STEM CELL TRIALS

Why don't stem-gene cell clinical trial sponsors count their stem cells?

James L. Sherley MD, PhD, the founder and president of Asymmetrex, answers this and many other questions.

Q. Who are stem-gene clinical trial sponsors?

A. Although currently most of the presentations at outsourcing clinical trials conferences are focused on the supply needs of pharmaceutical and biopharmaceutical sponsors, there is an emerging industry for the supply of stem-gene clinical trials. Stem-gene clinical trials fall into two categories. The first category evaluates treatments with human tissue stem cells, like hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). The vast majority of stem-gene clinical trials are for stem-cell treatments of this type. Examples of sponsors developing stem-cell clinical trials are Athersys, Pluristem, Celularity, Sorrento Therapeutics, and Talaris Therapeutics.

More recent and more highly publicised stem-gene clinical trials are gene therapy and gene-editing clinical trials. Well-known sponsors are Sangamo Therapeutics, Bluebird Bio, CRISPR Therapeutics, Beam Therapeutics, Editas Medicine, and Intellia Therapeutics. All gene therapy clinical trials are "stem-gene" clinical trials because the therapies target tissue stem cells (usually HSCs) to ensure that the effects of transduced genes or gene edits are maintained for long periods. Only tissue stem cells provide this essential treatment quality. Other cells in the body mature, die, and are lost rapidly.

Q. What do stem-gene cell clinical trial sponsors need?

A. Sponsors of stem-gene clinical trials need all the usual trial execution resources supplied by vendors for pharmaceutical and biopharmaceutical clinical trials. But they also have supply needs that are unique to their special treatments. These include the tissue stem cells and the gene vectors that constitute their treatments.

As in other new clinical trial disciplines, companies in this industry have either created or in-licensed the technologies needed for producing their treatments. In most cases, their treatment basis is a key proprietary element of the sponsors' business models. This feature makes it challenging for vendors to successfully supply such services in this early period. However, like all current mature areas of clinical trials supply, as the stem-gene clinical trials industry matures, sponsors will extend their clinical programs to outsourcing even the production of their treatments to gain the advantages of more economical and efficient expert outsourcing.

Q. Why don't stem-gene clinical trial sponsors count their stem cells?

A. This article is titled with the above question and is full of related questions. Many reading this article are already puzzled by the title. Of course, companies conducting stem-gene clinical trials know the number of stem cells in their treatments, don't they? Another question. They must know the dosage of stem cells in their treatments, right? If not, how can they design clinical trials whose outcomes they can soundly interpret? How do they certify the quality of their treatments if they don't know how many stem cells – natural, expanded, genetically-engineered, or gene-edited – are in them? Those well-versed in the challenges of tissue stem-cell expansion know that expanded cell products often have far fewer stem cells than their starting preparation. In addition, patients who are compared in stem-gene clinical trials usually get independent stem cell treatments, not treatments sampled from the same pool or bank. So, how do companies know that that they are comparing treatment outcomes for the same stem cell dosage? They don't.

Some who are willing to acknowledge this wide-spread stem cell counting problem in stem-gene clinical trials may suggest that it is not a problem. After all, the same problem exists for the one approved stem cell medical treatment, HSC transplantation (HSCT), and it seems to be doing fine. Though convenient, this assessment is naïve. During the development of bone marrow HSCT therapy, and subsequent related mobilised peripheral blood HSCT

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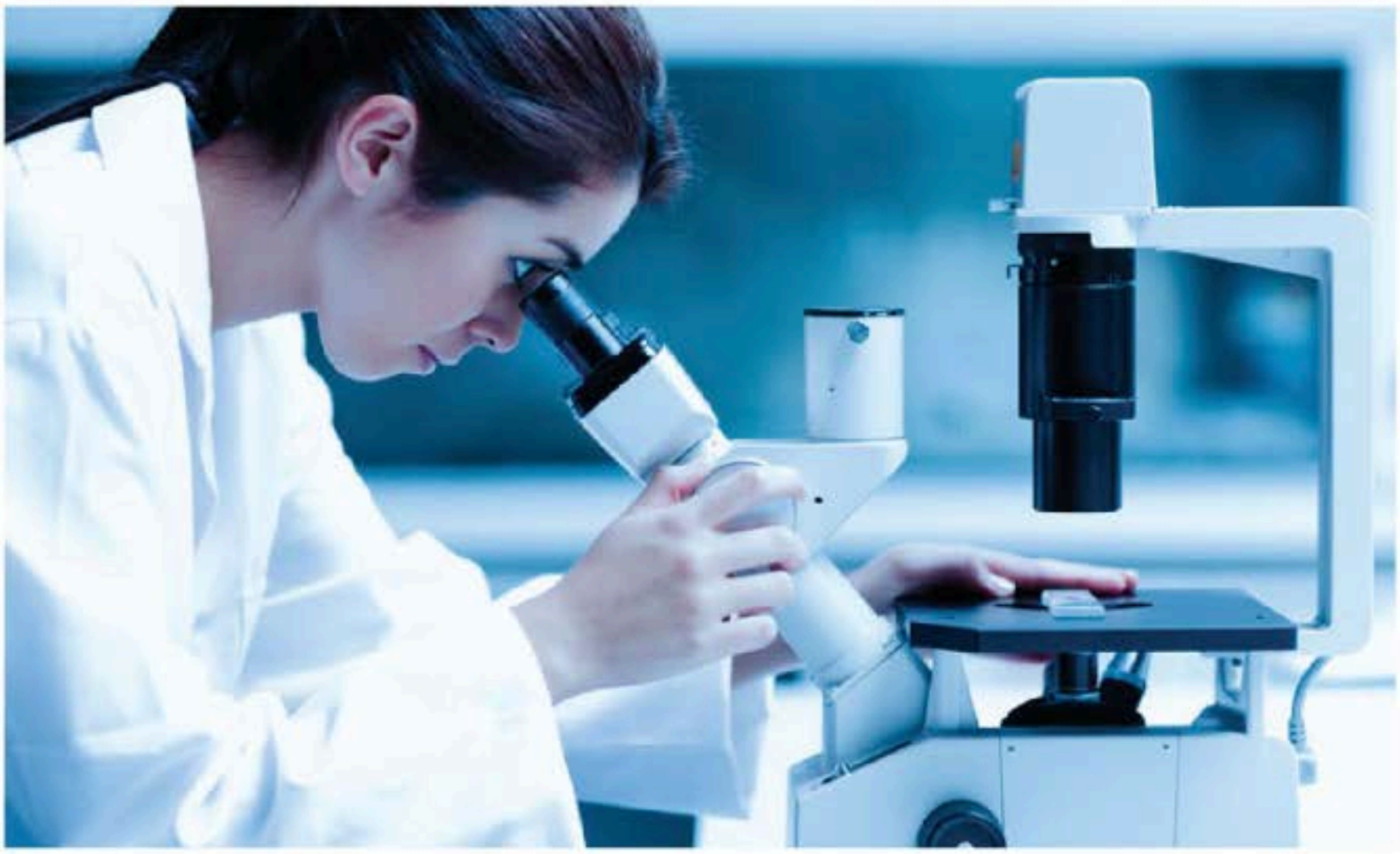

therapy, doctors learned that a high threshold number of total cells was important for ensuring treatment success.

Although doctors are still unable to determine the specific dosages of the rarer HSCs, for these treatments, total cell count is an adequate surrogate for HSC dosage. Not so for HSCs in umbilical cord blood units that are used to treat children. As many as 18% of cord blood units fail children because their unknown HSC dosage is inadequate. In these early days of stem-gene clinical trial practice, similar detrimental effects are certainly at play.

So far, the answer to the title question has not been provided. Here it is. Until very recently, no method was available to quantify the dosage of tissue stem cells. Several technologies are commonly misrepresented as able to determine stem cell dosage. However, experts in tissue stem cell medicine know that they can't. The first is flow cytometry, which is perhaps an understandable error. Flow is very sensitive, but relies on specific biomarkers to detect and quantify sub-types of cells. However, there are no biomarkers that specifically identify tissue stem cells. The biomarkers commonly used in flow, like CD34 and CD90, also detect more abundant non-stem committed progenitor cells, which do not have the long-term tissue cell-renewing ability of tissue stem cells.

The colony-forming unit (CFU) assay is widely used to evaluate and certify cord blood units for clinical use. Like flow, it also detects committed progenitor cells, but cannot distinguish them from HSCs. The one previous assay able to distinguish stem cells from committed progenitor cells is the SCID mouse-repopulating cell (SRC) assay. Some stem-gene companies use it, but it is an assay looking for a better solution. A single dosage determination requires as many as 50 mice and 16 weeks to get a result that is highly unreliable; and it only works for HSCs.

Q. Why should stem-gene clinical trial sponsors count their stem cells?

A. The simple answer to this question is if they do, they can reduce their costs, design and evaluate their clinical trials better, and improve the effectiveness of their treatments. A second equally important answer is that now they can. A new method called kinetic stem cell (KSC) counting was recently reported for conveniently counting any human tissue stem cells, including HSCs and MSCs. New attention to knowing the stem cell dosage of treatments is also developing in regulatory agencies like the FDA. So, the present moment may be ideal timing for supply vendors to begin considering tissue stem cell counting as an important stem-gene clinical trial supply need. ●