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DNA Binding Polyamides and the Importance of DNA Recognition in their use as Gene-Specific and Antiviral Agents

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Abstract

There is a long history for the bioorganic and biomedical use of N-methyl-pyrrole-derived polyamides (PAs) that are higher homologs of natural products such as distamycin A and metropin. This work has been pursued by many groups, with the Dervan and Sugiyama groups responsible for many breakthroughs. We have studied PAs since about 1999, partly in industry and partly in academia. Early in this program, we reported methods to control cellular uptake of polyamides in cancer cell lines and other cells likely to have multidrug resistance efflux pumps induced. We went on to discover antiviral polyamides active against HPV31, where SAR showed that a minimum binding size of about 10 bp of DNA was necessary for activity. Subsequently we discovered polyamides active against two additional high-risk HPVs, HPV16 and 18, a subset of which showed broad spectrum activity against HPV16, 18 and 31. Aspects of our results presented here are incompatible with reported DNA recognition rules. For example, molecules with the same cognate DNA recognition properties varied from active to inactive against HPVs. We have since pursued the mechanism of action of antiviral polyamides, and polyamides in general, with collaborators at NanoVir, the University of Missouri-St. Louis, and Georgia State University. We describe dramatic consequences of β-alanine positioning even in relatively small, 8-ring polyamides; these results contrast sharply with prior reports. This paper was originally presented by JKB as a Keynote Lecture in the 2nd International Conference on Medicinal Chemistry and Computer Aided Drug Design Conference in Las Vegas, NV, October 2013.

Introduction

Polyamides (PAs) that recognize and bind the minor groove of DNA have been studied extensively by a number of groups, including those of Dervan [1-3], Sugiyama [4-7], Lee [8-11], Laemmli [12-14], Kodadek [15,16] and others [17-19]. Over the course of that extensive work, a set of binding rules was developed primarily by the Dervan group to allow prediction and control of polyamide-DNA interactions in the minor groove [3,20-34].

We have been engaged in several collaborative N-methylpyrrole/ N-methylimidazole (Py/Im) polyamide projects over the years [35-42]. One project involved design of polyamides to repress cyclooxygenase-2 (COX-2) gene expression by targeting the binding site of ETS (E26 transcription factor) transcription control superfamily member Ets-1 in the COX-2 promoter, followed by study of the detailed thermodynamics of interactions between active PAs and their Ets-1 target [37]. Another project discovered, and is developing, antiviral agents for high-risk, cancer-causing Human Papillomavirus (HPV), and also encompasses understanding the mechanism of action of these antiviral compounds [36,38,41]. During the course of these projects, we have made and studied the chemical, biological and biophysical properties of a number of polyamides of different sizes, from six to twenty-six heterocyclic rings. Especially for larger compounds, many of our results have not followed the reported rules of PA-DNA recognition, so we have pursued the DNA recognition properties of our compounds with chemical, biochemical and biophysical methods [35,37,39,43]. We found excellent antiviral efficacy in human cell and tissue culture with compounds exceeding MW of 3000 [36,38,41], and note that Sugiyama and colleagues have reported no difference in cellular uptake of polyamides from 400-4000 in MW, as long as Im content was kept constant [44].

Testing the effectiveness of polyamides against HPV16, 18 and 31 in cell culture led to some surprising findings, in addition to a number of inventions [41]. In that work, monolayers of human keratinocytes and organotypic raft tissue cultures were used- both support maintenance of high-risk, cancer-causing HPV DNA, a circular, double-stranded molecule of about 8 kb. Levels of viral DNA in monolayer cultures were monitored 48 h after PA treatment using qPCR; viral DNA was measured relative to vehicle-treated controls in dose-dependent experiments with PAs that allowed calculation of IC₅₀ values. The raft cultures were studied for much longer times (up to 19 days after PA treatment in published reports [41], and longer in unpublished studies at NanoVir). Of note, only relatively long polyamides showed antiviral activity, i.e. those compounds expected to bind approximately a full turn or more of DNA. In addition, only a subset of these long polyamides showed activity against HPV. Furthermore, there was a hierarchy of anti-HPV activity: more compounds were active against HPV31 than against HPV16, and more compounds were active against HPV16 than against HPV18. To date, all compounds active against HPV18 are active against both HPV16 and HPV31, and all compounds active against HPV16 are active against HPV31 [41]. Small chemical changes to PA structure caused huge differences in activity, even when

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the nominal DNA recognition sites of the molecules were the same. Therefore, in order to determine the actual binding sites and affinities of the long, antiviral polyamides to wild-type HPV DNA sequences, we employed a variety of methods, including DNase I footprinting [45-48], affinity cleavage (AC) [28,49,50] and capillary electrophoresis (CE) [29,43,45,51-54]. To carry out the footprinting, we studied a number of DNA molecules, about 300-523 base pairs (bp) in length, that are part of the AT-rich, approximately 8 thousand bp double-stranded DNA (dsDNA) genomes of HPV16 and 18 [38,55-62].

Because we observed unexpected effects of β-alanine (β) positioning on antiviral efficacy, and because we had also previously seen unexpected consequences of positional β effects [37,39,41,63], we decided to investigate these effects in more detail with biophysical studies. Solubility limitations prevented some experiments from being carried out on long polyamides, so we worked with smaller polyamides, a series of 6- and 8-ring molecules with their own inherent interest because they are directed to the COX-2 Ets-1 binding site [37,39]. Note that β is reported to be a good substitute for N-methylpyrrolyl building blocks, one that generally improves or maintains the binding constant between polyamide and DNA [63-70]. Furthermore, incorporation of β or a related "molecular spring" [66] is necessary when working with long polyamides, in order to keep good alignment between hydrogen bonding groups on polyamides with those in the minor groove of DNA. In this area of research, it is therefore common to refer to a polyamide as having eight "rings" even if one or more of those rings has been replaced with β.

Methods
Synthetic chemistry
Synthesis and purification of polyamides was carried out by literature methods [71]. Compounds were characterized by HPLC/ms (ESI+), HRMS, and 500 or 600 MHz 1H NMR, 13C NMR and 2-D NMR techniques [37,39-42].

Biosensor surface plasmon resonance (SPR)
Measurements were performed with Biacore T100 and T200 SPR sensor systems as described [39]. A biotinylated hairpin DNA was attached to sensor chips functionalized with streptavidin. The DNA had the sequence 5'-biotin-CCTGGCCTCCTTTCGAGCCAAGG-3', where the bold, underlined region is the dsDNA recognition site for PAs KA1002, KA1007, and KA1055 and the italic T1 region forms the hairpin loop. DNA binding of PAs KA1063 and KA1065, and prior studies of KA1002 and KA1007, were described by a combination of orthogonal methods using several DNA targets; the methods included a novel fluorescence assay [40]. SPR as described above and quantitative DNase I footprinting analyzed by CE [51], and these results were reported in concert with other colleagues [37].

Results
One striking result is the relative antiviral activity against HPV16 of four molecules which are isomeric or nearly isomeric. These molecules are NV1020, NV1023, NV1028, and NV1030 as shown below, with their different internal β positions in bold text. The only other difference between these four compounds is at the γ turn. Please note that with over 100 PA compounds tested against HPV16, 18 and 31, we have not seen any advantage or systematic effect of using the chiral γ turn (R)-2,4-diaminobutyric acid, abbreviated as γ(NH2), in place of γ itself, even though the chiral reagent is reported to impart numerous beneficial properties on shorter PAs (including elimination of the reverse binding mode which we discuss below, and show in Figure 1) [72]. Here, we follow the literature naming conventions for PAs, where residues are referred to by their parent N-methylpyrrole and N-methylimidazole amino acid building blocks. Thus, dIm is the N-terminal des-amino-N-methyl imidazole-2-carboxylic acid, Py is 4-amino-2-carboxy-N-methyl pyrrole, Im is 4-amino-2-carboxy-N-methyl imidazole, γ is gamma-aminobutyric acid, which forms a hairpin turn for polyamides, Dp is dimethylaminopropylamine, NMe(CH2)3CH2NH2, and Ta is bis(aminoaryl)N-methylamine, NMe(CH2)3CH2NH2.

In the case of antiviral activity against HPV16, we have found better anti-HPV activity for Ta analogs much of the time, but there are a number of cases where the Dp analog is more active than its Ta counterpart, so there is no systematic preference for one amino tail over the other. A lack of preference was also found in the antiviral properties of PAs derived from γ and γ(NH2) as will be detailed elsewhere. NV1020, NV1023, NV1028 and NV1030 all recognize and bind identical DNA sites according to literature predictions (with W= A or T, the binding sites are either WGW7 or WWGW 7, depending on which binding mode one prefers) [24, 27]. However, the antiviral IC50 and IC90 values for these four compounds against HPV16, given in Table 1, fall into two dramatically different groups.

Interestingly, all compounds in Table 1 are relatively ineffectual against HPV18. For example, NV1028 has an IC50 of 0.7 μM and an IC90 10 μM against HPV18, while NV1030 has an IC50 of 0.42 μM and an IC90 10 μM against HPV18. Clearly, we wanted to understand the basis of these differences for such apparently degenerate PAs.

In order to map the position of NV1028 binding on HPV16 and 18, we performed DNase I footprinting following by capillary electrophoresis (CE), and also carried out affinity cleavage/CE [28,49-51] by attaching Fe(II) EDTA to the primary amine of the Ta group using literature methods to give NV1028-Fe (EDTA) [49,68]. A large study on the binding of NV1028 to HPV16 DNA is currently in press [73]. Using affinity cleavage, we identified fourteen binding sites for NV1028 in a section of the HPV18 including part of the LCR, spanning nucleotides 7647 to 157 of the circular, double-stranded DNA viral genome. The complete picture of PA-DNA binding is rather complex for discussion here, so we have provided a subset of data for two overlapping binding sites, a "forward" binding site with one mismatch and a "reverse" binding site with no mismatches (Figure 1A and B). By "forward orientation" we use the standard PA terminology where the N-C direction of the PA hairpin is oriented along the 5'-3' direction of the DNA. For the reverse orientation, the N-C direction of the hairpin is oriented along the 3'-5' direction of the DNA [74].

The dissociation constants for NV1028 at two HPV18 binding sites (1 and 2) are given in Table 2 and those same two binding sites are illustrated in Figure 1. The Kd values were determined by measuring the

| Compound | IC50 HPV16 (μM) | IC90 HPV16 (μM) | n (replicates) |
|----------|----------------|----------------|----------------|
| NV1020   | 5              | >10            | 4              |
| NV1023   | 5              | 10             | 2              |
| NV1028   | 0.10           | 1.3            | 4              |
| NV1030   | 0.13           | 1.3            | 4              |

Table 1: IC50 and IC90 values against HPV16 are shown for nearly isomeric polyamides NV1020, NV1023, NV1028 and NV1030, all with the same putative DNA recognition motif.
The particular helical nature of DNA gives a familiar 3' stagger to the cleavage patterns when cleavage occurs in the minor groove, which is the site of PA binding [79]. These comments help explain the appearance of Figure 1B.

In order to show the raw data used to generate both DNase I and affinity cleavage information by capillary electrophoresis, examples are given in Figure 2A-C.

To study the role of internal β residues in DNA recognition and binding thermodynamics, we turned to several series of smaller compounds that are more amenable to a number of thermodynamic techniques than the large, antiviral PAs. Some of these compounds are shown in Figure 3A-E. There are two parent compounds with all internal heterocycles, KA1002 and KA1063. Figure 3A shows KA1002, which has PA sequence dIm-Im-Py-Py-γ-Py-Im-Py-Py-β-Dp, and Figure 3D shows the control DNase I fragmentation (0 nM polyamide); (B) illustrates the region protected upon addition of 5 nM NV1028; (C) shows affinity cleavage where polyamide binds (the black bar above the sequence).
shows KA1063 with PA sequence dIm-Py-Py-γ-Py-Im-Im-Py-β-Dp. In a series of KA1002 analogs, two compounds were made that replaced one or the other bold Py shown in Figure 3 with β. The first analog shown is KA1007, Figure 3B, where the bold pyrrole in the top strand of hairpin KA1002 was replaced with β, and the second analog is KA1055, shown in Figure 3C, where the bold red Py of KA1002’s bottom strand was replaced with β. For additional comparison of the positional effects of β on PA-DNA binding parameters, the bold, blue Py of KA1063 (Figure 3D) was replaced to give KA1065 (Figure 3E).

In contrast to many literature reports [63-70], we found that the replacement of Py by β can have a significantly deleterious effect on PA-DNA binding. Figure 4 contains the relevant SPR data and global kinetic fits of that data. Thus, KA1002 binds DNA with a $K_d$ of 0.3-1.1 nM, depending on conditions (i.e. whether binding isotherms are obtained by fluorescence measurements of dye-labeled DNA in solution, by competition experiments for PA between labeled and unlabeled DNA [37,40] or by SPR at the solid-liquid interface [35,37,39]), but this weakens under those same experimental conditions (SPR, fluorescence or fluorescence competition [35,37,39]) to 35 - 83.4 - 325 nM upon substituting just one Py of the top strand with β to give KA1007 (Figure 3) [37,39]. In contrast, substitution of a Py on the bottom strand with β, giving KA1055, barely alters $K_d$ at all, with a measured value of 0.9 nM [39]. Similarly, the all heterocyclic KA1063 has a $K_d$ of 0.71 nM, but this increases to 70 or 106 nM, depending on measurement conditions, when a single Py is replaced with β to give KA1065 [35,37,39]. The reasons for these strong β effects could not be dissected into thermodynamic components $\Delta H$ and $T\Delta S$ because of solubility limitations and aggregation of the polyamides in isothermal calorimetry experiments, but we hope that new molecular designs will overcome these difficulties. Different aggregation states at different concentrations are likely the cause of the variations in $K_d$ measured by the various methods mentioned here. A slightly smaller, 6-ring PA proved sufficiently soluble to be amenable to complete and fruitful thermodynamic analyses [35,39].

**Discussion**

We have found that our long, antiviral polyamides are much more promiscuous at binding DNA than predicted by well-established rules of PA-DNA recognition. This promiscuity is based, we believe, on a large number of favorable enthalpic interactions such that one or more unfavorable interactions can be tolerated with no significant detriment to $K_d$. We have shown here that single base pair mismatches can still have $K_d$ values in the single digit nM region, similar to perfect match sites. Data on double and triple mismatches have been submitted for publication.

We should point out that the concept of “the binding constant to HPV16 or HPV18” has turned out to have no meaning, because we have discovered a large number of binding sites for various PAs on each HPV genome, essentially all with different binding constants, some with forward orientations, some with reverse orientations, some with orientations yet to be distinguished, and many with one or two mismatches. Furthermore, certain DNA sequences which we expected to bind particular PAs, e.g. NV1028, based on literature rules do not bind NV1028 at all. The details of these complex results will appear shortly for part of the HPV16 genome [73]. However, to date our results have covered about 50% of the HPV16 genome and about 20% of the HPV...
18 genome with 1–4 polyamides, and the binding sites and affinities in those genomes do not yet show any clear preference or higher affinity for active vs. inactive PAs. Furthermore, antiviral activity does not correlate with the $K_d$ values for PA-DNA binding events that we have characterized. In addition, we found poor correlation for reportedly degenerate aspects of PA sequences, such as $\beta$-alanine placement, with anti-HPV activity.

We do not yet have a molecular-level picture of the specific in vivo impact on the negatively supercoiled HPV episome of a large number of bound PA molecules, or how many PA molecules are bound per episome in a given cell. However, we started out to bind very specific viral DNA regions involved in replication and binding viral proteins and ended up with molecules able to bind many more sites on the 8 kb viral genome than expected. It is certainly tempting to invoke this promiscuous binding as a partial explanation of the broad-spectrum anti-HPV activity discovered for a subset of active compounds [41]. We will soon be able to compare the binding patterns for NV1028 on HPV16 and HPV18 DNA over quite a wide range of their genomes, to see if this sheds light on the relatively poor anti-HPV18 activity for this compound and dramatically better anti-HPV18 activity for related compounds.

Although the Py for $\beta$ exchange is reported in a great many cases to either improve or leave unchanged the $K_d$ for PA-DNA interactions and to improve properties of intermolecular DNA alkylation efficiency by reactive PAs [63–70], we have found quite a number of cases where swapping $\beta$ for Py is highly damaging to PA-DNA binding interactions. Most of these studies, whether our groups or by other groups, have been done on relatively similar, 6-8-ring polyamides. This set of seemingly contradictory results is certainly puzzling, and we don’t suggest that any prior results from other groups are incorrect. We instead conclude that it may not be possible yet to write completely general rules for PA-DNA recognition when $\beta$ is involved. Why would this be the case? The $\beta$-alanine unit has a very different hydrophobic surface area and set of possible shapes than the PA heterocycles Py and Im, and $\beta$ may be particularly sensitive to local changes in minor groove width and other DNA structural parameters that are (1) governed by DNA sequence context and (2) altered by complexes between DNA and minor groove-binders [80,81]. In fact, we have already begun to show such sequence context-driven effects to be important for PA-DNA recognition [39]. Therefore, although the small PAs we studied are quite far from our active antiviral compounds in molecular weight, there are definite parallels between 8 ring PAs and 14-ring or larger PAs in the currently unpredictable nature of how Py/$\beta$ substitutions affect biological and biochemical activities. We hope to expand the understanding of molecular recognition with polyamides so it reaches the levels we have begun to expect from the literature.

Conclusions

Recent work has discovered an entirely novel mechanism of action for polyamides as antiviral agents [36]. That work, largely by CF and TGE, used gene expression arrays, siRNA libraries and pharmacology to show how active antiviral polyamides elicit a DNA Damage Response (DDR) to destroy viral DNA when used to treat HPV-positive, precancerous cells [36]. No such response was triggered by inactive polyamides, nor was the equivalent DDR elicited in HPV-negative cells or in cells having integrated HPV. Evidence was also found of HPV episomal DNA in multiple, unusual supercoiled states. These findings lead us to suggest that the interaction of polyamides with viral DNA sequences in the context of a small circular episome is the key to triggering events that ultimately result in viral DNA elimination. An important challenge now is to find the molecular and biophysical links between polyamide-DNA interactions (or other polyamide interactions) and activation of the DDR. We have established that the location of $\beta$-alanine building blocks can be much more complex than the literature led us to predict. These complications caused $\beta$ depending on positioning of this aliphatic building block, and had large consequences for (a) the biophysical parameters of 8-ring polyamides binding to DNA [35,37,39,40] and (b) the ability of nearly identical 14-ring polyamides to show antiviral activity in human cell and tissue culture [36,38,41] against HPV16, 18 and 31.

Disclosure

JKB and CF hold major ownership positions in NanoVir, LLC.

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References

1. Li BC, Montgomery DC, Puckett JW, Dervan PB (2013) Synthesis of cyclic Py-Im polyamide libraries. J Org Chem 78: 124–133.
2. Raskatov JA, Meier JL, Puckett JW, Yang F, Ramakrishnan P, et al. (2012) Modulation of NF-kB-dependent gene transcription using programmable DNA minor groove binders. Proc Natl Acad Sci USA 109: 1023–1026.
3. Cho J, Parks ME, Dervan PB (1995) Cyclic polyamides for recognition in the minor groove of DNA. Proc Natl Acad Sci USA 92: 10389-10392.
4. Kawamoto Y, Bando T, Kamada F, Li Y, Hashiaka K, et al. (2013) Development of a new method for synthesis of tandem hairpin pyrrole-imidazole polyamide probes targeting human telomerases. J Am Chem Soc 135: 16468-16477.
5. Zhang HF, Wu YL, Jiang SK, Wang P, Sugiyama H, et al. (2012) Recognition by nonaromatic and stereochemical subunit-containing polyamides of the four Watson-Crick base pairs in the DNA minor groove. ChemBioChem 13: 1367-1374.
6. Yasuda A, Noguchi K, Minoshima M, Kashiwazaki G, Kanda T, et al. (2011) DNA ligand designed to antagonize EBN1 represses Epstein-Barr virus-induced immortalization. Cancer Sci 102: 2221-2230.
7. Fujitani M, Jiao Z, Saito I, Sugiyama H (1999) Synthesis of pyrrole-imidazole-ducarmycin polyamide and its sequence selective DNA alkylation. Nucleic Acids Symp Ser: 249-250.
8. Satam V, Babu B, Chavda S, Savagian M, Spholm R, et al. (2012) Novel diaminimidazole and pyrrole-containing polyamides: Synthesis and DNA binding studies of mono- and diaminophenylimPy*Im polyamides designed to target S-AGCGTG-3’. Bioorg Med Chem 20: 693-701.
9. Mackay H, Brown T, Sexton JS, Kotecha M, Nguyen B, et al. (2008) Targeting the inverted CCAAAT Box-2 of the topoisomerase IIalpha gene. DNA sequence selective recognition by a polyamide-intercalator as a staggered dimer. Bioorg Med Chem 16: 2093-2102.
10. Lacy ER, Le NM, Price CA, Lee M, Wilson WD (2002) Influence of a terminal formamido group on the sequence recognition of DNA by polyamides. J Am Chem Soc 124: 2153-2163.
11. Lacy ER, Cox KK, Wilson WD, Lee M (2002) Recognition of T*G mismatched base pairs in DNA by stacked imidazole-containing polyamides: surface plasmon resonance and circular dichroism studies. Nucleic Acids Res 30: 1834-1841.
12. Maeshima K, Janssen S, Laemmli UK (2001) Specific targeting of insect and vertebrate telomeres with pyrrole and imidazole polyamides. EMBO J 20: 3218-3228.
13. Janssen S, Durussel T, Laemmli UK (2000) Chromatin opening of DNA satellites by targeted sequence-specific drugs. Mol Cell 6: 999-1011.
14. Janssen S, Cuver O, Müller M, Laemmli UK (2000) Specific gain- and loss-of-function phenotypes induced by satellite-specific DNA-binding drugs fed to Drosophila melanogaster. Mol Cell 6: 1013-1024.
15. Liu B, Koddek T (2009) Investigation of the relative cellular permeability of DNA-binding pyrrole-imidazole polyamides. J Med Chem 52: 4604-4612.
35. Koeller KJ, Davis Harris G, Aston K, He G, Castaneda CH, Thornton MA, et al. (2014) DNA Binding Polyamides and the Importance of DNA repair genes controlling human papillomavirus (HPV) episome levels under different thermodynamic signatures for DNA minor groove binding with an alpha-substituted-gamma-aminobutyric acid as a 5'-TG-3' reader in the DNA bases of a DNase I footprint by the use of dye primer sequencing on capillary DNA sequencer. Biotechniques 29: 1034-1041.

36. Wang S, Bashkin JK, Bashkin JK, Wilson WD (2012) Correlation of local effects of DNA sequence and position of β-alanine inserts with polyamide-DNA complex binding affinities and kinetics. Biochemistry 51: 9796-9806.

37. Durepura CM, Bashkin JK, Aston K, Koeller KJ, Gaston KR, et al. (2012) Fluorescence assay of DNA-DNA interactions. Anal Biochem 423: 176-183.

38. Edwards TG, Koeller KJ, Slomczyńska U, Fok K, Helmus M, et al. (2011) HPV episome levels are potently decreased by pyrrole-imidazole polyamides. Antiviral Res 91: 177-186.

39. Crowley KS, Philion DP, Woodard SS, Schweitzer BA, Singh M, et al. (2003) Controlling the intracellular localization of fluorescent pyrrole analogues in cultured cells. Bioorg Med Chem Lett 13: 1565-1570.

40. He G, Koeller KJ, Harris GD, Durepura CM, Bashkin JK (2012) DNA binding properties of a large antiviral polyamide via capillary electrophoresis. Abstracts of the 243rd American Chemical Society National Meeting, 2012, San Diego, CA, USA, BIOL-254.

41. Nishijima S, Shinohara K, Bando T, Minoshima M, Kashiwazaki G, et al. (2010) Cell permeability of Py-Im-polyamide-fluorescein conjugates: Influence of molecular size and PyLin content. Bioorg Med Chem 18: 978-983.

42. Wilson DO, Johnson P, McCord BR (2001) NonradiochemicalDNAase I footprinting by capillary electrophoresis. Electrophoresis 22: 1979-1986.

43. Floreancig PE, Swalley SE, Trauer JW, Dervan PB (2000) Recognition of the Minor Groove of DNA by Hairpin Polyamides Containing α-Substituted-β-Amino Acids, J Am Chem Soc 122: 6342-6350.

44. Neamatli N, Mazumder A, Sunder S, Owen JM, Tandon M, et al. (1998) Highly potent synthetic polyamides, bist dialcynamics, and lexitropsins as inhibitors of human immunodeficiency virus type 1 integrase. MolPharmacol 54: 280-290.

45. Dabrowiak JC, Goodisman J, Kissingler K (1990) Thermodynamic data from drug-DNA footprinting experiments. Biochemistry 29: 6139-6145.

46. Farkas ME, Tsai SM, Dervan PB (2007) Alpha-diaminobutyric acid-linked hairpin polyamides. Bioorg Med Chem 15: 6927-6936.

47. Swalley SE, Baird EE, Dervan PB (1997) Discrimination of 5'-GGGG-3', 5'-GGCG-3', and 5'-GGCC-3' Sequences in the Minor Groove of DNA by Eight-Ring Hairpin Polyamides, J Am Chem Soc 119: 6693-6691.

48. He G, Vasileeva E, Bashkin JK, Durepura CM (2013) Mapping small DNA ligand hydroxyl radical footprinting and affinity cleavage products for capillary electrophoresis, Anal Biochem 439: 99-101.

49. Mitra S, Shcherbakova IV, Altman RB, Breenowitz M, Laederach A (2008) High-throughput single-nucleotide structural mapping by capillary automated footprinting analysis. Nucleic Acids Res 36: e63.

50. Zianni M, Tessanne K, Merighi M, Lagarina R, Tabita FR (2006) Identification of the DNA bases of a DNase I footprint by the use of dye primer sequencing on an automated capillary DNA analysis instrument. J Biomol Tech 17: 103-113.

51. Yindeeyoung Y, Schell MA (2000) Footprinting with an automated drug-DNA footprinting experiments. Biochemistry 29: 6139-6145.

52. Garner-Hamrick PA, Fisher C (2002) HPV episomal copy number closely correlates with cell size in keratinocyte monolayer cultures. Virology 301: 334-341.

53. Stubenrauch F, Laimins LA (1999) Human papillomavirus life cycle: active and latent phases. Semin Cancer Biol 9: 379-386.

54. Meyers CM (1999) Artificial system for the production of infectious human papillomavirus. Patent US 5994415 WO 1999004811A1.

55. Laimins LA (1993) The biology of human papillomaviruses: from warts to cancer. Infect Agents Dis 2: 74-86.

56. Coutlee F, Bobo L, Abbass H, Dalabetta G, Hook NE, et al. (1992) Detection of HPV-16 in cell lines and cervical lavage specimens by a polymerase chain reaction-enzyme immunoassay assay. J Med Virol 37: 22-29.

57. Park JS, Rader JS, Wu TC, Laimins LA, Currie JL, et al. (1991) HPV-16 viral transcripts in vulvar neoplasia: preliminary studies. Gynecol Oncol 42: 250-255.

58. Bradford CR, Zaacks SE, Androphy EJ, Greigore L, Lancaster WD, et al. (1991) Human papillomavirus DNA sequences in cell lines derived from head and neck squamous cell carcinomas. Otolaryngol Head Neck Surg 104: 303-310.

Citation: Koeller KJ, Davis Harris G, Aston K, He G, Castaneda CH, Thornton MA, et al. (2014) DNA Binding Polyamides and the Importance of DNA Recognition in their use as Gene-Specific and Antiviral Agents. Med chem 4: 338-344. doi:10.4172/2161-0444.1000162
63. Turner JM, Swalley SE, Baird EE, Dervan PB (1998) Aliphatic/Aromatic Amino Acid Pairings for Polymide Recognition in the Minor Groove of DNA. J Am Chem Soc 120: 6219-6226.

64. Baird EE, Dervan PB (1996) Solid Phase Synthesis of Polyamides Containing Imidazole and Pyrrole Amino Acids. J Am Chem Soc 118: 6141-6146.

65. Herman DM, Baird EE, Dervan PB (1998) Stereocchemical Control of the DNA Binding Affinity, Sequence Specificity, and Orientation Preference of Chiral Hairpin Polyamides in the Minor Groove. J Am Chem Soc 120: 1382-1391.

66. Trauger JW, Baird EE, Dervan PB (1996) Extended hairpin polyamide motif for sequence-specific recognition in the minor groove of DNA. Chem Biol 3: 369-377.

67. He G, Vasilieva E, Harris JGD, Koeller KJ, Bashkin JK, et al. (2014) Binding Studies of a Large Antiviral Polyamide to a Natural HPV Sequence, Biochimie DOI:10.1016/j.biochi.2014.02.011.

68. Rucker VC, Melander C, Dervan PB (2003) Influence of β-alanine on hairpin polyamide orientation in the DNA minor groove. Helv Chim Acta 86: 1839-1851.

69. Ramos JP, Babu B, Chavda S, Liu Y, Plaunt A, et al. (2013) Affinity and kinetic modulation of polyamide-DNA interactions by N-modification of the heterocycles. Biopolymers 99: 497-507.

70. Leblanc B, Moss T (2009) DNase I footprinting. Methods Mol Biol 543: 37-47.

71. Vashisht Gopal YN, Van Dyke MW (2003) Combinatorial determination of sequence specificity for nonmolar DNA-binding hairpin polypeptides. Biochemistry 42: 6891-6903.

72. Lee M, Shea RG, Hartley JA, Kissinger K, Pon RT, et al. (1989) Molecular recognition between oligopeptides and nucleic acids: sequence-specific binding of the naturally occurring antibiotic (4S) (+)-anthelvencin A and its (4R)(-) enantiomer to deoxyribonucleic acids deduced from proton NMR, footprinting, and thermodynamic data, J Am Chem Soc 111: 345-354.

73. Taylor JS, Schultz PG, Dervan PB (1984) DNA affinity cleaving: Sequence specific cleavage of DNA by Distamycin-EDTA-Fe(II) and EDTA-distamycin Fe(II). Tetrahedron 40: 457-465.

74. Urbach AR, Love JJ, Ross SA, Dervan PB (2002) Structure of a beta-alanine-linked polyamide bound to a full helical turn of purine tract DNA in the 1:1 motif. J Mol Biol 320: 55-71.

75. Dervan PB, Urbach AR (2001) The importance of β-alanine for recognition of the minor groove of DNA. Essays Contemp Chem 327-339.

76. Swalley SE, Baird EE, Dervan PB (1999) Effects of γ-Turn and β-Tail Amino Acids on Sequence-Specific Recognition of DNA by Hairpin Polyamides. J Am Chem Soc 121: 1113-1120.

77. Trauger JW, Baird EE, Mrksich M, Dervan PB (1996) Extension of Sequence-Specific Recognition in the Minor Groove of DNA by Pyrrole-Imidazole Polyamides to 9-13 Base Pairs. J Am Chem Soc 118: 6160-6166.

78. Han YW, Kashiwazaki G, Morinaga H, Matsumoto T, Hashiya K, et al. (2013) Effect of single pyrrole replacement with β-alanine on DNA binding affinity and sequence specificity of hairpin pyrrole/imidazole polyamides targeting 5'-GGCG-3'. Bioorg Med Chem 21: 5436-5441.

79. Minoshima M, Bando T, Sasaki S, Fujimoto J, Sugiyama H (2008) Pyrrole-imidazole hairpin polyamides with high affinity at 5'-GGCG-3' DNA sequence; influence of cysteine methylation on binding. Nucleic Acids Res 36: 2889-2894.

80. Tevis DS, Kumar A, Stephens CE, Boykin DW, Wilson WD (2009) Large, sequence-dependent effects on DNA conformation by minor groove binding compounds. Nucleic Acids Res 37: 5550-5558.

81. Hunt RA, Munde M, Kumar A, Ismail MA, Farahat AA, et al. (2011) Induced topological changes in DNA complexes: influence of DNA sequences and small molecule structures, Nucleic Acids Res 39: 4265-4274.