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Applying Quantitative Systems Pharmacology, Mathematical Modeling and Machine Learning Techniques to Drug R&D, Applied BioMath is Modernizing Drug Discovery, Drug Development and Clinical Trials

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CEOCFO: ***Dr. Burke, we spoke about a year ago. Would you tell us what has transpired over the last year for Applied BioMath?***
Dr. Burke: In short, exponential growth. Our team has grown from three to more than twenty. Our repeat business rate is extremely high, approximately 85%. This would be even higher were there not a transition period between finishing our first project and getting our second one. It is like we cannot get out there fast enough, early enough, and often enough. It's a good problem to have.

CEOCFO: ***What changed for you?***
Dr. Burke: I do not think anything has changed. It was our plan, my partners Joshua Apgar and Andrew Sutherland and I, all along to focus on what we can do very well: delivering the highest quality of science and results and not over-promising. We work with our collaborators to develop practical and usually fast timelines and we deliver on them. We also focus on brand recognition and market penetration.

CEOCFO: ***The tagline on your website is Revolutionizing Drug Invention. Would you tell us how?***
Dr. Burke: Similarly to how mechanical, aeronautical, and electrical engineering employ the hard sciences to optimally design bridges, cars, wings on planes, and computer chips, respectively, we are creating a new and innovative engineering approach in drug R&D. We use physics, biology, mathematical modeling, high-performance computing, and high-quality data to de-risk projects. We help our collaborators identify which of their projects to prioritize and which to deprioritize. For example, we can help identify which roadblocks they can move or which ones they have to navigate. We help predict the failures much earlier – with the killer experiment, to help reduce late stage attrition rates. This helps our collaborators prioritize their resources and their experiments. We identify which projects they should accelerate so when they get to the clinic they are more likely to get there faster, with potentially a best in class drug, and more likely to assess proof of clinical concept, so they are more successful. Also important: we help identify which projects are too difficult to develop, so they do not waste up to $100 million on these projects. This is what we call Model Aided Drug Invention, or Pharmacological Engineering, or Systems Pharmacology.

CEOCFO: ***How do you weigh some of the factors that you evaluate and if it is border-line, which side do you come down on?***
Dr. Burke: We can approach a problem either conservatively or extremely optimistically, and the computer allows us to test the full spectrum in-between. Our approach involves many factors, such as types of diseases we are targeting, types

of data, and drug mechanisms, and all of these factors are varied to create the conservative or optimistic scenarios, more commonly thought of as best and worst-case scenarios. If we find that under the best-case scenarios they are not going to be successful, or have a low likelihood of being a success, we can advise them not to work on that project. Under the worst-case scenarios, if our results show a slam-dunk and that they will win under every single consideration that we thought of, that is fantastic! It is important to look at both best and worst-case scenarios, and all in-between, so there are no surprises as they advance toward the clinic. One advantage we have is that our technology enables us to simulate and assess an entire spectrum of possibilities quickly. For example, if we are investigating a cancer treatment and the size of the tumor might be small to very large, why don't we do a simulation with every single possibility from small to large?

To elaborate on the first part of your question, what do we consider? We develop a single mathematical model based on the biophysics of the disease and of the drug mechanism of action with model parameters, like k-ons, k-offs, affinities, cell or protein turnover rates: real, measurable features that collaborators can prioritize and design experiments around. When we have that single model, we can change model parameters systematically, enabling us to recapitulate in vitro assays or animal studies or human data. We can choose to weigh some of the data or mechanisms more heavily or less, depending on which we believe more and which we believe less. Also, we can identify which parameters have the most effect on our desired outcome so we know which ones are most important to understand and study – all to make better human predictions early. The holy grail is when we find parameters that can work for all or almost all of these considerations, so for example, they only have to do lead-generation once, possibly saving six months to a year of R&D and maybe a half a million to $2 million dollars in that calendar year, or the clinical trial is designed properly so they're more likely to assess proof of clinical concept. That's a huge win! When they go into the clinic and they are doing their Phase I and Phase II predictions before clinical trial design, then they know, for example, that they are dosing high enough and frequently enough in Phase I that they can hit the disease hard enough and still be safe in Phase II. These abilities are extremely valuable because of the time and money they can save. It all centers around the model acting as a central repository of data and hypotheses so they can test a lot of different scenarios before they go into the clinic.

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CEOCFO: ***When you are providing a result to a client, what do they typically look for and what can you provide?***
Dr. Burke: One of the most common pieces of feedback we receive from our customers is that they appreciate our transparency and methodology, because it helps them trust the results that we deliver. We ideally meet with our partners every three weeks or so. Sometimes it is a little more in the beginning of a collaboration, or near a milestone transition. Our collaborators see us as valued team members. We meet frequently and collaborate closely so that they see how the model is developed. Their expertise and ours is used to build the model diagram, and we work together to understand the data. They see how the model is built and where it is strong and where it is weak, they see how flexible we are when new questions come up, some of which we never would have thought of without to model enabling the scientific method. All of this is critical because when our champion needs to present the results of our modeling to their senior leadership, they understand and are comfortable with the model, model results, and the value, which is what we, and our partners, want. We love it when they can do that well!

CEOCFO: ***Does a company's risk tolerance come into play or is it up to them once they see the facts?***
Dr. Burke: Our partners do not have to tell us at all if they have used our decisions or not. We are also agnostic in the approach. We are not going to get a raise or promotion whether or not the project moves forward. That is, our predictions are purely scientific. When we make our predictions, quantify risk and success, our collaborators trust our predictions. This is important, because project teams want to make the right decision, but it is often tough to kill a project that they've been working on for 2-5 years. We help them make decisions in a rational way.

Through feedback that we request from our partners, we know that more often than not, they do follow our recommendations. We also know that because we have such a high repeat business rate. All of the work that we have done with our partners for regulatory agencies, such as IND support, all of our recommendations have been accepted by the government regulatory agencies. We have never had any push-back or any negative comments, which is great and extremely rare. In some instances, our recommendations enabled our partners to be more aggressive in the clinic, than by

using traditional approaches, for example by starting at higher doses. This saves our partners a lot of time and money, but most importantly, it is more ethical for patients, because the higher dose will still be safe but the patient's dose is more likely to be within the therapeutic window. The fact that we are getting no negative feedback from the FDA, that we are getting high repeat business rate, and that our feedback tells us that our partners followed our recommendations – this is exciting and good, positive feedback to get.

CEOCFO: ***Is there one process? If a company turns to you, depending on what they are looking for you to do, does everything get the same process or are there different levels that you offer?***
Dr. Burke: At a high level, our process is in many ways the same. There is the business side where we have to get the confidentiality agreement and service agreement in place and then execute the statement of work. We also try to be consistent in assessing which projects we accept. When we have our scope meeting, we look at their questions and their timelines and data and we assess the feasibility of the project on our end. We are not going to work on a project where we do not think we can help, whether there is just not enough data, not enough time, or that the ROI is low, for example. We want to ensure that our partners are happy with our work and our project timelines. Biology is hard. We do not want to develop an 'uber model' of 'everything' because we just will not be able to answer everyone's question in time and have confidence in our results.

At that level, our process is always the same. Beyond that, each project varies a bit since we work on various therapeutic platforms and disease indications. We tailor each statement of work, model, and analysis to our partner's timelines, needs and data that they have. Sometimes we use mechanistic PK/PD, sometimes a quantitative systems pharmacology model, sometimes a traditional PK/PD model, sometimes machine learning or statistical approaches. Due to our team's vast diversity of knowledge and experience, we bring the right math, to the right questions, on the right timelines, with good ROI.

CEOCFO: ***You mentioned your staff includes people with different disciplines. When someone comes into your organization do you scope out if they can communicate with people in the other disciplines? Is that an issue?***
Dr. Burke: Yes. Always. Communication is key not only for our success inside of Applied BioMath, but it's also important that the modeler, biologist, computer scientist, mathematician, pharmacologist, enzymologist, and our engineers communicate clearly and concisely with the vast array of disciplines on our partner's project team. To be successful, we need to translate and understand our partner's needs and project issues, which allows us to translate within their teams too. We have to be those translators, not only within Applied BioMath but also with our partners. Biology is hard enough and drug discovery is hard enough; now imagine throwing in mathematics, engineering, and computer science.

CEOCFO: ***What surprised you through the whole process of founding, developing and growing Applied BioMath?***
Dr. Burke: How much our partners really need our analyses. Almost always, our strongest antagonists become our strongest proponents within other organizations. This is always exciting.

CEOCFO: ***What is ahead or what would you like to see a year from now?***
Dr. Burke: I would like to say that in a year's time we might have forty employees, if not more. I would like to say that when you think of mechanistic PKPD modeling, when you think of quantitative systems pharmacology, or machine learning techniques applied to drug R&D, you think of Applied BioMath. We are working on very exciting therapeutics with very exciting and cutting-edge companies. I think that we're helping our partners improve or save patients' lives. All confidential. As we work with our partners, they will present our work – show how we're helping them help patients. How we're innovating drug invention in R&D –bring engineering approaches to help invent better drugs or not work on failures. I want these stories heard. In time, they will be. We are still young and growing, in our infancy, but when people think of model-aided drug invention approaches, helping our partners to develop better drugs, faster, and for less money, it would be ideal if Applied BioMath is the first thing to come to people's minds.