Financier, Jeffrey Epstein, Accelerates the Course of Evolution at Harvard

Evolution is always on the move but nowhere has it been more in flux than at Harvard University. Indeed ten years ago, an Austrian biologist and mathematician called Martin Nowak, at the Advanced Institute for Studies at Princeton, met with an unknown New York financier called Jeffrey Epstein, to discuss the evolution of language. Epstein was by then an established philanthropist in the sciences. But what emerged was far more pragmatic than the first evolutionary theory of irregular verbs. What emerged was an entire department at Harvard, under Nowak's direction, to study the evolution of human diseases with the primary use of mathematics.

The department, called the Program for Evolutionary Dynamics or PED, was no ordinary department. Epstein established it in August 2003, with an unprecedented $30 million dollar gift to the university. It quickly became one of the first of its kind to study the mathematical evolution of micro biology, notably cancer, infectious diseases and viruses such as HIV—in view of advancing their treatment.

And by creating the first mathematical models of how human cancer cells, viruses and bacteria evolve, Nowak and his graduate team have been able to identify groundbreaking aspects about these diseases and steps to treat them more effectively.

The somewhat calculated meeting between the two men first occurred in March of 2000 when Epstein, with a passion for cutting-edge science, flew Nowak to his island in the US Virgin Islands to host a conference on the evolution of language. It was an obscure topic, but Epstein, familiar with Nowak's HIV work at Princeton, wanted to get to know the scientist intimately and if that involved furthering Nowak's current research on language, so be it.

At that time, Nowak was head of the Program in 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 cells. Before going to Princeton, Nowak had been the head of the mathematical-biology group at Oxford University. His motivation for research differed from Epstein's. While they were both enraptured with unraveling the big questions about existence, Nowak is a practicing Roman Catholic and a declared humanist with a desire to serve society. Epstein on the other hand, is first and foremost

a problem solver, interested in strategy and intellectual puzzles. He is equally devoted to physics, artificial intelligence, and the human brain. According to Nowak, Epstein 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 had no interest in purely humanistic endeavors. He has given to countless organizations to further early and primary education, notably in the U.S. Virgin Islands, where his foundation is based. But his essence is in uncovering the big questions, a possible but perhaps insatiable desire.

Epstein was not amateur philanthropist or science groupee. By 2003, 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. According to *New York Magazine*, he is one of the largest donors to individual scientists around the world, granting up to $200 million a year. He was also a member of the New York Academy of Science, a member of Rockefeller University's board, and actively involved in the Santa Fe Institute, the Quantum Gravity Program at the University of Pennsylvania, and the Mind, Brain & Behavior Advisory Committee at Harvard. Epstein himself had studied physics at the Cooper Union in New York and mathematics at the Courant Institute in New York and moved on to teaching calculus and physics at the Dalton School in Manhattan. Within a couple of years, he was quickly recruited into options trading on Wall Street and applied his mathematical wit to the markets, focusing on the then popular Black Scholes model.

But Epstein's heart remained in the pure sciences. He was fascinated by fundamental questions on the one hand, and as a fervent businessman, eager to apply scientific theory to the real world. It was this combination that drew him to Nowak. For Nowak's work embodied both large theoretical concepts about evolution and also focused on the treatment of disease with the use of evolutionary mathematics. Epstein could not only probe a brilliant mind about the origins of life, but, with his connections at Harvard, was able to provide Nowak a powerful platform to put his pioneering medical research into immediate practice.

So in August 2003, with the cooperation of Lawrence Summers, then president of Harvard, the Program for Evolutionary Dynamics (PED) set up for business under the direction of Nowak, who was made a professor of mathematics and biology at Harvard.

PED's math models soon led to key discoveries towards combatting diseases of all kinds. In 2012, Nowak and two postdoctoral students, Benjamin Allen and Ivana Bozic, developed the first mathematical model of how human colon-cancer cells evolve and how they become immune to inhibitor-drug therapy. Their research was conducted at the request of the Pathology and Oncology Department at Johns 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 the growth of colon-cancer cells, Nowak and his team showed that the KRAS gene is not actually activated or "switched on" by inhibitor therapy; rather, a small percentage of colon-cancer cells with an already activated KRAS gene are immune from the start and come to dominate 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 fight secondary and tertiary resistance, the researchers at Johns Hopkins are now exploring the effects of using 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 cancers.

In 2010, Ivana Bozic and Martin Nowak co-authored a 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 drive tumor growth. The findings were essential to the researchers at Johns Hopkins and elsewhere because they demonstrated the importance of isolating a key minority of mutated tumor cells for effective inhibitor treatment.

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

In that same year 2010, the PED presented to Bert Vogelstein, professor and director of the Ludwig Center for Cancer Genetics and Therapeutics at the Johns Hopkins Kimmel Cancer Center and the Howard Hughes Medical Institute, a mathematical model showing the genetic evolution of pancreatic-cancer cells from initial mutation to non-primary malignant cells. What Nowak's team had found was surprising: that pancreatic cancer, one of the most lethal forms of

cancer, is not fast and furious as believed, but slow to develop. In fact, given the amount and type of genetic disparity between the cellular stages, it appears that it takes about ten years for an initiating mutation to grow to a parental, non-metastatic founder cell and another six years for cells to become malignant.

The findings highlighted the importance and real possibility of isolating pancreatic mutations prior to metastasis. Johns Hopkins scientists are now focusing on developing a pancreatic cancer screening method similar to the protocol used for breast and colon cancers. Though early stages of pancreatic cancer cause no known symptoms, the John Hopkins team is looking into pancreatic screening endoscopies for patients of a certain age.

Over the last two years, Nowak and his team have also collaborated with the Johns Hopkins to develop a database to map and predict the effect of drugs on the HIV virus. Like cancer cells, HIV often develops resistance to drug cocktails. This is a major problem for patients and the trial and error of clinical trials can be hugely debilitating. Using data collected from thousands of blood tests on more than 20 anti-HIV drugs, the model calculates each drug's ability to suppress viral replication and avoid resistant HIV strains. The model also factors in different drug combinations and dosages, and information about the patient such as blood type, age, and sex to arrive at the most precisely engineered predictor of results for future patients.

Much has been written about the Program for Evolutionary Dynamics and Nowak's work. Nowak is also the honored recipient of numerous awards, a frequent guest lecturer and the author of several books. And while Jeffrey Epstein remains an obscure figure, tarnished now by a series of scandals involving underage women, one of which led to an 18-month jail sentence, he is nonetheless the talented catalyst, the accelerator of all this medical discovery. Whatever his ignominy, Epstein's continued bond with Nowak and PED emphasizes that nature is neither fastidious nor judgmental, nor is its dynamic always gradual. Discovery can be sparked into being by an unlikely combustion, pragmatically driven and above all, errs towards sustainability, its great self, no matter how outlying its' gaze.