

Commentary: Technological Trajectories and Stem Cell “Dominant Design”

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For the Burrill & Company Stem Cell Report March 2007, I wrote an article that proposed that if a dominant design were to emerge in the stem cell industry, the successful design would have a cell type that possesses a set of core attributes in order to win the allegiance of the marketplace. Now, collaborating with Ray Wood, the Managing Director of Cell Therapies Pty Ltd, herein, we expand on the premise of the primary article and further discuss the likelihood and attributes for the emergence of a dominant design in the stem cell industry. First of all, we need draw a distinction between a dominant cell type and a dominant commercial design. By utilizing the concept of technology “factors” or “trajectories,” we will provide an outline of how the coincidence of multiple technological solutions and commercial dynamics (each with their own development path or “trajectory”) will influence the makeup and timing of a dominant design. We will attempt to highlight the usefulness of academic business research in strategic planning and implementation for an emerging market such as cellular and tissue therapy.

We further develop the overall definition and notion (as described by James M. Utterback in *Mastering the Dynamics of Innovation*, 1994), of dominant design, briefly review the important stem cell specific attributes that likely will be required, and introduce the concept of *technology trajectories* and how these will affect the emergence of dominant design. We believe that while the characteristics of a functional stem cell type may contribute to the emergence of dominant design in the stem cell industry, we contend that complementary technologies (trajectories) will not only enable the manifestation of a dominant design, but will determine the pace at which it emerges, and thereby provide investors with opportunities to pick winners.

Dominant Design and the Emerging Stem Cell Industry

A dominant design in a product class is, by definition, the one that wins the allegiance of the marketplace. According to Utterback, dominant design is conceptually broader than merely technical structure, competition and progress; there are and will be technological factors and, we believe, “trajectories” that will be critical to the emergence of a dominant design in the stem cell industry. First, we’ll describe the emerging state of the industry, and consider Utterback’s description of what is typical in an emerging industry: Either a single or a number of pioneering discoveries is made that underpins the possibility that an initial product or technology (for the purposes of this discussion, the discovery and application of human stem cells) can create a growing market that begins to take shape around that product or technology (for example, identification and availability of multiple cell types, their clinical significance and related manufacturing or enabling tools). As the market for a clinical application is proven, new competitors enter to either expand the market or take market share with their own product versions. New companies are formed to capture value from a combination of technological advantage and proven clinical outcome (examples include developments in stem cell isolation methodologies, cell expansion devices and allogenic banking). Utterback explains that at this early stage, “no firm has a ‘lock’ on the market,” and “no one’s product is really perfected (technologically, clinically or commercially). The market and industry are in a fluid stage of development. Everyone – producers and customers – is learning as they move along.” As a result, Utterback points out, this environment [that of an emerging industry] is conducive to market entry by many firms, given that capital exists and technical barriers can be overcome.

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"...both producers and customers are experimenting. Even as new companies enter with uniquely designed products, established firms are busy perfecting their original designs...and customers are not yet so wedded to any particular design or company that they will not experiment with something new. Industry standards at this stage are usually rudimentary, when they exist at all."¹

Today this point is illustrated by the fact there are over 350 stem cell-related companies and thousands of research laboratories operating in this field worldwide.² (www.stemcellresearchnews.com) Without doubt, the stem cell industry is in a formative or fluid state of innovation and as of yet; no dominant design has emerged for the production and delivery of a dominant cell type or a dominant commercial business model. We do however draw your attention to an important difference between Utterback's research and the emerging cellular therapy market. For cellular therapies there are well established industry standards (e.g., cGLP/cGMP/cGTP), an aggressive regulator with absolute power, and a disconnect between the ultimate beneficiary (the patient) and the purchaser (health care insurers and public health budgets).

An important question for the investment community is whether or not a dominant design in the stem cell industry will occur and if so will it be recognizable? If the emergence of a dominant design is a signal that an important shift is about to take place with respect to the pace of innovation and the number of competing firms, the ability of managers and industry watchers to receive that signal—or even better, to predict the emergence of dominant design—should be important with respect to their product designs, R & D programs, and targeted process development.¹ The following describes the base technology in the stem cell industry as well as the concept of technological trajectories with respect to a dominant design leading to a description of a number of the key technology trajectories that, in our opinion are likely to contribute to the emergence of a dominant design.

Important Stem Cell Attributes

According to Utterback, dominant designs most often satisfy multiple qualifications in terms of the interplay of technical possibilities and market choices instead of only optimizing a select few criteria. Today, the com-

petitive landscape revolves around the identification and production of sufficient quantities of a cell type which has a demonstrable and useful therapeutic benefit. The methodology to isolate, expand, and produce a specific category of cells is important, but until the therapeutic effect is established, the market is insensitive to how the cells are produced. Presently, the market is focused on identifying, and claiming IP rights, to cells that demonstrate therapeutic effect and can be shown to have versatility, accessibility, and safety. The following attributes and characteristics will play key roles in the emergence of a dominant design in the stem cell industry.²

Versatility

Versatility, or plasticity, is defined as the ability to differentiate into one or more cell types. To be considered a potential cell for multiple therapeutic endpoints, one would envision a dominant cell type that is highly versatile, and this will likely afford great economies of scale in banking stem cells for clinical use.^{4, 5, 6, 13}

Accessibility

Ease of accessing the therapeutic stem cell will contribute to the dominant design. The emerging cell types within the industry need to be easy to isolate, manufacture and purchase/license. As the industry matures and competitive pressure focuses more on developing cells for specific therapeutic application, the ability to manufacture and deliver stem cells in large quantities will be an imperative for commercial success. More specifically, for a clinical application, cells will most likely be partially differentiated before being introduced into a patient.¹⁴ Pre-differentiated cells represent a more controlled material, which is already set on a path to creating a cure or becoming desired tissue.

Safety

An important characteristic of any dominant stem cell type slated for transplantation/therapeutic use will be the lack of transplantation side effects, and for embryonic stem cells, a proven inability to form teratomas *in vivo*. Researchers are defining approaches to inhibit teratoma formation by eliminating the tumorigenic cells prior to injection^{11, 12}, but ultimately, it may be simpler (i.e. regulatory and otherwise) to choose a cell type

that simply does not have tumorigenic potential as a defining characteristic.⁵ In order for any stem cell therapy to enter the clinic, many issues will need to be addressed beyond the stem cell itself, including, but not limited to, autologous vs. allogenic, genetically modified, mode of delivery, and the need to immune modulate and/or induce tolerance.²

Autologous and Allogenic Sources

While the business community would like to see allogenic (read: banked lowest cost, immediately available cells) as the preferred cell type, there is no clear clinical evidence yet that allogenic cells can deliver clinically useful outcomes, whereas autologous transplantation has been shown to be at least safe and to have low to no side effects. A number of groups are working with what appear to be partially or fully immune-privileged cells. A commercial business model based on a bank of allogenic cells would appear to be the preferred model. However, the development of low-cost automation techniques could deliver economically viable autologous transplantations.

Clinical Outcomes

To date there appears to be a split in the clinical results along the following lines: For regenerative tissue, allogenic banked cells such as mesenchymal stem cell (MSCs) would appear to be the preferred deliverable. For cells that require some hemopoietic differentiation, purified CD34+ cells are promising. Whereas dendritic cells (DC's) and more lately, "T" cells, would appear to be the front runners in the race to deliver a viable and commercially sustainable therapy.

Concurrently or perhaps alternatively, intellectual property rights held by competing firms may ultimately drive a dominant commercial design in the stem cell industry. As the stem cell patent landscape continues to populate and evolve, freedom to operate issues will become prevalent.² Firms holding broad rights to stem cell inventions may or may not be able to block co-claimants and initiate joint ventures with complimentary intellectual property holders and block fast-followers from competing through the forcing of licensing of claims—thus enforcing a dominant design. An industry growth-limiting factor is the abil-

ity to use stem cells for basic research and ultimately therapeutic purposes, and this is itself dependent on a business environment that allows access to the required cell lines. Technology transfer, limitations in Government funding for stem cell research and intellectual property rights currently define accessibility in the United States and a number of countries. However simplistic it may sound, actually gaining access to a source of stem cells will be critical to the manifestation of dominant design in the stem cell industry.

Technological Trajectories and Dominant Design

Factors other than specific cell characteristics will affect the materialization of dominant design in the stem cell industry. Chief among these factors, according to Utterback, are¹ a firm's access to collateral assets², industry regulation and government intervention³, strategic maneuvering by individual firms, and⁴ communication between producers and users. For the purpose of this discussion, we will focus on the third factor—namely, strategic maneuvering by individual firms. The product strategy followed by a firm relative to its competitors may determine which firm's product design becomes dominant—an observation described by Cusumano, Mylonadis and Rosenbloom⁹ as "strategic maneuvering." Demonstrating this concept is the study of the videocassette recorder standards done by Cusumano et al. These researchers determined that one reason that JVC's VHS system won market dominance over Sony's Betamax was the different strategies followed by these two firms. Strategically, JVC established alliances in Japan, then Europe, and finally in the United States; alternatively, Sony chose to go it alone, stressing its reputation and deliberately avoiding alliances or contracts that would impinge on its vertical integration for this important new market. It was primarily JVC's partnering strategy, and neither the technical advantages (design attributes) of VHS, the firm's collateral assets, nor government regulation that made VHS the dominant design. In fact, VHS was technically inferior in many ways to its Betamax rival.¹ A similar example is the IBM-PC dominance over Apple in the consumer (mass) computer market.

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It can be argued that the cellular therapy market (however nascent) is different from the VCR or computer markets in that there is a prescribed approval process (clinical trials), an aggressive independent regulator (the Food and Drug Administration) and an impartial purchaser (BlueCross/Blue Shield/insurer).

Importantly, the stem cell firm whose product strategy involves forming key partnerships (strategic maneuvering) to gain access to the critical technologies (technological trajectories) other than the cell itself may drive the emergence of dominant design in the industry. There is an overlap and interrelation between dominant design emerging in a market and the often multiple technological trajectories that are required to enable the market's maturation and durability³. There are three phases or classes of a technology trajectory: Discovery, development/evolution, and deployment. We note that the staging or availability of key technologies in these three classes can hold back or drive a market's growth and the emergence of dominant design. The cell therapy market is itself emerging from a phase of basic scientific discovery and is proceeding through a phase of clinical discovery where "what cell does what in which disease or indication" is the industry's focus. A successful clinical trial result (validation that the identified cell has a useful therapeutic effect) enables the quantification of markets and via a round of fund raising progression to a development or evolutionary phase where purposed delivery methods and "a saleable product" emerge to meet early adopters' needs. Today the cellular therapy market is entering a phase where a number of independent technological trajectories will need to intersect before dominant design emerges.

To produce a cellular therapy there is, in general, a sequence of steps involving the collection and preparation of starting material, then the separation, expansion, sorting, modifying/loading, testing and packaging of the product. While there are differences if the therapy is autologous, allogenic, banked or fresh, the steps to produce the cells are similar and will be dependent upon the availability of very similar technological solutions. The following section describes examples of important technological trajectories in each of the discovery, developmental, and deployment phases that we believe can drive the emergence of a dominant design.

Technological Trajectories Impacting the Stem Cell Industry

Discovery Phase: High Resolution Melting

Polymerase chain reaction (PCR) amplification and detection has become a preferred researcher's tool for molecular detection and has become a dominant design in its own field; however, it has been a slow off-line, low-volume tool. More recently, a technological innovation has emerged. High-resolution melting (hrm) is an integration of a quantitative real time PCR system with a downstream analysis technique to deliver rapid low cost DNA sequencing for the identification and quantification of mutations and molecular phenotype.^{7,8} While initially being directed to speeding up research, this capability can be applied as a release criteria for a cellular production process to rapidly and definitively define cell populations and to provide quantification data not previously available in "production time." In other words, this data can be obtained before product release and at a molecular level, making it possible to identify DNA mutations with resolution and specificity not previously possible. This trajectory will enable faster, lower-cost, adequately sensitive, and cell-specific data. For personalized medicines, specific mutations can be identified and tailored therapies delivered at a commercially acceptable cost and time frame.

An ability to replace and maintain the long-term expression of genes that are inherited and deficient (gene transfer and ultimately therapy) in diseases such as haemophilia is likely to lead to significant but niche markets. The selection of an optimal cell type for the delivery and verification of predictable outcomes will be critical developments that can lead to a dominant design.

Development/Evolution Phase: High-Speed Cell Sorting

This technological trajectory shifts previous off-line instrumentation into the production process. It increases speed and cell volume while simultaneously reducing and eliminating research oriented features to deliver a narrower but optimized set of performance characteristics directed at cell production. The Gigasort cell sorter from Cytonome LLC (www.cytonome.com) could enable a new class of production processes. Gigasort is a very high-speed, functionally closed cell counter. This innovation is specifically designed as a dedicated

production tool for the identification and separation of complex combinations of narrowly defined and quantified cell populations. By incorporating a removable cassette into the design, functionally closed code of Good Manufacturing Practice (cGMP) principles can be implemented. Furthermore, this cell sorting technique has a claimed sorting speed an order of magnitude greater than that of conventional cell sorters but with a low impact on cell viability. If this is accurate, the cell throughput is sufficient to now consider complex multi-parameter phenotype sorting in series with the cell production process. This new class of sorting technology can move cell processing closer to pharmaceutical performance levels with better quantification and reproducibility of production outputs.

There are a number of similarly novel cell sorter developments emerging. Some will be expensive but very high-speed, while others will be low cost and cell-specific. Importantly, the availability of cell selection based on cell phenotype and other precise characteristics has not previously been available, and new approaches to cell production and selection can be now expected. An example of another approach is based on a low-cost cell-specific sorter design such as that manufactured by Aldagen (www.aldagen.com). This company has invested in the development of a low-cost delivery platform to identify and sort ALDH+ cells for use in multiple clinical indications. They are currently in phase II and III trials for cardiac and limb ischemia. Their business model is based on a dedicated device to deliver ALDH+ cells. ALDECOUNT is an FDA-approved in-vitro diagnostic use (IVD) product for the identification and enumeration of low side scatter, ALDH^{br} cells by flow cytometry.

Deployment Phase: Integrated Automation to Deliver Functionally Closed Processes

The Automation Partnership (TAP) (www.automation-partnership.com) has developed automation hardware to deliver the multifunctional integration of clean room functions for flask-based cell processing. The beneficial attributes of this technological trajectory are speed, reliability, repeatability, tighter tolerances, and lower unit cost of production. TAP has produced an integrated incubation, cell counter, robotic arm, cell counter, class 350 hood, dispensing, and filling device to replicate

an operator and a clean room hood. The device is an extension of production equipment used in pharmaceutical manufacturing, and claims proven reliability and robustness. This class of automation, when proven to be reliable and with acceptable "up time," can drive down the unit cost of a cellular therapy and enable a dominant commercial design.

A complementary but critically enabling development is the availability of novel delivery devices such as catheters to deposit cells directly into the myocardium, or the redesign of the traditional injection needle tip using micro machining techniques to significantly increase the number of viable cells delivered directly to the site of interest.

Patents and proprietary supply lines can be expected to influence the deployment phase. For example, some cytokines are not routinely available (e.g., IL15) whereas others (such as CSF) may be. Currently, cells need cytokines to mature or to direct their tracking to the target tissues. The relationship between the cell producer and the cytokine producer in terms of freedom to operate and the availability of critical supplies can determine the growth rate and emergence of a dominant design.

Conclusion

Utterback notes that dominant design usually takes shape following the flurry of radical product innovation when market feedback is rapid and performance, features, and functionality of the product are far more important than price to demanding lead users. As market observers and managers, we feel that a firm's capacity for strategic maneuvering to gain access to enabling technological trajectories will be its single most important success factor. Strength in any one aspect will be insufficient; a firm's agility and ability to secure access to the current enabling technologies will determine its commercial success. It is likely to be a long time (at least 10 years) before a dominant design for the cellular therapy market emerges, and so far the impact of the regulator (TGA) and the reimbursement agencies have yet to be quantified.

While we have provided examples of innovation for this industry that can impact the cost and speed of product delivery, there will need to be a number of clinical breakthroughs before a dominant design emerges. Once the dust has settled on the contest for

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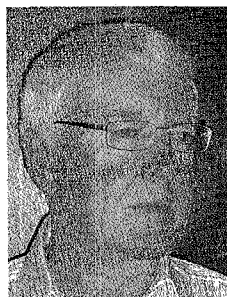
clinical efficacy and product innovation, the competitive engagement shifts to a new battleground: process innovation and lowest-unit cost. As soon as a therapy for a significant market is validated, there will be a refocus on cost-effectiveness. Firms that are unable to make the transition toward greater process innovation are unable to compete effectively and very often fail.¹ The emergence of open and transparent phenotype data will be a measure of the industry maturing. For example, what cell population is being used in which application, and what cell types are and are not included in a "product" will become both clinically and commercially critical. Additionally, once a dominant design emerges, the basis of competition changes radically whereby the ecology of competing firms shifts from one characterized by many companies and unique product designs to one of a few firms with similar product designs.¹ Finally, we believe that there will be multiple or at least serially dominant designs over a matter of decades, leading in the very long term to a single cell therapy market dominated by lowest cost delivery.

The emergence of a singularly successful clinical trial could have a powerful impact on the development of future technological innovations and a dominant design within this industry. The efficiency of the "translation" of results of such a trial to other clinical indications can drive the emergence of a dominant design. Alternatively, market economics may determine the dominant business model through the control of reimbursement policy. A company's ability to lobby and negotiate favourable reimbursements could be as valuable as, and more strategically important than, a first-in-class patent, lowest unit cost or adherence to the current dominant design.

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FOOTNOTES

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