Seeking Serendipity

BY EMILY PEARLMAN

When Dr. Peter Walter was approached by one of his graduate students with an unusual finding, a shorter-than-expected mRNA molecule, he brushed the student aside, telling him to "go back and repeat the experiment, and try not to degrade your mRNA this time." When it became clear that this peculiar result was not erroneous, however, he paused. "Let's try to make some sense of this," he said.

It all started with a simple question: How do different parts of the cell communicate with each other? When unfolded proteins build up in the endoplasmic reticulum (ER)—the cell's protein folding factory—the ER sends out an SOS signal to the nucleus. Like any good mission control center, the nucleus responds by expressing rescue genes that help the ER mitigate its stress. Walter and his graduate students wanted to elucidate the molecular details of this signaling pathway, known as the unfolded protein response (UPR).[1]

What they found was entirely novel and unexpected. The buildup of unfolded proteins in the ER activates a pair of molecular scissors, which snips a small segment of genetic material out of the middle of a particular piece of mRNA. With this segment missing, the mRNA can be translated into a protein that binds to DNA and activates expression of ER stress-response genes.[1] This was the first example of an mRNA splicing reaction serving as a molecular switch; the process, it turns out, is conserved across eukaryotes from single-celled yeast to humans. It breaks all of the conventions of mRNA splicing, which

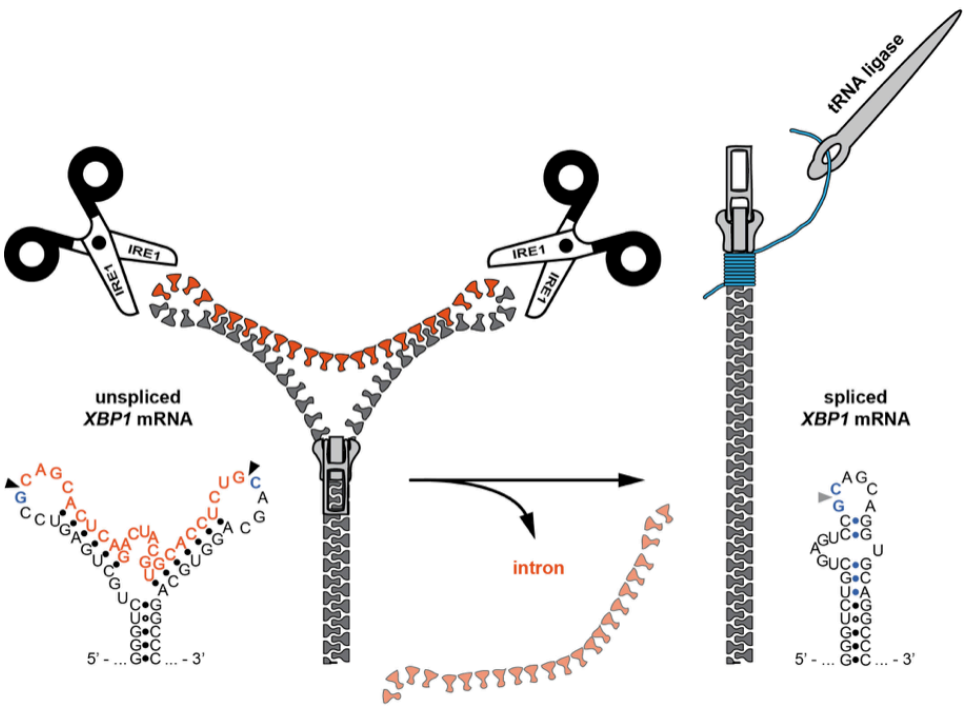

Figure 1: An mRNA splicing reaction activates the unfolded protein response. *When IRE1 senses a buildup of unfolded proteins in the endoplasmic reticulum, it cuts XBP1 mRNA, removing an intron. The resulting spliced mRNA is translated into the XBP1 transcription factor, which activates expression of stress-response genes. Image licensed under CC BY-NC-ND 4.0.*

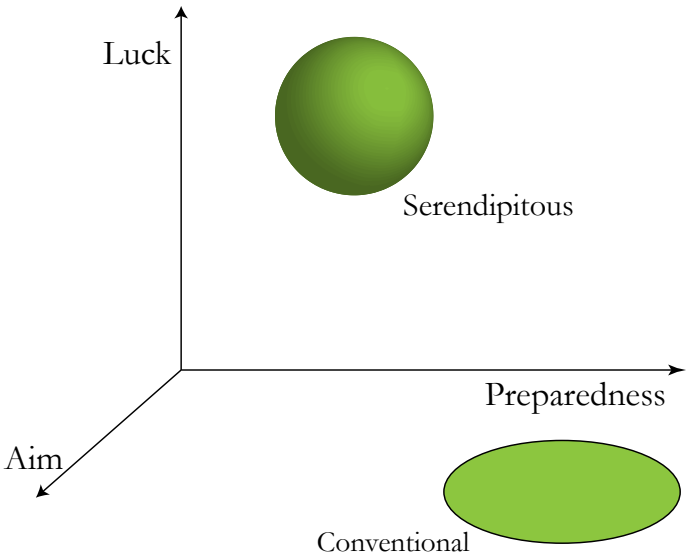

Figure 2: Serendipity lies at the intersection of luck, aim, and preparedness, while conventional scientific approaches often dismiss the role of luck in discovery. *Image adapted from source.*

normally takes place in the nucleus and requires dozens of different enzymes. "Nothing made sense," Walter tells me. "It was a beautiful moment."

The history of science is filled with these beautiful moments. In 1928, Alexander Fleming discovered penicillin, the first antibiotic, when he noticed patches devoid of bacteria on a petri dish contaminated with mold.[2] In 1943, Albert Hofmann inadvertently discovered the psychedelic properties of LSD when he absorbed some of the compound through his ungloved fingertip; three days later, he intentionally ingested LSD and rode his bicycle home from the lab while experiencing wild hallucinations.[3] In 1963, Arno Penzias and Robert Wilson were measuring radio signals from nearby galaxies when they noticed a strange background noise in their data. The noise wasn't due to pigeon droppings, as they initially expected, but was actually the cosmic microwave background radiation, a key piece of evidence for the Big Bang Theory.[4] The list goes on and on.

In fact, when you look closely, nearly all discoveries involve an element of serendipity. This notion of unexpected and beneficial discoveries has long fascinated scientists and philosophers alike.[5] Serendipity is more than simple luck or accident; it requires the ability to recognize when unexpected results are significant and the flexible mindset to pursue these unexpected results further.[6] Louis Pasteur put it perfectly in an 1854 lecture: "In the fields of observation, chance favours only the prepared mind."[2] Scientific discovery thrives here, at the intersection between chance and wisdom.

Walter's investigation of the UPR doesn't end here. After deciphering how the ER communicates with the nucleus, he began searching for molecules that stopped that chatter. Aberrant activation of the UPR throws cells into a state of chaos, so it's associated with many diseases; inhibitors of the UPR are promising candidates for therapeutics. Starting with a pool of hundreds of thousands of molecules, he subjected them to a series of tests, weeding out unlikely candidates at every step. At the end of Walter's screen, only one molecule remained: ISRIB, or integrated stress response inhibitor. Intimately related to the UPR, the integrated stress response alters protein expression in response to intra or extracellular stress.

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This screening approach, which Walter describes as "disease agnostic," is unconventional in that he began without the intent of curing a specific disease. The current paradigm of grant allocation can make it difficult to receive funding for this type of untargeted biological research. More often than not, grants drive researchers to address particular problems, a process that discourages flexibility and makes it hard to change directions in light of unexpected developments, stifling serendipity.[7] Furthermore, funding agencies are more likely to support projects where successful outcomes can be predicted with reasonable certainty, in order to maximize their returns.[8] This is not to say that all research should be curiosity-driven—unexpected findings can arise from targeted studies as well—but curiosity-driven research should be given a chance.[4]

After discovering ISRIB, Walter's next move was to call up his colleague, Nahum Sonenberg, to see if he had any materials that would be useful for studying ISRIB's effects on protein translation. Though the contents of his lab freezer didn't wind up being useful, during their conversation, Sonenberg happened to mention an interesting project related to protein translation in the brain that his postdoc, Mauro Costa-Mattioli, was working on. Coincidentally, the very step of translation that ISRIB acts on is involved in long-term memory formation. This connection set off a cascade of scientific discovery; subsequent work by Walter's research team and others revealed ISRIB's remarkable capacity for cognitive enhancement. ISRIB's mechanism of action is not yet entirely clear, but it likely reverses the global decrease in protein translation caused by aberrant activation of the ISR (which is implicated in some neurological

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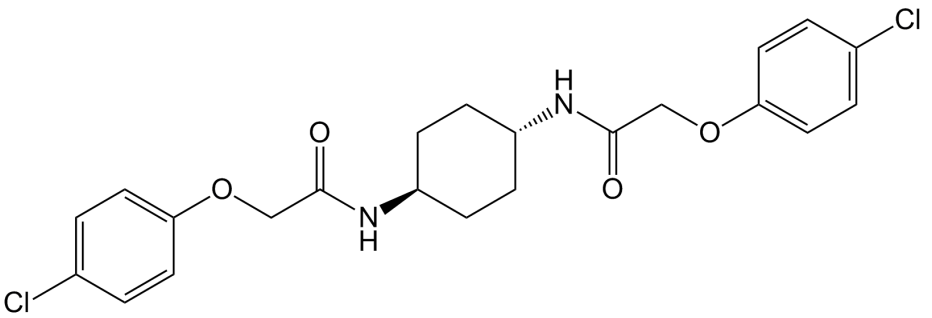

Figure 3: Molecular structure of the integrated stress response inhibitor (ISRIB). *Dr. Walter came across ISRIB in his screen for small molecule inhibitors of the unfolded protein response (UPR). ISRIB interferes with the integrated stress response, restoring normal protein production to the cell, and shows potential to treat a broad spectrum of diseases.*

diseases), restoring long-term memory formation and normal cognitive function.[9]

If not for this phone call, ISRIB's cognitive enhancement properties may have gone undiscovered, or at least unrecognized for many years. "It changed the spectrum of what we could do with ISRIB entirely," says Walter. Serendipity is thus critical not only at the individual level, but also at the community level. External features of a researcher's environment, including their network of colleagues, influence their aptitude for recognizing and following up on serendipitous findings. Serendipity is enhanced when researchers with different expertises and perspectives are brought together in a collaborative setting; colleagues from different disciplines may have previously unrecognized insight or alternative interpretations of unexpected results.[2] Serendipity is also enhanced in settings where knowledge is regularly shared and results are published early.[6]

ISRIB human trials haven't begun yet, but the results of mouse studies are nothing short of amazing: old mice, when treated with ISRIB, are able to solve difficult mazes significantly faster than their placebo-receiving counterparts.[8] In addition to treating age-related cognitive decline, ISRIB has shown a good deal of promise for treating traumatic brain injuries.[10]

None of this was obvious when Walter started out. He was just trying to answer the simple question, "How does one part of the cell communicate with another?"

His story certainly doesn't end here. It's just a matter of seeing where the meandering path of discovery leads him next. He reminds us that scientists are explorers, forging ahead into the universe of the unknown, following the guiding star of serendipity.

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IMAGE REFERENCES

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3. *Figure 2*: see reference 8.
4. *Figure 3*: Image made by author.