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Revolutionary Trojan Horse Type Platform that can Deliver Large Molecules across the Blood-Brain Barrier to Treat Severe Neurological Diseases

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"By generating a 'Trojan horse' out of our Trojan Horse antibody and the missing enzyme, we have created a next generation of ERT that treats both, the somatic disease burden and also crosses the BBB to address the cognitive disease burden. Why is this so important? As I said, now for the first time we are able to add years to the life, but also life to the years of our patients."- Dr. Mathias Schmidt, Ph.D.

CEOCFO: ***Dr. Schmidt, what is the focus for ArmaGen today?***
Dr. Schmidt: ArmaGen has developed a platform to bring biotherapeutics across the blood-brain barrier (BBB). Let me briefly tell you why this is important. Recombinant biotherapeutics, which were invented almost thirty years ago, have revolutionized the way we treat serious and life-threatening diseases. However, the last white spot in the landscape of human organs that is not addressed by biologics is the brain. The reason for that is that nature invented the BBB to prevent large molecules, including pathogens or toxic molecules, to cross the BBB and wreak havoc on the brain. What was a great invention by Mother Nature, is the most significant impediment towards exploiting biologics to address diseases with very high unmet medical needs like Alzheimer's, Parkinson's disease, multiple sclerosis, and other serious diseases affecting the brain.

CEOCFO: ***What has ArmaGen developed?***
Dr. Schmidt: ArmaGen has developed a Trojan Horse platform that can bring large molecules across the BBB. We know that there are certain receptors at the BBB that can transcytose larger molecules into the brain that are needed for physiological functions. One of those molecules is insulin. We all know that insulin is exclusively made in the pancreas, but has an important physiological role in the brain. The way that this is solved is that this molecule is bound by the insulin receptor and transcytosed from the blood circulation into the brain. ArmaGen is exploiting this very mechanism by having developed an antibody against the insulin receptor. By fusing a payload with therapeutic effector function to the antibody, we generate a therapeutic molecule that can travel across the BBB very much like insulin. Like a Trojan Horse, this fusion protein then brings the therapeutic payload into the brain.

CEOCFO: ***Does it ever worry you that you can trick the brain? How can you accomplish this? Why are we able to trick the body in different ways that are helpful?***
Dr. Schmidt: This platform and technology sounds intuitive. However, the entire pharmaceutical industry and researchers have struggled for decades to trick the human body and to trick the brain to bring large molecules across the BBB. Our Founder and Chief Scientific Officer, Dr. William (Bill) Pardridge, M.D., has basically dedicated his entire scientific career to come up with a platform solution that is applicable to almost any kind of central nervous system (CNS) disease. Importantly, it is also safe enough for human application and efficacious enough to bring a sufficient amount of the therapy across the BBB.

CEOCFO: ***What are you working on today?***
Dr. Schmidt: Although the platform is broadly applicable, ArmaGen's focus is in a disease area that is called Lysosomal Storage Diseases (LSD's): To explain this very briefly, the lysosome is the trash can of the cell that degrades and recycles

molecules that are not needed anymore. Now, there is a range of inherited monogenic diseases where some of those enzymes that degrade the “trash” are missing or not functioning properly. As a result, the substrate starts to accumulate in the lysosome. It forms inclusion bodies which have a detrimental effect on the cell and the entire human body, finally resulting in the pathology of the disease. Affected patients suffer from a variety of symptoms including enlarged spleen or liver, loss of hearing and/or vision, skeletal malformations, cardiac and lung dysfunction, and importantly, mental retardation, cognitive and motor deficits. Before the invention of enzyme replacement therapies (ERT’s), many of these patients would not have reached their second decade of life. An ERT is basically a recombinant form of the missing enzyme that is given to the patient as a weekly infusion. About 15 years ago, those ERT’s became available to patients and these therapeutics have changed the way we treat those diseases and have added many years to the lives of the patients. However, as large molecules, ERT’s do not cross the BBB. Thus, the patients are still left alone with their cognitive disease burden. This is exactly where ArmaGen kicks in: By generating a ‘Trojan horse’ out of our Trojan Horse antibody and the missing enzyme, we have created a next generation of ERT that treats both, the somatic disease burden and also crosses the BBB to address the cognitive disease burden. Why is this so important? As I said, now for the first time we are able to add years to the life, but also life to the years of our patients. Also, from the payer’s perspective, this is not an add-on therapy to an already very expensive treatment. We are talking about over $200,000 per year of treatment for such a patient. We expect that our fusion proteins will make the first generation of ERT’s obsolete.

CEOCFO: ***Where is it today in the development process?***
Dr. Schmidt: Today, our lead molecule, AGT-181, is in a Phase II clinical trial in pediatric patients. It is designed to treat children affected with MPS I or Mucopolysaccharidosis Type I (Hurler syndrome). This disease comes in various manifestations. Hurler is the most severe form and Hurler Scheie is a more attenuated form. We started safety studies in adult patients in the United States and in Brazil. In Brazil, we are already in Phase II in pediatric patients. After three and six months of treatment, we assessed their cognitive function and offered the patients to remain on the drug if they feel is it of benefit for them. Until now, all patients who have finished the six-month period stayed on the drug. Interim results were recently presented at the World Lysosomal Storage Disease Symposium in San Diego, CA, by Dr. Roberto Giugliani, principal investigator of the trial in Brazil. In short, Dr. Giugliani showed evidence that for the very first time was possible to improve the cognitive function in these patients who would otherwise cognitively decline.

CEOCFO: ***Is the medical community overall onboard with what you are doing? Do they understand the concept and what you have been able to do?***
Dr. Schmidt: Yes, very much! The interim data that Dr. Giugliani presented was received with a lot of attention and with strong encouragement from many pediatricians. We constantly reach out for feedback to the medical community and it is the pediatricians who encourage us strongly to develop this molecule as aggressively as we can. AGT-181 is one of the very few approaches that is offering a realistic hope for a change in the cognitive outcome of this disease patient population. Pediatricians know about the fate of their patients and they want to change it, and we want to be their partners. As the mother of one patient said, “hope is a terrible word until we turn hope into action.” I feel blessed working in an area where we are aligned together with parents and physicians to work toward a better tomorrow of these young and fragile patients.

CEOCFO: ***Are you seeking funding, investment, or partnerships as you continue your work?***
Dr. Schmidt: We are currently talking to investors, and aim to expand the number of existing partnerships with the pharmaceutical industry in areas in which partners have potentially promising effector molecules. An example would be a pharmaceutical company that is working on an effector molecule for the treatment of Alzheimer’s disease, but lack a technology to bring that effector molecule across the BBB. We also get approached by disease foundations or patient advocacy groups who know about our preclinical programs and who want to support them so that they become available to patients earlier.

CEOCFO: ***How do you personally deal with having something that can potentially help so many people, but it is a long arduous process to get it moving?***
Dr. Schmidt: Sometimes it is heartbreaking. Patients can’t wait and since working in this disease area, the sense of urgency has received a very different meaning to me. A mother of a child affected with another form of MPS recently told me, “I wish my child rather had cancer because with cancer there is hope. I know exactly what the prognosis of my daughter is and I know that at the age of three years she will start losing her cognitive functions and I know that she will die from the disease.” Listening to her and knowing we have a program, but cannot develop it faster due to lack of funds and resources is heartbreaking to me. The mother’s words have become one of the greatest motivating factors to us.