CASE STUDY

How Syngene's **safety tox package** helped Cytopeutics to advance its cell therapy drug to the Clinic

Syngene

Putting Science to Work

Overview

Cytopeutics was searching for a partner to prove the safety of its cell therapy products (e.g., hMSCs) prior to submission to regulatory authorities in the Asia Pacific region and National Pharmaceutical Regulatory Agency, Malaysia. The company was interested in conducting clinical trials for disease indications like autoimmune and other diseases.

Cytopeutics partnerned with Syngene to conduct safety and tumorigenicity studies in appropriate animal models (including immunocompromised) for its hMSC product as per regulatory guidelines. The data was used to design human clinical trials prior to NDA filing. Based on these studies, Cytopeutics went on to receive Malaysia's precedent CTX license under Cell and Gene Therapy for the manufacturing of its hMSCs for clinical and investigational use.

About the client

Cytopeutics (Malaysia) is a trusted provider of mesenchymal stem cells (MSC) for clinical trials and treatment in Asia-Pacific. With nearly two decades of experience in evidence-based research in collaboration with scientists worldwide, Cytopeutics today is at the forefront of cell therapy programs. The company is currently exploring the potential for multicellular immunotherapy, including cytokine-induced killer cells (CIK) and polarized M2 macrophages.

The requirement

Cell therapy research is an advanced therapeutic form of treatment that requires customized cell therapy products and services to meet product milestones. It makes use of Human Mesenchymal Stem Cells (hMSCs), which are multipotent stem cells capable of renewing themselves and differentiating *in vitro* into different kinds of tissues.

Cytopeutics was searching for a partner to prove the safety of its cell therapy products (e.g., hMSCs) prior to submission to regulatory authorities in the Asia Pacific region and National Pharmaceutical Regulatory Agency, Malaysia. The company was interested in conducting clinical trials for disease indications like autoimmune and other diseases.

The Cytopeutics team visited and selected Syngene based upon our scientific expertise, quality of work, and rapid turnaround time. After a series of technical discussions, Cytopeutics decided to partner with Syngene for preclinical Safety Assessment studies of their investigational new cell therapy product. The selection was based on Syngene's technical and innovative capabilities in cell and gene therapy. The scope of work was as follows:

- Maximum tolerable dose (MTD) in BALB/c mice
- 7-day, 28-day, 90-day toxicity studies in BALB/c mice
- 26-week tumorigenicity studies in transgenic B-NDG mice (NOD.CB17-Prkdcscid IL2rgtm1/BcgenHsd)

The Solution

From the beginning of the assignment, Syngene's Safety Assessment team worked collaboratively with the Cytopeutics team to execute the project. The initial task was to design preclinical safety tox studies that are acceptable to the regulatory agency. Syngene's Safety Assessment team prepared the study designs for all the studies, including relevant endpoints.

Dose selection is critical for the successful conduct of safety studies. As a part of the MTD study, we identified the dose which produces toxicity and the dose which is well tolerated. In subsequent *in vivo* toxicology studies, we tested the dose ranging from clinical dose to maximum tolerated dose. Later, as a part of formulation preparation, we counted the cells to arrive at the appropriate target dose level.

Since sterile handling of the cell therapy product is imperative for the success of the studies, we ensured sterility at every step – from formulation to administration. To start with, the Test item vials stored in a liquid nitrogen storage tank were removed, thawed, and processed only in biosafety cabinets. Further, the cells were diluted in normal saline and centrifuged and counted using an automated cell counter.

For the tumorigenicity study, we housed immunocompromised mice (SCID mice) in individually ventilated cages (IVC) and administered the doses in a biosafety cabinet. The parameters evaluated in the studies included general health status, food consumption, body weight, clinical laboratory parameters (hematology, serum chemistry), local tolerance, macroscopic pathology (gross observations), and microscopic pathology (histopathology) at terminal sacrifice.

We monitored tumor formation for over six months and conducted microscopic pathology for all tumors. In the 26-week tumorigenicity study, we used DLD-cells derived from a human colon cancer cell line as the positive control to assess the reliability of the assay.

In all, Syngene conducted five preclinical studies and submitted the report to Cytopeutics in tune with regulatory requirements. As a result, Cytopeutics could demonstrate its cell therapy product's safety and move on to clinical trials and product registration as per timelines.

Conclusion

Cell therapy products are live and dynamic, requiring customized case-by-case preclinical programs. By partnering with Syngene, Cytopeutics was able to conduct safety and tumorigenicity studies in appropriate animal models (including immunocompromised) for its hMSC product as per regulatory guidelines. The data was used to design human clinical trials prior to NDA filing. Recently, Cytopeutics also received Malaysia's precedent CTX license under Cell and Gene Therapy for the manufacturing of its hMSCs for clinical and investigational use.

Based on their positive experience, Cytopeutics decided to collaborate with Syngene for yet another cell therapy product – *in vitro* stroke model studies and an extremely complex project. The studies have since been completed successfully.

Cytopeutics' successful partnership with Syngene demonstrates Syngene's capability in this emerging science and marks it out as a preferred partner for stem cell therapies across the drug discovery continuum.

> "As a pioneer in stem cell research and treatment in Malaysia, Cytopeutics Sdn. Bhd. has worked extensively with Syngene on multiple preclinical projects such as safety (toxicity and tumorigenicity) and proof-of-concept studies for our new investigational product. We were consistently impressed with how efficiently the studies were initiated and progressed, within the stipulated timeline, despite the incredibly tight schedule and budget. We are extremely pleased with Syngene's outstanding quality of work, excellent professionalism, and the high level of dedication of each team member to our studies. With Syngene's help, we could complete our preclinical studies in time to support our clinical trials and product registration requirements. We look forward to working together again."

Dr. Chin Sze Piaw
Clinical and Research Advisor, Cytopeutics Sdn. Bhd., Malaysia

To know more about our Safety-Tox studies or to contact our experts, please click here

Syngene

Putting Science to Work

About Syngene

Syngene International Ltd. (BSE: 539268, NSE: SYNGENE, ISIN: INE398R01022) is an integrated research, development and manufacturing services company serving the global pharmaceutical, biotechnology, nutrition, animal health, consumer goods and specialty chemical sectors. Syngene's more than 4700 scientists offer both skills and the capacity to deliver great science, robust data management and IP security and quality manufacturing at speed to improve time-to-market and lower the cost of innovation. With a combination of dedicated research facilities for Amgen, Baxter and Bristol-Myers Squibb as well as 2 Mn sq. ft of specialist discovery, development and manufacturing facilities, Syngene works with biotech companies pursuing leading-edge science as well as multinationals, including GSK and Merck KGaA.

For more details, visit www.syngeneintl.com or write to us at bdc@syngeneintl.com

Stay Connected