New Approaches in Radiopharmaceutical Development

John Babich Talks with Lale Kostakoglu About Current and Coming Trends in Diagnostics and Therapeutics

John Babich[1] and Lale Kostakoglu[2]

[1]*Ratio Therapeutics, Inc., Boston, Massachusetts; and* [2]*NYU Langone, New York, New York*

Lale Kostakoglu, MD, a professor in the Department of Radiology at NYU Grossman School of Medicine at NYU Langone (New York, NY), talked with John Babich, PhD, about his work in advancing radiopharmaceutical research from the academic setting through early commercial development and acquisition for clinical integration. Dr. Babich is cofounder, president, and chief scientific officer of Ratio Therapeutics (Boston, MA) and was recently a professor of Radiopharmaceutical Sciences in Radiology at Weill Cornell Medicine (New York, NY).

Dr. Kostakoglu: *Thank you for talking with us today. You're the cofounder and currently president and chief scientific officer of Ratio Therapeutics. Your career has spanned the boundaries between high-profile academics and radiopharmaceutical science and industry. What inspired your journey and your career choices?*

Dr. Babich: At the end of the day, what gets me most excited is to be able to help a patient. We push very hard in our respective roles in science and medicine to convert the knowledge we develop into innovations that can actually reduce suffering. The ways in which a small, incremental change can catapult the whole field are exciting. If I look back at my career, I've had the good fortune to work with wonderful people who mentored me and gave me unique opportunities. If I hadn't had those doors opened by the right people, my path would have been very different.

Dr. Kostakoglu: *You have developed novel radiolabeled compounds in biotech companies, including Noria Therapeutics, which was later acquired by Bayer, and Molecular Insight Pharmaceuticals, which was ultimately acquired by Lantheus. Is such acquisition by big pharma the natural evolution of drug development for start-up biotech companies?*

Dr. Babich: It certainly wasn't our intention to do that with either company, but it's a maturation or an evolution period because of translational requirements that are just too massive for a small company to undertake on its own. Large pharma and venture capitalists have only recently recognized the value of targeted radiotherapeutics. I would say that 10 years ago the field of radioligand therapy (RLT) was not recognized as such. At some point, you really need a larger pharma company to take you to the next level from a clinical development perspective. Because they don't want the early-stage risk, of course, the large companies will watch and wait. One certain thing is that large pharma is looking for innovative small companies for the next innovation. It is a nice, symbiotic relationship. Most of these big companies also have their own investment arms or investment mechanisms. That's the ecosystem in which we live.

John Babich, PhD

Dr. Kostakoglu: *Let's talk about your company. What sets Ratio Therapeutics apart from other theranostic companies? What is Ratio's edge?*

Dr. Babich: I think our competitive edge is our superb and diverse team of experts. We merge radiopharmaceutical experience with outstanding medicinal chemistry and radiochemistry expertise, deep understanding of the impact of pharmacokinetics with mathematic modeling, and medical physics experience. The collective knowledge of the group means that we can look at a problem holistically. We have novel technologies that allow us to manipulate the pharmacokinetics of targeting radiotherapeutics. How do you design into the molecule the ability to target and be retained? We have a platform we refer to as Trillium, which is a trifunctional construct made up of a targeting moiety, an albumin-binding moiety, and a chelate to carry the nuclear payload. Noria, my predecessor company, did a deal with Bayer on our Trillium prostate-specific membrane antigen (PSMA) asset. They've taken that compound to the clinic with an ^{225}Ac version of that molecule. Lots of work went into optimizing the Trillium PSMA construct. Ratio has all the tools and know-how to do that for other targets. We also did a deal with Lantheus on a fibroblast-activation protein (FAP) PET diagnostic, again optimizing targeting using the Trillium scaffold. Of course, the pharmacokinetic profile of a therapeutic is different from a diagnostic perspective. We spent a lot of time fine-tuning the affinity to FAP and then picked a chelator that could be labeled with a variety of radionuclides (copper, gallium, or ^{18}F attached to aluminum as aluminum fluoride). So, we have all these toolkits. We'll be moving forward with a FAP therapeutic this year, and that, again, is going to be on the Trillium scaffold. I think that's a uniquely powerful technologic platform.

Dr. Kostakoglu: *Would the overall residence time of the small molecule, by entering the tumor multiple times, come close to the residence time of a peptide or an antibody?*

Dr. Babich: What we see is that we have the ability to change the pharmacokinetics in the plasma from, say, minutes to hours. We don't want to go out to days; we don't want it to look like an antibody. Other factors are at play, some pertaining to the actual structure and others having to do with the binding affinity. It's not always easy to get really high affinity with small molecules. Our med/chem colleagues at Ratio spend a lot of time fine-tuning

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molecules to boost affinity. Another piece to the puzzle is fairly new, and that is a unique actinium chelate we refer to as Macropa (https://ratiotx.com/). This is an interesting chelate introduced to me by Justin Wilson, PhD, who was at Cornell when we met and is now at the University of California Santa Barbara. This chelate is uniquely suited to actinium—you can label actinium quantitatively at micromolar ligand concentrations at neutral pH at room temperature in 5 min. Now we have added to that portfolio a library of novel chelates that allow us to make variations on this theme. Having a library of chelates is another of Ratio's unique technology platforms. At the end of the day, it's understanding the problem and then having a lot of bright people around the table with the right tools to solve that problem.

Dr. Kostakoglu: *That's certainly the key.*

Dr. Babich: What did Edison say? Success is 90% perspiration and 10% inspiration. I think we generate a lot of perspiration in our company.

Dr. Kostakoglu: *Therapeutic index is the key, obviously, but to increase that, should the monospecific radioligands be replaced by heterodimeric ligands targeting multiple receptors?*

Dr. Babich: It's a great idea. There is now literature coming out on heterodimers that bind to different targets. This is interesting from a couple of perspectives. The agent that we choose to target those tumors is not going to be on every cell or at the same expression level—almost in some sort of gaussian distribution. How many of these tumors in the body are going to be curable based on this heterogeneity of expression? What if you could add another dimension to that, for example, FAP plus $\alpha_v\beta_3$? So we go in with an $\alpha_v\beta_3$-binding domain, and then we attach a FAP-binding domain. Now we're going to attack 2 different targets, thereby virtually increasing the target expression. I think it's something that requires a lot of thought, effort, and experimentation, because heterodimers have real legs. In the later stages of disease, cancers start to lose expression of targets and begin to express FAP and probably other targets. Heterobifunctional targeting for certain cancers is likely a really good concept.

Dr. Kostakoglu: *Although we're not there yet, we currently have at least β- and α-labeled molecules. What about sequential treatment with a β to start and then continuing with an α?*

Dr. Babich: You know how hard it is to do any kind of clinical trial. How do you set up that paradigm from a clinical trial perspective? Probably in a randomized setting, one arm gets α first, then β, and then another gets β first followed by α. It is challenging to recruit enough patients. I think it's a good concept, but the feasibility may not be high. It's always interesting to see what a pharmaceutical company wants to do versus what a National Institutes of Health grant would support. I know Scott Tagawa, MD, MS, at Cornell Medical College has been contemplating these kinds of combinations, an α on, say, the antibody J591 and lutetium on a small-molecule PSMA inhibitor. How do these combinations play out? He's been pioneering this thought process. There are many questions: Will α particles pick up micrometastases? Will β particles take care of larger metastases? These will be answered by microdosimetric calculations. In the end, however, you need statistically powered, well-designed, and feasible clinical trials.

Dr. Kostakoglu: *We also know that single treatments are usually not as effective as combination treatments. What would be the most effective orthogonal treatment combination for FAP-based RLT?*

Dr. Babich: That's a good question. Immunooncology holds the promise of being able to turn on your immune system in a way that's quite specific. It doesn't always do it specifically, and lots of tumors don't get turned on. The team under Silvia Formenti, MD, in radiation oncology at Cornell is looking to use external-beam radiotherapy to stimulate the immune system in such a way that when you give a checkpoint inhibitor or some kind of stimulant to the immune system, you would "hijack" the inflammation caused by the irradiation. Although these are noncytocidal radiation doses, they may be cytotoxic or inflammatory, so that you actually start to create a reaction center with which the immune system begins to engage. My corollary is that I think targeted radiotherapeutics have a lot more to offer there for a couple of reasons. One is that with a lutetium or an actinium product much more of the mass of the tumor is stimulated by the radiation. Then we can give targeted immunooncologic agents. That, to me, is really fascinating, because we can look at what the quality of the radiation is, how that affects response, and then we can look at the dosing schedules. These are really important questions, because what if you could give a relatively modest dose of a radiotherapeutic to turn on the immune system and then give immunooncologic drugs? How exciting would that be for the oncology community? These hypotheses need to be tested. The external-beam work with immunooncology hasn't yet been super compelling, but I think it's also just begun. Maybe the combination of immune checkpoint drugs, the radiation, and something that enhances this bridge should be tested (such as a radiation sensitizer). It is also interesting to see the ongoing studies on the radiation sensitizer effect of poly(ADP-ribose)polymerase inhibitors on β-emitting labeled molecules.

> "We also have to recognize that a lot of the DNA and RNA sequencing work is not really giving us new targets. We have to find practical solutions to understanding cancer targets. The topographic assessment of what's actually on cancer cells as opposed to what's in their RNA or their DNA is something that generally has to happen in oncology and that will have a direct impact on us as theranostics investigators."

Dr. Kostakoglu: *I agree with you wholeheartedly. Going back to your imaging agent. You have finished the phase 1 trial with ^{64}Cu-RTX 1363S. What's next?*

Dr. Babich: That project has now been taken over by Lantheus. We intentionally did it as a discovery project to deliver a clinical candidate to Lantheus. We did the phase 1 in healthy volunteers. I don't want to speak for Lantheus, but my understanding is that they're well on their way to putting that into the clinic in the United States. I don't have more details at the moment, but I know it's in the plans.

Dr. Kostakoglu: *What about the therapeutic FAP you are pursuing? What phase are you in?*

Dr. Babich: We're planning right now to enter the clinic this year with an actinium version of our FAP therapy candidate molecule. It will be a standard phase 1 dose-escalation study.

Dr. Kostakoglu: *How different is your FAP molecule from other existing molecules?*

Dr. Babich: We have very good retention time in tumors. I think that was the key for us to move to the clinic. I can't say much more

about that other than that was the goal of the project. We were able to deliver a very attractive diagnostic FAP ligand to Lantheus. Then we had to expand our medicinal chemistry efforts to understand how we could get retention of a FAP ligand that was going to be sufficient to actually contemplate therapy. We were able to do that. Our excitement, right now, internally, is to move that into the clinic. Our goal is to file the Investigational New Drug application by the end of January 2025 so that we could be in the clinic by mid year.

Dr. Kostakoglu: *The increase in retention is on the basis of the Trillium platform and the novel radiochemistry of the construct?*

Dr. Babich: I would say that everything contributed to the improved performance of the therapy candidate. That's one of the nice things about this space. The tail doesn't always wag the dog, but the dog's not a dog without a tail. So everything comes together appropriately. We learned a lot in this effort.

Dr. Kostakoglu: *That's wonderful. Is your Trillium platform based on machine learning? Are you using artificial intelligence (AI) in your radiochemistry developments?*

Dr. Babich: As my partner Jack Hoppin, PhD, CEO of Ratio Therapeutics, would say, we use AI, but it's "actual" not "artificial" intelligence. There's a lot of trial and error. We're not in the AI space yet. There's a very interesting article that came out recently in *Chemical and Engineering News,* asking "Is AI in drug development a hype?" (https://cen.acs.org/sections/discovery-reports/AI-drug-discovery.html). I would suggest reading it. One area in which AI is quite useful is in in silico techniques. If you have an understanding of crystal structures, there's some very sophisticated software (Schrödinger's being one), where you can actually see the molecule and the crystal structure. Although that's not AI per se, it allows you to do in silico work before you get your hands dirty in a lab. Because every model is a model of reality and not the reality itself, this becomes much more interesting. We tested some ideas using these kinds of concepts while I was at Cornell, and it was directionally accurate but not, I would say, absolutely accurate. I think there's still a way to go with all these techniques.

Dr. Kostakoglu: *The other interesting point is that this new age of theranostics has brought a multimillion-dollar industry with investment for the field. Is it challenging to convince investors in an exploding field like this, with multiple competing stimuli from all sources?*

Dr. Babich: I think going back to what I said earlier, things have a moment in time when they become very exciting. It's probably easier today than it was in 2010 to raise money for a radiopharmaceutical company. Human nature in general tells us that there's a fear of missing out. There are more options for people who have an idea and want to start a company. I think it's always the long term. I mean, these companies need a lot of capital. So it's not that you start off with $5 million and maybe you're in a makeshift office or you're working out of your home. Once you start to spend that $5 million, then you need $15 million, and then you need $30 million. This is a beast that's not easily fed. It becomes harder to get the next tranche of money as it becomes larger. You have to have good data, and data win the day. The current environment is much better than it was 10 or 15 years ago, but surely macroeconomics can change that, as could a change in regulatory perspective. It is a dynamic environment!

Dr. Kostakoglu: *One last question, what should be the priority in radiochemistry research for the next 5 years?*

Dr. Babich: That's an interesting question. I think one answer is the continued evolution of our understanding of how to use radiopharmaceuticals. This goes back to your earlier question about how we start to think about combinations for RLT. How are immunooncologics incorporated? The concept of heterobifunctional compounds is another big one. How do you manipulate things that are not necessarily manipulable by themselves? The literature suggests that if you give androgen deprivation, PSMA expression increases, but it's not tripling. It goes up a little bit. How do you improve delivery? How do you improve retention? That is key. We also have to recognize that a lot of the DNA and RNA sequencing work is not really giving us new targets. We have to find practical solutions to understanding cancer targets. The topographic assessment of what's actually on cancer cells as opposed to what's in their RNA or their DNA is something that generally has to happen in oncology and that will have a direct impact on us as theranostics investigators. I think we need more targets and a better understanding of where those targets are and how to go after them.

Dr. Kostakoglu: *Thank you so much, John. I really enjoyed talking to you about this ever-evolving and exciting platform, and I'm sure our audience will love it.*