MISSION STATEMENT

Our mission is to educate healthcare professionals and patients on the SDHB genetic germline mutation as well as its role and impact in this orphan disease, namely **Pheochromocytoma** and **Paraganglioma** respectively…

APRIL 2022

"NEWSLETTER"

SDHB PHEOPARA COALITION

The SDHB PheoPara Coalition is a volunteer organization whose mission it is to first educate healthcare professionals and patients on the SDHB genetic germline mutation as well as its role and impact in this orphan disease.

Pheochromocytomas and Paragangliomas are neuroendocrine tumors and those patients who present with an SDHB genetic germline mutation are unfortunately associated with higher rates of malignancy.

Our goal is to focus on supporting research, which will lead to effective treatments of the SDHB form of the disease. To accomplish this objective, we conduct fundraisers as well as attempt to gain access to other potential investors so that we can provide educational and research grants to advance science in this important and underserved area. We also partner with other organizations and academia to try and learn more about the disease and what treatment options might exist that could be effective.

We have also created a website that we hope will be a resource to patients and healthcare professionals alike where they can access information on the symptoms of the disease,

the diagnosis, and the location of medical centers and doctors that can provide assistance today.

PHEOCHROMOCYTOMA / PARAGANGLIOMA

Q: What has been the impact of Covid-19 on patients?

A: The coronavirus disease (COVID-19) pandemic has caused global devastation for many patients including those with pheochromocytoma and paraganglioma. We know that those with cardiovascular diseases, diabetes, cancer, immunodeficiencies, and respiratory disorders are more likely to suffer from severe COVID-19 illness.

Interestingly, many of the above-mentioned health-related problems are present in patients with pheochromocytoma and paraganglioma. It is well known that most of these tumors regardless of metastatic status, produce and secrete catecholamines, particularly epinephrine and norepinephrine. Both epinephrine and norepinephrine act through adrenoceptors located on almost all organs and tissues of the human body. Pheochromocytomas (rarely paragangliomas) that secrete epinephrine can cause tachyarrhythmia and other heart performance disturbances. On the other hand, norepinephrine-secreting tumors can cause hypertension. Overall, nearly 90% of these patients have hypertension (sustained or episodic) and many of them have tachycardia. Chronically elevated catecholamines can lead to deleterious remodeling of coronary, cerebrovascular, and other organ-related arteries, predisposing a patient to stroke, myocardial infarction, and microvascular ischemia in setting of superimposed hemodynamic stressors (often caused by episodic tumoral catecholamine release). Furthermore, chronic hypertension can lead to myocardial thickening, eventual heart failure or cardiomyopathy. Given that catecholamines decrease insulin release (via adrenoceptors,), some patients present with hyperglycemia or diabetes and may require insulin treatment. As previously described, hyperglycemia is associated with impaired immune cell function responsible for fighting infections (including COVID-19). Furthermore, immunosuppression is present in all oncology patients, especially in those with metastatic disease. Respiratory problems are common for patients with multiple and/or large lung metastatic lesions. Chronic elevation of catecholamines can also cause vasoconstriction of blood vessels that supply the lungs, further exacerbating lung hypoxemia. Therefore, the presence of any catecholamine-producing and secreting pheochromocytoma or paraganglioma is a rare yet important example of how a patient with these tumors are more susceptible to severe COVID-19 illness.

For the reasons outlined above, it is pertinent that patients with pheochromocytoma or paraganglioma take measures to avoid contracting COVID-19. These measures include wearing protective face masks and respirators, being up to date on vaccinations and boosters, and taking care of their overall health in terms of diet, stress, and exercise.

Pharmacologic treatment of patients with pheochromocytoma or paraganglioma is based on the inhibition of alpha or beta-adrenoceptors to counteract the deleterious effects of catecholamines on many organ systems. Alpha-adrenoceptor blockers (e.g., doxazosin, phenoxybenzamine) are the drug of choice for patients who present with hypertension and vasoconstriction of vessels supplying vital organs (heart, kidneys, or intestines). Beta-adrenoceptor blockers are the drug of choice for patients who present with tachyarrhythmia (most commonly sinus tachycardia). The administration of both alpha- and beta-adrenoceptor blockers should optimize blood pressure (less than 130/90) and heart rate (less than 80). These target values might not be possible in all patients, however, efforts to reach the recommended values should be attempted. Furthermore, since catecholamines increase blood glucose levels, avoidance of inappropriate sugar intake is strongly advised. Optimal or near optimal glycemic control should be attempted with close monitoring of blood glucose levels at home and use of anti-hyperglycemic agents and insulin if prescribed by a physician. All patients with these tumors should be well hydrated (1-2 liters a day) and to have adequate salt intake. Low intensity exercise (such as walking) is recommended whereas high intensity exercise (strenuous biking or running) is contraindicated (due to its effects on catecholamine levels).

Continuing to follow COVID-19 precautions, maintaining a healthy lifestyle, and using appropriate pharmacologic medications will undoubtedly result in better health-related outcomes in patients with pheochromocytoma and paraganglioma. In conclusion, patients with pheochromocytoma and paraganglioma are at greater risk for COVID-19 related morbidity and mortality due to chronically elevated catecholamine levels, which directly correlate to the comorbidities and risk factors that have been well-studied in the development of severe COVID-19 illness.

Reference:

Gubbi, S., Nazari, M.A., Taieb, D., Klubo-Gwiezdzinska, J., Pacak, K. Lancet Diabetes Endocrinol. 2020; 12:978.

The comments shared above are kindly provided by Karel Pacak, MD, PhD, DSc., at NIH in Bethesda, MD…

PRESIDENTS REPORT - 2021

I would like to begin my remarks by acknowledging the many challenges that we have faced in 2020 and 2021 respectively due to Covid-19. The SDHB Coalition like so many other small companies and organizations has been significantly impacted in this regard. Despite these hurdles, our board has continued to work hard to spread the word about this orphan disease by using and updating various communication vehicles including social media and our website to help achieve our communications

objectives. Unfortunately, we were unable to hold our successful annual fundraising galas in both 2020 and 2021. This has clearly put a strain on our financial resources but, we were still able to leverage our resources and fund limited research to better understand this disease, the role of the SDHB germline mutation, and its impact on patients and their prognosis. One of our objectives as an organization is to act as a catalyst to find ways to address this disease, and hopefully find effective treatments in the future.

During 2020 and 2021, we have supported the following research activities:

At the **University of Alabama**, we continue to support the research scientist-surgical oncologist team who are studying SDHB signaling mechanisms that drive pheochromocytoma and paraganglioma. UOA have produced very promising results so far and we can highlight several areas of interest. First and very importantly, they have advanced the study of pheochromocytoma and now are revising an important manuscript for a high impact journal that shows a major advance in understanding the causes and identifying new treatment approaches. Furthermore, they have also identified research on how SDHB mutations alter metabolism, mitochondrial dynamics and identified tumorigenic signaling mechanisms consistent with their original scientific hypothesis. In addition, they have also developed novel animal mouse models of the disease, are identifying new diagnostic biomarkers, and are testing new targeted drug therapies with the goal of moving effective treatments to clinical trials. Finally, they have identified improved drug delivery systems using biomimetic nanoparticles with higher efficiency and lower toxicity. This excellent progress in the last year will be the subject of new publications in 2022 and beyond.

At the **University of Columbia**, we continue to support the establishment of a PC/PG registry, comparing gene expression profiles following exposure to epigenetic agents with controls, and evaluating the cytotoxicity of agents that alter gene expression. In addition, Columbia is also working on methylation profiling in patients and relatives. Importantly, good progress is being made especially with registry and this continues to be ongoing.

In 2020, we approved new funding for a project at the **University of Melbourne** in Australia with an objective of identifying changes in the genes that regulate cell behavior to better understand what initiates the process of spreading to distant sites and to identify precision treatments for patients. This study continued in 2021 and we are working closely with the architects on their findings.

Furthermore in 2020, we agreed to support a project at the **University of Florida** that will perform large scale metabolic analysis on an outstanding set of 50 novel PCC/PGL frozen tumor samples to interrogate the consequences of alterations in the SDHB cascade and identify perturbed metabolic pathways. This will enable scientists to better understand the metabolism in the PCC/PGL cells. In 2020 and 2021 the work continued; however, it was decided that they needed to expand the number

of fresh frozen samples to 100, which they did. A more comprehensive metabolomics is currently being performed to assess the extent to which the polyamine pathway is upregulated in SDHB mutated tumors. Potentially targeting the polyamine pathway is important because cells are not able to survive without this pathway. This study was delayed due to Covid and is continuing now into 2022 to initiate experiments to test polyamine inhibitors both in vitro and in vivo.

Another Research initiative that we started in 2019 in combination with the Pheo Para Alliance and the Paradifference Foundation is an agreement with the **Broad Institute of MIT and Harvard** to develop a Pheochromocytoma and Paraganglioma tumor dependency map. This project was designed to be three-year project and so we are 2 ½ years in. The idea was to collects tumor samples and hopefully develop possible drug repurposing opportunities that will be effective against these rare tumors. This study started but encountered delays due to COVID 19. In the upcoming months, they will continue to further evaluate collected samples. However, this is a very challenging mission because there is no PCPG cancer cell line in the world yet. That has not deterred the Broad institute as they continue to iterate model derivation strategies that might enrich the pheo/para tumor cell growth that is needed to move the project forward.

Regarding **communications** and our goal to **increase awareness**, we have created new Facebook, Instagram and LinkedIn accounts / pages and started adding new content and infographics that can be used on monthly basis or as needed to update the social media platforms. We are also sending out email blasts via Mailchimp to our target audience to ensure useful and timely information is being disseminated to our many sponsors, contributors and donors. As a result of these outreach efforts, we are receiving individual donations through Facebook and Instagram respectively. We continue to share and distribute “YouTube” videos that describe the disease in detail for both healthcare professionals and patients and have posted them on our website. In fact, we have just produced several smaller educational vignettes that are being shared on our website and other social media program platforms. In addition, we have developed a one-page informational leaflet that describes the symptoms and treatments available for the disease which is available online. We are also in the process of updating our newsletter which provides a wealth of good information which we hope can be helpful to both patients and healthcare professionals alike.

Our objectives for 2022 are as follows:

1. To continue to spread the word about the existence of the SDHB PheoPara Coalition, and to fulfill our stated mission. We expect to hold our first virtual gala on April 28th, 2022.

2. We want to look at adding additional board members who can serve in the future and provide ongoing continuity for the Coalition. We will also review our committees and see if we can identify

more volunteers who would like to serve. In 2021, we added two new members to our subcommittees who we believe have the potential to hold board positions in the future.

3. To support at least 1 or 2 good and new SDHB scientific projects which will lead to a better understanding of the role of the SDHB germline mutation in this disease and effective treatments.

4. To finalize our marketing plan and start implementation with the objective of increasing brand awareness of SDHB Pheo Para Coalition and the SDHB germline mutation as well as its role and impact in this orphan disease. And to raise money from different sources to support treatments that can help treat this disease. The marketing plan has been updated and is ready for implementation during 2022.

5. Continue to look at social media opportunities which will allow us to spread the word to different audiences.

SDHB PHEO-PARA COALITION ANNUAL GALA - 2022

The SDHB PheoPara Coalition will hold its annual gala on April 28, 2022 as a **"VIRTUAL"** event.

The annual fundraising gala was cancelled in 2020 and 2021 due to Covid. This has had a significant impact on our financial resources but we still have been able to support some key research projects .

SPONSORS / CONTRIBUTORS OF THE SDHB PHEO-PARA COALITION ANNUAL GALA – 2020/2021/2022

Diamond:
Progenics / Lantheus
Havas Health
Citius Pharmaceuticals

Platinum:
Orexo US, Inc.
Clarion Healthcare
Joseph Papa / Bausch Health
Tim & Joanne Rothwell
Prasco

Gold:
Zeus Scientific
Ferring Pharmaceuticals

Silver:
Sanofi

Eisai
ProMIS Neurosciences

Bronze:
Fred & Noreen Hassan

Crystal:
Goran Ando
Radius Health
Almirall
Amgen
Frank's Big & Tall Men's Shop, Inc.
Gary & Dawn Bernstein
New Jersey Risk Managers
Nick & Ellie Colucci
Rutgers Cancer Institute
Robert & Anne Essner
Hugh O'Neill

Patron:
Anthony Greco
Greg & Nancy Irace
Thomas Scientific
Nick & Debi Rothwell
Lithan Networks
Pollock Brothers
Susan Esposito
Michael Evanisko
Carl Sailer
Jim & Patsy Meisterich
Judy O'Hagan
Jill DeSimone
Bhavesh Ashar
Hendry Construction Services
Nova Rose Special Events
Xiaokui Zhang
Shabnam Kazmi

WHY ARE WE FOCUSED ON THE SDHB GENE?

Patients who present with an SDHB genetic germline mutation are unfortunately associated with higher rates of malignancy. Furthermore, there are no cures for this disease and the treatments are

inadequate. Today, we lack effective chemotherapeutic and radiation therapies that can give these patients hope and help them survive this orphan disease.

Pheochromocytoma and Paraganglioma represent a significant health problem. Patients with these conditions not only face the symptoms caused by the overproduction of catecholamine's, but they also run the risk of recurrence or metastatic spread even after successful surgery for the primary tumor. This is especially true with inherited conditions such as the SDHB gene mutations.

Patients with SDHB genetic mutations face more challenges than those who develop sporadic pheochromocytoma or paraganglioma. Tumors are more likely to be multi-focal and are more likely to occur at a young age. For patients with SDHB mutations, the risk for recurrence or metastatic spread is much higher than for sporadic patients or for patients with other inherited forms of the disease.

At present, surgery remains the only truly effective means of managing SDHB patients. Multiple surgeries over one's lifetime are the rule rather than the exception for these patients. While progress has been made in understanding the molecular pathways involved in the development of these tumors, we still lack the critical models necessary to accelerate the development of effective systemic treatment for these tumors when they recur or spread to distant sites.

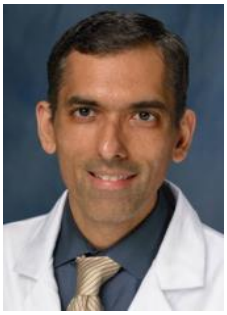
THE SDHB PHEOPARA COALITION "HALL OF FAME"…

PAST RECIPIENTS AND HONOREES…

Awardees of The SDHB PheoPara Coaliton Science Award – 2019
(Note: Awards actually received by recipients in 2022 due to Covid-19 delays…)

James Bibb received bachelor's and master's degrees with honors from Murray State Univ. and the Univ. of Kentucky respectively before completing his doctorate in Cellular and Developmental Biology at the State Univ. of New York at Stony Brook. His doctoral thesis characterized the poliovirus receptor protein in Eckard Wimmer's laboratory. Dr. Bibb's postdoctoral training was conducted in the Laboratory on Molecular and Cellular Neuroscience at the Rockefeller Univ. under the direction of Paul Greengard. His work on the regulation of dopamine neurotransmission was cited in the Nobel Prize in Physiology for Medicine in 2000. Dr. Bibb became a tenured full professor in 2014, has over 90 publications. He is Professor and Vice Chair of Research and the Champ Lyons Endowed Chair

for General Surgery and appointed faculty in the Departments of Neurobiology, Neurology, the UAB Comprehensive Cancer Center. Dr. Bibb's lab has approached the problem of neuroendocrine cancers from a neurobiology perspective. Research on brain injury led him to the realization that mechanisms of synaptic plasticity and neuronal metabolism overlap with mechanisms that cause neuroendocrine (NE) cancers. Combining Dr. Bibb's expertise in signal transduction with outstanding clinical expertise is leading to important advances in understanding the causes of pheochromocytoma and paraganglioma and, hopefully, new treatments to NE cancer patients.



Dr Hans Gayee completed his Doctor of Osteopathic Medicine degree at the University of North Texas Health Science Center at Fort Worth. He later trained at the Johns Hopkins University/Sinai Hospital Internal Medicine program for his internship and residency. Dr. Ghayee then pursued his fellowship training in Endocrinology & Metabolism at the University of Texas Southwestern Medical Center (UTSW) at Dallas. While at UTSW, he was Chief Fellow and later joined as faculty. As a faculty member, he was awarded the prestigious "Daniel Foster, MD Clinical Teaching Award" by the UTSW endocrine fellows in 2012 and 2014. In 2015, he was recruited to the University of Florida (UF) to become the Director of Endocrine Neoplasia and Chief of Endocrinology & Metabolism at the Malcom Randall VA Medical Center. Dr. Ghayee was recognized with the "Outstanding Faculty in Endocrinology Award" at UF in 2018. Besides clinical care, teaching, and administrative duties, Dr. Ghayee also runs a translational research laboratory. His research focuses on understanding pathways that drive pheochromocytoma/paraganglioma growth and differentiation. He has actively been involved in studying metabolism of pheochromocytoma/paraganglioma particularly in *SDHB* mutated cells. Dr. Ghayee continues to be inspired by his patients to find ways to bring novel treatment strategies from the bench back to the bedside.

Recipients of The SDHB PheoPara Coalition Leadership Award - 2019

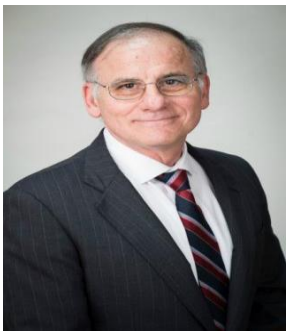
Scott Tourville joined ZEUS Scientific in 1987. Since acquiring the company with his brother John in 1998, he has focused on transforming ZEUS into an industry-leading *in vitro* diagnostics company through organic growth, licensing arrangements, and acquisition. Scott has established successful strategic partnerships and relationships with other leading companies to provide complete diagnostics solutions, including reagents, instrumentation, and automation for the clinical diagnostic market. Previously Scott was ZEUS' VP of finance and controller; prior to that he worked as an accountant for Matsushita Electric Corporation (now Panasonic). He earned a bachelor's degree in accounting from Lycoming College and has earned his CFP® certification through the Certified Financial Planner Board of Standards.

Robert DeLuca joined OREXO US as President in May,2013. During his nine-year tenure he has led the U.S. company from its inception and is responsible for commercializing Orexo's first product, Zubsolv, in the opioid use disorder treatment category. He has more than 30 years of industry experience at several multinational pharmaceutical companies and brings to OREXO a demonstrated track record of success in the pharmaceutical industry. He has extensive executive leadership experience with a combined background in global commercial operations, marketing, market access and sales. Additionally, he is considered a commercial leader especially in the Market Access and Value-based disciplines. He has progressed through senior roles of increasing responsibility at Schering Plough, Berlex, Pharmacia and Sanofi.

Robert is a New Jersey licensed pharmacist and graduated from St. John's University in New York City. He practiced retail pharmacy for three years post licensure prior to entering the corporate arena. DeLuca is a co-chair of the SDHB PheoPara Coalition Gala for the past 10 years and also has

memberships in the Academy of Managed Care Pharmacy (AMCP) and the American Pharmacists Association.

Awardees of The SDHB PheoPara Coaliton Science Award - 2018



Antonio Tito Fojo MD., PhD – Professor of Medicine at CUMC, Co-Director Adrenal Center, Columbia University. During his time at the National Cancer Institute, Dr. Fojo established a highly successful research program that began by exploring agents to reverse drug resistance and evolved to understanding its molecular basis. He identified rearrangements of the MDR-1 gene as a novel mechanism of drug resistance in several cancers, a molecular event recently demonstrated as being very important in ovarian cancer. He has also been involved in research on microtubule-targeting agents, establishing interference with microtubule trafficking, rather than mitosis, as the mechanism of action for these important drugs. All of this evolved into a focus on the origins of endocrine cancers including pheochromocytomas and paragangliomas and the development of therapies for endocrine and neuroendocrine malignancies.

Steven K. Libutti, MD., FACS – Director of Rutgers Cancer Institute of New Jersey and Vice Chancellor for Cancer programs, Rutgers Biomedical and Health Sciences. Dr. Libutti also serves as Senior Vice President of Oncology Services for RWJBarnabas Health and is a tenured Professor of Surgery at Rutgers Robert Wood Johnson Medical School. Dr. Libutti's research focuses on developing novel cancer therapies through an understanding of the tumor microenvironment. His work also focuses on a better understanding of the tumor suppressor genes . Dr. Libutti is a leader in regional cancer therapy, the management of endocrine tumors and tumor targeted gene therapy.

Recipients of The SDHB PheoPara Coalition Leadership Award - 2018

Leonard L. Mazur – Chairman Citius Pharmaceuticals, Inc**.** Mr. Mazur is an entrepreneur and pharmaceutical industry executive. Presently, he is the Executive Chairman of Citius Pharmaceuticals, Inc. Mr. Mazur serves as Chairman of the Board of Trustees at Manor College and is a member of the Board of visitors for Temple University's College of Liberal Arts. He is the co-founder of Akrimax Pharmaceuticals, LLC, a privately held pharmaceutical company specializing in producing cardiovascular and general pharmaceutical products.

Awardees of The SDHB PheoPara Coaliton Science Award – 2017

Karel Pacak,MD,PhD,DSc, FACE - Chief of the Section of Medical Neuroendocrinology NICHD at the NIH**.** Dr. Pacak is a board-certified endocrinologist as well as the current and tenured Chief of the Section on Medical Neuroendocrinology of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the National Institues of Health (NIH) IN Bethesda, MD. He heads the Pheochromocytoma and Paraganglioma Program at NICHD/NIH. He established one of the most productive, internationally recognized and patient oriented research programs and has devoted his scientific career to clinical and translational research in these tumors. Dr. Pacak, together with his colleages and collaborators, introduced a novel biochemical test – measurement of plasma free metanephrines – that was clinically incorporated into the diagnosis of pheochromocytoma; a novel clonidine suppression test; and new reference ranges for plasma free metanephrines in pediatric patients. Furthermore, he introduced a new nuclear imaging method into the diagnostic localization of pheochromcytoma and a "flip-flop" theory in the functional imaging of SDHB – related pheochromocytoma using (18F)-FDG PET scanning.

Katherine L. Nathanson, MD - Professor of Medicine, in the Division of Translational Medicine and Human Genetics,at the Perelman School of Medicine of the University of Pennsylvania. She also serves as the Deputy Director of the Abramson Cancer Center. Dr. Nathanson is one of the first physicians in the country to offer clinical genetic testing for patients with pheochromocytomas and paragangliomas . Dr.Nathanson clinically cares for patients with inherited susceptibility to these diseases. She is conducting research into the somatic (tumor – specific) mutations in pheochromocytomas and paragangliomas, co-leading the cancer Genome Atlas effort.

Recipients of The SDHB PheoPara Coalition Leadership Award - 2017

Joseph Papa – Chairman of the Board, Chief Executive Officer Bausch & Lomb. Mr. Papa has been serving on the Board since May 2016. He has more than 35 years of experience in the pharmaceutical healthcare and specialty pharmaceutical industries, including 20 years of branded prescription drug experience. Mr. Papa has led and been in leadership roles for a number of major companies within the pharmaceutical industry that include Perrigo, Watson, Pharmacia, Searle and Novartis to name a few. His long-term commitment and leadership within the industry and continued support of the SDHB Coalition make him a deserving recipient of this award.

Goran A. Ando, MD – Former Chairman of the Board of Novo Nordisk. Goran Ando joined EW Healthcare Partners in 2007 as a Senior Advisor. Dr. Ando brings to EW Health Partners 35 years of experience as one of the most experienced and respected leaders in the global pharmaceutical industry. Dr Ando served as Chairman of the Board of Novo Nordisk, a global pharmaceutical company with $100 billion market capitalization until April 2018. Dr. Ando began his career in 1978 and has provided leadership to companies such as Pfizer, Bristol-Myers, Glaxo and Pharmacia. Most people who have served in the pharmaceutical industry are aware of Dr. Ando's accomplishments and commitment to the industry as a whole and he is undoubtedly a very deserving recipient of this award.

Awardees of The SDHB PheoPara Coaliton Science Award – 2016

James Lee, MD – Chief of Endocrine Surgery at Columbia University, the Medical Director of the NY Presbyterian Hospital Endocrine Service Line, Vice Chair of New Media, and Co-Director of the Thyroid, Parathyroid and Adrenal Centers. Dr. Lee's accomplishments and achievements are too many to share in this space, suffice to say that he is a dedicated and highly respected professional who actively participates in and supports our cause and we are very appreciative of his efforts in this regard.

SDHB PHEOPARA COALITION --- BOARD (OFFICERS & DIRECTORS)

Timothy Rothwell,
President

Xiaokui Zhang, Ph.D.,
Vice President

Tiffany Hendry,
Secretary

Nicholas Rothwell
VP & Treasurer

David (Rick) Keefer,
Board Director

Sheila Buchbinder, MD
Board Director

Curtis Quigley,
Board Director

CONTACT US:

The SDHB PheoPara Coalition
3943 Greystone Drive
Doylestown, PA 18902
Email: info@sdhbcoalition.org
Website: www.sdhbcoalition.org

THE SDHB PHEOPARA COALITION

is a 501(c)(3) not-for-profit organization…

Your contribution and support are greatly appreciated. Please click on link below to make a donation…

"DONATE HERE…"