Since Huggins and Hodges established the link between prostate cancer and testosterone in 1941, androgen deprivation therapy has remained a cornerstone for systemic treatment of prostate cancer. In 1979, the first prostate cancer patient was treated with a GnRH agonist at the Laval University Medical Center in Quebec City, Canada with credit of this discovery by Dr. Fernand Labrie. In 1985, gonadotropin-releasing hormone (GnRH) agonists were first approved by the FDA for the treatment of prostate cancer. Common trade names of GnRH agonists include leuprolide (Lupron), Trelstar, and Zoladex. These GnRH agonists take the place of the physiologic, pulsatile, intrinsic GnRH which is secreted from the hypothalamus gland. As a result, this desensitizes the pituitary gland and ultimately causes down-regulation of the receptors which prevents further pituitary secretion of leutinizing hormone, in turn arrests testicular secretion of testosterone. Unfortunately, GnRH agonists can cause an initial flare or surge of testosterone which may last from 2-4 weeks before medical castration is achieved. What exactly does this mean? These surges can be associated with potentially devastating effects with patients having widespread disease including the potential for spinal cord compression in patients with spinal disease or significant worsening in bladder outlet obstructive symptoms in patients with locally advanced disease.
On the contrary, GnRH antagonists [such as degarelix] can produce immediate suppression of testosterone without any surge and usually achieve adequate testosterone suppression within 48 hours. As a result, this prompted the discovery of GnRH antagonists which directly block the GnRH receptor and prevent signaling downstream. The prototype GnRH antagonist was Abarelix which was approved by the FDA in 2003. Unfortunately, a minority of patients sustained hypersensitivity reactions including anaphylaxis. As a result it was withdrawn from the U.S. market. More recently, degarelix [brand name Firmagon], a new-generation GnRH receptor antagonist with low histamine-release was approved by the FDA in December 2008. Degarelix, fortunately, has not been associated with a significant risk of allergic reaction or anaphylaxis. The common side effects of degarelix are similar to those of GnRH agonists including transient injection-site reactions. The pivotal trial which proved degarelix to be equivalent, or non-inferior, to leuprolide was published in December 2008 in BJU International by Klotz et al. This was a phase 3 trial which demonstrated that degarelix was clearly not inferior to leuprolide at maintaining low testosterone levels over a 1 year period. In fact, degarelix induced testosterone and PSA suppression better than leuprolide. Incidentally, an additional difference between the two was a lower incidence of urinary tract infections while using degarelix compared to leuprolide. In November 2009, Tombal et al in European Urology, provided results from a Phase 3, multicentre, randomized trial comparing degarelix to leuprolide in 610 patients. The objective of the trial was to compare activity in respect to PSA recurrence-free survival. Patients receiving degarelix showed a significantly lower risk of PSA progression or death compared to those on leuprolide. PSA recurrence occurred mainly in patients with advanced disease and in those with baseline PSA >20. PSA recurrences occurred almost exclusively in patients with metastatic prostate cancer or high baseline PSA during this study.
Before the discovery of PSA, urologists relied on serum prostatic acid phosphatase (PAP) and serum alkaline phosphatase (S-ALP) to assess the status of men at risk for or under treatment for metastatic prostate cancer. Alkaline phosphatase is a blood test which is often elevated in patients with metastatic disease as a marker of bone turnover. Hence, escalation of alkaline phosphatase can be a concern for progressive metastatic disease. In November 2009, Shröder et al in BJU International, published the results of a randomized, phase 3 trial comparing changes in alkaline phosphatase levels in patients on degarelix and leuprolide. This trial demonstrated that in patients with metastatic disease or those with PSA ≥50 at baseline achieved greater reductions in alkaline phosphatase levels while on degarelix compared to leuprolide. This implied the possibility that degarelix offers a longer time to progression as well as a survival benefit compared to GnRH agonists. Over the next few years, prostate cancer therapy will become increasingly tailored to meet the needs of individual patients with specific disease characteristics with continued development of novel, targeted therapies. Nonetheless, endocrine therapy will remain a critical pharmacologic cornerstone and it would be anticipated that new treatments in relation to hormone blockade will continue to evolve. Analysis of the current data suggests that degarelix may provide an advantage over traditional GnRH agonists in relation to faster and more efficient testosterone and PSA suppression, absence of a testosterone surge (risking potential complications such as spinal cord compression and bladder outlet obstruction), and better control over of the disease with respect to progression of bone metastases.

Dr. Jeffrey Turner is a native of Southern California, having grown up in Orange County and attended the University of Southern California. He was the first student to graduate from USC’s 3-year accelerated science program with a bachelor’s degree in Biological Sciences. Subsequently, he was employed
as a research associate at UCLA in infectious diseases and molecular biology. He completed his medical training in Vancouver, British Columbia. He has also trained clinically at MD Anderson Cancer Center with a focus on genitourinary malignancies. He is board certified in medical oncology and internal medicine. After two years of training, he graduated from fellowship in June of 2009 with a focus on both prostate and renal cell carcinomas. His most recent publication was an expert opinion on Finasteride in July 2010. He has been working with Dr. Bob Leibowitz at Compassionate Oncology Medical Group since July 2009.