2026 Boehringer ClinicalPath Forum

Plenary Session

Time: 09:40–10:10

Title: Real World Evidence & Contemporary Drug Development

Speaker: Dr. K. Arnold Chan, TriNetX

Abstract: Real-world evidence (RWE) is rapidly transforming the landscape of contemporary drug development and regulatory decision-making. Traditionally utilized for post-marketing surveillance and pharmacovigilance, RWE is now increasingly integrated into earlier stages of drug development, including clinical trial design, external control arm construction, and evidence generation for regulatory submissions. This presentation will review the evolving global trends in RWE adoption and discuss how regulatory agencies are incorporating real-world data into modern drug development frameworks. Special attention will be given to hybrid trial designs that combine conventional randomized clinical trials with synthetic or external control cohorts to improve efficiency while maintaining scientific rigor.

The session will also highlight recent advances in healthcare data platforms and artificial intelligence that enable large-scale, high-quality evidence generation. Through examples from international practice, Professor Chen will demonstrate how federated data networks preserve data privacy while supporting multinational research collaborations. The role of AI in transforming unstructured clinical records into regulatory-grade evidence will also be discussed, including applications in health technology assessment and reimbursement review. Attendees will gain practical insights into how RWE is reshaping clinical research, accelerating innovation, and supporting evidence-based decision making across healthcare systems.

Special Session

Time: 16:00–16:30

Title: Unlocking New Opportunities for Healthcare Sovereign AI Through Data Integration

Speaker: Peter Wu Ph.D. CEO, Taiwan AI Cloud / Taiwan Health and Bio DataBank Technology INC

Abstract: AI 在醫療領域的價值，不僅在於演算法突破，更在於建立完整的智慧醫療生態系。透過可信任且可治理的醫療資料、臨床流程整合平台，以及充足的算力與數位基礎建設，AI 可協助醫療體系提升效率與決策品質，例如病歷摘要、護理交班、健保申報及個案管理等應用。醫療 AI 亦是主權 AI 的重要落地場景，未來需確保資料安全、權限管理、流程可追蹤及結果可驗證，建立可信任的 AI 治理架構。台灣結合健保資料、生醫研發、ICT 及雲端科技優勢，有機會發展可輸出的醫療 AI 平台，推動醫療由反應式照護邁向預測式健康管理。

Track A｜Cardiovascular-Renal-Hepatic-Metabolic（CRHM）

Time: 10:30–11:00

Title: Beyond Guidelines: Residual CRM Risk in the GDMT Era

Speaker: Dr. David Cherney, Canada

Abstract:

一、GDMT 時代下仍未被滿足的殘餘心腎代謝（CRM）風險

儘管以 RAAS 阻斷劑、SGLT2 抑制劑與 MRA 為基礎的指引導向藥物治療（guideline-directed medical therapy, GDMT）已顯著改善心腎代謝（cardiovascular-renal-metabolic, CRM）疾病患者的預後，臨床上仍有相當比例的患者持續進展至器官損傷、心衰惡化與末期腎病。此一「殘餘風險」的核心成因之一，即在於過度且不當的醛固酮（aldosterone）作用未被充分阻斷。醛固酮除了在腎臟調控鈉鉀恆定外，其受體亦廣泛表現於心肌、血管內皮與平滑肌、巨噬細胞等組織，過量的醛固酮會促進發炎、氧化壓力、血管僵硬與心腎纖維化，成為 GDMT 之外持續驅動疾病進展的重要殘餘因子。

二、MRA 的侷限：醛固酮突破/逃逸、MR 非依賴性與非基因體途徑

MRA（mineralocorticoid receptor antagonist）雖能於受體端阻斷醛固酮作用，但單純阻斷受體無法完整涵蓋醛固酮的所有致病途徑。首先，長期使用 RAAS 阻斷劑（ACEi/ARB）或 MRA 的患者，常出現「醛固酮突破/逃逸（aldosterone breakthrough/escape）」現象，即循環醛固酮濃度反彈上升；此現象已被證實與更差的器官預後及疾病進展風險相關。其次，醛固酮除經典基因體途徑（genomic）作用外，尚具有 MR 非依賴性（MR-independent）與非基因體（non-genomic）的快速作用途徑，這些途徑往往無法被 MRA 有效攔截。此外，鹽分、皮質醇及發炎介質等亦可造成醛固酮非依賴性的 MR 活化。凡此種種，都使得單靠受體阻斷難以完整消弭醛固酮所驅動的殘餘 CRM 風險。

三、醛固酮合成酶抑制（ASi, vicadrostat）：從源頭阻斷的新契機

醛固酮合成酶抑制劑（aldosterone synthase inhibitor, ASi）如 vicadrostat（BI 690517），透過抑制 CYP11B2 直接減少醛固酮的生成，從「源頭」降低醛固酮負荷，理論上可同時涵蓋基因體與非基因體、MR 依賴與非依賴的多重致病途徑，並可望降低醛固酮突破/逃逸所帶來的殘餘風險，提供較 MRA 更全面的器官保護潛力。此外，臨床上有一群症狀相對不明顯、程度較輕微的原發性高醛固酮症（primary aldosteronism）患者常被低估或漏診，ASi 從合成端抑制的機轉，或許能一併涵蓋此類長期承受過量醛固酮的高風險族群。vicadrostat 在第二期臨床試驗中對 CYP11B2 展現高度選擇性（250x 相對於皮質醇合成之 CYP11B1），可有效降低血漿醛固酮並顯著減少蛋白尿（UACR），且無論是否併用 empagliflozin 皆可觀察到相似的療效，目前同時有四個第三期試驗 (EASi Trial Series) 中進一步驗證其心腎保護成效。

講者將與各位深入探討 GDMT 時代下仍持續存在的殘餘 CRM 風險、傳統 MRA 在醛固酮突破/逃逸及非基因體途徑上的侷限，以及醛固酮合成酶抑制（ASi）如何從源頭更全面地阻斷醛固酮的多重致病作用，為這些棘手的高風險患者開啟更完整器官保護的治療新契機。

Time: 11:00–11:30
Title: Beyond Glycemic Control: The Rise of Cardio-Renal-Metabolic Care in NICE 2026
Speaker: Dr. Mimi Z. Chen, UK
Abstract: This meeting will focus on the **early use of SGLT2 inhibitors in combination with metformin** as a key treatment strategy for type 2 diabetes in the UK. The speaker will provide perspectives from both a NICE committee member and a practicing clinician, discussing the rationale behind current NICE recommendations. Beyond glucose lowering, SGLT2 inhibitors have demonstrated significant cardiovascular and renal protection, supporting their use early in the disease course to reduce future cardiorenal complications.

And this session will also explore the health economic implications of early intervention, including the potential to reduce heart failure hospitalizations, slow chronic kidney disease progression, and decrease long-term healthcare costs for the NHS. In addition, real-world clinical experience from the UK will be shared, highlighting the effectiveness and safety of SGLT2 inhibitors in routine practice. Finally, the discussion will address remaining barriers to implementation despite established reimbursement, including delayed disease identification, clinical inertia, variability in healthcare professional awareness, and patient concerns regarding treatment, while considering potential strategies to overcome these challenges.

Time: 11:30–12:00
Title: From Inflammation to Fibrosis: CKD/HF/CVD Continuum
Speaker: Dr. Javed Butler, US
Abstract: Despite advances in guideline-directed medical therapy (GDMT), patients with chronic kidney disease (CKD), heart failure (HF), and cardiovascular disease (CVD) continue to experience substantial residual cardiorenal risk. Increasing evidence identifies aldosterone as a key driver of inflammation, oxidative stress, endothelial dysfunction, and fibrosis across the heart, kidneys, and vasculature, contributing to progression along the CKD–HF–CVD continuum. This presentation reviews the biological mechanisms underlying aldosterone-mediated organ injury, highlights the challenges of aldosterone breakthrough and non-genomic signaling pathways that may

persist despite current therapies, and discusses emerging therapeutic strategies, including upstream aldosterone synthase inhibition, as a potential approach to further mitigate inflammation, fibrosis, and residual cardiorenal risk.

Time: 13:00–13:30
Title: Interconnection between Type 2 Diabetes Mellitus and Ischemic Stroke: Pathophysiology, Risks, and Management
Speaker: Dr. Georgios Tsivgoulis, Greece
Abstract: Type 2 diabetes mellitus (T2DM) and ischemic stroke are closely linked diseases that pose a major global health burden. Individuals with diabetes have a substantially increased risk of stroke, while stroke survivors with diabetes often experience more complex clinical management and poorer long-term outcomes. Understanding the interplay between these two conditions is essential for improving prevention, acute care, and secondary risk reduction.
This presentation will provide an overview of the mechanistic and clinical connections between T2DM and ischemic stroke, including shared vascular risk factors, metabolic disturbances, and the impact of diabetes on cerebrovascular health. The session will also review the epidemiology and clinical consequences of this relationship, highlighting key considerations across the continuum of care, from primary prevention to acute stroke treatment and long-term management.
In addition, emerging developments in cardiovascular and cerebrovascular risk reduction strategies, multidisciplinary care, and evidence-based approaches to optimizing outcomes in patients with diabetes and stroke will be discussed. Through a comprehensive review of current knowledge and clinical perspectives, this lecture aims to enhance understanding of the diabetes-stroke continuum and its implications for everyday clinical practice.

Time: 13:30–14:00
Title: Advancing Obesity Management: Liver and Cardio-Kidney-Metabolism Holistic Care
Speaker: Dr. Jaime Almandoz, US
Abstract: Obesity is a chronic, progressive disease that drives a wide spectrum of

obesity-related complications (ORCDs), including metabolic dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes, cardiovascular disease, and chronic kidney disease. Modern obesity management is therefore shifting from a weight-centric approach toward preserving organ health through comprehensive, long-term care.
This presentation will review a practical framework for assessing obesity and its related complications, followed by recent advances in anti-obesity pharmacotherapy, including the latest phase 3 clinical evidence. Practical considerations for translating evidence into clinical practice—including individualized treatment goals, continuity of care, treatment persistence, and adverse event management—will also be discussed.
By integrating evidence-based therapies with a holistic approach to liver and cardio-kidney-metabolic health, clinicians can better address the diverse consequences of obesity and optimize long-term outcomes for people living with this chronic disease.

Time: 14:00–14:30
Title: Transforming Obesity and MASLD: Recent Advances of Multi-Receptor Therapies
Speaker: Dr. Vincent Wong, Hong Kong
Abstract: The treatment landscape of metabolic dysfunction-associated steatotic liver disease (MASLD) is evolving rapidly with the emergence of disease-modifying therapies. As obesity and MASLD are increasingly recognized as closely interconnected diseases, treatment is extending beyond weight reduction alone to improving liver health and long-term metabolic outcomes.

Recent clinical evidence has demonstrated the potential of incretin-based therapies to improve hepatic steatosis, steatohepatitis, fibrosis-related outcomes, and cardiometabolic health. Building on these advances, multi-receptor therapies, particularly GLP-1/glucagon receptor agonists, represent a promising strategy to address obesity and liver disease through complementary metabolic effects. In parallel, liver-directed therapies, including FGF21 analogues, are broadening treatment options for patients across different stages of MASLD.

Drawing on the latest clinical evidence, this presentation will examine how these emerging therapies are reshaping the management of MASLD and discuss their evolving

roles within an integrated treatment strategy aimed at improving both metabolic and liver health.

Time: 14:50–15:20
Title: Precision Nephrology: TRPC6 & Podocyte Biology
Speaker: Dr. Matthias Kretzler, US
Abstract:

一、FSGS 的疾病成因與足細胞的核心角色

局灶性節段性腎絲球硬化症（focal segmental glomerulosclerosis, FSGS）本質上是一種足細胞病變（podocytopathy）。足細胞為腎絲球濾過屏障的關鍵結構，屬於高度分化、再生能力極為有限的細胞；一旦受損或流失，往往造成不可逆的濾過屏障破壞，臨床上表現為蛋白尿，並逐步進展為節段性硬化。FSGS 的成因高度異質，可概分為原發性（與免疫機轉及循環中通透性因子相關）、遺傳性（涉及足細胞細胞骨架與鈣離子訊號調控的基因變異，如 TRPC6）以及次發性（適應性血流動力學變化）等不同型態。正因致病機轉多元且交錯，FSGS 在診斷分型與治療決策上皆具相當挑戰性。

二、當前的醫療未滿足需求與治療困境

現行 FSGS 的治療多仰賴非專一性的免疫抑制策略，如類固醇與鈣調磷酸酶抑制劑（calcineurin inhibitors），並輔以 RAAS 阻斷劑控制蛋白尿。然而，臨床反應差異極大，相當比例的患者屬於類固醇抗性（steroid-resistant），且長期使用免疫抑制劑伴隨顯著的副作用與安全性負擔。目前尚缺乏針對 FSGS 致病機轉的專一性核准治療，許多患者最終仍進展至末期腎病（ESRD），需接受透析或腎臟移植，且移植後復發風險偏高。加以疾病早期症狀不明顯、診斷常有延遲，使得針對足細胞損傷源頭、能延緩病程的標靶治療成為迫切的未滿足需求。

三、TRPC6 抑制為何可能為 FSGS 患者帶來效益

TRPC6（transient receptor potential canonical 6）是表現於足細胞的鈣離子通道；

其功能增益型（gain-of-function）變異或過度活化，會導致鈣離子過量內流、細胞骨架結構受損，進而引發足細胞損傷，此機轉已在相關研究被證實與 FSGS 的發生有密切相關。以 Apecotrep 為代表的 TRPC6 抑制劑，透過恢復足細胞內鈣離子恆定、保護足細胞完整性，期能減少蛋白尿並延緩腎功能惡化，提供一個有別於傳統免疫抑制、直接針對致病機轉的標靶治療新選擇。

講者將與各位深入探討 FSGS 的疾病成因與足細胞損傷機轉、當前臨床照護中常被低估的困境與未滿足需求，以及 TRPC6 抑制作為新興治療策略，如何可能為 FSGS 患者開啟嶄新的治療契機。

Time: 15:20–15:50
Title: Albuminuria as a Systemic Cardiovascular Risk Marker: From Asian Cohorts to Clinical Action
Speaker: Dr. Juliana C.N. Chan, Hong Kong
Abstract: 白蛋白尿不僅反映腎絲球損傷，更是全身性內皮功能異常與心血管風險的重要指標。即使腎絲球過濾率正常，白蛋白尿仍與心血管事件及死亡風險增加相關。本演講將探討白蛋白尿的病理機轉、亞洲實證及臨床判讀，並說明如何透過持續性確認白蛋白尿及適當使用腎素血管張力素系統抑制劑、SGLT2 抑制劑及其他心腎保護治療，將風險辨識轉化為具體臨床行動，降低心血管與腎臟不良風險。

Track B | Oncology + Respiratory & Inflammation

Time: 10:30–11:00
Title: Bridging Autoimmunity and Lung Fibrosis: Deciphering the Pipeline of Novel Immunomodulatory Molecules
Speaker: Dr. Justin Oldham, US
Abstract: Interstitial lung diseases (ILDs) comprise a heterogeneous group of disorders characterized by varying degrees of inflammation, immune dysregulation, and

progressive fibrosis. Recent advances in molecular phenotyping, biomarker discovery, and translational research are transforming our understanding of disease mechanisms and creating new opportunities for precision medicine. This presentation will explore emerging breakthroughs in ILD, with particular emphasis on autoimmune-associated ILD and the identification of novel therapeutic pathways.

Dr. Oldham will review key biological mechanisms implicated in fibrotic progression, including epithelial dysfunction, immune-fibrotic crosstalk, fibroblast activation, and vascular remodeling. The session will highlight the development of next-generation therapies targeting pathways beyond conventional anti-fibrotic treatments, including but not limited to PDE4B inhibition with nerandomilast, IL-11 blockade, and soluble guanylate cyclase activation etc. These innovative approaches aim to simultaneously address inflammation, fibrosis, epithelial injury, and vascular abnormalities that contribute to disease progression. The integration of molecular biomarkers and precision medicine strategies will also be discussed as tools to improve patient stratification and optimize therapeutic outcomes. This overview will provide clinicians with an updated perspective on the rapidly evolving ILD treatment landscape and future directions in translational research.

Time: 11:00–11:30
Title: Pulmonary Fibrosis Basic Research and Mechanistic Insights into Nerandomilast
Speaker: Dr. HongGang Zhou, China
Abstract: Pulmonary fibrosis is driven by complex interactions among epithelial cells, endothelial cells, immune cells, and fibroblasts, ultimately leading to irreversible tissue remodeling and loss of lung function. Recent advances in basic science have revealed that dysregulation of the immune-fibrotic microenvironment serves as a central driver of disease progression. This presentation will review current insights into the cellular and molecular mechanisms underlying pulmonary fibrosis and discuss how these discoveries are guiding the development of targeted therapies.

A major focus will be the mechanism of action of nerandomilast, a preferential phosphodiesterase-4B (PDE4B) inhibitor. By preserving intracellular cyclic AMP signaling, nerandomilast exerts anti-inflammatory, immunomodulatory, and anti-fibrotic effects across multiple cell types, including macrophages, fibroblasts, epithelial

cells, and endothelial cells. Preclinical data suggest that the drug can inhibit fibroblast activation, reduce profibrotic macrophage signaling, stabilize endothelial barriers, and support epithelial repair. Evidence from diverse animal models of pulmonary fibrosis and autoimmune-related ILD will also be reviewed. The presentation aims to provide a mechanistic understanding of how targeting the PDE4B/cAMP pathway may represent a novel strategy for modifying disease progression across a broad spectrum of fibrotic lung diseases.

Time: 11:30–12:00
Title: Bronchiectasis: Past, Present, and Future – From Historical Challenge to Unmet Needs
Speaker: Dr. Sanjay Chotirmall, Singapore
Abstract: Bronchiectasis is a chronic and progressive respiratory disease characterized by persistent airway inflammation, recurrent infections, impaired mucociliary clearance, and progressive structural airway damage. Despite its substantial clinical burden, particularly in Asian populations, treatment options remain limited and many patients continue to experience frequent exacerbations, declining lung function, and reduced quality of life. Recent advances in disease biology have identified neutrophil-driven inflammation as a central mechanism contributing to ongoing airway injury and disease progression.

This presentation will review the historical evolution of bronchiectasis management and discuss current unmet clinical needs. Particular attention will be given to the emerging role of dipeptidyl peptidase-1 (DPP1) inhibition as a novel therapeutic strategy. DPP1 regulates activation of neutrophil serine proteases, which are implicated in airway inflammation and tissue destruction. Clinical data from the AIRLEAF and related development programs will be reviewed, highlighting the efficacy and safety profile of DPP1 inhibitors such as verducatib in reducing exacerbation risk and targeting disease-driving biology. The session will also provide an overview of the future bronchiectasis treatment pipeline and discuss how precision medicine approaches may help identify patients most likely to benefit from targeted therapies. Together, these advances signal a promising new era in bronchiectasis management.

Time: 13:00–13:30

Title: Navigating the Landscape of HER2 Altered NSCLC: Disease Biology and Current Unmet Needs

Speaker: Dr. Jii Bum Lee, Korea

Abstract: HER2-altered non-small cell lung cancer (NSCLC) represents a distinct molecular subset associated with unique biological characteristics, significant disease burden, and limited treatment options. HER2 mutations, most commonly exon 20 insertions, occur in approximately 2–4% of NSCLC cases and are frequently observed in younger patients, females, and never-smokers. Despite advances in molecularly targeted therapy, outcomes with first-line platinum-based chemotherapy and immunotherapy remain suboptimal, highlighting a substantial unmet medical need. Although antibody–drug conjugates such as trastuzumab deruxtecan have improved outcomes in previously treated patients, challenges remain regarding durability of response, treatment sequencing, and toxicity management.

Zongertinib is a next-generation, HER2-selective tyrosine kinase inhibitor designed to address these challenges. Preclinical studies have demonstrated potent activity across HER2-mutant models while sparing wild-type EGFR, potentially improving therapeutic selectivity and tolerability. Structural and mechanistic analyses suggest enhanced targeting of HER2 alterations compared with earlier HER-family inhibitors. In HER2-altered cell lines, zongertinib has shown promising antitumor activity, supporting its continued clinical development. Early clinical findings from phase 1a studies further indicate encouraging efficacy and safety in patients with HER2-mutant NSCLC. This presentation will review the epidemiology and biology of HER2-altered NSCLC, current standards of care and unmet needs, and the scientific rationale supporting zongertinib as a potential new treatment option.

Time: 13:30–14:00

Title: Beaming Hope in HER2-mutant NSCLC: Evolution of HER2 Tyrosine Kinase Inhibitor

Speaker: Dr. Ross Soo, Singapore

Abstract: The development of HER2-targeted therapies has transformed the treatment landscape for HER2-mutant non-small cell lung cancer (NSCLC), a molecular subset historically associated with limited treatment options and poor clinical outcomes. Beamion Lung-1 is a pivotal study evaluating zongertinib, a highly selective HER2 tyrosine kinase inhibitor designed to maximize anti-tumor activity while minimizing wild-type EGFR inhibition. This presentation will provide a comprehensive review of the key findings from Beamion Lung-1 and their implications for clinical practice.

Particular focus will be placed on efficacy outcomes, including objective response rate (ORR), progression-free survival (PFS), and duration of response (DoR) across patients with HER2-mutant NSCLC. In addition, intracranial activity will be explored, highlighting the potential role of zongertinib in addressing the major unmet need of central nervous system (CNS) progression and brain metastases in this patient population. Safety data from Beamion Lung-1 will also be reviewed, with emphasis on the favorable tolerability profile and the low incidence of EGFR-mediated toxicities observed with selective HER2 inhibition. Finally, the presentation will discuss the ongoing clinical development program and how emerging evidence may shape the future treatment algorithm for patients with HER2-mutant NSCLC.

Time: 14:00–14:30

Title: HER2 Expression Heterogeneity and HER2 Alterations in NSCLC: Implications for HER2-targeted Therapy

Speaker: Dr. Yeh-Han Wang, Taiwan

Abstract: Accurate molecular diagnosis and effective implementation of biomarker testing are critical to optimizing outcomes for patients with HER2-altered cancers. As HER2-targeted therapies continue to evolve, there is an increasing need to establish efficient diagnostic pathways and testing ecosystems that enable timely identification of eligible patients. This presentation will review current diagnostic methodologies for HER2 alterations, including next-generation sequencing (NGS), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH), highlighting their complementary

roles, advantages, and limitations in routine clinical practice. The challenges associated with tissue-based testing and the emerging role of liquid biopsy (circulating tumor DNA, ctDNA) in detecting HER2 alterations will also be discussed.

Special emphasis will be placed on the testing landscape in Taiwan, including available testing platforms, workflows across major medical centers, turnaround time considerations, quality assurance practices, and integration within local reimbursement frameworks. Practical recommendations for implementing HER2 testing in real-world clinical settings will be shared.

Beyond lung cancer, the presentation will explore the broader potential of HER2-directed therapies across solid tumors. The biological rationale for targeting HER2 amplification and overexpression across tumor types will be reviewed, together with emerging clinical evidence from basket studies evaluating zongertinib in non-lung malignancies, including breast, gastric, and colorectal cancers, supporting the continued expansion of precision oncology approaches.

Time: 14:50–15:20
Title: Going beyond Individualization of Sequencing of Treatment for ES-SCLC: DLL3 Combination
Speaker: Dr. Tatsuya Yoshida, Japan
Abstract:

Extensive-Stage Small Cell Lung Cancer (ES-SCLC) remains among the most aggressive and formidable malignancies in oncology. While the landmark CASPIAN and IMpower133 trials established chemoimmunotherapy as the frontline standard of care, the biology of SCLC drives rapid resistance and swift progression, leading to relapse within months for most patients. Overcoming this therapeutic plateau and breaking through the frontline "survival ceiling" is a critical unmet need. At the ClinicalPath Forum, we will discuss how pioneering DLL3-targeted T-cell engager combinations aim to address this clinical bottleneck.

Time: 15:20–15:50

Title: From Registry to Therapy: Decades of epNEC Experience and the Potential of DLL3 in Treatment

Speaker: Dr. Ming-Huang Chen, Taiwan

Abstract:

Extrapulmonary neuroendocrine carcinoma (epNEC) is characterized by high aggressiveness and profound clinical heterogeneity. Even with standard frontline chemotherapy, therapeutic efficacy remains limited, and subsequent-line treatment options are highly fragmented with no established standard, highlighting a stark unmet medical need. The accumulation of Taiwanese real-world evidence has become instrumental in elucidating the disease profile and current treatment landscape of epNEC. Furthermore, emerging therapeutics such as DLL3-targeted T-cell engagers offer a promising new direction. At the ClinicalPath Forum, we will pivot from registry data and integrate clinical experience to deeply explore the therapeutic challenges and future development of epNEC management.