Food and Drug Administration
Center for Biologics Evaluation and Research
Cellular, Tissue and Gene Therapies Advisory Committee

SUMMARY MINUTES
Meeting #47, May 14-15, 2009
Hilton Hotel, Gaithersburg, MD

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Guest Speakers
Ira J. Fox, M.D.
Bernhard Hering, M.D.
Gunnar Knutsen, M.D., Ph.D.
John Miller, M.D., Ph.D.
John R. Papp, Ph.D.
Scheffer C.G. Tseng, M.D., Ph.D.
Kenneth Zaslav, M.D.

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Danielle Cubbage

Designated Federal Officer
Gail Dapolito

* Consumer Representative
** Industry Representative

The summary minutes for the May 14-15, 2009 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee were approved on September 18, 2009.

I certify that I attended the May 14-15,2009 meeting of the Cellular, Tissue and Gene Therapies Advisory Committee and that this report accurately reflects what transpired.

//s//
Gail Dapolito, Designated Federal Officer

//s//
Walter Urba, M.D., Ph.D., Chair

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The Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) met in open session on May 14-15, 2009 at the Hilton Hotel, Gaithersburg, MD.

On May 14, the Chair called the meeting to order and introduced the members and consultants. The Designated Federal Officer read the conflict of interest statement into the public record. This statement identified members and consultants of the Committee with an appearance of a financial conflict of interest, for whom FDA issued waivers to participate. Copies of the waivers are available from the FDA Freedom of Information Office.

In open session the Committee discussed the following topics: 1) the potential for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) transmission by human cells, tissues, and cellular and tissue-based products (HCT/Ps) that are recovered from the reproductive system, gestational tissues, or other sources and, 2) animal models for porcine xenotransplantation products intended to treat Type 1 diabetes or acute liver failure.

Topic I: The Potential for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) Transmission by Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps) that are Recovered from the Reproductive System, Gestational Tissues, or Other Sources

The FDA described the goals and focus of this topic; provided background information on relevant communicable disease agents or diseases (RCDADs) including current requirements for donor screening and testing and presented a literature review on animal models of CT and NG infections, and reports of human CT and NG infections of HCT/Ps recovered from the reproductive system, gestational tissues or other sources. Following the FDA presentations, Guest Speakers presented on 1) the infectivity of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* and the epidemiology of these bacteria in the United States (John Papp, CDC); 2) the current scope of utilization of human amnion (Scheffer C. G. Tseng, Bio-Tissue, Inc) and; 3) the current screening and testing practices for donors of cord blood (John Miller, National Marrow Donor Program).

The Open Public Hearing followed the presentations. There were no requests to address the Committee during the Open Public Hearing.

Following the Open Public Hearing the Committee addressed the following discussion questions:

Question 1: Please comment on the potential for transmission of *C. trachomatis* and *N. gonorrhoeae* by HCT/Ps that are recovered from the reproductive system or gestational tissues, for example: amniotic membrane and placenta, or cells recovered from these tissues; cells recovered from menstrual blood; foreskin; placental/umbilical cord blood derived cell products.

- The Committee discussed issues related to cord blood procedures and whether cells may become contaminated during harvesting and processing and whether CT and NG can survive freeze-thaw cycle in the medium that is used to store cord blood cells.

The Committee agreed that infection of cord blood samples could likely occur during harvesting. It was suggested that a simple laboratory experiment could provide data on survival during freezing and thawing.

- The Committee discussed the risk of CT infections in cord blood and the availability of treatment options. The Committee estimated that the risk for CT infections in cord blood would be approximately 1 in 100,000 samples and pointed out that CT is an easily treatable organism with a single course of azithromycin, while NG can only be treated with third generation cephalosporins and often goes into persistence.

- The Committee agreed that the potential for transmission exists if women were infected with either organism. There was no consensus among the Committee regarding a requirement for CT and NG testing of cord blood donors/products. Some Committee members stated testing should not be required as the risk of false-positive results when using DNA amplification test for CT and NG would outweigh the benefit of testing. Additionally, the available literature does not suggest that the likelihood of transmission is high via this HCT/Ps. It was stated that the majority of the presented papers on transmission of CT and NG via HCT/Ps were poorly written, with poor methodology, and that many were not published in well known peer reviewed journals. Neonatal infections of CT (and likely also NG) are relatively rare as a result of improved screening of women during pregnancy for CT and NG. Much of the Committee's discussion related to screening and testing of donors was predicated on an assumption that women delivering babies in the US are unlikely to be infected with CT or NG, however this assumption has not been proven. It is likely that only 40-50% of women in the United States are actually tested during pregnancy according to the CDC recommendations.

  Some members stated testing requirements of donors would be reasonable because it is not known if the risk of transmission is zero and there is an expectation that the pool of donors will expand in the future. Testing of cord blood products is also reasonable as infections may occur during processing of the tissues. Additionally, in the absence of reported transmission via these HCT/Ps, it is difficult to conclude whether or not to require screening and testing for CT and NG.

  Other members pointed out that whether there should be a requirement for donor testing should depend on which particular tissues are donated. For example, if one product goes into only one patient, the risk is much lower than if the cells are harvested, expanded, and used to treat many patients (all of the cells originating from only one donor). It was suggested that screening (vs. screening and testing) would be sufficient in most cases; with weighing out the risk-benefit ratio before mandating any screening and testing. Several committee members agreed that screening is sufficient at this time. The major screening criteria agreed upon by the Committee was a requirement for "prenatal care." There was a recommendation that pregnant women who do not receive prenatal care be excluded from donations. One member stated that no premature rupture of the membranes, term delivery, no chorioamnionitis and no sepsis should be mandated for donors.

The Committee also discussed the cost of testing and stated that the cost for tests for uro-genital infections in public institutions is approximately $25 per test (combined NG and CT testing), and in the private institutions between $80 and $90 per test.

- Several times during the discussion the question of the lack of epidemiological data outside of the U.S. arose. The Committee was concerned whether there should be different criteria for the donors of HCT/Ps outside of the U.S. It was pointed out that the incidence of CT infections in Europe and other industrialized countries is lower than in the U.S. However, members were concerned about donors from South America and Asia, as the incidence of CT and NG may be high in these regions.

  One member implied that as most donors of amniotic membrane are from the U.S., these donors may not have to be tested. However, donors of cord blood should be tested, since there is much cord blood imported from foreign countries. There was consensus from the Committee that donors of menstrual blood should be tested for CT and NG.

Question 2: Please comment on whether additional HCT/Ps should be considered for potential risk for transmission of *C. trachomatis* and *N. gonorrhoeae* (e.g., cells recovered from bladder and kidneys)

- There was no consensus among the Committee whether additional HCT/Ps should be considered for potential risk and testing. Some members stated screening of donors of bladder and kidney cells would be sufficient. It was pointed out that CT and NG do not colonize the upper urinary tract,. Other members felt that testing of the donors of any fluids that go through the genitourinary tract should be required. HCT/Ps from the upper genital tract could get contaminated during harvesting if the donor is infected and asymptomatic male carriers might not be aware of infection during a screening interview.

Following this discussion, the session for Topic I was adjourned.

Topic II: Animal Models for Porcine Xenotransplantation Products Intended to Treat Type 1 Diabetes or Acute Liver Failure

FDA's decision to allow the initiation of a first-in-human clinical trial using a xenotransplantation product is based on careful examination of all available preclinical data, as well as the clinical indication and review of the proposed clinical trial protocol. This overall appraisal is greatly dependent on the selection of appropriate animal models that can be employed to evaluate safety and demonstrate substantial pharmacodynamic activity of the xenotransplantation product.

The FDA speaker provided background information and described the goals and focus of the session. The Open Public Hearing followed the FDA presentation. There were no requests to address the Committee during the Open Public Hearing.

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Guest speakers presented considerations for animal models of acute liver failure (Dr. I. Fox; University of Pittsburgh) and of type 1 diabetes (Dr. B. Hering; University of Minnesota) for the evaluation of the safety and efficacy of porcine cells/tissues to treat patients with these diseases.

Following the guest speaker presentations, the Committee addressed the following discussion questions:

Animal Models of Acute Liver Failure (ALF)

1. ***Please discuss the limitations and capabilities of available animal models of ALF to assess the safety and clinical activity of bioartificial liver assist devices containing porcine cells or tissues as a bridge to spontaneous recovery or liver transplantation. Please consider the following in the discussion:***

    a. ***The ability of the animals to model the clinical manifestations and laboratory abnormalities of ALF in humans.***

    b. ***Treatment duration and the ability to repeat the treatment, as would likely be required by the clinical condition of ALF patients.***

    c. ***Study endpoints – the changes in laboratory values and clinical responses in test animals that would be considered clinically meaningful and predictive of potential clinical benefit in patients***

The Committee discussion focused on the utility of existing ALF animal models to determine the potential risks of extracorporeal blood circulation devices (Bioartificial Liver [BAL] assist system) containing porcine hepatocytes or porcine hepatic tissue when used to treat humans presenting with acute liver failure. The above-listed considerations were used to guide the discussion. General discussion centered on the inability, thus far, of results from existing ALF animal models to translate into clinical success. The following points by the Committee are highlighted:

- There was no Committee consensus that there is a need for preclinical testing of the BAL system prior to initiation of a clinical trial Some Committee members noted that a conservative, well-designed trial in a predetermined patient population should be allowed to proceed. This point of view is based on the premises that the patient population is desperately ill and that there are no established or theoretical safety concerns. However, given the a priori assumption of risk inherent in xenogeneic products, it is not clear that this perspective is applicable to these products.

- Other Committee members expressed reservations regarding the use of this type of xenotransplantation product in humans without adequate testing first in an animal model, stating that the use of a xenotransplantation product is not without risk, thus an understanding of the biological actions of the xenotransplantation product in animals that model the clinical presentation of ALF to the extent possible will potentially help to mitigate/better define some of these risks.

- However, in general the Committee agreed that if testing of the product – the extracorporeal liver assist system containing porcine cells – needed to be conducted, the ALF model should be a large animal.

- Extra-hepatic toxicities, such as hypoglycemia and renal failure, are manifested in many ALF animal models; these toxicities may not reflect the human condition. These toxicities may impact overall survival or limit the ability of the model to display a relevant treatment effect that successfully translates to patient outcome.

- The pathological conditions of concern in patients with ALF include: limited survival duration, coagulopathy, hepatic encephalopathy, significantly elevated intracranial pressure (ICP), and hyperammonemia. Other pathologies, such as acidosis, can generally be treated, thus are not of notable concern. The Committee consensus as to the top three abnormal conditions that contribute to the death of the ALF patient were elevated ICP, ammonia levels, and prothrombin times (PT). The ideal animal model of ALF should thus at least reflect these three pathologies.

- Of these three endpoints, discussion regarding monitoring of the ICP was more widely discussed. Although the Committee agreed that this parameter should be monitored, the technology to enable continuous or even repeated monitoring of ICP in the animal does not appear to have been mastered. Several Committee members noted that such monitoring could possibly be achieved for a limited duration in a large animal through the use of a telemetry device implanted in the brain.

- Determination of survival is an important endpoint; however, short study durations (hours to days) are often seen in studies using ALF animal models, depending on the severity of the model and the fact that the animal needs to be anesthetized to test the BAL system. Thus this testing scenario does not reflect the clinical situation, as ALF patients generally present in less extreme condition and can usually survive for days to weeks under intensive medical care. These short windows will limit an adequate assessment of survival and will not allow for the ability to administer multiple BAL treatments in the animal model.

- Although encephalopathy/coma is a key pathology of ALF patients, this condition/endpoint cannot be assessed because the available models anesthetize the animals for the study duration until termination.

- Some Committee members agreed that the nonhuman primate model of ALF, as presented by Dr. Fox's work, may be appropriate as a model, as long as the model recapitulated the three agreed-upon pathological endpoints.

- The use of *in vitro* studies to supplement the preclinical data via characterization of porcine cell viability and function was also briefly discussed.

Animal Models of Type 1 Diabetes (T1D)

2. ***Porcine islet products are currently under development to treat Type 1 diabetics who are chronically metabolically unstable. Please discuss the limitations and capabilities of available animal models of Type 1 diabetes that can be used to assess the safety and clinical activity of porcine islet cell transplantation. Please consider the following in the discussion:***

    a. ***The ability of the animals to model the immunological and metabolic manifestations of Type 1 diabetic patients.***

    b. ***Treatment duration and the ability to re-transplant, as would likely be required by the chronic clinical condition of Type 1 diabetic patients.***

    c. ***Study endpoints – the changes in laboratory values and clinical responses in animals that would be considered clinically meaningful in diabetic patients.***

    d. ***The intended clinical immunosuppression regimen, as applicable.***

The Committee did not question the use of the nonhuman primate (NHP) as a model of T1D, as presented by Dr. Hering. The Committee focused its discussion on the very detailed pivotal study design using this model that was presented by Dr. Hering. Dr. Hering's major points regarding the necessity for use of the model are in accord with the current position of the International Xenotransplantation Association (IXA). For the details of this study design, the reader is referred to the slides presented by Dr. Hering. The above-listed considerations were used to guide the discussion. The following points of discussion by the Committee are highlighted:

- The Committee understood the limitations of the small and large animal models and was in general agreement with: 1) the rationale for the pig-to-NHP model; 2) the modality of diabetes induction (primarily streptozotocin-induced) without causing other nontarget toxicities (i.e., renal); 3) the study duration needed to confirm efficacy[1] and assess safety; 4) the need for islet re-transplantation and subsequent monitoring for sensitization (humoral and cellular); and the various study endpoints specified in Dr. Hering's talk (i.e., C-peptide levels, HbA1c levels, blood glucose levels, insulin independence).

- Measurement of insulin dependence and insulin doses, glucose levels, C-peptide levels, HbA1c, mixed meal tests, etc. (per the study design presented by Dr. Hering) are good surrogates to address secondary pathologies, such as hypoglycemic unawareness and microvascular disease. However, there is no animal model of hypoglycemic unawareness.

[1] Proportion of recipients maintaining fasting blood glucose levels of <150 mg/dl and non-fasting levels of <200 mg/dl at 6 months in the absence of exogenous insulin or in the presence of greatly reduced insulin requirements. It is suggested that this endpoint be met in ≥5 of 8 consecutive NHPs; follow-up should be for a period of ≥6 months after the initial transplant in all cases and ideally for 12 months in at least 1 or 2 successful cases.

- Regarding attainment of efficacy: NHPs secrete 10-fold more C-peptide than pigs, while humans only secrete 2-fold more C-peptide compared to pigs. Therefore control of normoglycemia in the NHPs may prove more difficult compared to humans.

- If used, immunosuppressant regimens in NHPs are a major source of toxicity and the ability to maintain immunosuppressed NHPs in a healthy state long-term is a major challenge. The use of agents that are not licensed can be an added complication. This issue of immune rejection may be less of an issue in the future if cells from genetically engineered pigs are used. In addition, incremental approaches to the use of tolerance therapies, novel cell encapsulation modalities, humanized antibodies, immune receptor-specific fusion proteins, and a bioartificial pancreas are possible future tools for use in animal models.

- Porcine C-peptide is difficult to measure when encapsulated islets are transplanted without concurrent immunosuppression. There is speculation that there is an antibody response that prohibits an accurate measurement of C-peptide; insulin may be a more appropriate endpoint measure in certain circumstances, such as transplant of encapsulated islets. More investigation in this area will be helpful.

- The potential for xenotransplantation after allotransplantation should be considered since alloreactivity does not appear to sensitize the immunosuppressed individual to the xenogeneic islets.

- The need for imaging modalities to measure islet cell mass *in vivo* both in animals and in the patients was recognized.

- Preclinical studies should take into account that more than one islet source may need to be considered for an individual patient over the life of their disease.

- The Committee understood that: 1) the pig-to-NHP model pivotal study design as presented by Dr. Hering reflects the current consensus of an international group of experts in this field and 2) this study design will be published under the auspices of the IXA.

Following this discussion the meeting was adjourned and reconvened on May 15.

On May 15, the Chair called the meeting to order and introduced the members and consultants. The Designated Federal Officer read the conflict of interest statement into the public record. Following the introductions, FDA recognized the service of retiring members of the Committee with a short ceremony to present plaques and letters for appreciation from the Agency.

In open session, the Committee 1) heard updates on guidance documents from the Office of Cellular, Tissue and Gene Therapies, Center for Biologics Evaluation and Research, and the Center for Veterinary Medicine and 2) discussed clinical issues related to the FDA draft guidance "Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage."

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Committee Updates

The Committee received information on 1) the process for development of FDA guidances and 2) several recently published guidances developed in the Office of Cellular, Tissue and Gene Therapies. The new guidances included 1) manufacturing guidances for cell and gene therapy investigational new drug applications; 2) human tissue practices guidance and 3) guidance for manufacturing of human cells, tissues and cellular and tissue based products. In addition information on several guidances, developed within the last year, in conjunction with other Offices and Centers in FDA was provided.

Topic III: Clinical Issues Related to the FDA Draft Guidance "Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage"

The FDA speaker provided background information on the draft Guidance and described the goals and focus of the session. Guest Speakers provided information on 1) treatment options for articular cartilage repair (Kenneth Zaslav, Advanced Orthopaedic Centers) and; 2) issues concerning clinical outcomes in long-term trials of cellular therapies for cartilage repair (Gunnar Knutsen, University of Tromsø, Norway).

During the Open Public Hearing, the Committee heard comments from one firm (Genzyme) related to the clinical section of the draft Guidance.

Following the Open Public Hearing the Committee addressed the following discussion questions:

1. At the 38th CTGTAC meeting, the Panel stated that improvements in pain and function are the most important clinical benefits but that these outcome measures can be assessed reliably only by use of a scale that dissociates pain from function. FDA incorporated this advice into the draft guidance, which states that an adequately designed clinical trial of a product for knee cartilage repair should ". . . identify changes in pain and/or physical functioning as the primary endpoint for confirmatory clinical studies."

Some comments received on the guidance have suggested additional clarity regarding the primary endpoints would be beneficial.

Please discuss whether there is a single validated instrument or summary measure that is able to measure changes in both pain and function and takes the effect of activity on these into account, or whether there are specific sub-domains of the instruments referred to in the guidance or other instruments that can be used as a primary or co-primary endpoint.

- The Committee agreed that improvement in both joint pain and joint function should be considered as the outcomes that best capture a clinically meaningful benefit. Trials of biologics that are intended for the repair of cartilage defects should therefore be designed with a primary efficacy endpoint that evaluates the change in both pain and function. However, the committee did not believe that there is a single validated instrument that can be used to measure both joint pain and function. Separate validated instruments are recommended for the use of measurement of both joint pain and function.

2. Regarding overall trial design: The suitability of non-inferiority design for trials of cartilage repair products was raised in a number of the public comments. The 38th CTGTAC Meeting was not charged directly to address this question, and FDA has found it challenging to determine, with reliability, a quantitative treatment effect for comparators (such as microfracture), which is a requisite for designing a non-inferiority trial. We believe that, based upon current clinical knowledge, a treatment effect size for an available therapy that can be used as an active concurrent control has not been established with precision sufficient to employ a non-inferiority trial design.

Please comment on superiority and non-inferiority trial designs for pivotal studies of cartilage repair products.

- Some panel members expressed concern that although microfracture surgery has been employed as a comparator in many studies of biologics used to repair knee cartilage defects, the acceptability of microfracture as a control procedure is questionable (e.g., no consistent treatment effect size has been determined for microfracture and microfracture outcomes are highly dependent on the age of the patient). Some panel members noted that incorporation of a non-treatment arm into the clinical trial may provide useful data, but there may be ethical concerns. Most of the members believe that superiority trials are necessary to evaluate the efficacy of these products

3. The draft guidance states that MRI and histological assessments of the repaired cartilage should be considered secondary efficacy endpoints. Some of the public comments to the draft guidance propose that MRI and histological assessments be utilized as primary efficacy endpoints.

Please comment on whether there is substantial new information that should be considered with respect to revision of the recommendation in the draft guidance that MRI and histological assessments be considered secondary efficacy endpoints

- Overall the comments emphasized that histological and MRI assessments can be appropriate as secondary outcomes, as these analyses may be capable of providing added insight into the mechanism of repair. However, the fields have not progressed to the point that MRI- or histological-based analyses should be considered as acceptable primary outcomes for trials of biologics used to repair cartilage defects.

Following this discussion the meeting was adjourned on May 15.

For more detailed information concerning this session presentation and committee discussion summarized above, please refer to the meeting transcripts available on the FDA website at http://www.fda.gov/AdvisoryCommittees/default.htm.