

Issue 48 Summer 2022

Endocrine Views

Opinion and news from the European Society of Endocrinology

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Supporting your career in research

In this issue

Insights into neuroendocrinology
Launching European Hormone Day
ECE 2022: the many highlights



European Society
of Endocrinology



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Astrocytes (red) interspersed among neurons (green) in the brain.
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Editorial



The joy of meeting in person at ECE 2022 in Milan, Italy, spills into this issue, as we recall the highlights (page 3), the ESE Award winners (page 16) and exciting new initiatives, such as European Hormone Day (page 4). On page 5, we reflect on the words that our President, Martin Reincke, shared in his address.

The future of ESE was prominent in Martin's address, including the new Research Roadmap, which will be a vital document in the development of European endocrine research. ESE seeks to support the research community at all levels. In this issue of *Endocrine Views*, we take this to heart, highlighting ESE initiatives and tips from successful researchers in our field.

On page 7, ESE Science Committee Chair, Martin Fassnacht talks about his own experience in endocrine research, the ways in which ESE supports researchers, and the Society's plans for the future. On pages 8–9, you can learn from leading researchers Márta Korbonits, Daniela Cota, Ruben Nogueiras and Cynthia Andoniadou as they share their advice.

I am delighted that Niki Karavitaki joined us as Guest Editor for this issue. As my fellow ESE Focus Area Lead in Pituitary and Neuroendocrinology, she helped curate our content in this area. This includes the exciting and continuing debate on the naming of PitNETs versus pituitary adenomas, summarised eloquently for us by Ashley Grossman and Ken Ho on page 10.

Our focus on neuroendocrinology continues on page 12, where Ariane Sharif and Vincent Prévot discuss their captivating studies on the communication between GnRH neurones and glial progenitors that leads to puberty.

Barriers to gender equity in medicine and research sadly remain. In this light, we welcome the new initiative EUWIN (European Women in Endocrinology), which was launched at ECE 2022 (see page 4). We are also pleased to have an analysis of the current issues influencing gender balance, with ideas for future progress, from Joy Wu (page 11).

Finally, we bring you highlights from ESE journals, including the new ESE Guideline on endocrine side effects of immune checkpoint inhibitors (page 13), and a study into the COVID-19 pandemic's impact on rates of precocious puberty in girls (page 14).

There is something for everyone here!

Justo P Castaño
Editor, *Endocrine Views*

Areas of interest in this issue:



Awards



Events



Reproductive and Developmental Endocrinology



COVID-19



Pituitary and Neuroendocrinology



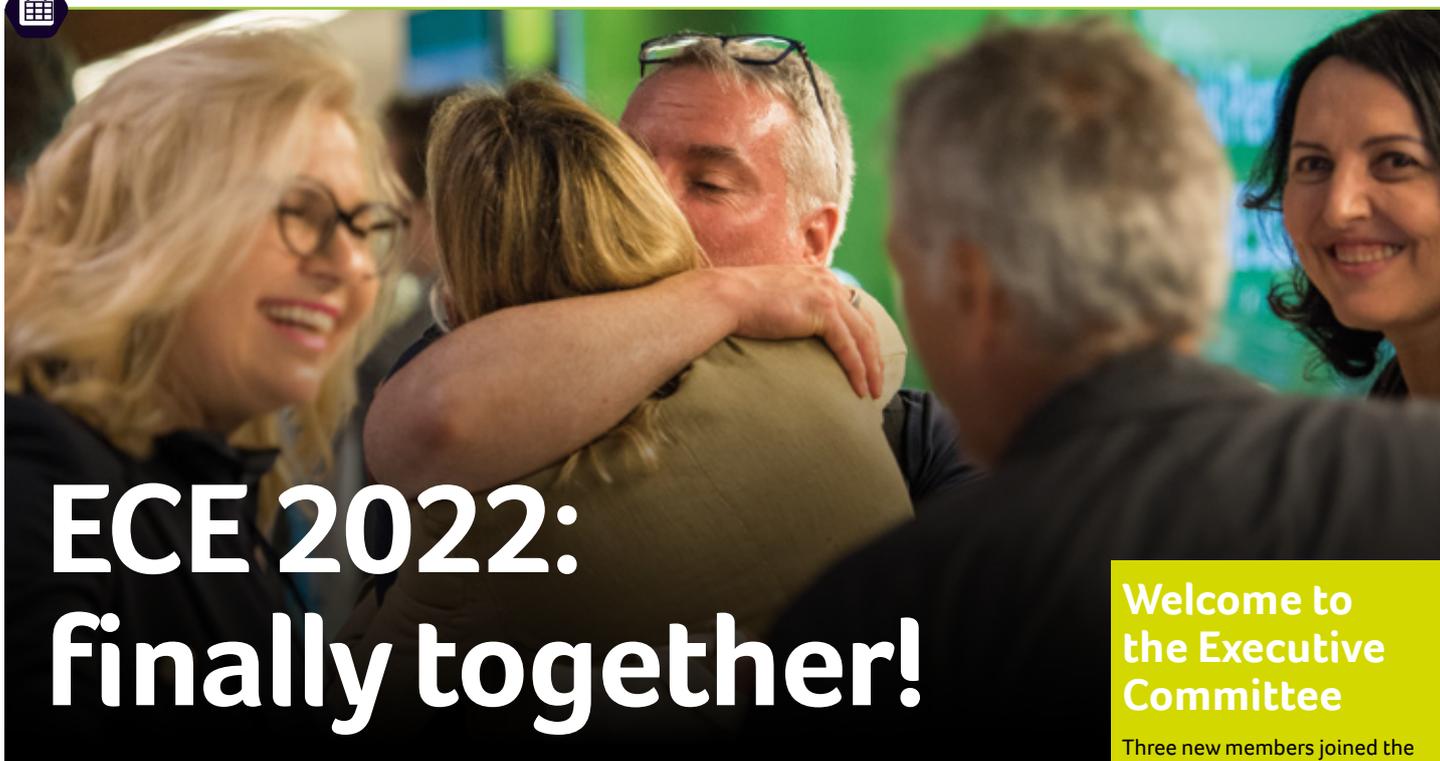
Research



Endocrine-related cancer



Publications



ECE 2022: finally together!

When attendees were asked what they most liked about the 2022 Congress in Milan, the majority said that what made them happiest was being together again at a live meeting.

ECE 2020 and ECE 2021 were virtual because of the pandemic. Although very well-attended, the enthusiasm in those years was slightly different and the atmosphere less joyful. At ECE 2022, we could really feel a novel, enthusiastic atmosphere. People were smiling at each other, embracing friends, and actively participating in their favourite sessions.

We had an extraordinary and exciting opening day, which perfectly anticipated the spirit of the whole Congress. Alongside the Geoffrey Harris Award (the Society's most prestigious prize) and the *European Journal of Endocrinology* Award, for the first time we witnessed the lecture by the recipient of the Transatlantic Alliance Award. The winner of this joint ESE and Endocrine Society prize, Shlomo Melmed, talked on 'Growth hormone: an adult endocrine misnomer'. Photographs

of these and other Award recipients are on page 16.

As always, our goal was to maintain both basic and clinical science at the highest levels and to involve all participants in discussions with faculty members. Delegates could start each day with an early morning 'warm-up' at the Meet the Expert and New Scientific Approaches sessions, before plunging into a programme of outstanding plenary talks, symposia, joint sessions and debates, as well as rapid and oral communications selected from each ESE Focus Area, and diverse posters. Every early morning and afternoon, members of the Programme Organising Committee (POC) and Focus Area Leads presented a Daily Spotlight, anticipating and summing up the highlights of the day.

Amongst the many exciting basic science lectures, one highlight was Manuel Tena-Sempere's talk on

how the brain decodes nutritional signals for fine control of puberty onset. This is a hot topic, since we are witnessing how early obesity is linked to disturbed puberty and is bound to adverse health outcomes in both sexes. We also had superb presentations on new developments in the fields of extracellular vesicles, microRNAs and single cell -omics, as well as sessions related to endocrine-disrupting chemicals: an increasingly relevant topic in endocrinology.

The outstanding presentations by clinical specialists included talks on advances in our understanding of pituitary disorders, how artificial intelligence could change our view on assisted reproduction, the latest developments in rare endocrine tumours, nutritional and metabolic aspects of the thyroid, a clinical update on parathyroid disorders, insights into hormones and emotions, the transition from childhood to adulthood, and the very topical 'Diabetes remission: from dream to clinical goal'.

There were many joint sessions with other organisations, and the events for nurses had a great impact, as did the activities for the ESE Young Endocrinologists and Scientists (EYES), which focused on artificial intelligence and reproduction. The ESE Council of Affiliated Societies (ECAS) delivered a session entitled 'Europe needs more endocrinology'. The reach of the Congress was extended by industry symposia and Hub sessions, as well as patient group sessions.

ECE 2022 attracted almost 3000 attendees on-site and over 1000 online. It was a feast of basic,

Welcome to the Executive Committee

Three new members joined the ESE Executive Committee in May.

Maria Chiara Zatelli (Italy)
ESE Secretary

Cynthia Andoniadou (UK)
ESE Congress Committee Chair

Stavroula Paschou (Greece)
EYES Committee Co-Chair
(ex-officio member)

Grateful thanks are due to retiring Executive Committee members Mónica Marazuela, Riccarda Granata and Eva Coopmans for their valuable contributions.

translational and clinical science, thanks to the great commitment of our outstanding speakers, excellent Chairs, and unique community of friends and colleagues. Its success was due to the contributions of the POC, the ESE President and President-Elect, and all the Executive Committee members. We warmly acknowledge the ESE staff, particularly the Event Manager, for their valuable and tireless support.

At last we return to real life, to enjoy science, friendship and shared experiences, expecting to continue each and every year with this incredible Congress. The POC is already working on the programme for ECE 2023, and we will be waiting for you in Istanbul!

Riccarda Granata
ESE Congress Committee Chair
Carlos Diéguez
POC Basic Lead
Beata Kos-Kudła
POC Clinical Lead



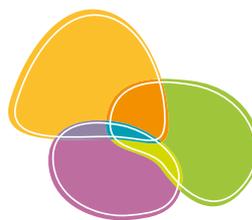


Annual date to mark hormones

On 23 May 2022, ESE launched the first ever dedicated awareness day for hormones – European Hormone Day (www.europhormoneday.org). This annual event will alert policymakers and the public to the central role of hormones in health and in addressing disease.

The European Hormone and Metabolism Foundation (ESE Foundation) and partner societies collaborated with ESE on the launch. The focus for 2022 was on European and national decision makers, encouraging them to pay close attention to hormones when drafting policies. With this aim, the launch included the Milano Declaration: a statement presenting some of the main challenges and potential solutions in endocrinology, reiterating messages from the ESE White Paper.

Ewa Kopacz, Vice-President of the European Parliament, welcomed European Hormone Day, saying, 'I fully support this important initiative and the recommendations of the Milano Declaration. We should raise awareness of the importance of hormone health!'



European Hormone Day

Because Hormones Matter
23 May 2022



Ewa Kopacz speaking at the launch of European Hormone Day



The launch of EUWIN at ECE 2022

ECE welcomes EUWIN

European Women in Endocrinology (EUWIN) was launched at ECE 2022 (www.eese-hormones.org/euwin).

Founded by Cynthia Andoniadou (UK), Wiebke Arlt (UK) and Jenny Visser (The Netherlands), the group will improve opportunities and diversity for women in European endocrinology and within ESE, enhancing collaboration and supporting the career advancement of young female trainees and investigators.

After the launch, Wiebke commented, 'Thank you to all the women (and men) who came to the EUWIN launch and came up with lots of exciting ideas in the brainstorm networking session!'

From the ESE Office

I hope everyone is looking forward to a good summer break. As I write, we are still in 'recovery mode' – in the best way – from a fabulous Congress in Milan. We enjoyed excellent endocrine science, as well as interacting face-to-face with colleagues and friends for the first time in 3 years.

Justo Castaño, Editor of *Endocrine Views*, expressed it perfectly in a Tweet after ECE 2022: 'I'm happy and sad. Real congresses were going to be replaced by virtual meetings, so they said ... Guess what: NO WAY! I return home full of energy, ideas, challenges and, most of all, hugs, love, smiles. Friendship cannot be substituted and research needs friends.'

I cannot improve on that, Justo, and can only echo those perfect words.

The ESE Team has, indeed, come away from the Congress with renewed energy to deliver for all of our members. We are working on a number of substantial projects. Just to select two, we are starting to develop a European Research Roadmap for endocrinology, which will outline the specific research needs and programmes in endocrine health and disease that will contribute to better health in Europe. It is a challenging project, but is immensely important for European endocrinology, to better define our future focus. We are also working on the implementation of an ESE Academy, which will support our

endocrine community at mid-career stage, and aims to foster future endocrine leaders, educators and advocates. We aim to launch this in the autumn.

Finally, I would like to welcome the new members of our ESE Team. Natalie Dass has taken on the role of Business Development Manager, supporting our Strategic Partnerships Director, Dirk De Rijdt, in their work on ESE's relationships with industry. Janice Clay has joined us as a Senior Marketing Executive, supporting Victoria Witherby on marketing activities for the Society. I also congratulate Victoria on her new role as Marketing, Communications and Membership Manager, which is an essential new role to support our developing Society.

Please do get in touch with me if you have anything to discuss. I wish you all a wonderful summer!



Helen Gregson
Chief Executive Officer, ESE
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‘Who are we and where are we going?’

In his Presidential Address at ECE 2022, Martin Reincke shared his perspective on the past, present and – importantly – future of your Society.

The questions ‘Who are we and where are we going?’ were considered long ago, by the German philosopher and poet Novalis (1772–1801), in his quest to address the relationship between soul and science during the Age of Enlightenment. Today, we find ourselves asking these questions again, but in the context of your Society.

In my first year as your President, I have become increasingly aware of ESE’s many strengths. It is one of the youngest European scientific societies, and has benefited throughout its 16 years from strong leadership from an enthusiastic and engaged Executive Committee and its other, very active, Committees, the dedication of its focused staff and, especially, the support it receives from you, its members.

Uniquely representing the field of endocrinology at the European level, ESE displays a strong, unifying purpose in patient care, education, research, and policy and advocacy. It is growing rapidly (an increase in membership of 10% year on year).

Our past performance against our 2017–2021 strategic plan, under the stewardship of previous leaders, particularly AJ van der Lely

and Andrea Giustina, has been astonishing:

- a growth in membership of 34%, to exceed 5000 individual members
- an increase in early career membership from 24% to 30% of total members
- our association with 53 national societies and 12 specialist societies, to represent more than 23 000 endocrinologists across Europe
- the publication of our White Paper ‘Hormones in European Health Policies’, which was welcomed by European policymakers
- elevated Impact Factors for *European Journal of Endocrinology* (now 6.664) and *Endocrine Connections* (3.335)
- the launch of the European Hormone and Metabolism Foundation (the ESE Foundation), an independent organisation, which will run the newly launched annual European Hormone Day
- the expansion of educational activities, including ESE Talks, Clinical Updates, Spotlight on Science, with 27 events in 2021
- transformation of ECE 2020 and ECE 2021 into digital events
- the launch of our rapidly growing Patient Advocacy Group Affiliate Membership.



What is our Society?

Last year, I had the privilege of working with the Executive Committee to define the strategy for the next 5 years (2022–2026). This led us to examine our Society’s current position, and to identify its activities. In addition to our phenomenal Congresses, ESE is a successful publisher, with two respected journals – and maybe more in future. We are active in policy and advocacy, striving for increased awareness of hormones in Europe, and occupying a strong position. Your Society is an educator, with many associated activities and courses. We are also very much engaged in research.

This illustrates that your Society is much more than ‘a Congress’ or ‘a membership’.

In considering the new strategy, there were several areas we had to take into account: the Society’s financial and environmental sustainability, our policy and advocacy focus, improving our scientific outreach, ensuring diversity and inclusion, enhancing services to members, and the necessary growth of our team and infrastructure. The significant growth of our team over the last 5 years has been accompanied by a commensurate growth in supporting infrastructure. Consequently, we have a world-class team to help deliver our strategy.

A Society on the move

The strategy we have set is supported by four ‘pillars’, each of which comprises many ‘bricks’, contributing to our stated aim of ‘**shaping the future of endocrinology by uniting, supporting and representing our community**’. Those pillars are shown in the Figure. You can find further details at www.ese-hormones.org/about-us.

What the future holds

You can expect to hear more about several exciting initiatives in the coming months and years. Here are just a few of them:

- The **Research Roadmap** is an initiative which will be equivalent in stature to the White Paper, reflecting the development of endocrine research within Europe, to better support the research community at all levels.
- The **ESE Academy** will develop the next generation of leaders in endocrinology, in Europe and beyond.
- **Global collaboration** will see us working more with other international and national societies.
- **Digital transformation and infrastructure development** will underpin our development and better support you, our members.

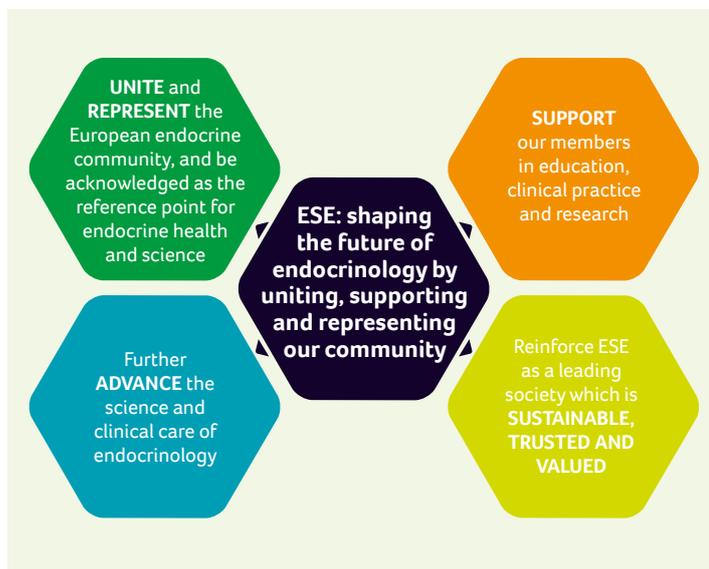
You will recall Novalis, and his consideration of the questions ‘Who are we and where are we going?’ These are, in fact, very good questions to ask about our Society – and about ourselves! It was in one of his poems that Novalis concluded that ‘We are always going **home**’. In that way, I hope that our Society, which is (and always has been) endlessly moving forwards, is itself heading ‘home’.

Thank you for your support as we continue the journey together.

Martin Reincke

ESE President

@EsePresident





Success for Observership Programmes

The 5 years since the EYES Clinical Observership Programme (COP) was first envisaged have seen much international upheaval. Despite that, we kept striving for a future of free knowledge and equal opportunities for early career investigators around the globe.

The first round in 2020 attracted 26 applicants. This year, the second round received 40 applicants from 16 countries, with the chance to attend an expanded list of 11 COP centres.

The results were announced at ECE 2022. We congratulate COP grant recipients **Selvihan Beysel** (Turkey), **Marta Borges Canha** (Portugal) and **Mirko Parasiliti Caprino** (Italy). We are also delighted for our self-funded awardees: **Nestan Bostoganashvili** (Georgia), **Paolo Facondo** (Italy), **Irene Gagliardi** (Italy), **Gabriela Handzlik** (Poland), **Adam Maciejewski** (Poland), **Mia Manojlovic** (Serbia), **Brett Mansfield** (South Africa) and **Nino Matas** (Croatia).

With the continued support of the Executive and Science Committees and the ESE Team, we launched the new EYES Research Observership Programme (ROP), with 6 fantastic centres. It was immediately well-received, attracting 33 applicants from 15 countries in this, its first round.

Our successful ROP grant recipients are **Jowita Halupczok-Zyła** (Poland), **Narjes Nasiri Ansari** (Greece) and **Emre Sedar Saygılı** (Turkey). The self-funded awardees are **Fabio Bioletto** (Italy), **Roxana Dumitriu** (Romania), **Elisa Rossini** (Italy) and **Valentine Suteau** (France).

This is a milestone worthy of celebration! The EYES Observership Programmes have proved that early

career investigators everywhere aspire towards academic mobility and international experience. We will keep developing the EYES COP and ROP to become an integral part of the European endocrinology programme, as a step towards unification of a pan-European

eyes 
ESE young endocrinologists
and scientists
looking forward

curriculum in endocrinology. We will do so in true EYES spirit: excited about what the future holds!

Antoan Stefan Šojat
EYES Co-Chair and Observership Programme Lead

‘We launched the new EYES Research Observership Programme... It was immediately well-received.’

Early career grants

The Bioscientifica Trust exists to distribute funds to early career scientists and clinicians in biomedicine and the life sciences. Its aim is to improve research and clinical outcomes by facilitating co-operative research, by means of the following types of small grants.

Standard Grants typically <€5000

To further endocrine research or delivery of service for academic, clinical or public benefit, led by early career applicants.

Travel Grants typically <€2000

To facilitate new, international collaborations or the exchange of knowledge/skills, or the dissemination of new endocrine-related science to wider audiences.

Scientific Meeting Grants up to €10,000

To support small, tightly focused meetings of 10–20 attendees on specific topics.

There are three grant rounds per year; the next deadline is 31 August 2022. Applications are competitively assessed by the Trustees, and full details, including the application process, can be found at www.bioscientificatrust.org.

Stavroula A Paschou
Bioscientifica Trustee

 **BIOSCIENTIFICA**
TRUST

Hypoparathyroidism Patient Forum

Over 150 participants took part in the first ESE Hypoparathyroidism Patient Forum, held online on 26 March 2022. They included patients, their families, and those who treat and care for people with hypoparathyroidism.

Clinical and patient experts discussed the following areas:

- Symptoms of hypoparathyroidism
- Current standards in hypoparathyroidism care: practical problems and limitations
- Hormone replacement therapy: new developments and future prospects.

Simultaneous translation into French, Spanish and Italian allowed wider participation, and the Q&A session (pictured) saw the experts asked many questions by a very interactive audience.

The full programme and recordings of the sessions are available at www.es-hormones.org/1esehypoparapatientforum.



The Hypoparathyroidism Patient Forum is an ESE pilot project, which brings clinical experts and patient group representatives together from across Europe to identify the needs of patients with hypoparathyroidism. We thank Andrea Giustina (Italy), Heide Siggelkow (Germany), Natalie Grosset (Hypoparathyroidism France) and Tanja Richter (Netzwerk Hypopara, Germany) for organising this event, and Takeda for supporting it through a restricted grant.



An interview with Martin Fassnacht

Martin Fassnacht is Chair of the ESE Science Committee, which supports scientific research in endocrinology in Europe, including funding, education, policy and public relations. Here, we talk to Martin about his life in endocrinology, ESE's support for research, and much else besides.

How did you become interested in endocrinology?

There was a 'magic moment' at the end of my first year of medical school. In a lecture entitled 'Introduction to clinical medicine', Bruno Allolio introduced us to the world of hormonal diseases. In his enthusiastic and inspiring talk, I heard of acromegaly and Cushing's syndrome for the first time, and became 'hormone-addicted' for the rest of my medical life.

What would you have done if you had not studied medicine?

I would probably have been a teacher. I love to work with people.

What are your main interests in the field?

At heart I am an 'adrenalist'. For a long time, we have searched for better treatment for adrenocortical carcinoma. This is a little bit like searching for a needle in a haystack; despite many efforts by ourselves and others, we have not yet found the 'magic bullet'. However, as an 'adrenal community', we have made significant progress in the last 20 years. We also work on more common adrenal diseases. Currently, I have a vision of a long term clinical trial in patients with adrenal incidentaloma, to clarify whether or not autonomous cortisol secretion requires active treatment.

What is the secret to success in endocrine research?

For all researchers, the key challenge is to ask the right questions at the right time and to try to answer them. For this purpose, a good team of coworkers is crucial. And for this, you finally require funding – and the best chance to get funding is to have good ideas and an enthusiastic team...

How is ESE supporting education and training for researchers?

Complementary to the successful education programme for clinicians, we are aiming for tools that

are especially useful for young researchers in different areas of endocrinology. Thus, the Science Committee established the ESE Spotlight on Science webinars, and we will restart the ESE Summer School in July (www.eese-hormones.org/eese-courses/eese-summer-school-2022).

What will Summer School's return mean for ESE and attendees?

We are all suffering from the contact restrictions of the last 2 years. Science thrives on the exchange between colleagues, and Summer School is the ideal place for such an exchange with experts from all over Europe. Here young endocrinologists (scientists, and also clinician scientists) can experience cutting edge science first hand. More senior researchers benefit from meeting enthusiastic young fellows in a nice environment. It's a perfect win-win situation – obviously also for ESE. The fact that we can now revitalise this important event is really great.

How does ESE help members secure EU and other research grants?

Our members told us that identifying the right call is often a relevant bottleneck. So, we dedicated part of the ESE website to European Research Funding (www.eese-hormones.org/research/european-research-funding), providing a comprehensive summary of all kinds of funding opportunities.

Members have also told us (and we know from our own experience) that writing successful grant applications is long and complex. This is particularly true for proposals that build on the development of European consortia, whose efforts need to be co-ordinated. Our recently adapted ESE-SEEDER-EU programme (www.eese-hormones.org/grants-and-awards/grants/eese-seeder-eu-programme) provides consultancy support for individuals or consortia during the

grant selection and writing process. We worked with Dr Yulia Matskevich, an expert in European Collaborative Research and Innovation, who brings a wealth of experience in international collaboration, both as a biomedical researcher and as a research manager.

The ultimate goal is to improve the chances of endocrine researchers in competitive funding calls from the EU and other international funding agencies.

What advice do you offer early career endocrinologists?

My main advice is to follow your instinct/gut feeling. The more you burn for your research, the more successful you will be. My second tip is to find a true mentor. Life is just much easier in the early years if you are supported by someone who is really interested in your career. I experienced this by myself as I was fortunate to be guided by Bruno Allolio. The third tip is to collaborate. Research in a team is more successful and is also more fun.

What further plans do you have for developing research within ESE?

From the Science Committee's point of view, the main goal is for ESE to become even more of a 'home' for basic and translational scientists. With this aim, the



Executive Committee is starting to develop a Roadmap for European Endocrine Research, which will outline the specific research needs in endocrine health and disease. It will make policymakers and other stakeholders aware of urgent topics in our field, lead to improved funding and, thus, contribute to better hormonal health in Europe. As a side effect, it will also demonstrate the attractiveness of endocrine research to young people.

We are also open to any suggestions from members for further improvements for scientists within ESE.

If you have a day off, where are we likely to find you?

Cycling! One of my highlights in recent years was an 'annual cycle week' with my teenage boys throughout different parts of the Alps.

And finally...

I am very happy and proud to be part of the ESE family. Especially, in light of this terrible war against Ukraine, it is important that we, as clinicians and scientists, demonstrate how well collaboration works, independently of nationality, religion etc.

'The Executive Committee is starting to develop a Roadmap for European Endocrine Research, which will outline the specific research needs in endocrine health and disease.'



Secrets of success

How do leading endocrinologists build their careers, their teams and their research? Here we ask four familiar faces from their world of endocrinology for their advice on the road to success.



Márta Korbonits

Professor of Endocrinology and Deputy Director of the William Harvey Research Institute, London, UK

The key ingredient to becoming a successful principal investigator is unrelenting curiosity for finding new questions, and finding joy in analysing data and sharing your work with others. The ability to enthuse others is vital: grant-giving bodies on one hand and your peers, collaborators and junior colleagues on the other.

Finding the right people to build a research team is often down to pure luck: who applies for your PhD studentship or postdoctoral position, who wants to join your lab with their own fellowship funding, who joins your department independently from you and then becomes a key collaborator. On the other hand, you try to find people you can work with, who have skills or resources you lack. Without collaboration, you are dead. When leading a team, it can be tricky to keep everybody happy, as aims and timelines are very different. It is important to think with the other person's head, and see where they see their advantage in the common work.

Securing grants is the most difficult task in a researcher's life – and it is getting more difficult. The recipe for success combines a good idea, good resources, high quality and novel techniques, relevant collaborators, previous publication of some work in the field, a crystal-clear hypothesis and workplan and supporting preliminary data.

It can also be challenging to identify the most productive areas for study. When there are several choices, I have often tended to go for the one where there is already supporting data (i.e. the safer but 'smaller gain' option). In contrast, others may do the opposite: selecting the pathway where nothing is known, hoping for bigger, more novel, findings. A balance of the two is probably ideal. It also depends on your resources. Do you have time, money and personnel to go for the more risky one? Bigger labs are definitely at an advantage here.

In terms of identifying the most effective journals for publication, and raising the profile of your work, things have changed a lot in recent years. The truth is, people will find your paper, wherever you publish. This may sound heretical, but I think the choice of journal is purely important for kudos, for your next grant or for your promotion at work... Where raising your profile used to rely on papers, abstracts and talks, social media brings a lot more opportunities. This is where younger colleagues are well ahead of the game!

If I could talk to my younger self, I would say, 'Be more of a risk taker, follow the ideas if they are exciting, and do not back down just because they sound crazy or too expensive.'

'The key ingredient to becoming a successful principal investigator is unrelenting curiosity...'



Daniela Cota

Research Director at INSERM, Neurocentre Magendie, Bordeaux, France

Let's face it, doing research can be extremely time-consuming and frustrating. However, I am convinced that there is no greater reward, intellectually speaking, than formulating your own novel and original hypothesis, and having the chance to prove that it is (hopefully!) true.

This intimate conviction has been my internal motor over the years since I serendipitously started working in research, and it has helped me build my research laboratory.

When asked how to be a successful principal investigator and establish a research team, I believe my answer is similar to what a successful entrepreneur would say about starting a business from scratch. Here are my top ten tips:

1. Be curious and bold, work on a research question that you really believe to be important.
2. Truly enjoy what you are doing (as you will spend most of your time doing it).
3. Have strong drive and passion, which can help motivate your team members, and be resilient. Being an optimist also helps, as it may take years to prove that your hypothesis is right.
4. Develop excellent writing and communication skills, to be able to illustrate your research hypothesis and data succinctly and convincingly. These qualities are a 'must' if you want to convince research agencies to invest in your work, and to target the most effective journals for publication.
5. Be an effective listener and accept feedback from others. Being open-minded and capable of really exchanging ideas allows you to design greater experiments, to recognise true value and to instil confidence in your students and postdocs.
6. Encourage creativity by regularly brainstorming and discussing ongoing projects and experiments with your team and your collaborators.
7. Do not hesitate to look for expertise if you or your team does not possess an aspect that is needed for a research grant, for a publication or for a new research technique that will help answer your research question. Always be open to reach out to potential collaborators.
8. When you manage a group of people, let them know that you recognise their value and their strengths, but also be honest about their weaknesses and areas for improvement. Make sure to build cohesion by giving your team members tools and space to build trust among themselves.
9. Like any relationship, clear communication with your team members is vital for a successful, happy environment. Be open, direct and have fun discussing science, but also be available to sharing everyday life events.
10. Be empathic and stay humble. My motto (in words attributed to the Greek philosopher Socrates) is 'I know that I do not know'.



'Do what you like the most ... Just do it, giving the best of yourself and fighting for it.'



Ruben Nogueiras

Associate Professor at the University of Santiago de Compostela, Spain

Motivation is the first step on the road to becoming a successful principal investigator. You need to get up every morning wanting to do research – otherwise it will be difficult to keep going, in an environment where we commonly face uncomfortable news, such as the failure of experiments, and the rejection of grant applications and papers.

Perseverance is also critical. As Thomas Edison claimed, 'Genius (or, in this case, success) is 1% inspiration and 99% perspiration.'

Finally, you must make good decisions, starting with your choice of PhD and postdoc supervisors, and then collaborators.

Finding the right people to build a research team largely depends on each university/research institute. At a personal level, this was a great challenge. It is particularly so at the beginning, when you are alone and do not have a real team to attract people. At that point, you need to split working at the bench and the desk. It is critical to teach the first students appropriately and to be realistic about what a very young and small research team can do.

Once the grants start to be awarded and the first papers are published, more students are interested and that is when selecting people is possible. It is extremely difficult to predict who will fit in the team, but an interview with each lab member and, if possible, a few days coming to the lab and knowing the daily work and environment are helpful.

Managing a group of researchers is definitely the most difficult part of the job. I had previously only been worried about my own projects, working in my own way and, suddenly, I needed to carry out a project with others. Nobody prepares us for this, and each personality is completely different. The same words can encourage some and annoy others. It is necessary to be flexible and always keep calm, trying to motivate each person and make them see that we are a team and that we will only succeed if we all share the same goal.

Writing grant applications is a stressful and uncertain activity. You never know what will happen, and it is impossible (at least for me) to know how to secure enough grants. Identifying your areas of interest is usually linked to your background in research, and that guides you to the appropriate calls. I have always chosen obesity-related disorders, as they represent a current health, economic and social issue. Within those, we focus on diseases that do not have an approved treatment, or that have treatments with limited efficacy.

I have not yet successfully found a way of targeting the most effective journals for publication! I guess that we always try to be ambitious but need to be realistic, evaluating our own work in an objective manner to choose the right journal. From that point, anything can happen, because the evaluation process is totally unpredictable. Sometimes, I believe that we have a really great and original story, but the Editors simply do not find it of interest. This means several years of work are taken down in a few hours. We need to be prepared for that: resilience, never give up!

If I could talk to my younger self, I would say, 'Do what you like the most. Do not listen to others. Just do it, giving the best of yourself and fighting for it.'



Cynthia Andoniadou

Reader in Stem Cell Biology at the Centre for Craniofacial and Regenerative Biology, King's College London, UK

I have found that a team gels through a shared work ethic, a positive attitude and passion for the topic. Expertise can be taught and acquired, so consider this when hiring.

When applying for grants, remember that timing is crucial. Apply when your CV and the project are at their strongest, not just because of an upcoming deadline. Substantial grants are built on a proven track record and/or solid preliminary data. It is therefore important to identify the data you will need to generate, ahead of time.

Clarity and logical flow are crucial. A positive state of mind helps when writing applications; exhaustion or bad moods can come across as a lack of enthusiasm! If you do not have certain experience that is needed for a project, collaborate with someone who has a strong proven track record in the area. Ask multiple colleagues to read your grant applications. Including non-experts will result in very insightful comments.

To help me effectively target journals for publication, I was once told 'always write your paper for the Editor', since they are the gatekeeper to getting your research published. This has turned out to be excellent advice. If the Editor is not keen, you will probably face an uphill struggle. Read journal mission statements carefully and know the target audience. If unsure, contacting the Editors of two or three key journals with pre-submission enquiries will help you decide. You should seek enthusiastic, rather than lukewarm, responses. If a paper is time-sensitive, consider submitting it to a respected appropriate journal with quick turn-around times. A high quality study will shine and can be well-cited, no matter the journal.

I am in favour of only publishing fully open access, but many top journals have prohibitive costs for this. There are therefore trade-offs between targeting suitable, highly regarded journals and affordability. If submitting to relevant society journals, check for discounts or waivers offered to members. For all journals, it is worth checking in advance if they operate fee waiver schemes for authors who truly cannot afford the cost.

Finally, if I could talk to my younger self, I would say, 'When choices regarding the direction of research need to be made, pursue work that you find most exciting. It makes light work of writing papers, grant applications and talking enthusiastically about your findings. Every couple of years, reassess the ongoing studies and your research plans for the next 5 years, which will help you stay on track.'

'A positive state of mind helps when writing applications; exhaustion can come across as a lack of enthusiasm!'



A matter of debate



In recent years, a debate on the terminology used for pituitary adenomas has arisen. This has involved the wider pituitary community, and the name 'pituitary neuroendocrine tumours' (PitNETs) has been proposed to replace 'pituitary adenomas'. Arguments have been presented for each option, and discussions are ongoing. This brief debate between two leaders in the field, **Ken Ho** and **Ashley Grossman**, aims to keep endocrinologists up to date and to facilitate a constructive dialogue on this hot topic.

There is no doubt that both parties provide thought-provoking comments encompassing, amongst others, the biology, pathology and clinical behaviour of these tumours. Evolution and progress rely on questioning and reviewing current practice while appreciating its merits. Reaching a consensus through productive conversation, engaging all relevant parties, is an urgent requirement in our small, but elegant, pituitary world. This will avoid confusion and conflict, and allow our discipline to move forward on this issue.



Join in this debate on Twitter!

We know there are many opinions on this topic. We encourage you to voice yours on Twitter.

To stimulate, join or start the discussion, tag @ESEndocrinology and use the hashtags #EVDebates and #PituitaryTumours, so we can listen and share!

The case for adenomas

Neuroendocrine tumour (NET) is misleading terminology that is detrimental to patients with pituitary neoplasms. NET has been proposed by pathologists to replace adenoma because pituitary cells express markers similar to 'NE' cells, and pituitary neoplasms bear some similarity to NETs in manifesting invasive and malignant behaviour.¹ This is a flawed proposition for the following reasons.

Biology: A NET label is a gross misrepresentation of the overwhelmingly benign clinical biology of pituitary neoplasms.^{1,2} The prevalence of pituitary neoplasms is 10% or more. Local invasiveness occurs only in 1 in 2000 and malignancy in 1 in 100 000 neoplasms.² Thus, 'NET-like' behaviour occurs in a minuscule fraction of pituitary neoplasms.

Taxonomy: The proponents contend that pituitary cells are NE cells because they express NE markers, such as synaptophysin, neurone-specific enolase and somatostatin receptors. These markers are also expressed in thyroid and adrenal neoplasms, which can also be invasive and malignant.¹ Should these other endocrine neoplasms not be classified as NETs? A name change confined solely to the pituitary, without a critical review of taxonomy, can only confuse the classification of tumours of the endocrine system.

Clinical consequence: Renaming adenomas does not change prognosis or reflect clinical reality. Clinical phenotype remains overwhelmingly benign.¹ In sharp contrast, NETs carry significant prognostic uncertainty. Cancer societies raise public awareness of NETs, citing metastasis in 50% at late diagnosis (www.nanets.net/education/about-nets); the Mayo Clinic states that NETs are cancers derived from NE cells (www.mayoclinic.org). A change in disease classification requires education of patients and health professionals. Labels associated with tumour and 'cancer' may alarm patients and families and engender inappropriate clinical decisions.³ The high risk of malignancy associated with NETs will likely lead to overtreatment, unnecessary testing, heightened anxiety and adverse insurance assessment.

A nomenclature change to NET grossly distorts pituitary adenoma biology, confuses the classification of endocrine tumours, does not change prognosis, but creates social and health care anxiety. NET is a tunnelled-view label, an unnecessary burden and liability for the patient with a pituitary neoplasm. There is no case for changing pituitary adenoma and carcinoma terminologies.

Ken Ho

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REFERENCES

1. Ho et al. 2021 *Journal of the Endocrine Society* 5 bvaa205.
2. Melmed et al. 2022 *Endocrine Reviews* doi: 10.1210/endrev/bnac010.
3. Dixon et al. 2019 *JAMA Oncology* 5 817–823.

The case for PitNETs

Lesions within the pituitary region are not uncommon, and the great majority, at least in adults and adolescents, arise from the class of the pituitary hormone-producing cells. These are neoplastic masses which may present with either hormone hypersecretory syndromes or problems related to local mass effects. Classically, these lesions were described as 'adenomas', defined as discrete benign neoplastic tumours, the word 'tumour' in this context relating to a local mass (from the Latin tumor, meaning swelling).

However, in recent years, specialist pituitary pathologists have identified increasing similarity between these lesions and other types of neuroendocrine tumour (NET), such that the International Pituitary Pathology Club has recommended that these tumours should now be known as pituitary NETs – PitNETs.^{1,2} The commonality in basic pathological features should then be combined with immunocytochemistry to identify the cell of origin, such as hormones and transcription factors for the pituitary. This also makes sense from the clinical point of view, as the term 'adenoma' is essentially inappropriate for tumours which, when large enough to require surgical resection, show marked aggressiveness in terms of treatment resistance, invasiveness and recurrence in 15% of cases, with a continuum between aggressive tumours and carcinomas.³

It has been argued that classic non-pituitary NETs show a wider spectrum of metastatic potential and, as such, patients may become anxious through the use of this term. However, appendiceal NETs <1cm (aNETs) and non-secretory pancreatic NETs <2cm (pNETs) show very little potential for metastasis, and almost always simply require no follow-up (aNETs) or simple surveillance (pNETs), much like PitNETs (formerly 'microadenomas'). Clinically, any patient with a pituitary tumour arising from pituitary cells will have the diagnosis, prognosis and therapy explained by an endocrinologist; the specific pathological description is relatively irrelevant. Considerations of healthcare facilities and insurance-related problems are not part of this basic clinical discussion. Thus, the term 'primary pituitary carcinoid' is nonsensical: all such pituitary tumours are either primary lesions arising from the pituitary or, rarely, secondaries from other tumours, such as bronchial NETs.

What's in a name? I believe we should carefully maintain scientific integrity in describing all pituitary tumours by precise pathology, while retaining our ability to discuss the clinical behaviour with patients without using outdated and inappropriate language.

Ashley Grossman

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REFERENCES

1. Asa et al. 2017 *Endocrine-Related Cancer* 24 C5–C8.
2. Asa et al. 2021 *Modern Pathology* 34 1634–1650.
3. Trouillas et al. 2020 *Reviews in Endocrine & Metabolic Disorders* 21 243–251.



How can we achieve gender equity in endocrinology?

Ongoing gender disparity in medicine is increasingly well-recognised, but seemingly slow to resolve. What is needed to address the situation?

The COVID-19 pandemic has highlighted the importance of endocrinology in the management of SARS-CoV-2 infections. With its disproportionate impact on women physicians and researchers, the pandemic has also called attention to gender disparities in medicine. Here, I will discuss both challenges and opportunities for advancing gender equity, with a focus on endocrinology.

A few caveats: first, while gender is not binary, most of the published studies on gender in medicine to date have collected data using a binary construct. Secondly, most of the data cited here are from the USA. The optimist in me hopes that this is because our European colleagues have achieved greater gender equity, but this may also reflect the need for more data from around the globe.

The lack of parity

Although women have exceeded 40% of medical school applicants in the USA for three decades, and currently make up 48% of assistant professors, gender parity at higher ranks has proven elusive. Only 27% of professors, 21% of department chairs, and 18% of medical school deans are women. There are many reasons for the attrition of women along their career progression. Women are paid less than men, even after adjusting for differences in sub-specialty, academic rank, work hours, research time and academic productivity.¹ This is of particular concern for endocrinology, in which 51% of active physicians and 71% of trainees in the USA are now female, because, as more women enter a specialty, the salary falls for all physicians in that specialty.²

Promotions in academic medicine are typically tied to metrics of recognition, yet women receive fewer speaking invitations, endowed Chairs, society leadership positions and society awards. In the field of diabetes research, women are underrepresented among society leadership and awardees.³ Despite having fewer opportunities for recognition, women are held to higher standards for promotion. Even after adjusting for years since training, specialty choice and research productivity, women are less likely to be promoted, and there has been no narrowing of this promotions gap over 35 years.⁴

Additional barriers

Women physicians in research face additional barriers. The most competitive candidates for faculty hires are often trained in elite laboratories, yet elite male faculty are significantly less likely to train women scientists.⁵ To establish a laboratory as a new faculty member requires substantial resources, but women receive significantly less start-up funding than men.⁶ Women also have less time available for research, spending more time on campus service, student advising and teaching at work, more time with patients in the clinic, and more time on domestic activities at home.

In clinical research, women have often been excluded or underrepresented as participants in clinical trials. For example, most insulins have not been rigorously tested in pregnant women.⁷ One approach to increasing the enrolment of women in clinical trials is to increase the number of women who lead clinical trials, yet women are underrepresented among the leadership of clinical trials.⁸

On top of this, women face greater gender bias and sexual harassment.⁹ It is therefore not surprising that women are more likely to leave their careers. These disparities are amplified for women belonging to groups underrepresented in medicine.¹⁰ When women leave medicine, society is deprived of their many contributions. While women publish fewer articles earlier in their career, their publication rates increase later and eventually exceed those of men.¹¹ And several studies demonstrate that women physicians have better clinical outcomes than men, especially among women patients.



The impact of the pandemic

Gender disparities in medicine have been further amplified by the COVID-19 pandemic, in which the abrupt closure of schools and childcare facilities, as well as the transition of clinical care and teaching to online platforms, disproportionately impacted the academic productivity of women faculty. There is danger that the 'Great Resignation' of workers burned out by the pandemic will impact the field of medicine, and that women will leave in greater proportions.

However, the pandemic also presents opportunities to reduce disparities in medicine. For instance, virtual meetings and conferences may allow a greater number of attendees who are no longer restrained by the demands of travel, and the delivery of telehealth has been widely embraced by endocrinologists.

The route forward

A concerted effort is needed on multiple fronts to promote gender equity in endocrinology. During the pandemic, I was invited to join a committee convened by the Clinical Research Forum to address pandemic-related challenges faced by women in research. We recently published a framework of action for institutions, societies and funding agencies, to better support women in the biomedical work force.¹²

Institutions can provide flexible funding for faculty impacted by care-giving, ensure equitable start-up packages, and provide mentorship and sponsorship to support career advancement. Professional societies, foundations and funding agencies can also provide funding for care-giving and advocate for culture change to promote gender equity.

For the sake of our colleagues and our patients, we must act to ensure that continued progress towards gender equity in endocrinology is sustained and not hindered by the pandemic.

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REFERENCES

- Jagsi et al. 2012 *JAMA* **307** 2410–2417.
- Bravender et al. 2021 *JAMA Pediatrics* **175** 524–525.
- Dunne et al. 2021 *Diabetes Care* **44** 1734–1743.
- Richter et al. 2020 *New England Journal of Medicine* **383** 2148–2157.
- Sheltzer & Smith 2014 *Proceedings of the National Academy of Sciences of the USA* **111** 10107–10112.
- Sege et al. 2015 *JAMA* **314** 1175–1177.
- DiMeglio et al. 2022 *Lancet Diabetes & Endocrinology* **10** 236–238.
- Whitelaw et al. 2021 *European Journal of Heart Failure* **23** 15–24.
- Jagsi et al. 2016 *JAMA* **315** 2120–2121.
- Westring et al. 2021 *JAMA Network Open* **4** e212723.
- Reed et al. 2011 *Academic Medicine* **86** 43–47.
- Davis et al. 2022 *Nature Medicine* **28** 436–438.

ESE supports equality

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An early postnatal pathway in puberty onset

Ariane Sharif and Vincent Prévot discuss the intimate communication processes between GnRH neurones and glial progenitors that lead to sexual maturation.

Master regulators of sexual maturation

The reproductive function of mammals is controlled by a small population of neurones that produce gonadotrophin-releasing hormone (GnRH). These neurones are mainly found in the preoptic region of the hypothalamus in rodents, whereas in primates, including humans, they are also present in the tuberal region of the hypothalamus.

They project to the median eminence, where they release GnRH into the hypothalamic–hypophysial portal system. GnRH thus reaches the anterior pituitary, where it stimulates the release of the gonadotrophins, luteinising hormone and follicle-stimulating hormone (FSH), which regulate the production of gametes and sex hormones. These peripheral steroid hormones then signal back to the hypothalamus and pituitary.

The fine-tuning of GnRH production and release, according to internal and external cues, is enabled by the neurones' integration into a complex network of neuronal afferents and glial partners. For example, the glutamate released by excitatory afferents to GnRH neurones stimulates their electrical activity directly, but also via the surrounding astrocytes, which respond to glutamate by producing the excitatory gliotransmitter prostaglandin E2 (PGE2).^{1,2}

The process of postnatal maturation

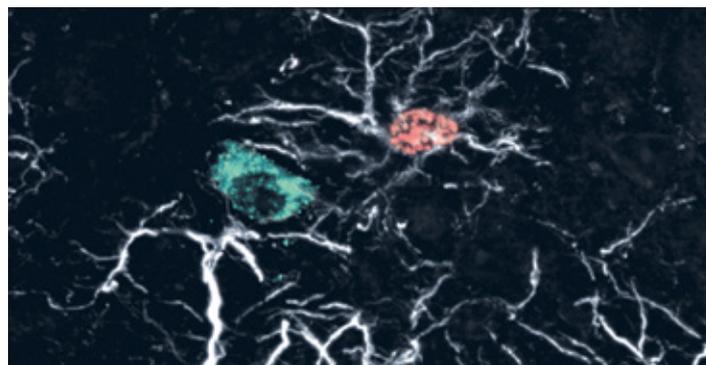
GnRH neurones are unique because, unlike the other neurones of the central nervous system, they originate outside the brain, in the olfactory placodes, and migrate into the forebrain during embryonic development.³ While their migration is completed by birth, a long process of postnatal maturation is required to allow GnRH neurones to acquire the firing and secretory patterns that trigger the onset of puberty.⁴ This period of postnatal maturation is marked by a major event, called minipuberty, which occurs in the infantile period: the second week of life in rodents and the end of the first month in humans. Minipuberty, which corresponds to the first central activation of the gonadotrophic axis, independent of the gonads, is essential for the initiation of gonadal maturation.^{5,6}

A major challenge in reproductive research is to identify the mechanisms that control the maturation of the gonadotrophic axis and the timing of puberty. A recent study revealed some of the epigenetic/genetic determinants that allow the postnatal increase in GnRH expression driving sexual maturation.⁷ However, the mechanisms regulating the integration of GnRH neurones into their neuroglial network during postnatal development, and the importance of this process for the onset of puberty and fertility, remained unexplored until now.

A critical time window

The infantile period includes a critical period for establishment of a partnership between GnRH neurones and astrocytes. In a study published in 2021, we showed that the first 2 weeks of postnatal life are marked by intense gliogenesis in the preoptic region of the hypothalamus in rats.⁸ We observed that cells born in the vicinity of the GnRH neurone cell bodies during the second week of postnatal life differentiate mainly into astrocytes and remain associated with their neuronal partner until adulthood. Inhibition of infantile gliogenesis in the environment of GnRH neurones by local infusion of an antimetabolic agent delayed the onset of puberty and disrupted oestrous cyclicity in adulthood.

Unexpectedly, we found that GnRH neurones enrich their glial environment during the infantile period via an active process. They release prostaglandin D2 (PGD2), which acts as a chemoattractant for surrounding glial progenitors by binding to the DP1 receptor. The attracted newborn cells then differentiate into astrocytes that escort GnRH neurones until adulthood.⁸



A GnRH neurone cell body (green, GnRH immunoreactivity) morphologically associated with an astrocyte (white, glial fibrillary acidic protein-immunoreactive cell processes) born during the infantile period (red, bromodeoxyuridine immunoreactivity). Image reproduced from Pellegrino *et al.* 2021⁸ ©The Authors.

In order to better understand the importance for their maturation of that recruitment of astrocytes by GnRH neurones, we blocked this process by locally infusing DP1 receptor inhibitors into the preoptic region during the infantile period. This treatment affected the integration of GnRH neurones into their neural network by decreasing the number of excitatory glutamatergic synapses around their cell bodies, and also the ability to respond to the excitatory gliotransmitter PGE2. This loss of excitatory neuroglial influences resulted in both reduced spontaneous electrical activity in GnRH neurones and blunted FSH release, which usually peaks at minipuberty in infantile female rats. The deleterious consequences of this lack of infantile astrocytic recruitment were also seen later in life, with a delayed onset of regular oestrous cyclicity.⁸

A target for endocrine disruptors

Endocrine disruptors are natural or manmade substances that interfere with the endocrine systems through mechanisms that are still poorly understood. Exposure to certain environmental pollutants, such as bisphenols or phthalates, disrupts the onset of puberty, fertility or sexual behaviour.⁹ These include bisphenol A (BPA), a common industrial plasticiser.

A study in rats has shown that exposure to very low doses of BPA during the early postnatal period affects infantile GnRH pulse frequency and tends to delay puberty.¹⁰ At these very low doses, BPA blunts the ability of GnRH neurones to recruit newborn astrocytes to their entourage during the infantile period,⁸ suggesting that the deleterious effects of BPA on sexual maturation involve, at least partly, an altered integration of GnRH neurones into their neuroglial network.

The route forward

Our results shed new light on the neural mechanisms underlying puberty onset and fertility acquisition, by revealing a previously unknown communication pathway between neurones and glial progenitors that unfolds during early postnatal life. Our work also identifies that process as a target for the adverse effects of BPA on sexual maturation. Future studies are needed to explore the underlying molecular mechanisms and to investigate whether they extend to other endocrine disruptors.

Ariane Sharif and Vincent Prévot

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REFERENCES

1. Prévot & Sharif 2022 *Journal of Neuroendocrinology* doi: 10.1111/jne.13104.
2. Clasadonte *et al.* 2011 *Proceedings of the National Academy of Sciences of the USA* **108** 16104–16109.
3. Casoni *et al.* 2016 *Development* **143** 3969–3981.
4. Prévot 2015 In *Knobil and Neill's Physiology of Reproduction*, edn 4, pp 1395–1439 doi: 10.1016/B978-0-12-397175-3.00030-2.
5. François *et al.* 2017 *Science Reports* **7** 46222.
6. Kuri-Häninen *et al.* 2014 *Hormone Research in Paediatrics* **82** 73–80.
7. Messina *et al.* 2016 *Nature Neuroscience* **19** 835–844.
8. Pellegrino *et al.* 2021 *Nature Neuroscience* **24** 1660–1672.
9. Lopez-Rodriguez *et al.* 2021 *Nature Reviews in Endocrinology* **17** 83–96.
10. Franssen *et al.* 2016 *Endocrinology* **157** 1740–1750.



Complications of checkpoint inhibitors

EJE Clinical & translational endocrinology from around the globe

A new ESE Clinical Guideline on the management of endocrine side effects of immune checkpoint inhibitors will be published soon in *European Journal of Endocrinology*.¹

Immune checkpoint inhibitors (ICI) have revolutionised treatment and now provide extended survival for patients with cancers that used to have very poor prognosis, such as malignant melanoma and lung cancer. These extraordinary effects come at the cost of significant autoimmune side effects, affecting multiple organs including endocrine glands. Indeed, up to one third of patients using cytotoxic T cell activator 4 (CTLA-4) and/or programmed cell death 1 (PD-1) or programmed cell death 1 ligand (PD-L1) antagonists experience endocrinopathies (Figure),² which pose diagnostic and treatment challenges.

Diagnosis

Nonetheless, the Guideline commends a systematic approach to diagnosis. As baseline minimum tests before each treatment cycle, we recommend morning (08.00–09.00) thyroid-stimulating hormone (TSH), free thyroxine, cortisol (with attention to any recent or current glucocorticoid treatment), glucose and electrolytes (Na, K, Ca). These tests should be repeated every 4–6 weeks, preferably before each treatment cycle starts.

When thyroid disorder is suspected or indicated by the initial tests, measurement of thyroid autoantibodies, namely anti-thyroperoxidase for hypothyroidism and TSH receptor-stimulating antibodies for hyperthyroidism, is helpful. When hyperglycaemia is present, the risk of diabetic ketoacidosis should be kept in mind (consider urine testing for ketones and blood pH measurement). If the risk of hypophysitis is substantial, we recommend analyses for other pituitary hormones, including adrenocorticotrophin (ACTH), luteinising hormone, follicle-stimulating hormone, oestradiol (pre-menopausal females), testosterone (males) and prolactin. Many symptoms of thyroid, pituitary and adrenal insufficiencies are unspecific and overlap with those caused by the malignant disease. Thus, diagnosis of endocrinopathies should be based on laboratory tests.

Endocrinopathies

Thyroiditis is the most common ICI-induced endocrinopathy, most often caused by PD-1 or PD-L1 inhibitors. In the vast majority of cases, there is release of thyroid hormones from an inflamed gland followed by hypothyroidism. Hyperthyroidism is transient and can often be managed with beta blockers only, while the hypothyroidism that follows often needs replacement therapy with levothyroxine. Thyroid dysfunction is often reversible, but can also be permanent. Graves' disease and subsequent hyperthyroidism is rare in the setting of ICI treatment.

Hypophysitis is the second most common endocrinopathy, most often caused by ipilimumab, a CTLA-4 inhibitor used either alone or in combination with a PD-1 inhibitor. Although TSH and gonadotrophin insufficiency can be reversible, ACTH deficiency is often permanent, dictating a need for life-long glucocorticoid replacement.

ICI-induced autoimmune diabetes mellitus is rare, but often presents acutely with diabetic ketoacidosis. Relatively low levels of glycosylated haemoglobin in relation to serum glucose levels indicate that destruction of pancreatic beta cells has been rapid. Patients often display the typical autoantibodies associated with type 1 diabetes, such as anti-glutamic acid decarboxylase and tyrosine phosphatase-related antigen 2, and have human leukocyte antibody genotypes typically found in type 1 diabetes. With such an abrupt debut, serum glucose should be used to monitor for diabetes (see suggestion for basal minimum tests above).

Primary adrenal insufficiency is a very rare complication, and only case reports have been reported in the literature. Some of these patients have been reported to harbour anti-21-hydroxylase autoantibodies, the biomarker used to diagnose patients with autoimmune primary adrenal insufficiency. Some patients develop multiple endocrine insufficiencies: for example, thyroiditis combined with either adrenalitis or autoimmune diabetes. ICI-induced hypoparathyroidism is extremely rare and only a few cases have been reported.

Treatment

The main treatment strategy is to replace missing hormones. There is no clear evidence for a benefit from high dose glucocorticoids, with the possible exceptions of severe thyroid eye disease and hypophysitis with enlargement of the pituitary gland affecting the visual apparatus. In fact, evidence indicates that use of high dose glucocorticoid (>7.5mg prednisolone) may reduce survival³ and reduce the chances of reversibility of the endocrinopathy. Prolonged use of high dose steroids carries the risk of inducing tertiary adrenal insufficiency, which may become permanent.

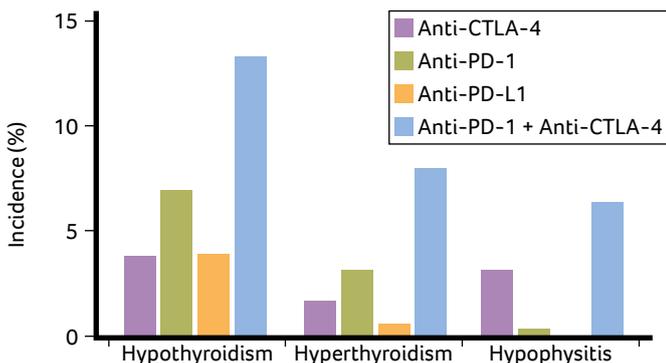
The presence of endocrine autoimmunity is no contraindication for continuation of ICI treatment. For patients with sustained and/or multiple endocrine deficiencies and good oncological prognosis, an endocrinologist should be involved in the ongoing endocrine care, with the exclusion of isolated hypothyroidism. It is crucial that patients are provided with adequate training and support to effectively manage their condition, including management of acute care interventions. Effective self-management can be supported through provision of appropriate education, empowerment and engagement activities. Specifically, patients with cortisol deficiency should be educated on how to adjust their glucocorticoid treatment during periods of intercurrent illness ('sick day rules'), and trained on the preparation and administration of glucocorticoid injection in the event of an emergency.⁴

The majority of the recommendations given in the Guideline are very weak or weak according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method. Many are also based on good clinical practice. This is due to a surprising lack of reports on endocrinopathies related to ICI therapy in large patient databases, which include data on adequately diagnosed ICI-induced endocrinopathies in patients followed up over time. As the range of ICIs is expanding, there is a need to establish registries with long term follow-up, not only to register side effects, but also to evaluate the outcome of oncologic and endocrine interventions.

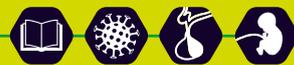
Stavroula A Paschou and Eystein S Husebye
Guideline Working Group

REFERENCES

- Husebye et al. 2022 *European Journal of Endocrinology* In Press.
- Barroso-Sousa et al. 2018 *JAMA Oncology* 4 173–182.
- Faje et al. 2018 *Cancer* 124 3706–3714.
- Husebye et al. 2021 *Lancet* 397 613–629.



Incidence of thyroid dysfunction and hypophysitis induced by different immune checkpoint inhibitors.²



Precocious puberty in the pandemic

Endocrine
CONNECTIONS



A recent study promoted by five paediatric endocrinology centres in Italy and published in *Endocrine Connections* found that cases of precocious puberty doubled in girls in Italy during the COVID-19 pandemic.¹ Stress caused by isolation and a sedentary lifestyle appear to be among the most likely causes.

Defining precocious puberty

The onset of sexual maturation before the age of 8 years in girls and before 9 years in boys is identified as precocious puberty. In Italy, it affects 1–6 live births per 1000. The child's body begins to transform into an adult prematurely, with an acceleration of the development of sexual characteristics and a rapid closure of the growth plates. Due to this process, affected children grow quickly in height, but adult stature is below average.

Incidence before and during the pandemic

In March 2020, to reduce the transmission rate of the SARS-CoV-2 virus and hospital bed saturation early in the COVID-19 pandemic, the Italian Government imposed a strict lockdown. The cases of precocious or early puberty observed in March–September 2020 in Italy were found to have more than doubled compared with the same period in 2019, as reported in a multicentre observational study involving five Italian paediatric endocrinology centres, co-ordinated by the Bambino Gesù Children's Hospital, Rome.

In total, 338 cases of precocious puberty were observed in 2020 versus 152 cases in the same period of 2019: an increase of 122%. The possible environmental factors involved in this increase were investigated using lifestyle questionnaires given to the patients' parents. The largest increase was observed in girls (328 cases in 2020 versus 140 in 2019: an increase of 134%), in particular during the second half of the observation period (92 girls between March and May 2020, compared with 236 girls between June and September 2020: an increase of 156%). There was no significant increase in cases in males (10 patients in 2020 versus 12 in 2019).

We have no explanation for this difference between sexes. We know, however, that precocious puberty is much less common in males than females, and in males it is more often the result of predisposing genetic mutations or organic diseases of the hypothalamus–pituitary area. We can hypothesise that the impact of environmental triggers, such as those related to the pandemic, is less significant on the timing of male puberty.

Comparing the populations of 2019 and 2020, there were no significant differences in clinical and anthropometric parameters (i.e. weight, height, body mass index, birth weight, age at onset of pubertal signs). Contrary to what was expected, no significant increase in weight (or, therefore, in body mass index) was observed in patients with onset of precocious puberty after the first 2020 lockdown. In 2020, on the other hand, there was a significant increase in cases of rapidly progressive precocious puberty (135 out of 328 girls observed in 2020, compared with 37 out of 140 girls observed in 2019: a range of increase from 26% to 41%).

Food habits and lifestyles

The results of the lifestyle questionnaires given to the parents of girls with precocious puberty showed a significant increase in the use of electronic devices (PCs, tablets, smartphones) in 2020 compared with 2019. This

'The cases of precocious or early puberty observed were found to have more than doubled compared with the same period in 2019.'

increase can be traced back to the introduction of e-learning (rarely used in primary schools before 2020), together with the persistence of their use in leisure time. A more prolonged use of electronic devices, already present before the pandemic, was reported in girls presenting with rapidly progressive precocious puberty in 2020.

Similarly, the first lockdown of 2020 also caused a drastic reduction in the outdoor physical activity of children and young people (see Figure). Physical activity was particularly poor in the 2020 subgroup of girls with rapidly progressive precocious puberty. This sedentary lifestyle was already evident before the pandemic.

With regard to eating habits, no significant increase in the consumption of meat or junk food was reported in the 2020 patients, despite an increased feeling of hunger.

Finally, more than half of the families of the patients observed in 2020 reported changes in behaviour (59%) and a significant increase in stress-related symptoms (63%).

The role of stress

Several studies have analysed the impact of COVID-19 and social isolation on the mental health of children and adolescents, reporting a significant increase in behavioural and emotional disorders following school closure. In particular, a study by the Neuropsychiatry Unit of Bambino Gesù Children's Hospital described post-traumatic stress disorder due to quarantine or social isolation in 30% of the children who were analysed.²

Findings also show a positive association between physical activity and psychological well-being in children and adolescents. Sedentary lifestyle, on the other hand, has been correlated with both an increase in depression and a perception of a less satisfactory quality of life. Furthermore, anxiety and a tendency to social isolation in prepubertal girls have been recently associated with an early pubertal onset.³

We now know that secretion of the hypothalamic hormone that initiates pubertal development (gonadotrophin-releasing hormone; GnRH) is regulated in the brain, but the mechanisms responsible are not fully understood. We could assume that stress-induced dysregulation of

Insights from the Editor

Puberty is one of those inevitable but poorly understood endocrine events that fills most parents with dismay, usually bringing a variety of stresses and behavioural disturbances into previously stable homes or disrupting school performance. It can be tough for all concerned. Precocious puberty, however, defined as thelarche before the age of 8 years, is a catastrophe that we really don't understand or manage very well.

Chioma and colleagues report the startling doubling of the rate of central precocious puberty in girls in five widely dispersed centres in Italy in 2020, the first year of the COVID-19 pandemic, in comparison with rates from 2019. These findings reinforce some previous smaller Italian studies, so it seems this is a real phenomenon. They demonstrate a markedly greater sedentary lifestyle and use of electronic devices in their patients – not a surprise – and although body mass index (BMI) was unchanged, there was a substantial mismatch between BMI and birthweight in this group of girls. This is consistent with the hypothesis put forward by de Zegher & Ibañez (*European Journal of Endocrinology* 2021 **185** L1–L2) that puberty is an adaptive response to escape from the 'ectopic' adiposity that results from greater postnatal weight gain in low birth weight infants. Exactly how such mechanisms work and, hence, how we can control them, remains a topic well worthy of research. Clues arising from reports such as this seem to be a valuable starting point.

Adrian Clark
Editor-in-Chief, *Endocrine Connections*



brain neurotransmitters is behind the increase in new cases of precocious puberty observed during the pandemic. Stress could act as a more powerful trigger on GnRH-secreting neurones in girls with additional risk factors, such as a sedentary lifestyle and excessive use of electronic devices already evident before the pandemic.

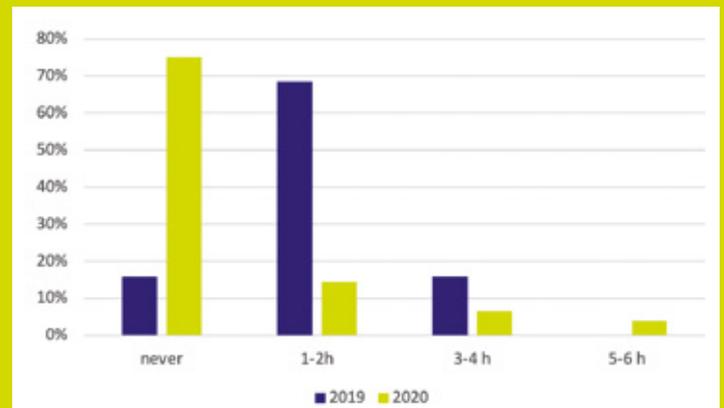
The verification of this hypothesis opens interesting perspectives for clinical research in coming years.

Laura Chioma, Carla Bizzarri and Marco Cappa

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REFERENCES

1. Chioma *et al.* 2022 *Endocrine Connections* **11** e210650.
2. Demaria & Vicari 2021 *Italian Journal of Pediatrics* **47** 58.
3. Knight *et al.* 2021 *American Journal of Epidemiology* **190** 431–438.



Overall weekly physical activity in 2019 and 2020 populations. Reproduced under CC BY-NC-ND 4.0 licence (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) from Chioma *et al.* <https://doi.org/10.1530/EC-21-0650> ©2022 The Authors.

2021 Impact Factors



ESE's journals have once again received impressive ratings in this year's Journal Citation Reports.

European Journal of Endocrinology has seen a 7% increase in its Five-Year Impact Factor (a long term measure of the impact of authors' research) to 6.805, thus cementing its place as the leading broad-scope, clinical and translational endocrinology journal.

Endocrine Connections has also secured an increase in Five-Year Impact Factor, reaching 3.635. This fantastic achievement is appropriate for one of the leading fully open access journals covering basic, translational and clinical endocrinology.

We thank our authors, reviewers, readers and Editorial Boards, who ensure that ESE journals are the best places for you to publish world-class endocrinology. Special thanks go to our Editors-in-Chief, Wiebke Arlt and Adrian Clark.

Vitamin D collection

The first *Endocrine Connections* special collection marks 100 years since the discovery of vitamin D with a series of reviews and recent research.

Eight articles have been published so far in the series, which is being commissioned and reviewed by Susan Lanham-New, Martina Rauner and Josef Köhrle. It will provide clinicians and researchers with a comprehensive update on the latest developments in the vitamin D field.

You can find it at <https://ec.bioscientifica.com/page/VitaminD>.



EJE Rising Stars

This new initiative from *European Journal of Endocrinology* (EJE) supports promising individuals whose exceptional achievements identify them as future leading clinical and translational endocrine researchers, with great potential to serve as Editors of EJE.

We congratulate the inaugural recipients of the award: **Sophie Bensing** (Sweden), **Avivit Cahn** (Israel), **Guido Di Dalmazi** (Italy), **Tim Korevaar** (The Netherlands), **Dan Niculescu** (Romania), **Svenja Nölting** (Switzerland), **Michael O'Reilly** (Ireland), **Cristina Olarescu** (Norway),

Nadia Schoenmakers (UK), **Roland Stimson** (UK), **Elena Valassi** (Spain), **Dimitra Vassiliadi** (Greece) and **Maria Yavropoulou** (Greece) (pictured below from top left to bottom right).

The award includes membership of the EJE Rising Star Reviewer Board for 2 years, a dedicated mentorship programme for future Editors of EJE and a travel bursary to attend ECE and the EJE Editorial Board meeting.

You can find out more at <https://eje.bioscientifica.com/page/rising-stars>.



ESE Clinical Updates

Reports from recent ESE Clinical Update webinars discuss the management of acromegaly, Cushing's and obesity. You can download them at www.ese-hormones.org/publications/ese-meeting-reports.

To find out more about the forthcoming ESE Clinical Update on Calcium and Bone, which takes place online on 4–6 October 2022, see www.ese-hormones.org/ese-courses/ese-clinical-update-on-calcium-bone-2022-online.



Celebrating success at ECE 2022

Honorary Membership



Clara Alvarez (Spain, left) and **Barbara Jarzab** (Poland) received Honorary Membership. Both were recognised for their long-standing support of ESE and the European endocrinology community at large. Clara served as a member of the ESE Executive Committee (2005–2009) and as Thyroid Focus Area Lead (2018–2020). Barbara is a former Secretary of ESE (2010–2014).

Special Recognition Awards



Ljiljana Marina (Serbia, left), **Camilla Schalin-Jäntti** (Finland, centre) and **Bulent Yildiz** (Turkey) received Special Recognition Awards at ECE 2022. Ljiljana was recognised for her valuable contribution to ESE and the ESE Young Endocrinologists and Scientists (EYES). Camilla received the award for her outstanding contribution as an Executive Committee member and her work as Chair of the Education Committee. Bulent was recognised for his long service on the Executive Committee (2014–2020), and his outstanding contribution as ESE Treasurer.

Award Lecturers and other recipients



AJ van der Lely
(The Netherlands)
Geoffrey Harris Award



Roland Stimson
(UK)
European Journal of Endocrinology Award



Josef Köhrlé
(Germany)
European Hormone Medal



Peter Rossing
(Denmark)
European Hormone Medal



Alberto Pereira
(The Netherlands)
Clinical Endocrinology Trust Award



Shlomo Melmed
(USA)
Transatlantic Alliance Award



Ruben Nogueiras
(Spain)
Jens Sandahl Christiansen Award



Cristina Olarescu
(Norway)
Jens Sandahl Christiansen Award

Young Investigator Award winners

The 2022 recipients are **Barbara Altieri** (Germany), **Lucas Bouys** (France), **Ana Carreira** (Portugal), **Giulia Del Sindaco** (Italy), **Aristidis Diamantopoulos** (Greece), **Typhanie Dumontet** (USA), **Ross Hamblin** (UK), **Nikolaos Nikolaou** (UK), **Joris Osinga** (The Netherlands), **Valeria Pecce** (Italy), **Carolina Pieterman** (The Netherlands) and **Louise Ramhøj** (Denmark).

Poster Award winners

The 2022 winning clinical posters were presented by **Alessandro Maria Berton** (Italy), **Georgios Papadakis** (Switzerland), **Giulia Rodari** (Italy) and **Joeri Walravens** (Belgium). The winning basic science/translational posters were presented by **Hamza Benderradji** (France), **Manuel D Gahete** (Spain), **Gloria Elena Silva Román** (Mexico) and **Chris Smith** (UK).

Save the date

For more information about any ESE event see www.e-se-hormones.org.

ESE Spotlight on Science

1 September 2022

Online

ESE Young Endocrinologists and Scientists (EYES) Annual Meeting

2–4 September 2022

Zagreb, Croatia

30th ESE Postgraduate Training Course in Clinical Endocrinology, Diabetes and Metabolism

29 September–2 October 2022

Tbilisi, Georgia

ESE Clinical Update on Calcium and Bone 2022

4–6 October 2022

Online

45th Symposium on Hormones and Cell Regulation

12–15 October 2022

Mont Ste Odile, France

EndoBridge 2022

20–23 October 2022

Antalya, Turkey

ESE Spotlight on Science

3 November 2022

Online

EuroPit 2022

20–23 November 2022

Annecy, France

ECE 2023

25th European Congress of Endocrinology

13–16 May 2023

Istanbul, Turkey

Deadlines

1 August 2022

45th Symposium on Hormones and Cell Regulation

Abstract submission deadline

26 August 2022

EndoBridge Clinical Cases

Submission deadline

1 September 2022

ESE Small Meeting Grant

Application deadline

30 November 2022

ESE Short-Term Fellowship

Application deadline