

The EHE Foundation (USA)
The EHE Rare Cancer Charity (UK)
The EHE Rare Cancer Foundation (Australia)
EHE Italia - Non solo Laura
EHE Canada



Quarterly Newsletter for the EHE Group
July - September 2021

the pledge

Edition 26



Welcome

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Welcome to our third quarter, 2021 edition of “**The Pledge**”, the quarterly newsletter of the EHE Group. We are excited by the levels of activity and interest we are seeing post the COVID19 pandemic.

Patient support and advocacy activities continue to expand; research is back up and running, with new projects being approved for funding; and our supporters are once again driving fundraising for EHE research. We have included updates covering all these areas in this edition, which we hope you will enjoy. Of course, as always, we also want to say a huge thank you to all our supporters for their contributions. **“Just Live”**.



Highlights

The 2022 EHE 360 Conference is taking shape

Following the success of the 2021 EHE 360 International Conference, The EHE Foundation is currently finalising arrangements for the 2022 EHE 360 conference which will take place in January next year! More information about this event can be found in this newsletter. Registration for the conference will be opening very soon, so please watch out for the announcement.

Two new EHE research projects approved

The EHE Foundation in the US completed its 2021 'call for research proposals' during the third quarter. Two new projects were accepted and will be funded by The EHE Foundation, with funding contributions also provided by The EHE Rare Cancer Foundation Australia.

European strategy progressing

The EHE Rare Cancer Charity (UK) became a full member of both SPAEN (Sarcoma Patients EuroNet) and EURORDIS (Rare Diseases Europe). The charity is now working with these organisations to build a European-wide EHE community network, including patients, clinicians and researchers.

Dr Stacchiotti joins UK Advisory Board

Following her wonderful work chairing the ESMO EHE Consensus Paper process through the end of 2020 and the start of 2021, The EHE Rare Cancer Charity (UK) is thrilled that Dr Stacchiotti has accepted the charity's invitation to join its own Advisory Board.

Fundraising favourites once again huge successes

After the trials of the COVID19 pandemic, we have been so pleased to see our supporters returning in force to raise funds for EHE research. The EHE Foundations 2021 EHE Fun Run and Walk, and the London Landmarks Half Marathon in the UK, have both proved to be hugely successful.

Kimberly's 'Keep Fighting' shirts honour EHE patients

Kimberly Young's 'Keep fighting' shirts, in honor of many EHE patients, with their names on the back, have also been hugely popular and deliver a powerful and heart-felt message of support.

Further details on these stories, and much more, can be found in this edition

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01 Patient Support and Advocacy

The EHE Group's patient support is provided through its worldwide Facebook page which connects with over 2,100 people across the globe, as well as more local social media platforms.

Our global page, driven by the tireless energy and contribution of so many of our members, most of whom are EHE patients themselves, continues to inspire and support our worldwide EHE community. It is this community that continues to warmly welcome and compassionately support anyone diagnosed with EHE, wherever they may live. It is also for this community that our EHE foundations work so hard to deliver increased awareness of EHE while striving to create ever-greater support and connectivity for our members. We thank all our supporters who have contributed to this critical part of our activity, examples of which are provided in this section.

Save the Date for the 2022 EHE 360 International Conference!

Building on the momentum and research progress success stemming from the inaugural 2021 EHE 360 Conference, The EHE Foundation is hard at work organizing the 2nd EHE 360 International Conference to be held on January 28 & 29, 2022. Please mark your calendars and join us for this two-day virtual event bringing together researchers, clinicians, patients, and advocates from around the world to advance the fight for treatments and a cure for EHE. Registration will be opening soon – sign up here to receive updates and registration information, or go to The EHE Foundation website at www.fightthehe.com. Here are further details on this virtual event:

Friday, January 28th
EHE Scientific Symposium
for Researchers & Clinicians

Friday, January 29th
Global EHE Patient Conference
for Patients, Clinicians, Researchers, and Advocates

European patient initiative growing

A key part of our patient support and advocacy programme is to engage with as many EHE patients as we can globally through our existing non-profit organisations. In Europe this campaign is being led by the EHE Rare Cancer Charity (EHERCC), and we hope will also be supported by our new Italian foundation “Associazione EHE Italia - Non Solo Laura”. Mariana Coutinho, European Coordinator for the EHERCC explained:

“The EHERCC is UK-based but also Europe-focused. Our goal is to establish a network of European patients so that we can ensure as many as possible have access to the knowledge, experience and information available from our global community, while also allowing us to share and engage with them on issues such as EHE studies, clinical trials, registries etc. This way they will be fully involved in all such initiatives while we will secure larger amounts of valuable data.”

The Charity is now joining three major European sarcoma and rare disease patient-representative organisations as part of its European strategy. Memberships of SPAEN (Sarcoma Patients EuroNet) and EURORDIS (Rare Diseases Europe) have been completed, while membership of ECPC (European Cancer Patient Coalition) is being finalised. Mariana continued:



“These established European bodies already have European engagement and reach, and we believe will be able to assist us. Hugh Leonard and I had our first call with SPAEN just this week to explain our objectives and found them to be super helpful and informative. They have offered to circulate a message from the Charity to all their European patient contacts to help us reach out to EHE patients everywhere. We are so grateful for this assistance.”

This patient initiative is also being run in parallel with a similar strategy to identify and create a network of sarcoma/EHE experienced clinicians across Europe. SPAEN have also offered to circulate a message from the Charity to their database of European sarcoma and general cancer clinicians. Hugh Leonard, Chair of Trustees of EHERCC, said:

“The Charity wants ultimately to have a comprehensive list of contacts for EHE experienced doctors and specialists in each European country. That way we can help new EHE patients get to the appropriate doctors, while at the same time we can keep these doctors informed about our EHE research and patient registries etc so that we maintain their interest in EHE. This also fits well with exciting discussions we are having with key European institutes about collaborative EHE research. Ultimately the whole idea of European-wide activities is already established through the EU and European-wide groups like Eurocan and ESMO.”

01 Patient Support and Advocacy

Running to Honor Others with EHE

Kimberly Young was just diagnosed with EHE in March and has already created a much needed awareness, fundraising, and unity within the EHE worldwide community. First, she won a design competition, which we shared in the previous edition of The Pledge. This time we applaud her for her **Just Live-Keep Fighting** T-shirt, which she designed to wear as she ran the Maine Marathon in October.

The concept is simple. The front of the shirt has a clear and powerful message to **keep fighting** and **Just Live**, the EHE community's motto. The back of the shirt is a list of submitted names, which Kim described:



“I plan to run in honor of our fight against EHE. I would love to have a t-shirt made with the names of fighters, survivors, and those we’ve lost to EHE, printed on the back of it to wear during the race. This is my first ever marathon and there is no stronger group of people that I would want to ‘have my back’ as I push through. A small 4-hour struggle on my part pales in comparison to what so many of you have gone through and continue to fight on a daily basis.”

Kimberly sold a stunning 109 shirts and raised \$1,200 for The EHE Foundation (US). She said:

“This donation is made in honor of everyone whose name graces the back!”

Kimberly also provided the design artwork to Samantha Parsons Hutton in Australia and Hugh Leonard in the UK, both of whom are working on printing the shirts locally. Kimberly is also working on producing a second edition of the shirt in the future as she knows some people were too late to include the names this time, but they will have the chance on the next version.

We wish Kimberly every success as she prepares for her race in October. We are grateful for her ongoing commitment to making a difference in our EHE community.

EHE at the Olympics

An important theme, that many of our members often come back to, is that life does go on despite an EHE diagnosis. They don't want their cancer to define them, nor control their lives. It is a message that is at the core of our **Just Live** motto. So we are delighted when EHE patients post stories, not about their EHE, but about challenges and achievements in their ongoing lives. Rosemary Collins from Australia surprised us all with just such a message with her wonderful post from Tokyo.



“Today, some good news to share. Next month it will be 10 years since I was diagnosed with EHE after years of misdiagnosis. Today I will umpire the final two medal races for the last sailing events of the Tokyo 2020 Olympics. I started officiating sailing because I was unable to compete for over a year whilst recovering from my first EHE surgery. Since then, I have officiated at high profile events like world championships around the world. For the past two weeks I have been a judge and umpire at the Olympics. It has been an incredible experience. I try to find the positives wherever possible. The Olympics is my silver lining.”

Congratulations Rosemary on such a wonderful achievement. **Just Live** indeed, or maybe in this case it should be **Just Sail**.

Mariana Coutinho takes on new role

As the EHERCC launched its European strategy, it quickly became clear that the charity needed some additional help to enable it to efficiently deliver this programme. The charity had no hesitation in reaching out to one of the EHE Group's existing European members, Mariana Coutinho, to see if she would be interested. Hugh Leonard commented:

“We were so pleased when Mariana said she would love to take on the role of European Coordinator for us. She has already established a great profile within European cancer circles, and is a wonderful advocate not only for the EHERCC, but for EHE patients everywhere. We are looking forward to working together as we build our European presence.”



Mariana is a Clinical and Health Psychologist. After her EHE diagnosis, in 2016, she became a patient advocate and joined several patient groups and organisations who work to improve the lives of those living with cancer. She has a special interest in the topic of cross-border healthcare and has contributed with her perspective on a political level, by attending meetings with decision makers and a public hearing at the European Parliament where she brought attention to the importance of making cross-border healthcare more accessible to cancer patients, especially those living with a rare cancer. She was part of the Rare 2030 Project (lead by EURORDIS) where together with other young patient advocates, she worked on the development of policy recommendations around rare disease policy in Europe. She is a member of the Steering Committee of Youth Cancer Europe where she also works as a researcher. She recently joined the EORTC Quality of Life Group as a Patient Expert. Mariana was born in Portugal, where she currently lives, and has received cancer treatment in the UK.

01 Patient Support and Advocacy

Sarcoma Awareness Month

July was Sarcoma Awareness Month and The EHE Foundation took the opportunity to spread awareness of EHE.

“July is Sarcoma Awareness month. Sarcomas are cancers that arise from the cells that hold the body together. These could be cells related to muscles, nerves, bones, fat, tendons, cartilage, or other forms of **“connective tissues.”** There are hundreds of different kinds of sarcomas, which come from different kinds of cells. EHE is a rare vascular sarcoma that originates in the cells that line blood vessels. Help us spread awareness about EHE and Sarcoma!”



We will continue to use every opportunity we can to spread awareness of EHE, and sarcoma more generally, as we work to find new treatments to combat and ultimately defeat EHE.

Dr Stacchiotti joins UK Advisory Board



Hugh Leonard was delighted to be able to confirm that Dr Silvia Stacchiotti had agreed to join the Research and Medical Advisory Board (RMAB) of the EHE Rare Cancer Charity (UK). The Advisory Boards of our different EHE foundations fulfil a critical role as they provide the research and medical expertise to support the Trustees and Directors. This is particularly important when the foundations are considering grant applications, as well as the strategy with regard to key areas of EHE research that we need to encourage and promote. Hugh Leonard commented:

“Of course Dr Stacchiotti is already well known to many of you. She has always been a champion of EHE research and clinical improvement. Dr Stacchiotti was a leading proponent of the use of Sirolimus in the treatment of EHE. Many of you will also remember that it was under Dr Stacchiotti’s guidance that ESMO (the European Society of Medical Oncology) undertook its EHE consensus meeting in December 2020.”

The meeting, with its goal being the “Development of the Consensus and Guidelines for EHE Treatment”, and chaired by Dr Stacchiotti, brought together over 90 EHE clinical and research specialists from across Europe, but also from the USA, Japan, India and other international centres. The resultant consensus paper was the first such document for EHE, and will form the foundation for future ongoing development of guidelines relating to EHE. Dr Stacchiotti has also been a member of the Advisory Board of The EHE Foundation in the USA for a number of years. Hugh went on:

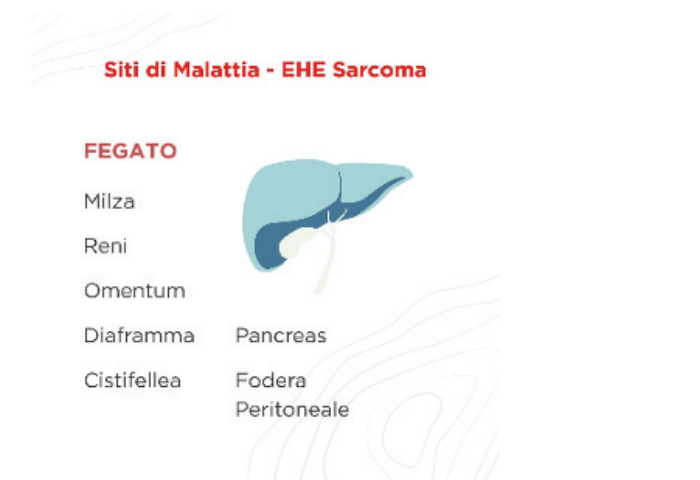
“We are so grateful, and very lucky indeed, that Dr Stacchiotti has agreed to join our UK charity as well. We welcome her and look forward to working with her as we seek to build a greater clinical and EHE focus across Europe.”

EHE Italia - Non Solo Laura

In the first half of 2021 we were able to report on the great news that our EHE community in Italy had established and launched an Italian foundation, ‘**EHE Italia - Non Solo Laura**’. This quarter saw the Italian foundation publishing further materials to explain not only their objectives, but also the facts about EHE.



Congratulations EHE Italia on continuing to promote your EHE plans and expanding awareness of this disease.



02 EHE Research

Our existing EHE research continues to produce exiting results. At the same time we continue to see a pipeline of new EHE proposals seeking funding and support. This leaves us excited by the potential of our research activity to deliver improvements in the care and treatment available for EHE patients everywhere. We hope that you also will find the research articles in this edition both inspiring and exciting.

2022 EHE 360 International Conference Update

In our previous edition of The Pledge, we were delighted to be able to report, after the success of the 2021 EHE 360 International Conference, that the 2022 event will take place on January 28th and 29th next year. Each of the two days will have a different audience focus, as follows.

Friday, January 28th
Researchers & Clinicians

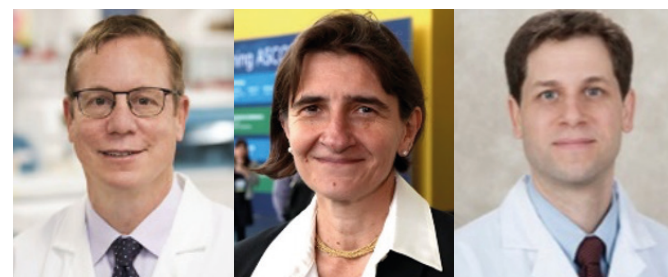
Friday, January 29th
Patients, Clinicians, Researchers and Advocates

Please save these dates for what will be another amazing occasion. This two-day, ground-breaking virtual event will bring together researchers, clinicians, patients and advocates to share information, openly collaborate, and advance the fight for effective treatments and a cure for Epithelioid Hemangioendothelioma (EHE). There will be no charge to attend the conference, but pre-registration will be required.

Registration will be opening shortly, so watch for the notifications in the near future.

Building on the important research and clinical management updates presented at the 2021 conference, the **2022 EHE 360** event will expand to include programming recognizing important EHE patient and caregiver needs and concerns. We can also confirm that an exciting group of research and clinical specialists have already committed to speak during the conference, so we hope you can make it.

The EHE Foundation is also honored to announce the **2022 EHE 360** International Conference Co-Chairs:



Brian Rubin
M.D Ph.D.

Silvia Stacchiotti
M.D.

Bill Tap
M.D.

EHE 360 is organized by The EHE Foundation as part of a patient-led research network, in collaboration with the EHE Rare Cancer Charity (UK), the EHE Rare Cancer Foundation Australia, key global patient advocacy groups, and our medical and industry partners. The EHE Foundation wants to thank their generous donors, volunteers and the support of the CZI Rare As One Project.

Manchester PhD continues

In our last edition of The Pledge, we reported on the progress made by Emily Neil in her PhD being funded by the EHERCC at Manchester University in the UK.

Emily had reported that TAZ-CAMTA1 expression caused activation of the DNA damage response pathway in endothelial cells, and was already apparent 4 hours after the addition of doxycycline to induce TAZ-CAMTA1 expression. During the third quarter, Emily sought to determine whether the results seen were as a result of actual DNA damage caused by TAZ-CAMTA1, or alternatively were due to a direct activation of the DNA damage response pathway by TAZ-CAMTA1.

Emily undertook an experiment that detects double strand breaks (DSBs) in DNA. In these experiments undamaged DNA remains in the comet 'head', whereas DNA containing DSBs migrates to form a 'tail'. This assay revealed that endothelial cells expressing TAZ-CAMTA1 had a greater percentage of DNA in the comet 'tail' compared to untreated control cells, suggesting that TAZ-CAMTA1 expression was causing DSBs (see Figure A). The percentage of DNA in the tail of endothelial cells treated with doxycycline was comparable to that of endothelial cells treated with H₂O₂, which was used as a positive control as it is known to cause DSBs. Overall, these data suggest that TAZ-CAMTA1 expression is rapidly causing DSBs in the DNA of endothelial cells. This results in the subsequent activation of the DNA damage response pathway which causes cells to arrest in S phase of the cell cycle, as was previously observed.

Fig A

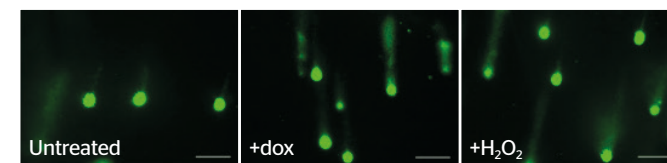


Fig B

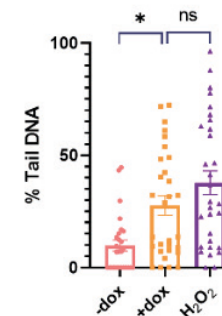


Fig: TAZ-CAMTA1 expression results in DNA damage

(A): Representative images from neutral comet assay to detect double strand breaks in DNA. Day 10 endothelial cells were either left untreated, incubated with dox for 24h to induce TAZ-CAMTA1 expression, or treated with 10μM H₂O₂ for 4h as a positive control for DNA damage. Scale bars = 50μm. **(B):** Graph showing the percentage of DNA in the comet tail for each of the three conditions. Statistical significance was determined by one-way ANOVA with Turkey's multiple comparisons test, *p=0.0127.

Next, Emily investigated hypertranscription as a potential mechanism behind the DSBs generated upon TAZ-CAMTA1 expression in endothelial cells. Hypertranscription is a state whereby global transcriptional activity is upregulated, and can result in replication stress, the generation of DNA damage and genomic instability. Previous RNA sequencing experiments revealed considerable changes in transcriptional output 24 hours after the induction of TAZ-CAMTA1 expression in endothelial cells. These experiments revealed that 1861 genes were significantly upregulated and 2665 were significantly downregulated in the cell population expressing high TAZ-CAMTA1 level compared to uninduced controls, demonstrating that transcription is vastly altered upon TAZ-CAMTA1 expression.

To further examine changes in transcription upon TAZ-CAMTA1 expression, an experiment was performed to measure RNA synthesised upon TAZ-CAMTA1 expression. In these experiments, doxycycline was added to induce TAZ-CAMTA1 expression for 4 or 24



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hours, and compared to doxycycline non-treated cells. These experiments revealed an increase in the amount of RNA synthesised in TAZ-CAMTA1 expressing cells at both 4 and 24 hours after doxycycline addition.

Together, these data suggest that upon expression, TAZ-CAMTA1 is causing an increase in global transcription in endothelial cells. Furthermore, this effect is already visible within 4 hours of TAZ-CAMTA1 expression, similar to the timing of the activation of the DNA damage response pathway in endothelial cells. This could therefore provide a mechanism behind the generation of DSBs by TAZ-CAMTA1. These experiments will need to be repeated to confirm the results.

Finally, Emily aimed to further characterise the activation of the DNA damage response pathway in endothelial cells upon TAZ-CAMTA1 expression as multiple pathways exist to repair damaged DNA. Homologous recombination (HR) is the predominant DNA damage response pathway for DSBs generated in S/G2 phases of the cell cycle; the phase at which TAZ-CAMTA1 expressing endothelial cells become arrested. Emily's provisional results suggest that HR might be impaired in TAZ-CAMTA1 expressing endothelial cells. If this is the case, cells with DNA damage will either become apoptotic, senescent, or the DSBs will be repaired by a different pathway before the cells re-enter the cell cycle. If the DSBs are repaired by an error-prone pathway, there is the potential to generate secondary mutations which overcome the cell cycle arrest imposed by TAZ-CAMTA1 expression.

To assess this potential mechanism of TAZ-CAMTA1 action, Emily aimed to determine if endothelial cells were able to overcome cell cycle arrest when exposed to doxycycline to induce TAZ-CAMTA1 expression for longer periods of time. This would be suggestive of increased genomic instability caused by TAZ-CAMTA1 expression, resulting in secondary mutation. In these experiments, endothelial cell cultures were induced or not with doxycycline for TAZ-CAMTA1 expression, then maintained in culture for 1 month. Every 3-4 days the media was changed and doxycycline maintained to sustain TAZ-CAMTA1 expression. After 2 weeks of incubation with doxycycline, endothelial

cells with TAZ-CAMTA1 expression began to form clusters. These cell clusters grew larger over the remainder of the experiment, suggesting that these cells were proliferating. The surrounding endothelial cells that were negative for TAZ-CAMTA1 expression, and the cell cultures not exposed to doxycycline, stopped proliferating once confluence was reached and changed very little throughout the course of the experiment. These findings are consistent with the hypothesis that impaired HR in TAZ-CAMTA1 expressing endothelial cells leads to the acquisition of secondary mutations which bypass cell cycle arrest and promote increased proliferation in a subset of cells. Further experiments will be required to confirm this mechanism of action.

MPhil Zebrafish projects started

In 2018 and 2019, the EHERCC funded a two year project to develop an EHE zebrafish model. This work was undertaken at the Bateson Centre, one of Europe's oldest and largest zebrafish facilities. The project proved to be challenging however, with the expression of TAZ-CAMTA1 in endothelial cells remaining stubbornly difficult to achieve.

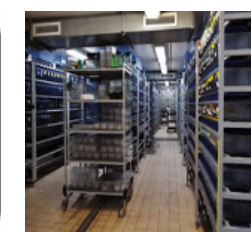
As a result, Dr Fredericus van Eeden, PI for the project, undertook a broad and detailed review of all results in 2020, both internally in the Bateson Centre, but also with contacts in the wider zebrafish and research community. As a result, a number of interesting initiatives were identified and a new research proposal, based around a one-year MPhil project structure was agreed and approved for funding by the EHERCC, with the assistance of the charity's Medical and Research Advisory Board.

This MPhil project has now started, seeking to address the surprising and persistent difficulties in getting the main oncoprotein that is at the root of EHE, TAZ-CAMTA1, to express in endothelial cells in the blood vessels. The review completed in 2020 suggested that this may have 2 causes:

1. The first is that there are elements in the DNA sequence that encodes the oncoprotein, that prevent it from being produced. To check this, the team are chopping the sequence first into big, and then smaller pieces, and seeing if any of these, block expression.
2. The second reason might be best described as “**feedback inhibition**”. In order to activate TAZ-CAMTA1 in endothelial cells, a particular well-tried and tested control sequence is used, known as the **fli1** promoter. Perhaps, when a little TAZ-CAMTA1 protein has been produced, it blocks the function of its own **fli1** promoter.

The team are making new DNA constructs to understand and solve this issue. Initial experiments cannot yet distinguish between reason one and two, but suggest the CAMTA1 part is at the root of the problem, and not TAZ. They are now chopping up CAMTA1 further, to home in on the precise area. If “**feedback inhibition**” is the issue, they have created a construct that uses a different promoter, which could bypass this problem. The next step will then be to inject these new constructs into fish to create transgenics.

We wish Dr van Eeden and Eleanor Markham, the MPhil student, every success with this project. Creating an EHE zebrafish model will provide a low cost and quick model with which to test EHE response to different drugs and compounds, and hopefully help us accelerate the identification of new treatments for EHE. We look forward to updating our readers about this fascinating project in future editions.



New research grants awarded

In the second quarter of this year, The EHE Foundation launched their first formal call for EHE research proposals. Four proposals were received and evaluated by The EHE Foundation and its Advisory Board. The EHE Foundation was delighted to be able to announce that two of the projects were approved for funding. Funding provided by The EHE Foundation will be complemented by funding provided by The EHE Rare Cancer Foundation Australia to support these projects.

Project 1: TAZ-CAMTA1 Regulation by the Calcium Sensor Calmodulin

The Principal Investigator for this project is John Lamar, PhD, based at Albany Medical College in Albany, New York.

Greater than 90% of all epithelioid hemangioendotheliomas (EHE) have a WWTR1-CAMTA1 translocation (gene mutation), and it is now understood that the fusion protein that results from this translocation, namely TAZ-CAMTA1 (TC), causes EHE and promotes its growth. This suggests that therapies that inhibit TC could be extremely effective treatments for EHE, as EHE is believed to be “addicted” to TC. However, to promote the formation of tumors, we also understand that TC must first bind to another family of proteins (transcription factors) in our cells called TEADS. Given the established roles for TAZ-TEAD and YAP-TEAD in other cancers, there is a significant ongoing effort to develop compounds to block the TAZ-TEAD and YAP-TEAD interactions. However, to date, this has largely been unsuccessful. Furthermore, YAP and TAZ have important functions in normal tissues so systemic YAP/TAZ-TEAD inhibition may cause adverse side effects.

Another promising approach is to target pathways required for TC activity, but which will not impact necessary YAP and TAZ function. The CAMTA1 portion of TC holds great promise because it is not part of normal TAZ or YAP, so targeting pathways that regulate the CAMTA1 portion of TC may block the



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cancer-forming fusion of TC without compromising YAP and TAZ function in other cells. The importance of functional proteins originating from CAMTA1 is unknown, and the regulation of the CAMTA1 protein itself is severely understudied. Dr Lamar therefore feels the lack of research focused on the CAMTA1 portion of TC is a potential opportunity that warrants further research.

Dr Lamar's laboratory has previously undertaken EHE research, partially funded by the EHE Group. His lab is now focused on identifying cellular pathways that can be targeted to inhibit the cancer-forming function of TC and understanding how these pathways regulate TC function. Their preliminary data shows that overexpression of the calcium-sensing protein Calmodulin dramatically represses TC transcriptional activity, suggesting that modulation of calcium-Calmodulin signaling may inhibit TAZ-CAMTA1.

In their proposed research, they will test the effect of Calmodulin and calcium signaling on both TC transcriptional activity and its cancer-forming function and determine the mechanism through which Calmodulin regulates TC. This work will use the *in vitro* and *in vivo* model systems developed by Dr Lamar's lab, as well as the genetically-engineered EHE mouse model developed by Dr Brian Rubin. If successful, this work has the potential to reveal a molecular pathway that could be exploited therapeutically to develop new treatments for EHE.

In summary, Dr Lamar's research will have three main research objectives as follows:

Aim 1: Test if Calmodulin represses TAZ-CAMTA1 activity and tumorigenic function.

Aim 2: Determine the mechanism of Calmodulin regulation of TAZ-CAMTA1; and

Aim 3: Determine if Calcium-Calmodulin signaling represses TAZ-CAMTA1 in mouse EHE cells.

Project 2: Investigating the early molecular mechanisms of WWTR1-CAMTA1 and YAP1-TFE3 gene fusions in driving the Epithelioid hemangioendothelioma (EHE)

The Principal Investigator for this project is Cristina Antonescu, MD, based at Memorial Sloan Kettering Cancer Center in New York.

Dr Antonescu's research proposal seeks to generate isogenic cell lines to recreate the same tissue with the physical properties as EHE tumors, using cutting edge CRISPR-Cas9 genome editing technology. Dr Antonescu's team will model the WWTR1-CAMTA1 proteins in human embryonic stem (hES) cells, differentiate these to endothelial progenitors, and then induce the expression of the WWTR1-CAMTA1 fusion. Their approach will also seek to identify other cancer-relevant translocations and how these too effect cells, and so hopefully identify new druggable targets. Moreover, using their extensive collection of frozen and archival samples, as well as the existing genomic data on EHE samples obtained through their international collaboration with a world leader in the field of sarcoma, they propose to define the transcriptional and epigenetic profiles of EHE tumors to unveil target vulnerabilities and identify potential new therapeutic approaches.

In summary, Dr Antonescu's research will have four main research objectives as follows:

Aim 1: Investigate the transcriptional and epigenetic profile of EHE tumors.

Aim 2: Establishing in vitro models of EHE to evaluate early steps of cellular transformation.

Aim 3: Investigate the epigenetic landscape of cells expressing the fusion in various cellular contexts by comprehensive epigenome mapping.

Aim 4: Developing in vivo models of fusion positive EHE.

We want to wish both Dr. Lamar and his team, and Dr. Antonescu and her team, every success in their respective EHE research projects, and look forward to sharing their research updates in future editions of The Pledge.

Biobanking is so important!

In our previous edition of The Pledge (Edition 25, April-June 2021) we included a full update concerning the biobanking activities of the EHE Group. We will not repeat all of that information here, but we would like to re-emphasise the core message about biobanking, which is:

“WE NEED YOUR HELP”

Samples collected in the biobank are a key part of EHE research. Blood, tissue, and fluids from people with EHE enable researchers to learn more about EHE, test possible treatments and find new drugs. Your sample donation to an EHE biobank might include:

- stored tissue from your original biopsy at diagnosis or upcoming biopsy;
- tissue from therapeutic surgery involving EHE tumour resection or removal;
- whole organs, following transplant;
- blood samples, collected during routine doctor visits over time;
- other fluids drained that will be discarded, e.g. if you have pleural effusion due to pleural involvement or ascites fluid.

Tissue that is removed during surgery is often discarded, but highly important to EHE research. Of greatest value to researchers is fresh tissue which can be used in the development of EHE cell lines. These cell lines are very difficult to develop, and we think there may only be one currently in the world. So every tissue donation opportunity is priceless.

There may be reasons why you do not want to donate to the biobank, and that is fine. Everybody must make their own decision, and if you chose not to, this will not in any way affect your medical care or clinical treatment. But if you are willing to donate, please don't put it off until another day. Donating is actually very

easy, with a bit of notification. Make contact with the relevant people now and they will work with you to ensure that you, and your samples, will be included in the biobanking process if at all possible.

And here are the key contacts:

In Australia:

Please contact the EHE Rare Cancer Foundation Australia (EHE-RCFA) at: info@ehfoundation.com.au if you have any queries regarding participating in the WEHI Stafford Fox Rare Cancer Research Program, or to notify the foundation of a recent/upcoming surgical procedure.

In the USA:

Contact Patty Cogswell, EHE Biobank Coordinator, on 1-919-619-1811, or at Biobank@fightEHE.org; or

Visit the EHE Foundation biobanking page at: <https://fightehe.org/ehe-biobank/>

In the UK:

Contact the EHE Tissue Coordinator at the National UK EHE Biobank at the Royal Marsden Hospital, at: EHEbiobank@rmh.nhs.uk; or

Hugh Leonard at the EHE Rare Cancer Charity (UK) at: hleonard@ehercc.co.uk; or

Visit the EHERCC biobanking page at: <https://www.ehercc.org.uk/national-ehe-biobank-uk>



02 EHE Research

MyPART is open to US and international participants

MyPART is the 'My Pediatric and Adult Rare Tumor' network. It is a group of scientists, patients, family members, advocates, and healthcare providers who want to help find treatments for rare cancers. They are working on childhood, teen, and young adult solid rare tumors that have no cures, and believe that working as a team will help them find treatments for rare cancers faster.

The MyPART scientific team is a team of doctors, nurses, scientists, and other staff, working together to improve the lives of children, adolescents, and young adults with rare solid tumors. The team members come from different locations within the United States and around the world, bringing diverse interests.

We also want to amplify that participation in MyPART is not restricted to US citizens. Mariana Coutinho, based in Portugal, has enrolled in the programme, and wanted to share important news with the group. Mariana posted:

“I just had a call with one of the research nurses involved in the MyPART study and I am so thankful for the opportunity to contribute to research on EHE but even more amazing is the fact that since this is a longitudinal study - where the researchers will track our health history over a long period of time (many years) - we can get a diagnosis confirmation and molecular tests done for free. Also, we can ask for the opinion of one of the oncologists involved in the study on our treatment plan at any given time, whilst we are enrolled in the study... for free as well! I am about to send a tissue sample from my primary tumor to the US, and I encourage any other EHE patients to engage in this international study... we can only benefit from this.”



Anybody wishing to learn more about the study can find information at the following web address: <https://www.cancer.gov/pediatric-adult-rare-tumor/about/what-is-mypart>

Here you can find a brief form to complete and submit to start the process. There are also numbers to ring. They can also be contacted by chat and email.

Understanding sarcoma

One of the challenges for newly diagnosed patients is simply understanding the complexity of cancer and the terminology associated with different treatments options. The EHE Foundation holds a library of scientific papers and articles related to EHE research and treatments. In August, the Foundation announced that they had added a new article on YAP1-TFE3 fused hemangioendothelioma. Contributors to the paper include EHE Foundation Advisory Board member, Dr Brian Rubin!

The library can also be found at: <https://fightehe.org/scientific-publications-articles/>



Researching 'scanxiety'

We often see our members posting questions or sharing their feelings about the anxiety they face as their next set of scans approach, commonly referred to as 'scanxiety' by cancer patients and cancer charities. Hugh Leonard was therefore pleased to be approached in the UK regarding research being undertaken into this phenomenon, with a request to inform our UK EHE community. Hugh explained:

“Sarcoma UK have just posted news of a new study they are doing with UCLH and Birmingham City University to try and better understand the effects of scanxiety. They need sarcoma patients to complete a questionnaire. It would be great for as many as possible to complete it.”

We believe the survey is still open. If you want to understand more about this research and the survey they want sarcoma patients to complete, you can find it at the link below. Good luck.

<https://www.myonlinesurvey.co.uk/ream/>



University College London Hospitals
NHS Foundation Trust

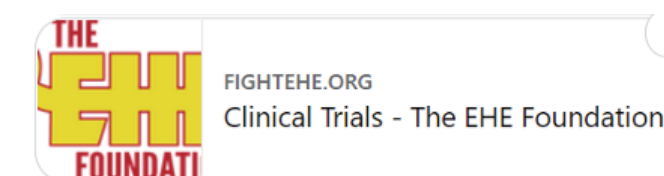


Clinical trials eligible for EHE

Medha Deoras Sutliff, Executive Director of The EHE Foundation, continues to share about clinical trials that may be open to eligible patients with EHE. The Clinical Trials database lists available US trials on The EHE Foundation's website.

“A patient's decision of which cancer treatment to receive is complex and unique. We provide an easily searchable list of clinical trials for EHE patients on our website. We continue to update the list to benefit patients and medical experts as they navigate through possible treatment options.”

The list can be found at: <https://fightehe.org/ehe-clinical-trials/>



03 EHE Fundraising

Fundraising activities are now back at pre-COVID levels. The determination of our EHE fundraisers is wonderful to see, driven by the simple desire to defeat EHE. We hope you find the following articles inspiring. If you do, we encourage you to think about how you might be able to mobilise friends, family and colleagues to help raise the funds we need to ensure we can not only maintain, but also expand our EHE research programmes. Fundraising does not need to involve massive campaigns or extreme sports. It is often the collation of many small sums that adds up to the funding we need.

London Landmarks Half Marathon back on!

After the disappointment of the 2020 event being cancelled one week before it took place, the EHERCC was delighted that the 2021 London Landmarks Half Marathon was back, on 1st August. The charity had a team of 36 runners taking part to raise awareness of EHE and also to raise funds for EHE research. The team was originally 40, but lost two runners to COVID while two had an accident driving to the station. Nobody was seriously injured, thank goodness, but that was sadly the end of their participation.

A week before the race, London had been enduring 35° heat and very high humidity, but runners awoke on race day to almost perfect running weather. Some of the 'EHEAwesome40' team gathered for a pre-race photo before taking on the 13+ mile course. It was a wonderful turn out by so many of our supporters, either running or cheering, and everybody who took part said that it had been a fantastic experience. At the end of the day the event helped raise over £22,000 for EHE research; a fantastic effort. We want to thank and congratulate all those who took part for this wonderful performance.



Amazing effort to support charities

Nicola Henderson has always had an amazing group of supporters. Kerry Marks, Leanne Woodruff, and several others, set out to raise funds for EHERCC and two other charities, while completing an arduous training regime, known as the "Bootcamp".

This included running while carrying a log, half marathons, and multiple other exercise regimes. Kerry Marks explained:

"Hi everyone - I will be doing the three peaks this weekend, along with a half marathon, carrying a 70kg log in September (along with my bootcamp commandos) to raise funds for EHE and what's brilliant is my work are going to match what I can raise!! Wow."



Nicola posted news of their amazing achievement:

"Hi fellow EHE family! I just wanted to share the amazing achievement of a group of my friends from my town in the UK who have just walked to the summit of 3 different mountains. The highest mountain peaks in England, Wales and Scotland! They completed it in 3 days and have so far raised over £6,000 for EHE research! They were also supporting a general cancer research charity and MIND for mental health! I wanted to share so I could

show them your comments as I said our EHE family would be so grateful. They showed pure grit and determination and I'm super proud of them!! Special shout out to Kerry and Darran, my best friends, who are always there to support me and our charity with fundraising, love you guys now get some rest!"



We send our congratulations to all the Boot Camp Commandos for the incredible energy and dedication shown in completing these events, and for raising over £6,000 for the EHERCC.



We want to thank Lee Ralph who organised the Bootcamp Commandos, and also everyone of the 19 brilliant women who put in so much effort and achieved so much. They are: Debbie Ralph, Shelley Player, Leanne Donoghue, Kirstie Worrall, Danielle Base, Jenna Totterdell, Andrea Simkova, Ceri Pugh, Laura Leach, Abigail Base, Nancy Stone, Emma Hemmings, Emma Rushent, Karen Fisher, Carly Morgan, Kerry Marks, Christina Leach, Paige Whittington, and Ruth Oram. You guys are all heroes. We are proud to have you on the front cover of this edition of **The Pledge**.

03 EHE Fundraising

2021 EHE Fun Run and Walk a huge success

The EHE Foundation in the US want to say a huge thank you to their wonderful participants, supporters, and sponsors for making the 2021 EHE Fun Run and Walk a tremendous success! Together, more than 900 supporters across the nation helped raise more than \$45,000. Thanks to the backing of their sponsors, every penny brought in for this event will go directly to EHE research.

This event does much more than create awareness and funding for EHE research. Each team represents an EHE patient with a very unique story. The EHE Fun Run and Walk allows teams of families, friends, and other supporters to rally together and show their unwavering support for their loved one and other EHE patients.



Julie Wahl, Vice President of The EHE Foundation commented:

“Year after year, we are amazed at the passion, drive, and dedication of our many supporters who help make the annual EHE Fun Run and Walk an extraordinary success. For many families, it’s a time to reflect on the wonderful support system that surrounds us and comes together in a positive and grateful atmosphere.”

Jennifer Mulligan of Team Joe supporters, the top team for 2021, was also very grateful for the wonderful support they received:

“We had a huge outpouring of support for Team Joe and we thrive on their love, energy, and commitment to not only our family, but for EHE patients across the nation.”



Teams came together in a nationwide rally to fight against EHE. The EHE Foundation is excited to share many of their photos on their website at www.FightEHE.org.

The EHE Foundation said:

“As a patient-led foundation, we understand the challenges of EHE, but take comfort in knowing we are there to support each other and are stronger together.”

We are blown away by the effort of every individual and team. A huge applause for the top teams: Team Joe, Team Laney, #EthanStrong, Team Kristen Leigh, #JonathansWolfPack, Rick’s Incredible Cancer Killers, Team Matt, #teamjenni, Love for Lisa, Tiff’s Tribe, and Team John.

Special thanks are also extended to our sponsors listed below. Thank you for helping The EHE Foundation continue to gain considerable attention as our organization and events grow each year. Rare cancers are often the victims of inequality in research and medical care, but you are helping us overcome this obstacle.”



Platinum Sponsors:

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Giombetti Associates
Hansen Distribution Agency
Monticello & Warren Animal Clinics
The Bright Solutions
Western Bat Specialists

Gold Sponsor:

V&P Hydraulics

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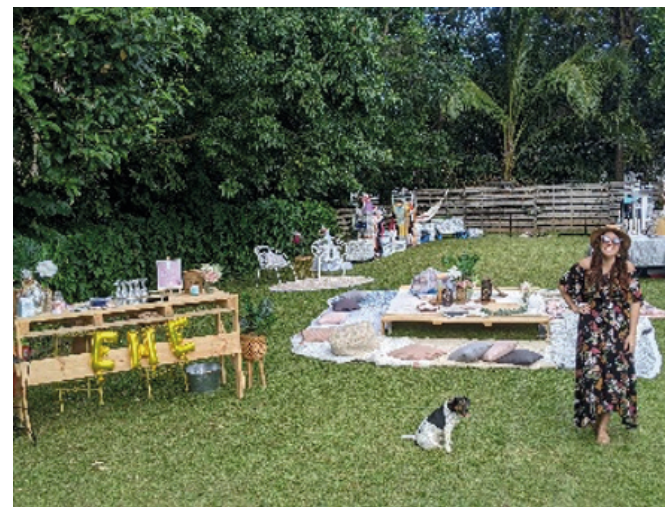
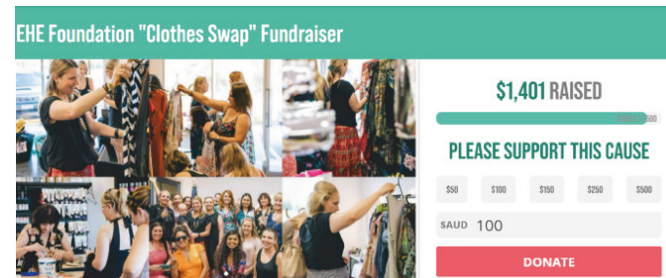
03 EHE Fundraising

Recycling for research

It is always amazing to see the different ways people have found to raise funds for great causes. In Australia, the wonderful Angela Siermans held her 3rd Annual EHE Clothes Swap party, on 31st July, in the tropical North of Australia, in a town called Cairns. Jane Biddlecombe explained:

“The Clothes Swap event is Angela’s way to show her support for a much-loved family member who was diagnosed with EHE, as well as to help in raising funds to support EHE research. It’s a fashionable and fun event, held in Angela’s garden, which was beautifully set up for the day. The event was well attended and raised over \$1,400 for the EHE Rare Cancer Foundation Australia. Equally important, the event helped start many conversations about EHE.”

We also want to thank a number of sponsors who helped make the event so successful. Thanks go to: We Love Nanny P; Bella Boutique Hire; Old Mate’s Farm; Caroline’s Yummy Cakes; Muddy’s Café; Annee’s Caphe; Blended Hair; Designs by Brize; Coconuts Restaurant; Marni Happy Crafter; The Ground Australia; Vintage Seeker; and Mi Piacé.



EHE Sarcoma Fall Fundraiser

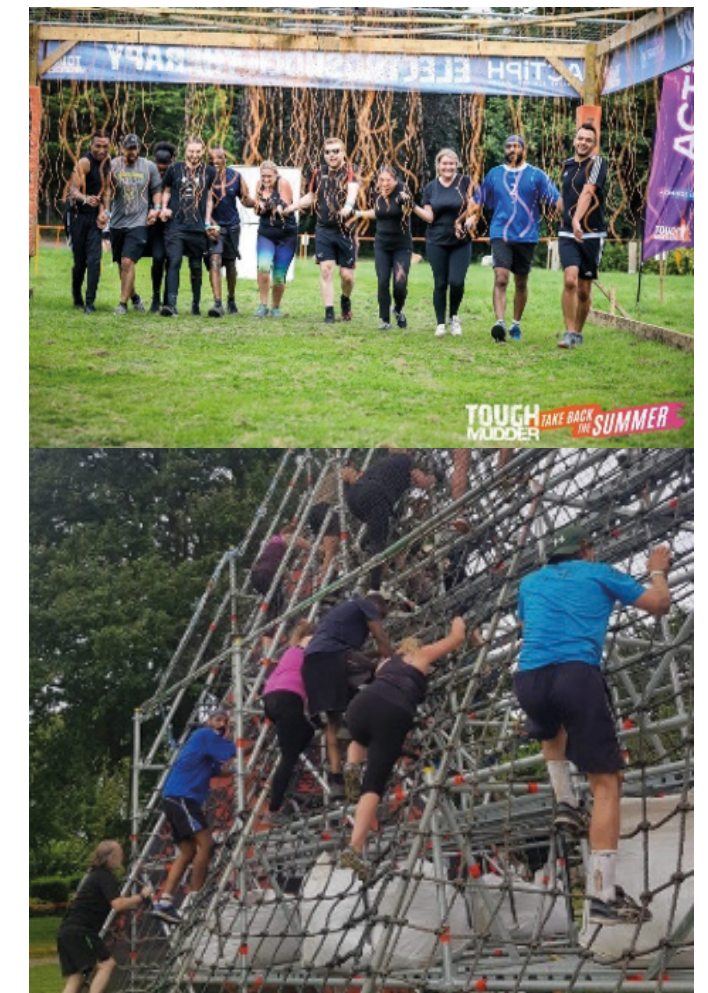
In mid-September, Fiona Louise posted news of two wonderful prizes donated by generous local businesses in the Caledon East area. The first was a Fall Porch or Garden Décor set with a bale, large planters, signs, pumpkins of different sizes etc, donated by Horseshoe Hill Farms, Rock Garden Farms, and Trustee Stan Cameron. The second was a TIN JAY wild bird feeder and large bag of bird seed, donated by Amy Davis and Davis Feed.



Fiona Louise will be raffling these prizes to raise funds for EHE research. We look forward to seeing the results of this raffle in October. We also want to join Fiona Louise in thanking the sponsors who donated these great prizes.

UK supporters take on Tough Mudder

Tough Mudder is an organisation in the UK that sets up assault courses to test participants to their maximum. Normally this involves large amounts of water and mud, and huge amounts of energy. In September, a group of employees from Raft Furniture, took on the Tough Mudder course in support of somebody they know who has EHE. As the weather had been so hot, the normally wet and soggy course was in fact rock hard and totally dry. But that did not stop the group having a great day during which they raised over £7,300 for EHE research. We want to thank everybody at Raft Furniture for their wonderful support.



04 And in other news...

Every quarter, people will post stories or short messages that are not necessarily related to EHE. We always include a small selection of these as we think it supports the spirit of so many of our EHE community, namely that they will not let EHE control or dictate how they lead their lives. They will **"Just Live"**! Here are the posts for this quarter.

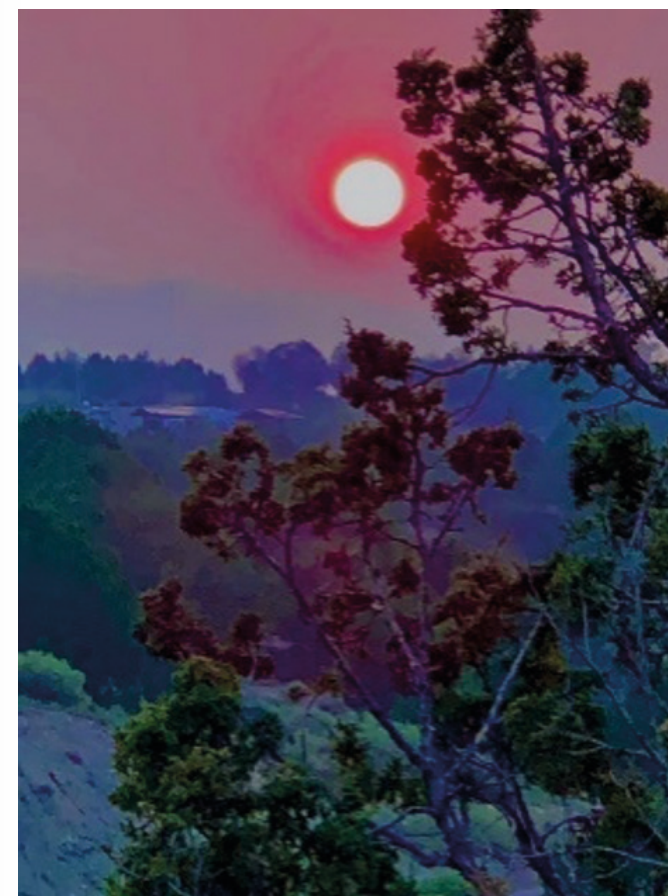
Carl Dickson posted news of his son's skiing exploits:

"Another great moment as to why we fight each day to live with EHE, my little guy just did his first backflip on snow at Mt. Hood, so proud. He is the youngest member of his team, can't wait to see how he does this up-coming season. I can't be there with him but cell phones are the next best thing, beats memorex! **Just Live** as best you can."



Carl Dickson also shared two photos after his latest procedure:

"My first morning walk after my procedure last week and what a gift, no real pain, which gave such an extra beauty to this early morning sunrise. No one else was around, just me, the silence and the sun, I was able to take it all in. Two nearly perfect painless nights of sleep, and a comfortable day yesterday, I'm ready to take life on again. The road ahead may be rocky but I am ready."



"Just thought I would share a picture for those that just can't get out. I watched this guy move from plant to plant for about 10 minutes... Hope you like it."





The EHE Foundation (USA)

www.fightehe.org

The EHE Rare Cancer Charity (UK)

www.ehercc.org.uk

The EHE Rare Cancer Foundation (Australia)

www.ehefoundation.com.au

EHE Italia - Non solo Laura

website not yet available

EHE Canada

website not yet available