

“Never Give Up”: An Essential Approach to Scientific Research

During his April 2013 *Hot Science – Cool Talks* outreach lecture on the University of Texas Campus, Dr. Andy Ellington told an important story about his lab’s biomedical research that underscored the importance of perseverance in scientific research. The ability to “never give up” is quality that applies to many aspects of life and inspirational moments of achievement; the sciences are no exception!

The Ellington lab is working on developing biomedical technology that could save many lives in developing countries: an inexpensive test for a deadly strain of tuberculosis that is resistant to drug treatment. Making progress on this technology has been very challenging; especially with regards to developing an effective method of detecting a tiny sequence of molecules embedded within a very complex set of genetic code (the code is also known as a DNA). An appropriate analogy for finding this target gene sequence would be to “find a needle in a haystack”. In order to “find the needle”, Ellington’s lab sought to develop a way to **detect** the target sequence, and copy it a huge number of times (**amplification**) in order to produce enough of the sequence to be reliably **reported** by a simple instrument in developing countries. It turns out this task was no simple matter, and required true perseverance to achieve a test that was sensitive enough to detect drug-resistant tuberculosis.

During his *Hot Science – Cool Talks* lecture, Andy Ellington describes an extraordinary science adventure (starting at minute mark 14:06) where his lab used computers to engineer genetic code sequences (parts of DNA) that represented tuberculosis, and biological molecules that caused two separate genetic code sequences to combine together. His lab constructed these biological molecules using computer simulations, and engineered the process to repeat itself thousands upon thousands of times over. The entire goal of this engineering feat was to create a tremendous number of tuberculosis molecules (amplification) so that it could be detected and reported by a simple test. Despite successfully engineering a way to amplify the number of molecules of tuberculosis, the amplification was not strong enough to be detected and reported. ***The lab had to try harder.***


The Ellington lab decided to engineer a process by which the reaction producing copies of tuberculosis DNA was itself copied many times over. This “stacked” the production lines that generated tuberculosis DNA, which increased the number of gene sequences exponentially. Instead of hundreds of copies of tuberculosis, they produced millions of them – all triggered by one original DNA sequence. This was enough tuberculosis to trigger a diagnosis! Guess what? This was still not going to work in a medical office. It turns out that the DNA had impurities that interfered with the detection process when it was amplified. ***The lab had to try harder.***

Dr. Ellington’s lab had to engineer a “stacking” method that produced purified copies of the tuberculosis DNA. They achieved the target level of purity, but it only produced thousands of pieces of tuberculosis DNA, not the millions they needed to trigger a proper detection. ***The lab had to try harder.***

They had to completely re-engineer the way they made copies of the Tuberculosis DNA, in a way that made enough copies to be detected, and at a purity level that did not produce interference in detection. They succeeded in this engineering feat.....and you guessed it...it was not good enough. Why? The amplification reactions took too long to occur to be practical on the front lines of medical offices. ***The lab had to try harder.***

Ultimately, Ellington's lab had to develop and combine several different methods in order to progress past these roadblocks in making a cost-effective and reliable test for drug-resistant tuberculosis. It will likely be years before they produce a test that is ready to deploy to developing countries. The process of achieving breakthroughs, insights, and progress in science requires tremendous perseverance!

Students should take encouragement from this story whenever they feel frustrated or intimidated by learning science topics which are difficult to them. That is normal, and part of the adventure!



A different woman, a different social revolution: monitoring drug resistant tuberculosis in Afghanistan

- Collect slide material
- Boil, centrifuge, collect supernatant
- Phenol chloroform extraction
- Nested PCR of *rpoB*
- Sequencing
- Analysis

- Gain a picture of the extent of rifampin resistance in primary tuberculosis isolates.
- Identify relative frequency of resistance-conferring mutations to set up interpretation of new resistance tests.
- Determine geographical distribution of resistance.
- Evaluate the feasibility of molecular mutation detection for the Afghanistan National Tuberculosis Program, utilizing the existing infrastructure as an alternative to phenotypic susceptibility testing.

Sources (including featured imagery):

- *Hot Science Cool Talks* Lecture: “Diagnosing Ourselves: Take Two Assays and Don’t Call Me in the Morning” by Dr. Andrew Ellington, April 4, 2013:
<http://www.esi.utexas.edu/k-12-a-the-community/hot-science-cool-talks/diagnosing-ourselves-biotechnology-in-your-back-pocket>