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# One Cancer Start-Up's Resolve To Crack The Mystery Of Metastasis

*An Interview With Rgenix Founders Masoud, Sohail and Saeed Tavazoie*

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## Executive Summary

Rgenix, a New York-based start-up co-founded by three prominent physician researchers, is taking aim at what it contends is the future of cancer treatment: finding drugs that shut off the biological chain reaction called tumor metastasis – the colonization of malignant cells throughout the body that ends up killing the majority of cancer patients.



MASOUD TAVAZOIE, CEO OF RGENIX

- > The company has a strong IP portfolio rooted in its founders' ties to Rockefeller and Columbia universities, with three investigational drug candidates now moving forward into clinical trials.
- > Rgenix's lead compound, RGX-104, is an oral small molecule LXR agonist that targets the ApoE gene to regulate cancer progression. A Phase Ib/II trial for an indication in lung cancer is beginning patient

enrollment; RGX-104 also carries FDA orphan drug designation for three other tumor types. The company has numerous ideas on potential partnering tie-ups to help drive its platform toward commercialization.

- Rgenix's messenger RNA small molecule/antibody platform conforms to an emerging consensus among researchers that proteins are the physics of cancer biology, revealing vital insights on how the most aggressive malignant cells activate, grow, spread, slow and stop, in real time. Such knowledge can be highly useful as a precision medicine tool, where RNA-based treatment and genetic profiling can work together to reveal gene alterations indicating a predisposition to metastatic relapse in individual patients.

In the fight against the seemingly random pathogenesis of cancer, one standout innovation is the ability to suppress the actions of specific genes that drive tumor progression in different cancers – the dreaded metastatic phase whose spread to other organs makes the disease a uniquely prolific killer. It is an unmet medical need of the highest order, yet most cancer research today centers on a rearguard mobilization of the immune system to find and destroy cancer receptors in individual tumors rather than address the underlying drivers of cancer growth and dispersion, across different malignancies. Yes, killing cancer cells in the tumor represents a step forward, but from the expectant eyes of the patient the ultimate test is death by metastatic disease – so shouldn't preventing that lead the future of cancer research?

Three entrepreneurs determined to answer this question are Masoud, Sohail and Saeed Tavazoie, the sons of immigrants from Iran with complementary backgrounds in cancer care and academic research. Sohail, a medical oncologist and cancer biologist, and Saeed, a systems biologist, run their own academic labs at Rockefeller and Columbia universities in New York, respectively; Masoud, also a physician scientist, trained as a clinical dermatologist.

In 2010, the three founded a private start-up, Rgenix Inc., to commercialize a cancer discovery platform based largely on their own research, with Masoud eventually taking the role of CEO. The aim of Rgenix is to develop novel small molecule and antibody therapies to slow or eliminate disease progression in cancer patients for which there are limited or no alternative treatments. It has taken nearly a decade, but the company is finally advancing to clinical trials with several compounds that will hopefully prove its thesis that finding and destroying the cancer cells responsible for initiating and promoting metastatic progression can be performed by a drug – one able to short-circuit this biological chain reaction and extend patient lives.

## Bench – And Bedside – Perspective

The three co-founders are motivated by what they have observed in clinical practice. Cancer is always one step ahead of science, which means that physicians have many patients for which there are no effective treatments. Thus, the simple premise of the new business was to invest in new approaches that might offer more hope. "As a physician I trained in oncology and was discouraged by seeing so many patients with metastatic disease die without much benefit from traditional therapies," said Sohail Tavazoie in an interview with *In Vivo*. "I continue to see that today despite the revolutionary progress cancer immunology has made in subsets of cancer like melanoma and NSCLC. That's what led us to the biology of metastasis – the therapeutic rationale behind Rgenix is finding in each cancer type the key gene that drives its progression in individual tumors and growth to other organs."

In contrast to the standard discovery route of sequencing cancer DNA to find mutations that drive malignancies, which is constrained by the fact that many patient's tumors do not have identifiable DNA mutations that are druggable, Rgenix's platform focuses on RNA and the proteins it regulates. RNA is now known to be more revealing than DNA in predicting the course of the disease. Specifically, the platform targets the non-coding micro-RNA that impacts the gene expression of so-called messenger RNAs (mRNAs) and the proteins that

regulate cancer behavior, and, by extension, key aspects of that behavior such as invasion/metastasis, angiogenesis, and immune evasion. The approach conforms to the recent consensus among researchers that proteins are the physics of cancer biology, revealing vital insights on disease progression: how malignant cells activate, grow, spread, slow or stop, all in real time. Hence the Rgenix platform does not seek to develop drugs to modulate RNA itself but instead zeros in on the proteins whose normal expression has been “deregulated” – made cancerous – through the pathogenic signaling of altered micro-RNAs. It is an important distinction, because disarming proteins that act as a cancer’s messenger can be done with high efficacy using a small molecule or antibody instead of a complex, autologous gene-based therapy.

## Do Cancers Have A Favorite Gene?

Tavazoie explains further the step-by-step process that guides Rgenix’s discovery platform. “Through systematic mapping of the micro-RNA landscape, we have discovered critical genes and proteins that exert extremely large effects on cancer progression. We then employ genetic, molecular, biochemical, pharmacologic and clinical association approaches to characterize the mechanism of action of the specific target protein. Next, we develop conventional small molecule and antibody therapeutics to engage the target and to move them forward as first-in-class cancer-fighting agents, all focused on those aggressive cancer cells that colonize different organs and will eventually kill you. From a clinical perspective, the target genes we have identified exert robust regulation of cancer progression across multiple pathologic processes, ranging from the phenomenon of innate immune suppression to angiogenesis in the tumor micro-environment.”

It may be too much of a simplification, but, as Masoud Tavazoie explains it, the method is disarmingly tumor agnostic. “We just tell the cancer to show us its favorite gene and confirm that with animal assays and then human tissue samples, after which we test a conventional small molecule or antibody drug against the protein target. In most cases, the drug target drives cancer progression using a mechanism that has a broad impact against an array of different cancers by, for example, suppressing the innate immune system. The premise is we learn to make the connections across cancers as we go along, with patient impact at the late-stage as our compass.”

As Rgenix CEO, Masoud has the task of communicating the company’s mission succinctly to investors, which now include blue chip names like Europe’s Sofinnova Partners, Novo Ventures, Alexandria Venture Investments, WuXi App Tec, and the Partnership Fund for New York City. For that, he channels his experience in treating patients. “As a clinician you have to step back and ask yourself what the patient wants, and the answer in every case is – a cure for their cancer. To do that, you start by asking what these patients end up dying from right now. The answer is metastatic disease. So our mission is to prevent what drives that process. It’s the future of cancer, where we can apply RNA biology and human genetics to identify not just patients at risk for cancer, but more precisely those facing the biggest risk of cancer mortality, with a higher probability of metastatic progression because of the genes they were born with or the genes that get deregulated in their tumors.”

One gene that has attracted the company’s attention is apolipoprotein E (ApoE), the deregulation of which has been implicated in tumorigenesis and progression, particularly for cancers of the breast and melanoma. “ApoE was among the earliest genes where researchers were able to show how its deregulation resulted in dyslipidemia, a process for which statin drugs were developed, and which are now very effective in reversing this condition,” Sohail Tavazoie tells *In Vivo*. “I believe this process is where the potential is in cancer as well, by uncovering those germ line genetic alterations that can predict metastatic relapse in individual patients further down the line.”

Tavazoie notes that Rgenix has produced preliminary evidence confirming in human studies that forms of ApoE can either inhibit or promote the likelihood of metastasis in patients with melanoma. For example, one

inherited allele (sub-type) of ApoE, present in about one-quarter of the human population, is protective for melanoma metastasis; while another form, present in about 15 per cent of humans, is destructive and promotes metastasis. “The challenge is finding which variant the patient is genetically pre-disposed to and then create a drug that can put the brakes on that biology, perhaps in combination with medicines already approved and known to activate the standard T-cell immune response.” He says what matters most is developing agents that by themselves will significantly modulate tumor growth – the foundation of the Rgenix platform.

## Pipeline Prospects: The Gang Of Three

Rgenix has seeded its pipeline with three key assets. RGX-104, the first, and most advanced, is an oral small molecule liver X receptor (LXR) agonist that targets the ApoE gene and is in development for the treatment of solid tumors. The initial focus for clinical development is in lung cancer although the company has obtained an orphan drug designation from the FDA in three additional indications: malignant melanoma stages IIB-IV, glioblastoma multiforme, and ovarian cancer.

In a Phase Ia dose escalation study completed and presented at the American Society of Clinical Oncology (ASCO) last year, RGX-104 demonstrated an overall favorable safety profile with evidence of innate immune stimulatory effect and anti-tumor activity, as a single agent. Adds Masoud Tavazoie, “We are positioning this as a first-in-class medicine, in combination with other agents, that highlight our therapeutic focus on major areas of unmet need. In our view, RGX-104 is the most advanced LXR agonist coming out of discovery to date. It’s also the only LXR agonist we know of that’s in clinical testing for cancer indications.”

The next step for RGX-104 is the imminent launch of a Phase Ib/II trial that will test the compound in combination with other agents in lung cancer indications. RGX-104 will be tested in combination with standard of care chemotherapy and the checkpoint inhibitor Keytruda (pembrolizumab) in first line non- small cell lung cancer (NSCLC) patients whose tumors lack expression of the PD-L1 protein, which is an area of high unmet need in the first-line therapy setting. RGX-104 will also be tested in patients with a particularly aggressive form of lung cancer – small cell lung cancer (SCLC) -- in combination with the chemotherapy drug docetaxel in the second-line setting. “We are seeking to demonstrate our unique mechanism of action works in combination with chemotherapy and checkpoint inhibitors in those patient subsets in lung malignancies that have not benefited, or benefited a small degree, from such combinations. The goal is to boost that benefit and thus slow or prevent the inevitable progression of metastatic disease and death,” Tavazoie told *In Vivo*. “In fact, from the early data, it appears the benefit goes beyond stimulating an immune response to suppress angiogenesis and prevent metastasis progression.” Rgenix has selected 17 trial sites for the RGX-104 Phase Ib study, with an estimated date for completion of patient enrollment in the second half of 2020.

The second asset, RGX-202, is another small molecule that the company is positioning for treatment of colon and other gastrointestinal cancers. Animal studies drawing on the Rgenix micro-RNA discovery platform have shown how the molecule creatine has a metabolic effect that accentuates survival of cancerous cells originating in the colon and rectum and helps them colonize in the liver, allowing these cancers to form metastases throughout the body. The investigational compound prevents cancer cells from taking up creatine, inducing in turn apoptosis (cell death) of metastatic cells in these animal studies.

At present, a Phase Ia monotherapy with dose escalation trial with RGX-202 is nearing completion. The plan is to start recruiting patients at seven US centers for a Phase Ib (RGX-202-001) trial in combination with the chemotherapy drug regimen FOLFIRI later this year, in patients with colorectal and gastric/gastroesophageal cancer. Interim data from the colorectal cohort is projected for the second half of 2021. “In many sub-sets of patients with colon cancer, such as those with KRAS-mutant tumors, there aren’t any approved targeted therapeutic agents that broadly target such tumors because it’s been difficult to identify druggable targets. We

have uncovered a key pathway that represents an attractive small molecule target, not only in the colorectal indication but perhaps extending to other gastric malignancies and pancreatic cancer as well. It's another example of our mission of creating new options for patients using our powerful target-discovery platform," said Masoud Tavazoie.

The third asset in play is RGX-19, is a pre-clinical candidate, a monoclonal antibody that targets the MerTK gene, which Sohail Tavazoie's lab at Rockefeller University originally identified as the trigger of tumor growth in triple negative breast cancer. It is now licensed exclusively to Rgenix. According to Sohail, "MerTK is a very interesting kinase which is expressed not only on cancer cells, but also on the immunosuppressive tumor cell that block the body's innate and adaptive immune response. Hence, RGX-019 targets both cancer cell proliferation and the immune response against tumors."

The company has initiated the enabling work to support an FDA IND application on the compound by 2021.

Because the MerTK gene is associated with the onset of a wide variety of cancers beyond breast cancer, including hematological cancers, progress on RGX-19 represents another area where Rgenix believes it can serve cancer patients whose individual conditions are not helped by current standard of care. However, on a competitive note, the oncologic effects of the MerTK gene has attracted significant interest among industry researchers. According to Informa's Biomedtracker service, five other companies – Ono Pharmaceuticals, Elsayls Biotech, Incyte Corp., Celldex Therapeutics, and AbbVie Inc., are involved in pre-clinical work on solid tumors; Ono also has a pre-clinical program for acute myelogenous leukemia (AML). Most of these compounds are small molecules, but Rgenix is employing an antibody approach that it believes will be best-in-class, given the antibody's specificity for MerTK and its ability to induce MerTK receptor degradation – a unique mechanism of action compared to these other approaches.

## IP Gravy From GSK

As a counter to the intensity of industry activity in cancer, Rgenix relies on a solid portfolio of IP, starting with its close ties to Rockefeller University, exemplified by the more than two dozen researchers working with Sohail Tavazoie in his dual role as head of the University's Meyer Laboratory of Systems Cancer Biology and the Black Family Center for Metastasis Research. The company's three pipeline candidates are derived from basic research conducted at the Tavazoie lab over the past decade. RGX-019, which focuses on MerTK gene expression and remains an attractive target for many other industry players, is patented around original animal study research that Tavazoie first published in 2010, long predating these other efforts.

"Rgenix has the credibility that many start-ups lack because it is grounded in a set of core principles around cancer progression and a powerful platform technology invented independently, in the academic setting. It is what attracted me to leave

## Rgenix's Roll Call On Precision Medicine

Cancer is a collection of diseases and symptoms that express differently in individual patients – thus all of Rgenix's clinical programs have a "precision medicine" component, a characteristic reinforced due to the unique target discovery approach used across these programs. Here are three examples covering each of the company's three compounds currently in development:

- Rgenix's candidate RGX-202 to suppress gastrointestinal tumor growth has a precision diagnostic strategy already incorporated into its clinical development. The FDA has lent its support to Rgenix's use of Creatine Kinase Brain-Type (CKB) to enrich for patients that, based on pre-clinical data, are more likely to respond in a

the venture capital field and join the company as its first outside employee,” said Rgenix chief operating officer, David Darst, in an interview with *In Vivo*. He also noted how Rockefeller helped jump start formation of the start-up by offering the three co-founders a license covering a full suite of IP protecting the micro-RNA protein technology, contingent on their raising at least \$2.5m, which was secured in 2013. A multi-year collaborative research agreement between Rgenix and the University allowed for amendments to the licensing package – eight to date – covering the three development programs’ pathways and targets as well as companion diagnostics that allow therapies to be personalized to the patient’s own disease profile (see *Rgenix’s Roll Call on Precision Medicine*).

“Overall, it’s a very close relationship,” said Darst. “In 2018 we moved toward a standard material transfer agreement (MTA) model as the University seeks more oversight of companies that interact with campus research. But we continue to work closely with Rockefeller’s technology transfer office. There is substantial institutional funding covering genetics and proteomics for cancer that will no doubt prove useful to us further down the line.” Nevertheless, ties between the two have matured. The platform has been brought in-house and the organic drug discovery engine is now led by Rgenix’s VP of R&D, Isabel Kurth, who is building a team of biochemists, computational biologists, and downstream drug development managers.

Not all of Rgenix’s technology originated in academia. Perhaps the company’s most ambitious move was the licensing in 2013 of the chemistry behind an LXR agonist developed at GlaxoSmithKline PLC and intended to treat atherosclerosis before it was shelved for increasing lipids in the blood. According to Darst, “we found that the drug activates our transcription factor and turns on ApoE, the gene we are most interested in for the effects we were seeking in our lead candidate, RGX-104, initially for lung cancer. It took about 10 months of negotiation, including GSK rejecting our first bid. In the end, Rgenix secured a favorable license, mainly because the deal legitimized our business model for RGX-104. We realized there was strong IP out there that could be licensed around a lead program from a major industry player like GSK.”

## Open To Playing Outside

Along with expanding its IP portfolio, Rgenix has raised a series of four equity funding rounds, beginning in 2013 and most recently in September last year, when a series C placement pulled in \$40m with Lepu Medical, a China-based medtech firm, in the lead. Lepu has no strategic rights to any Rgenix program. In total, the

Phase Ib expansion arm of its current trial in metastatic colorectal cancer.

- > Rgenix is evaluating several potential companion diagnostic markers (cellular, protein and genetic) in the target pathway of its lead candidate compound RGX-104, which is being evaluated with the LXR/ApoE gene in suppressing immune response in a variety of cancers, starting with lung cancer. After the Phase Ib/2 data read out at the end of next year, the company will consider incorporating them to enrich for patients more likely to respond in subsequent Phase II/III clinical trials with RGX-104.
- > The third pipeline candidate, RGX-019, a monoclonal antibody addressing tumor growth and immune evasion in several tumor types, including triple negative breast cancer, has shown in pre-clinical studies to have greater efficacy against tumor cells with higher levels of MerTK gene expression. Rgenix researchers plan to use a similar companion diagnostic approach for that program once it is in the clinic, likely in 2021, and potentially with a big pharma partner.



company has raised over \$80m to date, including an initial \$2.5m in seed money raised to trigger the license rights from Rockefeller University

According to Darst, roughly \$50m has been spent so far, which leaves the company with about \$30m in cash on hand to finance the transition into full-scale clinical trial work. "We have three novel targets along with a small team of about 20 full-time staff committed to advancing these candidates to FDA approval as quickly as possible," Darst said. "Even with reliance on dozens of outside consultants who we can draw on virtually rather than bringing them on full-time, it will be a challenge to expand in our base in New York City. A single patient in one of our clinical trials is for us a \$100,000 plus investment, which explains why the average cost for an approved drug ranges from a low of \$300m to as much as \$1.4bn. Our approach to partnering is grounded in this reality."

Darst tells *In Vivo* that as Rgenix transitions to Phase II and III for its lead and two secondary programs, it will be "definitely open" to working with other biopharma companies to secure FDA NDA approvals, generate more novel research targets, push work on the MerTK program into additional indications, and consider support to secure eventual approval for the lead molecule RGX-104 in foreign markets such as China, Japan and the EU. CEO Masoud Tavazoie adds that while to date Rgenix has been successful by pursuing its clinical program independently, on its own, future progress may demand a different set of drivers; thus, the key criteria required of any potential partner is "strategic fit." One area of interest is helping the company accumulate, evaluate and leverage data. "Our strong clinical data combined with our first-in-class compounds will determine if and how we raise more money, go public with an IPO, dialogue productively with regulators and attract partners. We intend to be very judicious in applying this tool to support the growth of our business."

## Future Forward

What comes next for Rgenix? Masoud said, "We have a lead first-in-class candidate that has demonstrated anti-tumor activity in patients, establishing proof-of-concept and proof-of-mechanism in a manner that, to us, shows our platform works. Now what needs to be done is to implement our clinical development plan, testing RGX-104 in those cancer patients most likely to benefit, leading eventually to an FDA approval in clinical settings of high unmet need with large commercial impact. That is the final bridge we must cross. And as we have put in place a strong clinical team, I am confident Rgenix will have at least one marketed product within the next four or five years."

Sohail added, "It may seem a long journey, but getting clinical responses from a novel agent in patients at an advanced stage of disease, doing it all in six years from the start-up of operations, is a matter of personal and professional pride to me. That's particularly true because, as a researcher who continues to see patients with cancer, I know how so many of them have limited time left. Rgenix is going to keep moving forward to extend that time – with approvals and therapies that provide meaningful clinical benefit to patients."