Abstract
Many human diseases such as cancer are the result of dysregulated gene expression networks due to the over-activity or over-supply of key transcription factors. Therefore, the regulation of transcription factor-DNA binding with small molecules holds immense promise in human medicine. Pyrrole-imidazole polyamides are programmable small molecules that bind strongly and sequence-specifically to the minor groove of DNA. In cell culture, Py-Im polyamides have been found to localize to the nucleus, display transcriptional inhibition of induced pathways and disrupt transcription factor occupancy at chromatin binding sites. Recent studies have examined the medicinal properties of Py-Im polyamides and demonstrated their ability to circulate in mouse plasma and localize to the nuclei of human cancer xenografts. In our prostate cancer program, we have targeted androgen receptor (AR)-DNA binding sites as well as those of ERG, an ETS transcription factor recently identified as a driver in prostate cancer progression. We have used a Py-Im polyamide targeted to the AR-DNA binding site to downregulate AR-driven gene expression, decrease AR occupancy at promoter and enhancer regions, and achieve cytotoxicity in prostate cancer cell lines. At the same time, Py-Im polyamides have been employed to abrogate the AR-driven transcription of ERG, reduce ERG protein levels, inhibit ERG-driven changes in gene expression, and decrease levels of ERG-dependent DNA damage. Importantly, ongoing studies of human prostate cancer xenografts indicate a reduction in tumor volume upon treatment with an AR-targeted Py-Im polyamide. Studies in ERG-dependent xenograft systems are underway.