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**Voice-Over:** *The BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast* and I'm Lynn Yoffee. About a third of all cancers are driven by mutations in RAS genes. Many RAS mutations make cells resistant to a lot of approved cancer therapies. Some members of the RAS gene family encode proteins that have a key role in cell signaling. When those genes are mutated, cells grow uncontrollably and evade death signals. So far, blocking RAS gene function has not worked.

It's such a challenging area of science that RAS proteins are considered by many as undruggable targets for therapy. Despite that, there's a highly competitive drug development landscape. The team at Revolution Medicines is undaunted, building a portfolio of compounds that inhibit critical signaling nodes in RAS and associated pathways. Pharma giant Sanofi had enough faith in Revolution's approaches that, in 2018, it partnered with the company, giving them $50 million upfront and up to $500 million in potential payments.

Revolution has been evaluating its lead asset, RMC-4630, in a multi-cohort Phase 1/2 program for a range of tumor types. This week, they hit the brakes on experiments pairing RMC-4630 with Roche and AstraZeneca drugs due to a lack of efficacy. Today, BioWorld's managing editor, Michael Fitzhugh, is joined by Revolution's president, CEO, and chairman, Mark Goldsmith, to discuss the company's challenges and progress. Welcome, Dr. Goldsmith.

**Dr. Mark Goldsmith:** Thanks very much for having me.

**Lynn:** Michael, take it away.

**Michael Fitzhugh:** Thank you very much. Revolution Medicines was founded in 2014 to develop medicines that could outsmart cancer. Tell me a little bit about what shaped that work has taken and how it helps you eventually identify a lead candidate.

**Dr. Goldsmith:** Thanks, Michael. It's a pleasure to be with you today. Revolution Medicines was predicated on the idea that many important new disease targets are classically undruggable by traditional means. We thought we could overcome these challenges by drawing both inspiration and even specific lessons from a billion years of evolution, and provided instructions about non-obvious strategies derived from nature and from natural products that we could use to drug new disease targets.

In fact, the name Revolution Medicines is the merging of two words, "redesigning" and "evolution." That's revolution. By that, we mean borrowing features of natural products that come out of that billion years of evolution to make new synthetic compounds that engage these targets that are otherwise very difficult to drug. We licensed chemistry from Dr. Marty Burke at the University of Illinois to help us do this.

Our strategy is to create very special compounds that will ultimately become differentiated drug candidates to use these compounds in order to probe human disease and human biology and advance the field and then combine the insights from our differentiated compounds with the scientific advances to take best-in-class approaches to treating these difficult cancers. As a company, we worked initially in several therapeutic areas.

Early on, we became increasingly focused on oncology and precision oncology specifically. As of a year or two ago, we are now fully, completely committed to RAS-addicted cancers. Our first two clinical-stage compounds are RMC-4630, an inhibitor of SHP2; and RMC-5552, an inhibitor of an associated target called mTORC1. We have a pipeline of very interesting RAS inhibitors that I hope we'll have a chance to talk about in this conversation.

**Michael:** Really, one of the things that I came across as I was reading about the company was that you refer to these targets as frontier targets in RAS-addicted cancer. Tell me just a little bit about why that phrasing. It's interesting.

**Dr. Goldsmith:** Well, we like to think that we're operating on the frontiers of cancer biology. In order to come up with something that will help patients who are not adequately served by today's medicines, we have to look to the frontiers of science. We have to identify targets that have important roles in disease pathogenesis and for which we could come up with interesting inhibitors or modulators of those targets. SHP2 is an example of such a target. RAS, the RAS family of oncogenic proteins, clearly represent those sorts of targets, so working on the frontiers and trying to push those frontiers with pioneering new molecules and new biologic insights.

**Michael:** One of the programs that you mentioned, the 4630 program, has matured along the way. You've brought a number of studies, early-stage studies of the candidate, both in monotherapy and in combination as a potential treatment for solid tumors, right?

**Dr. Goldsmith:** Yes. SHP2 is a tyrosine phosphatase. Very important as a convergence signaling node for many receptor tyrosine kinases that drive human cancer. It's a very difficult class of targets. Many pharmaceutical companies broke their picks trying to drug targets like SHP2 over the years, but we've succeeded in developing a very selective potent and well-behaved inhibitor called RMC-4630, which today is leading the field, the field of SHP2 inhibitors with its very attractive clinical profile.

With a great tool like RMC-4630, with a very scientifically talented organization, and a lot of unmet need and opportunities that need to be served, we've conducted a great deal of science over the years around the SHP2 target. We unexpectedly discovered that it is deeply connected to oncogenic forms of RAS that cause roughly a third of all human cancers. This was a new finding.

It subsequently was validated by others, but it made us realize that we were really a RAS company even though, at that point in time, we didn't have any specific inhibitors of RAS. We decided that we needed to approach RAS very holistically because RAS-addicted cancers are extremely wily. They're extremely resilient, resistant to various treatment approaches.

We felt we would need a holistic or combinatorial approach in order to outsmart those sorts of cancers. We're developing RMC-4630 as an inhibitor of SHP2, as part of that armamentarium, but it's only a part of it. I mentioned RMC-5552 as a second part. Both of these, we call "companion inhibitors" because we believe they would best be used, that is to be most effective if they're combined with other inhibitors.

The kind of inhibitors today we believe as the most important type of inhibitor to combine with these companions would be RAS inhibitors, direct inhibitors of RAS. For that reason, we've been developing a very exciting, new approach to inhibiting RAS itself. The idea is that we'll combine a RAS inhibitor with a RAS companion inhibitor and try to defeat the resistance mechanisms that are quite common in RAS-addicted cancers.

Now, before there were such things as RAS inhibitors, we call that-- In 2018, nobody had ever put a direct RAS inhibitor into a patient and tested its effect on a RAS tumor.

We weren't really certain that those mutations in RAS that look like they drive cancer could actually be an Achilles' heel of human cancers until that was done. Amgen and Mirati did those early experiments, which really convinced us that we should all be focusing on RAS itself. At that point in time in 2018, we had a really fine SHP2 inhibitor, RMC-4630, headed into the clinic.

There were no RAS inhibitors available and so we began looking for ways to find utility in the RMC-4630 compound itself, waiting until the day when the RAS inhibitors themselves would be available to be combined with RMC-4630. We came up with several companion inhibitor combinations, including combining with cobimetinib, the MEK inhibitor from Roche; or osimertinib, an EGF receptor inhibitor from AstraZeneca.

We felt the unmet needs were so significant that we really couldn't wait for the direct RAS inhibitors themselves to become available. We began combination studies using RMC-4630 with the MEK inhibitor and the EGF receptor inhibitor. Our partnership with Sanofi, our global partnership on SHP2, gave us the financial wherewithal to be able to do broad-based exploration. We knew that that would be quite difficult to combine some of these agents because of expected overlapping effects in normal tissues that could create additive toxicity.

Nonetheless, we felt it was important to try them. We believe you've got to be trying some new things that are on the leading edge or you're not working hard enough to create new clinical benefit. An important paradigm, I think, here is if we're trying multiple experiments to make sure that the experiments are not interdependent, in other words, make sure that they are independent clinical hypotheses so that while we might find one thing or another doesn't work, it doesn't read through to the next experiment that's already underway.

**Michael:** That's really exactly one of the things I want to ask you about. It was two of those experiments, the ones with combining RMC-4630 with cobimetinib and one with osimert--

**Dr. Goldsmith:** Osimertinib, yes.

**Michael:** Osimertinib. [chuckles] Two of those experiments, they fell short of internally set benchmarks. We wrote about that earlier this week and you guys made the decision with Sanofi, I think, in both cases to discontinue those trials. Can you just tell me a little bit about that decision-making process?

**Dr. Goldsmith:** Yes. Look, we felt that these were important experiments to try. We thought that they would be difficult to be successful with. Nonetheless, we tried them. As I said, we know that in drug development, some things will work out and some things won't. They were important enough to try and there wasn't anything better on the horizon. Now, as it turns out, we did see anti-tumor activity with RMC-4630 combined with cobimetinib.

In fact, we saw an objective response in a patient carrying a RAS mutation called G12V as in victory that's really never been treated before effectively with an approved drug. We did see clinical activity, but it just didn't meet our very high hurdle for what we would call success. Even though on some level, there certainly was a good indication of activity that confirmed that RMC-4630 is doing what we expected it to do.

Now, we have RAS inhibitors. We have RAS inhibitors because of Amgen's and Mirati's work and others who are now coming along behind them. We have our own RAS inhibitor program that really is a next-generation approach to RAS inhibitors. That's really what we would like to most combined with RMC-4630. Indeed, we have been doing the first part of that work in a combination study with Amgen on sotorasib, their KRAS G12C inhibitor. That's under the CodeBreak 101 C-study, which we might come back to.

The point I'd like to emphasize and I think you're really asking about is that the results of those first two combination studies that we did were not entirely unexpected. They were pretty difficult to imagine, a great degree of success on them. They just didn't meet our hurdle for going forward with, but they still gave us a lot of information. We don't think anything that we saw in those studies really reads through to the combination studies that we will be pursuing with direct RAS inhibitors.

**Michael:** You've had an academic career. You've been an investor. You've been a CEO of five companies over time. Is there strategic importance in taking that kind of risk in terms of even maybe, if you're not sure if something's going to work, having the latitude to figure it out to advance the science there?

**Dr. Goldsmith:** Very much so. We're working in an important area. We're talking about patients' lives here. If we only do experiments where we know what the outcome is before we do it, we're not really doing important science. We're not moving the field. We do extensive preclinical work to try to give us predictive insights, but those predictions aren't 100%. Some things will work and some things won't.

In tackling such an important problem, both as a physician-scientist myself, as a business person, our feeling was we need to tackle this in a big way. We can't go in with just a single experiment and it's success or failure. We either win or we lose. We have to go after this holistically. We've created a very rich pipeline. Arguably, a very competitive pipeline, both RAS inhibitors, which we, by the way, call RAS(ON) inhibitors for a particular reason, we might come back to, but RAS inhibitors plus our RAS companion inhibitors. It's a very extensive set of assets.

Figuring out exactly how to use them in combinations in which patients, how to dose them, and how to get the most out of it on behalf of patients is the mission of Revolution Medicines. It's what we're here to do and we're willing to take some knocks along the way if something isn't working out, but we feel quite encouraged by the ongoing work and look forward over the next 18 months or so as we really get to those treatment strategies that we're most excited about and that have, we think, the greatest opportunity for success.

**Michael:** Let's talk about the Lumakras combination and then move on to maybe talking about the RAS(ON) platform and things that have come from that. With Lumakras, I understand that you've got an ongoing Phase 1B combination with RMC-4630 in mutated non-small cell lung cancer and a Phase 2 on deck, right?

**Dr. Goldsmith:** Yes, that's right. We've been working with Amgen for a little over a year. They are today the commercial leader in KRAS G12C inhibitors. They've made very important advances, so we're thrilled to be working with them and we have a great relationship. As part of their CodeBreak 101 C-study, they are testing whether RMC-4630 can add clinical benefit beyond the benefit that's seen with sotorasib or Lumakras alone.

That's an important study. It's an exciting study. It's an exploratory study, meaning that they're testing it against a wide variety of tumor types and patients at different stages in order just to see can you find a clinical signal, and also mainly to figure out how you put those two together in terms of dosing and dose schedules. That's making good progress. They've not disclosed any of the data publicly from that work, but it is making progress and we're very happy that it continues.

Based on the totality of the evidence that we've seen in the field, in our own work pre-clinically, et cetera, we believe that it is now important to move into a more advanced study, a Phase 2 study using sotorasib or Lumakras in combination with RMC-4630, studying it in this particular case exclusively in lung cancer, in patients who have not yet been treated with a RAS inhibitor, and also studying it in patients who have varying genetic backgrounds in their tumors in addition to or as context for their KRAS mutation in order to figure out really which is the subset of patients that can most benefit from this combination.

We're really excited to be doing this study. We're in the process of ramping it up now. We're running it with and under our partnership with Sanofi, our global partner for development of SHP2 inhibitors, and in collaboration with Amgen who are providing a clinical supply for sotorasib. It's an exciting study. We look forward to enrolling our first patients in the not-too-distant future.

**Michael:** If things proceed on schedule, it's my understanding that you're looking for preliminary findings by the end of '22?

**Dr. Goldsmith:** That's right. Of course, we'll be monitoring every patient as they come through and looking to see what kinds of signals we can get out of it. I think by the end of 2022, we should have a good idea at a high level of what's the output from that study. We might not have a final data ready for presentation in a deep scientific format, but we should have the high-level results.

That's terrific because not only will it give us a chance to define what a registration study should look like based on the results of that, but also it informs us with regard to our own RAS inhibitors. Everything we do with RMC-4630 with sotorasib will provide some guidance and some insights that we can turn around and make useful when we're studying our own RAS inhibitors that as you know are coming online very shortly.

**Michael:** Help me understand the current pipeline a little bit. You mentioned the RMC-5552 program. I've got 6291, 6236. It's easy to get lost in the jumble of numbers, but tell me a little bit about the most advanced among those and which one's your own RAS inhibitor because, I apologize, I failed to identify that. [chuckles]

**Dr. Goldsmith:** Yes. Well, they're both our inhibitors.

**Michael:** They're both?

**Dr. Goldsmith:** Both of them come from Rev Med. Maybe just to provide context for this, when we concluded that we really were a RAS company and needed to develop direct RAS inhibitors in addition to these companion inhibitors, we looked through the field. We identified, hiding in the field, a next-generation technology for drugging RAS, which we thought could lead to more robust anti-tumor effects. That also could be applied broadly across many different mutant forms of RAS.

We used a different tool in our toolkit. We used a business tool and that is required a company, the company that had developed this technology called Warp Drive Bio. They had invested several years of very high-quality discovery stage work and a significant financial investment by their investors. We felt that that technology had real promise, so we merged it into our already existing, deepened, highly-complementary drug discovery capabilities.

Really, quite remarkably over the last couple of years, I think we've successfully turned it into a very sophisticated, differentiated, high-output, essentially industrial-grade drug discovery platform. The first two compounds to go to the clinic from this platform are those compounds, 6291 and 6236. We can shorten their names, 6291, 6236. These compounds are really quite exquisite molecules. They're elaborate. They require very advanced chemistry.

They do exemplify what we can do. The first one, 6291, is a highly mutant-selective inhibitor of the KRAS G12C mutant protein. It's highly selective and very potent and effective at suppressing its activity. On the other hand, RMC-6236 is also an exquisite molecule, but it's designed to inhibit the entire family of RAS proteins. In contrast to 6291, which is very selective, 6236 is very broad for its activity across the entire or nearly entire RAS family of proteins.

These are two, you might call them, bookends if you think about each of our assets as a book on a bookshelf. On one end, we have 6291. On the other end, we have 6236. Now, we're filling in between those two extremes, a variety of different inhibitors with lots of different jumbles of numbers to name them that have different ranges of selectivity that are designed and engineered specifically for different subsets of the RAS family of proteins because there are so many different oncogenic RAS proteins that can cause cancer.

Those will be brought forward in time. I might tell you about one or two of those in a moment. One thing I want to highlight is that this drug discovery approach, which started out fairly rudimentary, I'd say, in the early days, has now turned into a virtuous drug discovery cycle. Everything that each of our teams working on this does and learns from it translates very quickly into benefit for the other teams that are working in parallel with them across the company.

We have different teams for different targets, so we get better and better. As we get better, we get better at doing it. That has led to really amazing advances. Well, I think 6291 and 6236 are superb molecules and we're really excited to get them into the clinic in 2022. We're on track for INDs for each of those two compounds in the first half of 2022, so just around the corner.

While I'm excited about those, I'm also excited about how the platform is now enabled to approach this broader set of RAS targets and to do so with quite amazing chemical advances. We just reported just a week ago when we described the results of the first two 4630 studies. We also reported tremendous drug discovery progress on two specific mutant forms of RAS called KRAS G13C and KRAS G12D.

These are just molecular variants that are found in different patients than those who carry G12C. We showed phenomenal progress in drugging these two particular targets again just trying to provide a glimpse to folks who look under the hood at what sorts of things are coming out of our work. We will continue to move forward compounds like those inhibitors behind the first two. I think the next milestone for us actually later this year will be declaration of a third development candidate just behind 6291 and 6236. That will move towards an IND.

We would expect later this year to name the third in our series and then there will be more to come, I'm sure, in 2022 and beyond. Eventually, as these enter the clinic one by one, we'll also create the opportunity to combine them with our very own RAS companion inhibitors like RMC-4630 or RMC-5552. Even though we are a young and smallish company, we will quickly now get to the opportunity to combine within portfolio assets creating combination strategies tailored to different patients with different tumor types and different genotypes within those tumors.

**Michael:** It sounds like I'm going to be talking to you again very soon with-

[laughter]

**Michael:** -a number of these things. Before we wrap up, I just have a handful of questions that came up. As you were talking about those last programs with the 6291 program targeting KRAS G12C, is that going to be competitive with Lumakras at some point?

**Dr. Goldsmith:** It will be, we hope. That's the nature of the business we're all in, which is the leading edge folks get a position with clinical impact and a commercial progress. They're making fantastic progress and we're really happy for patients, but we're also trying to improve upon the initial successes that they've had. We know that 60% of patients who are treated with KRAS-- 60% of lung cancer patients treated with Lumakras don't show an objective response. More than half of patients don't show response even though 40% do.

There's a real benefit for many patients, but there are many patients who are left without that kind of benefit. There's real opportunity. Even among those who do show an initial objective response to Lumakras or even to adagrasib, the compound coming up from Mirati, most if not all of those patients will progress on monotherapy within a little over a year based on the data that had been published so far. There's still real unmet need here. We're excited about the progress that's been made and the impact that Amgen and Mirati and others will have in the field for sure, but we also are looking ahead.

This is a chess game. We constantly need to be looking several moves ahead and making sure that we're coming up with solutions that may be helpful to patients who simply are left out from the benefit of the first-generation inhibitors. We will at some point, I think, be competing head to head. In what format that will occur, I don't know. We'll see as time comes, but we do project based on the preclinical profile of RMC-6291 that it does have a real opportunity to provide additional benefit beyond that of the first-generation inhibitors.

**Michael:** The 6236 program, we're talking about real broad application. I often think about drugs as trying to be scalpels. Obviously, the opposite of a scalpel is not necessarily a sledgehammer. Can you just tell me briefly about the potential of having that broader targeting?

**Dr. Goldsmith:** Yes, well, a couple of things. First is that by having its broad potential, it means it may be used in multiple different tumor types, multiple different genotypes that are simply not served by G12C inhibitors. Actually, 85% of all new RAS cancers in the US are driven by something other than KRAS G12C. The vast majority of cancer patients are not going to be served by these RAS G12C inhibitors.

That's a real big opportunity and serious unmet need in lung cancer, colorectal, pancreatic, and other forms of cancer. That's exciting. I think a second feature that's much more subtle, sort of a scientific insight that often is overlooked, and that is that in a cancer that's driven by a mutant RAS, often, the normal forms of RAS that are in those tumor cells actually do contribute to the formation of cancer.

I know that that's a little bit of a troubling thought when we thought precision oncology was all about finding the cancer driver and crushing the cancer driver and everything's all over. It just turns out that it's not so simple. In the RAS-addicted cancers, which are really tirelessly addicted to RAS, they will exploit all of the RAS proteins or many of the RAS proteins that they can get their hands on within a cell in order to maintain viability.

Therefore, being able to inhibit more broadly across the RAS collection of proteins within a cell can provide significant benefit. That's a twist that hasn't been talked about much. We very much believe that there's good evidence for it, of course. I think what you're hinting at is the possibility that if you inhibit all the RAS proteins, will the patient be able to tolerate that? Will their normal tissues be able to tolerate that broader inhibitory effect of 6236?

I think the answer as we see it today is that there is a therapeutic window. There is a place to find a dose and a regimen to find that has the kinds of desired effects on the tumor, even dramatic effects on the tumor, but still be tolerable to the patient. Now, we have to prove that in humans, of course. There's good precedent for that. The early RTK inhibitors like erlotinib and gefitinib and even the blockbuster osimertinib is not selective for the mutant form of their target, their EGF receptor target.

They actually inhibit wild-type EGF receptors and patients can have some side effects from that, and yet they also gain, receive tremendous clinical benefit from being treated with those drugs. I think we already know that this is possible. In preclinical work with RMC-6236, we saw even more dramatic ratio of benefit to side effects, but we have to do that experiment in humans and we'll find out early on how well it's tolerated, what doses we can achieve, and whether or not what I just said translates into patient benefit.

**Michael:** Driving toward new insights, that seems like a pretty good place to wrap things up. I so appreciate you taking the time to talk to me about these programs today. It's been a pleasure talking to you.

**Dr. Goldsmith:** Thank you, Michael. I really appreciate your questions and the chance to tell you about Revolution Medicines.

**Lynn:** That was a fascinating discussion. Thank you, Mark and Michael. As always, BioWorld will continue to report on the incremental scientific, clinical, and business updates in this field. That's our show for today. If you need to track the development of drugs, turn to bioworld.com. Follow us on Twitter or email us at newsdesk@bioworld.com. Thanks for joining us.

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