Therapy Stories

Stop Codon Readthrough (PTC124)

Imagine that you are traveling on the road that makes Dysferlin protein. In order to obtain a full length dysferlin protein that makes healthy muscles, you need to get to the end of the road. However, somewhere along the road there is a washed out bridge that stops you from going further. A stop codon mutation is like the washed out bridge that prevents the cell from manufacturing a full length dysferlin protein. If the cells stops making the dysferlin protein before it is complete, the full length protein will never be made, and whatever that has been made will be too short to function, and will eventually breakdown and disappear. Therefore, you need to find another way to get to the end of the road. PTC124 is something that lets you get around the obstacles, like a new bridge, so you can continue and finish your journey to get a functional full length dysferlin protein.

Exon Skipping

Think of a mutated dysferlin gene as an electrical wire that has a fault somewhere in the middle. The idea behind exon-skipping is to remove the fault by rejoining the two ends of the wire around the fault. The resulting wire is shorter than the original one, but can still do the job.

A mutated dysferlin gene can also be thought of as a scratched CD. When you get to the damaged section of the CD, the music cannot proceed, but Exon Skipping is like skipping past the track where the scratched section is, so you can listen to the rest of the album.

Gene Editing

Think of the dysferlin gene as a string of holiday lights. If there is a defect in one of the bulbs, the whole string of light will not work. The way gene editing works is like replacing the faulty bulb, so that the whole string of light will work (i.e., make a full length functional dysferlin protein).

Chaperones

Proteins normally fold into predefined structures and when this folding gets messed up the protein cannot function. Think of the dysferlin protein as your hair and that you put curlers into your hair to make a specific look, just like the cell folds dysferlin to make a functional protein. Imagine, however, that instead of getting nice defined curls, your hair comes out all knotted and tangled up, so it doesn't look or act like it is supposed to. Some dysferlin mutations can cause a similar misfolding of the dysferlin protein so that it cannot function the way it should. Chaperones are small molecules that help the dysferlin protein fold correctly, like a comb that helps to smooth out the knots and untangle the hair.

Gene Therapy

You are a supervisor and have an employee who is not doing his job. The job needs to get done, but you are not able to fire the ineffective employee because he is the boss's son. So you bring in a new person who can do the job. Therefore, even though the ineffective employee is still there, the new employee does enough good work and the job gets done.

Immune Modulation

Think of the immune system as the fire department. If the immune system does not work correctly, it is like the fire department showing up when there is a fire in the neighborhood, but instead of dousing only

the house on fire, they also drench all the surrounding houses, causing more damage than the original fire did. What we need to do is to give the fire department the right instructions, so only the house on fire gets doused with water. In another words, we need to control the immune system by giving it the right chemical signals, so the immune system only targets the degenerated muscle cells, and does not cause damage to other healthy muscle cells.

Membrane Stabilization

Think of the cell membrane of muscle cells in a dysferlin patient as a weak and unstable dam. When severe storms come, the unstable dam will break and flood the town. Shoring up the dam will help reinforce the dam so that it becomes strong and stable and holds when the storms come, so that the town is safe.

Calcium regulation

Imagine that there is a leak in the floor and water is slowly seeping in, thereby damaging the furniture in the room. Calcium is like that rain water that enters through a crack in the cell membrane and causes damage in the cell. Now if we were to install a pump that pumps out this water (or calcium), then we can limit the amount of damage caused. The idea here is to regulate the amount of calcium inside the cell, without necessarily fixing the original crack in the floor (i.e., the cell membrane).

Repair Mediating proteins and drugs (Myoferlin substituting for dysferlin)

Think of dysferlin as part of the "tool kit" that cells use to repair damage, just like a hammer in a carpenter's box of tools when doing a repair job. If the hammer is not there, the carpenter can't do the repair the way he would normally do it. However, the carpenter could improvise and use something else as a hammer. While this tool might not be ideal for the job, it is better than nothing. There are possibly other proteins in the cell that could be made to do the job of the missing dysferlin protein.

Increased Regeneration – Stem Cell Therapy – Cell Death Regulation

Scenario: Suppose the muscle cells are like bubbles in a sink. We want to keep the sink full of bubbles, but the dysferlin deficient muscle cell bubbles rupture easily, leaving the sink with very few bubbles.

Increased regeneration: We can make bubbles faster to replenish the ruptured bubbles, so the sink will continue to be filled with bubbles, even if the bubbles keep bursting. In the case of a muscle that is lacking dysferlin, if we can increase the amount of muscle cells that the body makes (i.e. regeneration), then dysferlin deficient patients can keep getting new muscles, even if their muscle cells do not live very long.

Stem Cell Therapy: We can make bubbles from better detergents or use a better bubble maker, so the new bubbles will last longer in the sink and not burst quickly like the original bubbles. In the case of dysferlin deficiency, if we can introduce stem cells that have a healthy dysferlin gene, then the new muscle cells will not die quickly like the ones with a defective dysferlin gene.

Cell Death Regulation: Bubbles go through different phases before they burst. If we can prevent factors, such as wind, from causing early rupture of the bubbles, then the bubbles will last longer. Similarly, muscle cells go through different stages before they degenerate completely, and if we can stop muscle cells from dying at an early stage, these cells may have a chance to repair themselves, stay alive and be functional.