

# **REPORT TO CONGRESS**

## **The Appropriateness of the Inclusion of Adult Stem Cells and Birthing Tissues as New Types of Therapies in the C.W. Bill Young Cell Transplantation Program**

**Required by Section 2(c) of the Stem Cell Therapeutic  
and Research Reauthorization Act of 2015  
(Public Law 114-104)**

**Department of Health and Human Services**

**August 2019**



## Executive Summary

The Stem Cell Therapeutic and Research Reauthorization Act of 2015 (Public Law 114-104, Section 2(c)) requires that a report be provided to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives by the Secretary of Health and Human Services, working with others, regarding the appropriateness of the inclusion in the C.W. Bill Young Cell Transplantation Program (CWBYCTP) of adult stem cells and birthing tissues as new types of therapies for patients. For the purposes of this report, adult stem cells and birthing tissues are defined as cells or tissues derived from blood, bone marrow, umbilical cord, placenta, adipose tissue or other adult tissues that are used for purposes other than for hematologic or immunologic reconstitution.

The CWBYCTP is administered by the Health Resources and Services Administration, whose mission is to improve health outcomes and address health disparities through access to quality services; a skilled health workforce; and innovative, high-value programs. The purpose of the CWBYCTP is to help individuals who need a stem cell transplant from an unrelated marrow donor, peripheral blood stem cell donor, or cord blood unit. It does so by making information about bone marrow, peripheral blood, and cord blood transplants available to patients, families, health care professionals and the public; by providing a single point of access to identify suitably matched marrow donors and cord blood units; by increasing the number of unrelated marrow donors and cord blood units available for transplant; and by collecting data and expanding research to improve patient outcomes. The CWBYCTP currently facilitates transplants for over 70 diseases for which hematologic or immunologic reconstitution using bone marrow, peripheral blood, and cord blood have been demonstrated to be safe and effective. Bone marrow-derived stem cells, peripheral blood-derived stem cells, and cord blood-derived stem cells have clearly demonstrated safety and efficacy for hematologic reconstitution or immunologic reconstitution in settings such as the treatment of bone marrow failure syndromes, inherited hematologic disorders, and hematologic malignancies. Stem cells from these sources are considered by the medical community to be safe and effective for hematologic and immunologic reconstitution. These uses of stem cells have been incorporated into professional guidelines for the management of many different diseases, and there are several cord blood products approved<sup>1</sup> by the Food and Drug Administration (FDA) for use in hematologic and immunologic reconstitution.

Stem cells derived from allogeneic (cells from one individual to another) and autologous (cells from one's own body) bone marrow and peripheral blood, cord blood, as well as stem cells derived from adipose and other sources, are being investigated for the treatment of a wide variety of different conditions ranging from arthritis to neurologic disorders to cardiac diseases. In contrast to cellular products for hematologic and immunologic reconstitution, clinical trials have yet to demonstrate sufficient evidence to support the efficacy of such adult stem cells or stem cells derived from birthing tissues for the treatment of these diverse non-hematologic conditions. In addition to lacking demonstrated efficacy, significant safety concerns have been reported regarding adult stem cell and cord blood products used for purposes other than hematologic and immunologic reconstitution. Adult stem cells and birthing tissues are therefore investigational for these other indications.

The CWBYCTP currently facilitates access to potentially life-saving therapies that are generally accepted by the medical community as safe and effective: stem cells derived from blood, bone marrow, or cord blood used for hematologic or immunologic reconstitution. At this time, adult stem cells and birthing tissues as defined above fall into a different category of products: those that are investigational for their

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<sup>1</sup> FDA approval to market a biologic is granted by issuance of a biologics license under section 351 of the Public Health Service Act. For the purposes of this report, we will use the terms "approval" and "licensure", with respect to biological products, interchangeably.

intended uses. The inclusion in the CWBYCTP of such investigational products as adult stem cells and birthing tissues that require, but have not yet received, approval by FDA could give patients and providers the erroneous impression that these products are comparably safe and effective for their intended uses as are stem cell products used in hematopoietic stem cell transplants for hematologic and immunologic reconstitution and could be detrimental to product development because it will remove incentives for the conduct of clinical trials. Furthermore, it could undermine the regenerative medicine-related provisions of the 21<sup>st</sup> Century Cures Act, which encourage sponsors to obtain the needed clinical evidence toward the goal of obtaining marketing approval from the FDA. Supporting the intent of the 21<sup>st</sup> Century Cures Act will allow the greatest access for patients to safe, effective, and innovative cellular and tissue-based products.

In terms of access, the availability of investigational therapies to patients and providers is facilitated by information available on ClinicalTrials.gov, which is administered through the National Institutes of Health (NIH) in coordination with the FDA. There are statutory and regulatory requirements that certain clinical trials be listed in this publicly accessible database; other trials may be listed electively at the sponsor's or investigator's discretion. In addition to information relevant for patient participation, ClinicalTrials.gov also contains clinical trial summary results information.<sup>2</sup>

Based on the considerations discussed above, and the evolution of the field of stem cell-based therapies, the Department of Health and Human Services (HHS) makes the following recommendations:

1. The proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that:

The CWBYCTP should include only those adult stem cell and birthing tissue products, including those with new uses outside of hematologic or immunologic reconstitution, that:

- a) are utilized as treatments for serious or life-threatening conditions (1,2),
  - b) require donor matching if appropriate, and
  - c) have been demonstrated to be safe and effective as evidenced by FDA approval, or if FDA approval is not required, through adoption as a standard of care.
2. Based on the criteria above, the inclusion in the CWBYCTP of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time.
  3. As the science advances and new classes of cell-based products are developed that meet regulatory approval standards for safety and efficacy, it may be appropriate to include such products in the CWBYCTP. Therefore, reevaluation by HRSA, NIH, and FDA (in conjunction with appropriate expert consultation) of the status of adult stem cells and birthing tissues for potential inclusion in the CWBYCTP is recommended on a periodic basis (every two to three years or as needed), with issuance of a report on the outcomes of these evaluations when relevant.

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<sup>2</sup> See section 402(j) of the Public Health Service Act (42 U.S.C. 282(j)), as amended by section 801 of the Food and Drug Administration Modernization Act of 2007 (Public Law 110-85); 42 C.F.R. Part 11.

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## Statutory Mandate

The Stem Cell Therapeutic and Research Reauthorization Act of 2015 (Public Law 114-104, Section 2(c)) notes that “The Secretary of Health and Human Services, in consultation with the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Administrator of the Health Resources and Services Administration, including the Advisory Council on Blood Stem Cell Transplantation established under section 379(a) of the Public Health Service Act (42 U.S.C. 274k(a)), and other stakeholders, where appropriate given relevant expertise, shall conduct a review of the state of the science of using adult stem cells and birthing tissues to develop new types of therapies for patients, for the purpose of considering the potential inclusion of such new types of therapies in the C.W. Bill Young Cell Transplantation Program (established under such section 379) in addition to the continuation of ongoing activities. Not later than June 30, 2019, the Secretary shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives recommendations on the appropriateness of such new types of therapies for inclusion in the C.W. Bill Young Transplantation Program.”

Under the direction of the Secretary of Health and Human Services (HHS), the preparation of this report represents a collaborative effort by the Health Resources and Services Administration (HRSA), National Institutes of Health (NIH), and Food and Drug Administration (FDA) in consultation with the HHS Advisory Council on Blood Stem Cell Transplantation and other appropriate stakeholders, in fulfillment of this statutory mandate. The findings and recommendations herein represent the perspectives of HHS.

For the purposes of this report, adult stem cells and birthing tissues are defined as cells or tissues derived from blood, bone marrow, umbilical cord, placenta, adipose tissue or other adult tissues that are used for purposes other than for hematologic or immunologic reconstitution.

## Purpose of the C.W. Bill Young Cell Transplantation Program (CWBYCTP)

HRSA, whose mission is to improve health outcomes and address health disparities through access to quality services, a skilled health workforce, and innovative, high-value programs, is the federal agency that administers the CWBYCTP.

The Stem Cell Therapeutic and Research Act of 2005, P.L. 109-129, as amended by P.L. 111-264 (section 379(a)(1)) and P.L. 114-104, Stem Cell Therapeutic and Research Reauthorization Act of 2015, authorizes the:

- CWBYCTP – to increase the number of bone marrow and cord blood transplants for recipients suitably matched to biologically unrelated donors.
- National Cord Blood Inventory (NCBI) – to contract with qualified cord blood banks (CBBs) to meet the statutory goal of building a public inventory of at least 150,000 new, high quality, and genetically diverse cord blood units.
- HHS Advisory Council on Blood Stem Cell Transplantation – to advise, assist, consult with, and make recommendations to the HHS Secretary and the HRSA Administrator on matters carried out by both CWBYCTP and the NCBI Program.

The CWBYCTP provides a structure to facilitate allogeneic blood stem cell transplantation for over 70 diseases and collaborates with those in the blood stem cell transplantation field to address the need for allogeneic blood stem cell transplants for individuals in the United States (U.S.) who have leukemia, lymphoma, sickle cell anemia, or other inherited metabolic or immune system disorders

([https://bloodcell.transplant.hrsa.gov/transplant/understanding\\_tx/index.html#Diseases](https://bloodcell.transplant.hrsa.gov/transplant/understanding_tx/index.html#Diseases)).

The CWBYCTP provides a structure to facilitate blood stem cell transplantation with blood-forming cells from unrelated donors for individuals with leukemia and other life-threatening blood disorders. Through its Stem Cell Therapeutic Outcomes Database (SCTOD) function, CWBYCTP enables the collection of data on the clinical outcomes of those transplant recipients as well as data on blood stem cell products. The CWBYCTP implements five functions (i.e., bone marrow coordinating center, cord blood coordinating center, patient advocacy, single point of access, and outcomes database) through three major contracts awarded through a competitive process during September 2017. The following is a description of the major contracts:

- The Single Point of Access-Coordinating Center establishes a system for health care professionals and physicians searching on behalf of patients to search electronically for cells derived from adult marrow donors and cord blood units through a single point of access and supports coordination activities for bone marrow and cord blood transplants.
- The Office of Patient Advocacy establishes and maintains a system for patient advocacy, which serves patients searching for a bone marrow donor or cord blood unit through the CWBYCTP, from diagnosis through survivorship. The OPA engages in public and professional educational activities related to treatment options.
- The SCTOD collects, maintains, analyzes, and reports patients' outcomes data for all allogeneic (cells from one individual given to another) hematopoietic stem cell transplants and other therapeutic uses of blood stem cells, in a standardized electronic format.

## Outcomes Data Collection and Reporting Currently Facilitated Through Funding from the CWBYCTP

The SCTOD is administered through a contract that is in place with a private entity, the Medical College of Wisconsin. The SCTOD supports the collection, analysis, and reporting of outcomes data for all allogeneic hematopoietic stem cell transplants (HSCTs) performed in the U.S. and for allogeneic products provided from the U.S. to patients overseas. Further, the SCTOD also provides information about such transplants to patients, families, health care professionals, and the public, in fulfillment of the statutory mandate of the CWBYCTP. Also, a contractor of the SCTOD voluntarily collects information on other types of transplants, such as autologous hematopoietic stem cell transplants using stem cells derived from bone marrow or peripheral blood, and it also collects information on some cellular therapy products.

To date the SCTOD has primarily included therapies that have been FDA-approved (cord blood products) or that are accepted as safe and effective (bone marrow and peripheral blood stem cells) for the treatment of hematologic and immune system disorders. It includes data on both allogeneic and autologous bone marrow-derived and peripheral blood-derived stem cell transplants as well as cord blood transplants, which have been clearly demonstrated to be safe and effective for hematologic reconstitution in settings such as the treatment of hematologic malignancies.

Data are included in the SCTOD on allogeneic HSCTs occurring in the U.S., as well as HSCTs performed outside of the U.S. using a product procured through the federally-authorized CWBYCTP. The patient data included in the SCTOD are collected using the Office of Management and Budget-approved forms. Per the SCTOD contract requirement, patient data are collected immediately pre-infusion and immediately post-infusion as well as post-transplant at 100-days, 6-months, 1-year, and annually through 6 years after HSCT and every other year thereafter. Data collection for the SCTOD started in December of 2007; data for approximately 8,000 new allogeneic HSCT recipients are added each year. In addition to these data, the SCTOD contractor collects pre-transplant research samples from recipients and their related donors to

constitute a Related Donor Research Repository. Data derived from assays of these biospecimens are linked to the clinical outcomes data (e.g., SCTOD data) for research studies that evaluate genetic and immune-biologic as well as clinical phenotype data. However, the SCTOD contract does not provide funds for biospecimen assays.

## Consultations Performed Relevant to this Report

Consultations noted below include consultations performed relevant to HHS efforts to move the field of cell-based therapies forward; consultations on the state of the science of adult stem cells and birthing tissues included:

- 1) FDA Workshop, held September 8, 2016 – Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval

The focus of this workshop was largely on adult stem cell therapies. There were five sessions included: 1) Keynote and Regulatory Scheme; 2) Experiences in Product Development; 3) Views from Professional Societies; 4) Views from other Government Agencies; and 5) Patient and Society Experience and Expectations.

A complete agenda is provided as Appendix 1, and the full transcript of this workshop is available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM530238.pdf>.

- 2) Center for International Blood and Marrow Transplant Research (CIBMTR) Meeting, held August 10, 2017 – Regenerative Medicine Registry Meeting

This meeting, which included participants from CIBMTR, academic institutions, stem cell clinics, HRSA, and FDA discussed the possibility of establishment of a Regenerative Medicine Registry that could potentially capture data from a variety of cellular and tissue products used for purposes other than hematologic or immune reconstitution. Discussion at this meeting focused on the review of potential options for a registry to capture clinical information that could ultimately support several objectives, including fulfilling regulatory requirements, such as the submission of a biologics license application to the FDA, and determinations regarding product reimbursement by payors.

- 3) NIH-FDA Workshop, held December 6-7, 2017 – Regenerative Medicine Innovation Workshop: Focus on Adult Stem Cells

The focus of this workshop was the development of safe and effective regenerative medicine products. The workshop participants provided individual perspectives, including identifying critical gaps that need to be addressed to enable significant innovation and rapid advancement of regenerative medicine approaches. The ten sessions were: 1) Introduction, 2) Musculoskeletal Tissues and Integument, 3) Endocrinology, 4) Ophthalmology, 5) Regulatory Considerations for Stem Cell-Based Product Development, 6) Neurology, 7) Hematology, 8) Cardiology and Vascular Biology, 9) Opportunities in Clinical Trial Design, and 10) A Path to Treatment and Cures.

A complete agenda is provided as Appendix 2, and video recording of each of the sessions is available at [https://www.youtube.com/playlist?list=PL\\_ntiNjc6GvIOyKQ\\_j6RTWgahqzmt6nj3](https://www.youtube.com/playlist?list=PL_ntiNjc6GvIOyKQ_j6RTWgahqzmt6nj3).

- 4) CIBMTR Workshop, held October 25, 2018 – 2018 Cellular Therapy Registry Forum

The workshop focused on the inclusion of data from chimeric antigen receptor (CAR) T-cells in the CIBMTR Cellular Therapy Registry. The purpose of the forum was to discuss how to collect and analyze data in a way that is valuable to move the CAR T field forward. Later in the day, the meeting touched upon the

Center for Medicare & Medicaid Services (CMS) process for national coverage analyses and the incorporation of other cellular therapies into the CWBYCTP. The sessions at this forum were: 1) Objectives of the Forum and Overview of the CIBMTR Cell Therapy Registry, 2) Role of Registries in Developing and Evaluation of Cellular Therapies, 3) CAR T Cell Toxicities Reporting, 4) Cellular Therapy Center Accreditation and Data Auditing, 5) Long Term Follow-up, 6) Considerations for Capturing Biospecimens in Cell Therapy Recipients, 7) CMS National Coverage Analysis Process, 8) Role of Federal Agencies on Cellular and Gene Therapies, 9) CIBMTR's Perspective on Potential Inclusion of Cellular Therapies in CWBYCTP. The agenda for this meeting is included as Appendix 3.

5) A series of meetings of the Forum on Regenerative Medicine have been held under the auspices of the National Academy of Sciences during the period between 2016 and 2018

The October 16, 2016 Forum on Regenerative Medicine's first public workshop had the stated goal of developing a broad understanding of the opportunities and challenges associated with regenerative medicine cellular therapies and related technologies. Stakeholder groups, including research scientists, clinicians, and representatives from patient groups and industry, presented their perspectives and participated in discussions during the workshop, which focused on an exploration of the state of the science of cell-based regenerative therapies within the larger context of patient care and policy. The workshop rapporteurs prepared the proceedings as a factual summation of the session discussions.

The proceedings of this meeting are available online at: <https://www.nap.edu/read/24671/chapter/1>.

The Forum on Regenerative Medicine hosted a public workshop on June 26, 2017 to examine and discuss challenges, opportunities, and best practices associated with defining and measuring the quality of cell and tissue products and raw materials in the research and manufacturing of regenerative medicine therapies. Workshop participants were asked to explore what measurements, characteristics, and technologies may be important in the development of safe and effective new products and therapies.

The proceedings of this meeting are available online at: <https://www.nap.edu/read/24913/chapter/1>.

To further explore the various factors that contribute to successful regenerative engineering products, the Forum on Regenerative Medicine hosted a one-day meeting on October 18, 2018. The workshop explored factors and sources of variability in the development and clinical application of regenerative engineering products, characteristics of high-quality products, and how different clinical needs, models, and contexts can inform the development of a product. A broad array of stakeholders participated in the workshop, including academic and industry experts, regulators, clinicians, patients, and patient advocates

The agenda for this meeting is provided as Appendix 4.

6) HHS Consultation with the Advisory Council on Blood Stem Cell Transplantation (ACBSCT) of the U.S. Department of Health and Human Services (HHS) held March 11, 2019

This meeting was convened with a quorum of the ACBSCT, which included the ACBSCT Workgroup on New Uses for Adult Blood Stem Cells and Birthing Tissue. The purpose was to receive ACBSCT input, perspectives, and suggestions regarding a draft of this report.

During the discussion, and in written comments following the meeting, the Council members noted that the report provided a comprehensive review of the state of the science as it relates to considerations regarding the appropriateness of including additional adult stem cells and birthing tissues in the CWBYCTP. Members also noted that they agreed with the premise of and recommendations in the report and acknowledged the potential risks posed by unproven therapies.



Comments and questions focused primarily on the proposed criteria for inclusion of new cellular therapies in the CWBYCTP. With respect to the criterion that products are utilized as potentially life-saving treatments, members questioned whether inclusion should be restricted to life-saving measures, noting that other clinically relevant endpoints could be very important to patients. In response to this, the proposed criterion was modified to specify products that are utilized as “treatments for serious or life-threatening conditions.”

Regarding the criterion that products require donor matching, Council members asked about the rationale for limiting inclusion to those products that require donor matching, noting that there could be clinically important products in the future that would not require donor matching. In response to this, the proposed criterion was modified to specify products that “require donor matching if appropriate.”

Regarding the criterion that products have been demonstrated to be safe and effective as evidenced by FDA approval, Council members were supportive of the requirement for FDA approval of products included in the CWBYCTP, but questioned whether this threshold should be absolute, noting that some products may not be subject to FDA oversight. It was explained that the criterion addresses this situation by stating that if FDA approval is not required for a given product, safety and effectiveness can be demonstrated through its adoption as a standard of care by the medical community.

Council members indicated they agreed with the draft conclusion/recommendation that the inclusion of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time. They also indicated they agreed with the recommendation for periodic re-evaluation of including new products in the CWBYCTP, but noted that it would be helpful to define the periodicity of such reviews and to allow for review at any time there are significant changes in the field or new therapies that warrant review. In response to this suggestion, draft recommendation 3 was modified to specify periodic review every two to three years or as needed.

## Background on Stem Cell Therapies

Regenerative medicine, including classes of products such as adult stem cells and birthing tissues, is a rapidly emerging and expanding field that offers great potential benefit by the possibility of providing innovative treatments that may restore health and address unmet medical needs (3). Although there are many researchers working to understand the underlying basic biology, manufacturing processes, and critical quality attributes that will ultimately support the development of safe and effective adult stem cell and birthing tissue products, much remains to be learned. Representative vignettes of this research are provided in text boxes 1-3. Reflecting the current state of the science, today there is no FDA-approved adult stem cell product or stem cell product derived from birthing tissue, or birthing tissue products for use outside of hematologic or immunologic reconstitution.

### Hematopoietic Stem Cells and Birthing Tissues for Hematologic or Immunologic Reconstitution

Certain hematopoietic stem cell therapies offer the potential to treat diseases or conditions for which few treatments exist. For example, bone marrow-derived stem cells, peripheral blood-derived stem cells, and cord blood-derived stem cells have clearly demonstrated safety and efficacy for hematologic reconstitution or immunologic reconstitution in specific settings such as the treatment of bone marrow

failure syndromes and inherited hematologic disorders, the treatment of hematologic and certain other malignancies, and for the treatment of certain immunologic disorders (4).

The safety and efficacy of such stem cell transplantation are documented in hundreds of publications in the literature. For example, severe aplastic anemia was previously associated with high mortality. It is now curable in most eligible cases, particularly in children and younger adults, using hematopoietic stem cell transplantation (5). Transplantation of cord blood (derived from birthing tissues), when appropriate, has become integrated into standard clinical practice for the treatment of patients with acute leukemia, and its use has been associated with favorable long-term outcomes in relapsed or refractory hematologic malignancies (6). There are currently several FDA-approved cord blood products.

### Adult Stem Cells and Birthing Tissues for Other Uses

Stem cells derived from bone marrow, peripheral blood, and cord blood, as well as stem cells derived from other sources, such as adipose tissue, have been investigated for the treatment of a wide variety of different disorders.<sup>3</sup> These include rheumatologic diseases like osteoarthritis and rheumatoid arthritis; neurologic diseases such as stroke, Parkinson's disease, and amyotrophic lateral sclerosis; and cardiac conditions such as congestive heart failure (7, 8, 9). The scientific rationale for the use of adult stem cells or birthing tissues for the treatment of these disorders is that they can potentially replace missing or diseased cell types by differentiating based on local environmental factors into the needed cell type. Alternatively, adult stem cells or birthing tissues may have an immunomodulatory effect that is beneficial to diseases that have an autoimmune basis (10). These two mechanisms are also not mutually exclusive. However, data from definitive clinical trials evaluating the efficacy of adult stem cells or birthing tissues have yet to substantiate either of these alternatives as the mechanisms of action, and in fact, randomized clinical trials have yet to demonstrate clinical efficacy in a compelling manner (11, 12, 13).

#### DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 1

##### *Stem Cell Therapy for Age-related Macular Degeneration*

Age-related macular degeneration (AMD) is the leading cause of vision loss among people age 50 and older, affecting more than 10 million Americans. In advanced AMD, the retinal pigment epithelium (RPE) cells, which support photoreceptor function, lose function and atrophy, leading to the death of photoreceptors, and consequent vision loss. While there is no cure for AMD, some treatments may delay its progression or help to stop further vision loss. Stem cell therapies for AMD are being developed to restore vision through the regeneration of functional RPE tissue. Strategies of injecting suspensions of stem cell-derived RPE cells or RPE cell sheets with or without a scaffold are currently being explored by the research community. Human stem cell-derived RPE transplantation studies in rodents and pigs demonstrated restored visual function for 2-6 months and paved the way for clinical studies in humans. The results of early phase clinical studies conducted in Japan, the U.K., and the U.S. support the feasibility and safety of these strategies for treating AMD, but additional, larger trials are needed to assess efficacy. Significant challenges still need to be resolved, including how to prevent an immune response to patient-derived RPE cells and determine the optimal method for product preparation (i.e., RPE cell suspension versus cell sheets). A licensed cell therapy product for AMD is likely at least 5-10 years away.

*[See Appendix 5 for supporting references]*

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<sup>3</sup> The Stem Cell Therapeutic and Research Act of 2005, P.L. 109-129, as amended by P.L. 111-264 (section 379(a)(1)) and P.L. 114-104, allows cord blood units that are collected, but that are not appropriate for clinical use, to be made available for peer-reviewed research. The data resulting from such research uses are captured by entities other than the CWBYCTP. Cord blood units that are collected may also be made available for use in clinical trials that are conducted under Investigational New Drug (IND) applications on file with the FDA. Relevant findings of such investigational studies are reported to FDA under the IND application.

In addition to lacking demonstrated efficacy, adult stem cell products and cord blood used for purposes other than hematologic and immunologic reconstitution sometimes have been found to have significant safety concerns. For instance, attendees at a 2016 FDA public workshop discussed several cases of severe adverse events, and some of these cases have now been reported in the literature (14). Three individuals became blind, and a fourth had diminished vision due to stem cells injections into the eye (15). An individual received stem cell injections that caused the growth of a tumor compressing the spinal cord, and another received an injection of stem cells into the kidney that resulted in the need for surgical removal of the kidney (16, 17). Additionally, since that public workshop, other complications have been reported in the literature, including potentially life-threatening bloodstream infections (18). Other potential safety concerns for unproven treatments include the ability of cells to move from placement sites or change into inappropriate cell types due to the microenvironments into which the cells are placed. It should be noted that such safety concerns are likely underreported because the products are often administered outside of clinical trials.

Early phase clinical investigations of a wide variety of different applications of adult stem cell and birthing tissues are currently ongoing under appropriate regulatory oversight. However, despite the potential safety concerns and lack of documented efficacy noted above, many adult stem cell and birthing tissue products are currently being administered to patients as part of patient-funded clinical trials without appropriate FDA oversight or as part of commercial marketing operations in violation of FDA regulatory authorities.

It is worth noting that in its 2016 Guidelines for Stem Cell Research and Clinical Translation, the International Society for Stem Cell Research notes that “for the vast majority of medical conditions for which putative “stem cell therapies” are currently being marketed, there is insufficient evidence of safety and efficacy to justify routine or commercial use. Serious adverse events subsequent to such procedures have been reported and the long-term safety of most stem cell-based interventions remains undetermined.” (19)

Currently, there are no FDA-approved adult stem cell products or stem cell products derived from birthing tissue, or birthing tissue products for use outside of hematologic or immunologic reconstitution.

### Regulatory Framework for Stem Cell Therapies

Minimally manipulated bone marrow for homologous use, not combined with another article [medical product], is subject to HRSA oversight. With that exception, oversight of stem cells, including more than minimally manipulated bone marrow and bone marrow-derived stem cells used for other purposes, peripheral blood-derived stem cells, cord blood, as well as stem cells derived from other

#### DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 2

##### *Stem Cell Therapy for Heart Failure*

Heart failure (HF) is a condition in which the heart can't pump enough blood to meet the body's needs. Currently, HF has no cure. However, treatments—such as medicines, lifestyle changes, and assistive devices—can help people with the condition live longer and more active lives. Researchers continue to study new ways to treat HF and its complications, and one such avenue is stem cell therapy. Preclinical animal studies in rat, dog, pig and sheep models have explored the use of stem cells in regenerating the heart after heart attack, in chronic left ventricular dysfunction, and in non-ischemic HF. The effect of stem cells is postulated to be [largely related to paracrine activity](#), i.e., secretion of various types of growth factors that promote the development of new blood vessels, have anti-inflammatory effects, and reduce scarring and fibrosis. Early clinical studies have demonstrated the use of immune-privileged allogeneic stems cells to be safe but have not provided a compelling demonstration of efficacy. While these findings are promising, much remains to be learned before cell therapies for HF could become a reality, including determining the appropriate cell type, dosages, routes of delivery, and timing/intervals of treatment.

*[See Appendix 5 for supporting references]*

sources, such as adipose tissue, are regulated by the FDA. To date, the FDA has licensed eight cord blood banks to manufacture cord blood stem cells for hematopoietic and immunologic reconstitution.

FDA and HRSA have ongoing collaborations to share information and discuss applicable regulatory requirements and updates on relevant research or scientific issues related to hematopoietic stem cells for transplantations or other relevant products. FDA and HRSA representatives participate in the Interagency Hematopoietic Stem Cell Transplant Workgroup and the HHS Advisory Council on Blood Stem Cell Transplantation.

Adult stem cell products and birthing tissues are regulated under the FDA's regulatory framework for human cells, tissues, and cellular and tissue-based products (HCT/Ps). Under this risk-based framework, the criteria in the Code of Federal Regulations (CFR; particularly, 21 CFR 1271.10(a)) are used to determine whether HCT/Ps are regulated as drugs, devices, and/or biological products requiring FDA premarket review and approval, or whether they are appropriately regulated solely under section 361 of the Public Health Service Act and 21 CFR part 1271.

As described in FDA's final guidance for industry "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use," and in accordance with the regulations in 21 CFR 1271.10(a), some birthing tissue products can be appropriately regulated under section 361 of the Public Health Service (PHS) Act and 21 CFR part 1271 if they meet the criteria set forth in FDA's regulations, including that they are minimally manipulated and intended for a homologous use.<sup>4</sup> One example is amniotic membrane that is minimally manipulated and intended for a homologous use, such as covering skin wounds such as ulcers. In contrast, other birthing tissue products are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act. Examples of such birthing tissue-derived products regulated as drugs, devices, and/or biological products include amniotic membrane that is more than minimally manipulated or used for some purpose other than covering, and autologous cord blood when used for

#### **DEVELOPMENT OF ADULT STEM CELL AND BIRTHING TISSUE THERAPIES: RESEARCH VIGNETTE 3**

##### ***Stem Cell Therapy for Osteoarthritis/Joint Pain***

Osteoarthritis (OA) is a degenerative joint disease that affects approximately 27 million Americans and is most common in people older than 65. In OA, the cartilage breaks down, causing pain, swelling and problems moving the joint. Treatments focus on managing symptoms and may include lifestyle changes, pain and anti-inflammatory medications, physical therapy, assistive devices and joint surgery, none of which halt progression of disease or reverse damage. Adult stem cell-based therapy is proposed as a means to directly regenerate and repair the damaged tissue and/or to indirectly contribute to these processes by secreting factors that promote healing. Most preclinical proof-of-concept research has been conducted in small animal models; and while some studies have been performed in larger animals, additional preclinical studies in suitable animal models are needed to better understand how to control stem cell differentiation and proliferation *in vivo*. A few early phase clinical trials of cell-based therapies for OA have been conducted using stem cells harvested from a patient's own bone marrow; however, well-controlled clinical studies are needed to conclusively understand the safety and efficacy of this approach.

*[See Appendix 5 for supporting references]*

<sup>4</sup>FDA's regulations 21 C.F.R. 1271.3 provide definitions of minimal manipulation and homologous use. As defined in 21 C.F.R. 1271.3(f), minimal manipulation means:

- 1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;
- 2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

As defined in FDA's regulations at 21 C.F.R. 1271.3(c), homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

treatment of cerebral palsy or autism (or generally for any use except hematopoietic or immunologic reconstitution).

### Efforts to Expedite Progress Developing Adult Stem Cell and Birthing Tissue-based Treatments

Regenerative medicine is a rapidly expanding field that offers great potential. However, much remains to be understood regarding the science underlying these advanced therapeutic products as well as how to manufacture them consistently. Because of this, the 21<sup>st</sup> Century Cures Act (Public Law 114-255) tasked the NIH with establishing the Regenerative Medicine Innovation Project (RMIP) in coordination with FDA. The purpose of the RMIP is to accelerate the field of regenerative medicine by supporting clinical research, including clinical trials, on adult stem cells, including autologous cells, while promoting the highest standards for carrying out such research and protecting patient safety. The 21<sup>st</sup> Century Cures Act authorized \$30 million in federal awards over four years (2017–2020) for the RMIP and required award recipients to match the federal funds provided in at least an equal amount with non-federal contributions. Details of the FY 2017 and the FY 2018 solicitations and a list of awardees are available online at <https://www.nih.gov/rmi>.

To facilitate the efficient development of safe and effective adult stem cell-based therapies and further the field of regenerative medicine, NIH is establishing the Regenerative Medicine Innovation Catalyst (RMIC) program to provide key clinical services (phase appropriate cGMP assistance, regulatory support, and in-depth stem cell characterization).

As part of the RMIP program, grant recipients are expected to provide representative samples of the source stem cells and clinical-grade stem cell product for in-depth characterization through the RMIC, which is expected to conduct independent characterization of the source stem cell line and stem cell products being developed. The RMIC is expected to also provide a platform for sharing and analyzing of clinical trial data (if applicable) and cell product characterization data, thereby potentially enabling correlation of stem cell attributes with clinical outcomes.

Additional activities that are part of the RMIP collaboration between NIH and FDA are also ongoing. On December 6-7, 2017, the two agencies hosted a public Regenerative Medicine Innovation Workshop that brought together key stakeholders to explore the state of regenerative medicine clinical research involving adult stem cells with a focus on approaches to the development of safe and effective products (20). The individual perspectives shared at this workshop were instrumental in helping to identify some of the major needs, opportunities, and challenges in the regenerative medicine field. Particularly relevant to the discussion of adult stem cells and birthing tissues, multiple speakers at that workshop noted the current challenges with the appropriate characterization and reproducible manufacturing of stem cells for uses outside of hematologic reconstitution. The challenges of clinical development of such adult stem cell products were also noted.

The 21<sup>st</sup> Century Cures Act also included important regenerative medicine provisions that amended FDA's statutory authority, including provisions establishing the Regenerative Medicine Advanced Therapy (RMAT) designation program. This program is intended to help facilitate and expedite the development and review of regenerative medicine therapies, including certain cellular therapies. It does so through, for example, opportunities for early and frequent interactions between sponsors and FDA, with the goal ultimately of providing patient access to safe, effective and innovative regenerative medicine therapies. Details of FDA's efforts to implement the RMAT Designation Program in Calendar Year 2017 are included in Appendix 6.



These sections of the 21<sup>st</sup> Century Cures Act acknowledge a role for registries in the post-market setting for cellular and tissue-based products. However, they recognize that the best way to explore the promise of regenerative medicine products and get safe, effective, and innovative cellular and tissue-based products to patients – and to advance the field of regenerative medicine overall – is through clinical investigations under Investigational New Drug (IND) applications and through the submission of applications for marketing approval. These regenerative medicine-related provisions of the 21<sup>st</sup> Century Cures Act differentiate between products requiring premarket approval and those that do not and differentiate between investigational products and those that have been found by FDA to be safe and effective.

Building on FDA’s risk-based regulatory framework and the provisions in the 21<sup>st</sup> Century Cures Act, and with the goal of helping to support and facilitate the development and review of safe and effective regenerative medicine products so that they can be available expeditiously to patients, in November 2017 the FDA issued its comprehensive regenerative medicine framework. This was comprised of four guidance documents, two final and two draft (which have since been finalized), that built upon FDA’s existing risk-based regulatory approach (21). Under this framework, the FDA detailed its science-based process for helping to ensure the safety and effectiveness of these therapies, while facilitating development in this area.

To facilitate product development that will ultimately benefit patients, FDA is exercising considerable flexibility and encouraging developers of cell and tissue-based therapies to discuss with the Agency novel development plans that can help expedite development of these products. In fact, with an understanding of the challenges that developers of cellular products may face, the guidance “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions,” issued by FDA as part of the regenerative medicine framework, laid out a novel and efficient clinical development model by which sponsors of promising stem cell products could pursue review and approval by the FDA.

Developers of novel adult stem cell and birthing tissue products are also being encouraged to have early non-binding conversations with FDA regarding necessary regulatory aspects of product development through participation in the INTERACT program (Initial Targeted Engagement for Regulatory Advice on CBER Products) launched in 2018 by the Center for Biologics Evaluation and Research. These informal meetings can 1) assist sponsors conducting early product characterization and preclinical proof-of-concept studies, 2) initiate discussion for new delivery devices, 3) inform sponsors about overall early-phase clinical trial design elements, and 4) identify critical issues or deficiencies for sponsors to address in the development of innovative products.

Finally, at the time that FDA issued the regenerative medicine framework noted above, it also made clear its policy on enforcement and compliance in this area. Stem cell products otherwise requiring an IND application and Biologics License Application would need to come into compliance with the FDA’s regulations by November 20, 2020 at the latest. In the interval before that time, FDA noted that it would take regulatory action regarding products that posed significant safety or public health concerns. Such a policy was necessary because numerous stem cell clinics around the U.S. have been reported to be offering adult stem cell products and those derived from birthing tissues to treat a wide variety of conditions (22). These products are being purported to be safe and efficacious for many different conditions and patients are paying out of pocket for them, sometimes tens of thousands of dollars, even though they are not approved by the FDA, nor are they even being studied under an IND.

## Proposed Criteria for Inclusion of New Cellular Therapies in the CWBYCTP

The purpose of the CWBYCTP is to help patients who need a potentially life-saving transplant from an unrelated bone marrow or stem cell donor or from a cord blood unit by facilitating the matching of donors

and recipients and by making information about transplants and their outcomes available to patients, families, health care professionals, and the public. In keeping with this programmatic purpose and the mission of HRSA to improve health through access to quality services, the proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that the Program should include only those adult stem cell and birthing tissue products with new uses outside of hematologic or immunologic reconstitution, that:

- a) are utilized as treatments for serious or life-threatening conditions (1,2),
- b) require donor matching if appropriate, and
- c) have been demonstrated to be safe and effective as evidenced by FDA approval, or if FDA approval is not required, through adoption as a standard of care.

## Key Findings Regarding Inclusion of Adult Stem Cells and Birthing Tissue Products in the CWBYCTP

HRSA, NIH, and FDA have a shared goal of providing access to safe and effective products. As an embodiment of the HRSA mission to improve human health through access to quality services and care, a central goal of the CWBYCTP is to promote patient access to suitably matched bone marrow and cord blood transplants in potentially life-saving settings. These procedures are widely accepted by clinicians as representing a standard of care in certain settings, such as in the case of relapsed acute leukemia.

As noted above, through the SCTOD, the CWBYCTP collects outcomes data in a standardized electronic format on the use of suitably matched bone marrow and cord blood transplants for hematologic and immunologic indications. The hematologic and immunologic stem cells provided by suitably matched bone marrow and cord blood are relatively similar to one another; the outcome measures are similar or the same for the various applications that the different products are used for (e.g., non-relapse mortality); and, as a result, the data can meaningfully be analyzed across the products.

Adult stem cells and birthing tissues for other investigational applications (i.e., other than hematologic and immunologic reconstitution) represent a diverse array of products that are used for experimental interventions for different diseases with widely different outcome measures. Their use at this time inherently does not represent a standard of care for disease management. While such applications hold promise, at present they are without proven safety or efficacy, and in some instances, have resulted in significantly adverse patient outcomes. Information regarding the clinical trials investigating these products and the results of these trials is useful to patients interested in enrolling in such studies and is also of potential interest to the public. However, for many products in early stage clinical development (e.g., phase 1 clinical trials), and for all products in advanced stages of clinical development (e.g., phase 2 or phase 3), this information is already available in a congressionally-mandated and federally-funded database, ClinicalTrials.gov, which is dedicated to this purpose.

The inclusion in the CWBYCTP of adult stem cells and birthing tissues that require premarket review and approval by the FDA, but for which FDA approval has not been granted would have the CWBYCTP overseeing the maintenance and dissemination of information about some products with proven effectiveness and some products that are purely experimental. The intermingling in the same database of products that have been determined to be safe and effective for their intended uses with investigational treatments that have not had such a determination may pose risks to patient safety when patients seek out products they have seen in the CWBYCTP database without understanding that they may not have been fully tested or proven to be both safe and effective. It is likely that many, if not most, of these investigational products will never be proven safe and effective. However, patients are likely to be confused and possibly even be misled regarding which CWBYCTP products are effective, and which products are investigational. Furthermore, such a mingling of proven effective and unproven products in the CWBYCTP could be

detrimental to public confidence in potentially life-saving bone marrow-derived, peripheral blood-derived, and cord blood-derived stem cell transplants and could undermine the goal of the CWBYCTP in its mission to ensure access to and improve patient outcomes from these treatments.

The appropriate registry for investigational products currently being tested in clinical trials and pending regulatory approval is ClinicalTrials.gov, the congressionally mandated and federally funded database administered by the NIH in coordination with the FDA. The database includes information regarding certain clinical trials studying FDA-regulated products (regardless of whether the product being studied is approved, licensed, or cleared by FDA), including phase 2 and later clinical trials subject to the statutory and regulatory requirements for registration, and, since January 18, 2017, all NIH-funded clinical trials (including phase 1 studies). Sponsors and investigators may voluntarily submit information to ClinicalTrials.gov for those clinical trials that are not NIH-funded and do not study an FDA-regulated product in a phase 2 or later clinical trial. ClinicalTrials.gov facilitates patient access to and participation in clinical trials and facilitates public access to summary results information from clinical trials. It is an important and unique public information resource for those interested in learning more about products under development whose safety and efficacy have yet to be established for their intended uses.

Finally, inclusion of investigational cell-based products derived from adult stem cells and birthing tissues in a government-sponsored health services program like the CWBYCTP could be detrimental to adult stem cell and birthing tissue product development overall. Products listed in a registry sponsored by the CWBYCTP could be mistaken as being the equivalent of safe and effective. If such inclusion results in the continued marketing of unapproved products, it could greatly reduce or eliminate the incentive for legitimate product development and private sector investment in accordance with all applicable regulations. Furthermore, it could undermine the regenerative medicine-related provisions of the 21<sup>st</sup> Century Cures Act, which encourage sponsors to obtain the needed clinical evidence toward the goal of obtaining marketing approval from the FDA.<sup>5</sup> Supporting the intent of the 21<sup>st</sup> Century Cures Act will allow the greatest access for patients to safe, effective, and innovative cellular and tissue-based products.

## Recommendations

Based on the considerations discussed above, and the evolution of the field of stem cell-based therapies, HHS makes the following recommendations:

1. The proposed criteria for inclusion of new cellular therapies in the CWBYCTP are that:

The CWBYCTP should include only those adult stem cell and birthing tissue products, including those with new uses outside of hematologic or immunologic reconstitution, that:

- a) are utilized as treatments for serious or life-threatening conditions (1,2),
- b) require donor matching if appropriate, and
- c) have been demonstrated to be safe and effective as evidenced by FDA approval, or if FDA approval is not required, through adoption as a standard of care.

The purpose of the CWBYCTP underpins this recommendation. The CWBYCTP exists to help patients who need potentially life-saving transplants from unrelated bone marrow or stem cell donors or from cord blood units by facilitating the matching of donors and recipients and by making information about transplants and their outcomes available to patients, families, health care professionals and the public. Key concepts in this purpose are reflected in the proposed criteria: treatments for serious or life-threatening conditions that are based, if appropriate, on material from an unrelated donor and that require suitable matching.

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<sup>5</sup> Sections 1001(b)(4)(D), 3033, 3034, and 3036 of the 21<sup>st</sup> Century Cures Act, Public Law 114-255.



The CWBYCTP currently facilitates access to potentially life-saving therapies that are generally accepted by the medical community as safe and effective: stem cells derived from blood, bone marrow, or cord blood used for hematologic or immunologic reconstitution. At this time, adult stem cells and birthing tissues as defined in this report fall into a different category of products: those that are investigational for their intended uses. Furthermore, such uses do not uniformly address serious or life-threatening conditions, in distinct contrast to the use of stem cells derived from blood, bone marrow, or cord blood used in HSCT for hematologic and immunologic reconstitution.

2. Based on the criteria above, the inclusion in the CWBYCTP of adult stem cells and birthing tissues for uses other than hematologic and immunologic reconstitution is not recommended at this time.

The use of adult stem cells and birthing tissues for other uses holds significant promise for the treatment of life-threatening conditions. However, such applications are presently experimental, have not been proven safe and effective, and therefore do not meet the criteria described above for inclusion as new cellular therapies in the CWBYCTP.

The inclusion in the CWBYCTP of such investigational products as adult stem cells and birthing tissues that require but have not yet received approval by FDA could give patients and providers the erroneous impression that these products are comparably safe and effective for their intended uses as are stem cell products used in HSCT for hematologic and immunologic reconstitution and could be detrimental to product development. This is a disservice to patients and the public and to the field of cell-based therapies.

3. As the science advances and new classes of cell-based products are developed that meet regulatory approval standards for safety and efficacy, it may be appropriate to include such products in the CWBYCTP. Therefore, reevaluation by HRSA, NIH, and FDA (in conjunction with appropriate expert consultation) of the status of adult stem cells and birthing tissues for potential inclusion in the CWBYCTP is recommended on a periodic basis (every two to three years or as needed), with issuance of a report on the outcomes of these evaluations when relevant.

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## Appendices

Appendix 1. FDA Workshop Agenda: Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval, September 8, 2016.

Appendix 2. NIH-FDA Workshop Agenda: Regenerative Medicine Innovation Workshop: Focus on Adult Stem Cells, December 6-7, 2017.

Appendix 3. Center for International Blood and Marrow Transplant Research Workshop Agenda: 2018 Cellular Therapy Registry Forum, October 25, 2018.

Appendix 4. The National Academies of Sciences, Engineering, and Medicine Forum on Regenerative Medicine Workshop Agenda: 2018 Forum on Regenerative Medicine Meeting, October 18, 2018.

Appendix 5. Supporting References for Research Vignettes.

Appendix 6. FDA Regenerative Medicine Advanced Therapy Report to Congress FY2018.

## Appendix 1

### FDA Workshop Agenda: Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval, September 8, 2016

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#### **Public Workshop: Scientific Evidence in the Development of Human Cells, Tissues, and Cellular and Tissue-Based Products Subject to Premarket Approval - Agenda September 8, 2016**

Food and Drug Administration  
White Oak Campus - 10903 New Hampshire Ave  
Building 2 Great Room B&C  
Silver Spring, MD 20903

**8:30 - 8:40**      **Welcome/Opening remarks:** Celia Witten, PhD, MD

**8:40 - 9:45**      **Session 1: Keynote and Regulatory Scheme**

- 8:40-9:10: Keynote address: Irving Weissman, MD, *Stem Cell Biology and Regenerative Medicine*
- 9:10-9:15: Questions to keynote speaker
- 9:15-9:45: Steven Bauer, PhD, *FDA Perspectives on Scientific Evidence and HCT/P Development*

**9:45 -11:40: Session 2: Experiences in Product Development**

- 9:45 -10:05: Jacques Galipeau, MD, *How Mechanistic Studies on Mesenchymal Stromal Cells Inform Design of Human Clinical Trials for Autoimmune Ailments – The Fitness Paradigm*
- 10:05-10:25: Michael Matthay, MD, *Mesenchymal Stem Cells for Treatment of ARDS Patients: Challenges & Lessons Learned in Pre-Clinical Testing, FDA Approval, and Ongoing Clinical Trial*

**10:25 - 10:40: Break**

- 10:40-11:00: Gregory Russotti, PhD, *Drivers and Methodologies for Making Cell Therapy Process Changes*
- 11:00-11:20: Dennis Clegg, PhD, *Development of ES-derived Retinal Pigmented Epithelium on a Scaffold for Age-related Macular Degeneration*
- 11:20-11:40: Christopher Breuer, MD, *The Development and Translation of the Tissue Engineered Vascular Graft: From the Bench to the Bedside and Back Again*

**11:40 - 12:20: Panel Discussion 1:** Galipeau, Matthay, Russotti, Clegg, Breuer, Weisman

**12:20 - 1:20: Lunch**

**1:20 - 2:20: Session 3: Views from Professional Societies**

- 1:20-1:40: Jonathan Kimmelman, PhD, *Ethics, Evidence, and Regulatory Approval for Cell-Based Interventions*
- 1:40-2:00: Massimo Dominici, MD, *Dissecting Unproven Cellular Therapies: The International Society for Cellular Therapy (ISCT) Position*
- 2:00-2:20: Peter Rubin, MD, *Clinical Adipose-Based Therapies*

**2:20 - 2:40: Session 4: Views from other Government Agencies**

- 2:20-2:30: Kristy Pottol, *Delivering Mission Ready Medical Solutions to the Warfighter*
- 2:30-2:40: Martha Lundberg, PhD, *Enabling Development of Regenerative Medicine Technologies and Therapies at the NHLBI*

**2:40 - 2:55: Break**

**2:55 - 4:15: Session 5: Patient and Society Experience and Expectations**

- 2:55-3:15: Jeffrey Kahn, PhD, *Societal Perspectives on Development and Oversight of Novel Cell-Based Therapies*
- 3:15-3:35: Brian Mansfield, PhD, *Perspectives of Stem Cell Therapy for Orphan Inherited Retinal Dystrophies*
- 3:35-3:55: Thomas Albin, MD, *Severe Visual Loss After Intravitreal Injection of Autologous Adipose Tissue-derived Stem Cells for Age-related Macular Degeneration*
- 3:55-4:15: Michael Miller, MD, PhD, *Glioproliferative Lesion of the Spinal cord Arising from Exogenous Stem Cells*

**4:15 - 4:50: Panel Discussion 2: Kahn, Kimmelman, Dominici, Rubin, Pottol, Lundberg, Mansfield, Albin, Miller**

**4:50 - 5:00: Closing Remarks: Irving Weissman, MD**

## Appendix 2

### NIH-FDA Workshop Agenda: Regenerative Medicine Innovation Workshop: Focus on Adult Stem Cells, December 6-7, 2017



With a focus on the development of safe and effective RM products, the workshop will identify critical gaps that must be addressed to enable significant innovation and rapid advancement of RM approaches and will explore issues related to product development and standards, regulatory science, and clinical applications. The framework for Sessions II–IV and VI–VIII is a set of key [questions](#) designed to identify the scientific, technical, and operational challenges as well as to highlight strategies for enabling major transformative advances and the development of clinical applications using adult stem cells. These challenges and opportunities will be explored through the lens of scientific overviews and case studies of clinical science and product development in specific scientific areas that will serve as springboards for in-depth discussions while emphasizing cross-cutting issues with broad applicability to many areas of RM clinical research.

## AGENDA

### DAY 1 Wednesday, December 6

#### 8:00 AM Session I: Introduction

- **Gary Gibbons, MD**, Workshop Co-chair; Director, National Heart, Lung, and Blood Institute, NIH
- **Peter Marks, MD, PhD**, Workshop Co-chair; Director, Center for Biologics and Evaluation Research, FDA
- **Francis Collins, MD, PhD**, Director, NIH
- **Scott Gottlieb, MD**, Commissioner, FDA
- **Sally Temple, PhD**, Scientific Director, Neural Stem Cell Institute

#### 9:15 AM Session II: Musculoskeletal Tissues and Integument

Co-moderators:

- **Stephen Katz, MD, PhD**, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
- **Martha Somerman, DDS, PhD**, Director, National Institute of Dental and Craniofacial Research, NIH
- **Anthony Oro, MD, PhD**, Professor, Dermatology, Stanford University
- **Anthony Ratcliffe, PhD**, President and CEO, Synthasome, Inc.

## Panel Perspectives

- **Constance Chu, MD**, Professor and Vice Chair Research, Department of Orthopedic Surgery, Stanford University
- **Janice Lee, MD**, Clinical Director, National Institute of Dental and Craniofacial Research, NIH
- **Pamela Robey, PhD**, Chief, Skeletal Biology Section, National Institute of Dental and Craniofacial Research, NIH
- **Dennis Roop, PhD**, Professor, Dermatology, University of Colorado Denver
- **B. Lynn Allen-Hoffman, PhD**, Senior Vice President Regenerative Medicine, Stratatech—A Mallinckrodt Company; Professor, Department of Pathology and Department of Surgery, University of Wisconsin School of Medicine and Public Health
- **Joshua Hare, MD**, Director, Interdisciplinary Stem Cell Institute, University of Miami
- **Steve Bauer, PhD**, Chief, Cellular and Tissue Therapies Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

## Discussion of Key Questions

### Open Q&A

11:00 AM Break

## 11:15 AM Session III: Endocrinology

Co-moderators:

- **Nancy Bridges, MD**, Chief of Transplantation Branch, Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, NIH
- **Griffin Rodgers, MD**, Director, National Institute of Diabetes and Digestive and Kidney Diseases, NIH
- **José Oberholzer, MD**, Director, Charles O. Strickler Transplant Center, University of Virginia Health System
- **Felicia Pagliuca, PhD**, Co-Founder and Vice President of Cell Biology Research and Development, Semma Therapeutics
- **Bernhard Hering, MD**, Professor of Surgery and Medicine and Eunice L. Dwan Chair in Diabetes Research, University of Minnesota
- **Jon Odorico, MD**, Professor of Surgery, Director of Pancreas Transplantation, Co-Director of Islet Transplantation, Division of Multi-Organ Transplantation, University of Wisconsin—Madison
- **Klearchos Papas, PhD**, Professor of Surgery, University of Arizona
- **Daniel Pipeleers, MD, PhD**, Professor, Director Diabetes Research Center, Brussels Free University—VUB, Belgium
- **Mo Heidar, PhD**, Cell Therapies Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

1:00 PM Lunch

## 2:00 PM Session IV: Ophthalmology

Co-moderators:

- **Nitin Gogtay, MD**, Director, Office of Clinical Research, National Institute of Mental Health, NIH
- **Paul Sieving, MD, PhD**, Director, National Eye Institute, NIH



### Presentation: State of Clinical Science and Case Study

- **Dennis Clegg, PhD**, Professor, Center for Stem Cell Biology and Engineering, University of California, Santa Barbara
- **David Gamm, MD, PhD**, Associate Professor, Ophthalmology and Visual Sciences, University of Wisconsin–Madison
- **Leonard Levin, MD, PhD**, Professor and Chair, Department of Ophthalmology, McGill University, Montreal, Canada
- **Kapil Bharti, PhD**, Stadtman Investigator, National Eye Institute, NIH
- **Derek Hei, PhD**, BlueRock Therapeutics
- **Sophie Deng, MD, PhD**, Professor of Ophthalmology, University of California, Los Angeles
- **Don Fink, PhD**, Cell Therapies Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

3:45 PM Break

### Moderator:

- **Steven Oh, PhD**, Deputy Director, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA
- **Deborah Hursh, PhD**, Senior Investigator, Cellular and Tissue Therapies Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA
- **Michael Matthay, MD**, Professor, Medicine and Anesthesia, University of California San Francisco

### What are the major product development challenges that must be overcome to accelerate progress in the stem cell field?

- **Deborah Hursh, PhD**, Senior Investigator, Cellular and Tissue Therapies Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA
  - **Anthony Ting, PhD**, Vice President of Regenerative Medicine, Head of Cardiopulmonary Programs, Athersys, Inc.
  - **Michael Matthay, MD**, Professor, Medicine and Anesthesia, University of California San Francisco
  - **Martha Lundberg, PhD**, Program Director, Program Director, Tissue Engineering and Regenerative Medicine, National Heart, Lung, and Blood Institute, NIH
  - **Kelley Rogers, PhD**, Federal Technical Program Manager, Office of Advanced Manufacturing, National Institute of Standards and Technology
- i. Where is there opportunity for collaboration among stakeholders to support product development with adult stem cells, e.g., how can government agencies best partner with each other and stakeholders to move this field forward?
  - ii. What government underwritten networks, consortia, or other resources would be of value in this space (e.g., PACT)?

- iii. What are the key regulatory science questions for stem cell based products that would facilitate translation in this field?
- iv. Are there additional guidances FDA could provide that would provide clarity to sponsors?
- v. Are there assay methods that are ripe for standardization in this field?
- vi. What aspects of government funding and/or regulation affect ability to predict commercial development in this field?

5:30 PM    Adjourn

Co-moderators:

- **Candace Kerr, PhD**, Program Officer, Division on Aging Biology, National Institute on Aging, NIH
- **David Owens, PhD**, Acting Deputy Director, Division of Extramural Research, National Institute of Neurological Disorders and Stroke, NIH
- **Robert W. Mays, PhD**, Vice President of Regenerative Medicine and Head of Neuroscience Programs, Athersys, Inc.
- **Lorenz Studer, MD**, Director, Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center
- **Sean Savitz, MD**, Professor and Frank M. Yatsu Chair, Department of Neurology, University of Texas Health Science Center, Houston
- **Su-Chun Zhang, MD, PhD**, Professor, Neuroscience and Neurology, University of Wisconsin—Madison
- **Scott Burger, MD**, Principal, Advanced Cell & Gene Therapy, LLC
- **Ilyas Singeç, MD, PhD**, Head, Stem Cell Research, National Center for Advancing Translational Sciences, NIH
- **Jane Lebkowski, PhD**, Chief Scientific Officer, Asterias Biotherapeutics
- **Thomas Finn, PhD**, Cell Therapies Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

9:45 AM    Break

Co-moderators:

- **W. Keith Hoots, MD**, Director, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute, NIH
- **Anne Pariser, MD**, Deputy Director, Office of Rare Diseases Research, National Center for Advancing Translational Sciences, NIH
- **Donald Kohn, MD**, Professor of Microbiology, Immunology and Molecular Genetics and Pediatric Hematology/Oncology and Director, Human Gene and Cell Therapy Program, University of California, Los Angeles
- **Robert Negrin, MD**, Chief, Division of Blood and Marrow Transplantation, Stanford University

## Panel Perspectives

- **Harry Malech, MD**, Chief, Genetic Immunotherapy Section, National Institute of Allergy and Infectious Diseases, NIH
- **Kateri Moore, DVM**, Professor, Department of Cell, Developmental and Regenerative Biology, Mount Sinai
- **David Scadden, MD**, Professor of Medicine, Harvard University
- **Linda Kelley, PhD**, Senior Member and Technical Director, Moffitt Cancer Center
- **Robert Sackstein, MD, PhD**, Professor, Dermatology and Medicine, Harvard University
- **Helen Heslop, MD, DSc**, Professor, Medicine and Pediatrics, Baylor College
- **Andrew Byrnes, PhD**, Chief, Gene Transfer and Immunogenicity Branch, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

11:45 AM Lunch

## Co-moderators:

- **James Anderson, MD, PhD**, Director, Division of Program Coordination, Planning, and Strategic Initiatives, NIH
- **Denis Buxton, PhD**, Associate Director, Basic and Early Translational Research Program, Division of Cardiovascular Diseases, NIH
- **Eric Rose, MD**, Professor, Department of Population Health Science and Policy, Mount Sinai School of Medicine
- **Karen Christman, PhD**, Professor, Bioengineering and Associate Dean, University of California, San Diego
- **Laura Niklason, MD, PhD**, Nicholas M. Greene Professor in Anesthesia and Biomedical Engineering, Yale University
- **Nicanor Moldovan, PhD**, Director of 3D Bioprinting Core at IUSM/IUPUI and Associate Research Professor, Indiana University-Purdue University
- **Doris Taylor, PhD**, Director, Regenerative Medicine Research, Texas Heart Institute
- **Lemuel Moyé, MD, PhD**, Professor, Biostatistics, University of Texas Health Science Center, Houston
- **Deborah Hursh, PhD**, Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

2:30 PM Break

## Moderator

- **Ilan Irony, MD**, Deputy Director, Division of Clinical Evaluation, Pharmacology, and Toxicology, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA
- **Larissa Lapteva, MD**, Associate Director, Division of Clinical Evaluation, Pharmacology, and Toxicology, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

### Panel Perspectives & Discussion of Session Questions

- **Larissa Lapteva, MD**, Associate Director, Division of Clinical Evaluation, Pharmacology, and Toxicology, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA
- **Sean Savitz, MD**, Professor and Frank M. Yatsu, MD Chair, Department of Neurology, University of Texas Health Science Center, Houston
- **Eduardo Marbán, MD, PhD**, Director, Heart Institute, Cedars-Sinai
- **Anne Pariser, MD**, Deputy Director, Office of Rare Diseases Research, National Center for Advancing Translational Sciences, NIH

- i. What are the opportunities with design of studies investigating adult stem cell products?
- ii. What are the major challenges for patient recruitment and efficient product development?
- iii. What platforms/stakeholders, other than the manufacturing companies and the FDA, are currently in existence to support product development with adult stem cells?

### Co-moderators:

- **Peter Marks, MD, PhD**, Workshop Co-chair; Director, Center for Biologics and Evaluation Research, FDA
- **Amy Patterson, MD**, Chief Science Advisor, National Heart, Lung, and Blood Institute, NIH
- **Rachael Anatol, PhD**, Deputy Office Director, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA
- **Tom Bollenbach, PhD**, Chief Technology Officer, Advanced Regenerative Manufacturing Institute
- **Ruben Carbonell, PhD**, Chief Technology Officer, The National Institute for Innovation in Manufacturing Biopharmaceuticals
- **John Elliott, PhD**, Cell Systems Science Group Leader, National Institute of Standards and Technology
- **Joshua Hare, MD**, Director, Interdisciplinary Stem Cell Institute, University of Miami
- **Janet Lambert, MBA**, CEO, Alliance for Regenerative Medicine
- **José Oberholzer, MD**, Director, Charles O. Strickler Transplant Center, University of Virginia Health System
- **Anthony Oro, MD, PhD**, Professor, Dermatology, Stanford University
- **Sally Temple, PhD**, Scientific Director, Neural Stem Cell Institute

- **Peter Marks, MD, PhD**, Workshop Co-chair; Director, Center for Biologics and Evaluation Research, FDA
- **Amy Patterson, MD**, Chief Science Advisor, National Heart, Lung, and Blood Institute, NIH

## Key Questions for Clinical Sessions

For given specific applications:

1. What are the major scientific, technical, and operational challenges that must be overcome to accelerate progress in the field?
2. With regard to cell-based therapies:
  - a. What is the optimal stage of cell maturation and differentiation to facilitate safe and efficacious RM therapy?
    - i. In what specific areas is research needed to further define and thus guide decisions on the optimal stage of cell maturation and differentiation?
  - b. How can cell integration and physiologic function be optimized to promote therapeutic effect?
  - c. How can this function be stabilized and sustained?
  - d. How can immune tolerance be enhanced?
  - e. What tools exist and/or need to be developed to:
    - i. Deliver cells to appropriate sites in vivo?
    - ii. Monitor cell function in situ?
    - iii. Track cell fate in situ?
    - iv. Promote self-healing and in vivo repair?
3. What are the primary product development challenges surrounding RM cell-based interventions/products in:
  - a. Scaling-up production (increasing batch size)?
  - b. Scaling-out manufacturing (replicating batches)?
  - c. Single use technologies
  - d. Process analytical technologies
  - e. Modularization
4. What are key attributes of proposed RM interventions/products that demonstrate their readiness to be advanced into clinical trials?
  - a. Critical quality attributes
  - b. Critical process parameters
  - c. Material attributes
5. What are the key regulatory science questions that should be addressed in the next one, three, and five years?

### Appendix 3

## Center for International Blood and Marrow Transplant Research Workshop Agenda: 2018 Cellular Therapy Registry Forum, October 25, 2018

### 2018 Cellular Therapy Registry Forum October 25, 2018

Bethesda North Marriott Hotel and Conference Center Rockville,  
MD

Time	Topic	Presenter
7:45	Breakfast	
8:00	<b>Objectives of the Forum and Overview of the CIBMTR CT Registry</b>	Pasquini
8:20	<b>Role of Registries in Developing and Evaluation of Cellular Therapies</b>	Horowitz
8:40	<b>CAR-T cell Toxicities</b> <ul style="list-style-type: none"> <li>• CRS Grading</li> <li>• Neurotoxicity Grading</li> <li>• Discussion</li> </ul>	Neelapu Santomasso
9:50	Break	
10:05	<b>CAR T cell Toxicities Reporting</b> <ul style="list-style-type: none"> <li>• Overview of the REMS program (FDA)</li> <li>• Pharma perspective (Novartis)</li> <li>• Pharma perspective (Kite)</li> <li>• Centers perspective</li> <li>• Development of an Effective and Streamlined Reporting Process for CAR-T Related Adverse Events</li> <li>• Discussion</li> </ul>	Baird Karimattam Chonzi Nikiforow Perales
12:00	Lunch	
12:45	<b>Cellular Therapy Center Accreditation and Data Auditing</b> <ul style="list-style-type: none"> <li>• Immune Effector Cells and FACT Accreditation</li> <li>• CIBMTR Proposal for Cellular Therapy Auditing</li> </ul>	Warkentin Christianson
1:20	<b>Long term follow-up</b> <ul style="list-style-type: none"> <li>• Long Term follow up in recipients of cell and gene therapies</li> <li>• Direct patient contact and PRO in cell therapies</li> </ul>	Heslop Shaw
2:15	<b>Considerations for capturing biospecimens in cell therapy recipients</b> <ul style="list-style-type: none"> <li>• Approaches to Identify and Track Predictive Biomarkers for Immunotherapy Response and Adverse Events in Hematologic Diseases</li> <li>• Overview of FDA guidance on RCR testing</li> <li>• Approaches for CT Registry</li> </ul>	Paczesny  Schultz Spellman
3:15	Break	
3:30	<b>CMS National Coverage Analysis Process</b>	Szarama

<b>4:10</b>	<b>Role of Federal Agencies on Cellular and Gene Therapies (FDA, HRSA and NIH)</b>	Witten Kuramoto- Crawford Patterson
<b>5:30</b>	<b>CIBMTR's perspective on potential inclusion of cellular therapies in CWBYCTP</b>	Rizzo
<b>5:50</b>	<b>Concluding Remarks</b>	Pasquini
<b>6:00</b>	Adjourn	

## Appendix 4

The National Academies of Sciences, Engineering, and Medicine Forum on Regenerative Medicine Workshop Agenda: 2018 Forum on Regenerative Medicine Meeting, October 18, 2018

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# *The National Academies of* SCIENCES • ENGINEERING • MEDICINE

*Board on Health  
Sciences Policy  
Forum on  
Regenerative  
Medicine*

## Exploring Sources of Variability Related to the Clinical Translation of Regenerative Engineering Products – A Workshop

October 18, 2018

National Academy of Sciences Building  
*Lecture Room*  
2101 Constitution  
Avenue NW  
Washington, DC  
20418

### **Statement of Task:**

The emerging and multidisciplinary field of regenerative engineering aims to repair, regenerate, or replace damaged tissues in the body using a combination of principles and technologies from advanced materials science, developmental/stem cell biology, and immunology. The term “regenerative engineering,” used here to encompass regenerative medicine and tissue engineering, reflects the growing number of research and product development efforts that incorporate elements from both fields. Because regenerative engineered therapies rely on live cells and/or scaffolds, there are inherent challenges in quality control associated with variability in source and final products. Each patient recipient, tissue donor, and product application is unique and therefore the field faces complexities in the development of safe and effective new products and therapies that are not faced by developers of more conventional therapies. To further explore the various factors that contribute to successful regenerative engineering products, an ad hoc committee will plan a one-day public workshop in Washington, DC. Invited speakers and participants may discuss factors and sources of variability in the development and clinical application of regenerative engineering products, characteristics of high-quality products, and how different clinical needs, models, and contexts can inform the development of a product. Speakers may also discuss ways to reduce variability and ensure consistent, high-quality products and improve patient outcomes, share lessons learned, and highlight opportunities for collaboration. A broad array of stakeholders may take part in the workshop, including academic and industry experts, regulators, clinicians, patients, and patient advocates. The ad hoc committee will develop the workshop agenda, select and invite speakers and discussants, and may moderate the discussions. Proceedings of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures.



## AGENDA

8:30 a.m.      **Opening Remarks**

JAY SIEGEL, *Forum Co-Chair*  
Scientific  
Advisor  
Tycho  
Therapeutics,  
Inc.

SHARON TERRY, *Forum Co-Chair*  
Chief  
Executive  
Officer  
Genetic  
Alliance

8:35 a.m.      **Charge to Workshop Speakers and Participants**

MARTHA LUNDBERG, *Workshop Co-Chair*  
Program Director, Division of Cardiovascular  
Sciences Advanced Technologies and Surgery Branch  
National Heart, Lung, and Blood  
Institute National Institutes of  
Health

KATHY TSOKAS, *Workshop Co-Chair*  
Regulatory Head of Regenerative Medicine & Advanced  
Therapy Johnson & Johnson

8:45 a.m.      **Stage Setting – The Impact of Variability on Regenerative Engineering Products**

GUILLERMO AMEER  
Daniel Hale Williams Professor of Biomedical Engineering and Surgery  
Director, Center for Advanced Regenerative Engineering  
Northwestern University

<b>SESSION I: USING CASE STUDIES TO IDENTIFY THE SOURCES OF VARIABILITY ASSOCIATED WITH REGENERATIVE THERAPIES</b>
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Session Objective:

- To gain a better understanding of the sources of variability associated with regenerative engineering products through a series of case studies.

*Session Moderator: Cato Laurencin, University Professor, Director, Institute for Regenerative Engineering, University of Connecticut*

9:05 a.m.      **CASE STUDY 1: VARIABILITY IN THE USE OF MESENCHYMAL STEM CELLS FOR TREATING CARDIOMYOPATHY**

**IVONNE HERNANDEZ SCHULMAN**

Professor of Clinical Medicine  
University of Miami Miller School of Medicine

9:20 a.m.      **CASE STUDY 2: SOURCES OF VARIABILITY IN PRECLINICAL AND CLINICAL RESEARCH ON STEM CELL THERAPIES FOR ALS**

CLIVE SVENDSEN  
Kerry and Simone Vickar Family Foundation Distinguished Chair in Regenerative Medicine  
Cedars-Sinai Medical Center

9:35 a.m.      **CASE STUDY 3: VARIABILITY IN THE DEVELOPMENT OF CELLULAR THERAPIES**

DAVID STRONCEK  
Chief, Cell Processing Section  
Department of Transfusion Medicine  
NIH Clinical Center

9:50 a.m.      Panel Discussion with Speakers and Workshop Participants

10:20 a.m.      **Break**

**SESSION II: CONSIDERING THE FACTORS THAT CONTRIBUTE TO PATIENT VARIABILITY AND APPROACHES TO ADDRESSING THOSE DIFFERENCES**

Session Objectives:

- Discuss factors that contribute to patient variability such as a patient's genetics, the severity of their condition, past treatments, the placebo effect, and the patient's built environment/geography.
- Examine the feasibility of a precision medicine approach that would target the right patient with the right regenerative engineering therapy.

*Session Moderator: Brian Fiske, Senior Vice President, Research Programs, Michael J. Fox Foundation*

10:35 a.m.      JENNIFER ELISSEFF  
Morton Goldberg Professor  
Wilmer Eye Institute and Biomedical Engineering, Translational Tissue Engineering Center  
Johns Hopkins University

10:50 a.m.      JOSEPH WU  
Director, Stanford Cardiovascular Institute  
Simon H. Stertzer, MD, Professor of Cardiovascular Medicine & Radiology  
Stanford University School of Medicine

11:05 a.m.      STEVE BADYLAK  
Professor of Surgery  
McGowan Institute for Regenerative Medicine  
University of Pittsburgh

- 11:20 a.m. FLAGG FLANAGAN  
Chief Executive Officer & Chairman of the Board  
Discgenics
- 11:35 a.m. Panel Discussion with Speakers and Audience Members
- 12:05 p.m. **Working Lunch**

### SESSION III: THE IMPORTANCE OF ADDRESSING VARIABILITY IN DONOR TISSUES AND CELLS

#### Session Objectives:

- Consider the sources of variability among donor tissues and cells such as the source (e.g., bone marrow, adipose, cord blood), the dose, route of administration, and culture conditions, among other factors.
- Discuss methods to address the variability among source tissues and cells so that patients receive a consistent and effective product.

*Session Moderator: Martha Lundberg, Program Director, Division of Cardiovascular Sciences,  
Advanced Technologies and Surgery Branch, NHLBI*

- 1:00 p.m. ANDREW FESNAK  
Assistant Professor of Clinical Pathology and Laboratory Medicine  
University of Pennsylvania Perelman School of Medicine
- 1:15 p.m. GEORGE MUSCHLER  
Staff Member, Department of Biomedical  
Engineering Cleveland Clinic
- 1:30 p.m. ALLISON HUBEL  
Professor of Mechanical  
Engineering University of  
Minnesota
- 1:45 p.m. Panel Discussion with Speakers and Audience Members
- 2:15 p.m. **Break**

### SESSION IV: THE IMPORTANCE OF ADDRESSING VARIABILITY AND MEETING QUALITY EXPECTATIONS IN THE MANUFACTURING SETTING

#### Session Objectives:

- Explore the translational research priorities for the maturing of the fields of tissue science and regenerative engineering.
- Describe advances in preservation technologies needed to sustain fragile cells and tissues under biologically optimized conditions for storage, shipment and handling.
- Discuss metrics for reproducibility, robustness, and user-friendliness that will enable the broad distribution of products.

*Session Moderator: Krish Roy, Robert A. Milton Endowed Chair and Director, Center for ImmunoEngineering,  
Georgia Tech*

- 2:30 p.m.      CARL BURKE  
BioTherapeutics  
Development  
Johnson & Johnson
- 2:45 p.m.      MICHELE MYERS  
Senior Director, Cell Process  
Development  
Cell and Gene Therapy Platform  
GSK
- 3:00 p.m.      ERIK FINGER  
Assistant Professor, Department of  
Surgery University of Minnesota
- 3:15 p.m.      Panel Discussion with Speakers and Workshop Participants

<b>SESSION V: EXPLORING OBJECTIVE METRICS AND OUTCOMES FOR CLINICAL TRIALS AND THE REGULATORY APPROVAL PATHWAY</b>
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Session Objectives:

- Discuss ideas for objective metrics and reliable approaches to interpreting the outcomes of clinical trials of regenerative engineering therapies.
- Explore how variability in regenerative engineering products can affect the regulatory approval pathway.

*Session Moderator: Kathy Tsokas, Regulatory Head of Regenerative Medicine & Advanced Therapy, Johnson & Johnson*

- 3:45 p.m.      KAREN CHRISTMAN  
Scientific  
Co-Founder  
Ventrix
- 4:00 p.m.      PETER MARKS  
Director  
Center for Biologics Evaluation and Research  
U.S. Food & Drug Administration
- 4:15 p.m.      Panel Discussion with Speakers and Workshop Participants
- 4:35 p.m.      **Final Panel Discussion**
- CARL BURKE  
KAREN CHRISTMAN  
ALLISON HUBEL  
PETER MARKS  
CLIVE SVENDSEN

5:00 p.m.      **Final Remarks from Workshop Co-chairs**

MARTHA LUNDBERG, *Workshop Co-Chair*  
Program Director, Division of Cardiovascular Sciences  
Advanced Technologies and Surgery Branch  
National Heart, Lung, and Blood Institute  
National Institutes of Health

KATHY TSOKAS, *Workshop Co-Chair*  
Regulatory Head of Regenerative Medicine & Advanced  
Therapy Johnson & Johnson

5:10 p.m.      **Adjourn**

## Appendix 5

### Supporting References for Research Vignettes

#### Vignette 1: Age-related Macular Degeneration

- i. Schwartz SD, et al. Subretinal transplantation of embryonic stem cell-derived retinal pigment epithelium for the treatment of macular degeneration: an assessment at 4 years. *Invest Ophthalmol Vis Sci* 2016; 57: ORSFC1–9.
- ii. Mandai M, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. *N. Engl. J. Med.* 2017;377:792–793.
- iii. da Cruz L, et al. Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. *Nat Biotechnol* 2018; 36: 328–337.
- iv. Kashani AH, et al. A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. *Sci Transl Med.* 2018;10: 1–11.
- v. Sharma R, et al. Clinical-grade stem cell–derived retinal pigment epithelium patch rescues retinal degeneration in rodents and pigs. *Sci Transl Med.* 2019. Jan 16: 11, 475, eaat5580.
- vi. Tu HY, et al. Medium- to long-term survival and functional examination of human iPSC-derived retinas in rat and primate models of retinal degeneration. *EBioMedicine.* 2018;39:562–574.
- vii. Mandai M, et al. iPSC-derived retina transplants improve vision in rd1 end-stage retinal-degeneration mice. *Stem Cell Rep.* 2017;8:69–83.
- viii. Koss MJ, et al. Subretinal implantation of a monolayer of human embryonic stem cell-derived retinal pigment epithelium: a feasibility and safety study in Yucatan minipigs. *Graefes Arch Clin Exp Ophthalmol.* 2016; 254: 1553–1565.
- ix. [nei.nih.gov/health/maculardegen](http://nei.nih.gov/health/maculardegen)
- x. [www.macular.org/what-macular-degeneration](http://www.macular.org/what-macular-degeneration)
- xi. [www.allaboutvision.com/conditions/amd.htm](http://www.allaboutvision.com/conditions/amd.htm)

#### Vignette 2: Heart Failure

- i. Westerdahl DE, et al. Allogeneic mesenchymal precursor cells (MPCs): an innovative approach to treating advanced heart failure. *Expert Opin Biol Ther.* 2016 Sep;16(9):1163–9.
- ii. Perin EC, et al. A Phase II dose-escalation study of allogeneic mesenchymal precursor cells in patients with ischemic or nonischemic heart failure. *Circ Res.* 2015 Aug 28;117(6):576–584.
- iii. Ascheim DD, et al. Mesenchymal precursor cells as adjunctive therapy in recipients of contemporary left ventricular assist devices. *Circulation.* 2014 Jun 3;129(22):2287–2296.
- iv. Yau T, et al. Intramyocardial injection of mesenchymal precursor cells and successful temporary weaning from left ventricular assist device support in patients with advanced heart failure: A randomized clinical trial. *JAMA.* 2019 March;321(12): 1176–1186.
- v. Curfman G. Stem cell therapy for heart failure—an unfulfilled promise? *JAMA.* 2019 March;321(12): 1186–7.
- vi. [www.nhlbi.nih.gov/health-topics/heart-failure](http://www.nhlbi.nih.gov/health-topics/heart-failure)

#### Vignette 3: Osteoarthritis/Joint Pain

- i. McIntyre JA, et al. [Intra-articular Mesenchymal Stem Cell Therapy for the Human Joint: A Systematic Review](#), *Am J Sports Med.* 2018 Dec;46(14):3550–3563.
- ii. Borakati A, et al. [A Systematic Review And Meta-Analysis of Clinical Trials of Mesenchymal Stem Cell Therapy for Cartilage Repair](#) *Curr Stem Cell Res Ther.* 2018 Feb 23;13(3):215–225.
- iii. Alcerro JC, Lavernia CJ, Stem Cells and Platelet-rich Plasma for Knee Osteoarthritis: Prevalence and Cost in South Florida, *J Am Acad Orthop Surg.* 2018 Nov 28 [Epub ahead of print]

- iv. Broeckx S.Y., et al. The use of equine chondrogenic-induced mesenchymal stem cells as a treatment for osteoarthritis: a randomized, double-blinded, placebo-controlled proof-of-concept study. 27 February 2019 BEVA Equine Veterinary Journal.  
<https://doi.org/10.1111/evj.13089>
- v. Broeckx S.Y., et al. Equine allogeneic chondrogenic induced mesenchymal stem cells are an effective treatment for degenerative joint disease in horses. *Stem Cells and Development*, Vol. 28(6). Published Online: 8 Mar 2019 <https://doi.org/10.1089/scd.2018.0061>
- vi. Cabon Q, et al. Long-term safety and efficacy of single or repeated intra-articular injection of allogeneic neonatal mesenchymal stromal cells for managing pain and lameness in moderate to severe canine osteoarthritis without anti-inflammatory pharmacologic support: pilot clinical study. *Front Vet Sci*. 2019 Feb 5;6:10. doi: 10.3389/fvets.2019.00010. eCollection 2019
- vii. Gugjoo MB, et al. Mesenchymal stem cell basic research and applications in dog medicine. *J Cell Physiol*. 2019 Feb 20. doi: 10.1002/jcp.28348. [Epub ahead of print]
- viii. [www.arthritis.org/about-arthritis/types/osteoarthritis/what-is-osteoarthritis.php](http://www.arthritis.org/about-arthritis/types/osteoarthritis/what-is-osteoarthritis.php)

## **REPORT TO CONGRESS**

### **Applications for Regenerative Medicine Advanced Therapies**

**Required by Section 3035 of the  
21<sup>st</sup> Century Cures Act (Public Law 114-255)**

**Food and Drug Administration  
Department of Health and Human Services**



## **Executive Summary**

This report to Congress is being provided in accordance with section 3035 of the 21<sup>st</sup> Century Cures Act (Cures Act), Pub. L. 114-255, which was enacted on December 13, 2016. This report provides information on the efforts taken by the Food and Drug Administration (FDA or the Agency) to implement a new designation program established under the Cures Act for regenerative medicine therapies to expedite their development and review, as well as information about applications for approval of such products. The information provided covers the period from enactment of the Cures Act on December 13, 2016, to the end of calendar year (CY) 2017 on December 31, 2017.

## I. Introduction

The Cures Act was enacted on December 13, 2016. The legislation includes a variety of provisions that affect the activities of FDA and other agencies within the Department of Health and Human Services (HHS) on a broad range of topics related to the development, review, approval, and delivery of medical products, including regenerative medicine. Section 3035(a) of the Cures Act requires that the Secretary of HHS report information regarding applications for approval of regenerative advanced therapies (referred to by FDA as “Regenerative Medicine Advanced Therapies” or “RMATs”) with respect to the previous calendar year. This provision provides:

*(a) REPORT TO CONGRESS.—Before March 1 of each calendar year, the Secretary of Health and Human Services shall, with respect to the previous calendar year, submit a report to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives on—*

*(1) the number and type of applications for approval of regenerative advanced therapies filed, approved or licensed as applicable, withdrawn, or denied; and*

*(2) how many of such applications or therapies, as applicable, were granted accelerated approval or priority review.*

## II. Accelerated Approval for Regenerative Advanced Therapies

Regenerative medicine is a rapidly expanding field that has the potential to treat serious or life-threatening diseases or conditions (referred to as “serious conditions” in the remainder of this report), particularly in patients with unmet medical needs. The Cures Act includes several provisions related to regenerative medicine. In particular, section 3033 of the Cures Act builds on FDA’s existing expedited programs available to regenerative medicine products and amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to establish a new program to foster their development and review through the new RMAT designation. A drug (including a biologic) is eligible for RMAT designation if (1) it is a regenerative medicine therapy,<sup>6</sup> (2) it is intended to treat, modify, reverse, or cure a serious condition, and (3) preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs in such disease or condition.<sup>7</sup> A sponsor may request designation concurrently with, or any time after, the filing of an investigational new drug application (IND); FDA is required to respond to the request within 60 days.

Upon designation, sponsors of RMATs are eligible for increased and earlier interactions with FDA to help facilitate efficient development programs for, and expedited review of, such

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<sup>6</sup> Regenerative medicine therapy is defined in section 506(g)(8) of the FD&C Act as “includ[ing] cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and Title 21 of the Code of Federal Regulations Part 1271.”

<sup>7</sup> Section 506(g) of the FD&C Act.

therapies, including early discussions of any potential surrogate or intermediate endpoints to support accelerated approval. In addition, an application for approval of an RMAT may be eligible for priority review and accelerated approval if supported by clinical data at the time it is submitted and approved, respectively. If an RMAT is granted accelerated approval, section 3033 also addresses potential ways that sponsors may satisfy post-approval requirements.

As explained in more detail below, due to the relatively recent establishment of the RMAT designation program, there are not yet any applications for approval of RMATs filed, approved or licensed, as applicable, withdrawn, or denied, and, accordingly, no such applications for RMATs have been granted priority review or accelerated approval. Still, FDA's robust efforts to implement the RMAT designation program in CY 2017, described below, have laid the foundation to help support a strong pipeline of innovative regenerative medicine therapies.

### **III. Efforts to Establish the RMAT Designation Program**

Following enactment of the Cures Act, FDA's Center for Biologics Evaluation and Research (CBER) immediately moved forward with implementation of the new RMAT designation program, receiving the first RMAT designation request on the day after the Cures Act was signed into law. In addition to responding to individual sponsor requests for RMAT designation and other inquiries about the designation program, CBER engaged in a concerted effort to educate stakeholders about the new designation program. This included posting information on its website about the designation program in early 2017,<sup>8</sup> and participating in webinars and stakeholder meetings on regenerative medicine throughout the year.

In November 2017, as part of its comprehensive regulatory framework for regenerative medicine products, CBER published a draft guidance on expedited programs that are available to regenerative medicine therapies, including information about the new RMAT designation program.<sup>9</sup> The draft guidance also describes the regenerative medicine therapies that may be eligible for RMAT designation—including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271), as well as gene therapies that lead to a durable modification of cells or tissues (including genetically modified cells).

### **IV. RMAT Designations and Applications for Approval of RMATs**

As noted, CBER received the first request for RMAT designation on December 14, 2016,

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<sup>8</sup> Available at <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm>. Please also see "This is Not a Test: RMAT Designation Goes Live; FDA Voice blog" (March 2017), available at <https://blogs.fda.gov/fdavoices/index.php/2017/03/this-is-not-a-test-rmat-designation-goes-live/>.

<sup>9</sup> Expedited Programs for Regenerative Medicine Therapies for Serious Conditions – Draft Guidance for Industry (November 2017), available at <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585414.pdf>. When finalized, this guidance will represent FDA's thinking on the topic.

immediately after the Cures Act was signed into law. Between enactment of the Cures Act on December 13, 2016, and December 31, 2017, CBER received 43 requests for RMAT designation and acted upon 34 of those requests, with 7 still pending an action and 2 withdrawn by the sponsor. CBER granted 13 RMAT designations during this time (38 percent of those acted upon). CBER acted upon all of the designation requests received at least 60 days prior to December 31, 2017, within the 60-day period required under the statute. The table below summarizes this information.

### **Regenerative Medicine Advanced Therapy Designations**

<i>Year</i>	<i>Requests Received</i>	<i>Requests Granted</i>	<i>Requests Denied</i>	<i>Requests Pending</i>	<i>Requests Withdrawn</i>
<i>CY 2016<sup>10</sup></i>	3	0	3	0	0
<i>CY 2017</i>	40	13	18	7	2
<b>Total</b>	<b>43</b>	<b>13</b>	<b>21</b>	<b>7</b>	<b>2</b>

Between December 13, 2016, and December 31, 2017, no applications for approval (biologic license or new drug applications) for RMATs were filed, approved or licensed, as applicable, withdrawn, or denied.<sup>11</sup> Consequently, no applications for approval of RMATs were granted priority review or accelerated approval between December 13, 2016, and December 31, 2017. Since many of the benefits of RMAT designation are accrued during frequent interactions with FDA early in the development process, sponsors who were close to completing their clinical trials or submitting applications for approval at or around the time of establishment of the RMAT designation program in December 2016 were unlikely to request RMAT designation.<sup>12</sup> Moving forward, FDA anticipates that a number of RMAT-designated products will enter the approval phase of their development programs.

## **V. Conclusion**

FDA is committed to facilitating the development and review of RMATs to help ensure they are licensed or approved and available to patients with serious conditions as soon as it can be determined that they are safe and effective for their intended uses. FDA's implementation of the regenerative medicine-related provisions of the Cures Act, including the new RMAT designation program, is a key part of the Agency's efforts to encourage the development of innovative, safe, and effective products using the tools provided by the Cures Act.

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<sup>10</sup> CY 2016 covers December 13, 2016, when the Cures Act was enacted, to December 31, 2016.

<sup>11</sup> We note that "filed, approved or licensed, as applicable, withdrawn, or denied" refer to actions that FDA would take on an application submitted for marketing approval, e.g., a biologic license or new drug application, for an RMAT-designated product, rather than an action FDA would take on a request submitted for RMAT designation.

<sup>12</sup> For example, CBER approved biologics license applications for three gene therapies in 2017 that were not designated as RMATs, but would have been eligible for RMAT designation as regenerative medicine therapies if such designation had been requested by their sponsors and they had met the other criteria. The approved gene therapies received Breakthrough Therapy designation during their clinical development.

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