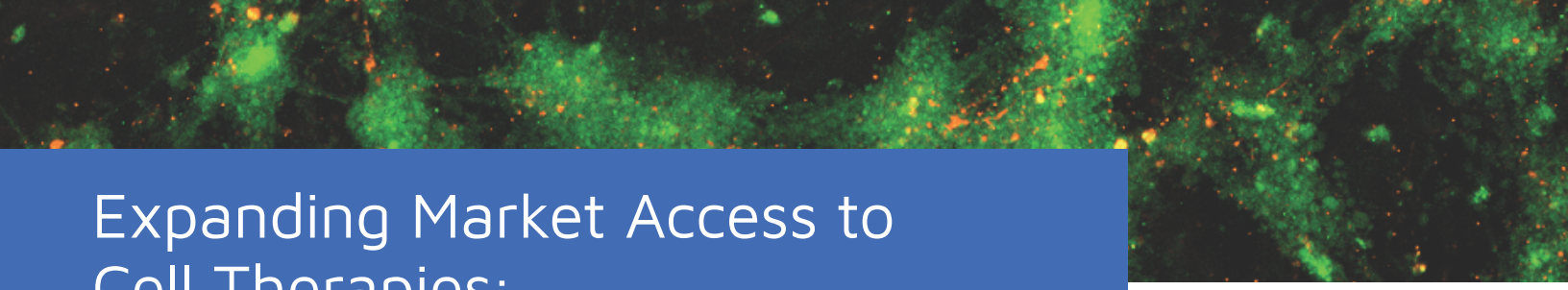

Expanding Market Access to Cell Therapies:

Plan Early to Scale Manufacturing Later

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Cell and gene therapies are no longer a promise for the future. They are here today.

In fields like oncology, pediatrics, and hematology, gene and cell therapies are revolutionizing care for chronic and terminal diseases.

However, with the exception of patients lucky enough to be enrolled in a clinical trial, the majority of patients do not have access to these life-saving drugs. Often the limitation is the cost.

For example, the life-saving gene therapy to treat children with spinal muscular atrophy, Zolgensma produced by Novartis, carries a price tag of $1.7 million[1].

Zolgensma is not alone:

- Novartis' cell therapy for cancer, Kymriah is priced at $375,000 to $475,000, depending on the indication.
- Spark's Luxturna for retinal disease costs $850,000.
- CSL Behring's hemophilia B gene therapy, called Hemgenix, is the most expensive drug in the world, priced at $3.5 million[2].
- Bluebird Bio has two regenerative therapies priced at nearly $3 million each. One treats a blood disorder called beta thalassemia and the other a neurological condition, cerebral adrenoleukodystrophy, which is terminal. When countries with government-supported healthcare refused to pay the asking price, Bluebird Bio simply withdrew the products from the European market, leaving patients without an option[1].

The Numbers Behind the Price

The public assumes that these price tags are excessive and reflect the greed of an industry. However, the numbers do not support that claim. While traditional chemical drugs have a profit margin of approximately 80%, Anthony Davies of Dark Horse Consulting indicates that none of the current regenerative therapies are anywhere near the 80% mark and some are being marketed with no profit margin[3].

Eric David of Aspa Therapeutics explains that the cost of manufacturing a gene therapy can be as high as $1 million and that does not include the costs of developing the therapy, running the clinical trial, or building the manufacturing facility[4].

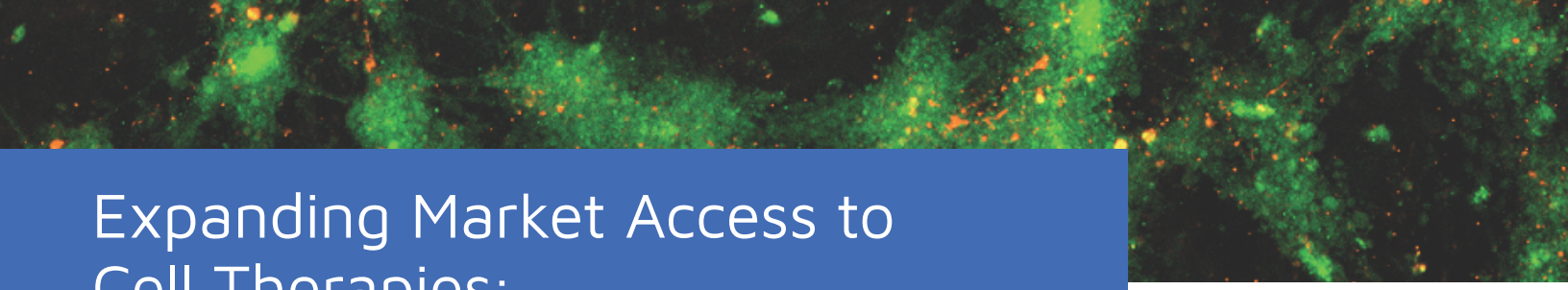
As Anthony Davies explains, the current situation is not sustainable[3].

Changes in the Reimbursement Landscape

As more regenerative therapy options come to the market, patients will demand access to the treatments, often using the court system. Payment options will be devised to absorb the costs. One option is for manufacturers to provide a product guarantee or refund the cost in a pay-for-performance model[4]. This possibility is a slippery slope that will be more costly for the manufacturer both in the refunds when the desired outcomes are not achieved and in litigation costs over whether the product claims were met or not.

Another option is private add-on insurance plans that are specific to cell and gene therapies, which carry a hefty premium. The result would be that only the wealthy could afford the treatments, limiting market access and penetration of the products.

Alternatively, Congress could move to limit payments on specific products reimbursed by government entities such as Medicaid, the VA, and Medicare. Such actions are already



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taking place for low-cost drugs such as insulin, thus it would not be surprising to see Congress move in this direction for regenerative medicines. Certainly, other countries have negotiated lower rates for life saving gene therapies based on the country's GDP or other metric[1].

Needed Changes in Manufacturing

Cell and gene therapies will likely never be as cheap to produce as most "pill in a bottle" drugs. However, their production costs can be reduced when price is a considered factor early in the development process.

Analytical models of market use can be instructional. For example, a comparison of allogeneic versus autologous stem cell treatments compared to standard chemotherapy to treat relapsing follicular lymphoma revealed that for patients over 65, standard chemotherapy was preferable for both cost and treatment effectiveness, but for younger patients the cell therapy was more beneficial and cost-effective and surprisingly, autologous treatments were more cost effective than allogeneic[5].

Manufacturers would be wise to focus on the pricing of the product early in the development phase. For too long, the US human health reimbursement system has been viewed as a limitless pile of cash. But the regenerative medicine field is showing that there are limits to the cost of treatments to an individual patient that, when exceeded, simply price the product out of the market.

Those of us in the regenerative medicine space often hear that as more treatments enter the market, there will be gains of scale that will reduce the price. However, many of the early indications targeted for cell and gene therapies have focused on rare diseases, where scale will always be limited.

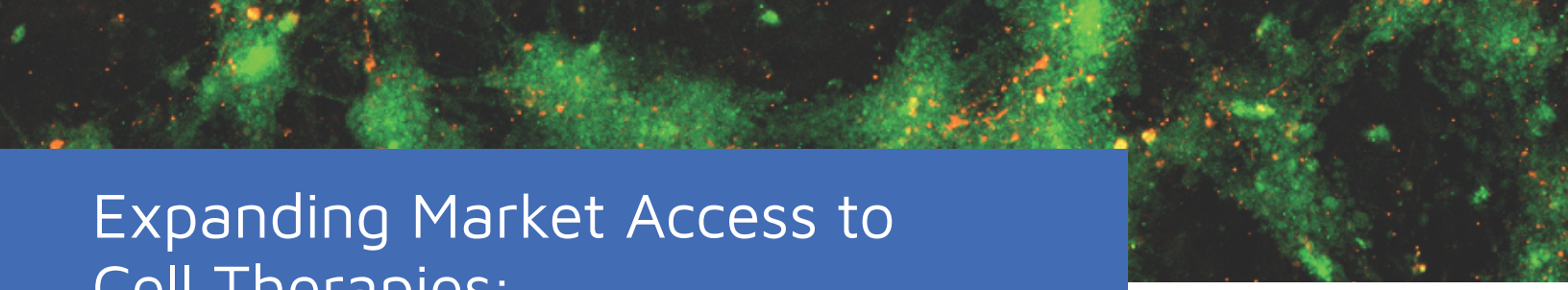
Instead, manufacturers need to consider the cost of production during the development phase. At Likarda, we were forced to think about cost at each step in the research and development of our products, because we have both human health and animal health applications for our cell therapies.

When developing a product for the veterinary market, price is a major constraint. For example, while working on a cell therapy to treat diabetes, we determined that 80% of the final cost of the product would be in the cell expansion and differentiation protocols. Analysis of our cost of goods (COGs) revealed that approximately 40% of that cost was the differentiation growth factors. Thus, when working on a differentiation protocol to convert induced pluripotent stem cells into insulin-producing cells, we analyzed each component used in the protocol.

Changes were made to the protocol based on a cost-benefit analysis. For example, we completed a series of experiments to reduce the amount of the most expensive component, Activin A. Even a slight reduction in the amount had no effect on the differentiation efficacy, but greatly reduced the COGs. Some components, such as latrunculin A, thought to be important in maturation of the cell product, had such a small effect that the product was not compromised by eliminating it completely.

In some cases, we were able to switch expensive growth factors for less expensive factors. The result is a product that, prior to achieving manufacturing scale, costs less than $1500 to produce for a canine diabetes veterinary product. Obviously, applying the same product to the human market will add costs, but should still be within a range that will be accepted by the current health care reimbursement providers, while affording a better profit margin for the manufacturer and considerable benefits to the patients.

If a biologic product requires a delivery system for protection from immune attack or to target the therapy to the desired location, that delivery system needs to be integrated into the therapeutic early in the development process. Likarda designs unique hydrogel delivery systems to optimize our clients' products. With the right hydrogel, the therapy can be more effective by:



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1. Targeting the therapy to the optimal site of action in the body
2. Optimizing the function of the therapy
3. Increasing the in vivo durability of the product
4. Protecting the therapy from immune attack

Matching the right delivery system to the therapeutic results in lower doses meaning reduced cost to the patient while still maintaining a beneficial profit margin. As politicians and the public make drug price controls a goal, those of us in the field of regenerative medicine must consider cost during the early design of the therapeutic, including the consideration of integrating a delivery system into the final product.

If you want to discuss the potential of an optimized cell therapy delivery system for your exact needs, please contact Likarda at **816.605.6440.**

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