HEADLINE

Over the last two decades, our understanding of cancer at the level of cells and molecules, has increased exponentially. The new era of genomics is the most promising time ever in cancer research, but it also presents great challenges. We have more data and deeper insights than ever before, but to make sense of it requires not only talent and dedication, but also collaboration. No one person can hope to unravel the mysteries of cancer by himself, but dedicated scientists, working together and building on each other's discoveries can make remarkable contributions to the improvement of patient care and ***Research*** for a **Cure.**

That is the story and the mission of NFCR, fostering scientific research from the lab bench to the bedside. It is also the story of NFCR Project Director Curt Civin, a pediatric oncologist specializing in leukemia research at the University of Maryland School of Medicine in Baltimore.

Dr. Civin revolutionized the field of leukemia research with his breakthrough discovery of CD34, the first — and still the best — marker of hematopoietic stem-progenitor cells ever found. Curt Civin's isolation of the hematopoietic (blood-forming) stem cell opened entirely new directions in bone marrow transplant research, and led directly to cures for patients. The CD34+ transplantation technology created by the team of scientists in Dr. Civin's laboratory has been widely applied, and thousands of patients owe their lives to this new approach to treating cancer.

Since the discovery of CD34 — and, in part, because of it — the relative 5-year survival rates for all types of leukemia have increased dramatically. Yet despite these advances, there is still so much that needs to be done. Although patients with acute myeloid leukemia (AML) have shared the improvement in outcomes, AML remains the deadliest form of leukemia.

Research into the molecular basis of cancer shows that AML patients with the worst response to current therapies are those whose cancers have mutations in a gene called p53, one of the most important molecules in the body for protection against cancer. Their p53 no longer functions. When p53 no longer functions, what can be done to help these patients?

The answer may lie in a recently discovered class of cellular molecules called microRNAs. These tiny bits of RNA — previously thought to be the "molecular sawdust" left over from the break-down of much larger RNA molecules—have been discovered to have vital functions of their own. MicroRNAs profoundly influence which of each cell's genes are made into proteins. A single microRNA may control the amounts of hundreds of different proteins in our cells

If expressing individual genes can be likened to turning on light switches one at a time, microRNAs can be thought of as flipping circuit breakers, switching on entire buildings at once. In the cancer cell, entire pathways or sets of pathways — involved in cell growth or division, for example — can be activated by a single microRNA. A single microRNA may also be able to shut down a cancer cell.

Dr. Civin's NFCR-funded research is focused on miR-34, a quintessential tumor-suppressor microRNA. When a mutant cell contains enough miR-34, the presence of miR-34 initiates a molecular self-destruct sequence that destroys the cell in a process called apoptosis.

It turns out that miR-34 is absent or present at only extremely low levels in most leukemia cells. It is as if leukemia cells have managed to cut the power to the apoptosis circuit.

Dr. Civin's exciting new research strategy is to restore miR-34 to the leukemia cells and reset the circuit breaker for tumor suppression to activate the leukemia cells' own natural machinery to induce them to destroy themselves through apoptosis. But miR-34 is a molecular cancer molecule that has never been targeted previously. How best to target miR-34 and initiate the molecular self-destruct sequence in leukemia?

MALARIA TREATMENT FOR CANCER PATIENTS

Dr. Civin set out to translate his findings for the benefit of patients in the clinic. This is where the collaborative nature of cancer research was most evident, and most crucial. Scouring the libraries and databases of existing clinical drugs, Dr. Civin's team was able to identify a set of drugs that were able to increase the amount of miR-34a in target cells. The most promising of these drugs came from an unexpected source.

It turns out that nearly two thousand years ago, Chinese herbalists described the use of the Artemisia annua plant as a remedy for malaria. The active ingredients isolated from this plant, known as Artemisinins, are now a standard treatment for patients with severe malaria, and they are routinely administered with no major toxicity. Dr. Civin's studies also revealed that, in addition to their anti-malarial effects, these Artemisinins also increased the levels of miR-34 in cells.

Would they be able to do this in leukemia cells as well?

Back in the laboratory, research conducted by Dr. Civin discovered that not only can Artemisinins increase the levels of miR-34 in leukemia cells with functioning p53 — inhibiting their growth — but they can also achieve this result in leukemia cells with mutant p53 — the leukemia cells that carry the worst prognosis for AML patients.

This could be a breakthrough discovery: this is the first drug that up-regulates miR-34 in a way that is both independent of p53 and safe for clinical use. Clinical trials testing the efficacy of Artemisinins in AML patients will be underway in the very near future, bringing this new AML treatment into the clinic.

This is an entirely new approach to treating AML. Researchers focused on malaria are not thinking about leukemia; researchers focused on leukemia are not thinking about malaria – but with a willingness to share information and think critically across disciplines, scientists can recognize the potential of different treatments. In this case, they will repurpose a malaria drug as a novel treatment for cancer — a new treatment that provides new hope and might lead to cures. Dr. Civin's innovative research offers promise that this can be accomplished.

What future might Dr. Civin's research hold? Might this drug or this approach be applicable to other types of cancer? Might there be other microRNAs that are critical for cancer? Might there be other cancer drugs — safe, effective, and readily available — that are languishing on the shelves, waiting for scientists like Dr. Civin to repurpose them?

With your support and by working together, we will answer these questions. From basic science to new treatments, Dr. Civin's work has both exemplified and advanced the mission of NFCR: ***Research*** for a **Cure.**