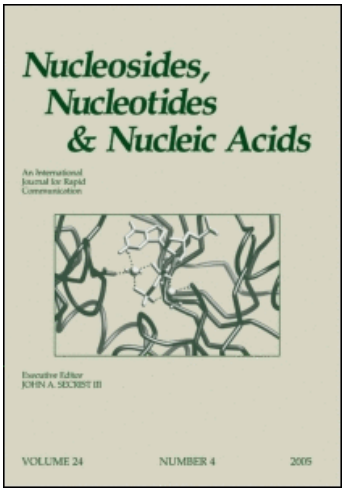

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Biological Properties of Antisense Oligonucleotides Conjugated to Different High-Molecular Mass Poly(Ethylen Glycols)

G. M. Bonora[a]; E. Ivanova[b]; N. Komarova[b]; D. Pishiniyi[b]; P. Vorobjev[b]; V. Zarytova[b]; S. Zaramella[c]; F. M. Veronese[c]
[a] Pharmaco-Chemico Dept., University of Cagliari, Cagliari, (Italy) [b] Institute of Bioorganic Chemistry - Novosibirsk, (Russia) [c] Dept. of Pharmaceutical Sciences, University of Padova, Padova, (Italy)

To cite this Article Bonora, G. M. , Ivanova, E. , Komarova, N. , Pishiniyi, D. , Vorobjev, P. , Zarytova, V. , Zaramella, S. and Veronese, F. M.(1999) 'Biological Properties of Antisense Oligonucleotides Conjugated to Different High-Molecular Mass Poly(Ethylen Glycols)', Nucleosides, Nucleotides and Nucleic Acids, 18: 6, 1723 — 1725
To link to this Article: DOI: 10.1080/07328319908044834
URL: http://dx.doi.org/10.1080/07328319908044834

NUCLEOSIDES & NUCLEOTIDES, 18(6&7), 1723–1725 (1999)

BIOLOGICAL PROPERTIES OF ANTISENSE OLIGONUCLEOTIDES CONJUGATED TO DIFFERENT HIGH-MOLECULAR MASS POLY(ETHYLEN GLYCOLS).

G. M. Bonora[$*], E. Ivanova[#] N. Komarova[#], D. Pishiniyi[#], P. Vorobjev[#], V. Zarytova[#], S. Zaramella[&], and F.M. Veronese[&].
[$]Pharmaco-Chemico Dept. - University of Cagliari - Cagliari (Italy)
[#]Institute of Bioorganic Chemistry - Novosibirsk (Russia)
[&]Dept. of Pharmaceutical Sciences - University of Padova - Padova (Italy)

ABSTRACT: The effect of the different structures of high-molecular weight poly(ethylen glycol) chains on the biological properties of the conjugated antisense oligonucleotide has been investigated and compared.

The chemical conjugation of antisense oligonucleotides with high-molecular mass poly(ethylene glycols) (PEGs) has been proposed to overcome some major drawbacks in their pharmacological application, owing to the advantageous amphiphilicity and absence of toxicity of this polymeric moiety[1]. Recently the PEG molecule has been also proposed as soluble supports in the liquid-phase synthesis of oligonucleotides, and this synthetic method has been applied to the production of oligonucleotides conjugated both to linear high-molecular weight monomethoxy poly(ethylen glycol) (MPEG) [2] as well as to a new branched derivative $(MPEG)_2$ [3].

The thermal denaturation of the two duplexes formed by equimolecolar concentrations of linear and branched MPEG (M.W. = 10.000 Da) conjugated with a sample 12mer antisense and of the complementary target were examined. Only a very little reduction of the duplex stability was observed for the two derivatives when compared to the native sequence (FIGURE 1). The effect of the stabilization against the enzymatic degradation

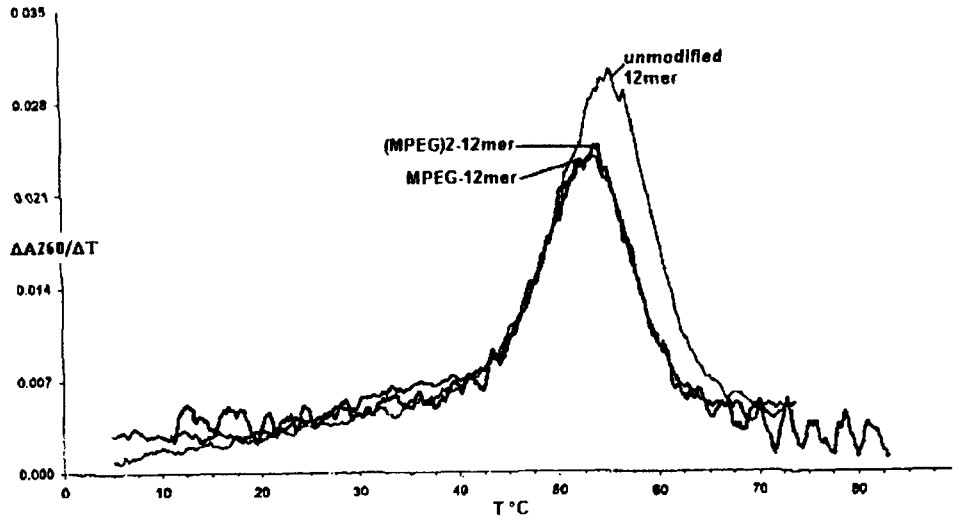

FIGURE 1. Melting behavior :I[st] derivative curve of A_{260} as a function of temperature

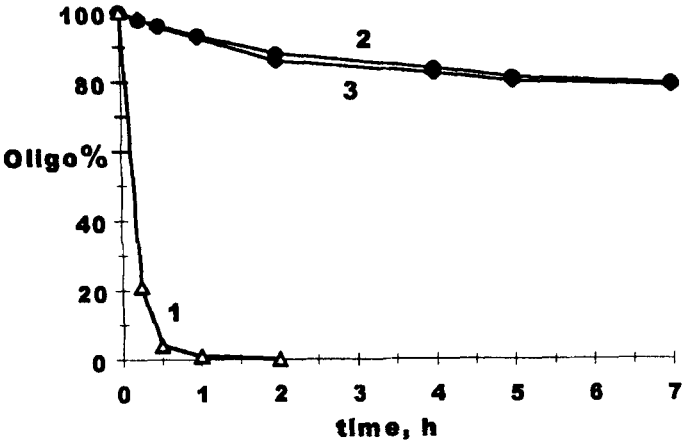

FIGURE 2. Enzymatic stability of : **1.** unmodified 12mer, **2.** MPEG-conjugated, and **3.** $(MPEG)_2$-conjugated against a 1:1 mixture of diesterase and 5'-nucleotidase.

was also investigated .The experimental conditions were the same reported in the previous paper [2], but a lower temperature (20 °C) was employed to better differentiate between linear and branched MPEGs effect (FIGURE 2).

It has been confirmed that the introduction of an high-molecular weight MPEG component stabilizes its oligonucleotide conjugated against the enzymatic attack, with an almost equal effect between the linear and the branched component, and without hampering their regular duplex-formation capability.

REFERENCES

1. Tarasow, M. T. ; Timmermeier, D. ; Zyzniewski, K. *Bioconjugate Chem.* **1997** ***8***, 89-93 and references therein included.
2. Bonora, G. M. ; Ivanova, E. ; Zarytova, V. ; Burcovich, B. ; Veronese, F. M. *Bioconjugate Chem.* **1997** ***8***, 793-797
3. Burcovich, B. ; Veronese, F.M. ; Zarytova, V. ; Bonora, G.M. *Nucleosides Nucleotides* **1998**, in press.