

PNA comes of age: from infancy to maturity



'The PNA story is truly an amazing one.'

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Ten years have now passed since the publication, in the December 1991 issue of *Science* [1], of the landmark article describing the unusual properties of the first peptide or polyamide nucleic acid (PNA). Since then, we have witnessed a tremendous flurry of activity caused by this seminal discovery: hundreds of scientific papers are presently published in the area of PNA research and dozens of patents cover the use of PNA in a variety of biotechnological and diagnostic applications. Emerging PNA-based technologies now promise many innovative developments, and potential PNA-derived therapeutics could advance the treatment of drug-resistant infectious diseases and be employed as a successful cure for cancer. Consequently, several biotech and pharma companies are intensely engaged in the PNA business.

I have been involved with PNA research virtually from its inception, revealing some of the features of PNA and contributing in several applications of PNAs as biomolecular tools and diagnostics. My impression of this unique class of molecules was expressed in 1995 by Mark Matteucci, then Director of Bioorganic Chemistry at Gilead Sciences (Foster City, CA, USA): 'The PNA story is truly an amazing one.' In this editorial, I would like to highlight some lessons from that story. I hope that these points will encourage and inspire those scientists who are eager to further research into this promising drug.

Lesson one: even rational drug design can yield fortunate surprises

Occasionally, a rational search for a new drug can result in the unexpected. The recent PNA development represents a bright and vivid example.

PNA is a synthetic pseudopeptide DNA/RNA mimic, which was functionally designed to be a sequence-specific DNA groove binder [1]. Unexpectedly, it was found that PNA binds to the designated site of duplex DNA by strand displacement, forming an exceptionally stable invasion triplex – the P-loop. This unusual mode of ligand–DNA interaction was found to be useful for DNA diagnostics and molecular biotechnology assays [2], some of which were rapidly developed and their number is continuing to grow each year. As a result, so-called PNA openers became a powerful biomolecular tool with numerous applications [3–6]. Site-directed triplex-forming strand invasion makes PNA a promising lead for gene therapeutic drugs [7,8].

Furthermore, it was realized that PNA has a robust antisense and similar RNA-targeting potentials, which are advantageous, in some aspects, over those of common oligonucleotides and their analogs [9,10]. Thus, there is a strong belief that the PNA methodology could readily generate potent antisense and anticancer therapeutics, along with the new types of antiviral and antimicrobial drugs. At present, the need for novel antivirals and antimicrobials is enormous because of the global HIV epidemic, escalating worldwide antibiotic resistance and the threatening expansion of protozoan infections in the Developing World. By contrast, the progress in these directions is somewhat slow. Therefore, it is satisfying that the PNA-based prototypes of some antimicrobial drug candidates are now under development [11,12]. In addition, efficient PNA hybridization to RNA analytes has yielded sensitive diagnostics for enteric, and other, pathogens [13,14].

The unplanned outcome of the rational structure-based PNA design is not an unprecedented situation for drug discovery and development. Acetylsalicylic acid – or aspirin – is another famous example: purposely synthesized as a salicylic acid derivative primarily for use in treating fevers, pain and inflammation, it now looks promising for preventing cardiovascular diseases and certain cancers [15].

Lesson two: initial major limitations to the drug efficacy could be overcome

From the very beginning, there appeared to be little doubt that PNA would become a useful biomolecular tool with many applications [1,16]. But there was skepticism that PNA-based drugs could ever be developed, which was based

on potential substantial limitations of the *in vivo* efficacy of PNA. Insufficient aqueous solubility and poor spontaneous cellular uptake could limit the potential therapeutic applications [2,16,17]. Also, the PNA gene-targeting strategy was limited by the requirements of low salt conditions and mainly purine DNA targets [6–8,18].

Because of these problems, some companies and academic research groups significantly curtailed, or even completely cut, their initial involvement in PNA research. But those who were more enthusiastic about the development of PNA-based drugs did not give up and have recently made significant progress that partially, or completely, dismissed all original difficulties with PNA [7,8,19–22]. Several effective approaches for intracellular PNA delivery and subcellular trafficking [19,22] and the enhancement of PNA solubility [23] were successfully demonstrated. Important advances have been made enabling the PNA to be used under physiological ionic concentrations, as well as extending the PNA sequence repertoire for gene-targeting purposes far beyond the homopurine motif [21,24].

These achievements will certainly aid in developing the PNA therapeutic potential to the full. Accordingly, this places PNA among the most promising nucleic acid drug candidates. It is also a well-deserved reward to the PNA advocates.

Lesson three: a fruitful idea could generate numerous offspring

There were previous attempts to combine some fragments of nucleic acids and proteins within so-called nucleopeptides or nucleoamino acids to acquire a new functionality [25–27]. However, none of them was as prosperous as in the PNA case. The success of PNA has stimulated the synthesis of numerous PNA modifications and the search for other related nucleic acid analogs [2,28,29]. To demonstrate how large the current PNA-like group of prospective drugs is, here is the list of some of these relatives: APNA, α -PNA, aepPNA, F-PNA, HypNA, NAAP, pPNA, and Z-OPA, along with DNA-PNA, peptide-PNA and PHONA-PNA chimeras.

Inspired by PNA, all these novel polyamide-based nucleic acid derivatives significantly extend the abilities of DNA/RNA mimics in terms of their future biomedical applications. This booming growth of the PNA-related family indicates that a clever conception in the field of drug design has a strong creative potential.

Epilogue

As the short PNA story shows, persistence in reaching the goal can make all the difference. Importantly, 10 years of PNA is a relatively short time period for such a notable success given that it usually takes 20 years to translate the drug research into clinical applications. I am very optimistic,

as are many of my colleagues, that this unique class of molecules will ultimately result in new powerful drugs: there is every prospect that in its second decade PNA will realize in full its enormous practical potential. So, Happy Birthday, PNA!

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Clovis-age sites in North America are overlain by a thin, discrete layer with varying peak abundances of (i) magnetic grains with iridium, (ii) magnetic microspherules, (iii) charcoal, (iv) soot, (v) carbon spherules, (vi) glass-like carbon containing nanodiamonds, and (vii) fullerenes with ET helium, all of which are evidence for an ET impact and associated biomass burning at ≈ 12.9 ka. Ten Clovis and equivalent-age sites were selected because of their long-established archeological and paleontological significance, and, hence, most are well documented and dated by previous researchers (see SI Table 2). Two are type-sites where unique PaleoAmerican projectile point styles were first named: the Clovis-point style at Blackwater Draw, NM, and the Gainey-point style at Gainey, MI. When Qi Xingchen transmigrated, he transmigrated into a fiction book set in the entertainment industry as cannon fodder and was lucky enough to have an entire family of cannon fodder. The kind of cannon fodder whose names would only appear once on their tombstone and were all eventually killed off by the male protagonist. With regards to this, Qi Xingchen understands that what goes around comes around. He only prays to go through the entire plotline such that he can return to the real world. But when he understands his family's style "CF (cannon fodder) Dad: I bought a private airplane for you, it's currently at the apron beside our family's mine. Is that enough for you to play around for half a month? CF older brother: Here's a Hollywood co-production film and the hottest IP drama... In genre studies, a coming-of-age story is a genre of literature, film, and video that focuses on the growth of a protagonist from youth to adulthood ("coming of age"). Coming-of-age stories tend to emphasize dialogue or internal monologue over action, and are often set in the past. The subjects of coming-of-age stories are typically teenagers. The Bildungsroman is a specific subgenre of coming-of-age story. A brief description of the manga I Became a Legend a Decade Later After Telling My Comrades to Leave Everything to Me and Retreat First: The Hero's party was attacked by a large group of powerful devils. The party will no doubt be annihilated if this were to go on. One member of the party, the strongest mage, Rakku decided to stop the enemies in their tracks. Show more. MANGA DISCUSSION. Local Disqus. Leave a Reply Cancel reply. Your email address will not be published. Required fields are marked *. Name *. Email *. Website. Save my name, email, and website in this browser for the next time I comment. 5 Comments. Specter. "The PNA story is truly an amazing one." Vadim V. Demidov, Senior Research Scientist and Freelance Science Writer, Center for Advanced Biotechnology, Boston University. Ten years have now passed since the publication, in the December 1991 issue of Science [1], of the landmark article describing the unusual properties of the first peptide or polyamide nucleic acid (PNA). PNA is a synthetic pseudopeptide DNA/RNA mimic, which was functionally designed to be a sequence-specific DNA groove binder [1]. Unexpectedly, it was found that PNA binds to the designated site of duplex DNA by strand displacement, forming an exceptionally stable invasion triplex "the P-loop.