Mark Roth

Mark Roth's pioneering work on hydrogen sulfide has spawned Ikaria, a company exploring the molecule's potential to modulate the body's metabolism and perhaps one day turn hibernation into profitable clinical applications.

A capricious curiosity has prompted Mark Roth to jump routinely into enticing, unexplored research fields during his career. Since 2000, however, his research focus has been firmly set on unraveling the intriguing biology behind hydrogen sulfide (H_2S), a molecule with potential in the treatment of hypoxic/ischemic conditions and even 'hibernation-on-demand' applications.

Roth, a cell biologist at the Fred Hutchinson Cancer Research Center in Seattle and adjunct faculty member in biochemistry at the University of Washington School of Medicine, is known for pushing boundaries and has received due credit for it. In 2007, he was awarded the MacArthur Foundation's Fellowship (nicknamed the 'genius' grant) of $500,000 for his work on H_2S. That same year, Clinton, New Jersey-based Ikaria—the company he formed to commercialize clinical applications for the H2S—merged with another firm in a transaction valued at $670 million.

Roth's interest in H_2S was sparked by the miraculous reports of winter accident victims who survive long periods without breathing. In 1999, Anna Bagenholm, a Swedish doctor, survived nearly an hour trapped underwater beneath ice flows after falling into a river while skiing. Triggered by the drop in temperature, her body entered a quasi-hibernation state, her metabolic rate slowing to a near standstill.

Roth wanted to induce the condition chemically so the compounds might be given to trauma patients suffering blood loss after a car accident or in the battlefield.

One way to stop metabolic activity is to curb oxygen consumption. Roth hit on a molecule capable of achieving it while watching a documentary about caving in Mexico. Cavers have to wear masks to protect themselves from the gas H_2S, which at high doses kills in minutes by blocking oxygen receptors and starving cells of oxygen. Roth speculates that H_2S—a by-product of cell metabolism and naturally present in blood—kills only in excess by overwhelming the cells; oxygen consumption grinds to a halt. In contrast, exposure to minute doses of H_2S would likely reduce oxygen demand enough to slow cellular metabolism.

Roth wanted to test that hypothesis, but he had neither the money nor the equipment to carry out his experiments. What's more, he had no track record in suspended animation, which was dominated by hypothermia research.

But Mark Groudine, the Fred Hutchinson's deputy director, bought into Roth's request for support. That was, as it turns out, a wise decision. In 2005, Roth made headline news worldwide when *Science* published his results showing that exposing mice to tiny doses of H_2S induced a state of reversible hibernation. The treated animals survived up to six hours, apparently unscathed, in tanks from which nearly all the oxygen had been removed.

After that, investors lined up to back Ikaria, then based in Seattle, which was launched in 2005 with $10 million in venture capital.

From a tiny company, Ikaria swelled overnight to roughly 350 employees in 2007, when it merged with INO Therapeutics, in Clinton, New Jersey. INO had already developed a global market for inhaled nitric oxide, also a toxic gas produced by cell metabolism, which is used to facilitate oxygen perfusion in cyanotic babies. Thanks to the merger, the new company—now officially dubbed Ikaria Holdings—had the funds to carry H_2S research all the way through clinical trials. With nearly 500 employees, Ikaria is now valued at roughly $500 million, Roth says.

Ikaria's chief science officer, Csaba Szabo, believes its potential market is huge. H_2S may someday satisfy unmet needs in trauma, heart attack, stroke, sepsis, lung injury and more. There are two patent categories: Roth and the Fred Hutchinson have a patent that covers medical applications with H_2S, which Ikaria has rights to; and Ikaria has its own patented H_2S formulation.

According to Szabo, Ikaria has since reformulated its H_2S product into a proprietary, injectable liquid (sodium sulfide) that lacks the gas' more noxious properties, particularly its rotten-egg smell. Ironically, however, Ikaria's clinical investigations with H_2S have diverged from Roth's groundbreaking forays into trauma. For instance, the company is currently running proof-of-concept phase 2 trials with that product, known as IK-1001, in patients undergoing pulmonary bypass surgery, he says. Meanwhile, Szabo and Roth describe H_2S's mode of action differently. Szabo describes it as a hormone that "enhances hemodynamic parameters and cardiovascular function." He adds, "It dilates blood vessels, scavenges free radicals and it inhibits the damaging adhesion of neutrophils to endothelial tissues on the inside of blood vessels. So, this is much more than metabolism—the story started there but it's gone off in different directions."

"Tiny doses of H_2S induced a state of reversible hibernation."

Roth still focuses on H_2S's capacity to slow metabolism "like a dimmer switch" depending on how much is given. He admits he doesn't know how it performs this function, noting that H_2S—a gas that sustained primordial life billions of years ago—likely binds with thousands of receptors conserved throughout evolution.

Skeptics wonder if H_2S will ever achieve its clinical goals. A recent study by Andrew Redington, division head in cardiology at the University of Toronto's Hospital for Sick Children, could not replicate Roth's mouse findings in piglets, prompting speculation that H_2S's metabolism-slowing effect might not be attainable in large animals, including humans. Sam Tisherman, a surgeon at the University of Pittsburgh Medical Center, who investigates suspended animation in pigs, concedes that "questions surrounding efficacy in large animals still need to be answered."

Meanwhile, Roth—who retains an advisory position with Ikaria—is plowing forward with his own research. His most recent published findings show that H_2S improves survival of rats suffering from extreme blood loss. Roth is said to be working with pigs, but would not comment on the results. "I'm pleased that Ikaria's going off in new directions," an upbeat Roth says. "And I'll be looking forward to the outcomes of their clinical trials."

Charlie Schmidt, Portland, Maine