



2017 PSBR High School Essay Contest
Grand Essayist

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Biomedical Research and My Life

Drug development is a long process, so is growing up. The development of Jakafi by the Incyte Corporation to treat myelofibrosis has spanned the course of my life. The JAK discovery program was initiated in 2003, just as I was entering preschool. At that time, the JAK-STAT pathway was known to be involved in blood diseases, so Incyte commenced their discovery program to look for chemical inhibitors that would block the kinases in this pathway. Meanwhile, I was busy with my own discovery program of how to turn my wooden blocks into a castle.

The first major breakthrough came in 2005, as I began kindergarten. Researchers discovered that virtually all patients suffering from myelofibrosis have the JAK2 V617F mutation in their blood cells. Patients homozygous for the V617F mutation tended to experience higher degrees of fibrosis and scarring than those unaffected by it; this is because the V617F mutation causes JAK2 to be constantly active and insensitive to cellular controls. Just as I was learning how letters become words and beginning to see the world in a new light, so too did the researchers after understanding the role of this critical mutation in myelofibrosis. Incyte chemists then targeted their approach to finding inhibitors in this pathway that would turn off JAK2 to prevent more malignant cells from being produced. As I played and explored in kindergarten, researchers played with and explored the JAK-STAT pathway, and upon my graduation to grade school, the compound ruxolitinib was synthesized. More commonly known as Jakafi, ruxolitinib successfully inhibits JAK2, shutting down the uncontrolled production of cells and thus aiding patients with myelofibrosis.

This groundbreaking development then moved to the next phase, testing in animals, right as I was moving into second grade. Just as elementary school children can't leave anything untried or untested, neither can drug developers. The first step to ensure the safety and efficacy of Jakafi was to test the drug on mice. These mice were genetically programmed to have the V617F mutation, and thus develop myelofibrosis, making them the perfect model to test different doses of Jakafi. After conducting numerous murine trials, researchers concluded that Jakafi significantly reduced malignant growth in the spleen and increased the survival rate of mice treated with Jakafi compared to the control groups of animals.

Immediately following Jakafi's success in murine models, Incyte launched Phase I of its clinical trials. Drug testing is like learning the times tables in elementary school; once I succeeded in the 3s I moved right onto learning the 4s. In June of 2007, Jakafi was first administered to a myelofibrosis patient, a significant milestone in the drug's development, just like learning the whole multiplication table. The purpose of this first, small-scale trial was to identify the maximum tolerated doses of Jakafi, along with the safest and most

effective dose. After evaluating different doses in 153 participants, researchers concluded that a 15mg twice-daily starting dose was the safest and most effective. Phase II of clinical trials provided supporting evidence that this was the acceptable dose and ensured Jakafi's safety in a larger sample size.

The launch of Phase III in 2010 occurred alongside my graduation from elementary school, two monumental occasions. Randomized trials within large populations characterized Phase III, which evaluated Jakafi's effectiveness, searched for side effects, and compared Jakafi to the best available therapy. Jakafi was thrown into the real world and compared to current treatment options, just like I was when I entered a large middle school. No more recess or small trials, this was real life. Overall, Jakafi proved to hold its ground among other therapies and emerged as a new and successful option in treating myelofibrosis. In fact, Jakafi was the first in its class to inhibit JAK2 as a means of treating this disease. After just one year of testing in Phase III, the FDA approved Jakafi for the treatment of myelofibrosis in 2011. Phase III and FDA approval flew by, as did my middle school career. By the time Jakafi hit the market I was already entering high school. Jakafi developed in conjunction with my life, from my first steps all the way up to entering high school, and every little breakthrough along the way.

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