Developing Cell-based Technologies

Strategic Challenges from Drugs to Tissue Transplants

The dynamic nature of cell therapy and its many therapeutic possibilities means that the successful commercial development of a cell-based clinical product often hinges on pivotal choices made in development. This makes a sound strategy for the targeting and development of cell-based technology essential. This report outlines how to design and execute an effective strategy for cell-based technologies from biomolecule delivery to tissue graft.

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The Challenge

Cells can be used as delivery vehicles, as persistent transplants and as tissue grafts. Cell-based therapy offers several potential advantages over single biopharmaceuticals like the delivery of complex mixtures of biological factors, the potential for responsiveness and interaction with the host, physiological function and in some cases, structure. When asked how one knows when a cell-based technology is ready for clinical trials, the short answer is, when you know what you can do, you can target what needs to be done. That is, when the scientific foundation is in hand and the technology is sufficiently developed to reach a therapeutic target that is capable of achieving the therapeutic goal. Not all cell-based therapies will reach the same targets nor will targets reach a therapeutic goal with equal effectiveness. The challenge is finding the best application for a technology and the best way to use the technology.

The Best Strategy

As with any new technology, core technical competency, a combination of general scientific and technical proficiency, and proficiency in using the specific technology (fig. 1), will usually be under developed, and certain aspects of the biological basis of the cell technology will still be unclear, making assessment of a therapy's potential and how best to use it hard to gauge. While often viewed as the unavoidable risk of new technology, it isn't a reason to enter the clinic prematurely. Development risk can be mitigated by considering what strategy would bring together the therapeutic target, cell-based approach and host environment in the strongest, most competitive way to reach the therapeutic goal (fig. 2). The issue is then whether a specific tech-

nology fits the strategic need and, if it does, what challenges will have to be overcome to reach the therapeutic target effectively.

Host Influence

The therapeutic power of a cell-based therapy will depend on its ability, either to beneficially counteract, interact with, and/or withstand the host environment. The host environment is made up of cells of the tissue in a certain biological state, the signalling being produced by these cells, and the extracellular molecular context of the host tissue (fig. 2). It is dynamic and will change in both potency and character over time. Each biological condition will have its own collective signature based on the dominant biological process at the time. Each signature will present both benefits and challenges to cell-based therapies.

Product Approach

There are three basic approaches to using cells in the clinic:

1. Cells used as drugs or for the delivery of biomolecules
2. Cells used as a transplant where the cells must persist to be effective
3. Cells used as a tissue grafts to re-establish tissue function and/or structure.

While each approach may be uniquely suited for certain indications, there will also be overlap. Each approach will have its strengths and drawbacks and should be chosen with the therapeutic target and host environment in mind. This requires having an understanding of the biological basis of the cell-based technology as well as the biological and disease processes at work in the host. The combination indicates what has to be achieved at a mechanistic level to reach the therapeutic target in the context of the host environment. If the therapeutic goal is to overcome native tissue response, it stands to reason that the more biological power built into the strategic design and use of a technology, the more effective the resulting therapy will be. Product strategies will be a balance of strengths over weaknesses based on: biological mechanisms, the state of the technology and clinical feasibility.

Drivers of Successful R&D

While strategy is your road map, there are four cardinal drivers that fuel the generation of clinically and commercially important output: knowledge, clarity, skill and performance.

- Knowledge is about how well information is processed into working knowledge that can drive decision-making. Knowledge is an early driver in determining technology strategy and targeting. It also drives scientific proficiency, which impacts ongoing technology development and execution.
- Clarity refers to a sense of the path ahead. It represents the product vision, evolving with time into a development plan. It is focused on what it will take to achieve commercial output. Clarity draws on key competencies (internal and external) (fig. 1) to purge potentially damaging naiveté. It is an early driver in technology strategy and targeting. It is also critical for successful execution of the strategic product plan.
- Skill refers to how well a team can apply science to achieve objectives and overcome scientific and technical hurdles.
- Performance is to how well competencies and technology (fig. 1) are brought together for efficient execution of the product plan. It draws on knowledge, clarity and skill.

Factors Important to Cell Therapy

While the four cardinal drivers apply to all life science development, there are factors that specifically address the safety and effectiveness of cell-based therapy. In addition to the influence of the host environment, they are: robustness, stability and functional capacity.

Reproducibility and predictability will determine robustness. It speaks to the ability of the cell-based product to deliver the same cell population and the same effect to each patient. This can be a particular challenge for autologous cell therapies because of the inherent variability of the cell source. While robustness encompasses the process and with it chemistry, manufacturing and controls (CMC), it goes beyond process to the biological result of the process.

Stability refers to the ability of a cell-based therapy to remain controlled in its growth and differentiation, as well as on target under relevant clinical conditions. Evidence of this control is particularly important when implanting non-committed stem cells.

All cell therapies rely on functional capacity for effectiveness. Specific cell compositions will vary in their functional capacity depending on their biology and the target indication. The more committed the cells are to a specific cell lineage, the more functional capacity the cells are likely to have. For example, an islet-like cell will have less inherent functional capacity than a pancreatic islet progenitor cell. The high functional capacity of fewer cells will trump low functional capacity of many. An additional bonus is that it naturally yields greater robustness and assurance of stability. Func-

Fig. 1

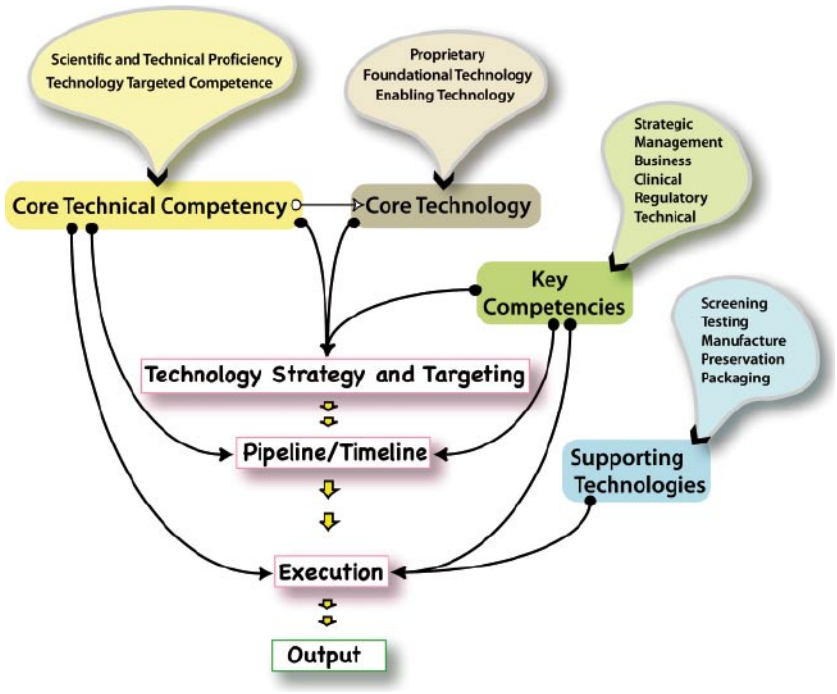
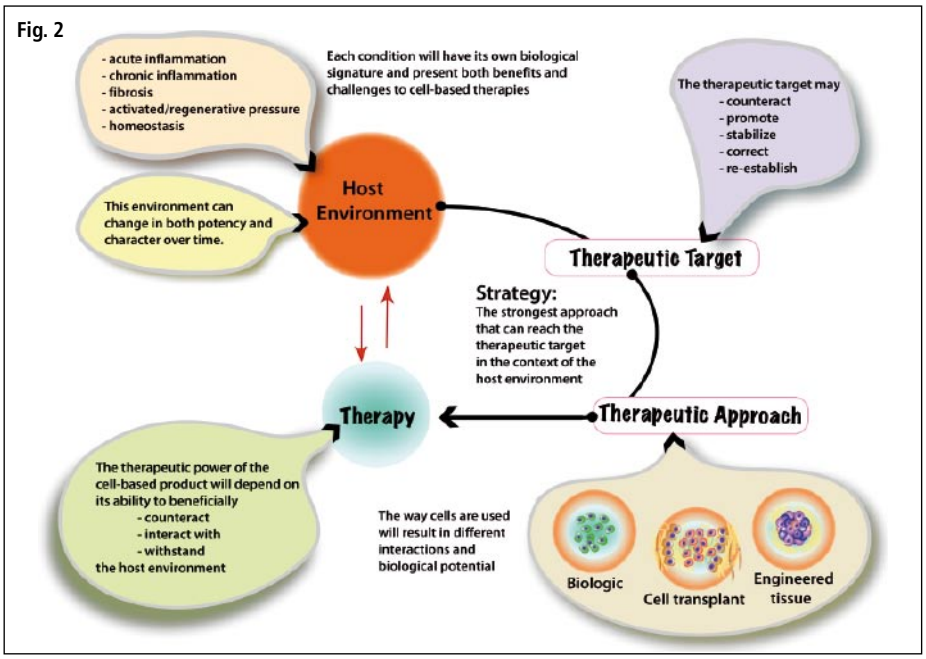


Fig. 2



tional capacity is challenging and an important strategic consideration when the cell source is a multi-potent stem cell population.

Conclusion

Successful development of cell-based therapies involves significantly more than just growing and delivering cells. Even promising technology can flounder without a deliberate strategy and strong execution. Potential can be turned into output by:

- Remaining cognizant of the special considerations involved in developing a cell-based therapy
- Developing the four cardinal drivers for R&D success
- Formulating a strategy that plays to the biological strengths and competitive advantage of your technology
- Choosing well-matched clinical targets

With that, cell-based therapies can fulfill their potential.

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