Correction

SCIENCE AND CULTURE

Correction for "Science and Culture: Putting a game face on biomedical research," by Esther Landhuis, which appeared in issue 24, June 14, 2016, of *Proc Natl Acad Sci USA* (113:6577–6578; 10.1073/pnas.1607585113).

The editors note that on page 6577, left column, first paragraph, line 1, "In 2011" should instead appear as "About a year ago." The article has been updated online.

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Putting a game face on biomedical research

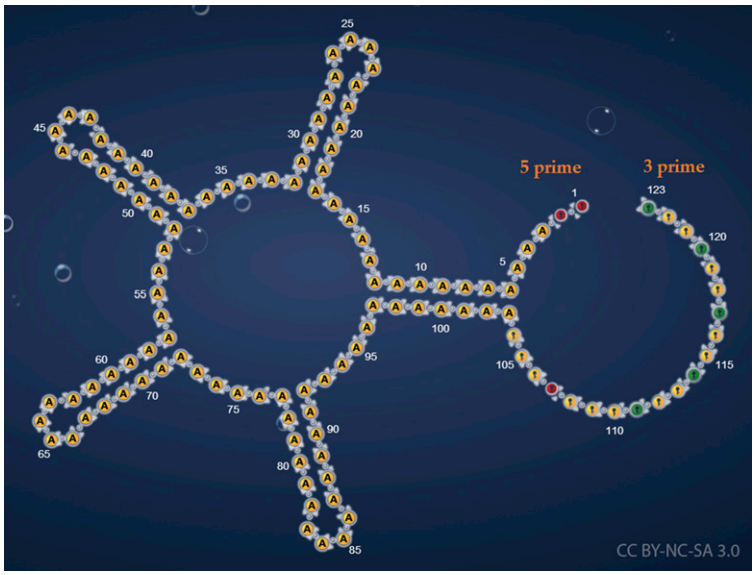
Esther Landhuis, *Science Writer*

About a year ago, game developer David Edery shocked his collaborator Sandy Anderson, a mathematical oncologist, with a provocative question: "If I could kill the patient really quickly, would that be useful?" It sounds cruel, but is rather typical thinking for game developers. Edery was essentially asking: "Would you learn something if I broke your system?"

Edery, cofounder of a Seattle-based video game company called Spry Fox, was probing how to best design a game that had a serious purpose. Edery and Anderson aspire to build a research tool that uses crowdsourcing to uncover general principles about how tumors and their microenvironment evolve during the course of disease: for example, a pattern of growth in cancer X can be treated with drug A followed by drug B. As game players figure out how to move parameters to treat—or kill—a virtual patient, they could bring new insight into the development of treatment strategies. "I was taken aback," Anderson says of Edery's question. "I'd never thought about it like that."

Anderson, who studies tumor growth at the Moffitt Cancer Center in Florida, met Edery in December 2014 at a first-of-its-kind NIH workshop seeking to forge collaborations between biomedical researchers and game developers. "We'd been following the game community for some time," says NIH workshop coorganizer Jennifer Couch. She noted the success of earlier games, such as Foldit (1), a protein-folding game, and Eyewire (2), which invites citizen scientists to help map the brain. "It was obvious to us that there are opportunities to use games to do research," says Couch, a program officer with the NIH Big Data to Knowledge initiative, a data-sharing and data-mining effort that launched in 2012.

The 2014 workshop is just one indication of growing interest in applying game technologies and approaches to biomedical research. Inspired by the excitement of workshop participants, last year the NIH announced it would award $2.5 million to 6–10 research projects that advance biomedicine through crowdsourcing and digital media. (In early April of this year, Anderson and Edery found out that they were among the grantees.) And in February, a gaming and citizen science milestone: a paper describing insights into RNA molecule design became, some say, the first peer-reviewed publication of research initiated and carried out by citizen scientists: in this case, players of the web-based game EteRNA (3).



Biomedical researchers and gamers have come together to devise novel interactive games that tackle disease. EteRNA (from which this image was taken) encourages players to design RNA molecules that could help scientists devise new medicines or therapies. Image courtesy of Eli Fisker.

Gaming the System

Game developers have skills that could be put to good use in this era of "big data," especially with increasing efforts to use crowdsourcing. Developers are good at rendering things in real time, optimizing hardware, and thinking about data pipelining, says Couch. "We wanted to get some of that thinking to bear in the biomedical space," she notes.

During a 15-minute "speed-dating" session at the 2014 NIH workshop, Edery explained to Anderson about a game's "engine," the set of rules that defines how players do things. In turn, Anderson gave Edery a crash course on tumor heterogeneity and the ways in which he uses mathematical models to study cancer growth. Not all cells in a tumor are the same, Anderson explained. Some die in the presence of a drug while others thrive [see also "Capturing cancer's complexity" in PNAS (4)].

Timing also matters. Administering chemotherapy early can produce a long-term response, but therapy given later could accelerate the growth of the tumor (5). Essentially, says Anderson, you can devise a mathematical model that predicts how the tumor cells comprising a heterogeneous mass grow, invade, and interact with each other and their surrounding environment. This model, he says, can help predict how fast a cancer progresses and even how it responds to treatment.

As the two chatted, Edery and Anderson began to wonder if Anderson's models could serve as the engine for a game that challenges players to explore trade-offs between treatment response and toxicity as they try to cure an evolving cancer. For example, the players could learn that tumor cells become resistant to drug X if it's administered too early, or that drug Y works better when combined with drug X but costs too much based on the financial constraints specified in the game. "Players are great at finding smart strategies to beat competitors, only this time the competitor is cancer and the strategies are cancer treatments," says Anderson. Now the two collaborators, having won one of the NIH awards, are starting to design the game, and hope to launch it within a year. They expect it will serve both as a vehicle for outreach and a means to devise smart treatment strategies.

Playing with RNA

In the case of EteRNA, nonexpert players use problem-solving to design complex RNA molecules. RNA-folding aberrations underlie a number of brain disorders, including Parkinson's; and for some viruses, RNA elements are critical for replication. "What if we could tackle a brain disease or a retrovirus by targeting the RNAs involved?" asked EteRNA cocreator Rhiju Das, a computational biochemist at Stanford University.

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—Sandy Anderson

EteRNA consists of puzzles in which players arrange RNA's building blocks—the nucleotides adenine, cytosine, guanine, and uracil—into sequences they think will adopt a target shape. Players vote on which ones they think will fold up best. Top-voted designs get synthesized in Das' laboratory. Each gets scored using a technology called high-throughput SHAPE, which rates the molecule's likelihood of adopting the target shape. (The same RNA strand can fold in multiple ways, but certain sequences are better than others at stabilizing the molecule in the desired shape.) Based on their molecules' scores in these wet-laboratory experiments, players can learn how to improve their designs in subsequent puzzles.

Unlike other scientific games that motivate players with points or badges, EteRNA was "designed to appeal to people who get a real rush out of practicing the scientific method," says Das, who worked with computer scientist Adrien Treuille of Carnegie Mellon University. Both were postdoctorates in David Baker's University of Washington laboratory, where Foldit was developed.

Within a week of going public in 2011, the game attracted more than 5,000 players and currently has around 100,000. Many have no formal training beyond high school biology or introductory college chemistry. Even so, over time EteRNA players have learned enough about RNA folding to devise designs that outperform those generated by computer algorithms created by experts (6). "Some of these players are like the best graduate students we have at Stanford," Das says. "They're reading literature and mastering the science."

But EteRNA players weren't content simply designing molecules and earning scores. They wanted the raw data showing how each loop, each twist, and even how individual nucleotides contributed to the overall score. So every few weeks advanced players talk with game developers in an hour-long online "dev chat."

Before long, EteRNA players started forming and testing hypotheses based on their own questions: for example, what kinds of shapes make an RNA molecule especially hard to design. To their surprise, the gamers discovered that repetitive symmetry poses significant design challenges. If the same substructure appears multiple times, it's easier for a given RNA sequence to adopt multiple shapes that compete with each other and misfold in solution, says Jeff Anderson-Lee, a top EteRNA player and longtime computer systems manager at the University of California, Berkeley. He and several other gamers reported these insights in the *Journal of Molecular Biology* (3).

"The players were the ones who had the idea, and they were the ones who did the analysis," Das says. EteRNA players are now designing molecules not only with certain shapes but also for specific functions and diseases. For example, players have come up with "switch designs": RNA structures that fold differently in the presence of certain chemicals. EteRNA's most recent challenge invites players to design RNA molecules that can act as a sensor for signature tuberculosis genes.

More games are likely to follow. To encourage partnerships between game developers and biomedical researchers, the NIH built an online collaboration space (citscibio.org), which launched in February of this year. And Anderson and Edery weren't the only pair that hit it off at the 2014 workshop. Couch says that she was struck by just "how interested [these two groups] were in working together."

1 Khatib F, et al.; Foldit Contenders Group; Foldit Void Crushers Group (2011) Crystal structure of a monomeric retroviral protease solved by protein folding game players. *Nat Struct Mol Biol* 18(10):1175–1177.
2 Kim JS, et al.; EyeWirers (2014) Space-time wiring specificity supports direction selectivity in the retina. *Nature* 509(7500):331–336.
3 Anderson-Lee J, et al.; Eterna Players (2016) Principles for predicting RNA secondary structure design difficulty. *J Mol Biol* 428(5 Pt A):748–757.
4 Williams SC (2016) News feature: Capturing cancer's complexity. *Proc Natl Acad Sci USA* 112(15):4508–4511.
5 Robertson-Tessi M, Gillies RJ, Gatenby RA, Anderson AR (2015) Impact of metabolic heterogeneity on tumor growth, invasion, and treatment outcomes. *Cancer Res* 75(8):1567–1579.
6 Lee J, et al.; EteRNA Participants (2014) RNA design rules from a massive open laboratory. *Proc Natl Acad Sci USA* 111(6):2122–2127.