THEMATIC REVIEW

Pacak–Zhuang syndrome: a model providing new insights into tumor syndromes

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Abstract

This article is a summary of the plenary lecture presented by Jared Rosenblum that was awarded the Manger Prize at the Sixth International Symposium on Pheochromocytoma/Paraganglioma held on 19–22 October 2022 in Prague, Czech Republic. Herein, we review our initial identification of a new syndrome of multiple paragangliomas, somatostatinomas, and polycythemia caused by early postzygotic mosaic mutations in EPAS1, encoding hypoxia-inducible factor 2 alpha (HIF-2α), and our continued exploration of new disease phenotypes in this syndrome, including vascular malformations and neural tube defects. Continued recruitment and close monitoring of patients with this syndrome as well as the generation and study of a corresponding disease mouse model as afforded by the pheochromocytoma/paraganglioma translational program at the National Institutes of Health has provided new insights into the natural history of these developmental anomalies and the pathophysiologic role of HIF-2α. Further, these studies have highlighted the importance of the timing of genetic defects in the development of related disease phenotypes. The recent discovery and continued study of this syndrome has not only rapidly evolved our understanding of pheochromocytoma and paraganglioma but also deepened our understanding of other developmental tumor syndromes, heritable syndromes, and sporadic diseases.

Introduction

In this invited article, we summarize our plenary lecture, entitled ‘Pacak-Zhuang Syndrome: A Model Providing New Insights into Tumor Syndromes,’ presented by Jared Rosenblum MD, who was awarded the Manger Prize (Young Investigator Award), at the Sixth International Symposium on Pheochromocytoma/Paraganglioma (ISP) held in Prague, Czech Republic on 19–22 October 2022 which gathered the leading experts in every aspect of pheochromocytoma and paraganglioma (PPGL), including genetics, diagnosis, pathophysiology, and treatment. Since its inception, the ISP has had a central mission to improve the lives of patients with PPGL by bringing basic and clinical researchers together to foster discoveries that would improve our understanding, diagnosis, and treatment options for these patients. Through significant organizational efforts, the ISP has enacted changes that have led to an accelerated pace of discovery and a deeper understanding of the pathophysiology of these
catecholamine-producing tumors that have a high rate of metastatic disease and mortality related to the sequelae of catecholamine excess such as heart attack and stroke.

A key initiative born out of collaboration between several key attendees of the First ISP launched the first ‘Pheochromocytoma and Paraganglioma: an Endocrine Society Clinical Practice Guideline,’ which contributed to the recent division of these tumors into three main molecular clusters by Fishbein et al. – pseudohypoxia, Wnt-related, and kinase signaling (Lenders et al. 2014, Fishbein et al. 2017). Subsequent collaborative efforts also born out of subsequent ISP meetings led by Tothill et al. resulted in a further recent clinically relevant stratification of these rare tumors based on the tumor microenvironment (Zethoven et al. 2022), which was also presented at the Sixth ISP meeting in 2022. These and other critical discoveries related to the role of hypoxia-inducible factors (HIFs) in oxygen sensing and polycythemia, particularly hypoxia-inducible factor 2 alpha (HIF-2α), which is encoded by EPAS1 (Safran et al. 2006, Lee & Percy 2011, Semenza 2011), spurred the discovery of a new syndrome of PPGL, somatostatinomas, and polycythemia – Pacak–Zhuang syndrome – caused by a mosaic gain-of-function mutation in EPAS1 (Zhuang et al. 2012), which is central to pseudohypoxia signaling pathways.

The discovery of this syndrome has uniquely highlighted the key fundamental differences between hypoxia-inducible factor 1 alpha (HIF-1α) and HIF-2α and how molecular pathogenesis leads to differing clinical disease phenotypes. For example, as we will describe below, we have discovered that this syndrome, in addition to PPGL, has unexpected malformations of the central and peripheral nervous system and vasculature, which we believe reflects the abundant yet restricted tissue expression of HIF-2α throughout development, such as across the developing sympathetic nervous system (Tian et al. 1998, Favier et al. 1999). This is opposed to the distribution of HIF1α, which is ubiquitously expressed at low levels. Further, we have found that studying this syndrome has led to a deeper understanding of the clinical presentation and behavior of this syndrome compared to other PPGL syndromes. For example, patients with this syndrome present at a young age almost exclusively with noradrenergic (NA) biochemical phenotype and abdominal or retroperitoneal PPGL (Table 1), which we believe reflects the critical role of HIF-2α in the development of the sympathoadrenal tissues.

While we have begun to uncover some answers, there is certainly more to be discovered. For example, we believe that the altered catecholamine production in these patients may reflect an altered physiologic baseline and hypoxia feedback system that will require further investigation, perhaps involving the development of the carotid bodies, which is known to be dependent on HIF-2α (Percy et al. 2008, Fielding et al. 2018, Macias et al. 2018). As such, it was our distinct honor in this plenary lecture to review our initial discovery of this syndrome and highlight how continued study of this syndrome has led us to uncover previously unrecognized disease phenotypes that reflect the impact of the timing of these acquired genetic defects.

### Initial discovery

As the first report shows (Zhuang et al. 2012), our initial discovery of Pacak–Zhuang syndrome was the product of a keen clinical acumen, a high index of suspicion, and a strong translational collaborative effort between basic and clinical sciences. Based on the robust network established by the ISP, two unrelated young patients were referred to our pheochromocytoma/paraganglioma program at the National Institutes of Health for evaluation and management of paragangliomas. PPGLs tend to occur in hereditary patterns with mutations in a variety of pathways, as alluded to above (Fishbein et al. 2017). However, neither of these patients (one from the USA and the other from Croatia) who both had the same rare tumor and rare blood disorder, PPGL and polycythemia, had any affected family members or defects in any known disease-causative genes on germline testing. Both of these disorders are often due to heritable mutations in pathways related to hypoxia or pseudohypoxia signaling (Percy et al. 2008, Lee & Percy 2011, Semenza 2011, Fishbein et al. 2017). This led us to believe that the constellation of findings in these patients – rare neuroendocrine tumors derived from the neural crest and polycythemia – was due to a spontaneous genetic defect in the same pathway that occurred early enough in somatic tissue but not the germline in both patients to lead to pathologies in multiple organ systems.

At the time, defects in genes putatively related to hypoxia signaling pathways such as VHL (von Hippel-Lindau), EGLN1, and SDHx (succinate dehydrogenase complex genes) had been associated with neural crest tumors prior to our discovery (Neumann & Wiestler 1991, Dahia 2006, Kaelin & Ratcliffe 2008). However, not only had no defects in HIF genes been identified in these tumors, but regulation of erythropoietin production, the key hormone regulating production of red blood cells, had been initially mistakenly attributed mainly to HIF1α (Haase et al. 2010).
Table 1   Characteristics of patients with Pacak–Zhuang syndrome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
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<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Age at onset of the diagnosed condition (years)</td>
<td>Birth</td>
<td>2</td>
<td>7</td>
<td>Birth</td>
<td>7</td>
<td>2.3</td>
<td>2</td>
<td>17</td>
<td>31</td>
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<tr>
<td>Polycythemia</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PPGL</td>
<td>14</td>
<td>15</td>
<td>8</td>
<td>18</td>
<td>35</td>
<td>16</td>
<td>39</td>
<td>56</td>
<td>31</td>
</tr>
<tr>
<td>Ampullary somatostatinoma</td>
<td>29</td>
<td>17</td>
<td>–</td>
<td>22</td>
<td>35</td>
<td>–</td>
<td>39</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Severity of polycythemia at presentation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>PPGL characteristics (Rosenblum et al. 2021)</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Vascular malformations (Rosenblum et al. 2021)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>–</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Ocular malformations (Dmitriev et al. 2020, Rosenblum et al. 2021)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Variant analysis (Wang et al. 2022)</td>
<td>EPAS1</td>
<td>A530T</td>
<td>P531S</td>
<td>D539N</td>
<td>A530V</td>
<td>Y532C</td>
<td>D539N</td>
<td>A530V</td>
<td>D539N</td>
</tr>
<tr>
<td>VAF (%)</td>
<td>100</td>
<td>80.20</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>66.60</td>
<td>67.00</td>
<td>–</td>
<td>48.80</td>
</tr>
<tr>
<td>Blood</td>
<td>25.46</td>
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<td>Negative</td>
<td>1.72</td>
<td>Negative</td>
<td>0.34</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>BMC</td>
<td>35.60</td>
<td>–</td>
<td>Negative</td>
<td>2.74</td>
<td>1.40</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
<td>4.60</td>
</tr>
<tr>
<td>Hair</td>
<td>54.00</td>
<td>–</td>
<td>Negative</td>
<td>2.26</td>
<td>–</td>
<td>16.00</td>
<td>Negative</td>
<td>–</td>
<td>0.34</td>
</tr>
<tr>
<td>Nail</td>
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<td>–</td>
<td>Negative</td>
<td>0.42</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
<td>1.80</td>
</tr>
</tbody>
</table>
| Characteristics of our cohort of patients with Pacak–Zhuang syndrome identified to date based on literature review and retrospective chart review are provided. Patient numbers correspond to those in Rosenblum et al. (2021), which cross-references patient numbers in other published articles concerning this cohort (Darr et al. 2016, Robert et al. 2019). These include sex, presence of disease phenotypes such as polycythemia, paraganglioma (PPGL), ampullary somatostatinoma, vascular malformations, and ocular malformations, age of onset of each phenotype, and frequency of the variant EPAS1 allele (VAF; percent) detected in multiple tissues tested. The severity of polycythemia at presentation is also provided; however, most patients were already undergoing routine phlebotomy at the time of referral to our institution. All patients in our cohort had NA biochemical phenotype. Six of nine patients in this cohort had metastatic disease from their abdominal or retroperitoneal (A/RP) PPGL; one patient (patient 5) has a lesion at the jugular foramen (JF) with PET imaging signature consistent with a PPGL. Metastatic disease was determined in retrospective chart review based on PET imaging features, such as bone lesions, per the World Health Organization criteria, and/or histopathologic confirmation of invasion of resected lymph nodes when available. All patients had vascular malformations and ocular malformations, except patient 6, who did not have sufficient radiologic evaluation to assess ocular malformations. Vascular malformations may include enlarged dural sinuses and vein of Galen, rete mirabile of the jugular vein, and subfascial cavernous malformations of the neck. Ocular malformations may include persistent fibrovascular membranes, optic disc anomalies such as morning glory anomalies, hemangiomaticus lesions, and tortuous and/or dilated vessels. Tissues tested by digital droplet polymerase chain reaction (ddPCR) include resected tumors, blood, bone marrow concentrate (BMC), hair, saliva, nail, and urine. Other variant analyses such as prothrombin, erythropoietin receptor (EPOR), hypoxia-inducible factor 1 alpha (HIF-1α), Janus kinase 2 (JAK2), prolyl hydroxylase 1/2 (PHD1/2), succinate dehydrogenase (SDH) B/C/D, and von Hippel–Lindau (VHL) were performed with Sanger sequencing and were negative in all patients except patient 9, who had a G20210A variant prothrombin allele. A/RP, abdominal or retroperitoneal; F, female; JF, jugular foramen; M, male; N, no; NA, noradrenergic; PPGL, pheochromocytoma and paraganglioma; VAF, variant allele frequency; Y, yes.
2013). Under baseline conditions (normal oxygenation or normoxia), HIFs are constantly produced but rapidly degraded by the proteasome after hydroxylation by prolyl-hydroxylases (PHDs) and association with VHL, which is an E3 ubiquitin ligase (Kaelin & Ratcliffe 2008, Semenza 2011). However, under low oxygen conditions, or hypoxia, PHDs are inactivated and HIFs are stabilized and translated to the nucleus, where they regulate many key genes involved in vessel growth and maintenance, red blood cell production, and tumorigenesis (Kaelin & Ratcliffe 2008, Semenza 2011, Jochmanová et al. 2013). Thus, we hypothesized that a genetic defect in one of the HIFs may explain the presentation of these patients. By evaluating the multiple primary PPGL resected from both patients, we demonstrated that these tumors expressed downstream targets of hypoxia signaling, suggesting that these tumors, but not the germline tissue, carried the same genetic defect in a gene related to hypoxia signaling (Zhuang et al. 2012). By performing targeted Sanger sequencing, we found hotspot variants in the oxygen degradation domain of EPAS1 in multiple tumors from each patient but not the matched blood samples (Zhuang et al. 2012). Further, we showed that the variants identified in both patients disrupted hydroxylation and VHL-mediated proteasomal degradation (Zhuang et al. 2012). This confirmed our suspicions that this new syndrome is caused by early somatic mosaicism of gain-of-function mutations in EPAS1. Later, we did confirm low VAF in the blood and other normal tissues of these and other patients with this syndrome referred to us for evaluation of PPGL (Pacak et al. 2013, Wang et al. 2022).

While our discovery that this sporadic syndrome is caused by mosaic gain-of-function mutations in EPAS1 did provide essential insights into many longstanding questions such as how two unrelated patients could have the same PPGL syndrome and what the role of HIFs, particularly HIF-2α, is in the pathogenesis of these tumors, it raised additional critical questions. For example, some of these patients presented with vision problems that we and others assumed were due to the sequelae of catecholamine excess, such as hypertension, but that did not progress clinically the way in which such secondary phenomena might be expected to do so. Thus, prompted by these new questions, we developed a transgenic mouse model bearing the mutation corresponding to that discovered in the index patient to further our investigations (Wang et al. 2019). We have found this model, which recapitulates the human disease phenotype including noradrenergic biochemical phenotype, polycythemia, and increased number of somatostatin positive cells in the ampullary region of the duodenum, to be critical to our continued translational studies (Wang et al. 2019).

**Continued investigations**

Many outstanding studies have investigated the loss-of-function of HIFs by targeted knockout or germline deletion and found a variety of phenotypes ranging from embryonic lethality to cardiovascular malformations (Dunwoodie 2009). Further, several studies have studied models of indirect gain-of-function of HIFs by generating, for example, loss-of-function of EGLN1 or VHL based on variants identified in families with PPGL or polycythemia syndromes (Dunwoodie 2009, Arsenault et al. 2013, Fielding et al. 2018, Wang et al. 2018). However, prior to our discovery, there had been no studies of the direct gain-of-function of EPAS1 (HIF-2α). Based on our initial report and new findings as described above, we generated a transgenic mouse model bearing a mosaic variant allele corresponding to that identified in our index patient and demonstrated that this model effectively recapitulates key aspects of the syndrome, including the polycythemia and NA biochemical phenotype, which, has since been recognized as a key distinguishing feature of the pseudohypoxia cluster PPGL (Wang et al. 2019).

By using an inducible knockin system, this model allowed us to effectively recapitulate the genetic pathogenesis of this syndrome, which, as described above, is a mosaicism. In brief, we established mice bearing the Epas1A529V variant using TALEN-mediated homologous recombination (Wang et al. 2019, Rosenblum et al. 2021). We introduced this point mutation, A529V (GCA>GTA), which corresponds to the variant (A530V) first detected in the index patient, into exon 12 of Epas1 in one allele distal to an inserted reverse-oriented neomycin resistance gene cassette, which was flanked by loxP sites in intron 11 (Wang et al. 2019, Rosenblum et al. 2021). In its native state, this cassette is expected to inhibit transcription of this altered Epas1 allele that we introduced (Wang et al. 2019). While this heterozygous mouse (Epas1+/Neo-A529V) produced in the first generation does not demonstrate polycythemia or the NA phenotype due to inhibition of the variant allele, crossing it with a transgenic mouse bearing the Cre recombinase under the control of the adenovirus enzyme IIa cyclization recombinase promoter (Ella-Cre) (Lakso et al. 1996) leads to the excision of the neomycin resistance gene cassette and transcription of the variant allele (Wang et al. 2019). We chose this promoter because it is expressed...
in most tissues but not all cells in the early embryo (Lakso et al. 1996). Thus, in this way, we can generate mosaic activation of the *EPAS1* variant allele, which recapitulates the human disease pathogenesis (Rosenblum et al. 2021).

### Ocular malformations

In continuing to follow the initially reported patients and evaluating newly referred patients, we have found that, as alluded to above, in addition to a multiplicity of neuroendocrine tumors at a young age, a majority of our cohort (n = 9) present with poor vision (Dmitriev et al. 2020, Rosenblum et al. 2021), which may at first seem unsurprising, considering these patients have chronic catecholamine excess. However, a close ophthalmologic evaluation over more than a decade has revealed that the stable poor vision in these patients is not solely due to sequelae of catecholamine excess such as high blood pressure. We found that these patients have a congenital malformation of the eye and associated vasculature called a morning glory anomaly, which includes a partial- or full-thickness defect through the retina, choroid, and sclera, and has been rarely reported in the literature prior to the discovery of this syndrome (Dmitriev et al. 2020, Rosenblum et al. 2021). Further supporting the developmental nature of the poor vision in these patients, we identified the same malformation in the transgenic mouse model (Dmitriev et al. 2020, Rosenblum et al. 2021). Further, we were able to identify remnant embryologic hyaloid vessels and membranes in both the patients and mouse model (Dmitriev et al. 2020, Rosenblum et al. 2021). These findings highlight the previously unrecognized critical role of HIF-2α in developmental malformations of the eye and associated vasculature. Further, these findings raise the question of which came first – are these malformations in the retina, choroid, and sclera due to direct effects of the gain-of-function variant of HIF-2α on parenchymal cells of those structures, or are they due to abnormal development of affected vascular endothelial cells? To gain a better understanding of the origin of these malformations, we evaluated our patients and transgenic mouse model for vascular malformations (Rosenblum et al. 2021).

### Vascular malformations and neural tube defects

Though rarely reported in the literature, morning glory anomalies and other vascular malformations of the eye are often associated with ipsilateral vascular malformations of the central nervous system with unclear etiology (Lenhart et al. 2006, Robert et al. 2019). While the underlying pathogenesis of this relationship is not understood, we felt, similar to metameric syndromes with vascular malformations (Lasjaunias et al. 2006), that this new syndrome, which is due to a mosaic genetic defect, may have additional vascular malformations. Indeed, evaluation of our cohort and the corresponding transgenic mouse model revealed a range of systemic vascular malformations (Rosenblum et al. 2021). These included cavernous malformations of the central nervous system, previously unreported subfascial cavernous malformation of the extrinsic spinal venous system, and rete mirabile of the carotid and jugular system, which has been rarely reported in humans (Fig. 1) (Rosenblum et al. 2021). Further, we believed that, in contrast to the current hypothesis regarding co-occurrence of PPGL and congenital heart malformations, which posits that PPGL are secondary to systemic hypoxia (Vaidya et al. 2018), that, in these patients, cardiac malformations may be due to a primary developmental effect of the somatic variant on the heart. In our investigations, we have found significant malformations of the heart, lung, and associated vasculature (unpublished), again raising the question of whether the parenchyma or vessels are primarily affected, or perhaps both, and highlighting the importance of further stratification of PPGL syndromes. Similar to the findings in the eyes of patients and the mouse model with this syndrome, in which vascular malformations coincided with malformations of the organ parenchyma, we found that vascular malformations of the head and neck often occurred at the site of neural tube defects of abnormal bony segmentation (Rosenblum et al. 2020).

To address the questions raised by these findings, we evaluated the variant allele frequency in tissue samples isolated from patients with the syndrome (Rosenblum et al. 2021). We found that, as reported previously, the seemingly unaffected or normal tissue surrounding the resected paraganglioma had a low VAF (~2–5%) while the tumor allele frequency was much higher (~60–80%) (Rosenblum et al. 2021). Further, the abnormal appearing vessels within and around these resected tumors had higher VAF (~9–50%) than the surrounding normal tissue (Rosenblum et al. 2021). These findings demonstrate that the previously unrecognized disease phenotypes such as vascular malformations are likely due to mosaic variant alleles in the affected tissue. Further, it suggested to us that the vascular malformations, which appeared to have increased vessel density and tortuosity and to primarily affect veins, are likely due to failure of regression of vessels from early development (Fig. 1) (Rosenblum et al. 2021).
**Discussion – broader implications**

The initial discovery of this rare PPGL syndrome has already had a tremendous impact on the field of PPGL research and informed diagnosis and treatment options. First, we are now aware of a PPGL syndrome that, to our knowledge, behaves differently than other PPGL syndromes. For example, these patients present at a young age with a multiplicity of large tumors rather than with a high number of small metastatic lesions, although they usually later develop in about 60% of these patients (Table 1), as determined by retrospective chart review and systematic review of the literature (Därr et al. 2016). While these numbers were determined from our small cohort (nine patients), it is the largest cohort of these patients to date and should guide our understanding until larger studies are possible. Second, we now have a strong pathophysiologic understanding of other associated disease phenotypes such as developmental ocular malformations that explain the poor vision in these patients, which is in direct contradistinction to the classical assumption that this is potentially reversible sequelae of catecholamine excess. Finally, the discovery of the central role of HIF-2α in this syndrome and in pseudohypoxia cluster PPGL has led to the development of the first personalized treatment for these patients – Belzutifan (trade name: Welireg) (Merck) – which has recently received Food and Drug Administration

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**Figure 1**

Molecular pathogenesis of vascular malformations in Pacak-Zhuang syndrome. Top: The sequence of HIF-2α is shown with the variant (A530V) identified in the index patient with this syndrome. We found that this variant leads to stabilization of HIF-2α by preventing its association with prolyl hydroxylase domain-containing protein 2, as shown in the structural render, and subsequent proteasomal degradation mediated by the von Hippel–Lindau protein. This stabilization leads to constitutive hypoxia signaling that we have shown is insensitive to increasing oxygen tension. Bottom: By continued investigation of patients with this syndrome and the corresponding mouse model that we generated, we have found that malformed vessels, such as those found in the eye and various systemic vascular malformations listed here, have higher VAF than surrounding normal tissue, which leads to a failure of normal developmental venous regression. Reproduced, with permission, from Rosenblum et al. (2021), JCI Insight, volume 6, e144368 (https://doi.org/10.1172/jci.insight.144368).
approval for renal cell carcinoma in VHL disease and has been shown to have remarkable outcomes in treating these PPGL and signs of catecholamine excess with one specific report in a patient with Pacak–Zhuang syndrome (Kamihara et al. 2021). This report, while very promising, only evaluated the effect of Belzutifan on PPGL, catecholamine production, and polycythemia. This may have wider impact in patients with tumors or diseases due to pseudohypoxic signaling. For example, though there is ongoing debate, it is believed that oncogenesis in PPGL carrying variants in succinate dehydrogenase B (SDHB) is due, at least in part, to activation of HIF2α, likely due to inactivation of PHD2 and hypermethylation due to inhibition of ten–eleven translocation enzymes (Morin et al. 2020). In light of our recent findings, it is very important to know the effect of Belzutifan, which represents the first targeted personalized treatment for such a PPGL syndrome, on these additional disease phenotypes in critical organs such as the eye and brain.

Moving forward, as this and new personalized therapies with a chance of cure are developed, it is critical to assess the effect on all of the disease phenotypes of these rare diseases. Further, we must determine the long-term effect of these new treatments. For example, are the resolution of these disease phenotypes permanent and what happens when the treatment is withdrawn? Patients will need to be followed in dedicated specialized programs with the capabilities to answer these questions.

Studying this syndrome has suggested to us that continuing to stratify these and other rare diseases such as other developmental tumor syndromes, heritable syndromes, mosaicisms, and other sporadic diseases in light of the genetics, for example, the timing of acquired genetic defects, will be critical to prognostication and treatment paradigms. We have been afforded a brief window into the natural history of these new disease phenotypes in these patients over the last 12 years, in which they have been largely stable, as opposed to the cardiovascular sequelae of catecholamine excess seen in other PPGL patients (Nazari et al. 2020).

Several studies in other syndromes that have heritable, mosaic, and sporadic forms such as neurofibromatosis have suggested that the natural history of these forms varies considerably (Kahrer-Sawatzki et al. 2004, Kerr et al. 2018, Ejerskov et al. 2021). Moving forward, we feel that we can apply this paradigm to PPGL syndromes, as highlighted by our continued studies of Pacak–Zhuang syndrome. This may greatly inform our decisions regarding treatment interventions, particularly as these new discoveries and understandings lead to the development of additional therapies such as Belzutifan. Further, in light of these new personalized therapies that are now available, we feel it is now more important than ever to perform and disseminate studies that guide the clinical identification of these rare syndromes, which will allow proper patient selection and the greatest chance at successful treatment. For example, we have learned that, while it can be extremely challenging to detect low variant allele frequency in non-tumor tissue, as with any somatic mosaic disease, Pacak–Zhuang syndrome can be diagnosed with a high index of suspicion based on the clinical characteristics described herein and repeated testing (Table 1) and has a significant impact on clinical management, such as the selection of appropriate therapies including Belzutifan (Wang et al. 2022, Toledo et al. 2023).

In fact, there are additional ongoing trials, such as one evaluating the combination of a new small molecular inhibitor of HIF-2α with everolimus and other immune-oncology agents in advanced or relapsed renal cancer and other malignancies sponsored by Novartis (NLM, NCT04895748) that may warrant such considerations very soon. For example, we may find that treatments with greater side effect profiles that offer only a chance of remission and no change of cure may not be warranted. We feel it is likely that, in these scenarios, personalized targeted curative therapies such as Belzutifan and this new small molecular inhibitor currently in trial may be a better option for these patients. Continued study of these rare diseases and associated models in translational programs through broad collaborative networks such as the ISP and its outgrowths will pave the way forward and deepen our understanding of the underlying pathophysiology of these diseases. This will allow us to make more informed decisions regarding patient care.

Studying rare diseases such as PPGL, which greatly inform our broader understanding of not only cancer biology but also the pathogenesis of other pathologies such as the new disease phenotypes we have discovered, requires a strong global collaborative effort such as those spurred by the ISP. Further, the continued development and safe use of targeted personalized medicine based on these discoveries requires dedicated translational centers and programs dedicated to further understanding disease pathogenesis, developing novel treatments, and improving the outcome of patients with these and other diseases.

Declaration of interest
The authors have no relevant conflicts of interest to disclose.
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