Significance of Mentoring

By Peg Ford

According to Wikipedia, "Mentorship is a personal relationship in which a more experienced or more knowledgeable person helps to guide a less experienced or less knowledgeable person. However, true mentoring is more than just answering occasional questions or providing ad hoc help. It is about an ongoing relationship of learning, dialog, and challenge." This description of a mentor was to prove accurate for me, as I describe my recent experience as a Patient Representative Stakeholder Reviewer in the funding applications for the Patient-Centered Outcomes Research Institute (PCORI) Cycle II Merit Review Assessment of Prevention, Diagnosis, and Treatment Options. To say that it was challenging and absorbing is an understatement!

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Allow me to quote from my instructions, "PCORI's review process embodies the uniquely patient-centered, outcomes-focused mission of PCORI: patients and stakeholders, as well as scientists, review applications against PCORI's review criteria. Because PCORI's review process differs from other peer review processes in important ways, PCORI requires that all reviewers complete online training." I was to discover this statement was not misleading.

After the informative online training, I received the applications I was to review, and to my surprise, not one was about ovarian or any kind of gynecologic research (my specialty). This was a new challenge to undertake, and the process would require a great deal of time and effort to accomplish the work by the deadline. Each grant request was to be reviewed on the basis of 3 main criteria: innovation/potential for improvement, patient-centeredness, and team and environment. An overall score and an outline of strengths and weaknesses would then be passed along to the research panel. At the in-person Merit Review Panel Meeting, the grant requests would be discussed and voted on.

I generally face challenges with a determination to succeed, but this time, I thought perhaps I had taken on a task that either I could not or would not have time to finish. However, I had someone in my corner who thought differently—my PCORI Mentor, Debra Madden, who assured me I was capable and did so with grace, talent, and encouragement. She never equivocated for a moment in her emails, or on that important telephone call about my ability to not only finish the job, but to get it done by the deadline. In one of her emails, she wrote, "I've always been a bit of a collector of quotes that I've found inspiring. I wanted to share this one with you, thinking you might like

it as well. *Reach high, for stars lie hidden in your soul. Dream deep, for every dream precedes the goal.* —Pamela Vaull Starr." I did finish, and before the deadline! And I hope to be a mentor like Deb to inspire others to go beyond what they thought they were capable of.

Now, reflecting on the experience, I thought about a story I wrote several years ago. I hope that by sharing it here, I will acknowledge my debt of gratitude to Deb, and that this story will serve as a reminder about the inner critic that, still at my age, can stop me from facing my fears and growing beyond anything I thought possible.

Up Up Up Over the Rainbow

There once was a Bluebird born into this world full of excitement and inner passion to experience all that life had to offer. For hours, this little Bluebird, named Charlie, would sit and watch the birds that knew how to fly. He would gaze in awe at how high they could fly and with such a feeling of complete freedom. He wanted this for himself and could hardly wait for the day it would come true.

As twists of fate happen, a Cardinal moved into the neighborhood just days before the time arrived for Charlie to test his wings. Charlie sensed the Cardinal was not happy and often kept to himself. "How sad," thought Charlie, for, unlike the Cardinal, he was anxious to learn to fly so he could go and meet other birds and experience life!

One day the sun rose a little more brightly and the air seemed tinged with electricity. The day had arrived for Charlie to leave the nest and fly!

Continued on page 10

Significance of Mentoring

Continued from page 9

He awoke happy, full of excitement and anticipation. He knew he was ready! His heart started to beat faster and faster. He thought his little breast was going to explode with the expectation. He was ready!

Just as he said to himself, "Okay, here I go!" with his natural inclination to just fall out of the nest, the Cardinal, sitting in the next tree, shouted to him, "That's not the RIGHT way. You will only kill yourself! Jump off. Do it the right way!" With this, Charlie's heart started racing. Regaining his balance, he sat down, immobilized by fear. He sat, and sat, and sat. It was hard for him to breathe being so confused and anxious.

His little body was trembling and he felt so lost. Looking high in the sky, he saw an Eagle soaring proudly and effortlessly. Charlie sighed. Why hadn't he been born an Eagle so he too could fly so freely and so confidently?

Days passed and little Charlie kept very still, waiting for some clue or idea to help him out of his predicament. Anything would help him feel better about himself. If jumping out of the nest,

like the Cardinal said, was the right way to fly, then why did it feel so wrong to him? Charlie sat doubting himself more and more. Charlie's depression grew, and not even the beautiful sun rising in the morning or watching the other birds could make him even want to try to spread his wings. What was supposed to be his flight to freedom and expression only brought him sadness and misery. He looked around and only saw the critical eye of the Cardinal watching his every move. He felt trapped, useless, and wishing he had not been born. Obviously, he was a mistake.

One day, from high up, a wise old Owl, who had observed what happened, said, "Trust yourself, Charlie. Listen to your heart. Go for it. Don't worry about if you are doing it right." "But," Charlie replied, "the Cardinal said I was doing it wrong. I'm supposed to jump off rather than fall out." The Owl kindly responded, "The Cardinal thinks he is helping, but he is so focused on what others are doing that he forgets he does not have all the answers. Also notice," the Owl continued, "he is so busy telling you that you are not doing it right and watching your every move, that he is not flying and getting on with his own life."

Like magic, right at that moment, a teenage Bluebird flew down and landed next to Charlie and said, "Hey, come with me. The Eagles have this neat nest

Continued on page 12

Serious Adverse Reactions
Infections were the most common type of SAE reported in both studies with 8 patients (8%) in Study 1 and 26 patients (31%) in Study 2 experiencing a serious infection. Serious adverse reactions reported in > 2% of patients in Study 1 were sepsis and pyrexia (3%). In Study 2, serious adverse reactions in > 2% of patients were fatigue (7%), supraventricular arrhythmia, central line infection, neutropenia (6%), hypotension, hyperuricemia, edema (5%), ventricular arrhythmia, thrombocytopenia, nausea, leukopenia, dehydration, pyrexia, aspartate aminotransferase increased, sepsis, catheter related infection, hypophosphatemia and dyspnea (4%).

Most deaths were due to disease progression. In Study 1, there were two deaths due to cardiopulmonary failure and acute renal failure. In Study 2, there were six deaths due to infection (4), myocardial ischemia, and acute respiratory distress syndrome.

Discontinuations
Discontinuation due to an adverse event occurred in 21% of patients in Study 1 and 11% in Study 2. Discontinuations occurring in at least 2% of patients in either study included infection, fatigue, dyspnea, QT prolongation, and hypomagnesmia.

Peripheral T-Cell Lymphoma
The safety of ISTODAX was evaluated in 178 patients with PTCL in a sponsor-conducted pivotal study (Study 3) and a secondary NCI-sponsored study (Study 4) in which patients received a starting dose of 14 mg/m^2. The mean duration of treatment and number of cycles in these studies were 5.6 months and 6 cycles.

Common Adverse Reactions
Table 2 summarizes the most frequent adverse reactions (≥ 10%) regardless of causality, using the NCI-CTCAE, Version 3.0. The AE data are presented separately for Study 3 and Study 4. Laboratory abnormalities commonly reported (≥ 10%) as adverse reactions are included in Table 2.

Table 2. Adverse Reactions Occurring in ≥10% of Patients with PTCL in Study 3 and Corresponding Incidence in Study 4 (N=178)

	Study 3 (N=131)		Study 4 (N=47)	
Adverse Reactions n (%)	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**
Any adverse reactions	*127 (97)*	*86 (66)*	*47 (100)*	*40 (85)*
Gastrointestinal disorders				
Nausea	77 (59)	3 (2)	35 (75)	3 (6)
Vomiting	51 (39)	6 (5)	19 (40)	4 (9)
Diarrhea	47 (36)	3 (2)	17 (36)	1 (2)
Constipation	39 (30)	1 (<1)	19 (40)	1 (2)
Abdominal pain	18 (14)	3 (2)	6 (13)	1 (2)
Stomatitis	13 (10)	0	3 (6)	0
General disorders and administration site conditions				
Asthenia/Fatigue	72 (55)	11 (8)	36 (77)	9 (19)
Pyrexia	46 (35)	7 (5)	22 (47)	8 (17)
Chills	14 (11)	1 (<1)	8 (17)	0
Edema peripheral	13 (10)	1 (<1)	3 (6)	0
Blood and lymphatic system disorders				
Thrombocytopenia	53 (41)	32 (24)	34 (72)	17 (36)
Neutropenia	39 (30)	26 (20)	31 (66)	22 (47)
Anemia	32 (24)	14 (11)	29 (62)	13 (28)
Leukopenia	16 (12)	8 (6)	26 (55)	21 (45)
Metabolism and nutrition disorders				
Anorexia	37 (28)	2 (2)	21 (45)	1 (2)
Hypokalemia	14 (11)	3 (2)	8 (17)	1 (2)
Nervous system disorders				
Dysgeusia	27 (21)	0	13 (28)	0
Headache	19 (15)	0	16 (34)	1 (2)
Respiratory, thoracic and mediastinal disorders				
Cough	23 (18)	0	10 (21)	0
Dyspnea	17 (13)	3 (2)	10 (21)	2 (4)
Investigations				
Weight decreased	13 (10)	0	7 (15)	0
Cardiac disorders				
Tachycardia	13 (10)	0	0	0

Serious Adverse Reactions
Infections were the most common type of SAE reported. In Study 3, 25 patients (19%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, 11 patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections. Serious adverse reactions reported in ≥ 2% of patients in Study 3 were pyrexia (7%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis, (4%), febrile neutropenia, abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnea, and dehydration (2%). In Study 4, serious adverse reactions in ≥ 2 patients were pyrexia (17%), aspartate aminotransferase increased, hypotension (13%), anemia, thrombocytopenia, alanine aminotransferase increased (11%), infection, dehydration, dyspnea (9%), lymphopenia, neutropenia, hyperbilirubinemia, hypocalcemia, hypoxia (6%), febrile neutropenia, leukopenia, ventricular arrhythmia, vomiting, hypersensitivity, catheter related infection, hyperuricemia, hypoalbuminemia, syncope, pneumonitis, packed red blood cell transfusion, and platelet transfusion (4%).

Deaths due to all causes within 30 days of the last dose of ISTODAX occurred in 7% of patients in Study 3 and 17% of patients in Study 4. In Study 3, there were 5 deaths unrelated to disease progression that were due to infections, including multi-organ failure/sepsis, pneumonia, septic shock, candida sepsis, and sepsis/cardiogenic shock. In Study 4, there were 3 deaths unrelated to disease progression that were due to sepsis, aspartate aminotransferase elevation in the setting of Epstein Barr virus reactivation, and death of unknown cause.

Discontinuations
Discontinuation due to an adverse event occurred in 19% of patients in Study 3 and in 28% of patients in Study 4. In Study 3, thrombocytopenia and pneumonia were the only events leading to treatment discontinuation in at least 2% of patients. In Study 4, events leading to treatment discontinuation in ≥ 2 patients were thrombocytopenia (11%), anemia, infection, and alanine aminotransferase increased (4%).

6.2 Postmarketing Experience
No additional safety signals have been observed from postmarketing experience.

7 DRUG INTERACTIONS

7.1 Coumadin or Coumadin Derivatives
Prolongation of PT and elevation of INR were observed in a patient receiving ISTODAX concomitantly with warfarin. Although the interaction potential between ISTODAX and Coumadin® (a registered trademark of Bristol-Myers Squibb Pharma Company) or Coumadin derivatives has not been formally studied, physicians should carefully monitor PT and INR in patients concurrently administered ISTODAX and Coumadin or Coumadin derivatives *[See Clinical Pharmacology (12.3)]*.

7.2 Drugs that Inhibit or Induce Cytochrome P450 3A4 Enzymes
Romidepsin is metabolized by CYP3A4. Although there are no formal drug interaction studies for ISTODAX, strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase concentrations of romidepsin. Therefore, co-administration with strong CYP3A4 inhibitors should be avoided if possible. Caution should be exercised with concomitant use of moderate CYP3A4 inhibitors.

Co-administration of potent CYP3A4 inducers (e.g., dexamethasone, carbamazepine, phenytoin, rifampin, rifabutin, rifapentine, phenobarbital) may decrease concentrations of romidepsin and should be avoided if possible. Patients should also refrain from taking St. John's Wort.

7.3 Drugs that Inhibit Drug Transport Systems
Romidepsin is a substrate of the efflux transporter P-glycoprotein (P-gp, ABCB1). If ISTODAX is administered with drugs that inhibit P-gp, increased concentrations of romidepsin are likely, and caution should be exercised.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D *[See Warnings and Precautions (5.5)]*.

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and resulted in adverse effects on the developing fetus at exposures below those in patients at the recommended dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus.

Romidepsin was administered intravenously to rats during the period of organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day. Substantial resorption or post-implantation loss was observed at the high-dose of 0.5 mg/kg/day, a maternally toxic dose. Adverse embryo-fetal effects were

Significance of Mentoring

Continued from page 11

high on the top of this tree, and we're all wind sailing from their platform." "Wait," said Charlie, "how did you learn to fly?" "Well, it felt right for me to fall out backward at first," said his new friend, "and since then, I have practiced taking off frontward. Boy, it sure did give my mother a scare the first few times I fell out backward! I knew she held her breath each time I did it, but she only had words of encouragement for me and was proud of my efforts. Then, unbelievably, my flock admired me for my uniqueness, and I started teaching others how to do my move. They were scared out of their wits to try. Imagine that! What came to me naturally, others were frightened just to attempt, and they soon appreciated how easy it was for me. My mother said I had been given a special gift. Boy, did this make me feel good about myself. Now I only do my backflips in bird shows and on days I want to be reminded of my mother's words of encouragement to keep growing and trusting myself."

With this, his new friend flew away effortlessly. Charlie looked around and very abashed said out loud to himself, "Sometimes you've just got to say 'what the heck' and go for it!" With this, he took a deep breath and with his little body trembling in terror, fell out of the nest. The Cardinal was, of course, observing all of this and yelled out, "You're not doing it right! You're going to kill yourself!"

Charlie fell straight toward the ground. His immediate reaction was that he had made a mistake. The earth was moving closer and closer! But suddenly, his natural instincts took over and he flew! Yes, awkwardly and wildly with erratic movements, but he was flying! He landed on a branch within earshot of his new friend, who smiled and said, "Hey, man, that was cool! Could you show me how you made those moves? I'll meet you at the Eagle's nest!"

With this, his new friend took off to the top of the tree to the Eagle's nest. Before Charlie joined him, however, he flew to a branch near to where the Cardinal shook his head in disbelief.

Charlie spoke from his heart how he felt humiliated and discouraged when the Cardinal told him he was not doing it right. He shared how much this prevented him from trusting himself and how insecure and fearful he had been, scared even to try. The Cardinal listened without comment. Relieved by sharing his feelings with the Cardinal, Charlie took off. In his own unique and shaky way, Charlie started to fly to the top of the tree. Looking back over his shoulder, to his wonder, Charlie noticed that the Cardinal had flown up to the wise old Owl and was listening intently to every word the Owl was saying.

Our little Bluebird, Charlie, went on to learn how to soar to new heights. You may not believe it, but one rainy day he risked flying higher than he had ever done before, and he and his best friend flew over the rainbow! A songwriter caught the Bluebirds flying and composed a song about freedom and flying over the rainbow. That song is famous to this day.

What happened to the Cardinal? He is still hanging around his favorite tree. Except now he wind sails from the Eagles' platform, demonstrating his graceful ability and setting an example for others to follow.

He learned that day from the wise old Owl and Charlie that it is more important to show others by example how to fly. For the greatest gift we can give to each other is to applaud one's courage, rather than clip one's wings! ●

noted at romidepsin doses of ≥0.1 mg/kg/day, with systemic exposures (AUC) ≥0.2% of the human exposure at the recommended dose of 14 mg/m²/week. Drug-related fetal effects consisted of folded retina, rotated limbs, and incomplete sternal ossification.

8.3 Nursing Mothers
It is not known whether romidepsin is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of ISTODAX in pediatric patients has not been established.

8.5 Geriatric Use
Of the approximately 300 patients with CTCL or PTCL in trials, about 25% were > 65 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects; however, greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment
No dedicated hepatic impairment study for ISTODAX has been conducted. Mild hepatic impairment does not alter pharmacokinetics of romidepsin based on a population pharmacokinetic analysis. Patients with moderate and severe hepatic impairment should be treated with caution *[See Clinical Pharmacology (12.3)]*

8.7 Renal Impairment
No dedicated renal impairment study for ISTODAX has been conducted. Based upon the population pharmacokinetic analysis, renal impairment is not expected to significantly influence drug exposure. The effect of end-stage renal disease on romidepsin pharmacokinetics has not been studied. Thus, patients with end-stage renal disease should be treated with caution *[See Clinical Pharmacology (12.3)]*

10 OVERDOSAGE
No specific information is available on the treatment of overdosage of ISTODAX.

Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 2.2 fold the recommended human dose based on the body surface area, included irregular respiration, irregular heart beat, staggering gait, tremor, and tonic convulsions.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., clinical monitoring and supportive therapy, if required. There is no known antidote for ISTODAX and it is not known if ISTODAX is dialyzable.

12 CLINICAL PHARMACOLOGY
12.2 Pharmacodynamics
Cardiac Electrophysiology
The effect of romidepsin on the heart-rate corrected QTc/QTcF was evaluated in 26 subjects with advanced malignancies given romidepsin at doses of 14 mg/m² as a 4-hour intravenous infusion, and at doses of 8, 10 or 12 mg/m² as a 1–hour infusion. Patients received premedications with antiemetics. No large changes in the mean QTc interval (> 20 milliseconds) from baseline based on Fridericia correction method were detected in the trial. Small increase in mean QT interval (< 10 milliseconds) and mean QT interval increase between 10 to 20 milliseconds cannot be excluded because of the limitations in the trial design.

Romidepsin was associated with a delayed concentration-dependent increase in heart rate in patients with advanced cancer with a maximum mean increase in heart rate of 20 beats per minute occurring at the 6 hour time point after start of romidepsin infusion for patients receiving 14 mg/m² as a 4-hour infusion.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity studies have not been performed with romidepsin. Romidepsin was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Romidepsin was not clastogenic in an *in vivo* rat bone marrow micronucleus assay when tested to the maximum tolerated dose (MTD) of 1 mg/kg in males and 3 mg/kg in females (6 and 18 mg/m² in males and females, respectively). These doses were up to 1.3-fold the recommended human dose, based on body surface area.

Based on non-clinical findings, male and female fertility may be compromised by treatment with ISTODAX. In a 26-week toxicology study, romidepsin administration resulted in testicular degeneration in rats at 0.33 mg/kg/dose (2 mg/m²/dose) following the clinical dosing schedule. This dose resulted in $AUC_{0\text{-inf.}}$ values that were approximately 2% the exposure level in patients receiving the recommended dose of 14 mg/m²/dose. A similar effect was seen in mice after 4 weeks of drug administration at higher doses. Seminal vesicle and prostate organ weights were decreased in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m²/day), approximately 30% the estimated human daily dose based on body surface area. Romidepsin showed high affinity for binding to estrogen receptors in pharmacology studies. In a 26-week toxicology study in rats, atrophy was seen in the ovary, uterus, vagina and mammary gland of females administered doses as low as 0.1 mg/kg/dose (0.6 mg/m²/dose) following the clinical dosing schedule. This dose resulted in $AUC_{0\text{-inf.}}$ values that were 0.3% of those in patients receiving the recommended dose of 14 mg/m²/dose. Maturation arrest of ovarian follicles and decreased weight of ovaries were observed in a separate study in rats after four weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m²/day). This dose is approximately 30% the estimated human daily dose based on body surface area

16 HOW SUPPLIED/STORAGE AND HANDLING
Keep out of reach of children.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published[1-4] *[See References (15)]*.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling.

17.1 Instructions
- Nausea and Vomiting
  Nausea and vomiting are common following treatment with ISTODAX. Prophylactic antiemetics are recommended to be used in all patients. Advise patients to report these symptoms so that appropriate treatment can be instituted *[See Adverse Reactions (6)]*.
- Low Blood Counts
  Patients should be informed that treatment with ISTODAX can cause low blood counts and that frequent monitoring of hematologic parameters is required. Patients should be instructed to report fever or other signs of infection, significant fatigue, shortness of breath, or bleeding *[See Warnings and Precautions (5.1)]*.
- Infections
  Patients should be informed that infections may occur during treatment with ISTODAX. Patients should be instructed to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems *[See Warnings and Precautions (5.2]*.
- Tumor Lysis Syndrome
  Patients at risk of tumor lysis syndrome (i.e, those with advanced stage disease and/or high tumor burden) should be monitored closely for TLS and appropriate measures taken if symptoms are observed *[See Warnings and Precautions (5.4)]*.
- Use in Pregnancy
  If pregnancy occurs during treatment with ISTODAX, female patients should be advised to seek immediate medical advice and counseling. *[See Warnings and Precautions (5.5)]*.
- Patients should be instructed to read the patient insert carefully.

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Celgene Corporation
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