/dmid/

Presentation by James Yang

James Yang, M.D. Surgery Branch, NCI presented his group's work on systemic therapies for metastatic melanoma. Response rates are low with current therapies including high dose IL-2. This NCI approach includes surgically resecting tumor for the preparation of tumor-infiltrating lymphocytes (TILs). Recipients are immunosuppressed prior to receiving TILs. Several case studies and their respective responses were discussed, ending in a cumulative response rate of 49%. Subsequent approaches, including TBI were also reviewed with good outcomes. However, Dr. Yang concluded, that this therapy, is not available to anyone outside of NCI. The technique has been developed for four centers but investigators have not been able, thus far, to obtain coverage for the hospital associated costs. (See presentation 2).

During the discussion the Stakeholders asked if Dr Yang had approached industry as a potential founding source. Dr Yang responded that the corporate entities they had engaged expressed reservations about how they could earn a profit on such a therapy.

Presentation by Lazlo Radvanyi

Lazlo Radvanyi, PhD, MD Anderson Cancer Center, discussed the advantages of their adoptive T cell therapy protocol. Their approach is similar to NCI (See presentation 3). Major cost drivers at MD Anderson include the overhead for the GMP facility, quality control testing, and non-reimbursable apheresis costs. He estimates manufacturing costs at $21,000 per patient, exclusive of apheresis costs. Increased supply costs due to vendor changes were discussed as impacting the cost of cell product production. This model could also be applicable to other solid tumors such as ovarian cancer. Dr. Radvanyi explained that the R01 and even the generous funding from his own institution might not adequately cover production costs. On a direct cost analysis, media, cytokines such as IL-2, and other reagents pose the most significant expenditures. Facility requirements and required number of expansions to patient ratio were also reviewed. In conclusion the speaker summarized that the funds to support this production are covered by the institution, institutional discretionary funds and grants. Insurance reimbursement covers only the clinical standard of care and high dose IL-2 component. Apheresis for other related therapies is also expensive and lacking in coverage. He concluded by stating that production costs for such therapies limit the number of patients with access to them and also hinders technology development to improving the therapy. (See presentation 4).

Presentation by Carl June

Carl June, MD, Abramson Center at University of Pennsylvania, presented their approach to adoptive T cell therapy for progressive multifocal leukoencephalopathy (PML). They use CD3/CD28 activated T cells. Since T cell therapy is effective in the allogeneic setting, they are working on achieving similar success in the autologous setting. Dr. June reviewed their approach to adoptive T cell therapy and clinical scale expansion which costs in excess of $15,000 per patient. Culture medium is the largest driver of their manufacturing costs. He then reviewed the success in the multiple myeloma setting and

phase I/II trials. He shared results of the first successful randomized multicenter adoptive immunotherapy trial – results included accelerated immunological recovery. Other studies and related case studies were also presented for discussion. Dr. June concluded that adoptive transfer of autologous co stimulation leads to long term immune reconstitution. Clinical trial costs cannot be supported with grants alone and PML is an orphan disease, nearly uniformly fatal in the non-HIV setting. There is a lack of biotechnology industry support for such technology and pharma/biotech companies have indicated they will require randomized Phase II efficacy data, which will be extremely expensive to obtain. (See presentation 5).

Presentation by Thomas Finn

Thomas Finn, Ph.D, OCTGT, FDA presented a review of cost recovery regulations and procedures for cell and gene therapy products and medical devices. He opened with a discussion of differences between IDEs (for devices) and INDs (for cell therapy products). With IDE rules, the manufacturer must only notify FDA of its intent to charge for cost recovery. With INDs, the sponsor must request cost recovery and this must be approved prior to charging for the therapy. He discussed the current rule [21 CFR 312.7(d)] and the proposed rule [21 CFR 312.8] which has not been finalized. The proposed rule merely provides additional clarification and does not significantly change the current rule. The sponsor must justify why the requested charges are not just part of the normal cost of doing business. The costs recovered must be uniquely and directly attributable to the product being manufactured. It is limited to manufacturing costs and does not include clinical trial related expenses. Total development costs and costs to build a new facility that would be used for a licensed product are not covered under the regulation. Early stage research and development and preclinical studies are also not covered. In cases where there is significant inequality in manufacturing costs from patient to patient (for example, due to administration of placebo versus investigational product), it is not appropriate to average costs, because patients cannot be charged for products they don't receive. Costs which could be included/covered and required supporting information were presented as well as the mechanism for requesting cost recovery associated with an IND and timelines. Cost recovery is approved for a one year period but is renewable. Dr. Finn provided examples of direct costs (allowable) and indirect costs (not allowable) as well as the agency's intent to modify regulations covering expanded access. He summarized by reviewing the intent of cost recovery and provided additional resources for further information. (See presentation 5).

In discussion it was pointed out that cost recovery did not necessarily solve a cell therapy manufacturer's problems. Even if a manufacturer were able to charge to recover costs, the manufacturer still has to find a third party payer willing to reimburse. The Stakeholders explained that larger institutions might have the ability to absorb the costs but not all do, and that facilities might have discretionary funds to support clinical trials but not for production costs. FDA asked whether turning away patients who cannot afford to pay for the therapy might somehow bias or skew the data and asked how this is handled. The skewed data could be an issue because the patients that are treated are likely healthier because they have some form of insurance coverage. The participants

agreed it was a potential issue with no clear resolution. Subsequent discussion included the potential for unblinding in the situation where patients might see their bill and whether or not it included production costs.

SAFETY TESTING OF EMBRYONIC STEM CELL LINES

Presentation by Marie Csete

Marie Csete, MD, Ph.D, CSO, California Institute for Regenerative Medicine (CIRM) presented their view on safety assessment and progress with human embryonic stem cell (hESC)-derived cellular therapies. She discussed the major concerns shared at the April 2008 FDA Cellular, Tissue and Gene Therapies Advisory Committee and the CIRM approach to this issue. She reviewed the status of gene therapy trials and unintended consequences. The implications of donor transmitted diseases and potential xenogeneic contaminants were described. The allogeneic immune response was discussed and the speaker highlighted the differences among cell types. Graft survival is a key variable that must be assessed accurately. It was noted that there are significant differences between animal models and human reactions. The central nervous system (CNS) presents unique opportunities but the optimal form of patient monitoring is biopsy, which presents problems. Various approaches were reviewed and CIRM will host an immunology workshop is February 2009 to discuss. The major concern from the April FDA meeting was the development of teratomas. However, subtle chromosomal abnormalities may also present challenges. Other technical hurdles, include stem cell migration, scale up and poor animal models were discussed. Dr. Csete presented a model trial design for phase I/II. She shared the disease team planning awards (by disease) and the CIRM considerations for evaluation in the risk to safety continuum. Lessons learned from failed muscular dystrophy trials were discussed. She concluded by sharing that CIRM had already funded $1 billion so far but that terminal differentiation from hESC is more difficult than anticipated, and that a global or team effort is needed to be successful. The presentation then focused on the differences in adult stem cells and hESCs. (See presentation #6).

During the discussion period, FDA asked about the rationale for the decision regarding which patients are treated first. The presenter explained that animal models were the key, and that large animal models are desperately needed. The Stakeholders commented that source material is not discussed very often. How important is it to prospectively derive new cell lines under GMP conditions versus qualifying those we have? The presenter replied that cell lines can be re-derived under GMP conditions but that some master cell banks were derived before the ethical issues were addressed. She expressed that the medical history of the donor should be available and the donors should be contactable in the future.

Presentation by Mahendra Rao

Mahendra Rao, MD, Ph.D, Invitrogen discussed issues to consider for safety testing of hESCs. His presentation focused on outlining the important regulatory issues that may affect moving hESCs forward into the clinic. Production issues, considerations for animal studies and testing panels for safety were discussed. These three models for therapeutic approaches were discussed in detail. He stressed that the final products must be qualified by appropriate testing. Animal studies must address immune system issues and safety issues must include issues relating to consent. Karyotype stability presents a unique challenge as some information may not be meaningful due to random translocations in the normal population. There is little consensus in the community as to the significance of karyotypic changes in ES derived lines. The problem of contaminated cells is compounded because there is not a mechanism of action for how the cells work or the mechanism varies among cell lines. This situation is similar to vaccines where one has a product but does not know all of the details relating to the active ingredient. Assays for teratoma formation present many variables and the assay can be difficult to perform, control and interpret. Ectopic distribution is another important issue. There is a need to standardize tumorigenicity assays including length of follow up. The speaker then discussed two more problematic areas: a) epigenetic changes and their effects; and b) potency assays. Each was discussed in detail with its unique challenges including the lack of a simple predictive in vitro assay and equivalence data.. He also cautioned that some entities might be tempted to select a cell type based on the regulatory pathway rather than the optimal or preferred cell type. (See presentation #7).

FUTURE MEETING AND CONCLUSION

Dr. Gunter then began the meeting conclusion with a call for suggestions for future agenda items. Suggestions included the following:

1. Pre-licensing inspection of umbilical cord blood establishments.
2. Private (family) cord blood banking and crossing over of inventories for public and research use
3. Discussion of the term “homologous use”, as used to define FDA Part 351 vs 361 regulation of cell therapy products, as well as the international implications.

The meeting was adjourned at 4:45pm with the next meeting to occur in 2009.