# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Insights Into Cell Therapies for Patients With Inflammatory Bowel Disease

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**G&H** Why has there been interest in using cell therapies to treat patients with inflammatory bowel disease?

**LC** For a long time, it seemed like it was only possible to harness the power of an individual molecule or protein, and delivering it became the ultimate challenge. Finding a way to encapsulate or administer it and then get it to the site of action became the fundamentals of therapeutic development. The reality was that nature had done this already. Living cells, whether human or bacterial, had evolved to do exactly what we wanted. They were making the molecules that were going to be critical, whether as a detriment to the pathophysiology of a disease or to the benefit of healing something. The challenge then became identifying the right cell types that perpetuate either the good or the bad, and learning how to enrich those, until suddenly it was realized that perhaps the cells themselves could be used. This opened up an entirely new concept of how to think about treating a disease. The power of a cell could be harnessed to make complicated molecules and eliminate expensive biosynthesis. This could be done not only to make one molecule but many that together have a specific outcome that is of interest, perhaps suppressing an immune response or promoting mucosal healing. The best thing about this approach is that these cells naturally are going to want to go to their site of action; that is what they have evolved to do. Thus, cell therapies hold promise for being able to tap into much more complicated therapeutic concepts and being able to treat across multiple molecules and endpoints using the native substances that are either helping patients or causing their disease, rather than trying to use an approximation made in a laboratory through synthetic biology or biochemistry.

**G&H** On which types of cells has research focused so far for inflammatory bowel disease?

**LC** Many cell therapy approaches have been applied in Crohn's disease. The most familiar are some of the mesenchymal cell therapies. A lot of these products are allogeneic, which means that the cells come from someone else. In contrast, in autologous cell therapy, the patient's own cells are being used. Allogeneic mesenchymal therapies have undergone phase 2 and 3 studies in Crohn's disease for healing the intestine as a mucosal therapy and also as a therapy for fistulizing disease. Allogeneic mesenchymal cells are currently on the market in Europe but have not come to the United States yet. The phase 3 studies have been somewhat mixed. Part of the lack of success for some of these therapies in Crohn's disease likely has been because these cells do not have the ability to perpetuate the aforementioned beneficial effects to function as cells and go to the site of action, engraft, and make things better. In fact, the patient's own immune system usually prevents allogeneic mesenchymal therapies from having a lot of those functions because they are foreign and so are destroyed by the patient's immune system. Instead, there is reliance that allogeneic cells contain certain unknown growth factors or signals that are released when these cells die and help repair tissue.

Not completely understanding the biology and mechanisms of very early mesenchymal therapies likely translated to very inconsistent results. Now with second-generation cell therapies in Crohn's disease, we are thinking about how cells circulate and function. We are trying to develop allogeneic cells that are not prone to being destroyed by a patient's immune system and have the ability to function as cells rather than just functioning as vectors to release whatever is inside of them.

Some companies are also coming back to the idea of harvesting autologous cells (eg, epithelial stem cells or mesenchymal cells) from patients and are thinking more about what cells are being harvested. There is not just one type of mesenchymal stem cell or even hematopoietic stem cell; there are many different types. Probably the most prime-time example of a cell therapy for the treatment of Crohn's disease has been the use of stem cell transplantation for patients with severe refractory Crohn's disease. This involves harvesting hematopoietic stem cells from the patients, giving them high-dose chemotherapy to eradicate inflammatory cell populations, and then trying to restore healthier immune cells from their own immune stem cells to reset their immune system.

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As mentioned, Crohn's disease is where a number of these therapies have come to the market in Europe. A lot of cell therapies such as hematopoietic stem cell transplantation are undergoing investigation in both Europe and the United States. Many interesting cell therapies are in the pipeline, some of which are allogeneic one-size-fits-all approaches. Therapies using different types of allogeneic regulatory T cells are starting to get into early-phase studies. Similar things are being seen in ulcerative colitis. There have been interesting discussions in this disease involving CAR T-cell therapies, which engineer cells to attack other cell types such as certain B- or T-cell populations. Companies have even begun to explore the use of CAR T cells to attack certain myeloid cell populations.

There was a phase of initial hype for cell therapies and just giving stem cells to patients because perhaps these cells could do something and they were believed to be safe. This has now transitioned to a new phase of cell therapies where we are being much more intelligent about how to select the right types of stem or effector cells and how to make sure they are doing what we want at the right site. There is going to be a significant change in the way we start to think about the management of disease, maybe not so much in the next few years but probably over the next 5 to 10 years as some of these therapies become available.

**G&H** How are these cell therapies being dosed?

**LC** This therapeutic approach changes the way we think about drug dosing. We are no longer thinking about drug dosing necessarily in terms of pharmacokinetics, the concentration of something in the tissue. Now we are thinking in terms of the number of live cells or how do those cells persist and/or change the local environment. For cell therapies, dosing should ensure that a sufficient number of these cells make it to the tissue of interest. Similarly, for allogeneic cell therapies, we should be sure that the dose is able to go and do what we want it to do, although we may not be able to measure metrics such as engraftment. As we start to get into cell therapies whose intended role is to go to the tissue and promote healing or destroy a specific cell population that is causing problems, I think we are going to find that dosing is going to be highly individualized. There will likely be many companion diagnostics that indicate what these cells are doing and whether they are persisting or targeting the right cell population. This has been seen in the cancer world. As a patient's cancer relapses, there are ways of boosting cell therapies with repeated dosing or companion cells, and we dose these therapies based on the ability of these new cells to take hold, for instance, in bone marrow, and form a stable relationship. As cell therapies evolve, the concept of dosing may very well become highly individualized because it is not going to be as simple as giving a drug and making sure it maintains a certain concentration. It is going to be a more complicated system of making sure these cells are able to get to where they should be and have the intended effect.

**G&H** What methods of administration have been studied?

**LC** One is an indirect method in which cells can be administered into the circulation. For instance, when performing hematopoietic stem cell transplantation, the stem cells are harvested and then administered into the

blood. These cells have trafficking molecules built into them that help them go back to bone marrow, which is their home, where they can take up residence and do their job as a cell therapy. One concern is that, depending on the cell therapy, it may not have the type of homing mechanisms where the provider can put it into circulation and expect it to go back to its site.

Other companies are looking at the idea of local administration or injecting cells directly into the tissue of interest. Tissue-directed administration of cell therapies even applies to live biotherapeutics, which use bacteria as a therapeutic. Although for most live biotherapeutics, administration aims to get these organisms into the correct location in the intestine, in some of these cases, companies have even been thinking about injecting bacteria directly into certain tissues where they want them as a way to produce an effect. Mesenchymal cell therapies have involved injection directly into fistulas after preparing the fistula tract and creating an environment that may be more conducive to the cells taking hold. This sometimes involves not only preparing the site of administration, but putting the cells in the right matrix. Companies are thinking about how to generate matrices to improve tissue renewal and cell engraftment, which is the real function of cell therapy.

**G&H** What appears to be the potential for using these therapies for long-term remission in inflammatory bowel disease?

**LC** This is where the concept of cure can get tossed around. That is because there is potential to put in healthy cells that are independent of whatever environment may be contributing to the pathophysiology of inflammatory bowel disease. Additionally, from an allogeneic standpoint or even a gene therapy standpoint, there is the potential to harvest someone's cells and fix the genetic risk in those cells before they go back into the patient. Therefore, there is the potential to change the entire trajectory of a cell population by having perfectly engineered allogeneic cells or considering the patient's own cells that have been fixed of any genetic problems. When thinking about cure for Crohn's disease or ulcerative colitis, there are two schools of thought. One is eliminating any risk that could possibly exist that increases the onset of the disease, such as removing a patient's genetic or environmental risk so they never develop the disease in the first place. Another concept is somehow being able to return patients back to a predisease state after disease onset. If we could restore cells and get them to forget their role in the pathophysiology of Crohn's disease, and then put back these corrected cells that do the right things, we could have the ability maybe not to cure all patients, but perhaps to put them into incredibly durable long-term remission. Therefore, understanding how cells acquire bad behaviors in Crohn's disease and which cells do not have these bad behaviors, as well as being able to differentiate and change between the two cell states, suggests this idea of the perfect reset. There has been much interest in this in the context of hematopoietic stem cell transplantation. Can the entire immune system be reset? Can all of the cells be made to forget, or do some cells remember? Cell therapy offers an incredible opportunity to explore these ideas. Although it may well be that small molecule– or protein-based therapies will be developed that help to re-engineer a cell in vivo, for the moment, being able to find the right cells, harvest them, expand them, give them back to patients, and make sure that these are the cells that do not know bad behaviors brings patients a little closer to a realistic long-term durable remission.

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One question would be whether patients need to keep receiving these cells. If we can make sure these cells take hold and that we are putting in cells that can renew themselves and continue to do their job, there is a chance that we may not need the patient to come back for multiple doses of multiple therapies. Perhaps this could be done in a few rounds. This is something that is being explored. Where the field has to go is identifying how bad behaviors were acquired by cells, finding the cells that do not know those behaviors yet, and learning to enrich the cells through cell therapy.

**G&H** Are there any safety concerns with using cell therapy to treat inflammatory bowel disease?

**LC** With these cell therapies that involve putting in foreign cells or cells that perhaps were engineered to grow well or fast, a concern always becomes that the cells

grow too much and this would be a risk of developing something along the lines of cancer. However, in general, this has not been shown to be a significant risk for cell therapies that have gone to clinical trial in Crohn's disease, only a theoretical one. With that being said, I think this will depend on the cell therapy itself. Certainly, therapies such as CAR T-cell therapy require the administration of chemotherapy to create space for these cells to grow, which creates its own set of risks. What will likely end up happening is that the risks of cell therapies will be like the early days of biologics, where it was thought that just because they were antibodies, they shared similar risks. We will likely come to understand that not all cell therapies are the same, and a lot of the risks of cell therapy will depend on their intended function, for example, whether we intend the cell to engraft and maintain a home there for a long time or whether the cell is supposed to be there for a specific time and then over a week or two gradually wash its way out of the body.

Another theoretical concern, especially with allogeneic products, is that sometimes patients are being exposed to immune antigens they have never seen before. There may be a risk, if there are certain proteins or mismatching, that there could be aspects of how those cells provoke an immune response that may be unintentional. This is sometimes seen with certain cellular therapies such as CAR T-cell therapies and is something to watch out for on a case-by-case basis.

**G&H** What are the most important next steps in research in this area?

**LC** Important steps include continuing to build infrastructure at institutions to be able to administer cell therapies and performing the right types of translational studies to make sure these cells are doing what they are intended to do and are going to their site of action. With those steps, we are going to see a lot more advances. Also critical is ensuring that earlier-phase studies are being performed in disease states. A lot of what we have come to understand from cell therapies may not be transferable from one disease to another, and the way cells may function in healthy patients may not be the same as how they function in patients who have Crohn's disease, for instance. Although it is also important to consider early-phase studies in healthy volunteers, there is much to be learned about the pathophysiology of inflammatory bowel disease by ensuring that the people being studied are the ones we intend to give the therapy to over the long run.

***Disclosures***

*Dr Cohen is a consultant for Orchard Therapeutics.*

## Suggested Reading


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