Dear Shareholders,

Since becoming CEO of Regulus in June of 2015, this communication marks my first annual shareholder letter. I am very pleased to summarize last year's achievements and provide you with our vision for the future, based on the exciting promise of our strategic focus and leadership in developing therapeutics that allow for control of microRNAs and their potential role in many medically important diseases.

2015 was a Pivotal Year

2015 was an important year of growth and maturation for the company, with meaningful progress made in advancing our drug discovery and development pipeline against validated microRNA targets. Most notably, with the rapid operational progression of our clinical pipeline, we finished the year with three different programs in clinical development all in important disease categories - we believe this further solidifies our leadership position in the field.

We strengthened our science and business in several meaningful ways: we filed three investigational new drug applications in the US, two clinical trial application in different counties in Europe, presented multiple key data sets at major medical meetings, realized several partner milestones with the advancement of our portfolio, and strengthened our leadership team. I am proud of the achievements accomplished by the team here at Regulus, together with the support of the consultants, advisors and investigators we work with, which have led us to our favorable position today. Regulus has a well balanced portfolio with an exciting lead program, RG-101, in development for chronic Hepatitis C (HCV) infection; an orphan disease program, RG-012 in development to treat the rare genetic kidney disease called Alport syndrome; and RG-125 which entered the clinic late last year in partnership with AstraZeneca for NASH and type 2 diabetes.

At Regulus, we are firmly focused on disease areas of high unmet medical need that represent global health problems, such as HCV. According to the CDC, up to 185 million people are chronically infected with HCV worldwide and more than 500,000 people die annually from HCV. While very important advances have been made in the medical treatment of HCV in the last several years with the introduction of orally administered direct-acting antivirals, significant opportunities remain to further advance standard-of-care to provide the potential to cure this infection on a global scale. Our lead program, RG-101, targets the HCV host factor, microRNA-122, providing a different mechanism to target the virus, which, in combination with other direct-acting antivirals, holds the potential to dramatically shorten treatment durations and improve patient compliance. We believe that RG-101 has a promising profile and may be a powerful agent in emerging combination regimens to address difficult-to-treat genotypes and to potentially expand upon the current therapies available to clinicians treating HCV patients.

RG-101's profile to date is very encouraging – it's potent, durable and pan-genotypic with compelling efficacy in combination with approved oral agents, positioning RG-101 as a potential backbone therapy in an evolving commercial landscape. We have received positive feedback and interest from leading key opinion leaders in the field who recognize the potential of novel agents such as RG-101 to address this global health issue.

We are also excited about our second program, RG-012, and its opportunity to help patients with a rare, genetic kidney disease, Alport syndrome, affecting approximately 20,000-30,000 people in the US and a similar number in Europe. In 2015, we achieved important milestones in the program through completion of the Phase 1 study and advancement of our longitudinal patient disease observational study called Athena, which aims to chronicle the kidney function decline and associated disease pathology for this disease over time. Currently, there are no approved therapies for patients with Alports, providing a significant opportunity for RG-012, if proven safe and effective.

Great Culture is at Our Core

To complement our external successes, we are focused on building a highly engaged and productive team of Regulites who work synergistically to solve complex problems. Our unique and empowering corporate culture is shaped by our four core values that we live by – integrity, teamwork, conviction and excellence, and we incorporate these values into everything that we do. Maintaining our vibrant culture is our lifeblood, and because of this, we believe that Regulus has the potential to become the next great biopharmaceutical company headquartered in San Diego.

Looking Ahead in 2016

This year, we have the critical opportunity to advance our therapeutics pipeline to multiple valuable inflection points. The development of RG-101 has been accelerated and further key clinical trials in Europe and the United States will be initiated. We also expect to report additional combination data from multiple clinical trials, and obtain clarity on a regulatory path for approval. In addition to our work with RG-101, we expect to initiate a Phase II study of RG-012 in Alport syndrome patients, which if successful, may serve as a registration study for the program. We also expect to nominate at least one new candidate for clinical development from our research portfolio. In our preclinical pipeline, we are currently working on validating multiple new microRNA targets where we believe we can develop new therapeutics in diseases of significant unmet need that represent important advancements over currently available therapeutic options.

Thank You

On behalf of the Board of Directors, the management team and all our employees, I want to thank you, our shareholders, for your continued support of Regulus and our mission. We remain steadfast in our belief that through our scientific focus and leadership, we have the potential to create high impact medicines based on microRNAs.

Paul C. Grint, M.D.
President & CEO