

# Eureka! My Path to Studying the Epigenome

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## Story Key Points

Cherish all the new knowledge that you acquire. You will realize how valuable it is when you least expect it.

Doing science is like goldmining. You never know where the eureka moment will happen.

It may not be a bad thing to face failure in early life because you will then understand its necessity for growth.

Remember that your family will always have your back.

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To go to college in China, almost every high school student has to take the College Entrance Examination, or Gaokao (高考). The Gaokao score will exclusively determine a student's admission into universities. However, a very small group of students can get guaranteed-admission to top universities before the Gaokao. The pre-requirement is that a student needs to get the first-prize in the National Science Olympiad. I wanted to be one of those students.

With this goal in mind, I studied college chemistry in high school so that I could ultimately compete for the first-prize in the National Chemistry Olympiad and avoid taking the Gaokao. Gradually, I fostered a deep interest in chemistry because of its combined simplicity and complexity. I did very well in chemistry and felt prepared for the Chemistry Olympiad test. I was very confident that I could get the first-prize. I dreamed of being admitted to the best college in China to continue my interest in carbon chemistry. I am not joking when I say that, as a high school student, I actually fantasized about the electrical potential of single-layer graphene! Though at that time, I knew nothing about the subsequent Nobel prize-winning research from Dr. Andre Geim and Dr. Konstantin Novoselov.

I imagined nearly all kinds of good outcomes. However, everything suddenly changed and was kicked in the face by reality. I still remember that I was just too excited or perhaps too nervous to calm down during test. I remember failing to even approximate 6.993 to 7 in a chemical formula calculation which led to a loss of 13 out of the 100 available points. As you can guess, I failed the Chemistry Olympiad and missed all my expectations. All the work I had put in for the past two years seemed like a waste.

It was extremely heartbreaking and it almost destroyed me completely. I actually remember locking myself in a room. I felt hopeless as I didn't know what to do. I also did not want to do anything. I was afraid of seeing anyone. But in my heart, I wanted to have someone to share my sadness and frustration. I wanted to find someone to tell me, "Hey Bo, don't worry about it. You've done well enough."

My mom was this person for me. At the time, she had been someone I truly trusted. I still do. She is a positive person and has always been very optimistic. However, like most kids, I did not want to let her down. After a long internal struggle, I finally summoned the courage to call her to let her know what had happened. I spoke to her in a very low voice and said, "Mom, I did very badly in today's test and I... lost ...um... everything." Immediately after saying these words, tears poured out of my eyes and I could not stop.

There was some silence for a few seconds. It felt like years. "Bo," she slowly uttered. "One test does not mean anything. You can compete in the Gaokao and I believe you can still go to your dream school."

I could not speak and kept crying silently. Then my mom said something that later became very important to me. "Bo, it may be true that you did not do well in the exam, but your hard work will last forever. You never know how rewarding the knowledge you have acquired will be until you actually need it."

In fact, I did not believe in these words at that time. But my mom's words ultimately put me back on the road to recovery. I knew that I had to face my failure in the Chemistry Olympiad head on and go back to prepare for the Gaokao again.

The failure in Chemistry Olympiad changed my path in college. I wanted to continue pursuing my studies in chemistry but later changed to studying biological sciences at the China Agricultural University. However, it was quickly evident to me that the chemistry aspirations I harbored in my heart never changed. I tended to understand biological processes naturally from a chemistry point of view. I can't emphasize enough how beneficial this turned out to be. I found myself easily understanding how Cytosine pairs with Guanine in a DNA double helix, and how protein is built using amino acids. I also appreciated the breakthrough of using chemical tools to identify the mysterious abscisic acid receptors in plant biology. Gradually, I found the effort I put in during the Chemistry Olympiad paying off. I started to believe in what my mom had said to me. Then what happened later totally reinforced this thought.

The turning point came when I joined Dr. Chengqi Yi's lab at Peking University for my undergraduate thesis research. Dr. Yi brought me into the field of epigenetics which is the study of inheritable changes in gene function without changing DNA sequences. Our genome is more than just A, T, G and C. But it includes multiple derivatives as represented by 5-methyl-cytosine (5mC), 5-hydroxymethyl-cytosine (5hmC), 5-formyl-cytosine (5fC) and 5-carboxyl

-cytosine (5caC). One of the main challenges in epigenetics at that time was to profile the genome distribution pattern of DNA modifications, called epigenomics. I hoped my chemistry background could help to develop chemical tools to study DNA modifications.

Well, it definitely helped a lot! Unexpectedly, a eureka moment came during a mid-night brainstorming session. Here is the mini-story. At that time, everyone was focusing on the formyl group of 5fC to develop tools. But I looked more at the chemical structure in its integrity. The eureka moment came when I noticed an amino group next to the formyl group, which together gives potential for chemical labeling. We could label 5fC through a well-known quinine-synthesis chemistry as shown in my organic chemistry textbook. I was shocked and couldn't fall asleep for the whole night. What an idea!

On the second morning, I rushed to my advisor's office to talk with him about this idea. Chengqi was super impressed and envisioned its potential in analyzing epigenomes. We started the project right away. Soon, I identified several chemicals which label 5fC selectively and efficiently. It was just beautiful that this 5fC-labeling induced a complete C-to-T transition mutation at 5fC sites thus allowing us to directly read out the 5fC distribution map through DNA sequencing. We named this method as 'fC-CET' (Cyclization-Enabled 5fC-to-T Transition). Through fC-CET, we discovered that 5fC is enriched in active promoters and enhancers thus marking the most active genomic regions. Ultimately, this story led to a pioneering publication in *Nature Methods* ([Xia, B. et al, 2015](#)), one of the leading scientific journals focusing on methods and technologies. I never thought I could be part of and also take a leading role in this cool project as an undergraduate student. But I strongly believe that my previous background in chemistry was instrumental in the project's success.

Though, the magic did not stop with the publication. The chemistry we had developed and our understanding of the underlying mechanisms provided us a lot of potential applications. For example, we applied this chemistry to the extreme resolution at the single-cell level. This allowed us to glimpse the epigenome dynamics in rare biological samples like pre-implantation embryos. We found that 5fC sites predict gene expression program during mouse embryonic development ([Zhu, C. et al 2017](#)). What awesome chemistry!

Suddenly, I fully understood my mom's words: "You never know how rewarding the knowledge you have acquired will be until you actually need it." My original efforts in the Chemistry Olympiad were in fact not a waste. It is worth to remember that failure is almost necessary and the associated struggle is worth it. It may not be a bad thing to face failure in the early life. In fact, failure is the greatest teacher. Don't let minor setbacks derail your progress. This is especially true in scientific research. Doing science is like goldmining. You never know where the eureka moment will happen. You have to believe that at some point in the future, you will reap the benefits from the struggle.

I am deeply thankful to my mom for having my back all those years. So, I ended up telling her this story. Though she knows almost nothing about chemistry or biology, I can tell she understood from her proud smile. Perhaps she foresaw this many years ago.