The EHE Foundation (USA)
The EHE Rare Cancer Charity (UK)
The EHE Rare Cancer Foundation (Australia)

Quarterly Newsletter for the EHE Group
July – September 2020

the pledge

Edition 22

Photos *for life*

Contents

Welcome

Welcome to the 22nd edition of “**The Pledge**”, the quarterly newsletter of the EHE Group, covering the third quarter of 2020.

The extreme situation due to COVID19 has continued as the world grapples with the pandemic. Some of the activities of the EHE Group that had been curtailed, due to lock-down and social distancing, have begun to slowly re-emerge, but are still significantly affected. We however remain totally focused on all our core objectives.

As always, we hope that you enjoy the contents of this edition, and once again we want to say a huge thank you to all our supporters for their contributions. ***“Just Live”.***

Highlights

EHE research restarts after COVID shutdown

After a three month global shut down that brought a halt to EHE research, we were delighted to see projects at the University of Manchester and Albany Medical College again making exciting progress.

The EHE Group launches its first ever wall calendar

A project team led by Anna Wydro launched the EHE 2021 wall calendar, asking members to submit their favourite landscape photographs. The resultant calendar is spectacular and is now available.

Dr Rubin provides EHE overview for PALs

Dr Brian Rubin took time out of his hectic schedule to provide an overview of EHE for The EHE Foundation's newly formed Patient Advocate Leaders (PALs), together with Directors and Trustees from the EHE Group worldwide.

UK Charity launches its volunteers programme

Mike Rich, new part-time Executive Director of the UK charity, launched his survey of members, asking if they could spare some time to help. The response was fantastic.

Membership continues to grow

The EHE Patient Support Facebook page membership rose to nearly 1,900 by the end of the third quarter.

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

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Just live

01 Patient Support and Advocacy

The EHE Group will always endeavour to provide support to everybody diagnosed with EHE, wherever they may live, and to increase awareness and understanding of EHE. These two goals combined are at the core of the patient support and advocacy objectives that are passionately pursued by all three of the EHE foundations.

That support and advocacy is provided thanks to the tireless energy and contribution of so many of our members, many of them being EHE patients themselves.

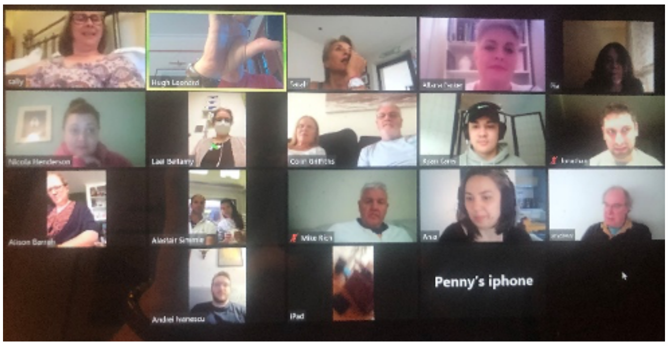
We therefore want to thank all our supporters who have contributed to this critical part of our activity, examples of which are provided in this section.

UK Charity holds its first group video conference

The EHE Rare Cancer Charity UK held its first ever video conference on 14th July. Chair of Trustees, Hugh Leonard was delighted to invite not only the UK members but many participants from other countries.

> “We hope not to go on for too long, but would like to tell you what the charity is up to, introduce a few people, get excited about the EHE research we are funding, even more excited about the international collaboration that is in progress, and our fundraising objectives. Most of all we would like to get your feedback as to anything you would like to see happening or any ideas you have. After all, you are the guys that we are really doing this all for.”

The participation was excellent. EHERCC were particularly grateful to Dr John Lamar from the Albany Medical College, who explained his EHE research project to the group and was able to also answer some questions. After the presentation section, there followed a lively discussion about things that the charity should be doing. Hugh commented: *“With energy and passion like that in the group, we are going to achieve so much.”*



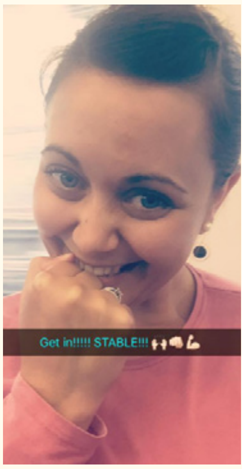
EHERCC send their thanks to everybody who participated and hope to do a follow up call before the end of the year.

Nicola Henderson posts some great news...

Nicola Henderson is a regular contributor to our group. Nicola not only has to live with EHE but in 2019 underwent a liver transplant due to the tumours in her liver progressing.

The transplant process was stressful to say the least, and many people only realised what an emotional rollercoaster a major transplant is when they read her posts. So everybody was delighted when she posted her news:

> “So after my last few scans have shown growth, I have now just received a stable result! It’s been so tough this year with not knowing what treatment is best etc but after being on Celebrex for 6 months, things appear to have settled down. I couldn’t be more grateful! Got to go back in 8 weeks. This photo is me punching EHE in the face!!! JUSTLIVE!”



... and then shares her story

Despite all the turmoil and anxiety Nicola has faced with her EHE and transplant, she has always been keen to share her story to help others. In July she was asked by Share Your Wishes, an encouraging and inspiring web site raising vital awareness for organ donation in the UK, to tell her story, and through the telling encourage others to talk about their organ donation decisions.

As always, Nicola did this providing an honest and open narrative of her journey with EHE and her liver transplant. She is also happy to answer any questions people may have. And at the end of the article, Nicola summed up what the transplant means to her, and then posed a simple question:

> “I get to spend extra time with my son and husband and this situation is only temporary. Hopefully soon I can get back to living the life I’ve been given to the full. The biggest thing the transplant has given me is a more certain future and being able to see my little man grow up! I was living with such fear before. So if anyone has not registered as a donor yet I would ask you to ask yourselves “would you or a family member take an organ if needed?” If the answer is yes ...”

Well done and well said Nicola.

01 Patient Support and Advocacy

Just Live...

A key aspect of living with EHE for members is a determination to keep going, and not let EHE take control of your life. This was at the heart of the adoption by the group of the ***"Just Live"*** heartbeat motif seen at the bottom of these pages and throughout our campaigns. A part of the patient support initiative within our EHE family includes sharing ***"Just Live"*** stories, to encourage and motivate everybody.

In July, Lael Bellamy shared the story that her son, Foster, and a friend had just embarked on a cross-country trip to Malibu where they intended to surf with their companion Oliver, a corgi. We love the idea of Oliver catching the waves, alongside Foster. It's hard to think of a better ***"Just Live"*** story.

...and never give up!

Alongside our ***"Just Live"*** motif, another common mantra for our EHE Family is ***"never give up"***. This was again amplified in the third quarter by Jennifer Mulligan. ***"Some words of wisdom or advice.... Never give up! Hold me accountable for saying this!"***

Jennifer's son Joe had just had his 3 month scans and the results of Joe's MRI showed something back near the same area. Jennifer went on:

> "Initially our insurance wanted to deny scans every 3 months. We fought an appeal (MSKCC did) and won, but the institution was willing to do it in spite of insurance denial which we are grateful for. Thank god we did not give in to every 6 months. We don't know yet what the final plan will be, but Joe feels strong. My husband is amazing and my rock. But I am a fighter and so many of you are, too!"

Jennifer was calling her insurance company to let them know their denial could have led to even bigger problems 3 months on.

Thanks Jennifer for reminding us to ***"never give up"!***

Mike Rich launches volunteers survey

In our last edition of The Pledge we introduced Mike Rich who is taking on the role of executive director of the EHERCC on a part time voluntary basis. Mike's immediate focus was to try and identify and coordinate the charity's supporters and so access voluntary help that will be so valuable. Mike explained:

> “Hi. I am doing some volunteer work for the EHE Rare Cancer Charity. Part of what we hope to do over the next year is to bring people together to collaborate and cooperate to help the charity and its supporters. To do that we are trying to get an idea of how people would like to get involved, how much time they have and what their interests are. If you would like to help the EHE Rare Cancer charity it would be great if you could spend 10 minutes (or less if you are quick) and fill in this very brief survey. With many thanks.”


Mike Rich

Late in September Mike was able to update the group with news of the response:

> “What a great response we have had to our survey. So far we have had pledges of time amounting to over 25 hours of activity a week. The great thing is that the time is split between 16 people so nobody will become overwhelmed with any tasks and it will work for the long term. In just over a week, we have had pledged the time of a part-time member of staff which is just fantastic.”

Mike explained that he would now be spending a bit of time analysing the responses and pulling together a set of activities that fit in with the time pledged and the interests that people have shown. In the meantime, Mike would like anybody who has not filled in the survey, and thinks they can spare 30 minutes or more of help, to let us know. In fact, even if you don't think you have the time now, the charity would love to hear if you may be interested.

If you do want to complete the survey and have not had the chance, you can find it at:

www.surveymonkey.co.uk/r/GFX5K9B

01 Patient Support and Advocacy

New German connection

A key aspect of helping patients wherever they may live in the world is being able to access sarcoma experts, ideally with EHE experience. This is an ongoing objective for Lisa Hartle De Young, an administrator of the EHE Facebook support group, and Director of Patient Liaison Services for The EHE Foundation, a non-profit organization in the US. Lisa's patient liaison role is not restricted to the US. She works tirelessly to support patients in 71 countries across the globe, and is always looking for new sarcoma resources as well as researchers to join our cause.

In August, Lisa cultivated a new relationship with a researcher and pathologist at University of Münster, Dr. Eva Wardelmann, who is a founding member of the German Sarcoma Foundation alongside EHE specialists, Dr. Sebastian Bauer of Essen and Dr. Peter Reichardt of Berlin. Dr Wardelmann receives more than 1500 soft tissue tumors per year for second opinions. Lisa encourages EHE patients in Germany to *"Please contact this sarcoma resource should you need additional assistance in Germany."*

Learn more about the German Sarcoma Foundation at: **https://www.sarkome.de/sarkom-stiftung**

Thanks to Lisa for her ongoing dedication as she continues to seek to improve the cancer journey of EHE patients everywhere.

The EHE Foundation is grateful to their Advisory Board

The EHE Foundation is committed to moving forward in the fight against EHE, but recognising that their Board of Directors are neither clinical oncologists nor research scientists, the Foundation has established a core group of specialists within its Advisory Board. Jenni Case Kovach, President of The EHE Foundation, wanted to recognise the Advisory Boards contribution following their latest meeting:

> "We are grateful for our panel of EHE medical experts, our Advisory Board, who are a critical asset to our mission. Today we held our annual meeting and are excited about what is in the future for EHE research. Here's a snapshot of some of the attendees in action. To learn more about our advisory board we invite you to visit their section on our website at https://fightehe.org/advisory-board/"

Sachin Sarcoma Society meeting for EHE patients

We are always excited when we see other groups around the globe helping patients with EHE, such as that posted by Rashi Kapoor in July, relating to the Patient Support Group Meeting being held by the Sachin Sarcoma Society, based in Delhi, and hosted by Mr Ashish Rana, whose mother has EHE.

We hope that the zoom meeting went well and look forward to more EHE activity and updates in the future.

Sachin Sarcoma Society

organises

Patient Support Group Meeting

for

Epitheliod Hemangioendothelioma Patients

on

zoom

Interested people, please contact
Ashish Rana +91 9999555399

www.sachinsarcomasociety.org

Lifelines to Cancer Survival

On 28th December 2002, Mark Roby collapsed following a five mile run. Five days later he was diagnosed with EHE and told that there was no treatment for it. Mark immediately started researching and reaching out to people across the globe. One key doctor eventually told Mark he would have to learn to keep himself alive.

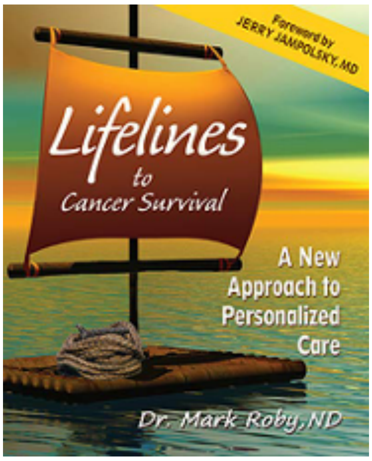
Mark set about doing exactly that, and then wrote his brilliant book, *Lifelines to Cancer Survival*. Mark explains:

> “My book outlines my journey but also documents tools, testing, and other modalities to fight EHE. It also features interviews with other patients and many research and clinical experts in areas such as molecular profiling, immunotherapy, nutrition, fundraising and many more.”

The book is highly rated and is still on sale at Amazon. Mark also donates 50% of the proceeds from the book to The EHE Foundation. We want to congratulate Mark on writing such a great book, and of course thank him for his generosity for donating.

Mark (left) just before his transplant.

Mark (centre) six years later.



01 Patient Support and Advocacy

Another virtual success

A key objective of the EHE Group is to try and share information and knowledge about EHE, and a large range of diagnostic and treatment modalities, so that our members remain informed and can engage more meaningfully with their own clinical teams.

Jane Gutkovich, Emeritus Board Member of The EHE Foundation, is passionate about sharing information. In September, Jane coordinated the latest of her virtual events, a workshop on the use of PET scans and their role in treating and diagnosing EHE.

The event was a huge success. Christy Webb Richardson summed it up well with her post about the workshop by stating,

> “A BIG SHOUT-OUT and THANK YOU to Jane Gutkovich for sharing through ZOOM so much good information with us this afternoon on PET scans! It was also great seeing some of your faces and sharing questions and info with each other. Hope we can do this more often!”

We know that Jane has plans for more virtual workshops in the future, and will be sharing details soon. As always we want to thank and congratulate Jane for her excellent work.

Dr Rubin supports the PALs

During the second quarter, The EHE Foundation (US) launched its PAL (Patient Advocate Leader) Program, which is a new volunteer opportunity for US-based patients and caregivers. The PAL Program expands patient support and ensures patients have a voice in the foundation’s initiatives. The 2020 PAL participants consists of a group of diverse, passionate, and highly motivated volunteers. Congratulations to Amy Baghdadi, Molly Gibson, Leah Heinrich, Sandy Meaders, Keren Stern, and Jennifer Mulligan. Learn more about these amazing volunteers at **https://fightehe.org/pal-program/**

One of the PAL Programs goals is to educate patient advocates. So Dr. Rubin graciously presented an overview of EHE biology and various aspects of his ongoing research to the PAL participants. Management and trustees/directors from our international groups also joined The EHE Foundation.

Dr Rubin’s presentation was extremely informative and the Q&A session provided the opportunity for many of the participants to ask further questions. This discussion was recorded and will soon be available on The EHE Foundation website.


TAZ is regulated by the Hippo pathway to control growth, organ, and cell size

Hippo pathway regulates organ and cell size (“tumor suppressor” pathway)

EHE Photos for Life initiative launched

One of the common themes of our EHE Facebook page are the wonderful photos posted by our members, a selection of which are included in the ***"...and in other news"*** section at the end of each edition of The Pledge. It was because of this that Anna Wydro first raised the idea of using photography, and the wonderful photos, to help promote the EHE cause, raise awareness, create a greater community spirit within our membership, and also to assist in fundraising. Anna explained:

> **"There are so many ways that photography can be used. Photographs can provide a unique link and relationship between people, while at the same time being uplifting. How we use these photos needs to be carefully planned, but I genuinely believe there is huge potential."**

Anna has established the EHE Photos for Life group and has started to communicate her ideas and reach out to the group worldwide. Her first project was to create the EHE Group's first-ever wall calendar for 2021. Anna noted:

> **"It's a great example of what we can achieve. We have photos from members from all over the globe which is a fantastic representation of our global community and the growing collaboration amongst us all as we work to find new treatments for EHE. The wonderful photos remind us of the beauty in the world which can be psychologically and spiritually important for people battling a rare disease. We have already had lots of lovely and warm feedback. We have been able not only to provide a calendar, but have also included information about our EHE Group, information about EHE itself, and a diagram to show the EHE research that we are helping to fund globally, so we are also raising awareness. And perhaps most importantly, we have included a memorial page to remember all those whose lives were cut tragically short by this horrible cancer."**

You can see more about the calendar in the fundraising section below. We congratulate Anna on this great initiative and cannot wait to see what will be next to come out of EHE Photos for Life.

To see the calendars (there is a UK version and an international version) just go to the single page calendar website at **http://ehecalendar2021.info/** where you can click to open and see the whole calendar. In the UK the calendars cost £12.50 each. Prices for other countries are shown on the website. Printing has all been funded by one of our supporters so every pound you spend on calendars will go to EHE research.

02 EHE Research

COVID19 continued to have a major impact on research through the third quarter of 2020, although some of our researchers were able to slowly restart work in their labs.

We have provided updates for those projects where further progress was made. But as the research taking place is still limited, we have again taken the chance to provide an overview of some of the areas of EHE research that the EHE group is helping to deliver.

Last quarter we focused the overview on research in the UK. This quarter we are focusing on projects in the USA.

Progress through the quarter

EHE presented at major conference

It was with mixed feelings that Jane Gutkovich posted the news that EHE had, for the very first time, been presented at one of the largest European cancer symposiums, the European Society of Medical Oncology symposium, or ESMO. Jane noted:

> “This is huge - the first time EHE has had this sort of profile. However, the difficult news is that the presented data relating to a number of different systemic treatments again demonstrated how heterogeneous EHE is and how there are no reliable biomarkers (yet!) to determine the right drug for each patient. There is so much more work that needs to be done!”

And the conclusions of the paper reflected these observations:

> “Systemic therapies available for advanced sarcomas exhibited limited activity in EHE... The identification of new active compounds, especially for rapidly progressive cases, is needed.”

Our EHE community already understands the limitations of current treatments for EHE. It is why we cannot relax for one moment; why we will continue to strive to raise funding so that we can promote further EHE research, so that new treatments can be found.

University of Manchester PhD is back up and running

Previously Emily, the PhD student, reported that she had determined differences in cell cycle progression between endothelial cell populations that express TAZ-CAMTA1 or not, using flow cytometry. Furthermore, she had started generating samples of 4 endothelial cell populations to send for RNA sequencing; TAZ-CAMTA1 high, TAZ-CAMTA1 low, TAZ-CAMTA1 negative, and non-induced cells. Unfortunately, this was interrupted in March when the University of Manchester campus was closed due to the coronavirus pandemic, leaving the team unable to access the laboratory. They returned to the lab in July, but social distancing guidelines have resulted in limited laboratory access and core facilities essential to their research running a reduced service.

Since returning, Emily has begun the final two experiments needed to generate samples for RNA sequencing. Having completed this stage, the cells were then harvested and sorted into the populations mentioned above 24 hours later, using GFP as a marker of TAZ-CAMTA1 expression levels. Her aim is to have this completed and the samples sent off to be sequenced before the end of October. Furthermore, she is beginning to investigate a role for mechanical stimuli, such as extracellular matrix stiffness and cell density, in regulating TAZ-CAMTA1 activity in endothelial cells. TAZ is widely reported to be regulated by various mechanical stimuli, via Hippo pathway dependent and independent mechanisms, and therefore this could also be relevant to TAZ-CAMTA1 regulation.

02 EHE Research

John Lamar's research restarts at Albany Medical College

Dr Lamar's team have been able to re-enter their lab and have been able to undertake some additional research.

They have completed a mouse experiment using the NIH3T3-TAZ-CAMTA1 expressing cells and this shows definitively that TAZ-CAMTA1 renders the cells tumorigenic and metastatic.

> **"We will now start to use this xenograft mouse model to test our candidate TAZ-CAMTA1 regulators. We can also label these cells so we can track their spread in the mouse (metastasis) and monitor tumor burden over time using an imaging device. So we can use this mouse model to test potential therapies. We also have a new in vitro (in a petri dish) assay optimized to test the ability of TAZ-CAMTA1 to render cells cancerous. This will allow us to rapidly test candidates, so we know which to focus on in the more expensive and time-consuming experiments in the mice."**

They have also completed some additional work with the leading candidate (of the 6 proteins they identified) that appear to repress TAZ-CAMTA1 activity.

> **"So far we know that if we overexpress this protein, called AMPK, we can repress TAZ-CAMTA1 activity. If we treat cells with a small molecule that is supposed to activate AMPK we see a moderate reduction in TAZ-CAMTA1 activity, but not as strong as if we over express AMPK. We are still trying to work out if this is because the small molecule does not effectively activate AMPK or if there is just not enough AMPK in these cells under normal conditions. We also found that the endogenous AMPK in these cells is repressing TAZ-CAMTA1, because if we inhibit AMPK the activity of TAZ-CAMTA1 goes up significantly. This is obviously not what we want therapeutically, but it is an important finding because it suggests that in these cells the existing AMPK pathway can regulate TAZ-CAMTA1, so if we can find a more effective way to activate this pathway or target another protein in the pathway, it may be a therapeutic approach for EHE."**

New paper links different underlying gene mutations for two EHE sub-groups

Jonathan Granek, Director of the EHE Rare Cancer Foundation Australia, was delighted to be able to share a new paper with the EHE community that for the first time shows that the two main sub-groups of EHE, one with the TAZ-CAMTA1 gene mutation (90% of EHEs) and the other with the YAP-TFE3 gene mutation (10% of EHEs) do have convergent oncogenic properties.

The common link appears to be the interaction of the Ada2a-containing histone acetyltransferase (ATAC) complex with both TAZCAMTA1 and YAP-TFE3, indicating that the histone acetyltransferase complex is an oncogenic driver in EHE and potentially other sarcomas.

Furthermore, the paper notes that ATAC complex is an enzymatic transcriptional cofactor required for both fusion proteins in EHE, and therefore may represent a unifying therapeutic target for this sarcoma.

The study also revealed well known YAP/TAZ target genes and genes that have not previously been identified as YAP/TAZ targets

Overview of projects that the EHE Group has contributed to

The EHE Group continues to support EHE research in the USA, Canada, the UK and Australia. In this edition of the pledge we have provided a summary of the main projects in the USA that the group has been supporting. We hope you find these project summaries informative and inspiring as they have been enabled through the wonderful fundraising support we have received from many of you, and are why we are able to make progress in our battle against EHE.

Funding of Post-doctoral researcher


Dr Rubin

In mid-2016, the funds from our first grant award were used to recruit Dr Che, a post-doctoral researcher, who joined Dr Rubin's team late that year. Dr Che immediately took a lead role in the work of the lab. She has been particularly instrumental in leading Dr Rubin's therapeutic drug screening project.

Another major area of focus for Dr Rubin has been his Genetically-Engineered Mouse Model (GEMM), and in Q32019, Dr Rubin had some exciting news:

> **“We have been successful in developing the first GEMM of EHE. After several years of planning, genetic engineering, mouse breeding and waiting, we recently saw the first EHE in our mouse model. These lesions appear to be very similar, if not identical, to human EHE in appearance and they are positive for vascular differentiation markers, confirming that they exhibit vascular differentiation, just like human EHE. Furthermore, these lesions arise in the same constellation of tissues that EHE occur in humans. We will spend the next several months developing cell lines from these tumors as well as characterizing the tumors at the molecular (RNA and DNA) level. This model is remarkable and truly does represent a breakthrough. It will open up a lot of potential studies for us and our collaborators.”**

It is hard to exaggerate the importance of this breakthrough. Having no animal model for a cancer makes many key research streams either impossible or very difficult, and with rare cancers like EHE, this limitation is exacerbated by the lack of human tissue samples to work with. So this really is a very exciting development indeed, and one for which we send our congratulations to Dr Rubin and all his team.

Pre and post-trial biopsies in trametinib clinical trial


Dr Schuetze

We were delighted in 2017 to see Dr Rubin's pre-clinical research data leading to an EHE-specific clinical trial of the MEK inhibitor, trametinib, on patients with advancing EHE, led by Dr Schuetze from the University of Michigan. The enrolment of the first 14 patients, required for phase one of the project, was quickly achieved. In late 2018 the disease response required to allow progress into phase two was seen and the second phase of patient recruitment was started. At this point, the trial is fully enrolled.

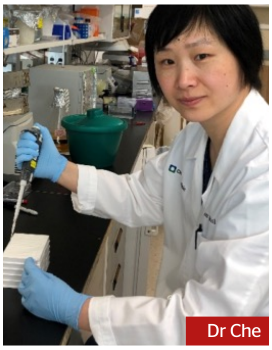
A key aspect of the trial is understanding what effect trametinib has had on patients' tumours. To do this, patients are asked to undergo pre-and post-trial biopsies which will be evaluated in Dr Rubin's lab. These biopsies were not included in the original project funding, and we were therefore pleased to be able to support this grant request.

The trial is still progressing. We hope that positive results will continue, and that Dr Rubin's biopsy analysis will lead to greater understanding of how EHE has been affected, and ways in which the treatment may be enhanced, both to achieve better results in the future, and identify possible new treatment options.

02 EHE Research

Overview of projects that the EHE Group has contributed to (continued)

Therapeutic drug screening project


Dr Che

Dr Che's main area of focus in the Rubin lab has been drug screening to find drugs that target TAZ-CAMTA1. Dr Che developed an innovative assay, designed to screen a huge number of potentially therapeutic compounds to assess their ability to impact the key interaction between TAZ-CAMTA1 and TEAD4. TEAD4 is the transcription factor that binds to our DNA and then recruits (joins to) TAZ-CAMTA1, which in turn transcribes further proteins, which in some combination are believed to be affecting the cells and driving EHE. If Dr Rubin can find a compound that blocks this process it may provide a tool with which to manage EHE progression.

In 2018, the EHE group funded the acquisition of proprietary technology that was used within the screening assay. In addition, the grant funded access to the Case Western Reserve Screening Core where 50,000 different molecules within the Chembridge small molecule library were screened.

And results were exciting, as Dr Rubin explained:

> **“We identified a single compound that made its way through the complete screening pipeline, a series of tests designed to identify a compound with the potential to treat EHE. We are now working with Dr Shaun Stauffer, a medicinal chemist, to understand the mechanism by which our candidate compound works. This will allow us to modify our compound to make it more like a drug. We are also pursuing a larger format drug screen to identify other compounds that inhibit TAZ-CAMTA1.”**

Identifying possible new drugs for rare diseases is at the very successful end of the spectrum of research outcomes. We are therefore excited about the results of this project and Dr Rubin's ongoing development of a potential new drug to control and manage EHE.

Can existing cell processes control EHE development and progress

Dr John Lamar's research at the Albany Medical College is testing the hypothesis that the TAZ-CAMTA1 fusion protein may be controlled by proteins and mechanisms independent of the Hippo pathway. If true these could then be used to inhibit TAZ-CAMTA1 function and treat EHE.


Dr Lamar

Starting in mid-2019, Dr Lamar's team first showed that their YAP/TAZ-TEAD reporter system provides a fast and quantitative measurement of TAZ-CAMTA1 transcriptional activity. The team also optimized Western Blot conditions for the detection of the TAZ-CAMTA1 fusion when exogenously expressed in human or mouse cells. Using the constructs that Dr Brian Rubin provided, they were able to express the TAZ-CAMTA1 fusion protein in either NIH3T3 cells (mouse fibroblasts) or HEK293 (human embryonic kidney) cells and show that it dramatically increased the activity of their transcriptional reporter assay. (The NIH3T3 and HEK293 cell lines provide two separate systems to study candidate regulators of TAZ-CAMTA1). They also confirmed that a mutant form of TAZ-CAMTA1 unable to bind TEADs has very little transcriptional activity. The team then established NIH3T3 cells stably expressing the TAZ-CAMTA1 fusion and confirmed stable expression and increased TEAD transcriptional activity by Western Blot and reporter assay, respectively.

Towards the end of the year the team used the NIH3T3 TAZ-CAMTA1 cells and their transcriptional reporter assay to test 11 candidate proteins for their ability to repress TAZ-CAMTA1 transcriptional activity. Excitingly they found that six of these genes significantly repressed TAZ-CAMTA1 activity and that this repression was consistent across several experiments. Each of these six proteins has roles in existing cellular pathways so, if they can find a way to activate these pathways in EHE cells, it could inhibit TAZ-CAMTA1-mediated tumour growth. This is the hypothesis that Dr Lamar's research will next test. Lastly, the team performed a pilot in vivo experiment and found that NIH3T3 TAZ-CAMTA1 cells form tumors in mice, which suggests that they can use these cells for in vivo experiments that test if their candidates influence TAZ-CAMTA1 tumor growth.

EHE research and activity at Memorial Sloan Kettering Cancer Center in New York

1 Dr Christina Antonescu Research Grant

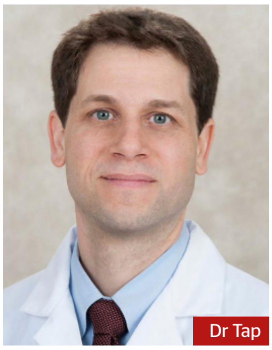
Dr Antonescu

The EHE Foundation has continued to fund a research grant to Dr. Christina Antonescu, Director, Bone and Soft Tissue Pathology at Memorial Sloan Kettering, New York, for her research entitled a ***"Molecular and Immune Characterization of EHE Clinical Subtypes";*** a comprehensive study of EHE genetics and the tumor microenvironment. The study will map intra-tumoral molecular differences between various subtypes of EHE, as well as variations in immune cells infiltrating and surrounding EHE tumors. The objective of this research is to identify potential targets for various types of treatments including immunotherapy.

The EHE Group was particularly excited when earlier this year the Sloan -Kettering team of scientists lead by Dr. Antonescu published their first EHE paper containing the findings from the first phase of the study funded by the EHE Foundation. This research paper, entitled ***"Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets"*** can be found at:

https://www.nature.com/articles/s41379-019-0368-8

2 International Center of Expertise in EHE Research established



Dr Tap

In addition to the grant provided to Dr Antonescu, and with the support of The EHE Foundation and our generous donors, Memorial Sloan Kettering Cancer Center in NYC will work over the next 3 years to establish an ***"International Center of Expertise in EHE Research".***

The project will be led by Dr. William Tap, Chief, Sarcoma Medical Oncology Service, and Dr. Cristina Antonescu, at MSK.

Goals include creating an EHE clinical database and tissue/blood biobank; instituting a multidisciplinary EHE patient care team focused not only on clinical presentation, but also pathology findings; launching a comprehensive research program to include various genetic projects, immunotherapy, development of EHE models and multiple drug screenings; developing a central EHE Collaborative Core by providing tissue and genomic data to other researchers studying EHE.

02 EHE Research

Tissue donation in the USA

The EHE Foundation in the USA continues to partner with Pattern.org on tissue donation. Pattern.org enables cancer patients to direct their tumor tissue to researchers working on building cancer models. The Foundation's partnership with Pattern.org empowers EHE patients to be directly involved in cancer research.

Tissue and medical data shared by patients through Pattern.org help scientists develop next generation cancer models, which will be made widely available to the research community. Using these models, researchers can identify cancer's key points of vulnerability and accelerate drug development. Pattern.org, was launched by the Rare Cancer Research Foundation (rcrf.org) a 501(c)3 non-profit dedicated to curing rare cancers through strategic investments and collaborations that catalyze effective research and accelerate deployment of promising therapies.

The EHE Foundation is also collaborating with Pattern.org and The Broad Institute to further the development of an EHE cell line. Cell lines are the main model to study cancer behavior and response to various therapies. Cell line development can be a very complex process which begins with coordination between patients and providers on tissue donation. EHE patients are demonstrating exceptional understanding of the importance of donating their tissue to research and the EHE Foundation will continue to support patients by providing easy access to a well-coordinated tissue donation program.

If you are facing surgery or indeed any procedure that you feel may result in tissue or fluid samples being available for this important programme, please feel free to contact Lisa DeYoung, Director of Patient Services, on **925-9986693** or at **lisadeyoung@fightehe.org.**

As part of its growing focus on the capture of EHE fluid and tissue samples, The EHE Foundation (US) was delighted to also announce the recruitment of Patty Cogswell in the role of Biobank Director. Patty has already initiated work on establishing the EHE Biobank in the USA.

03 EHE Fundraising

As we said in our last edition of The Pledge, we are continuing to work with all our brilliant supporters to get our fundraising activities back up and running through the second half of the year. This will be a significant challenge, but one we cannot ignore. And our supporters did not let us down. Some of the fundraising activities that restarted in the last quarter can be found below..

We also noted that this year is the 5th anniversary Year for The EHE Foundation in the USA, The EHE Rare Cancer Charity (UK), and The Rare Cancer Foundation Australia. In the last edition of The Pledge we celebrated The EHE Foundation's birthday by sharing some of their fundraising events over those five years. In this edition we are celebrating with the EHE Rare Cancer Charity, and have again shared some of the fundraising events of the past five years. We hope you enjoy this brief trip down our fundraising memory lane.

Could you be a Matching Donor?

The EHE Foundation is hoping to repeat the fantastic success it had in past years with a matched funding campaign around **#GivingTuesday.** To repeat that success the Foundation is looking for individuals, companies or other groups to provide matched funding, which will be able to multiply the impact of each donation received on **#GivingTuesday.**

The EHE Foundation posted news of the event and a call for help.

> “Do you know a generous donor looking for an amazing cause to support? In preparation for this year's #GivingTuesday (on Dec 1st), we are hoping to extend our partnership with additional matching donors. Matching donations are tax deductible, start at $1K, and can be made by an individual, group, company, or foundation.”

#GivingTuesday is a global movement to celebrate and encourage giving after Thanksgiving, Black Friday, and Cyber Monday. It is The EHE Foundation's largest annual fundraisng event. Rare cancers have many added obstacles, but together our tight-knit group is making astounding progress in research, support, and awareness.

If you can assist, or you know somebody or an organization that may be able to help, and you would like more information, please contact Jenni Kovach at jennikovach@fightehe.org or LeeAnn Conner at leeannconner@fightehe.org.

03 EHE Fundraising

Easy money from Amazon Smile

In many of our past editions we have posted news to remind people of the ability to collect free money from online shopping sites like **'Amazon Smile'** and **'Easy Fundraising'.** This edition of The Pledge is no different as several of our members have high-lighted this form of fundraising in these difficult times.

In the UK Allana Parker asked people to share an explanatory video, created by Anna Wydro, of how to shop through **smile.amazon.co.uk** and raise funds for the EHE Rare Cancer Charity:

> "This year has hit charities HARD!! The last thing on people's minds is giving to charity, but rare cancer charities like the EHE Rare Cancer Charity rely so much on these donations. So how about you give to charity but it costs you nothing?? By following Anna Wydro's great video, you can register with Amazon Smile, and every time you buy on Amazon they give to EHERCC!! Just follow those simple instructions and you will hear me and every other person here in the UK with EHE whispering **"Thank You"** in your ear!"

Adrianna Glennie also posted news about her purchasing with Amazon Smile and the total donations made to the EHE Rare Cancer Charity in the UK.

If you are not already an AmazonSmile member, **sign up** on your web browser

You have generated £1.53
as of September 09, 2020

Every little bit counts

When millions of supporters shop with AmazonSmile, charitable donations quickly add up.

Ehe Rare Cancer Charity (Uk)
has received as of August 2020
£206.48

Exactly the same concept is available in the USA. There The EHE Foundation asks its members to buy on line through **smile.amazon.com** (instead of amazon.com) and select The EHE Foundation as their recipient for donations. And these funds are definitely important. Lisa Hartle De Young and Nancy Castle both posted updates:

> "Great job EHE Amazon shoppers! Amazon Smile is the philanthropic arm of Amazon and they donate a portion of purchases to the EHE Foundation each quarter. It's FREE money donated on the same exact products and pricing as regular Amazon. In the quarter we raised $556 through Amazon Smile who have now donated just under $6,500 to The EHE Foundation."

On the bottle for EHE research

It is hard to fundraise in these difficult times, but Fiona Louise found an easy way in Canada to keep funds rolling in.

> “In Ontario bottles sold with wine, beer or liquor are sold with a small deposit. I have been asking neighbours to drop off their empties and I return them for the deposit. While my driveway does look like I have a significant drinking problem, so far in July alone I have returned $387 worth of bottles. I think if I get enough people in the habit of dropping off on my driveway I could easily make over $1000 a year.”

Well done Fiona. People are only donating a dollar or two each with their bottles, and for that small donation they also get rid of the hassle of taking them back. It is such a great way to raise what could be over $1,000. Keep going.

Allana Parker’s friends are fundraising for the EHERCC

In September Allana posted news that two more of her fantastic support network are raising funds for the EHERCC. *“A couple of my wonderful friends, Donna Watson and Amy Mills, are once again helping the EHE Rare Cancer Charity.”*

Donna explained:

> “Myself & Amy Mills are going to be carrying out a charity event in October to support our dear friend Allana Parker who battles everyday with EHE rare cancer. This cancer is rare which is why we need your support so that research can be carried out to cure this terrible disease.
> Last year was alcohol free for 1 month, and I raised £235! We would love to beat this. This year we are exercising before or after work for 31 consecutive days, biking, walking or running for 2 miles a day a pretty big challenge to us as we haven’t exercised for months.”

> “A just giving page will be uploaded soon, please support us, every little helps. We will also have charity boxes in both Beautique & Hair Affair.”

We cannot thank Donna and Amy enough for taking up this challenge. Fundraising has been very hard through 2020, for obvious reasons, so the EHERCC could not be more grateful for every penny raised. And we look forward to reporting how they got on in our next edition.

03 EHE Fundraising

5th Annual EHE Fun Run and Walk – Registration is still open

Registration remains open for **The EHE Foundation's 5th Annual EHE Fun Run and Walk.** This family fun event is for all ages and abilities. It is also virtual, which means it can be done anywhere you are. Simply register, receive your race packet in the mail (based on when you register), choose to do a 5K (3.1 miles) or 1K (.62 miles), and complete it when it is convenient for you. You can do it alone or with others who register. You can join a ***"team"*** to walk in honor of or in memory of a loved one. You can also leave a note of inspiration. **100% of the donations and profits from this event will be dedicated to EHE research.** The price of $30 includes a t-shirt, race bib, EHE bracelet, temporary ***"Just Live"*** tattoo, and shipping (US only). The Foundation has youth sizes XS to XL and adult sizes S to 2XL. If you are interested you can register at **www.fightehe.org.**

A special Thanks to our sponsors:

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Giombetti Associates
Hansen Distribution Agency

Gold Sponsors
Dolph & Associates
Fischman Outdoor Kitchens
Monticello & Warren Animal Clinics
Pure Skin Beauty
State Farm - Steve Botkin
V&P Hydraulic Products

Silver Sponsors
Midwest Dental
Team Diana Axness

Several people shared news and photos of their participation in the Fun Run and Walk. Shannon Estrem posted:

> “Better late than never, right? Finally got my walk in today with five of my besties in Othello, Washington. ***Just live friends!***”

Diana Axness shared a link to news of their event, where some of her friends did a horse and carriage drive for the EHE Fun Run and Walk. This received great local news coverage adding EHE awareness to their wonderful fundraising. Check out the story at: **https://kimatv.com/sports/content/moxee-women-out-on-a-wild-ride**

Leah Heinrich shared the photo of her and her little brother completing the event. As an EHE patient herself, she was happy to support the annual event in Pennsylvania. She said:

> “I support the EHE Foundation 5K because it’s a healthy way for me to give back to an organization that has given so much to me in my fight against EHE.”

03 EHE Fundraising

Anna Wydro drives the first ever EHE Wall Calendar for 2021

The third quarter saw Anna Wydro's idea of creating an EHE Wall Calendar for 2021 take off. Her idea was simply to use landscape photographs from around the world, donated by our members, to reflect the fact that our EHE family is also global. So posts went out asking anybody who had a great landscape photo of somewhere they love, or somewhere that looked stunning, to put it forward for the calendar.
Anna explained:

> “We want to cover all seasons, so don't worry about what season your photo represents. We also want to be able to say where the photo is of, so please tell us where the photo was taken, and if you can remember, the approximate time of year or maybe month?”

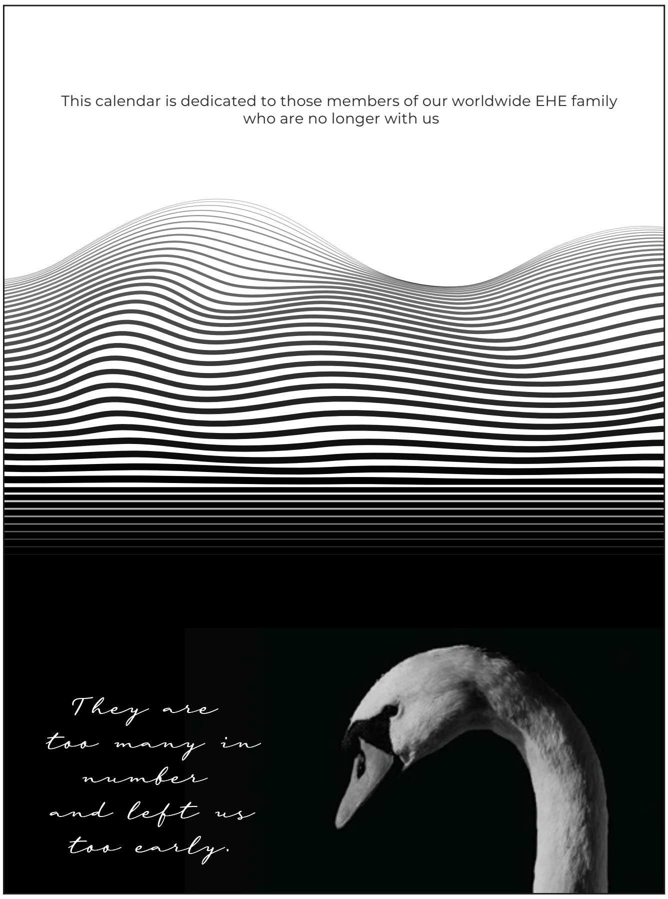
The response was fantastic with literally hundreds of photos submitted. Selecting the final twelve was so difficult, but in the end Anna was able to pick 12 stunning photos. At the time of issuing this edition of The Pledge the calendar has been finalised.

The EHE Group is also pleased to be able to confirm that all printing and shipping/postal costs have been funded by two or three of our supporters so that every pound or dollar you spend on calendars will go to EHE research.

In addition to the 12 photos, the calendar includes a memorial section, remembering all the members of our EHE family who are no longer with us.
Hugh Leonard explained:

> “We spend a lot of time talking about raising funds, research, patient support and advocacy. Those are all core objectives, but we also wanted to remember all our friends and family members whose lives have been cut short by EHE. We will never forget them.”

There are also information pages about EHE, the EHE Group, and the international research collaboration that we are jointly funding.



This calendar is dedicated to those members of our worldwide EHE family
who are no longer with us

*They are
too many in
number
and left us
too early.*

And now for those fundraising memories!

2015

'Team Henderson' held their first **race night** and so started an EHE fundraising dynasty!

Team Henderson
Race Night Team

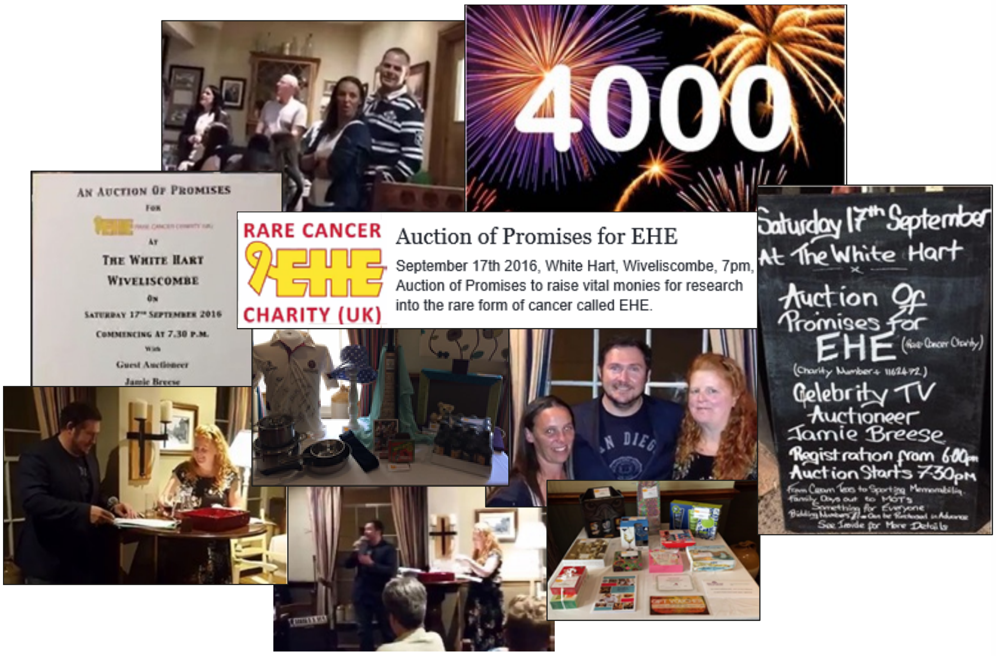
2016

Alastair Simmie and a small group of close friends cycled the length of the UK, from **Land's End to John O'Groats,** a ride of over 1,000 miles, in support of **Milly, Alastair's wife,** and completed the process with the **UK's first EHE charity ball**.

03 EHE Fundraising

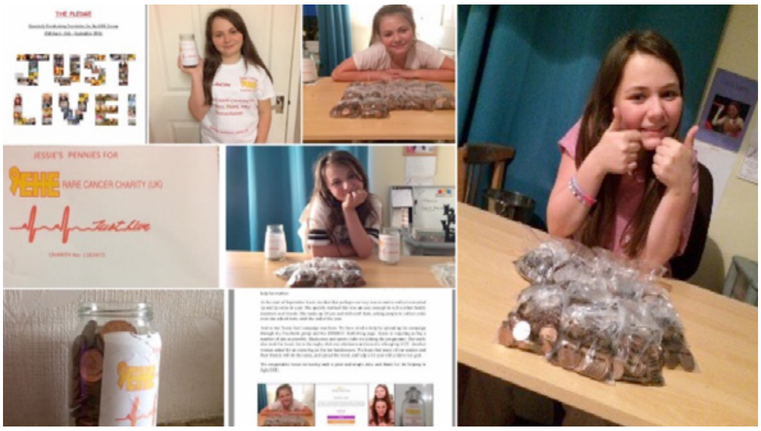
2016

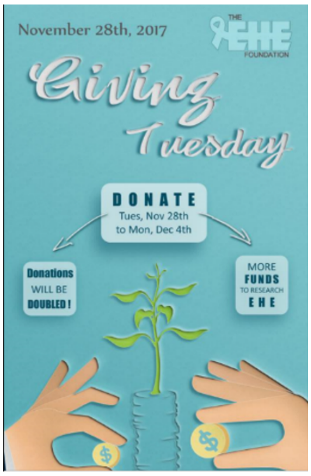
Tamzin Jones held her **Auction of Promises** at the White Hart in Wiveliscombe in the UK. Huge numbers turned up to take part and made the whole event a huge success.



2017

Jessie Hayman launched and ran her **Jessie Jars campaign** where she simply asked friends, family, school friends and the public, to collect their small and unwanted coins for EHE research.





On Giving Tuesday, 28th November, we have been offered matching for all funds we raise up to £10,000

WE ARE LIVE! Our campaign is live until midnight on 28th November

OUR TARGETS! £10,000 to raise £10,000 to match

With help from all our supporters we can secure £20,000 for critical EHE research. These funds will ultimately lead to the alleviation of suffering of EHE patients and save lives!

Please help us if you can!

The **UK** and **USA foundations** ran **matched funding campaigns for Giving Tuesday** with great success. The support from our members and the public was huge. The UK raised over **£100,000** while America raised over **$60,000** in just a week.

2018

The EHE Rare Cancer Charity took part in the **London Landmarks Half Marathon** and the **RideLondon100 cyclethon.**

2019

EHE charity ball, family fun day, and **super relay marathon** all completed in the UK.

WOKINGHAMPAPER.CO.UK

Wokingham pub's fun day helps raise funds for rare cancer charity - The Wokingham Paper

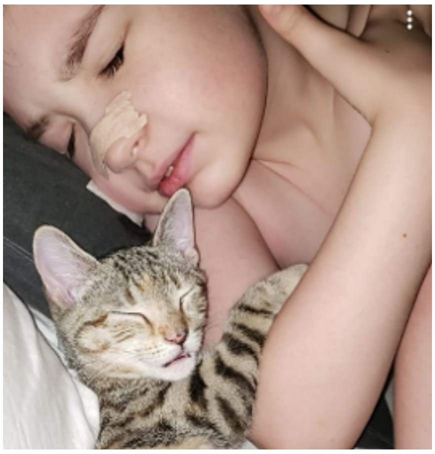
Charlie Medwin sets off to row **across the Atlantic Ocean** in support of **his brother Harry**, and to raise funds for EHE research.

04 And in other news…

Pet therapy

We always enjoy posts which involve our pets. Heidi Littlefield posted a great example with her son and their 3 month old cat having a snooze and a cuddle.

As Heidi commented **"I've never seen anything cuter. Pure love".**



A new arrival

New arrivals are always so special, so we were delighted to see SJ's post about the arrival of baby Jack.

> "James and I welcomed Jack to our lives on August 3! We are beyond overwhelmed with love and Joy! Best blessing ever. He's absolutely perfect and we couldn't be happier!"

A very special graduation

We were delighted in July when Aimee Ladd posted news and photos of her daughter's high school graduation. This was especially exciting as Veronica had been ill but recovered and was able on the day to attend the graduation.

> "High school graduation is a very special day for all parents and their children. However, when you have a child with cancer, it is a day that is extra special because it is a day that at one point in time or many, you were afraid you would never see. We were so excited yesterday that Veronica was healthy enough to attend graduation today. Congratulations Baby girl! You made it!!!"

Photo therapy

Carl Dickson posted this sunset photo.

> “Sunset in Eagle County as the fire burns in Piney Gulch. Like I always say you can find beauty even when life and nature throw difficult things your way.”

Anna Wydro and Artur Rozwalak posted this wonderful photo of the sunrise above Loch Lomond in Scotland, which they dedicated to our EHE family member Adrianna Glennie who had hoped to join them but had been unable to make it.

As always, Robinson Ortiz posted another photograph, with a positive quote from Charlie Mackes for everybody associated with EHE.

> “Sometimes just getting up and carrying on is brave and magnificent.”

Just live

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