Steve Lewis 00:10
Welcome to Speaking of Mol Bio, a podcast series about molecular biology and its trending applications in life sciences. I'm Steve Lewis and I'm excited to share my conversation with Dr. Christian Cobaugh today. Christian is the co-founder and CEO of Vernal Biosciences, which focuses on democratizing access to high purity mRNA. His background in mRNA research, discovery and process development spans nearly 10 years and his vision for the future of these technologies is fascinating. We hope you enjoy our conversation. We begin by asking Christian how he first got into the mRNA field and how he decided to start Vernal Biosciences in 2021.

Christian Cobaugh, PhD 00:54
I got involved in mRNA medicines when I was at Alexian Pharmaceuticals and we partnered with Moderna spent two years leading research and development as part of that. And one of the major limitations was our ability to continuously supply our mRNA discovery programs with high purity mRNA. Fast forward a couple of years and I went to Arcturus Therapeutics based in San Diego and led their mRNA program. And we really set up supply as a foundational technology so that we could rapidly go through mRNA discovery. Ultimately, I landed at Translate Bio, and I led process development there, where I really learned how to scale high purity mRNA. And it really opened up a lot of possibilities on the drug discovery and advancing clinical projects rapidly with high purity mRNA. And so when I left Omega Therapeutics, I thought that it would be a great idea to create what I had learned around mRNA supply and manufacturing as contract research and ultimately a contract development and manufacturing organization to supply innovator companies with high purity mRNA and all the other services that go along with that, such as the pDNA for the template, as well as lipid nanoparticle formulations. So we started just over three years ago, servicing research use needs, and we now basically sell the same type of services for GMP needs for clinical applications. The mRNA platform is growing more and more mature by the day, in terms of the use cases, as well as the stage of discovery and development.

Steve Lewis 02:45
And I think anytime you're talking about this kind of pace of innovation, it kind of goes hand in hand with the regulatory aspect. And I know that you mentioned the transition from Research Use Only to clinical. Do you mind talking about, a bit about that from your viewpoint?

Christian Cobaugh, PhD 03:02
What Vernal has done is created a culture of quality from day one. So even for research grade projects, we have leveraged a quality management system that institutionalizes and proceduralizes quality. But you know, at the end of the day, it really comes down to the culture, and how seriously people take this, you can go through all the training you want. But you know, what you're looking for are people who police their own work and police one another's work from a quality front. And that really makes the transition from a research project to a GMP project much easier to navigate. And in some cases, you can use some of the same people to go throughout the lifecycle of a project. And that continuity is incredibly important when it comes to the technical operations, as well as ensuring purity and knowing what can and can't be done with a particular project or what has or hasn't been done with a particular project. So from a quality perspective, we've always put the needs of the customer first, knowing that

ultimately these projects will land in the clinic. In terms of regulatory, which is sort of the partner of quality, you know, we have to know what the FDA, what the EMA and other regulatory agencies are expecting when it comes to the types of tests to be run and the specifications to be run. And at this point, that's still an ongoing negotiation, which is actually a healthy thing. Rather than getting locked into early generation technologies. You know, Vernal, and others continue to innovate using the best possible platform at whatever point in time to assess the quality attributes.

Steve Lewis 04:51
Can you tell me a little bit about the difference between an mRNA CDMO and perhaps a protein production CDMO?

Christian Cobaugh, PhD 04:58
It's a great question, I mean, our footprint is going to be a lot smaller. Our tanks, our reactors are, you know, a 10th of the size to get the level of the number of doses, for example. And so what that means is in the same amount of space as a protein-based manufacturer, you know, we might have more capacity for more projects, or we could deal with commercial projects much more readily, which tend to take up more space, and more infrastructure. The good news is that we actually borrow quite a bit from the process technologies that protein manufacturing uses. So we do use bio reactors, which can be dual purposed. We use chromatography systems for purification and TFF systems, which can readily be dual purpose. So while some folks might be prying for mRNA, specific technologies, we've been able to adapt quite readily with, you know, validated product families that have years and years of use, and, you know, plug right into the modern IT/OT networks that are validated for GMP. So you know, we're not reinventing the wheel when it comes to equipment in facilities. It I think, really, is more to the capacity when we make that comparison from protein to nucleic acids.

Steve Lewis 06:24
Certainly. What are some of the emerging application areas that you're seeing as you go to these conferences?

Christian Cobaugh, PhD 06:32
Well, I'll tell you what's hot is the personalized cancer vaccines. There's no mistaking that, within the next five years, we're going to be getting some commercial traction with those types of assets. You know, they take people with really aggressive disease, and they get personalized medicines into them within 60 days, in some cases. The clinical data, while it may not yet be transformative, is certainly buying time for these patients. And a lot of times in combination with other forms of therapy, including a neoadjuvant setting. So we're really pleased with the progress around personalized cancer vaccines, we think it's going to offer, you know, great hope for the next generation of the of immunotherapies. I am incredibly excited by the innovation that's going on in the non-viral delivery space. So Tessera, for example, shared a couple of weeks ago, the American Society for Gene and Cell Therapy conference, that in mice, they're able to reach editing levels and hematopoietic stem cells as high as 40%, which is likely to be transformative, at least in some of the hemoglobinopathies which do have really exciting recent breakthroughs in terms of medicines. But those medicines are very, very difficult in terms of the intensity on the patients, the price point, and they're difficult to read dose. You know, I like to say a great medicine can be dosed to affect safely. In case you know, the first time you didn't get a full

response. And so I think the delivery is starting to really drive, you know, some exciting potential payloads that will transform diseases that are currently only transformable through cell therapy assets.

Steve Lewis 08:23
And as we're talking a lot about personalized medicine, I think that that's been a really exciting topic for perhaps decades. And now we're at a point where we're actually seeing it in practice. For a company like Vernal, which is mRNA CDMO offerings, when you're talking about some of those really personalized approaches, do you see a need for nearby location, or colocation, even for scalability of these medicines, in terms of where the patients are?

Christian Cobaugh, PhD 08:58
I think we need to find ways to get away from that, because the last thing we want to do is, is for access to be determined based on your ability to either get to a center or to live near a center. You know, I think with the global logistics right now, particularly with mRNA, I think there's an opportunity to get things around the world fast enough so that we don't have to have full distributed manufacturing, you know, essentially, where we would have hospital pharmacies, you know, scattered around the world that are having to manufacture GMP mRNA and LMP mRNA and file it up. I think, I don't think that scales that effectively. I know that there are some technologies that are solving maybe the mRNA piece, but ultimately, it's still going to be a rather complex process. And unlike cell therapy, where I think location really does matter, on the mRNA side, we're not accepting anything into the process other than the patient's information. So in the case of personalized cancer vaccines, it's just data as to what their neoantigens might be. And then the work can occur virtually anywhere, so long as you have the logistics to return that to wherever the patient is, which is mostly a solved matter at this point, there's really nowhere on the planet where we can't get a frozen box to within two days.

Steve Lewis 10:31
Got it. And I could speak all day about the infrastructure developments that are happening and will continue to happen. But I want to take a moment to go a little bit lower level into kind of the molecular technologies. Do you mind sharing a bit about what you use at the very foundational level?

Christian Cobaugh, PhD 10:53
You know, process starts with essentially a protein sequence because ultimately, the mRNA is going to encode for a protein in order to be therapeutically or preventatively active inside of the body. So we're just using mRNA, as almost as if it were a pro drug, where upon the body activates it into a protein in this case. And so what we really need to get started, you know, anybody in the mRNA space is knowing what protein sequence you want to encode. And then from there, we gene synthesize, reverse transcribe that, obviously digitally, into a sequence and we do gene synthesis, to make a DNA template that now has the addition of untranslated regions. And in some cases, a Poly(A) region at the DNA level, most often that is cloned into a pDNA some type of a destination plasmid with a selectable marker as well as RNA polymerase promoter that needs to be immediately upstream of the mRNA cassette. And from once you get the pDNA it can be propagated and expanded in an E. coli strain purified using a plasmid prep technology, could be kit based. For larger scale and GMP, we have essentially developed our own technology around that. From there, the pDNA after the cells have been lysed are going through some type of a purification. On the case of the kits, often its affinity based like

silica, and then, you know, for GMP, we're using an ion exchange on that lysate. And then it gets buffer exchanged again, that can either be on column with the kits or in a TFF step with GMP. And then you're ready to linearize the plasmids. So on a molecular basis, we would use some type of a Type IIs restriction enzyme to linearize either downstream of the three prime UTR or downstream of an encoded Poly(A) region, and then move that forward into the in vitro transcription process, where that linearized plasmid is now being used as the mRNA template. The in vitro transcription process is powered in large part by a DNA dependent RNA polymerase, like T7 is probably the most popular enzyme to use it is a high producer. And in some cases, it's been engineered to eliminate double stranded RNA or truncation products. NTPs are also part of that reaction mixture. So that will literally polymerize a mRNA using that enzymatic process off of the pDNA templates. So that pDNA template is being reused, you know, throughout the process, you know, theoretically got several mRNAs being made simultaneously off of the same template as if, you know, you could imagine a train tracks with the RNA polymerase chugging its way down the mRNA, one polymerase sort of after another, and mRNA is being kind of spool off into the buffer. The RNA polymerase reaches the end of the template supposedly falls off we call it run off transcription. And the mRNA is then released into the buffer. The mRNA gets purified and, in some cases, you may have capped it during the transcription reaction with a cap analog or you may forward process that mRNA into an enzymatic capping step. And then that enzymatic capping step if you haven't transcribed the Poly(A) tail and that first step, that enzymatic capping step is also compatible with a Poly(A) polymerase which will add the three prime Poly(A) tail. And it's the cap and the tail, which are essential to initiate protein translation once that mRNA is into its target cell. And from there, the molecular biology is kind of over. We purify that mRNA, often with an affinity resin that captures Poly(A) tail. So anything without a Poly(A) tail, i.e. a truncation product, will flow through, and anything that remains is diluted in water. And then we forward process that into lipid nanoparticles for injection into mice or humans.

Steve Lewis 15:33
Are you in the market for a new PCR or gel electrophoresis instrument? If so, you should check out our virtual 3D Lab. From the comfort of your own device and at your own pace, you can interact with our PCR and gel electrophoresis instruments like never before. This immersive 3D tour of let you explore and experience what it's like to use the state-of-the-art instruments. To start your personal tour today, visit our website at www.thermofisher.com/molbiovirtuallab. That's forward slash mol bio virtual lab. And now back to the episode.

Steve Lewis 16:19
Where are some of the limiting factors in that process?

Christian Cobaugh, PhD 16:26
Well, purity is always an issue. These enzymatic processes relative to solid phase synthesis, they're like linearly scalable. And, you know, so long as you can control the temperature because there are some temperature shifts these enzymes like to work, you know, anywhere between 25 and say 42 degrees. But you know, purity is where, that that's where all the magic is right now. And that's, you know, where a company like Vernal fits in. Honestly, that IVT reaction, you know, at a small-scale level can be run in a in a thermocycler in a PCR tube, and there's, you know, nice kits that will purify that to, say, half a milligram level. But getting to levels of purity, where you really can start to underwrite your

preclinical results on a consistent basis. You know, that's always a struggle, I think, for small scale, chip-based production. And then obviously, scaling, you know, by the time you want to go to a much larger animal study, you know, that that's where you need to start to bolt together some of these, these technologies that are a little bit, look, they're not specific to mRNA, you know, we've talked about, you know, purification, being FPLC, and TFF driven approach. So, you know, so long as you have that equipment, you're kind of half the way home on adapting a lot of the exciting technology around purification. But, you know, this is a multidisciplinary workflow. And, you know, that's where Vernell can, you know, sort of speed things up for, for customers or jump in when they need to scale on kind of a case-by-case basis.

Steve Lewis 18:14
Yeah, that that makes sense in terms of, you know, input output considerations. If you take care of a lot of it upfront, you get the you benefits downstream, which is great.

Christian Cobaugh, PhD 18:26
Yeah, it's that old phrase quality and quality out.

Steve Lewis 18:30
Exactly. That's right. For the beginning of that process, you had mentioned DNA synthesis. Do you all do your own clonal DNA development? How does that process look?

Christian Cobaugh, PhD 18:43
We have a multi-pronged approach there. There's some projects that are just easier to outsource the gene synthesis and cloning. But then there's other projects where we start to bring in fragments, you know, we generally aren't going to do splicing overlap extension PCR, which is still sort of the work engine of gene synthesis. We'll bring fragments in and we'll assemble those fragments into a full gene. In some cases, we'll do an in vitro transcription right off the gene synthesis product. We have little tricks to try to achieve clonality around that. But it's, you're never going to be assured of commonality in any system, more than you can be assured of it through pDNA because we truly can do almost single plasmid based clonal screens with E. Coli. For a project where time is maybe not as important as the purity, pDNA is still a really powerful approach. We are starting to look at fully enzymatic processes through other companies that are out there, whether it's a plan rolling circle amplification, or some type of a high-fidelity polymerase. It is, you know, obviously going to be a mixed pool, because those have been manufactured off of an enzymatic process. But those are pretty close. And I think in some cases exceed the fidelity of an expanding E. coli culture. So we're, we're very keen to keep working with companies that do that.

Steve Lewis 20:27
What might somebody who is just learning about mRNA CDMO? What might somebody not know to ask? What am I missing?

Christian Cobaugh, PhD 20:37
That's a good question. I mean, number one, you know, how much experience folks have. What we're seeing is like a couple of different types of providers, there are those like us that have been mRNA from

day one and have been almost singularly focused on process technologies and innovation, in order to drive a high purity, and then to really fully understand the molecules we're working with. So the amount of analytical investments that we've made, not just in terms of equipment, but the procedures themselves, as well as the creation of reference standards. There's really not enough reference standards in this in this space yet. And so we've just had to build many of our own. That's one category, it's the real specialists that have thought about this from end to end. And then there's others who have mRNA, as part of a mix of, of many other service offerings. In the case of those companies, I think the good news is, you know, they have, you know, robust commercial operations, and, you know, good logistics, you know, they have a history of jumping on new technologies, and doing a good job. And then there's the third type of CDMO, which is essentially cleanrooms for hire with quality management, talented staff, and, you know, some technology that they can bring in, you know, we've covered, you know, the bio reactors and the FPLC. But these companies, you know, may have, you know, really good track record, just in general making GMP assets, but maybe kind of new to mRNA. And in a lot of cases, you're going to need to bring the process to them. So as a client, you know, you will have to have a robust process and analytical development package that you can transfer into them. That's not for everybody. You know, that's a fair bit of spend. So, you know, a lot of the customers we see, have a little bit of process knowledge, but ultimately, would rather not expend their capital on building something that they don't need, from inception of their business, through approval, and commercialization or partnering. You know, they want to really focus on what differentiates them, which is perhaps the way they discovered medicines or the type of therapeutic areas they're in, or, you know, some other platform technology, like their precision guided nucleases. And so, you know, what we're trying to solve for is how to companies do this on a transactional basis.

Steve Lewis 23:17
And it's, it's hard, right, all around getting those processes down and getting those controls in place, really, training and all of the operational considerations can ,honestly, they're undisciplined. Aside from the difficulty of the science itself.

Christian Cobaugh, PhD 23:35
Yeah, I mean, the number of technologies that we have here is pretty astonishing. And so this is where it gets difficult for innovator companies to do all of this themselves. Because, you know, the capital outlay alone, just in the different analytical instruments, again, it's really backbreaking and then you know, you've got to find people that know how to operate those pieces of equipment. So it's a lot of different disciplines to bring in house. And if you're not going to use it every day of the week, the math doesn't really work out, because you got to carry all that whether it's the capital or the people.

Steve Lewis 24:16
Capacity utilization is such a tremendous consideration with this kind of business model. I guess as we look forward to the next 10 years. I think I've seen a number of reports that the utilization may not be the issue. It's the actual physical facilities and equipment that are going to be the rate limiting step for scaling up some of these medicines. Do you agree with that?

Christian Cobaugh, PhD 24:42
I do. I mean, right now facilities. I mean, we went through, I think, a boom period during COVID. A lot of money came in, there was a lot of private equity that came in on facilities. And so facilities at the moment don't seem to be the bottleneck, the equipment bottleneck is starting to come down a little bit, as is the single use technology. So, you know, again on the GMP side, most of us want to use single use technologies these days to kind of reduce the quality, overhead, and the validations overhead, it's easier just to bring something in prevalidated, you know, attach it to your instruments and then dispose of it afterwards, as opposed to trying to clean it in place or something like that. And so that continues to be a bit of an issue, the access to just in time ordering around single use technologies. As a, you know, a well-managed business, we'd rather not carry too much of that in our warehouse, we'd rather order that as close to on-demand as possible, that's starting to get better, but it's still, it's, it's still a bit of an issue. The raw material costs, I think, continue to be a bit of an issue, competition is moving into the marketplace. So we think we're going to see that come down quite a bit over the next year, it's already come down a lot, but it's still it can constitute an unreasonably high fraction of project costs that could be tied up in raw materials.

Steve Lewis 26:20
This is going to be a really interesting space to continue to watch and see how it develops over the coming years. For somebody who might want to get into this space, what advice could you give?

Christian Cobaugh, PhD 26:33
Well, you know, one of the things you talked about was the complexity of these projects. Lay the project out from start to finish at a high level, don't take too long on proof of principle around process development or analytical development. In a lot of cases, you may not have your final sequence discovered, or you may have it discovered, but you want to make sure that it's you know, formulateable, and it continues to work in animal models as you kind of go up the value chain of animal studies. But, you know, we can do a lot in this field with prototypes. But again, if you got the final sequence locked, like there's low hanging fruit on the process development tree, as well as the analytical development tree, that is going to be valuable for you almost no matter what happens to the project, and it is therefore a wise investment to start making, you know, sooner rather than later. I mean, you can save yourself a lot of time and money in a GMP project if you've got it kind of sorted on that fundamental level.

Steve Lewis 27:48
And we love having entrepreneurs and founders on the podcast, and I'm curious with you as the founding CEO, and finding this kind of market opportunity, what advice would you give somebody who might want to follow in your footsteps?

Christian Cobaugh, PhD 28:08
I love this question. I mean, I think back to why I started this. I mean, I started this company, because number one, I was I'm passionate about mRNA medicines, and democratizing access to these. You know, I live with the conviction that mRNA medicines are going to change the health of the world for the better. So you know, find something upon which you have a ton of passion and conviction and possibly have lived through some pain points. Because you'll understand the marketplace that you're trying to

solve. And I mentioned some of those pain points, you know, throughout my journey of mRNA medicines that dates back over 10 years you know. So yeah, marrying up that conviction with a market opportunity and then, you know, really going deep on technology and the operations of the business. Ultimately, though, what, what, what it really comes down to, is getting that culture, right and getting the right people to work with you. And it's, there's no alchemy there. It's just finding people that have the same sense of purpose, share in the passion that you do, and we'll figure out the rest.

Steve Lewis 29:24
It's really great guidance and advice. And this is a really fantastic emerging area that has many implications and positive impacts to come. Christian, this has been fantastic. Do you have any last points that you might want to share with our listeners?

Christian Cobaugh, PhD 29:43
Well I, first of all, Steve, I just want to thank you and your audience for taking the time to listen to this. You know, I hope that everybody has learned that, you know, mRNA is here. to stay, I think, you know, we've seen it derisked with the infectious disease, vaccines, the countermeasures if you will. But the future is long and laying out in front of us as days go by pay attention to what you know is going on out there in the advanced therapeutics world. And in a lot of cases, think about how an mRNA, if we solve one or two of, you know, problems may not be trivial, but how an mRNA can potentially replace some very difficult types of therapies that have challenges. Whether it's, you know, viral integration, or, you know, cell base conditioning, these are all great innovations that have happened, but how can mRNA you know, kind of take the edges off of those therapeutic approaches, you know, without reinventing the target biology, and, and, and I say that as an encouragement to the next round of innovators. You know, let's hear about the one or two problems that you have to solve so that we can all solve those collectively. And I think about delivery, for example, is one of those, those big ones, because the payloads are, frankly, they're not that hard to make. Comparatively speaking, so and, you know, even the gene editing reagents like they just kind of work. So like, you know, if we solve one or two problems, like let's put our heads down and focus on that and really change the world.

Steve Lewis 31:28
That was Dr. Christian Cobaugh, co-founder and CEO of Vernal Biosciences. Speaking of Mol Bio is produced by Matt Ferris, Sarah Briganti, and Matthew Stock. Join us next time for more fascinating discussion about the amazing world of molecular biology. Until then, I'm your host, Steve Lewis. Cheers and good science.