In Conversation with

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How is your work related to cell and gene therapy?

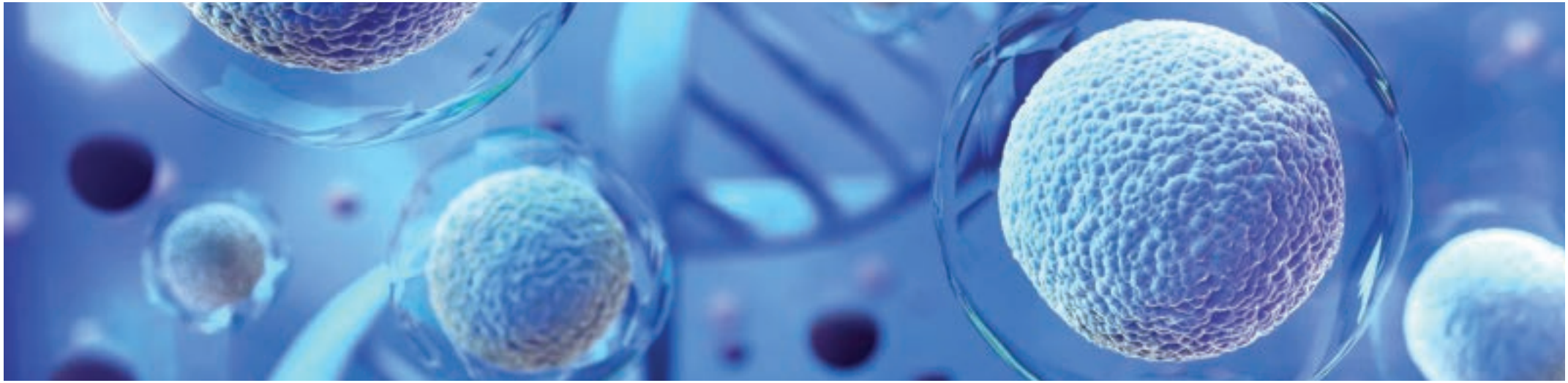
I work as a scientist in a CRO (contract research organizations), and my role involves helping pharmaceutical and biopharmaceutical clients test the efficacy of their cell and gene therapy products on a diverse pool of population.

Pharmaceutical companies often develop their products in-house and initially test them on small groups of patients to see if they are effective and safe. If the results of these initial tests are positive, the company may then try to bring the product to a larger market by conducting clinical trials on a larger group of people.

However, some pharmaceutical companies may not have the resources or capacity to conduct these larger clinical trials themselves, so they may reach out to CROs like the one I work for to help them run the studies and gather data.

CROs can provide the expertise and resources needed to conduct these studies and provide the data to the pharmaceutical companies to help them make decisions about whether to bring the product to market. When I work with a client, I try to understand the therapy they have developed and the disease they are targeting. I then work closely with hospitals or clinical sites that administer the therapy to patients and gather feedback on how the patients are responding, including any side effects or adverse reactions.

On my end, I provide the client with a readout on how the therapy is working at a molecular and cellular level. Based on this information, the client can then decide whether to bring the therapy to market. It's important to carefully assess the safety and effectiveness of these therapies to ensure that they are appropriate for use in a larger population.



Are the CRO companies just helping the innovators or are they themselves getting into the development of any kind of cell and gene therapies?

So CRO/CMO (contract manufacturing organizations) companies can be involved in developing and testing small molecule drugs, antibodies, and cellular therapies, either for their own purposes or on behalf of clients. Here at KCAS, we have teams in the biopharma and pharma departments that are responsible for developing small molecule therapies and testing their efficacy in-house.

Once they have been tested, they may be sent to clients for use in clinical trials or other types of studies. The CRO then receives patient samples and analyses the results of the therapy to assess its effects on the patient and its overall biological function. So, our company is involved in helping innovators develop and test their therapies. We have separate teams that work independently on these different activities.

What are the factors demanding the need of cell therapies?

There are several factors that are driving the growth of the cell and gene therapy industry. One major factor is the need to find new and more effective treatments for diseases like cancer, which have not seen much progress in recent decades with traditional therapies like chemotherapy and radiation. Another factor is the growing understanding of the role of cellular and genetic mutations in disease development and progression. We cannot take these therapies away from the market as they are still being used as the first line of therapy in the cancer treatment plan.

In response to this, researchers have developed adjuvant therapies, such as antibodies, which are intended to enhance the effectiveness of traditional therapies. However, these therapies have not always been effective, leading to the development of cell and gene therapies, which aim to retrain the patient's body to fight the disease. These therapies include cancer vaccines, which can help the immune system remember how to attack cancer cells if they reappear, as well as therapies using dendritic cells, mRNA-based cell therapies, and other approaches to create memory in the patient and prevent disease recurrence.

Yes, a lot of research is being conducted to develop therapies that can create memory within the immune system of cancer patients and make them strong enough to fight the disease if it spreads again. One approach that has shown promise in this regard is CAR-T cell therapy, which involves modifying T-cells, which are a type of immune cell that is naturally equipped to attack cancer cells. These modified T-cells are then administered back to the patient, where they can help to kill cancer cells and prevent disease progression.

One advantage of CAR-T cell therapy is that it is a very patient-specific treatment, as it involves taking cells from the patient and modifying them before administering them back to the patient. This can make it more effective than other types of therapies, which may not be as tailored to the individual patient's needs. However, CAR-T cell therapy is still a relatively new and emerging field, and more research is needed to fully understand its potential and limitations.

According to you, what are the challenges faced in the cell and gene therapies? Also, what are challenges faced by the researchers and the patients?

Yes, there are few challenges in this field as we are still learning about the effectiveness and success rates of these therapies. First, I would like to answer in terms of the challenges faced by the scientists.

Identifying the specific cellular and genetic changes that contribute to diseases like cancer is a major challenge for researchers in the field of cell and gene therapies. This can be a complex and time-consuming process, as diseases often have "cheat codes" that allow them to evade the body's normal regulatory processes and continue to grow and spread.

Additionally, developing mRNA therapies that can be translated into the specific proteins needed to perform specific functions in the body can be difficult due to the susceptibility of mRNA to degradation and the risk of inaccurate translation in cells. These and other challenges can make it difficult to develop and test new cell and gene therapies, but they are important to overcome in order to make progress in this field and improve the lives of patients with these diseases.

One of the biggest success stories that had got me excited in the past years is the treatment of SCID (severe combined immunodeficiency) or "bubble boy" disease in infants through gene therapy. SCID is a rare and serious immune disorder that affects infants and is characterized by a severe deficiency in immune system function.

In the past, the main treatment for SCID was bone marrow transplantation, which requires a long course of chemotherapy to prepare the patient's body for the transplant. However, gene therapy offers an alternative approach that can be less toxic and more effective for some patients. By taking hematopoietic stem cells from the patient, modifying them to express the required enzyme or protein, and then reintroducing them back into the patient's body, researchers and doctors can help to restore immune system function and improve the health of these patients.

Today, there have been a fair amount of former SCID patients who benefited from the gene-therapy and are now enjoying their childhood with healthy and intact immune systems. Stories like these make all the hard work and failures worth the journey for everyone involved in this process.

When it comes to the patients, managing the severe adverse effects (SAEs) of cell and gene therapies can be a major challenge for them. These therapies are designed to target specific changes at the cellular or genetic level, and they can sometimes have unintended consequences or side effects. Some of these side effects may be severe or long-lasting, and they can impact the patient's overall quality of life or ability to perform certain functions.

Additionally, patients may be more or less sensitive to these therapies due to genetic differences, which can make it difficult to predict how well a particular therapy will work for any given patient. These and other challenges can make it difficult for finding a universal cell and gene therapy for variable diseases, therefore it is important for researchers, clinicians, and CROs to work closely with patients and with each other to minimize the risk while ensuring the best possible outcomes.

How do you decide that patients require these therapies? Are there any criteria?

Each medication, or each drug has inclusion and exclusion criteria that are used to determine whether a patient is eligible for a particular cell or gene therapy. These criteria are usually based on factors such as age, sex, comorbidities (the presence of multiple diseases or conditions in a patient), and previous health history, including the patient's response to previous therapies.

For example, many CAR-T cell therapies have specific inclusion and exclusion criteria that are designed to ensure that the therapy is safe and effective for the patient. These criteria may include requirements related to the patient's age, sex, overall health and response to first line of therapies, as well as the type and stage of the disease being treated.

By carefully considering these and other factors, researchers and clinicians can help to ensure that patients receive the most appropriate therapies and achieve the best possible outcomes. So, I would say it is a very personalized medical decision made by the patient's provider based on who qualifies for what therapy.

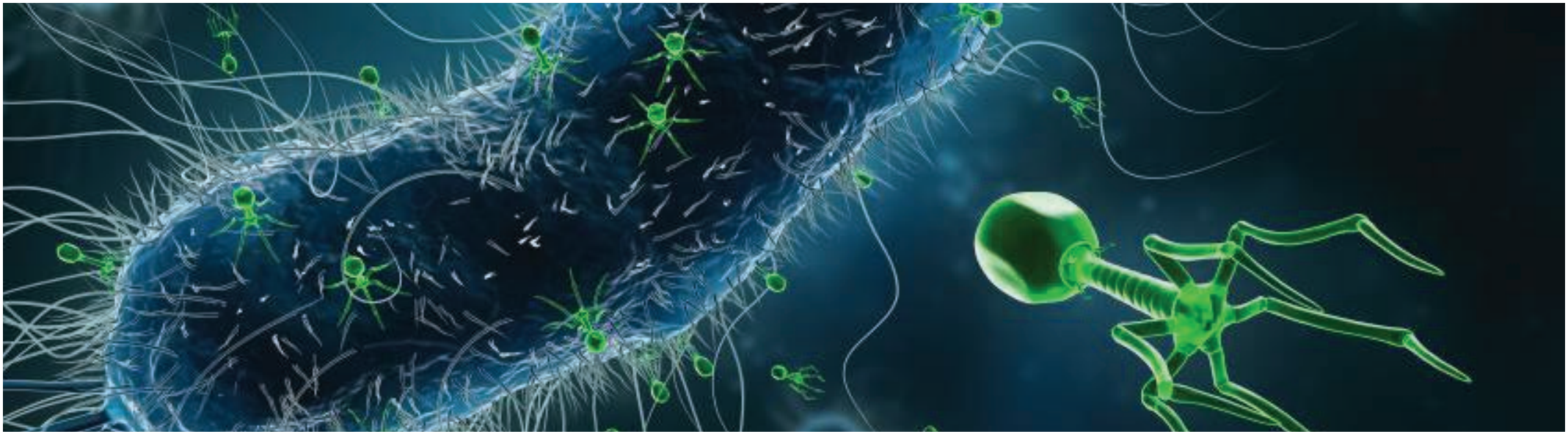
When it comes to clinical trials, is there any criteria that you will be selecting particular set of patients or is it same as you mentioned above?

The clients/sponsors are primary decision maker on setting up the inclusion and exclusion criteria for any clinical trials. Yes, there are several different types of clinical trials that may be used to test cell and gene therapies.

One type of clinical trial is a global trial, which is designed to be conducted on a global scale and may include patients from many different countries and regions. These trials often have relatively broad inclusion and exclusion criteria, and they may be used to test therapies for diseases that affect large numbers of people, such as COVID-19.

Another type of clinical trial is a basket trial, which is designed to test therapies for diseases that have a common underlying cause, such as a specific genetic mutation. In a basket trial, patients with different types of diseases may be eligible to participate as long as they have the specific mutation that the therapy is intended to target.

Finally, some clinical trials are population-specific, meaning that they are designed to test therapies for diseases that affect specific groups of people. These trials may be based on factors such as age, sex, or lifestyle, and they may be used to test therapies for diseases that are more common in certain populations.



Examples of such trials will be clinical trials undergoing to cure sickle cell disease.

What is a difference between the terminology cell therapy and gene therapy, as they are used individually also, and as cell and gene therapy together also?

Gene therapy involves the introduction of a functional gene into an individual's cells to correct a genetic deficiency or to treat a genetic disease. This can be done using a variety of methods, including using a vector such as a virus to deliver the gene to the target cells, or using gene editing technologies such as CRISPR to directly modify the genome.

Cell therapy, on the other hand, involves the use of whole cells or cell-derived products to treat a disease or condition. This can include using stem cells to regenerate damaged tissue, using immune cells to boost the body's immune response to cancer or infection, or using cells with a specific function to replace cells that are not functioning properly in the body.

CAR-T cells, genetically modified stem cells or immune cells are classic examples where both gene and cell therapies have been combined to achieve effective therapeutic approach.

So, when you combine these two strategies, and make one therapeutic product that becomes cell and gene therapy, but a lot of times people use them interchangeably.

In the past few years, cell therapy has become a hype, so what is the main factor that all the attention has come toward cell and gene therapy?

In last five to ten years, we have discovered a lot of cellular crosstalk including how one cell talk to other, how one inhibits other cell, how one cell can change the function of another cell etc. With advances in genome sequencing and other technologies, researchers have been able to identify specific genetic changes that contribute to diseases like cancer and other genetic disorders.

This has enabled the development of targeted therapies that can address these genetic changes, leading to more effective treatments for patients. Additionally, the success of some high-profile cell and gene therapies, such as the treatment of SCID (severe combined immunodeficiency) or "bubble boy" disease, has increased public awareness and interest in these therapies, which has further fueled their growth.

Additionally, the field of stem cell therapy has helped, as now we can make an organ-like structures on a petri dish where we can study how the organ is going to act in response to the new therapy, before expanding it to animals or to humans. So, with all these tools emerging in last decade it was evident that this field will bloom and explode in today's world.

What we have seen is most of the therapies which are developed are towards cancer, and after that it is either genetic disorders, or neurological disorders, so is it only applicable to only chronic diseases, or how do you decide to target a particular disease to develop a cell and gene therapy?

In summary, the focus on developing therapies for certain diseases is often driven by factors

such as market demand, funding, and availability of resources, as well as patient involvement in clinical trials. Chronic diseases such as cancer and genetic disorders are more likely to receive attention because they are more prevalent and have been studied for longer periods of time. Every day we learn something new about the rare diseases, that we have never heard of, so, these are diseases that happen in 1 in 10 million, and then we try to find the cause of these diseases. Therefore, rare diseases may take longer to identify and develop therapies for because they affect smaller populations and may be less well-studied. So, it's not that we don't want to solve all kinds of diseases with these strategies, it is that there are lot of genetic disorders or development disorders, we still are unaware about.

Personally I believe one of the biggest factors that decides the fate of a trial is the patient involvement in the clinical trials, without them volunteering not a single company in this world can release a drug out in the market. I have sincerest gratitude to our clinical trials volunteers who help us bring therapy from the bench side to the bedside one trial at a time.

Apart from Cancer, what are other current studies going on?

In addition to the diseases I mentioned, there are also studies being conducted on other conditions such as diabetes, heart disease, and genetic disorders like sickle cell anemia. There are also ongoing studies on using cell and gene therapies for regenerative medicine, which aims to repair or replace damaged tissues or organs.

A lot of cell and gene therapy studies are undergoing in the field of neurological diseases such as Alzheimer's, dementia etc. The whole mRNA-based therapy field is gene therapy that is now being used to treat infectious diseases and to develop better vaccines. However, there are a lot of studies which I may be missing that are undertaking in academic & research institutions and we would not be able to know about them until they get published. Many of these studies are still in the early stages of research, but they have the potential to significantly improve the treatment of a wide range of diseases and conditions

There are two sources for delivering cell therapies, autologous and allogenic. What is the difference between them, and which one is better?

It's worth noting that autologous cell therapies have the advantage of being more likely to be accepted by the patient's body, since they are derived from the

patient's own cells. This can reduce the risk of rejection and the need for immunosuppressant drugs. However, autologous therapies may not be suitable for all patients, as they may not have enough healthy cells to harvest for therapy. In these cases, allogenic therapies, which use cells from a donor, may be the only option.

It's also worth noting that allogenic therapies can still be successful if the donor cells are carefully selected and if the patient is given immunosuppressant drugs to reduce the risk of rejection. Thus, the method of treatment totally depends upon the patient's health status.

As you mentioned CAR-T therapies, and many other therapies such as Yescarta. Can you elaborate its benefits over others. Or can you elaborate the benefits of approved therapies over others.

I am knowledgeable about different CAR-T cell therapies currently available in the market. As I am not involved in treating patients, nor I am involved in making medical decisions, therefore I cannot say why a doctor will prescribe A vs B for certain patients. In general, the decision to use one cell therapy over another may depend on the specific characteristics of the therapy,

as well as the specific needs of the patient. Factors that may be considered include the type and stage of the disease being treated, the patient's overall health and medical history, and the potential side effects and long-term risks of the therapy. Ultimately, the decision will be made by the patient's healthcare team, which may include doctors, nurses, and other medical professionals, in consultation with the patient and their family.

When it comes to the role of manufacturers and CRO, what are there roles in terms of performing of clinical trials, further development of cell and gene therapy?

The role of the manufacturer (CMO) is to produce the cell and gene therapy according to the specifications given by the client, and the role of the CRO is to perform clinical trials to assess the efficacy of the therapy and provide a final report on their findings.

Let's consider a company that developed a CAR-T cell therapy and when the company tested it in a local hospital, they found 80% of the patients had positive response and tumor reduction with low SAE.

Now they want to take it across the country and treat patients with the same disease profile, but they don't have research facilities in every single state of the country. Therefore, to perform their nation-wide clinical trial, this company will select hospitals in different regions that will administer the therapy to the patient.

The role of the CRO in this scenario would be to oversee the clinical trial and ensure that it is conducted ethically and according to good clinical practice (GCP) guidelines.

This would involve coordinating with the participating hospitals, collecting, and analyzing data from the trial, and providing the final report to the company.

The company can then use this report to make decisions about the safety and efficacy of the therapy and to determine the next steps for its development and potential approval and marketing.

What is a regulatory scenario approval process related to cell and gene therapy? How much stringent it is?

It is very stringent. I will talk about FDA regulation because that is what am working with. In addition to the specific regulatory requirements for cell and gene therapies, the approval process for these therapies is also generally very stringent. This is because cell and gene therapies have the potential to have significant impacts on the body, and any adverse effects or unexpected outcomes could be very serious.

Therefore, regulatory agencies such as the FDA need to be confident that these therapies are safe and effective before they can be approved for use. This typically involves conducting clinical trials to test the therapy in humans, as well as reviewing data on the manufacturing, handling, and storage of the therapy to ensure that it is of high quality. There are various rules and regulations that instructs us on how we collect clinical samples, conduct our experiments, document our findings, and prepare our reports that we send out to the clients.

The regulatory approval process for cell and gene therapies can be time-consuming, but it is necessary to ensure that these therapies are safe and effective for patients. Furthermore, there are medical regulatory affairs, insurances, documentation regulations, and patient privacy and safety regulations that needs to be kept in mind and followed accordingly throughout the lifetime of the trial.

The biggest challenge associated with the cell and gene therapy is the cost, which is very high, so are the research fraternity or CRO's or manufacturers taking any kind of initiatives to reduce the cost of the cell therapies or is it possible to reduce the cost?

The cost of the therapy is depended on three things, firstly how easy it is to make that therapy: is it talking weeks or months? Second is the ease of storing and preserving the cell therapy: if it has longer shelf life that could lead to lowering the cost of the therapy, and vice versa. Third is the production volume, how much can we make in a single production of the therapy and whether the entire manufacturing process is reproducible?

The reason cell and gene therapy specially modified cell-based therapies are very costly because they are working with whole cells or modified cells, which has high cost of production, maintenance, preservation, shipping, and others.

If we can find cells which can be immortalized and is accepted in at least of the 60% of the population, then one can treat many patients with a single therapy. A research team from IIT Bombay is trying to develop gene therapy in India at a lower cost. Also, lot of therapies will get reduce in cost if they are produced locally in the country. So, if CRO's and CMO's, in India produce the therapy then that cost per treatment will be far cheaper than importing from other countries like USA. Overall, there is ongoing work in the field to try to reduce the cost of cell and gene therapies and make them more accessible to patients.

As the T-cells therapies are involving due you think that-cells therapies will be able to replace stem cells therapies in the future?

I don't think there is going to be any replacement at least not in next 10 years, I think there will be the combination of two different therapies, where stem cell therapies and T-cells therapies will be combined, and vice versa. So far, we have learnt that single therapies are not working as we want them to work, they still have lot of shortcomings.

So, based on the research point of view, one therapy is not going to work in a way we expect it to work in the patient population. But now we have lot of tools in this field, which is the most exciting part, as lot of things which we could not do due to animals were expensive, human drugs were expensive, so now we have found lot of alternative ways to do these studies and lot of assessment before we decide whether it should go to clinical trials or not.

What are the recent developments in the cell and gene therapy industry?

There are lot of exciting research happening every day in this field. As I have come from translational immunology background, what I am excited about is how the cell and gene therapy are being used in treating immune deficiency disorders, because these kids have been having very poor quality of life and they were dying at very young age.

So, to see a disease which I have studied in my high school as being untreatable and now finally in 2022 can be treated by the gene and cell therapy is nothing but an exciting time to be a scientist.

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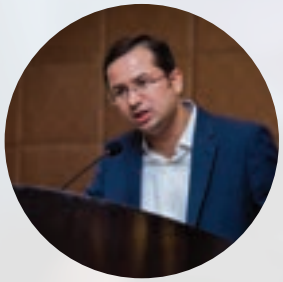

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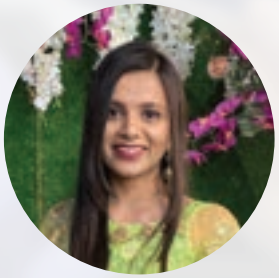

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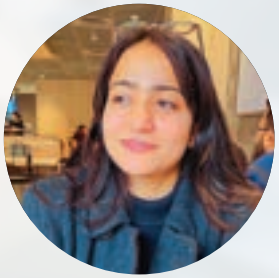

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