

A Science Financier, Jeffrey Epstein, Changes the Course of Evolution at Harvard.

If the scientist's job is to ponder the stars, the banker's is to funnel his vision into stellar panels. For while scientific theory can be enthralling, it's in danger of racking up lost gigabytes and circuitry dust. So every time a smart businessman comes along, with an interest in science, the public should pay attention, because not only can it lead to pragmatic accomplishments but can actually change the course of scientific enquiry.

Such is the case at Harvard. Evolution is always moving, but nowhere has it been more in flux than in Brattle Square. Indeed, ten years ago, an unknown financier, called Jeffrey Epstein, set up the Program for Evolutionary Dynamics at Harvard with a \$30 million dollar grant. His mission was not to coddle neo-Darwinian theorists (because honestly couldn't \$30 million be used to say, vaccinate the entire country of Zaire?) but to embolden a pragmatic use for the study of natural selection.

So in May 2003, with the cooperation of Lawrence Summers, then President of Harvard, the Program for Evolutionary Dynamics set up for business and, under the direction of Martin Nowak, a professor of Mathematics and Biology at Harvard, it revolutionized the way in which evolution is studied and utilized. The Program became one of the first of its kind to study the evolution of micro biology with the use of mathematics. It also became the first department to develop a mathematical model of how cancer cells evolve as well as infectious bacteria and viruses such as HIV. Now celebrating its 10th anniversary, the Program's models have led to key discoveries in combatting diseases of all kinds and have encouraged researchers around the world to do the same.

It all started in early 2000, when an obscure New York hedge fund owner called Jeffrey Epstein with a passion for cutting edge science, invited Martin Nowak to organize a conference on the evolution of language. Nowak was then Head of the Program of Theoretical Biology at the Institute for Advanced Study at Princeton and had already published a substantial amount of work on the mathematics of the HIV virus, infectious bacteria and cancer. Prior to his post at Princeton, Nowak had been the head of the mathematical biology group at Oxford University in 1995 and Professor of Mathematical Biology in 1997. His work was not just quixotic and theoretical but keenly implemental.

By 2003, Jeffrey Epstein already had a substantial career in science philanthropy. He had supported the research of many prominent scientists including, Stephen Hawking, Marvin Minsky, Eric Lander, George Church and Nobel laureate physicists, Gerard 't Hooft, David Gross and Frank Wilczek. He was also a member of the New York Academy of Science, a board member of Rockefeller University and actively involved in the Santa Fe Institute, the Quantum Gravity Program at the University of Pennsylvania, and sat on the Mind, Brain & Behavior Advisory Committee at Harvard University. Epstein himself was not a scientist *per se*. He had studied physics at the Cooper Union in New York, mathematics at the Courant Institute in New York, leaving both without a degree and moved on to teaching calculus and physics at the Dalton School in Manhattan. He was then scooped up into options trading on Wall Street and applied his acumen and mathematical wit to the markets.

But Epstein's heart remained in the pure sciences, fascinated by fundamental questions on the one hand and eager to apply scientific theory to the real world. It was this combination that drew him to Nowak. For

not only could Epstein probe a brilliant mind about the origin of life, the origin of evolution, but with his connections at Harvard, found a powerful platform in Nowak to put groundbreaking medical research into immediate practice.

One of the diseases that the Program has tackled successfully is colon cancer. In 2012, Martin Nowak and post-doctoral students, Benjamin Allen and Ivana Bozic, developed the first mathematical model of how human colon cancer cells evolve and specifically how they become immune to inhibitor therapy treatment. Their research was conducted at the request of the Pathology and Oncology Department at John Hopkins University. The Department was trying to understand how the KRAS gene in colon cancer cells becomes activated after inhibitor drug therapy, making the cells resistant to treatment.

By developing a mathematical model of colon cancer cell growth, Nowak and his team, showed how the KRAS gene is not actually activated or 'switched on' from inhibitor drugs but rather a small percentage of colon cancer cells with an already activated KRAS gene are immune from the start and evolve to predominance as the other cancer cells are destroyed by the inhibitor drug. The discovery was critical in changing the approach to inhibitor drug therapy. Instead of applying drugs in sequence to one another to fight secondary and tertiary resistance, the Pathology and Oncology Department at John Hopkins are now exploring the necessity of providing a cocktail of inhibitor drugs to capture all colon cancer cell types: those with the activated KRAS gene and those without. The same tailored approach is underway for other cancer types.

In 2010, Ivana Bozic and Martin Nowak co-authored a pivotal mathematical study that showed that most solid tumors contain 40 to 100 genetic mutations, but that on average only 5 to 15 of those actually drove tumor growth. The findings were essential to researchers at John Hopkins and other oncology departments because it highlighted the importance of isolating only a key minority of mutated tumor cells for effective inhibitor treatment.

"Mathematics in medical research reveals patterns that are otherwise hidden," Jeffrey Epstein remarked, who maintains a frequent presence at the Program. "It's exhilarating when a mathematician can determine molecular and cellular behavior with the precision of an engineer and share their findings with physicians."

In that same year, the Program of Evolutionary Dynamics presented to the John Hopkins School of Medicine, the Howard Hughes Medical Institute and others, a mathematical model showing the genetic evolution of pancreatic cancer cells from the time of initial mutation to non-primary malignant cells. What they found was surprising: that pancreatic cancer, one of the most lethal forms of cancer, is not fast and furious as suspected, but rather slow growing. In fact, given the amount and type of genetic disparity between the cellular stages, the model showed that it takes about 10 years for an initiating mutation to develop to a parental, non-metastatic founder cell and another 6 years for cells to become malignant.

The significance of these findings highlighted the real potential and importance of isolating pancreatic mutations prior to metastasis, if not in the blood, then as soon as a primary non-metastatic tumor develops.

Over the last two years, Nowak and his team also collaborated with John Hopkins School of Medicine to develop an ultimate database to map and predict the effect of drugs on the HIV virus. Similar to cancer,

resistance to HIV drug cocktails continues to be a major problem for patients and the trial and error of clinical trials can be hugely debilitating. By collecting data from thousands of blood tests of antiviral activity from more than 20 anti-HIV drugs, the model calculates each drug's ability to suppress viral replication and avoid resistant, mutant HIV strains. The model also factors in the performance of every possible drug combination, dosages, blood types, age, sex and other variables to arrive to the most precisely engineered predictor of results for future patients.

Ostensibly, Epstein's motivation for applied science varies from Nowak's. While Nowak is a practicing Roman Catholic, a declared humanist with a desire to serve society, Epstein is first and foremost a problem solver, interested in strategy, intellectual puzzles and interception. His interests are equally devoted to physics, artificial intelligence and the human brain. According to Nowak, he was fascinated with his Game Theory of Win Stay, Lose Shift and eager to see how it could be applied to the markets. That is not to say that Epstein doesn't espouse purely humanistic endeavors. He has given thoughtfully to countless organizations that help educate underprivileged children, notably in the US Virgin Islands where his foundation is based. But his essence is in uncovering the unsolved, a possible but perhaps, insatiable endeavor.

Much has been written about the Program for Evolutionary Dynamics and Martin Nowak's theoretical work in the evolution of language, his mathematical exploration of how pre-life evolved into life, and his work on spatial selection, cooperative, game, graph and set theory. Nowak himself is the recipient of the famed Weldon Memorial Prize, the Albert Wander Prize, the Akira Okubo Prize, the David Starr Jordan Prize, the Henry Dale Prize and is the author of several books including, *Super Cooperators*, *Altruism*, *Evolution*, and *Why We Need Each Other to Succeed*.

But it is the immediate and practical application of evolution that has been Jeffrey Epstein's focus and while he remains an obscure figure behind the academic spotlight, known now for a scandal for soliciting underage women, which led to an 18 month jail sentence, he is nonetheless the talented catalyst, the accelerator for all of this medical discovery. Whatever the disgrace, Jeffrey Epstein's continued bond with Martin Nowak and the Program for Evolutionary Dynamics emphasizes that nature is not fastidious, nor judgmental, nor is its dynamic always gradual: it can be sparked into being by an unlikely source, pragmatically driven and above all, errs towards sustainability, no matter how outlying its' gaze.