TransTech Alert
Transformational Technology

The Drug Delivery Technology That Could Completely Disrupt Healthcare

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Dear TransTech Reader,

This month we're presenting a technology to you that has the potential to transform medical science in ways that are almost unbelievable. The company that commands this new approach to medicine is not yet public, but you need to know it exists.

Should progress toward commercializing the revolutionary science at the heart of the company's platform continue, it will catapult the practice of medicine forward in ways that seem straight out of the world of science fiction. It could eventually make many modern medicines obsolete. It would enable treatments that are currently impossible and dramatically reduce the importance and profitability of current pharmaceutical manufacturing. It would even take business away from your local pharmacy.

In the last decade or so, we've seen many completely unexpected and transformational biotechnologies. The technology we're presenting today, however, may be the most unexpected and surprising breakthrough that I've ever encountered. Before we talk about what Nativis—the company that's developing this biotechnology—is working on, let's start with the basic science.

Electrostatic Surface Potential, a Ghost in the Cell

There is a component of electrical activity in all drug actions. You will recall from basic high school biology that atoms are made up of a nucleus and one or more electrically charged electron. Electrons exist in a state of constant motion outside of and surrounding an atom's nucleus.

Depending on the interplay of those electrons, atoms can join with other atoms to form molecules. When atoms share electrons, the force that holds the molecule together is referred to as "covalent." This is also known as a chemical bond. In such molecules, the movement of electrons is no longer a simple orbit as it is in a lone atom.

There are other interactions among electrons, though. Even if electrons do not form covalent bonds that keep a molecule together, electrons influence one another. They do this via electrostatic forces. Though each electron's interactions are incredibly small, they can have real impacts. Some are easily observable, even in our day-to-day macro world.

For example, when plastic wrap is unrolled, it often clings annoyingly to your hand. When that happens, you are experiencing electrostatic forces. If the bond were covalent or chemical, the molecules in your hand and the plastic wrap would fuse. Fortunately, that doesn't happen—a little bit of force separates the plastic wrap from your hand. You may even be able to utilize those electrostatic forces to do something useful, like attaching the plastic wrap to a bowl.

On a much smaller scale, electrostatic (noncovalent) forces influence most interactions among biological molecules. Most metabolic pathways are activated or deactivated by electrostatic forces. Even the interactions of the nucleotide pairs in our DNA are electrostatic. Most drugs, in fact, work through electrostatic forces. Many drugs interact as ligands with a receptor in the body, like a key to an electromagnetic lock. In most cases, however, ligands and receptors don't form permanent chemical bonds. Rather, they dock. They maintain their own structures but trigger other molecular actions. That docking takes place due to electrostatic forces.

Even when there is no molecular change happening, electrons are constantly active in their complex molecular orbits. It would be futile to try to describe that activity because much about the subatomic world remains a mystery, even to scientists who work in this field.

You may know, for example, about the particle–wave paradox. Electrons sometimes appear to behave as particles but other times as waves. It's easy to say that they're both, but it's much harder to understand why and how they exhibit that dual nature.

Whatever electrons are doing, however, they do it constantly. Let's call this behavior oscillation. Every molecule in your body is oscillating and electrostatically active. Even perfectly stable molecules that aren't undergoing any outwardly observable change of state are oscillating.

Because electrons oscillate continually, they create an active, albeit weak, electromagnetic field. This weak field exists in the extremely low-energy, low-frequency radio wave end of the electromagnetic spectrum. Until now, it has been unmeasurable with any precision.

Nativis scientists have pioneered the measurement of these fields and invented technology capable of measuring and recording their dynamic states in a time-domain series. We'll get into more detail later in this article, but now we're ready for the big overview of this technology.

Nativis scientists coined the term ultra-low radio frequency energy (*ul*RFE®) to describe the technology they use to measure and record the electrostatic signature profiles of molecules and their interactions. Extraordinarily, they have learned how to reproduce those specific electromagnetic fields to cause specific responses in biological systems.

The bonding of a particular ligand with a particular receptor creates a specific electromagnetic field. This field can now be measured and recorded. It's not, however, a single-frequency snapshot, because things are changing over time. It's more accurate to think of this recorded signal profile as a song.

This analogy shouldn't be too much of a leap, because ultra-low frequency radio waves and audible sound are both just energetic phenomena at very different frequencies. Everybody has seen the old Memorex commercial or the *MythBusters* segment of a glass being shattered by sound. I think this video by Saint Mary's University is a much better example of the relevant principle. If you watch the video, you'll see physical objects, in this case sand, being moved in changing predictable patterns by a precise sequence of tones.

Extend this principle to the molecular level and the potential of *ul*RFE becomes apparent. Sand, after all, is far, far larger than the molecular machines activated by drugs. Might it be possible to play an electrostatic "song" that would activate or deactivate molecular pathways?

The answer, I believe, is yes. Electrostatic interactions determine much of what takes place in our bodies. If Nativis can replicate the electrostatic interactions that take place in specific drug interactions, it is theoretically possible to trigger the same molecular responses without the need for drugs. In other words, they could produce the effects of a drug using an electromagnetic field. In effect, they would have virtual drugs with real-world impacts. Remarkably, there is already evidence that this is feasible.

We'll get to that evidence later. First, however, let's review the history of this developing biotechnology—which, by the way, includes submarine-tracking technology.

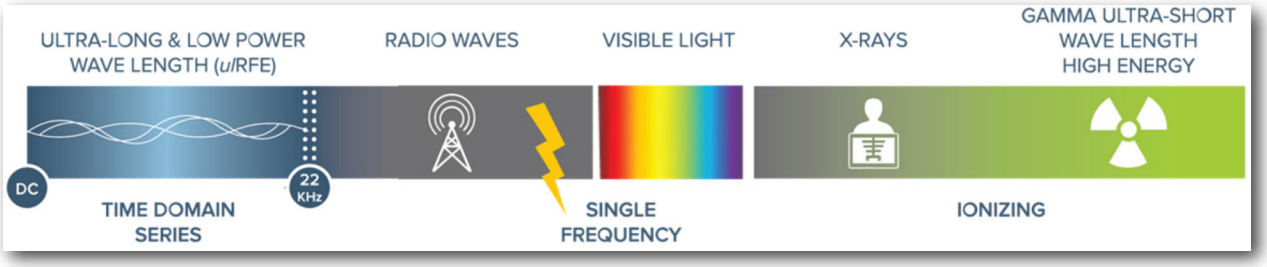
Developing the Technology Platform

In the last 80 years or so, there have been ongoing efforts by scientists and drug companies internationally to understand how electromagnetic fields interact with biological systems. This research is based on the fundamentals of molecular interactions. We've long known that the majority of molecular interactions, from water to the DNA double helix, are governed by their fundamental electrostatic forces. Scientists have naturally been interested in the possibility of manipulating these forces for beneficial purposes.

This is the line of research that sparked the interest of Nativis co-founder Mike Butters. Butters started his medical career as a nurse, but was driven to pursue his lifelong interest in radio-frequency engineering. At one point, he was involved in transferring innovative electronic technologies from Japan to the West. He also worked with European scientists who had developed crude experiments that attempted to measure, record, and replay the electromagnetic signals of chemistries in an attempt to elicit a biological response. Although these crude attempts did not reliably show effect, Butters still found their research compelling. This was an unrefined iteration of the technology that Nativis would go on to develop.

The challenge faced by researchers trying to harness electromagnetic waves to produce infinitesimally small oscillations of electrons was that they lacked instruments with the extreme sensitivity and a quiet enough electromagnetic environment needed to record them. As we have established, the complex and dynamic electromagnetic fields generated by a molecule are very weak. The energy signal given off is also extremely low-powered. Additionally, the frequencies involved have very long wavelengths.

In the electromagnetic spectrum, energy waves are measured by their wavelength. The shorter the wavelength, the higher the energy. For instance, on one end of the spectrum lie gamma radiation and X-rays with wavelengths shorter than one nanometer (one millionth of a meter). Further down the spectrum we find the range of wavelengths of visible light, between 300 and 700 nanometers. Even further down we have radio waves—the frequencies at which we transmit sound via radio—with wavelengths of about a meter. And beyond them there are the lowest-energy waves with wavelengths on the scale of a kilometer and up.



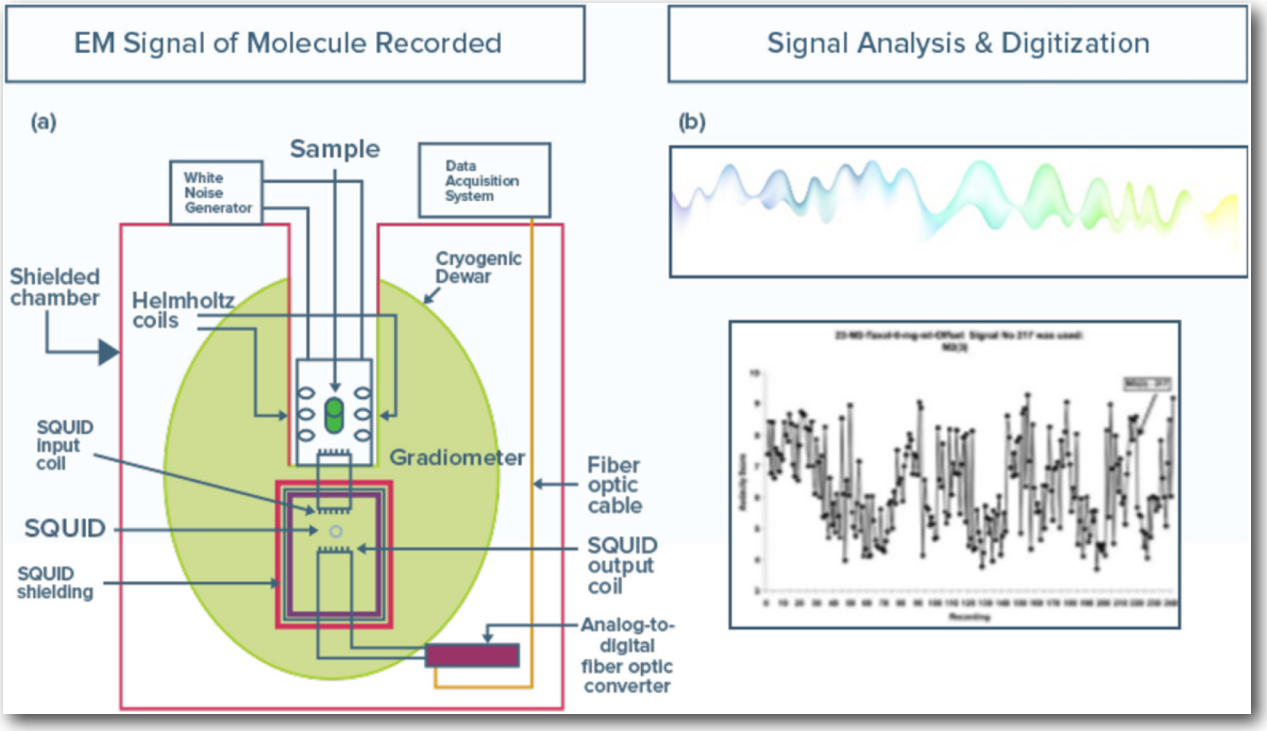
It is at this low end of the spectrum that we would find the radiation given off by electron movement in a potential drug molecule. This low energy level is why we need such a sensitive instrument to detect the signals.

Butters persisted in his efforts to record and harness the electrostatic surface potential of molecules. In addition to a tool sensitive enough to detect the electromagnetic signals of the individual electrons in a molecule, he needed the ability to remove the background noise of ubiquitous electromagnetic signals.

In his search for an appropriate tool, Butters contacted a researcher at the Oakridge National Lab who was working on superconductors. The Oakridge researcher brought to Butters' attention a technology known as SQUID, or superconducting quantum interfering device.

SQUID represents the most advanced magnetometer technology known, with the capacity to measure electromagnetic fields as small as 4 femtotesla, or 10^{-15} Tesla. (The unit was named after physicist and inventor Nikola Tesla; and for a frame of reference, the magnet in your refrigerator gives off a field of 0.01 Tesla, and a magnetic resonance imaging (MRI) machine gives off 1.5 to 3 Tesla.) Originally, SQUID-based technology was used to detect submarines, as its sensitivity allowed navies to measure minute changes in the Earth's magnetic field caused by the metal of a far-off submarine.

SQUID confers the ability to measure the electromagnetic waves generated by individual electrons in a molecule as they oscillate. Nativis can use SQUID to measure the specific electromagnetic fingerprints of a molecule and record their molecular "song." In combination with the proprietary Nativis Voyager® coil, which plays back the electromagnetic signals, SQUID unlocks the ability to directly influence metabolic pathways. This represents the dawning of a whole new field of medicine that previously only existed in science fiction.



Recording the Sound of a Drug

The first step in the process of creating an *ul*RFE treatment is to identify a target molecule with therapeutic benefits that can be reproduced. As explained earlier, *ul*RFE technology can only affect non-covalent molecular interactions; so drugs that rely on covalent bonding cannot be replicated. Fortunately, that leaves a wide variety of biological pathways open as therapeutic targets.

Most protein signaling interactions that occur in the body are non-covalent; and in fact, about two-thirds of all pharmaceutical drugs work through non-covalent, electrostatic interactions. This means, hypothetically, that two-thirds of all pharmaceutical drugs could be replaced or supplemented with electromagnetic waves.

The SQUID technology also requires that the molecules it measures be in solution.

Researchers record the electrostatic signature of the molecule and store this information as a digital WAV file. Nativis refers to these WAV files as cognates. A cognate can be "played back" using the Nativis Voyager system, producing an electrostatic signal similar to that generated by the chemistry from which the cognate is derived.

The Nativis Voyager system consists of a small controller, which holds and transduces cognates, connected to a coil antenna that creates an electromagnetic field within, which the cognate is delivered. This delivery system can be customized for specific treatment requirements. In early animal studies, the coil size was just large enough to generate a magnetic field that encompassed a dog's paw or a small cage. In later human trials for treatment of glioblastoma brain tumors, the coil has been designed as a headband that sits around the head like a crown or a hat.

To test their theories, Nativis scientists conducted early, unpublished experiments that compared the electromagnetic signals from glyphosate, a commercial herbicide, to the *ul*RFE cognate of the chemical. One group of pea sprouts was given chemical glyphosate, one was untreated, and the third was exposed to the electrostatic recording of glyphosate. The researchers' electromagnetic field produced the effects of the herbicide without the physical presence of the herbicide itself. According to company executives, the cost of their electrostatic herbicide treatment would be price-competitive with existing treatments. It would also have the advantage of having no runoff or any other environmental effect.

Based on the success of the glyphosate experiment, Butters and his team began developing a pipeline of possible applications based on the ultra-low radio frequency energy platform. The pipeline includes agricultural, veterinary, and human medical targets, among others.

The next proof of concept was the creation of the cognate of a taxane chemotherapy molecule, tested against cancer cells. Taxol, the oldest and perhaps most familiar chemotherapy drug on the market, was chosen because it is very well understood and in vitro experiments could be relatively easily performed. The company demonstrated in experiments, both in vitro and in vivo (mouse studies) that the taxane cognate disrupted cell division in cancer cells. These experiments provided the data that allowed Nativis to enter into human trials. More about that in a minute.

The Latest Research

In April, results from researchers at the Swedish Neuroscience Institute in Seattle and at the University of California at San Francisco, entitled "Precision knockdown of EGFR gene expression using radio frequency electromagnetic energy," were published in the *Journal of Neuro-Oncology*. You can purchase that study, but a poster in pdf form is online here.

Though the research was not conducted by Nativis, this was an important development for the company and its technology. The paper demonstrated that *ul*RFE can not only elicit the effects of signaling proteins in important metabolic pathways, but also affect gene expression directly. Specifically, it can affect the expression of oncogenes that can cause cancer.

One gene and its growth factor, epidermal growth factor receptor (EGFR), was knocked down both in vitro and then in vivo. Some EGFR drugs utilize small interfering RNA (siRNA), which blocks the cell's translation machinery, stopping messenger RNA (mRNA) from being turned into proteins. Nativis now has peer-reviewed evidence that it can mimic this effect, without the presence of the siRNA itself.

This is significant: Nativis has two broad product categories. Nativis technology can both specifically modulate metabolic pathways and can also produce the effects of a particular chemistry. The implication is that Nativis could not only make existing drug therapies less toxic and perhaps more effective, it could also create an entirely new way of hitting genetic targets. Who knows what other ways might be developed to utilize the underlying technology. The potential impact is enormous.

The Nativis technology has been in human trials for over two years, treating recurrent glioblastoma brain tumors—a particularly vicious brain cancer. To date, there have been no reported serious adverse events associated with the Voyager device. This is unusual in cancer clinical trials. Most importantly, the results so far have been very promising. Based on the early survival results in these trials, the company recently announced expansion of its study for patients with recurrent glioblastoma and has begun a phase I study for patients newly diagnosed with glioblastoma.

The Teijin Pharma Partnership

Obviously, even peer-reviewed journal articles and early clinical trial results don't prove that a technology is valid. Though the science behind the technology appears to be solid, researchers can make mistakes. If we only had preclinical studies and early clinical results, I would have far less confidence in this technology than I do.

A major source of my confidence, though, is the Nativis partnership with Teijin Limited. Earlier this year, Teijin completed due diligence and licensed the Nativis Voyager system to treat glioblastoma in Japan.

Teijin is a major Japanese chemical, pharmaceutical, and IT company founded almost a century ago. It is part of the Nikkei 225 stock index and is listed in the first section of the Tokyo Stock Exchange. As a private company, Nativis hasn't disclosed the size of the announced up-front payment or the additional milestone payments. We do know, however, that the Nativis agreement includes royalties.

As I mentioned above, Nativis has also shown efficacy in replicating the mechanism of the cancer drug Paclitaxol, also known as Taxol, as published in the paper "Non-Thermal Radio Frequency Stimulation of Tubulin Polymerization in Vitro: A Potential Therapy for Cancer Treatment." Taxol works by sabotaging the cellular scaffolding molecules known as microtubules in cancer cells. During mitosis, when cells duplicate their genomes and split into two cells, microtubules physically pull the two sets of chromosomes apart and place them in their new respective daughter cells. Taxol defeats this mechanism, resulting in failed cell division and subsequent apoptosis (programmed death) of cancer cells.

The *ul*RFE delivery of Taxol has multiple advantages. Firstly, the Voyager coil allows for more precise targeting of cancer cells, both anatomically and over a specific time period. This means that there would be even less damage to noncancerous cells. Secondly, after the treatment period, the coil turns off and the signal is no longer present in the body. There are no issues with the half-life of drugs remaining in the body from chemotherapy because there is no actual chemistry involved.

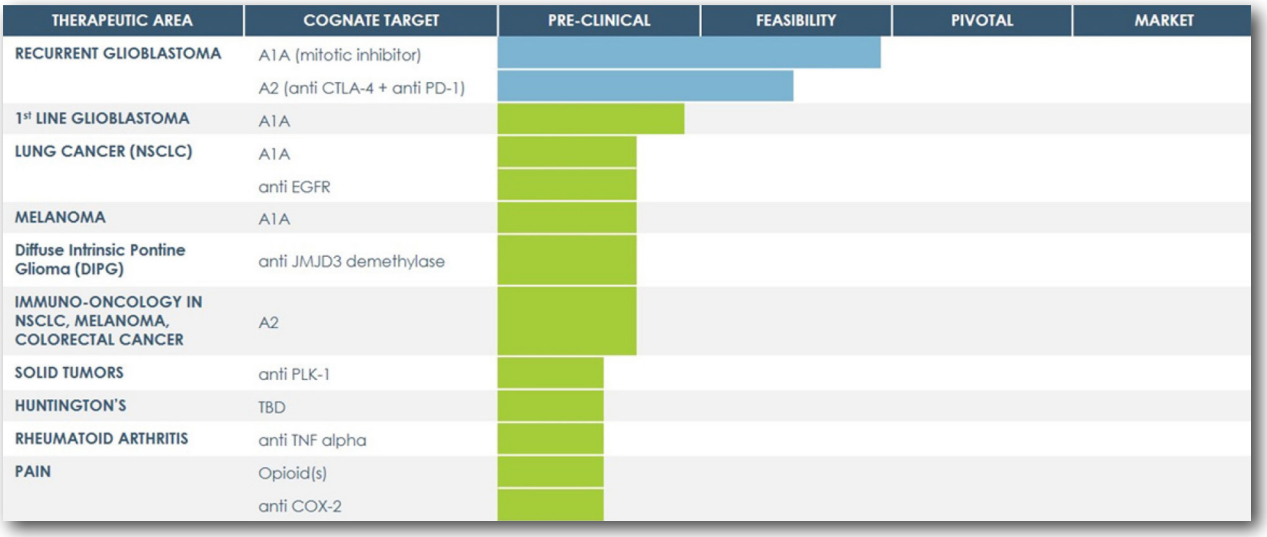
The Regulatory Opportunity

Looking at the regulatory pathway, the Nativis platform has an apparent advantage because it's not a drug. Rather, it is a medical device. Though the FDA and other nations' regulators might require additional testing for such a revolutionary technology, device approval has traditionally entailed a much shorter, cheaper, and more predictable regulatory pathway than is required for drugs.

The company has also begun preclinical work on an "ultra-rare" brain cancer, a glioma called diffuse intrinsic pontine glioma (DIPG). DIPG is a deadly brain cancer that afflicts about 300 children in the US each year. Unfortunately, these kids usually live less than one year, and to date, there has not been an effective treatment. Due to the unmet need and rarity of this disease, there is a regulatory pathway for Nativis technology that may allow FDA approval to commercialize a treatment for DIPG as early as 2019.

The pathway for agricultural uses would likely be shorter and cheaper still. Many opportunities exist in that sector. Nativis recently published data showing that a *ul*RFE cognate knocked down by 25–50% an mRNA that produces proteins that are toxic to algae. This may translate into increasing the overall productivity of algae, particularly in increasing the output of lipids. It could even increase alcohol production by yeast. In research conducted by one of Nativis' strategic partners, cognates of siRNA have demonstrated effectiveness in modulating photosynthetic pathways in plants.

While these markets outside the realm of human health present valuable potential opportunities, Nativis is currently focused on human health. The following graphic lists some of the company's areas of development.



Beyond oncology, Nativis has already recorded a cognate to knock down TNF-alpha, which is how the drug Enbrel targets rheumatoid arthritis. A cognate to deliver the anti-inflammatory effects of anti-TNF-alpha drugs could be delivered via a coil placed around your bed or pillow, so that every night, the chronic inflammation implicated in aging could be silenced. You could even theoretically treat an entire medical ward all at once with a room-wide electromagnetic coil.

The Transformational Impact of *ul*RFE Technology

I don't think we should be thinking about *ul*RFE in terms of individual drugs. Rather, we should understand that the long-term potential is the complete transformation of therapeutic delivery by changing the fundamental nature of therapeutics. Instead of pills and injections, we could have cognates transmitted into our bodies to produce health benefits without the drug residues that can create toxicities.

I asked a team of Nativis executives how they see the patent battleground developing. Could a drug company that owns rights to a drug molecule stop Nativis from activating the benefits of that drug using *ul*RFE? Their answer, loosely paraphrased, was, "We do not infringe on others' technology or drugs. Nonetheless, we recognize that legal challenges are a common tactic in highly competitive markets." There are, however, workarounds for that issue.

First, there are many generic and off-patent drugs that could be improved using the company's technology. The ability to activate beneficial pathways without the side effects caused by physical drugs could dramatically improve outcomes. The benefits of hundreds of older existing drugs could be delivered inexpensively. In many cases, the benefits could be improved.

Another strategy would be to collaborate with existing drug makers that could bring expertise, capital, and distribution networks to the table. I think established drug companies would prefer to collaborate than be bypassed.

Moreover, there are many biological pathways of interest to researchers that can't be targeted by drugs. Many could be addressed by *u*lRFE. In fact, the ability to directly activate biological pathways without physical drugs would revolutionize medicine. Treatments that are now considered impossible, including promising anti-aging therapies, would become practical.

In the world of video games and science-fiction movies, we often see injured people exposed to healing rays. Futurists generally believe that we will eventually see that promise made real. The Nativis technology appears to enable that vision. It does so, however, decades if not centuries before any prediction I've ever encountered.

The technology will probably be used first in clinics and hospitals. Eventually, however, it will necessarily move to the consumer market. In fact, it couldn't be stopped even if authorities tried. Right now, people are downloading software for 3D printable guns against the wishes of authorities everywhere. When drug cognates are available as readily downloadable WAV files, people will gladly purchase them for use in conjunction with the Nativis Voyager system.

A cognate-delivering device might be wearable or integrated into chairs and beds. Therapies would be personalized via artificial intelligences and downloaded directly to customers' devices as easily as music and video files are accessed today. This could revolutionize how we treat patients around the world—and for a very reasonable cost, regardless of where they live.

That's the big implication of *u*lRFE: the nearly complete digitization and personalization of therapeutic medicines. If the company's work continues to be validated, the science and business of medicine will be radically transformed. Freed from the complications of drugs, medical science will accelerate even more rapidly. Therapies will fall in price dramatically and be available to virtually everybody on the planet.

Entire industries will die, kicking and screaming, of course. However, for adopters and investors, it could be one of the greatest opportunities in the history of commerce.

For transformational profits,

Patrick Cox

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