Available online at www.sciencedirect.com
ScienceDirect
Biologicals 37 (2009) 103–107
IABS BIOLOGICALS
www.elsevier.com/locate/biologicals

Stem cell and cellular therapy developments

Michael Strong [a], Albert Farrugia [b], Paolo Rebulla [c,*]

[a] Northwest Tissue Center, Puget Sound Blood Center, USA
[b] Head, Blood and Tissues Unit, Office of Devices, Blood and Tissues, Therapeutic Goods Administration PO Box 100 Woden, ACT 2606, Australia
[c] Center of Transfusion Medicine, Cellular Therapy and Cryobiology, Department of Regenerative Medicine, Foundation IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Via Francesco Sforza 35, 20122 Milan, Italy

Received 9 January 2009; accepted 9 January 2009

Abstract

Recent discoveries on human and non-human stem cells have prompted the development of several studies aimed at the translation of laboratory evidences into novel clinical procedures collectively known as 'cellular therapy'.

In this regard, a number of features specifically related to the clinical setting require stringent evaluation, including, but not limited to: ethical appropriateness; donor and recipient informed consent; autologous versus allogeneic use; media and devices for cell collection, processing, characterization, storage and distribution; donor and recipient adverse events registration and management; risk-to-benefit and cost analysis; outcome analysis; production sites accreditation and management; regulatory oversight.

This article describes recent national and international developments related to the distribution of cells and tissues for clinical use. Moreover, an example is reported of the implementation of a cellular therapy production site compliant with good manufacturing practices (GMPs) in a large European University hospital.

Keywords: Tissue; Cells; GMP; Transplants

1. Changing paradigms in tissue distribution

Michael Strong, PhD, (dmichaelstrong@mac.com)

The first record of allograft transplantation dates back to the 16th century, with paintings depicting the physicians, Cosmos and Damien, transplanting a limb from a dead Moor onto a patient whose leg had been amputated. Modern day tissue banking was initiated in the U. S. Navy by an Orthopaedic surgeon in 1949 [1]. Since that time, a great deal of change has occurred in tissue banking. In the most recent survey by the American Association of Tissue Banks (AATB), the number of tissue donors recovered in the year 2000 was 18,021, which increased to over 23,295 in 2003. During this same period of time, the number of musculoskeletal grafts distributed increased from 675,370 to 1.28 million. This large increase in collections and distribution has been largely fuelled by the increased involvement of for-profit organizations and partnerships between non-profit tissue banks and for-profit device manufacturers. As a result, a large amount of money is being generated in this industry and has resulted in practices that have had an impact on the level of safety concerns by various agencies. In 2004, a report in the New England Journal of Medicine [2] described 14 patients with *Clostridium* infections associated with musculoskeletal tissue allografts. This resulted in emergency federal regulation that necessitated various record keeping requirements and validation data for prevention of infectious disease contamination. In 2005, a report described a number of hepatitis C virus (HCV) transmissions to several organ and tissue recipients from a donor that was antibody negative, but later determined to be nucleic acid reactive for HCV. This case generated much publicity because of the numbers of organs and tissues produced from a single donor and the resulting 44 transplants and 40 recipients. There were 32 recipients tested of which 5 were HCV positive

* Corresponding author.
E-mail addresses: dmichaelstrong@mac.com (M. Strong), albert.farrugia@health.gov.au (A. Farrugia), prebulla@policlinico.mi.it (P. Rebulla).

1045-1056/09/$36.00
doi:10.1016/j.biologicals.2009.01.003

infected. Many of these tissue recipient infections would have been prevented if recognition of infected organ recipients had resulted in notifying the tissue bank before tissue was processed and distributed [3].

The Centers for Disease Control (CDC) sponsored an organ and tissue safety workshop in 2005 to promote a better network within and between the organ and tissue community. From that workshop also came a number of recommendations including the development of unique donor identification system linking organs and tissues, clear mechanisms for adverse event reporting by health-care facilities, stronger information dissemination systems to a broader array of clinicians and health professionals as well as patients, and a notification algorithm for trace-back and trace-forward tracking. This system is now being developed by the United Network for Organ Sharing (UNOS) under contract from CDC and is called the Transplantation Transmission Sentinel Network (TTSN). In 2005, the Joint Commission (TJC) for the Accreditation of Hospital Organizations published standards relating to tissue storage and issuance. These standards require the assignment of responsibility for handling tissue within a hospital to a single coordinating entity. The oversight responsibility includes supplier certification, incoming inspection and logging in of tissue, traceability and record keeping, storage temperature monitoring, investigation of adverse outcomes, reporting tissue related infections to the tissue supplier, sequestering tissue reported by the supplier as contaminated, the notification of surgeons and recipients if tissue donors are subsequently found to harbor infection, and compliance with federal and state regulations if supplying tissues to any other facility. Hospitals in the US must comply with TJC requirements. In many cases, hospitals have turned to their blood bank, where many of these capabilities are already in existence. As a result, the AABB (formerly the American Association of Blood Banks) established a tissue task force to begin to develop guidance documents and assistance to blood banks to prepare for managing tissue within their facilities. The AABB Task Force, in an attempt to better understand how tissue was being managed within hospitals, prepared a survey that was distributed to hospital institutional members. The survey contained questions on tissue types, the breadth of responsibility, and facilities within hospitals responsible for tissue. Of the 904 institutional members invited to participate, 402 gave interpretable responses; 325 reported the use of allogeneic or autologous human tissue. The department of surgery (e.g. the operating room) (76%) was the most likely hospital department to have any responsibility for tissue use, followed by the blood bank (51%). Surgery departments were most frequently responsible for tissue handling, documenting use, and for adverse event reporting; for the latter category only 23% reported infection control responsibilities [4]. Recent workshops, sponsored by the AABB at the annual meeting, suggest that transfusion services in hospitals are more likely to be given increased responsibilities for many of these activities.

In May of 2005, the FDA published its final rule identifying the requirements for tissue banks in the recovery, processing and distribution of tissue in the US. During 2005, a report from the State of New York identified a serious problem with donor recovery being done outside of all standards and regulations. It was discovered that an organization was recovering donors from funeral homes without the permission of families, without adequate medical screening, and were, in many cases, falsifying records. Tissue was sold to a number of processing centers and distributed. Over 1000 donors were recovered during a 3-year period of time. Nearly 50,000 tissues were produced of which 15,000 could be recalled prior to transplantation. An estimated 25,000 tissues were distributed to hospitals and recipients of which 2000 could not be traced, an estimated 800 outside of the U.S. This identified, once again, the complications and difficulties of tracing tissues, particularly when there is concern about safety. As a result, legislation has also been proposed to better regulate this industry and has further emphasized the need for consolidation and monitoring of tissue distribution within the hospital setting. Thus, major changes are taking place in establishing better reporting systems and improving the ability of organizations to trace suspect tissues to recipients. The AABB, in collaboration with AATB and EBAA, is fully engaged in participation in this effort and has been working on guidelines and publications to assist hospital organizations in managing tissue in the future.

2. International regulatory oversight of cells and tissues

Albert Farrugia, PhD, (Albert.Farrugia@health.gov.au)

Therapeutic goods derived from biological sources have, with some exceptions, continued to be regulated along traditional principles until recently. This has led to regulatory models developed for mainstream pharmaceuticals being applied for biological products, not always with successful results. As the practice of transplantation medicine has grown to include more processed products, the risks to patients and the community have increased while the number of therapeutic benefits has expanded. With the ongoing advances in stem cell biology, bolder interventions are being attempted, and the expansion in therapeutic claims hints at being limitless. Concurrent concerns originating from the blood sector have put infectious disease risks foremost in the public, political and hence, regulatory-mind. Such concerns have underpinned the new regulatory pathways which agencies have developed over the past decade. While always conforming to national imperatives, such pathways have, probably unintentionally, assumed a number of common features [5]. In particular, an approach tailored to the level or risk, in contrast to the ‘one size fits all’ of traditional pharmaceutical paradigms, has been a common feature. Thus, with traditional transplantation products with little or no manufacture, minimisation of infectious risks and appropriate manufacturing principles have been deemed sufficient by most authorities. Challenges at this level include the hospital – manufacturing interface – as many of these products continue to be produced in a hospital environment with dedicated banking and processing facilities still reliant on hospital laboratories for essential services like infectious marker testing.