New horizons for endocrinology:

**EXPLORING ENDOCRINE CANCER**

Special features

PAGES 7-14

**COVID-19: DISCOVERING OUR ‘NEW NORMAL’**

Special features

PAGES 6, 18 & 26
A word from
THE EDITOR...

It seems an eternity since I wrote my last editorial, peak-pandemic. I think a COVID-19 month is equal to a non-COVID year, and I can barely remember life BC (‘before COVID’). Watching TV cricket highlights on ‘Ben Stokes day’ and the amazing Bowie set at Glastonbury, I find it hard to imagine being anywhere crowded ever again. Sadly, but inevitably, SfE BES 2020 will be virtual this year (you will find the programme on page 17), and we will have to wait a little longer before we can meet up to share our stories.

In this issue, we share some experiences of how endocrinologists have adapted during the pandemic. Risheka Walls and colleagues discuss running virtual endocrinology masterclasses (page 6), whilst Caroline Gorvin and Mark Turner demonstrate how to run a lab from our living rooms (page 18). On page 26, Steve Ball reflects on how rapidly things changed in March, and describes principles to consider as we rebuild our endocrinology services. You will find the Society for Endocrinology’s work looking at the future of endocrinology on page 22.

Then, reminding us there is life apart from coronavirus, we have some articles on the science of cancer, including those of the breast (page 7) and prostate (page 9) and neuroendocrine tumours (page 10). Caroline Maslin (page 14) writes about how it feels to be a patient living with cancer, how it affects lives in ways that are not immediately apparent. She emphasises the importance of discussing the consequences of treatments before irreversible decisions are made.

As our children go back to school, those not in key services go back to work, and COVID-19 cases rise again, I wonder where we will be in another 3 months. I hope we will not see a full blown second wave, although some will already have experienced local lockdowns. I hope you all had time away for well, team endocrinology.

HELEN SIMPSON
NEW HUB FOR CAREER ADVICE & SUPPORT

Check out our new collection of resources, providing tips and advice to help advance your career. You can find anything from CV help to alternative endocrine careers, for any career stage. Share your own with the community by sending them to careers@endocrinology.org.

See www.endocrinology.org/careers/career-resources-and-information.

ENDOCRINE SERVICES DURING THE COVID-19 RESET

The Association of British Clinical Diabetologists, in close collaboration with your Society and the Royal College of Physicians (London), has issued new guidance on which core diabetes and endocrine clinical services the NHS can provide in the face of major disruption and reduced capacity for clinical teams. It is hoped that it will provide a useful framework for clinical team leaders and managers during any further disruption of clinical services.


JOHN BEVAN’S CHARITY FUNDRAISER

We congratulate and applaud retired endocrinologist and senior Society member, John Bevan, who has raised almost £15,000 for charity during the COVID-19 lockdown by walking one million steps. As a stroke survivor, he decided to help some neglected charities during the pandemic by being sponsored to walk a million steps in his garden – equivalent to 417 miles. At a speed of just under 3mph, the walk took 145 hours and was completed on 1 July 2020. You can learn more and donate at https://uk.virginmoneygiving.com/MillionSteps.

BIOSCIENTIFICA LAUNCHES COVID-19 RESPONSE FUND

In reaction to the global coronavirus pandemic, the Bioscientifica Trust has launched a new COVID-19 response fund, providing up to £5,000/€5,000. This fund is aimed at early career scientists or clinicians to help address the disruption caused by the virus. The new fund can be utilised flexibly, for example to cover short term salary support, travel, equipment, consumable costs etc.

Find out more and apply at www.bioscientificatrust.org

CONGRATULATIONS TO OUR 2020 EARLY CAREER PRIZE LECTURERS

We are pleased to announce the winners of the 2020 Society for Endocrinology Early Career Prize Lectures.

Steve Millership from Imperial College London is our winning clinical/translational prize lecturer and was selected for his abstract, ‘Tracking of imprinted gene hypervariability and diet-induced deregulation in pancreatic beta cells.’

Kate Lines from the University of Oxford is our winning science lecturer and was selected for her abstract, ‘Targeting epigenetic mechanisms as a novel treatment for MEN1-associated tumours.’

Both winners will present their lectures at SfE BES Online.

WITH REGRET

We are sorry to announce the death of former Member and Society for Endocrinology Medalist, Professor Gerald Lincoln. A full obituary will appear in a future issue of The Endocrinologist.

SOCIETY GOVERNANCE REVIEW

We have started a project to review our governance structures and processes. This is to ensure that the Society is operating in line with current best practice and is therefore able to fulfil its mission in the most effective way. It is best practice to do a governance review every 5 years. The work will be led by members and Professor Karen Chapman has been appointed as Chair of the working group.

If you have any particular areas that you feel should be addressed please let us know at members@endocrinology.org and we will put you directly in touch with the working group. All members will be consulted on the recommendations that come out of the governance review before they go to Council mid-2021.

HELP IMPROVE SCIENCE REPORTING IN THE MEDIA

Become a Society Media Ambassador and share your expertise to improve media coverage of endocrine related topics. Find out more www.endocrinology.org/outreach/public-engagement.

NEW EDITORS AT CLINICAL ENDOCRINOLOGY

We are delighted to welcome Aled Rees (Cardiff) and Maralyn Druce (London) as the new Senior Editors of the Society’s journal Clinical Endocrinology.

You can find the journal online at www.onlinelibrary.wiley.com/journal/13652265.

SOCIETY CALENDAR

11 October 2020
YOU AND YOUR HORMONES
Content Editor Deadline
16–20 November 2020
SfE BES ONLINE

www.endocrinology.org/events for full details

GRANT AND PRIZE DEADLINES

28 October 2020
MEETING SUPPORT GRANTS

28 October 2020
PRACTICAL SKILLS GRANTS

11 November 2020
EARLY CAREER GRANTS

11 November 2020
ENDOCRINE NURSE GRANTS

2 December 2020
TRAVEL GRANTS

www.endocrinology.org/grants for full details of all Society grants and prizes

THE ENDOCRINOLOGIST | AUTUMN 2020 | 3
Reproductive and sexual health

Maternal obesity can affect the health of offspring and is associated with increased risk of metabolic disorders. Because it is linked to high birth weight, maternal obesity can programme an offspring’s mammary glands to develop carcinogen-initiated mammary tumours at a younger age. Maternal high fat diet during pregnancy was also associated with an increase in allografted mammary tumour initiation at a younger age. Maternal high fat diet during pregnancy was also associated with an increased risk of mammary cancer recurrence after tamoxifen administration. These responses were associated with an impaired tumour immune response characterised by altered T cell function. These findings suggest that maternal high fat diet in pregnancy increases offspring susceptibility to mammary tumour growth, cancer recurrence and suppression of tumour immune responses.

Read the full article in Endocrine-Related Cancer 27 469–482

PKA functions in metabolism and resistance to obesity

In follow up to Constantine Stratakis’ 2019 SfE BES Dale Medal Lecture, this article provides a comprehensive review discussing the role of the cAMP-dependent protein kinase (PKA) in co-ordinating metabolic responses. Presenting evidence from studies of human epidemiology, endocrine disease and obesity, combined with rodent knockout models, London et al. systematically evaluate the evidence for the roles of this ubiquitous signalling molecule and the upstream/downstream Gsα signalling pathway components. They cover aspects including tissue-specific functionalities of PKA/the PKA pathway via knockout animals, through roles of PKA in hypothalamic and central energy sensing, and energy sensing/storage and expenditure and insulin secretion.

Read the full article in Journal of Endocrinology 246 R51–R64

Anti-inflammatory effects of androgens in human vagina

Genitourinary syndrome of menopause (GSM) affects approximately 50% of postmenopausal women. It is characterised by vulvovaginal atrophy and lower urinary tract symptoms which adversely affect sexual health and general well-being. These symptoms are primarily a consequence of reduced oestrogens at menopause. However, androgens, which also decline with age, are increasingly recognised as important regulators of genital tissue function. Importantly, androgen treatment may have beneficial effects in the vagina by modulating inflammatory responses.

Maseroli and colleagues investigated whether androgens could modulate the inflammatory response in the vagina by assessing human vaginal tissues and human distal vagina smooth muscle cells isolated from postmenopausal women.

They investigated the expression of sex steroid receptors and assessed the effect of the selective androgen receptor agonist dihydrotestosterone (DHT) on inflammatory responses. The authors found that androgen receptor was expressed in vaginal smooth muscle cells and that DHT reduced basal secretion of pro-inflammatory cytokines, chemokines and growth factors. DHT also decreased secretion of cytokines induced by the pro-inflammatory stimulus lipopolysaccharide. These results suggest that androgens have an anti-inflammatory effect on vaginal smooth muscle cells which may have therapeutic benefit in the treatment of GSM.

Read the full article in Journal of Molecular Endocrinology doi:10.1530/JME-20-0147

Endocrine-Related Cancer

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ENDOCRINE-RELATED CANCER

High fat diet in pregnancy and mammary cancer recurrence in offspring

Maternal obesity can affect the health of offspring and is associated with increased risk of metabolic disorders. Because it is linked to high birth weight, it may also increase a daughter’s breast cancer risk and increase breast cancer mortality.

Zhang and colleagues used rodent models of premenopausal breast cancer to investigate whether maternal obesity could affect a female offspring’s response to tamoxifen treatment and risk of recurrence after tamoxifen administration. They found that maternal exposure to an obesogenic high fat diet during pregnancy could programme an offspring’s mammary glands to develop carcinogen-initiated mammary tumours at a younger age. Maternal high fat diet during pregnancy was also associated with an increase in allografted mammary tumour initiation at a younger age. Maternal high fat diet during pregnancy was also associated with an increased risk of mammary cancer recurrence after tamoxifen administration. These responses were associated with an impaired tumour immune response characterised by altered T cell function. These findings suggest that maternal high fat diet in pregnancy increases offspring susceptibility to mammary tumour growth, cancer recurrence and suppression of tumour immune responses.

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Mammographic screening from age 40 and breast cancer mortality

Breast cancer screening programmes in the UK offer mammograms every 3 years to women aged 50–70. However, the cost:benefit ratio regarding the public health benefits versus technical issues associated with screening women from the age of 40 remains under debate.

This randomised, controlled trial conducted by Duffy et al. investigated the effects of earlier mammogram screening for prevention of breast cancer mortality. A total of 160,921 participants were recruited into 23 breast screening units. They were stratified by general practice into yearly mammogram screening up to 48 years of age (intervention), or to standard care of no screening until invitation at ~50 years of age into the national screening programme (control). Participants were followed up for a median of 22.8 years.

A significant (~25%) reduction was seen in breast cancer mortality in the first 10 years of follow up in the intervention group. However, there was no significant reduction in the intervention group with follow up after 10 years.

Read the full article in Lancet Oncology doi:10.1016/S1470-2045(20)30398-3

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

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Read the full article in Lancet Oncology doi:10.1016/S1470-2045(20)30398-3
**CLINICAL ENDOCRINOLOGY**

Self-reported adverse lifestyle factors in men with sub-fertility

Sperm counts are falling, fertility is declining, and there are no pharmacological interventions to improve sperm quality. Add to that COVID-19 and the human race is clearly doomed.

Jayasena *et al.* describe lifestyle factors (LSFs) in a cohort of 1,149 male partners of couples under investigation for sub-fertility. Factors such as smoking, recreational drug use, alcohol, caffeine intake and obesity are known to affect fertility. In this study, 70% of men reported one or more LSFs affecting fertility, and 29% reported two or more. Education also correlated with sperm count, with those men achieving undergraduate education or higher having a higher sperm count. When asked, 79% of the men expressed a desire for more information about how to improve fertility, such as leaflets, videos, online educational resources and more education at schools.

There is evidence that reducing some of these factors improves sperm count, but no prospective studies currently show improvements in fertility. These data suggest, however, that optimising health by providing early health education and educational resources when considering fertility may be an effective strategy. Hopefully, there will be follow-up data to show efficacy of such an approach in the future.

Read the full article in *Clinical Endocrinology* 93 312–321

**ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS**

When primary hyperparathyroidism comes as good news

Clinicians in Varese report a case of a rarely observed consequence of primary hyperparathyroidism: multiple brown tumours initially misdiagnosed as malignant osteosarcoma. Brown tumours can occur when osteoclast activity is especially high, resulting in haemorrhage and fibrosis within the bone marrow. The brown colour is imparted by a build-up of haemosiderin.

For the 70-year-old patient reported in this case study, chest X-ray incidentally detected an 8cm axillary mass, showing local invasion on CT, concurrent with hyperparathyroidism. Giant cell-rich osteosarcoma was high on the list of initial diagnoses. Lesions were detected elsewhere in the skeleton. However, immunohistochemistry findings were not in keeping with malignancy and, instead, demonstrated haemorrhage and haemosiderin deposition. Parathyroid hormone levels, which were then measured, were elevated. Subsequent investigations led to the discovery of a large right-sided parathyroid adenoma. The patient was therefore treated with parathyroid surgery plus denosumab to improve bone density.

The authors reflect on the unusual nature of this case, in an era when primary hyperparathyroidism is frequently detected early, before complications have developed. They also comment on the value of the histopathology input, which led to the true diagnosis. This carried a profoundly different prognosis to the more sinister conditions initially suspected.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* doi:10.1530/EDM-20-0046

**ENDOCRINE CONNECTIONS**

Short term SGLT2 inhibitor use improves skeletal muscle insulin sensitivity

Sodium-glucose co-transporter 2 (SGLT2) inhibitors exert their actions within the kidneys, serving an important glucose-lowering effect in the treatment of diabetes mellitus. However, it is unclear if SGLT2 inhibitors can impact glucose sensitivity of skeletal muscle during short term administration.

Goto *et al.* examined 20 individuals experiencing T2DM and their response to a single week’s treatment with empagliflozin, a common SGLT2 inhibitor. The study measured relevant metabolic outcomes following SGLT2 inhibition, including low and high density lipoproteins and urinary glucose levels. In addition, the work measured skeletal muscle mass, through body composition using bioimpedance. This experiment revealed that 1 week’s administration of empagliflozin significantly decreases body mass index as well as overall fat and skeletal muscle mass. Plasma glucose also demonstrated reduced levels, indicating a decline in insulin concentrations.

The authors suggest that SGLT2 inhibitor-associated elevation of glucose metabolism may occur through skeletal muscle mitochondrial metabolism and intramyocellular lipid mobilisation. Whilst much work remains to be done to fully appreciate the mechanism and implications of SGLT2 inhibition for specific tissues, these experiments demonstrate that short term exposure to SGLT2 can evoke substantial shifts in body composition, plasma glucose and skeletal muscle.

Read the full article in *Endocrine Connections* 9 599–606

Role of MICOS assembly in crista formation

The ability of mitochondria to complete critical functions such as ATP generation and lipid metabolism is a product of their iconic structure. It has also long been understood that aberrances in the folds of mitochondrial cristae are associated with numerous, severe, life-limiting human conditions. Despite their clear importance to human health, the molecular processes dictating their form and also wider mitochondrial architecture are poorly understood.

Stephan *et al.* recently increased our knowledge in this area by using CRISPR-Cas9 to knock out individual genes of the human MICOS (mitochondrial contact site and cristae organising system) along with super-resolution microscopy techniques to capture images of the structure of single mitochondria. They discovered that individual proteins within the MICOS are associated with specific aspects of cristae formation, with each one playing a role in a highly co-ordinated organisation. Interestingly, they also found that cristae precursors are first formed prior to remodelling by the MICOS complex.

As a result of these experiments, they propose a new model for mitochondrial cristae formation in higher eukaryotes distinct from that in lower eukaryotes. This advancement in knowledge moves us towards a better grasp of the genetic and physical interactions that give rise to the unique energy-generating organelles inside our cells.

Read the full article in *EMBO Journal* doi:10.15252/emboj.2019104105

Administration of systemic corticosteroids and mortality from COVID-19

This month, JAMA published several studies looking at the efficacy of steroids in severe COVID-19. The REAMP-CAP paper suggested some benefit for hydrocortisone in patients, data analysis used complex Bayesian statistics, which are beyond the capability of this author to explain. The trial was stopped early and no treatment strategy met pre-specified criteria for statistical superiority, precluding definitive conclusions. However, the meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group showed benefits for corticosteroids more generally. This meta-analysis was of 7 randomised trials, across 12 different countries including 1,703 patients with severe SARS-CoV-2 infection in an intensive care setting, of whom 647 died. Patients received intravenous dexamethasone, hydrocortisone or (in a small number of cases) methylprednisolone. There were 222 deaths among the 678 patients randomised to corticosteroids and 425 deaths among the 1,025 patients randomised to usual care or placebo (summary odds ratio, 0.66 [95% CI, 0.53-0.82]; *P*<0.001 based on a fixed-effect meta-analysis). This is exciting news in the management of severe SARS-CoV-19. From an endocrinologist’s perspective, it does not affect the usual management of patients with adrenal insufficiency (AI) and the NHS England central pharmacy team are aware that hydrocortisone is a critical drug for AI patients, so are monitoring stocks on a weekly basis, which should provide reassurance for our patients.

THE C WORDS:
CONFERENCES IN COVID-19

WRITTEN BY RISHEKA WALLS, NIAMH MARTIN AND KARIM MEERAN

Conferences see thousands of like-minded people coming together to learn and network, and generate over £19 billion per year for the UK economy.

Endocrinologists are integral to general medicine and occupy much of the COVID-19 frontline, with consultants returning to night shifts and trainees manning a 7-day NHS. As our working lives changed, learning also saw a ‘new normal’. COVID-19 dominated journals and filled teaching slots, whilst specialty training vaporised. However, excess deaths outside COVID-19 were becoming a worrying reality;

At Imperial College London, we wanted to continue with our 12th Annual Endocrine Masterclass 2020. However, we recognised that an overhaul in our approach to large face-to-face teaching forums was needed.

Convenience is key
As reflected by the popularity of Uber and Amazon, convenience influences decisions. Anti-social shifts, high sickness rates and clinicians working from home meant that convenience was key in securing an interested audience.

We set up fortnightly bite-sized themed Masterclass sessions lasting 2 hours and divided into four subsessions. Each opened with a general overview, followed by case presentations from across the UK, and ended with expert discussions. These sessions were delivered via a Zoom meeting, easily accessible through any device with one click on a web link. Through regular, short sessions, we ensured numerous opportunities to attend with small fortnightly time commitments. Zoom also has the option to record sessions, so they could be watched ‘on demand’ later.

Feedback is vital for improvement, and yet conference feedback can only be actioned 12 months post-event. Through our short but regular sessions, feedback from one session was actioned for the following fortnightly session. For instance, the first session saw a demand for expert teaching on osteoporosis. We therefore adapted the following session by opening with an osteoporosis presentation and questions at the end.

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Effectively delivering an online conference with audience participation is an evolving process. All the presenters built in interactive questions, put to the audience via Mentimeter (www.mentimeter.com). The audience could test their own knowledge and views against that of fellow endocrinologists through summary graphs (Figure 1). The presenter was also able to ‘read the room’, gauge the audience’s learning needs and adapt subsequent discussions.

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Our Zoom platform saw the majority of questions asked by trainees, which contrasts with ‘live’ large conferences. Each talk generated seven to ten questions from the audience, with 70% from trainees. The freedom to type questions, combined with an appreciation of the level of knowledge amongst the audience through Mentimeter, empowers those less vocal to speak up.

WHAT’S IN IT FOR ME?
Learning is great, but learning with Continuing Professional Development (CPD) is even better. We proactively approached the Royal College of Physicians who approved each session for two CPD points. Points were obtained by photographing a QR code displayed intermittently throughout the session. This linked directly to a feedback page and resulted in 90% of candidates completing feedback on the day. As conference organisers, we stand to gain too, as such instantaneous feedback helps us plan and adapt the next fortnightly session.

Physical conferences have provided opportunities to visit new places, collaborate over coffee and mingle with friends and experts. Yet, we have all missed conferences through rota clashes, personal commitments or a tight budget. Once missed, the next opportunity is often 12 months away. Through our Zoom bite-sized Masterclass, we were able to deliver.

Figure 1. Mentimeter questions with audience responses from a case presentation about Cushing’s disease. (a) A word cloud where the audience could free-type an answer to the question ‘Give one complication of Cushing’s’: the more popular an answer, the larger the font size. (b) Audience answers to ‘What test should we do?’ (c) Audience answers to ‘What test is next if low dose dexamethasone suppression test (LDDST) does not suppress?’ It was clear from the large number who chose high dose dexamethasone suppression test (HDDST) that this area needed more explanation, so we could spend more time on the evidence that a HDDST is not a good test, and that guessing the source of ACTH would actually be more accurate than an HDDST. (d) Audience answers to ‘Does this patient have Cushing’s disease?’

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CANCER THERAPY

MICRORNAs IN PROSTATE CANCER THERAPY

WRITTEN BY SUE M POWELL, CLAIRE E FLETCHER AND CHARLOTTE L BEVAN

ANDROGEN RECEPTOR AND MICRORNAs

The androgen receptor (AR) is the critical driver of prostate cancer growth, both in early hormone-responsive disease and in advanced prostate cancer. Thus, the first-line treatment is androgen-deprivation therapy (ADT). However, resistance to this therapy usually develops after 2–3 years. This results in the emergence of lethal disease: so-called castration-resistant prostate cancer (CRPC). The mechanisms driving this progression remain largely unclear, although continued AR signalling despite depletion of circulating androgens is key, and may be partly driven by constitutively active AR variants (AR-Vs).

Notably, AR is the most microRNA (miR)-targeted oncogene in prostate cancer. MicroRNAs are small non-coding RNAs comprising around 22 nucleotides that bind to complementary sequences most often present within the 3'UTR of their target mRNAs, resulting in post-transcriptional regulation, usually, although not exclusively, negative. MicroRNAs can have oncogenic and/or tumour suppressive roles, with the potential to regulate a large number of genes/gene networks and thus have significant impact on disease outcome. Excitingly, they are also hormone-like, in that they are seemingly released (actively or passively) by tissues, circulate in the blood and so have the potential to act at distant sites, resulting in their description by the term ‘hormomiR’.

MICRORNA TARGETING AND AR REGULATION

Mapping of miR-RNA interactions in prostate cancer cell lines has shown that, as well as being the most frequently targeted oncogene in prostate cancer, the AR is in the top 5% of all miR-regulated genes, supporting the disease-relevance of miR-mediated AR regulation. Post-transcriptional modulation of AR activity by miRs is via altering transcript stability, translational efficiency and regulatory networks.

Studies have identified a number of miRs that directly target the AR, including the miR-30 family members, miR-30c-5p and miR-30d-5p, which were shown to have significantly reduced expression in metastatic CRPC (mCRPC) compared with healthy control tissues. However, direct AR-modulatory miRs not only act to suppress the AR but can also increase AR activity, sometimes functioning as oncomiRs. Data from our laboratory have shown that miRs-346 and 361-3p, both of which directly bind the AR 3'UTR, increased not only the activity and expression levels of the wild type AR, but also that of AR-Vs, as well as promoting variant-driven prostate cancer cell proliferation. This upregulation could provide a mechanism by which the cancer cells maintain AR activity even under androgen-depleted conditions.

Regulation of AR is not only achieved via the direct action of miRs, but also by a wide variety of protein factors, including co-repressors, co-activators, and pioneer and transcription factors. At least 200 different co-regulators are known to regulate the AR, many of which are themselves under miR control, thus constituting indirect miR regulation of AR activity. For example, the AR co-repressor SHP is repressed by oncogenic miR-141, which shows increased expression in prostate cancer, with the net result being increased AR activity. In contrast, AR activity is repressed indirectly by let-7c targeting of c-Myc, a transcription factor that positively regulates the AR gene.

Following the popularity of our sessions, they have continued fort nightly, and we have run an insulin pump course and further metabolic medicine sessions. Our annual Imperial Pituitary Masterclass in September was also will also be delivered on Zoom. Such virtual interfaces cannot replace physical conferences but, by embracing both physical and virtual conferencing in the future, maybe these particular ‘C words’ aren’t all bad and, for learning, perhaps we can have our ‘C’ake and eat it.

RISHEKA WALLS (née RATNASAPATHY), NIAMH MARTIN AND KARIM MEERAN

Specialist Registrar in Endocrinology, Diabetes and General Medicine and Honorary Clinical Research Fellow, Consultant in Endocrinology and Diabetes, and Professor of Endocrinology, Imperial College NHS Healthcare Trust and Imperial College London

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MicroRNAs are known to be dysregulated in CRPC when compared with hormone-responsive prostate cancer, with more decreased than increased at this later stage. CRPC-downregulated miRs often inhibit oncogenic processes such as proliferation, migration and invasion. An example of one such is miR-145-3p, which functions as a tumour suppressor in prostate cancer by inhibiting cell cycle progression and survival through its targeting and downregulation of genes such as MELK, BUB1 and CDK1, all of which have been shown to be predictive for patient survival.15

**ANDROGEN RECEPTOR VARIANTS**

Expression of alternatively spliced forms of AR, known as AR-Vs, is an important mechanism of ADT resistance. These variants lack the ligand-binding domain (LBD), and thus are constitutively active. Crucially, they are not responsive to ADT, since these therapies rely on the presence of the LBD. Thus, modulation of AR-V levels using miRs, including variant-specific miRs, may represent a novel therapeutic strategy for mCRPC.

Studies have shown that certain miRs, for example miR-124, are able to target the transcripts of both full-length AR and AR-Vs due to distinct binding sites within the 3'UTRs, and so lead to downregulation of both full length and variant AR.16

AR-Vs have distinct 3'UTRs when compared with the full length transcript (as shown in the Figure), which is likely to account for the ability of miRs to differently regulate them. The characterisation of these distinct sequences may lead to further identification of additional variant-specific miRs.

**THERAPEUTIC POTENTIAL OF MICRORNAS**

The challenge for all in the field of cancer research is identifying new therapies that will reduce mortality and morbidity. Excitingly, miRs have several ideal therapeutic properties: they are small, relatively inexpensive to synthesise, highly target-specific, and have the potential to be modified in order to improve in vivo stability and cellular uptake. They also display disease and tissue specificity. Several clinical trials of miR-based therapeutics in cancer have been reported.17,18 The majority utilise synthetic, complementary oligonucleotides which sequester the target miR, inhibiting its function within the cell. Such ‘antagomiRs’ have been reported to be well tolerated, with no long term adverse effects, as seen in phase II trials of anti-miR-122 and anti-miR-155.12

In support of pursuing AR-associated miRs as therapeutic targets in prostate cancer, new evidence is emerging which suggests that aberrant expression of miRs can modulate AR activity, including miRs-221/222. These were identified as upregulated in 90% of mCRPC cases when compared with primary tumours. This altered expression affected how cells are able to respond to androgen treatment, thus suggesting potential involvement of this miR family in the transition to CRPC.13

Dysregulated miRs can also promote cell survival, proliferation and the development of drug resistance. For example, increased miR-21 levels in mCRPC may contribute to docetaxel chemotherapy resistance by downregulating the expression of PDCDH, a known suppressor of tumorigenesis.19 Potentially, the identification of the most critical miR(s) associated with drug resistance will be the cornerstone for the design of therapeutics. To date, antagomiRs and miR mimics are two highly promising miR-based therapeutics. However, it is widely accepted that the effective, targeted delivery of miR therapeutics is still a major challenge that needs to be overcome before these can be used extensively in the clinical setting. With much ongoing research in this area, it can only be a matter of time before miR-based therapies, probably in combination with more traditionally hormone-based therapies, are used in advanced prostate cancer.

**SUE M POWELL, CLAIRE E FLETCHER AND CHARLOTTE L BEVAN**

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Breast cancer remains a significant NHS health burden here in the UK. Through inhibitors targeting oestrogen receptor α (ERα; tamoxifen), aromatase activity (anastrozole, letrozole), and HER2 (tratuzamab, pertuzumab), scientists have developed some impressive therapeutic advances.

Despite this, there remains a worryingly high recurrence rate for many patients who have undergone chemotherapy and/or biotherapy. Indeed, ERα-positive breast cancer patients treated successfully with surgery and aromatase inhibitors still have an approximately 20% chance of breast cancer recurrence. Thus, there remains an unmet need to develop new drugs to improve outcomes.

**THE PATHWAY TO DRUG DEVELOPMENT**
I have been fortunate to have been immersed in this research area for most of my scientific career. Indeed, through my work and the collaboration of many others, I’ve seen most aspects of the drug development of various novel compounds that target both hormone-dependent and hormone-independent cancers. Moreover, irusostat (a compound that I did much pre-clinical research on) has entered clinical trials and is now being considered for a range of hormone-dependent malignancies. However, this drug development path has been fraught with difficulties, but is an interesting story of the rollercoaster and sometimes brutal route from drug discovery to patient care.

Let’s start in 2004 when I joined Sterix Ltd, a spin-out company of Imperial College London, supported by Ipsen. It was my second postdoctoral position, and I had limited knowledge of drug discovery or even steroids. The next few years rapidly reversed this ignorance.

Unfortunately, I cannot claim to having discovered and initially developed irusostat (also known as STX64 or 667Coumate), a highly specific, highly potent steroid sulfatase (STS) inhibitor. This honour goes to the inspirational team of steroid biochemists Michael Reed and Alan Purohit (Imperial College London) and medicinal and biological chemist Barry Potter (University of Bath, now University of Oxford).

STS catalyses the desulfation of generally inactive sulfated steroids and thus is considered an important activating step for hormones. With regards to hormone-dependent breast cancer, the key steroid is oestradiol, which binds ERα to stimulate growth. Blocking oestradiol synthesis and action has been the cornerstone of breast cancer therapy for over 40 years. Aromatase and STS both synthesise oestrogen from steroid precursors (see Figure) and so inhibition of these pathways is an attractive therapeutic target.

**NAVIGATING CLINICAL TRIALS**
After preclinical success, irusostat was taken forward to a ‘first-in-class’ phase 1 clinical trial for patients with hormone-responsive breast cancer. Initial results were hugely encouraging, with a 5mg/kg oral dose of irusostat for 5 days resulting in 98–99% inhibition of tumour STS activity and significant reduction of serum levels of oestrone (by 76%), oestradiol (by 39%), dehydroepiandrosterone (by 41%), androstenediol (by 70%), androstenedione (by 62%) and testosterone (by 30%). Importantly, 4 out of the 14 patients recruited showed signs of stable disease: no mean feat in these difficult-to-treat patients who had progress on standard therapies.

Fortunately, these initial promising results were somewhat undermined due to a poorly designed follow-up clinical trial that had limited input from the original scientific team who had identified irusostat in the first place.!

Irusostat received a further knock to its progress through another clinical trial, this time in patients with endometrial cancer. Irosustat performed
well, with an increased number of patients with more stable disease (47%) compared with the current standard therapy (32%) – the progestin megestrol acetate (MA). However, overall, there was no statistically significant difference between the groups with regards to patient response or survival rates. Thus, the trial was halted early.

**OVERCOMING SETBACKS**

These setbacks made it increasingly challenging to garner support for STS inhibitors to advance further into clinical trials. But we had another therapeutic strategy up our sleeves that would help drive further irusostat clinical trials. This was the concept of dual aromatase sulfatase inhibitors, or DASIs.

As part of our company’s drug pipeline, we had been developing DASI compounds since the mid-2000s; these had shown excellent efficacy in preclinical models of breast cancer. Targeting both aromatase and sulfatase was a no-brainer and provided interesting chemical entities and novel dual action efficacy. These studies informed the way forward: clinical trials overseen by Cancer Research UK to test irusostat in combination with an aromatase inhibitor (the IRIS trial). This trial reported in 2017 and showed evidence of clinical benefit which underpinned the scientific concept of STS inhibition. Larger studies are now required, with further clinical development still on the cards.

Although I have now moved on from the further development of irusostat, my own research laboratory still heavily focuses on these areas of research, albeit in new, emerging ways. We have recently shown that STS inhibition may be beneficial in treating a subset of colorectal cancer tumours that are oestrogen-responsive and we continue to develop novel STS inhibitors with excellent potency. Thus, there remain many new drug development avenues in this area that should see new inhibitors of oestrogen metabolism playing an important role in cancer research for the foreseeable future.

**PAUL FOSTER**

Institute of Metabolism & Systems Research (IMSR), University of Birmingham

**REFERENCES**


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**PROGRESS IN UNDERSTANDING PANCREATIC NETs**

WRITTEN BY KATHERINE A ENGLISH, OMAIR A SHARIQ AND KATE E LINES

Pancreatic neuroendocrine tumours (PNETs) represent a spectrum of cancers that arise from the islet cells of the pancreas. PNETs are rare and reportedly account for 3–5% of all pancreatic tumours, with an incidence of 1–3 cases per 100,000 individuals per year. The incidence rate appears to be increasing. However, it is unclear whether this is a true increase or if it can be explained by improved detection on endoscopy and imaging.

Despite high profile cases, including Steve Jobs, Arethra Franklin and Irfan Khan, who have been diagnosed with and subsequently died from PNETs, there continues to be a lack of awareness and understanding of these tumours among the general public, and the medical and scientific communities. This may partly be explained by the relatively good prognosis and slow-growing nature of these tumours when compared with pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer.

However, a proportion of PNETs (e.g. poorly differentiated neuroendocrine carcinomas) are highly aggressive, with a median survival of 12 months, not dissimilar to that of PDAC. Furthermore, around 60% of patients present with metastatic PNETs, usually with liver metastasis, with a median survival of only 24 months.

Surgery is the mainstay of therapy for PNETs. However, this is often not curative due to advanced disease. Although currently available medical therapies have been shown to improve progression-free survival (surrogate marker for overall survival), many studies group PNETs with other types of NETs due to their rarity, making specific inferences regarding PNET outcomes challenging. Therefore, there is a need for more effective targeted treatments, based on an improved understanding of the molecular mechanisms that underpin the development of PNETs.

**PNET GENETICS AND EPIGENETICS**

Approximately 10–15% of PNETs occur as part of an inherited syndrome, such as multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau disease, neurofibromatosis type 1 and tuberous sclerosis complex 1 and 2. Of these, MEN1 is the most common hereditary syndrome associated with an increased susceptibility to PNET development (approximately 10%).

However, the majority of PNETs are sporadic, with a low mutational burden. Nonetheless, large-scale whole genome and exome sequencing studies have shown that the mutations most commonly found in sporadic PNETs involve the genes MEN1, ATRX and DAXX, which are involved in the epigenetic mechanisms of histone modification and chromatin
remodelling. Epigenetics (which literally means ‘above’ or ‘on top of’ genetics) refers to changes in gene expression that are not caused by alterations in the underlying DNA sequence.

Enzymes responsible for carrying out epigenetic modifications are known as ‘writers’, while those that remove modifications are referred to as ‘erasers’. Epigenetic ‘readers’ have the ability to recognise and bind to specific epigenetic modifications and recruit additional proteins that regulate gene transcription (Figure). In cancer, these mechanisms may be dysregulated, resulting in either upregulation of oncogenes or downregulation of tumour suppressor genes. Unlike genetic mutations, epigenetic changes are reversible, therefore drugs that target epigenetic mechanisms may represent a promising therapy for the treatment of PNETs.

In October 2019, we formed the Oxford NETs research team, within Raj Thakker’s lab at the University of Oxford. The focus of our group is to investigate different aspects of epigenetics in NETs (including DNA methylation and histone modifications) as well as testing of novel epigenetic-targeting compounds.

THE DNA METHYLOME OF PNETs

DNA methylation is essential for normal development through its ability to silence/’turn off’ specific genes. This process is required for cellular differentiation and homeostasis.

In DNA methylation, DNA methyltransferase (DNMT; an epigenetic writer) adds a methyl group to the DNA base cytosine (C) to form 5-methylcytosine (5mC), usually at the start of the gene sequence (promoter). This ‘mark’ can either be maintained or removed during cellular replication, or it can be actively removed by the epigenetic eraser ten-eleven-translocase (TET) to form 5-hydroxymethylcytosine (5hmC). In opposition to 5mC, 5hmC protects the promoter site and enables gene transcription.

Unbalanced DNMT and/or TET activity may lead to inappropriately methylated/‘switched off’ tumour suppressor genes or hydroxymethylated/‘switched on’ oncogenes resulting in uncontrolled cellular proliferation.

TARGETING HISTONE MODIFICATIONS IN PNETs

Histones, which package and condense DNA, can be epigenetically modified through the addition of methyl and/or acetyl marks to histone tails (read by epigenetic readers). This results in an open/‘relaxed’ form (euchromatin), which enables gene transcription, or an inaccessible/‘closed’ form (heterochromatin).

The bromodomain and extra-terminal domain (BET) proteins are a family of epigenetic readers that bind to a specific type of histone modification (acetylation) and recruit other proteins that regulate gene expression. Dysfunction of the BET proteins has been linked to many cancers, through the upregulation of cancer-related genes, such as c-MYC.

Our group has previously shown that the BET inhibitor JQ1 decreases proliferation in PNET cell lines and increases apoptosis of PNETs that develop in mice. However, the poor half-life and bioavailability of JQ1 mean that it is unsuitable for clinical development. Novel BET inhibitors with improved selectivity and tolerability profiles have recently been developed. We are currently testing these and a panel of novel compounds (e.g. writers and erasers) in preclinical PNET models, to identify candidates that could be further developed for clinical use.

The variable efficacy and limited treatment options available for advanced PNETs presents a challenge for healthcare professionals, scientists and – most importantly – patients. In the current era of precision medicine, overcoming this challenge through an in-depth understanding of the epigenetic mechanisms involved in PNETs and the investigation of therapies that target these pathways may identify a novel treatment approach for these tumours.

Overview of epigenetic mechanisms.
The Society recognises that industry is a crucial part of the endocrinology community and through our Corporate Support scheme we commit to facilitating dialogue between professionals in industry, academia and clinical practice. In doing so, we can better represent endocrinology as a discipline, identify its challenges and find better healthcare solutions.

For further information, visit www.endocrinology.org/corporate or contact sophie.tovey@bioscientifica.com.

HRA Pharma Rare Diseases is dedicated to bringing the best care and services to patients and is committed to supporting healthcare professionals all over the world.

We have over 15 years’ experience in rare and ultra-rare diseases and are passionate about improving the lives of people affected by these conditions. We recognise that people living with rare diseases often have severe and potentially life-threatening disabilities that impact not only their quality of life, but also the lives of those who care for them. Delays in diagnosis, together with the lack of effective treatments are just some of the challenges faced by people living with a rare disease.

By partnering with the community, we are committed to tackling current challenges, reducing the time to accurate diagnosis, enabling global access to treatment and offering effective options for the long-term management of rare diseases. Our purpose is to improve the quality of life and the experience of care. We are confident that through innovative ideas, robust science and a passionate and highly focused team, we can elevate the needs of patients living with a rare disease and help to narrow inequalities in the standards of care across the globe.

Together we fight, so no patient is left behind!

For more information, contact Sara Elgott, Rare Diseases Country Lead UK & Ireland s.elgott@hra-pharma.com
Pfizer is one of the world’s premier innovative biopharmaceutical companies, discovering, developing and providing over 100 different medicines, vaccines and consumer healthcare products that help save and transform the lives of millions of people in the UK and around the world every year.

For more than 25 years, Pfizer Endocrine Care has been committed to the advancement of endocrinology. This is demonstrated by our innovations in endocrine care: Pfizer UK was the first company to launch single-dose and multi-dose growth hormone (GH) delivery devices; it has built up the largest international databases of patients receiving GH therapy; and it produces the first and only GH receptor antagonist for the treatment of acromegaly.

The Society for Endocrinology has entered into a partnership level agreement with Pfizer. The agreement is first of its kind for the Society, and aims to deliver maximum benefit to both organisations and the broader aim of advancing endocrinology.

To find out more about what Pfizer are doing to support the NHS and patients in the UK, please contact Endocrine Country Brand Lead on +44 (0)1304 616161.

Paul Carroll, Chair of the Society for Endocrinology Corporate Liaison Committee, says
“The partnership recognises the Society for Endocrinology’s commitment to working with industry to achieve its objectives. It represents a true collaboration with an industry partner, working on joint projects for the benefit of endocrinology.”

James Steed, UK Lead for Endocrine Care at Pfizer, comments
“The NHS is changing in response to various pressures, and the needs of our partners and the people they care for reflect this. We believe that, through working in partnership, combining our skills, experience and resources, together we can tackle some of the greatest challenges facing the NHS today. The new partnership will strengthen Pfizer’s relationship with the Society, and ultimately improve patient care.”
CANCER AND FERTILITY: A PATIENT’S PERSPECTIVE

WRITTEN BY CAROLINE MASLIN AND RICHARD ANDERSON

Cancer concentrates the mind, but fertility isn’t your first thought when you receive a diagnosis. It is such an overwhelming time: you are at the complete mercy of your medical team and you want to protect the people closest to you. Your survival is paramount and it may only be on reflection, at a later date, that the importance of fertility can become something of a priority.

When you are diagnosed with cancer at a relatively young age, fertility is most likely going to be an issue. Whether due to surgery or another treatment, it will have an impact one way or another.

MY STORY

I was diagnosed with breast cancer in 2012 at the age of 36. I underwent chemotherapy, a mastectomy and a course of radiation. I was then put on the oestrogen inhibitor tamoxifen, which sent me into menopause by the time I was 38. In 2017, my cancer metastasised into my bones and lymph nodes but, after a successful course of immunotherapy and lifestyle changes, I am now one of those lucky ones ‘living with cancer’. I had children before my cancer diagnosis, but fertility was never addressed with me during my initial treatment. I was never asked if I had children or if I wanted children, or if I wanted more children. I feel that the doctor didn’t see it as a priority, which I can understand. But, after coaching others in the course of my voluntary work with a local cancer support network, it is very clear the loss of fertility can have huge impact on patients. We put our trust in our medical teams, but that leads to a loss of control on the patient’s part, which can have huge repercussions.

FERTILITY: AN OVERLOOKED ISSUE

Eight years down the line of treatment, and after supporting many clients through my voluntary work, it’s clear that the issue of fertility is something that is often overlooked or deemed unimportant at the time of diagnosis and treatment. Even when I did go through a period of serious reflection later on in my treatment, wishing I could have more children, it was a ‘fait accompli’ and I had to move on. I never talked to anyone, even my family, at the time I was 38. In 2017, my cancer metastasised into my bones and lymph nodes but, after a successful course of immunotherapy and lifestyle changes, I am now one of those lucky ones ‘living with cancer’. I had children before my cancer diagnosis, but fertility was never addressed with me during my initial treatment. I was never asked if I had children or if I wanted children, or if I wanted more children. I feel that the doctor didn’t see it as a priority, which I can understand. But, after coaching others in the course of my voluntary work with a local cancer support network, it is very clear the loss of fertility can have huge impact on patients. We put our trust in our medical teams, but that leads to a loss of control on the patient’s part, which can have huge repercussions.

MAKING THE DISCUSSION A PRIORITY

I know that fertility treatment is constantly evolving. But I believe that a medical team have a responsibility to address the issue with a patient as early as possible during diagnosis and treatment, in order for the patient to have time to process whether it is going to be a priority or not.

It goes without saying that a patient is overwhelmed by the information being thrust at them at this difficult time, but doctors need to give their patients a certain level of trust, to realise that they have the right to decide the importance of fertility in their future. I believe that a doctor has the responsibility to ‘plant the seed’ early on.

There is no need to overwhelm a newly diagnosed patient with all the options, as I know that it is an expert field. But ‘forewarned is forearmed’ and the right information could prevent a lot of problems down the line. We tend to deal with the fallout from cancer on a reactive basis, rather than having the information in advance.

Hopes and dreams are constantly changing, especially after a cancer diagnosis. Those who did not ever want children may suddenly long for them. They may divorce, remarry or want more children, or face many other life issues that we are presented with as human beings. What someone feels at 28 may be very different to what they may feel at 38 or 48.

A patient/person deserves to be provided with the information that they need to make a considered decision.

CAROLINE MASLIN

New quicker protocols for ovarian stimulation have been developed based on a ‘random start’, rather than being limited to specific stages of the menstrual cycle. Data on outcomes are limited; while there are emerging data that oocyte quality may be slightly reduced in women with cancer, good live birth rates can be achieved.

Caroline also raises the wish of many women who already have children to have more after diagnosis – the natural desire to complete their family. This contrasts sharply with NHS-funded assisted reproduction, which limits treatment to a first child.

RICHARD ANDERSON
MRC Centre for Reproductive Health, University of Edinburgh

REFERENCES


ENDOCRINE CANCER
Where next after ‘biggest and best’?
PUBLIC ENGAGEMENT WITH SCHOOLS

Last November, the Society for Endocrinology held what was described as its ‘biggest and best’ public engagement event for schools.

Since 2017, this initiative has become an established and distinctive part of the annual Society for Endocrinology BES conference. It provides school pupils with the opportunity to join delegates for a dedicated afternoon of insights into the world of endocrinology. Revealing the everyday face of the specialty, the event included opportunities to engage in hands-on interactive activities, and to meet the scientists, nurses and doctors who make up the Society’s membership.

I have always been passionate about creating inclusive scientific communities. Therefore, it has been a natural and proactive step to work within the Society to bring endocrinology to a wider audience, including pupils, who would not normally have the opportunity to experience such events. Consequently, I have had the pleasure to lead the organisation of the last two schools’ public engagement events, in Glasgow (2018) and Brighton (2019).

STEPPING UP FOR BRIGHTON

After Glasgow, Brighton was always to be a ‘step up’, with the support of outreach representatives from the two local universities and the STEM ambassador hub. We had a phenomenal response: over 100 pupils (14–16 years) and teachers from local schools wanted to attend. The location was also fantastic, as we had the large restaurant lounge at the Brighton Centre to work in, directly overlooking the seafront. Visualising the space and how it could be utilised is an essential part in planning any public engagement event. Along with the perfect place to set up an auditorium for the introductory ‘live’ show and the concluding Q&A session, we had a great networking area to position the tables and poster boards for the hands-on activities.

I opened the conference with an interactive presentation on ‘you and your hormones’, which of course had plenty of fake blood on hand, to demonstrate the main way hormones are transported around the body! Other props included Christmas tree lights with a ‘Post-it’ race to help express the different ways and speeds chemical messengers are transmitted around the body. Afterwards, there was the opportunity for everyone to get involved in the hands-on activities. The pupils also alternated between networking sessions to meet and talk directly to the scientists, doctors and nurses about their careers and what they really do.

This year, we encouraged activities that showcased the fantastic ideas members had developed through the Society’s Public Engagement Grant

I also developed ‘make your diagnosis’: where pupils become doctors for the afternoon.

‘Make your diagnosis’: where pupils become doctors for the afternoon.

‘Make your diagnosis’: where pupils become doctors for the afternoon.

The schools’ afternoon at the annual Society for Endocrinology BES conference has proved to be a great way to engage and inspire a future generation of endocrinologists. We are grateful to all the members who have volunteered each year to make it such a success. Visiting pupils and teachers have always been very positive, describing the event as fun and very educational, where they have learnt a lot about potential future careers.

WHERE NEXT?

Despite this great success, there are now questions around the future direction of such public engagement events at a time of social distancing. Just 4 months on from SfE BES 2019, the UK was placed in COVID-19 lockdown and, even with lockdown gradually easing, it’s hard to imagine the complete return to such an intense face-to-face and highly interactive hands-on format in the foreseeable future.

In the short term, there has been the cancellation of many planned events, as the sector re-orientates itself. One casualty was Clinical Update (now postponed from April 2020), where Heather Lampard (Society Careers and Engagement Officer) and I had already planned the public engagement training session for the day of the Career Development Workshop. Another personal loss was the Big Bang Fair at Kingston University (scheduled for June), with great plans to work with the Society and present the ‘human cell signalling relay’ and ‘make your diagnosis’ again.

FUTURE OPPORTUNITIES

New challenges present new opportunities. I recall conversations before COVID with teachers at Brighton, regarding their disappointment in having to choose between the students to bring and those to leave behind, due to limited availability at the venue for each school. There is the need to consider broadening reach, being more inclusive and flexible and perhaps not always tying down events to selected venues, spaces and time constraints. Certainly, in the immediate future, the online world offers many new possibilities but, even then, we will have to learn to deliver our message very differently!

NIGEL PAGE

Public Engagement Committee
Endocrine Ambassador, Kingston University London

The next application deadline for the Society’s Public Engagement Grant is in March 2021. See www.endocrinology.org/grants-and-awards/grants/public-engagement-grant for more details.
Connecting the endocrine community is more important than ever, which is why we invite you to join us at SfE BES Online from 16-20 November 2020. This stream-lined, digital conference will bring the latest developments in endocrinology direct to your screens, including the much loved ‘What is new?’ session, Medal Lectures and an in-depth look at the Future of Endocrinology post-COVID-19. Content will be available on demand for all registered delegates, so you can view at a time which suits you. The new SfE BES digital platform also offers opportunities to network and discuss developments in endocrinology, including live Q&A sessions with speakers and colleagues.

You must register in advance to access the CPD accredited programme and all on-demand content. Register now to secure your place www.endocrinology.org/sfebes2020/registration

Join or renew your membership www.endocrinology.org/membership/join-or-renew

Each day, SfE BES Online will offer an opportunity for one or more Endocrine Network to gather in a dedicated session organised by Network Convenors. These sessions will highlight key updates within the networks, as well as facilitate discussion time for all participants.

Endocrine Network topics:
- Adrenal and Cardiovascular
- Bone and Calcium
- Endocrine Consequences of Living with and Beyond Cancer
- Endocrine Neoplasia and Cancer
- Metabolic and Obesity
- Neuroendocrinology
- Reproductive Endocrinology and Biology
- Thyroid

For further information visit www.endocrinology.org/sfebes2020
**PRESIDENTIAL LECTURE**
Professor Robert Lefkowitz  
New York, USA  
The SfE BES Online programme includes the much anticipated Presidential Lecture from Nobel Laureate Professor Robert Lefkowitz. Professor Lefkowitz is best known for his groundbreaking discoveries revealing the inner workings of an important family of G protein-coupled receptors, for which he was awarded the 2012 Nobel Prize in Chemistry with Professor Brian Kobilka. The Presidential Lecture will focus on G protein-coupled receptors (GPCRs) molecular signalling and related pharmacology.

**MEDAL AND PRIZE LECTURE HIGHLIGHTS**
Enjoy an exciting programme of the following 10 Medal and Prize Lectures:

- **Dale Medal Lecturer**
  Professor Dame Frances Ashcroft  
  Oxford  
  Metabolic regulation of insulin secretion in health and disease

- **Society for Endocrinology Medal Lecturer**
  Professor David Ray  
  Oxford  
  Circadian control of inflammation and metabolism

- **Starling Medal Lecturer**
  Professor Davide Calebiro  
  Birmingham  
  Illuminating hormone receptors in physiology and disease

International Medal Lecturer
Dr David Mangelsdorf  
Texas, USA  
FGF21 and nutrient stress: eat and drink, but don’t get too merry

Transatlantic Medal Lecturer
Dr Daniel Drucker  
Toronto, Canada  
Incretins and cardiometabolic disease – an inflammatory perspective

European Medal Lecturer
Professor Nelly Pitteloud  
Lausanne, Switzerland

Jubilee Medal Lecturer
Professor Anne White  
Manchester  
POMC peptides: master regulators of the stress axis and neuroendocrine pathways in energy balance

CET Visiting Professor Lecturer
Professor Mirjam Christ-Crain  
Basel, Switzerland  
New diagnostic and therapeutic options in vasopressin-dependent fluid disorders

Clinical Endocrinology Trust Lecturer
Professor Fredrik Karpe  
Oxford  
Endocrine determinants of human fat distribution

British Thyroid Association Pitt-Rivers Lecturer
Dr Frederic Flamant  
Lyon, France  
Thyroid hormone and the timing of cortical circuits maturation

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**GET THE LATEST INFORMATION**
SfEBESONLINE

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**THE ENDOCRINOLOGIST | AUTUMN 2020 | 17**
LEARNING IN LOCKDOWN:
LAB IN YOUR LIVING ROOM
WEBINAR SERIES

Caroline Gorvin (Birmingham) and Mark Turner (Coventry) were instrumental in the development of the Society’s Research Skills: Lab in your Living Room webinar series – aimed at early career researchers locked out of their labs (accessible via the Members’ Area of the Society website at www.endocrinology.org).

Here they describe the series’ inception and aims, and how research has been affected during the COVID-19 lockdown.

HOW HAS THE LABORATORY SHUTDOWN AFFECTED YOUR RESEARCH?

Caroline: My research is entirely lab-based, so the shutdowns had a large impact on my work. This meant accepting that those last few experiments for fellowship applications were not going to happen. I spent all of lockdown writing: fellowship applications, a chapter and a review. Having a concentrated period of time to focus on this was beneficial as, ordinarily, I get preoccupied with lab work.

We returned to our labs in July. It’s very different – now we work in shifts and maintain social distancing – but it is nice to be back. It has meant I have restructured my time to have lab-focused days and at least 1 day a week working from home.

Mark: Having recently started at Coventry University, I had only just managed to get my research underway when the laboratories shut down. While it has been frustrating not having access to the labs to conduct the experiments, it has given me the opportunity to think more about the experiments I need to do when the labs are back running. Away from the lab, and like most people, the shutdown has given me the opportunity to write or finish off papers and apply for internal and external funding.

‘We returned to our labs in July. It’s very different – now we work in shifts and maintain social distancing.’

WHY DID YOU WANT TO GET INVOLVED IN THE RESEARCH SKILLS SEMINARS?

Caroline: As it wasn’t too long since I was a post-doc, I could relate to how difficult it would be for many early career researchers working at home. As a lot of data are now online, there was an opportunity to teach early career researchers how to use it for their own research. I also felt there was a gap that these webinars could fill: lots of societies were setting up seminars using the traditional model in which someone presents their research, and I was conscious of avoiding overlap. Many junior researchers were already anxious enough about losing research time and not having enough data, so seeing someone’s amazing data wouldn’t be beneficial to them.

Mark: It has seemed that there has been a wave of webinar series set up around the world, often with daily seminars being presented by leaders in their respective fields. It’s been a great opportunity to expand our knowledge into different areas of research. At the same time, it’s also been the chance to ‘upskill’ as several postgraduate students and early career researchers have got to learn new ways of analysing data or generating new findings from existing and publicly available datasets.

WHY DID YOU THINK THESE TOPICS WERE THE MOST IMPORTANT?

Caroline: I wanted them to be as accessible as possible to everyone. I realise not everyone has large amounts of funding, so I suggested topics that could use existing data and be analysed using freely available software. We tried to come up with topics that would be relevant to as many people as possible, while trying to incorporate cutting-edge techniques.

‘It’s been the chance to “upskill” as several postgraduate students and early career researchers have got to learn new ways of analysing data or generating new findings from existing and publicly available datasets.’

HOW DO YOU THINK THE SHUTDOWNS WILL AFFECT YOUR RESEARCH LONG-TERM?

Caroline: For me, the next few months will be particularly challenging. How will we teach new students within the lab while maintaining social distancing? Will our new students feel supported and part of the team?

Adapting how we work will be important to address these challenges. If we are to take positive points from this period, it is that we are lucky to have technology that allows us to keep in contact, and it is possible that organisations will be more willing to accept flexible working patterns in the future.
Mark: From a practical standpoint, I’m fortunate that the majority of my research is based in vitro and, while it’s frustrating to have to stop work because of shutdowns, it might not affect my research as much as researchers from other disciplines. However, if local lockdowns are announced with little warning, as we’ve seen recently, it is going to be a challenge to manage this without it causing significant disruption to research.

What are likely to be affected are funding opportunities, which undoubtedly will become more competitive, both in terms of the number of applications and the funding available.

Caroline: We discussed several other topics, including analysis of microscopy images and statistical analysis. It would be great to hear from early career researchers to find out what they would like to learn (via media@endocrinology.org).

Mark: I’d like to see image analysis. Images can give you a lot of information about your samples, which can be used to generate interesting and potentially useful data. I think it would be great to find out what applications and approaches can be used to get the most out of microscopy.

You can watch the Lab in Your Living Room series by logging into the Members’ Area at www.endocrinology.org. If you would like to present a webinar or suggest a topic, email media@endocrinology.org.

WEBINAR TOPICS AND PRESENTERS

ILDEM AKERMAN University of Birmingham
Differential gene expression analysis from RNA-sequencing data

FABIO SANNA University of Oxford
Publicly available data sources, a practical example

STUART MORGAN University of Birmingham
Genetic screens and functional genomics using CRISPR-Cas9 technology

TORYN POOLMAN University of Oxford
Data analysis using R

INÊS CEBOLA Imperial College London
Analysis of genetic association data with publicly available datasets

WATCH OUR CLINICAL SKILLS WEBINAR SERIES

These interactive sessions are free to Members and provide essential knowledge for trainees and recently appointed consultants in endocrinology and diabetes. The talks, delivered by experts, focus on selected topic areas to compliment learning for the MRCP(UK) Specialty Certificate Examination in Endocrinology and Diabetes this year. They are also indispensable for continued training of clinicians and nurses at all career stages.

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Topics include:
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• How to set up a nurse-led clinic
• Medicolegal aspects of nurse-led training
It is an honour to be selected as the incoming Editor-in-Chief of Endocrine-Related Cancer (ERC). Following in the footsteps of Charis Eng is a daunting task. She and her team have done an outstanding job for the past 8 years in expanding ERC’s well-deserved reputation as a top flight and highly rigorous journal.

Challenges for implementation of preventive, diagnostic and treatment measures to the community have been magnified in the COVID-19 pandemic, some of which have been highlighted by recent ERC publications. One example has been the difficulty in the consistency of mask-wearing due, in part, to shortages of materials, inadequate distribution systems, and cultural and social barriers. Simultaneously, social justice issues have also moved to the forefront of the public consciousness. The Black Lives Matter movement in the USA has energised the larger population against racial and ethnic inequalities following multiple well-documented tragedies.

‘Journals such as Endocrine-Related Cancer provide an opportunity to expand the scientific, racial, gender and ethnic diversity not only of research, but also of researchers in the field.’

One consequence of this social movement has been greater recognition that socially disadvantaged populations fare worse from COVID-19 and have unique barriers to implementation. Social determinants of health impact the outcomes from nearly all diseases worldwide, including diabetes and obesity, breast cancer, prostate cancer and others that are highly relevant to ERC. Several of these diseases disproportionately affect specific ethnic and racial minorities, independent of social disparities. ERC has an established interest in supporting research designed to understand the biological mechanisms for racial and ethnic differences in endocrine cancer frequencies and outcomes. Implementation and population science applied to diverse worldwide communities are areas of further emphasis for ERC.

Journals such as ERC provide an opportunity to expand the scientific, racial, gender and ethnic diversity not only of research, but also of researchers in the field. In addition to continuing to emphasise science relevant to healthcare disparities, we will be establishing early career pathways for peer reviewers and early career positions on the Editorial Board, with close attention paid to diversity.

The COVID pandemic and current social climate have served to emphasise the importance of the current strengths and future directions of ERC. Continued emphasis on high quality science, enabling communication to the community, and continued and expanded attention to diversity, will all be needed as we move our field forward together. I look forward to working with our editorial team and with all of you in achieving our mutual goal to improve the health of all individuals with endocrine cancers.

MATTHEW D RINGEL
Division of Endocrinology, Diabetes and Metabolism, and Cancer Biology Program, The Ohio State University Wexner Medical Center, and The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

ENDOCRINE-RELATED CANCER: PRESENT CHALLENGES AND NEW OPPORTUNITIES

WRITTEN BY MATTHEW D RINGEL

Having served previously as an ERC Associate Editor, as well as publishing in the journal and reading numerous outstanding high quality articles over the years, I am particularly excited to begin my new role. I am eager to work with the ERC Editorial Board, Bioscientifica, the Society for Endocrinology and the affiliated societies in continuing and expanding upon the work of my predecessors.

When I was asked to write this opinion piece for The Endocrinologist to begin my tenure, I thought deeply about the timing of this new role in the context of the COVID-19 pandemic and the international responses to current social and racial tensions in the USA.

The COVID-19 pandemic and its rapid spread throughout the world have impacted on our core social fabric. It has enabled new international collaborations, but also has exposed deep social divisions within our communities. At no time since the early days of the AIDS epidemic has biomedical research had such immediate impact on public policy and global public health. The critical importance of rigorous basic, translational, clinical and population science cannot be overstated.

Over the past 8 months, landmark studies have characterised key mechanistic elements behind SARS-CoV2 infection, enabled a deeper understanding of the molecular epidemiology of the disease, established preventive and life-saving clinical strategies, and developed new therapeutic compounds and vaccines with a joint goal to prevent and treat COVID-19. The pace of this work has been breathtaking, and its importance is crucial to control the virus. It is also clear that the impact of the research relies on successful implementation of the findings to the community. For example, vaccine effectiveness will depend not only on its efficacy in rigorous clinical trials, but also on production of adequate doses, cost management and individual adherence to vaccination recommendations.

There also have been important lessons to learn from errors that have slowed implementation of the best new science. These have included publication of manuscripts that were subsequently retracted and public policy decisions based on peer-reviewed but unconfirmed small data series, identified and popularised on social media. These experiences emphasise the crucial roles that scientific journals and peer review play as arbiters of publication of manuscripts that were subsequently retracted and public.

The urgency of rapid translation of science in the current situation is clear, and clarifies the need for a timely, rigorous and fair peer review process. Be assured that the high scientific expectations and outstanding peer review maintained by ERC’s authors, peer reviewers and editors will be continued, with a renewed commitment to enhance accurate and timely communication of key results to the scientific and lay communities.

Outstanding science is necessary, but not sufficient, to ensure translation into clinical research and, eventually, public policy. As an international journal, ERC seeks to support research in all aspects of endocrine oncology, including fundamental basic science, translational studies and clinical research, with an ultimate goal to improve the health of diverse populations worldwide through new discovery.
Discover the latest Impact Factors from the journals of the Society for Endocrinology and find out why they should be the home of your next publication.

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Impact Factor 4.041, the leading basic endocrinology journal

**Journal of Molecular Endocrinology**
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Impact Factor 2.592, 40% discount on publishing for Society members

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www.endocrinology.org/publications
New NHS Steroid Emergency Card AVAILABLE TO ORDER

As you know, the new NHS Steroid Emergency Card is an NHS-wide card supported by our recently published guidance (www.rcpjournals.org/content/clinmedicine/20/4/371).

We know many GP and hospital appointments are operating as telephone clinics for the time being. Hence, community pharmacy teams will initially issue most of these cards, whilst we are working within COVID-19 contingency plans.

There will be 3 ways of obtaining a card:

- Through community pharmacies – for patients with known adrenal insufficiency who have had the necessary patient education, or need a replacement card; patients may wish to show a clinical letter or similar, but that is not essential.
- From GPs when having a routine review, if primary care is managing steroid replacement.
- From hospital teams at next routine appointment.

The card can also be downloaded as a PDF, and added as a lock screen to mobile devices. Learn more from the Addison’s Disease Self-Help Group (www.addisonsdisease.org.uk).

The new card can be ordered through the usual NHS ordering mechanisms:

- Secondary Care: Xerox online portal www.nhsforms.co.uk. You may need to raise a non-catalogue requisition in Oracle, selecting supplier as Xerox, and we can process the requisition by raising the order with NHS Forms. The cost is £2.65 (excluding VAT) for 100 cards (one unit is 100 cards).
- Primary Care: PCSE online portal https://secure.pcse.england.nhs.uk/_forms/pcsssignin.aspx.

Our adrenal crisis web page is a source of all the relevant information, including published guidance, a downloadable PDF of the card and links to patient educational resources. The QR code on the card goes directly to the adrenal crisis web page (www.endocrinology.org/adrenal-crisis).

DR HELEN SIMPSON
Society for Endocrinology and RCP Patient Safety Committee

Innovative clinical practice? YOUR SOCIETY NEEDS YOUR HELP!

So much has happened over the last six months. The COVID-19 crisis has taught us much about adapting rapidly and effectively to maintain clinical care for our patients. Even before the crisis many centres around the UK had developed novel and innovative ways of working for the benefit of patients.

All too often, though, whilst such advances may have been implemented locally to good effect, their potentially broad application may not have been realised in the wider endocrine community. It is here that as a member of the Society you have the opportunity to make a real difference.

Steve Ball’s article (page 26) succinctly lays out a whole variety of issues pertaining to clinical care in Specialised Endocrinology in this new era. In relation to this, the Society have formed a working group that is examining the ‘Future of Endocrinology’. It aims to share best practice and to truly take a step back and question how services may be best configured. We are working to tight time frames to ‘capture the moment’ and see what can be done differently.

One part of this activity is to gather innovative service ideas as a central resource that may then be shared across the UK for the betterment of patient care. It is possible that you have developed something that is either simple or obvious to you, and assume that everyone else must be doing the same, but this is not always the case.

So, what can you do? Simply think of the three clinical service innovations of which you are either the proudest, or that has had the biggest impact for patients with endocrine disease at your centre or region.

JOHN NEWELL-PRICE
KRISTIEN BOELAERT
ANTONIA BROOKE
On behalf of the Society’s Future of Endocrinology working group

Send your thoughts to clinical@endocrinology.org for consideration by the working group.
Our strength is together

2020 has seen enormous challenges for the endocrine community. As a result the collective strength of our members and our Society has never been more important.

Continue with us for 2021 to ensure we remain strong together.

Renew your Society membership today

Use the renewal link in your inbox or renew online at endocrinology.org
Transcriptional enhancers can regulate one or more genes at varying distances and irrespective of their relative position (i.e., they can regulate genes either up- or downstream of them). In practice, the complex nature of transcriptional enhancers has hampered the identification of true diabetes risk effector genes and the translation of T2D GWAS variants into targeted therapies.

To address this problem, we applied promoter capture Hi-C to create a genome-wide map of promoter–enhancer interactions in adult human pancreatic islets. Using this approach, we identified target genes for approximately 80% of all active human islet enhancers (36,664 of 45,683 enhancers). More specifically, this map enabled the systematic identification of genes that are regulated by enhancers carrying T2D risk variants. We observed that T2D variants often interact with more than one gene and that, unlike what has been assumed until now, the nearest genes are not always the true targets of T2D susceptibility variants. Indeed, over 75% of loci with at least one T2D risk variant in an islet enhancer were assigned to novel target genes.

These results have major implications for the interpretation of past and future genetic signals identified in GWAS, as it is often assumed that GWAS variants are flagging the nearest gene. By bypassing the genome’s linear representation which is more commonly used, and putting genetic risk loci in the context of the genome’s 3D conformation, we have gained access to a collection of new putative diabetes risk effector genes.

We decided to validate our in silico predictions using CRISPR-Cas9 perturbations in a human pancreatic β cell in vitro model. To this end, we first inspected the epigenomic landscape of the human pancreatic β cell line EndoC-BH3 by performing an assay for transposase-accessible chromatin using sequencing (ATAC-seq) to profile all accessible chromatin regions in the genome, a proxy for active and regulatory sequences. Our analysis revealed that EndoC-BH3 cells recapitulate the epigenomic landscape of human islets.

**Summary of enhancer perturbations performed in this study to validate T2D enhancer variant-to-target-gene assignments (see also Miguel-Escalada et al. 2019).** CRISPRa, CRISPR activation; CRISPRi, CRISPR inhibition; NT, not tested; SNP, single nucleotide polymorphism.

<table>
<thead>
<tr>
<th>Enhancer SNP</th>
<th>Assigned genes</th>
<th>Genes affected by CRISPR</th>
<th>CRISPR/Cas9 validations</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11257655</td>
<td>CAMK1D, OPTN</td>
<td>CAMK1D, OPTN</td>
<td>✓ ✓ ✔</td>
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<tr>
<td>rs4237590</td>
<td>RFX3, RFX3-AS1, GLI53</td>
<td>GLI53</td>
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<td>rs7903146</td>
<td>TCF7L2</td>
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<td>✓ ✓ ✔</td>
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<tr>
<td>rs7163757</td>
<td>C2CD4A, VPS15C</td>
<td>C2CD4A, VPS15C, C2CD4B</td>
<td>✓ ✓ NT</td>
</tr>
<tr>
<td>rs1401419</td>
<td>CRY2, P21FNA</td>
<td>CRY2</td>
<td>✓ ✓ NT</td>
</tr>
<tr>
<td>rs12189774</td>
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<tr>
<td>rs7732130</td>
<td>S100Z, ZBED3, snoRA47, ZBED3-AS1, PDE8B, WDR41</td>
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<td>✓ ✓ NT</td>
</tr>
<tr>
<td>rs58692659</td>
<td>MDGA, ZFAND3</td>
<td>MDGA1, ZFAND3</td>
<td>✓ ✓ NT</td>
</tr>
</tbody>
</table>

**Figure 1.** Summary of enhancer perturbations performed in this study to validate T2D enhancer variant-to-target-gene assignments. (a) The only T2D risk credible set variant that maps to an islet enhancer is rs11257655, which is associated with expression of CDC123/CAMK1D. (b) The only T2D risk credible set variant that maps to an islet enhancer is rs11257655, which is associated with expression of CDC123/CAMK1D.

**Figure 2.** Islet promoter capture Hi-C (pCHi-C) analysis defines gene targets of enhancers bearing T2D-associated variants near CDC123/CAMK1D. (a) The only T2D risk credible set variant that maps to an islet enhancer is rs11257655, which is associated with expression of CDC123/CAMK1D. (b) The only T2D risk credible set variant that maps to an islet enhancer is rs11257655, which is associated with expression of CDC123/CAMK1D.
assignments, CRISPR-mediated activation of this T2D enhancer resulted (Figure 2b). Further supporting our not of the nearest gene, CDC123 from the risk variant (Figure 2a). Deletion of this T2D enhancer in EndoC-OPN, located >800kb Hi-C also enabled detection of a very long range interaction with a gene of this enhancer variant. Nevertheless, our analysis by promoter capture as the target previously, human islet eQTL studies had prioritised high chromatin accessibility and enrichment for Mediator and H3K27ac). One of the investigated T2D loci was, where a single achieved by co-expressing Cas9 with two single guide RNAs flanking the for CRISPR inhibition). In comparison, deletion of islet enhancers was effector domains (VP64-P65-HSF1 for CRISPR activation and KRAB enhancers with a catalytically inactive Cas9 (dCas9) tethered with specific them (Figure 1). Epigenomic modulation was achieved by targeting T2D epigenomic modulation of the target enhancers and/or by deleting them (Figure 1). Epigenomic modulation was achieved by targeting T2D enhancers with a catalytically inactive Cas9 (dCas9) tethered with specific effector domains (VP64-P65-HSF1 for CRISPR activation and KRAB for CRISPR inhibition). In comparison, deletion of islet enhancers was achieved by co-expressing Cas9 with two single guide RNAs flanking the target enhancers.

One of the investigated T2D loci was CDC123/CAMKID, where a single risk variant resides in an islet enhancer with classic enhancer features (e.g. high chromatin accessibility and enrichment for Mediator and H3K27ac). Previously, human islet eQTL studies had prioritised CAMKID as the target of this enhancer variant. Nevertheless, our analysis by promoter capture Hi-C also enabled detection of a very long range interaction with a gene that has not been previously implicated in diabetes, OPTN, located >800kb from the risk variant (Figure 2a). Deletion of this T2D enhancer in EndoC-βH3 cells led to marked downregulation of both CAMKID and OPTN, but not of the nearest gene, CDC123 (Figure 2b). Further supporting our in silico assignments, CRISPR-mediated activation of this T2D enhancer resulted in overexpression of CAMKID and OPTN, whereas CRISPR-mediated inhibition led to an opposite effect.

At the ZBED3 T2D locus, we observed a remarkable connectivity between the T2D enhancer and multiple genes in the locus (Figure 3a), which was corroborated by the CRISPR perturbation experiments in EndoC-βH3 cells (Figure 3b). Altogether, our experimental validations demonstrated that the detected chromatin enhancer–promoter interactions reflect functional chromatin interactions in human pancreatic islets.

This study has revealed 3D chromatin architecture analysis coupled with genome editing as a powerful framework for interpretation of T2D genetic association signals (Figure 4). Furthermore, the results shed light into unexpected regulatory links that may be affected by T2D susceptibility variants, bringing to our attention new potential players in T2D aetiology. Future functional investigation of these new T2D genes should illuminate their contribution to T2D risk processes.

INÉS CEBOLA
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8. Benazra M et al. 2015 Molecular Metabolism 4 916–925.
ENDOCRINIOLOGY: GETTING BACK TO BETTER

WRITTEN_BY STEVE BALL

What issues do we face in resetting, restoring and rebuilding clinical services in the COVID-19 era?

On 30 January 2020 (a date that now seems an age ago), the UK’s NHS declared a level 4 critical incident in response to the emerging global COVID-19 pandemic. On 17 March, the NHS Chief Executive Sir Simon Stevens and Chief Operating Officer Amanda Pritchard wrote to NHS Trust Chief Executives, instructing them to enact steps to maximise critical care capacity, prepare for the anticipated increase in hospital admissions and increase staff availability to support patient-facing roles. The instructions included a number of operational elements:

- the postponement of non-urgent elective surgery and other clinical activity
- accessing capacity in the independent sector
- support for remote working for staff at increased risk
- support for remote consultations and provision of advice and guidance for outpatient and primary care
- support for clinicians to work beyond their usual boundaries and specialties
- a move to block contract payments ‘on account’ with suspension of volume-based ‘payment by result’ tariffs and the underlying financial architecture and processes.

The pace and scale of the NHS response to the COVID-19 challenge was remarkable: testimony to the structures and processes of the organisation, and to the skills and attributes of those working within it. To many, it showed what could be achieved given the right conditions for change.

We now face a different challenge: how to reset, restore and rebuild clinical services paused over the last 6 months. Do we return to what we had, or is there an opportunity to achieve something better?

THE ‘NEW NORMAL’ IN CLINICAL ENDOCRINOLOGY

In keeping with many other specialist clinical services, endocrinology in the UK has evolved around local and regional requirements through processes that have been partly strategic, partly organic.

Some services are based in specialist centres, others within smaller hospitals that balance a range of generalist and specialist services. Some regions have well-established and functional clinical networks, while in others services remain in silos.

Nationally, we see variation in pathways, performance, matching of demand and training outcomes: variation we have looked to address over time with a range of success.

As in any large, complex system, effecting change within the NHS can be a slow process of small, iterative steps. We are now presented with a bigger, strategic opportunity and we have an ally in change: the NHS leadership.

In a letter to NHS Chief Executives on 29 April 2020, Sir Simon Stevens highlighted the opportunities to ‘lock in’ beneficial changes brought about during the COVID-19 response. A number of themes covering ‘lessons learned’ were emphasised as being key going forward:

- flexibility
- enhanced local system working
- clinical leadership
- remote working
- rapid scaling of new technology-enabled service delivery.

As we restore endocrinology services to the ‘new normal’ within this broader context, we have a window of opportunity to embed change at pace and scale, such that we go back to something better. What should be the vision for that change?

CHANGE IN HEALTH SERVICE DELIVERY: THE BROAD VIEW

A number of national groups have set out broad principles for resetting healthcare delivery as we emerge from the COVID-19 peak. There is significant common ground.

The Royal College of Physicians has set out nine priorities in resetting and relaunching services. A key principle is building in long term improvements, with specific reference to reducing health inequalities and improving access:

- supporting integration: redesign through co-production with primary care, social care and patients
- increasing the workforce
- encouraging protected time for quality improvement, service redesign and research
- supporting education development
- securing a new deal for international workers
- enhancing person-centred care
- enabling access and involvement in research for all
- making social care sustainable
- harnessing the potential of digital health.

The Health Foundation too has emphasised four key principles underpinning service restoration and reform:

- understanding and addressing the full extent of unmet need
- reassuring the public about using services
- looking after and growing the workforce
- improving, not just recovering, services.

ENDOCRINOLOGY

The Specialist Endocrinology CRG and Society for Endocrinology have been working on a range of initiatives.

A Specialist Endocrinology CRG consultation exercise on the future of clinical services reported in May 2020. The exercise identified strategic principles and specific operational elements capturing positive learning from the COVID-19 response that we recommended should be ‘locked into’ the reset and rebuild.

1. Over-arching principles:
   - enhanced support for remote consultations
   - wider engagement with primary and community care
   - co-design of care pathways with primary and community care
   - enhancing visibility of local clinical networks
   - improving access to endocrinology MDTs.

2. Improving delivery of specialist care:
   - clearer recognition of specialist centres.

3. Enhancing efficiency of outpatient services:
   - providing advice and guidance as an alternative to referral for outpatient review
   - assessment and triage of referral as standard practice in managing referrals
   - development of ‘confer before refer’ systems with primary care
   - supporting ‘direct to test’ pathways.
4. **Improving access:**
   - Developing and supporting patient group education via video technology
   - Development and implementation of patient-initiated follow-up.

5. **Training in endocrinology:**
   - Further development of allied health professional and clinical nurse specialist roles
   - Development and support of e-learning platforms.

To further inform and guide adaptation in service delivery, the Society for Endocrinology is supporting a working group exploring the future of endocrinology. This will include representation from patient groups and the Association of British Clinical Diabetologists, who have recently gone though a similar process to review services in diabetes. We look forward to seeing the output in the near future. Alignment, inclusion and a cooperative approach across the system will be important determinants of success.

**OBSTACLES AND CHALLENGES**

While there is genuine excitement about the opportunities, it’s important we recognise the scale of the challenge ahead. Reset and restore will not be straightforward.

After the usual drop in referrals from primary to secondary care over the Christmas–New Year period in 2019/2020, weekly referrals peaked at 385,563 in the week beginning 20 January 2020. There was a subsequent sharp fall. By mid-April 2020, routine referrals had decreased by 90% overall. Urgent and ‘2-week’ pathway referrals fell by 78 and 67% respectively. This shift reflected both decreased presentation of patients to primary care as we ‘locked down’ and reduced onward referral. While referrals have started to increase again, there is limited ability to ‘bounce back’ within the system.

The public remain wary; there is fatigue within a depleted clinical workforce — many of whom were redeployed to other roles; and making hospitals safe for both patients and staff has reduced capacity for traditional ways of working. In the short term, we risk a logjam as new incoming work meets that which was postponed from March–June, at a time when capacity is still limited. We cannot simply stop and reconfigure: the logjam will simply get bigger.

New ways of working with technology are both refreshing and challenging. ‘Remote by default’ will be the standard for outpatient consultations going forward, as we aim to deliver 80% of appointments non-face-to-face. While there are positives to this approach, there are some uncertainties. Subsequent face-to-face consultations may be required for a proportion of patients seen remotely and, although consultations may require less physical infrastructure, access to testing and laboratory data can be limiting. Those services with a functional electronic patient record (EPR) will be more adaptable than others. Institutions wishing to engage in EPR platforms now will find themselves approaching a large financial investment at a time of significant constraint. Maturity and capacity of the NHS digital infrastructure may limit the pace and scale at which we can engage and respond.

As well as clinicians, healthcare commissioners and managers have an important role to play in resetting and restoring services. Financial structures and accounting processes may need modification to reflect changes in mode of consultation and outcomes. Activity constraints (payment by result) versus block contracts need key reconsideration following service restarts. The real challenge may be for commissioners and managers to support clinical teams in doing the right thing: responsive funding packages being co-designed to support clinical innovation.

**IN CONCLUSION**

A pragmatic, balanced approach is needed to what lies ahead. While there are some ‘low hanging fruit’, it is crucial to establish the vision and principles behind the need for change, while building in the processes that will enable further progress over time. We need to ensure those processes are dynamic and agile, as we still face some uncertainty over when and how our clinical services will be asked to respond again. There is much to do. Get involved.

**STEVE BALL**

Society for Endocrinology Representative.
Specialised Endocrinology CRG

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**STAY INFORMED ON MANAGING ENDOCRINE CONDITIONS DURING THE COVID-19 PANDEMIC**

Read and contribute to our resource collection for your information and to share with your colleagues. Visit [www.endocrinology.org/covid19](http://www.endocrinology.org/covid19).

If you have documents to share, please send them to [clinical@endocrinology.org](mailto:clinical@endocrinology.org).
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Efforts to manage rare conditions must be focused on partnership, education and working to improve patient outcomes

Many patients have non-specific symptoms and delays in diagnosis could worsen prognosis

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Awareness of rare diseases is low

Rare diseases are often difficult to recognise and diagnose

Late diagnosis leads to more advanced diseases that are difficult to treat

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Join us in congratulating our 2020 Awardees, who will receive a wide range of benefits, providing opportunities for them to develop their careers and professional profiles.

Watch out for updates on their progress over the next 3 years.

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**CLINICAL ACADEMICS**

**ALEXANDER COMMINOS**
Imperial College London
Alex’s research focuses on reproductive endocrinology, and is funded by fellowships, lectureships and grants from the Wellcome Trust, NIHRC and MRC. He has received a number of prestigious prizes, including the Reproductive Science Prize (Endocrine Society), and the Society for Endocrinology’s Early Career and Clinical Endocrinology Trust Prizes. Alex currently sits on the Society’s Science Committee.

**JULIA PRAGUE**
Royal Devon and Exeter NHS Foundation Trust and University of Exeter
Julia qualified in 2008 from King’s College London School of Medicine and Dentistry at Guy’s, King’s College and St Thomas’ Hospitals, with a double distinction and first class honours. During her PhD at Imperial College, she completed the first study in humans of a neurokinin 3 receptor antagonist for menopausal flushes, published in *The Lancet*. She was awarded the North American Menopause Society New Investigator Award in 2017 and the Society’s Early Career Prize in 2018.

**PETER TAYLOR**
Cardiff University and the University Hospital of Wales
Peter completed his PhD in thyroid epidemiology, and his research focuses on the effects of common variation in thyroid status, thyroid hormone prescribing and thyroid screening in pregnancy. He has had considerable involvement in trials relating to the thyroid in pregnancy and thyroid eye disease. As well as receiving awards at both national and international conferences for his work, Peter has over 50 publications related to the thyroid field.

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**CLINICIANS IN PRACTICE**

**SAFWAAN ADAM**
The Christie Hospital, Manchester
Following graduation from the University of Cape Town, Safwaan undertook early postgraduate training in South Africa and New Zealand, before his specialist endocrinology training in the North West of England. He took time out of clinical training to pursue a PhD examining the metabolic and cardiovascular complications of obesity at the University of Manchester. Safwaan’s research has led to a number of presentations, publications and prizes. He has a particular interest in the use of ‘real world’ data analytics to inform clinical practice.

**JUSTYNA WITCZAK**
University Hospital of Wales, Cardiff
Justyna completed her MD at Cardiff University on the characterisation of circulating extracellular vesicles in human obesity. Her research was supported by the Lewis Thomas Gibbon Jenkins of Briton Ferry Fellowship from the Royal College of Physicians. Other research interests include thyroid disorders and type 2 diabetes. Justyna is a Committee Member of the Young Diabetologist and Endocrinologist Forum Wales.

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**SCIENTISTS**

**CLAIRE FLETCHER**
Imperial College London
Awarded a PhD in the molecular biology of prostate cancer in 2013, Claire was granted a Young Investigator Award from the Prostate Cancer Foundation (USA) in 2016 and an Imperial College/AstraZeneca Research Fellowship in 2018. She is currently establishing an independent research team within the Department of Surgery and Cancer at Imperial, to investigate functions of non-coding RNAs in hormone-dependent cancers and drug resistance, the role of obesity and peri-prostatic adipocytes in modulating therapy responses.

**TIJANA MITIC**
University of Edinburgh
Tijana obtained her PhD from the University of Edinburgh in 2010, where she completed a short postdoctoral placement. She then moved to a further successful postdoc at the Bristol Heart Institute (2011–2014) before taking a break from academia. In 2016, she was awarded a highly competitive part-time fellowship from the British Heart Foundation to restart her academic research. In 2019, she received a Fellowship of the Higher Education Academy. She now leads a research team investigating the epigenetic changes in hypoxia and during vascular injury.

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SOCIETY NEWS

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You and your Hormones

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Being a Content Editor tuned my creative writing and editing skills. Shanty Shah

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I first met Bernard in the early 1990s when he was Secretary-General of the Association of Learned and Professional Society Publishers (ALPSP). I was CEO of the Society for Endocrinology and starting to get involved with ALPSP committee work. At the time I had no idea that Bernard had earlier been a prominent neuroendocrinologist.

Bernard was born in Peckham in 1927 to a close family with no academic background. Bernard discovered fairly early that he preferred the kinds of play that created or achieved something. On leaving school at 16, Bernard began work as a lab assistant at the Wellcome Lab on Euston Road and spent three hours studying at Chelsea Polytechnic every weekday, after a full day’s work. After his matriculation, and being made a Fellow of the Chemical Society, he was called up and served his National Service in the Royal Navy, where he specialised in the maintenance of radar kit.

Bernard was then given a grant to study physiology at University College London. After graduating in 1952, he was awarded an MRC grant to study for his PhD in Geoffrey Harris’ new Department of Neuroendocrinology at the University of London Institute of Psychiatry. Geoffrey Harris’ theory was that ‘the hypothalamus produced some chemical factor, or factors, that controlled the release of the hormones from the pituitary gland’. It was Bernard’s experimental work on this with Professor Harris that led to the long-running and vituperative argument between Harris and Solly Zuckerman, on which Harris and Bernard were eventually proved right. I believe Bernard’s first published paper, on this subject, was in Nature.

After gaining his PhD in only two years, Bernard continued his research career and wrote many journal papers and book chapters during this period. I’m aware that many an endocrinologist recalls with affection using Bernard’s experimental work on this with Professor Harris that led to the long-running and vituperative argument between Harris and Solly Zuckerman, on which Harris and Bernard were eventually proved right. I believe Bernard’s first published paper, on this subject, was in Nature.

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As regards his personal life, Bernard had three marriages. His first marriage was to Heather, which produced his first two children, Susan and Iain, faltered partly in an attempt to discover what had caused him to be so antagonistic towards Geoffrey Harris and to hold to a view that was increasingly shown to be erroneous. I don’t think he ever really satisfied himself on that question, but I was pleased to be able to publish the book through the Society for Endocrinology in 2005, especially as both Bernard and Solly had been leading lights in the Society.

After his retirement, Bernard wrote a biography of Lord Zuckerman, partly in an attempt to discover what had caused him to be so antagonistic towards Geoffrey Harris and to hold to a view that was increasingly shown to be erroneous. I don’t think he ever really satisfied himself on that question, but I was pleased to be able to publish the book through the Society for Endocrinology in 2005, especially as both Bernard and Solly had been leading lights in the Society.

During his time at ALPSP, Bernard worked closely with Eileen Storrie. After her husband’s death, Bernard and Eileen kept in touch and married in 2005. I remember being astonished by the news, and then being immediately convinced it was a fantastic match – Bernard described it in his memoir as being ‘content … even blissful’. A happy ending, indeed, and well-deserved. Bernard died peacefully in his sleep at the end of July.

SUE THORN
Former Chief Executive of the Society for Endocrinology

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