Cell Banking for Cell and Gene Therapy

Regulatory, Ethical, and Scientific Considerations

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Regenerative medicine holds great potential for human disease management, with hundreds of cell and gene therapy (CGT) products for tissue/organ reconstitution or replacement in different stages of development and clinical testing for toxicity, safety, and efficacy. For example, currently more than 60 CGTs have marketing authorization (although many with only conditional approval) from central regulatory agencies worldwide (**1**). Those products are treating conditions such as hematopoietic malignancies, immunological disorders, and cartilage disorders. Most of those treatments use culture-expanded autologous or allogeneic cells — some of which are genetically modified, such as for chimeric antigen receptor (CAR) T-cell gene-therapy products.

Nevertheless, the tangible clinical promise of cell, gene, and tissue therapies also has brought about the emergence of tagalong marketing for services both legitimate and dubious, including speculative private human-cell banking services. By contrast with cord-blood banking (discussed below), such speculative companies focus on long-term cell storage with an unclear path to clinical translation. At present, they store

- cultured or unexpanded dental pulp cells from extracted teeth (pediatric and adult patients)
- peripheral blood mononuclear cells (PBMCs) for supposed future derivation of induced pluripotent stem cells
- PBMCs for future production of CAR T cells.

Most private cell banks charge a collection fee as well as monthly, yearly, multiyear, or lifetime storage fees. The rationale behind such services is that cryopreserved cells offer some type of "insurance" allegedly for future use in treatment of a range of diseases, depending on the cell source. For example, T-cell banks claim explicitly or implicitly that cryopreserved PBMCs originating from a small blood draw could be used for approved CAR-T therapies and for CAR-T therapeutic applications that are currently in preclinical stages. Such vague claims are problematic for a number of scientific, ethical, and regulatory reasons.

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Differences Between Public and Private Cell Banking

The issue of public-or-private banking of potentially therapeutic cells is exemplified by umbilical-cord blood banking, which now has been an option for over two decades. Two main types of cord blood banks are storing cord blood units for potential future use: for-profit private cord-blood banks and public cord-blood banks that usually are not for profit. The latter implement collections at certain hospitals throughout the world and store cord-blood units for future use by individuals who are candidates for hematopoietic stem-cell transplantation and have suitably matched units in those banks.

Private cord-blood banks are for-profit organizations that collect and store umbilical cord blood for families for a fee. In this case, families choose to bank their infants' cord blood so that it might be used later as a source of hematopoietic stem cells for the child or another family member. These cord-blood banks provide families with collection kits, generally depending on the mothers' obstetrics teams to collect umbilical cord blood upon delivery of a baby and transport samples to a company's cell processing facility. Currently, the American Academy

of Pediatrics (AAP) discourages parents from storing their infants' umbilical cord blood in such private banks as so-called "biologic insurance" against potential future diseases unless a sibling is present who could benefit from cord-blood transplantation for an approved medical indication (**2**).

By contrast, the AAP identifies public cord-blood banking as the "preferred method of collecting, processing, and using cord blood cells for use in transplantation" (**2**). A similar position has been adopted by the American College of Obstetricians and Gynecologists, which considers "public umbilical cord blood banking [to be] the recommended method of obtaining umbilical cord blood for use in transplantation, immune therapies, or other medically validated indications" (**3**).

For public banks, high standards of selection, collection, shipment, characterization for human leukocyte antigen (HLA) typing and cell counting, testing for infectious disease markers, and cryopreservation processing of donated units are essential to ensure the quality and safety of the cord-blood units for potential future transplantation. Within the United States, however, private cord-blood banking is much less regulated. Furthermore, a combination of strong financial incentives, limited interest or experience, and the opaque nature of the for-profit private cord-blood banking industry makes it unclear whether due processes are followed for collection, labeling, processing, shipment, chain of custody, testing, and characterization based on a 2011 regulatory guidance document (**4**).

Major safety concerns arise even for the very remote chance that umbilical cord-blood cells could be used in an autologous setting. The less-regulated nature of private cord-blood banks, their lack of standardized characterization and validated processing procedures, and the fact that it remains unclear how long umbilical cord-blood cells remain viable when cryopreserved and stored under unknown conditions pose such questions. The emotional vulnerability of parents who want to do everything possible for their children is akin to that of newly diagnosed cancer patients and their families.

For-profit enterprises might not reflect accurately the limitations of cell banking, including the low likelihood that a privately banked cord-blood unit ever will be used. Seldom (if ever) do they make transparent in their marketing or communications the lack of quality systems or validation of cell quality/quantity to serve as useful raw materials for future clinical applications. Furthermore, adding to the complexity of legal and ethical aspects of private banking is the issue of who carries the liability for the quality of cord-blood units: the physician who performs collection for private banking, the cord-blood bank itself, or the physicians who later use that cord blood bank for an approved or speculative indication?

Major SAFETY CONCERNS arise even for the very remote chance that umbilical cord-blood cells could be used in an autologous setting.

By contrast with public (and *some* private cord blood banks) that are subject to quality control through regulation and accreditation, commercial cell banking for other cell types is characterized by a number of shortcomings that limit the potential for clinical translation of the services offered. Advertising of those services often is characterized by dramatic overtones, emotional appeal through deceptive patient testimonials, and a sense of urgency — all of which are in discordance with the actual therapeutic potential of cryopreserved cells.

Furthermore, the range of purported therapeutic applications often is exaggerated or not supported by scientific evidence. For example, claims that dental stem cells of neural crest origin have the potential for use in endodermal cell replacement (e.g., endocrine, pancreas, and hepatocytes) conflict with the current state of the science in developmental biology. Additionally, the absence of a clearly defined regulatory pathway from banked cells to future cell-replacement therapies undermines their theoretical therapeutic value.

T Cells for CAR-T

All those problems are exemplified by T-cell banking for future cellular immunotherapies. CAR-T cell therapies have received marketing authorization in a number of jurisdictions — including the United States, European Union, Switzerland, Japan, Australia, and Canada — but only for a small subset of hematopoietic malignancies (mainly certain types of lymphoma and pediatric acute lymphoblastic leukemia) and only after failure of other treatment approaches. Intense research efforts are ongoing to develop CAR-T therapies with wider application (e.g., against solid tumors) and reduced systemic toxicity. But their routine clinical application beyond currently approved regulatory indications is far from established. Thus, the advertisement of T-cell

Problems with Speculative Cell Banking Services

- Unclear scientific rationale to suggest potential clinical use
- Lack of a defined regulatory pathway for clinical translation
- Lack of a standardized approach to ensure use of cryopreserved cells in cell/gene product manufacturing
- Inadequate disclosure of information to patients (does not enable proper informed consent)
- Vague, unsupported marketing claims of future clinical applications

banking services to healthy individuals, recently diagnosed cancer patients, those with cancers that are not known to respond to CAR T cells, or others as "insurance" against future cancer conditions does not correspond to realistic clinical therapy.

The number of T cells contained in a blood draw used for PBMC cryopreservation is highly unlikely to be sufficient to make for a sample that will be useful in clinical development of a CAR-T therapy. Furthermore, even if private banks could collect and store enough cells through an apheresis procedure, the potential need for T-cell genetic manipulation and expansion requires current good manufacturing practice (CGMP) conditions that seldom — if ever — are adhered to by profit-based services. Appropriate samples need to be taken for in-process and final-product release testing, and the chain of custody from cryopreserved cells to manufactured product must be clearly defined. Cell-banking services do not meet those conditions at present. Legal implications will make use of such banked cells by pharmaceutical companies or hospital-based cell therapy facilities highly unlikely. For example, who would be responsible if such banked cells were used for CAR T-cell production, but the final products either did not work or caused side effects?

Such issues exemplify the information asymmetry between providers of T-cell banking and the individuals who are considering cryopreserving their own T cells. In principle, a strong informed-consent process could help address those concerns; in practice, the potential risks such a process would pose to the cell-banking business model renders the very notion of informed consent problematic.

The business model for cord-blood banking presents certain parallels with that of unproven, direct-to-consumer cell-based interventions (**5**). In accordance with a previous publication by the International Society for Cell and Gene Therapy's

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(ISCT's) Presidential Task Force on the Use of Unproven Cellular Therapies, we attempt to define common characteristics of speculative cell-banking services (see box, above right). As such, the same concerns about truthful advertising and potentially deceptive practices in unproven "stem-cell" interventions may be applicable (**6–8**).

The Need for a Public Option

As offered today, private cell-banking services for future disease treatments are misleading. They can create false hope while capitalizing on consumer fears about future health issues. A clearer path from cell cryopreservation to clinical use would be necessary to justify these services and place them on a firmer ethical foundation.

Public cord-blood banks offer one useful template for banking other cell types for other purposes. It will be important for both public and private cell banks to create a realistic path to clinical use through close coordination with regulatory authorities and accreditation bodies as well as companies developing future cell and gene therapies that could potentially use banked cells. Questions of equity, sufficient representation of HLA-matching donors (in the case of allogeneic banks), and regulatory harmonization all need to be considered carefully (**9**). Cell banks also must be committed to accuracy in their marketing and communications.

Addressing all these concerns could help support the development of cell-banking approaches that can promote access to effective cell and gene therapies. Cell banking for clinical use is a long-term proposition, however. Patients, investors, and others all should be wary of offers to bank cells as "biological insurance" today.

References

1 *Patient Resources*. International Society for Cell & Gene Therapy (ISCT) Presidential Task Force (PTF) on the Use of Unproven and/or Unethical Cell and Gene Therapy:

Vancouver, BC, Canada, 2019; http://www.isct-unprovencellulartherapies.org/patient-resources.

2 Shearer WT, et al. Cord Blood Banking for Potential Future Transplantation. *Pediatrics* 140, 2017: e20172695; doi:10.1542/peds.2017-2695.

3 Rink B, Miller RS. Umbilical Cord Blood Banking. *Obstet. Gynecol.* 133, 2019: E249–E253; https://doi.org/10.1097/AOG.0000000000003128.

4 CBER. *Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps): Guidance for Industry.* US Food and Drug Administration: Rockville, MD, 2011; https://www.fda.gov/media/82724/download.

5 Srivastava A, et al. Part 1: Defining Unproven Cellular Therapies. *Cytotherapy* 18, 2016: 117–119; doi:10.1016/j.jcyt.2015.11.004.

6 Ogbogu U. Combating Unlicensed Stem Cell Interventions Through Truthful Advertising Law: A Survey of Regulatory Trends. *McGill J. Law Health* 9, 2016: 311–336; https://mjlh.mcgill.ca/publications/volume-9-issue-2-92-2016/combatting-unlicensed-stem-cell-interventions-through-truthful-advertising-law-a-survey-of-regulatory-trends/.

7 *A Brief Overview of the Federal Trade Commission's Investigative, Law Enforcement, and Rulemaking Authority.* Federal Trade Commission: Washington, DC, October 2019. https://www.ftc.gov/about-ftc/what-we-do/enforcement-authority.

8 Tressler C. *FTC Takes Aim at Deceptive Stem Cell Therapy Claims.* Federal Trade Commission: Washington, DC, 18 October, 2018; https://www.consumer.ftc.gov/blog/2018/10/ftc-takes-aim-deceptive-stem-cell-therapy-claims.

9 Azuma K, Yamanaka S. Recent Policies That Support Clinical Application of Induced Pluripotent Stem Cell-Based Regenerative Therapies. *Regen. Ther.* 4, 2016: 36–47; doi:10.1016/j.reth.2016.01.009.

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Further Reading on Cell-Bank Preparation and Characterization

Animal Cell Culture Methods. Mather JP, Barnes D, eds. Elsevier: Amsterdam, The Netherlands, 1998.

Annex 3: Recommendations for the Evaluation of Animal Cell Cultures As Substrates for the Manufacture of Biological Medicinal Products and for the Characterization of Cell Banks. *World Health Organization Technical Report Series* 978, 2013; https://www.who.int/biologicals/vaccines/TRS_978_Annex_3.pdf.

Armstrong SE, Mariano JA, Lundin DJ. The Scope of Mycoplasma Contamination Within the Biopharmaceutical Industry. *Biologicals* 38, 2010: 211–213; https://doi.org/10.1016/j.biologicals.2010.03.002.

Chen D, Hatfield CC. Root Cause Investigation of Unusual Results Experienced during Master Cell Bank (MCB) Testing and Characterization. *PDA J. Pharm. Sci. Technol.* 64(5) 2010: 465–470.

Databases and Data Sets. International Cell Line Authentication Committee, 2021; https://iclac.org/databases.

Ho K. *Manufacturing Process of Biologics: A Presentation.* European Medicines Agency: Amsterdam, The Netherlands, 2011; https://www.ema.europa.eu/en/documents/presentation/presentation-manufacturing-process-biologics-kowid-ho-afssaps_en.pdf.

Kim J-H, et al. A Report from a Workshop of the International Stem Cell Banking Initiative, Held in Collaboration of Global Alliance for iPSC Therapies and the Harvard Stem Cell Institute, Boston, 2017. *Stem Cells* 37(9) 2019: 1130–1135; https://stemcellsjournals.onlinelibrary.wiley.com/doi/full/10.1002/stem.3003.

Nims RW, Harbell JW. Best Practices for the Use and Evaluation of Animal Serum As a Component of Cell Culture Medium. *In Vitro Cell. Develop. Biol. — Animal* 53, 2017: 682–690.

Nims RW, Pierce PJ. Best Practices for Detecting and Mitigating the Risk of Cell Culture Contaminants. *In Vitro Cell. Develop. Biol. — Animal* 53, 2017: 872–879.

Nims RW, Reid Y. Best Practices for Authenticating Cell Lines. *In Vitro Cell. Develop. Biol. — Animal* 53, 2017: 880–887.

Position Paper on Re-Establishment of Working Seeds and Working Cell Banks Using TSE Compliant Materials. European Agency for the Evaluation of Medical Products: London, UK, 2002; https://www.ema.europa.eu/en/documents/scientific-guideline/position-paper-re-establishment-working-seeds-working-cell-banks-using-tse-compliant-materials_en.pdf.

Reid Y. *Authentication and Characterization of Animal Cell Lines: Towards Best Practices in Cell Culture*. ATCC: Manassas, VA; https://www.atcc.org/about/news_and_events/events/webinars/2014/authentication_and_characterization_of_animal_cell_lines.aspx.

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