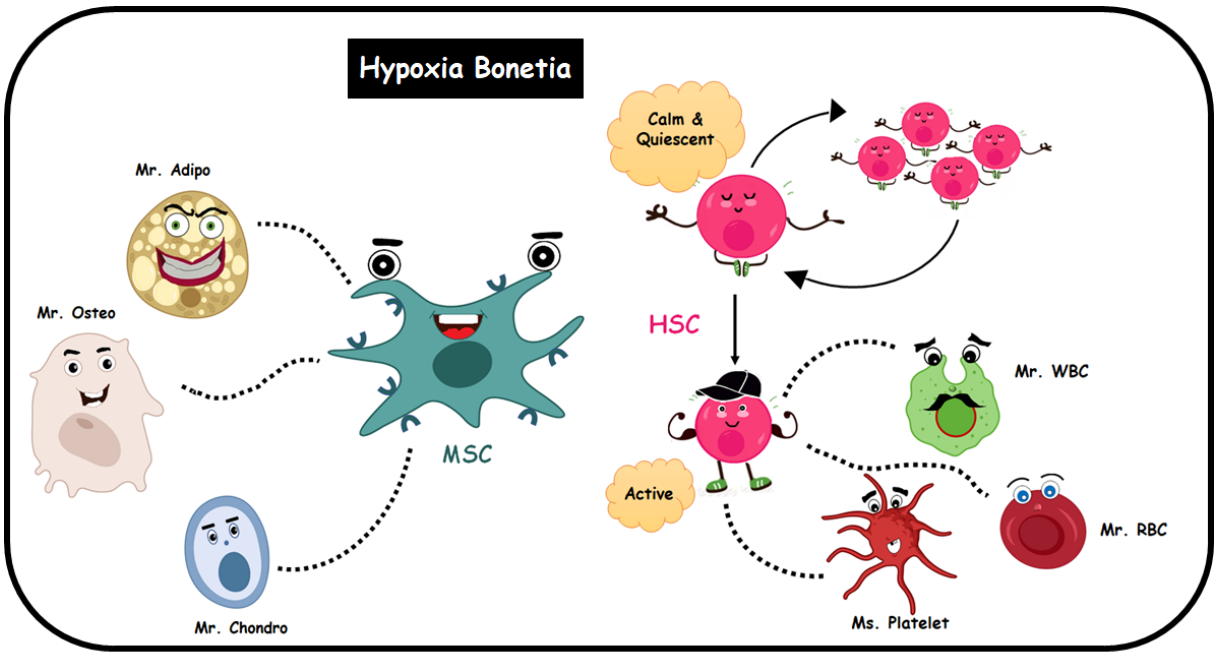
Dawn of the Stem Cells: From Rejuvenation to Regeneration

Once upon a time, there was a country called Hypoxia Bonetia (Bone marrow), known for its hypoxic (low oxygen) bone microenvironment. There lived two best friends called Mesenchymal stromal cell (MSC) and Hematopoietic stem cell (HSC).

MSC was a charming fellow with the inheritance of exceptional interactive and regenerative abilities. These abilities enabled him to differentiate his offspring into osteoblasts (Osteo), adipocytes (Adipo), or chondrocytes (Chondro), which make bone, fat, and cartilage tissues, respectively. He would also produce nutrient supplements for various other citizens of Hypoxia Bonetia, thereby helping them in their duties. MSC could complete his duties effortlessly because of his lovely *CXCR4* receptors that helped him manage his stress levels.



Unlike MSC, HSC was a submissive person. He would remain in a calm and quiescent state of mind for most of the time, regenerating copies of himself to maintain his stem cell reservoir. He called this his self-renewal mode. However, on the command of his government, he would quickly transition to an active phase and manufacture several cells, including RBCs, platelets, and WBCs. MSC was aware that HSC was dealing with a demanding responsibility, therefore as a best friend, MSC would always stay in touch with HSC and assist in his work. If communication was impossible for whatever reason, MSC would deliver HSC supportive supplements like proteins, nucleic acids, etc., wrapped like gifts in tiny packets called

microvesicles and exosomes to motivate HSC to self-renew and function efficiently. HSC and Mr. Adipo had never got along, so MSC would keep an eye on him while at work to ensure he didn't bully HSC. Moreover, MSC made sure that HSC maintained interaction with Mr. Osteo, who would also assist HSC in performing effectively. As time passed, MSC continued to support HSC in both calm and stressful conditions.

One fine day MSC and HSC got a day off, and they were having a great time at a cafe.

While sipping coffee, MSC said, “I’m bored of my monotonous life in Hypoxia Bonetia. I want to pursue something exciting and adventurous. I also wish to serve other countries which may require my help and spread joy to their families.”

With a startled expression on his face, HSC muttered to MSC, “Oh, you just hijacked my thoughts. I’ve been thinking the same lately. But I’m not sure what to do next.”

MSC and HSC kept staring at each other with eyes gleamed and grinned faces.

A voice came from the table behind MSC.

“HSC! You can be of tremendous value to different countries and states.”

MSC glanced around, annoyed, to see who was listening in on their conversation.

And he said, “Oh! Dr. Bella, it’s you. Then it’s alright! I thought who had the nerve in Bonetia to barge in our chat like this!”

Dr. Bella turned around, flashed a smile, and said, “there are so many countries that are ill and need HSCs to survive but are unable to do so because they do not have enough HSC members in them.”

HSC replied, “Oh!! That’s sad!! Dr. Bella, I want to help these countries. Can you tell me how I can do so?”

Dr. Bella responded. “To be of any use, you must leave Hypoxia Bonetia and travel to Incubatia (CO_2 Incubator) with me. There I will train you to undergo self-renewal and expand with superior functionality. Once this is completed, I will transplant you to countries suffering from various hematological illnesses, such as anemia and blood cancers, where you will serve

them and restore their quality of life. This procedure is known as hematopoietic stem cell transplantation."

Meanwhile, MSC continued to ponder, "Here I was, talking about leaving Hypoxia Bonetia and help other hosts, and Dr. Bella offers it to HSC. Huh! Seriously!"

HSC asked, "Dr. Bella, how are you going to enhance my functionality?".

Dr. Bella replied, "For that, I will have to first take MSC along with me to Incubatia."

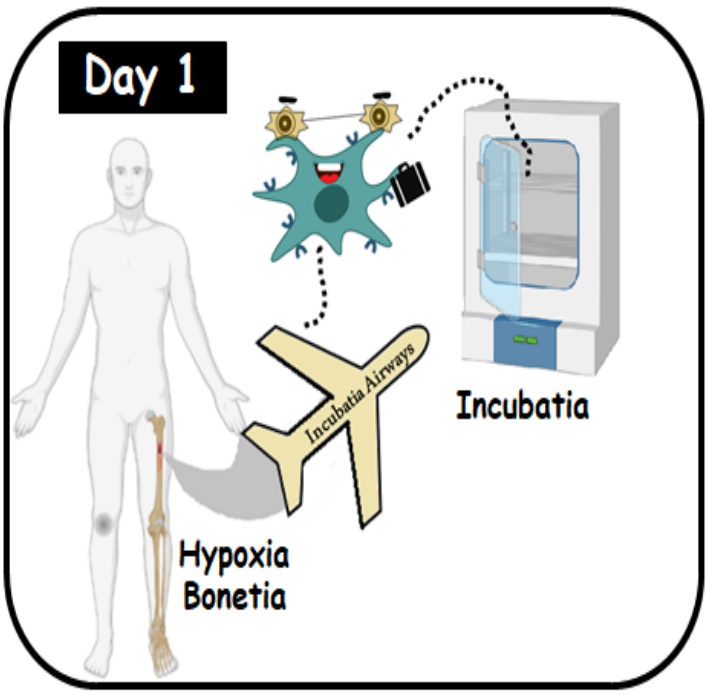
MSC, who was feeling resentful and unappreciated, spats the coffee out in astonishment.

MSC asked, "What about me? Why should I accompany you?"

Dr. Bella replied, "MSC, you are the key to this plan. HSC's functionality is enhanced by the friendship and support you provide. First, I will grow you alone for a month in Incubatia; after that, I will bring HSC to stay with you. This is when you will do what you always did in Hypoxia Bonetia for HSC, enhancing his functionality, mobility and expanding his numbers. And this will benefit us in treating countries suffering from different hematological ailments."

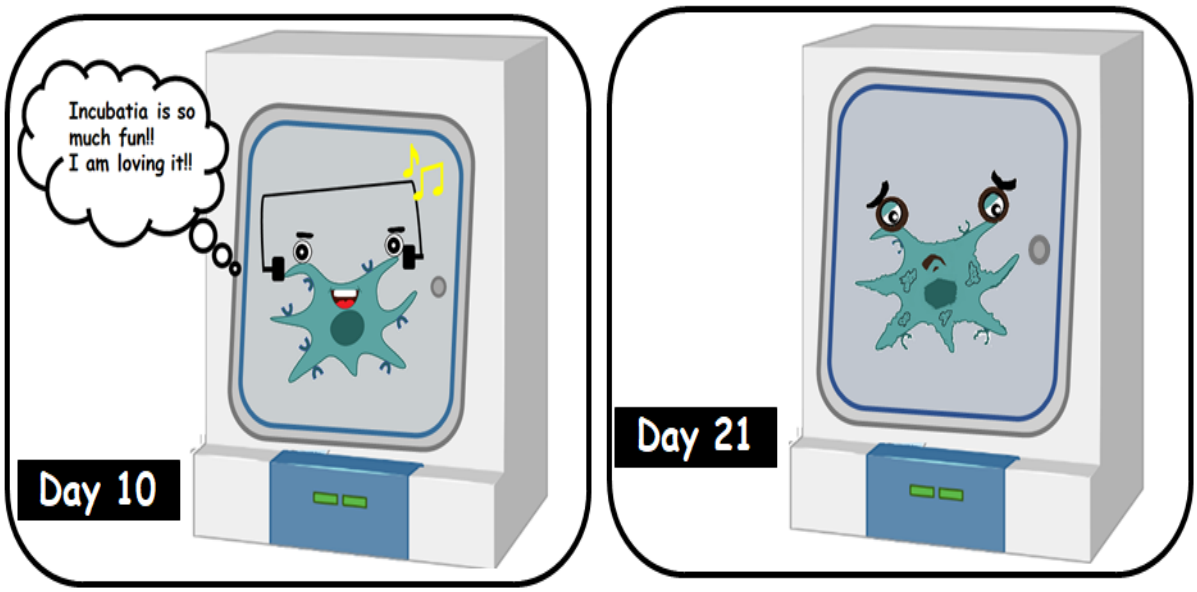
MSC couldn't keep the huge smile off his face because he was so proud of himself.

MSC responded in excitement, "So, Dr. Bella, when should we go on this adventure?"

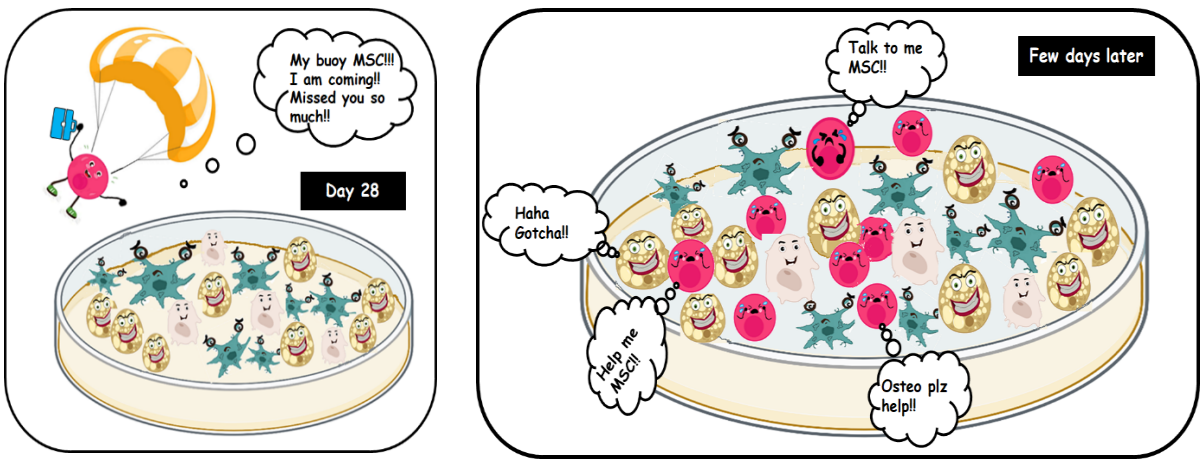


The overjoyed MSC arrived at Incubatia. Unlike Hypoxia Bonetia, this country had a hostile atmosphere with high oxygen levels. MSC tried to acclimatize to this different environment at first, but his health deteriorated over time, causing his appearance and functions to alter. He started to look pale and developed large sores on his face and body that resembled "fried egg morphology." His gorgeous *CXCR4* receptors began

to fade, resulting in excessive stress levels. Because of the increased stress, MSC reduced his ability to produce Mr. Osteo, and he began to accumulate fat droplets as Mr. Adipo seized command. He eventually reached a point where he could barely grow.



HSC reached Incubatia a few days later. Dr. Bella made HSC and MSC stay together as planned. HSC was delighted to see his friend, while MSC remained quiet. MSC had ceased producing the nutrient supplements that he used to gift HSC. He could not make Mr. Osteo, who was always supportive of HSC and also failed to protect HSC from Mr. Adipo's harassment. As a result, HSC experienced anxiety. HSC also began to lose its capacity to self-renew and to produce different immune cells and instead made only a few cell types. HSC tried to explain to MSC how his actions harmed HSC's functionality, but it was futile.



While performing routine tests, Dr. Bella observed that HSC was not working as she had anticipated him to. She asked HSC if he had any difficulties.

"Yes, there is some problem, but it is not with me," HSC responded meekly to Dr. Bella.

HSC continued, “the problem is with MSC. He has not spoken to me since the day I arrived; he is ill. And I believe his mood swings are impacting me, so I cannot perform my activities efficiently. "

Dr. Bella couldn’t help but wonder what could hurt someone as cheerful as MSC. Dr. Bella then discussed the issue with her department's head, Dr. Ciao.

Dr. Bella showed the state of MSC and HSC to Dr. Ciao.

Dr. Ciao examined them and concluded, "probably the new atmosphere was increasing the p38 stress signaling in MSC, which is why he is so fatigued."

Dr. Bella noted, "p38 signaling? Hmm!"

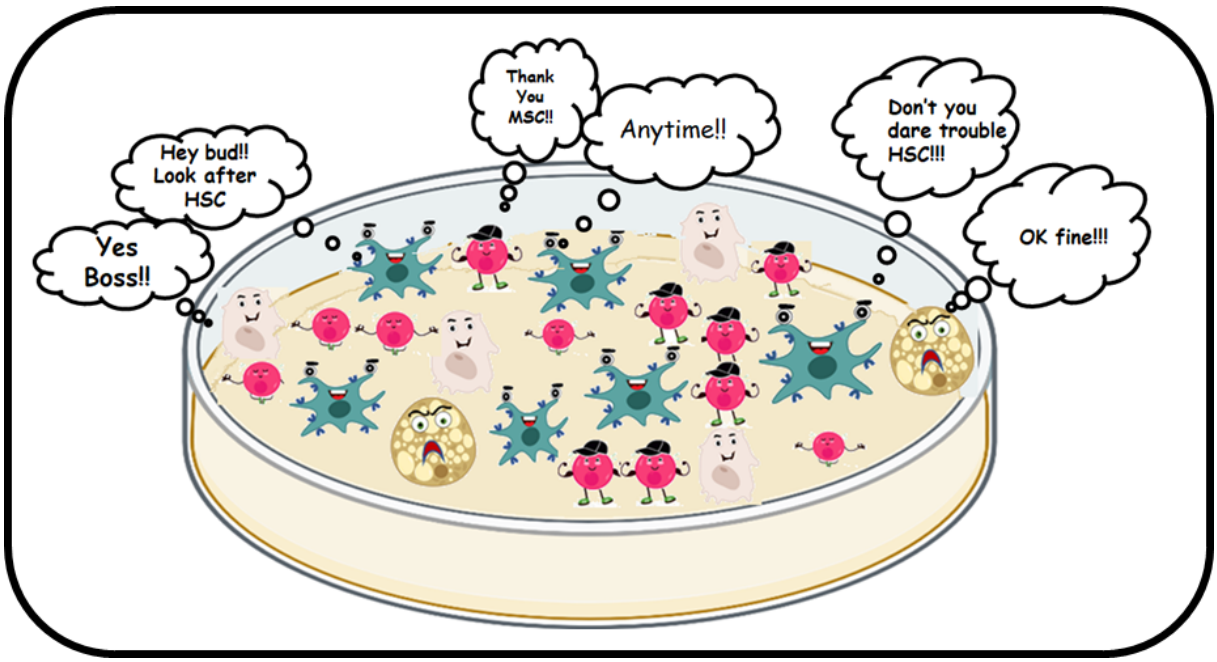
Dr. Ciao explained, "Yes! It is a stress signaling pathway that is triggered whenever someone is under any stress, anxious or depressed. In MSC's case, he is under both mental and physical pressure. He had to leave his homeland, so he is naturally homesick, and the oxygen-rich environment also adversely affects him."

Dr. Bella nodded.

Dr. Ciao continued, "To complete any work, one's mental and physical health must be prioritized. We can't change the environment in Incubatia, but we can put MSC on a rejuvenation therapy. Wherein we will treat MSC with a p38 inhibitor, which will lower his stress levels while simultaneously restoring his function."

Dr. Bella and Dr. Ciao then decided to treat MSC with PD169316, a medication that suppresses p38 stress signaling.

Within a few days following therapy, MSC began to feel rejuvenated. MSC regained his lost function and resumed his interactions with HSC. As a result, HSC was able to overcome his anxieties and recommenced normal functioning.



Dr. Bella was delighted to have finally accomplished what she had hoped for, as well as the fact that she could assist these closest friends in reuniting.

The rejuvenation therapy rekindled their friendship. In various foreign countries, MSC and HSC's triumphs flourished. And now they are both excited to serve the foreign lands of anemia, leukemia, lymphoma, and other diseased countries by their regenerative powers.

Moral of the story:

Challenges will always be a part of new beginnings; remember that asking for help is perfectly acceptable.

The author created the illustrations using BioRender.com, Publicdomainvectors.org, Paint, and PowerPoint.