Regulation of gene expression in all living cells rests upon selective interactions of regulatory proteins with specific nucleic acid sequences. In addition bacteria use short RNA transcripts to control the replication of plasmid DNA or translation of some mRNAs. Synthetic oligodeoxynucleotides have been used to block mRNA translation selectively (for review see Toullé & Hélène, 1988). The utilisation of oligonucleotides in vivo faces two main problems: (1) they penetrate rather poorly across cell membranes and (2) they are degraded by nuclease. The second problem has been solved by synthesising nuclease-resistant analogues of oligodeoxynucleotides. This can be achieved by replacing the phosphate group by a methylphosphonate or a phosphorothioate or by changing the anomeric configuration of the nucleoside units from β to α.

In this review I will briefly describe the approach we have been following to design new oligodeoxynucleotide derivatives that can be used to control gene expression at different levels. The binding of an oligonucleotide to its complementary sequence can be strongly enhanced by attaching an intercalating agent to one (or both) end(s) of the oligonucleotide. Besides increasing the binding strength the intercalating agent improves cellular uptake of the oligonucleotide and protects it against exonucleases. The oligonucleotide can be further substituted by a reactive group that can be activated chemically or photochemically to induce irreversible reactions in the target nucleic acid. In addition to binding mRNAs oligonucleotides can be designed to bind to duplex DNA, which opens new ways to control gene expression at the transcriptional level.

**Design of oligonucleotides covalently linked to intercalating agents as specific gene control elements**

The first question that is raised concerns the specificity of biological effects of synthetic oligonucleotides: what should be the minimum length that the oligonucleotide should have in order to recognise a single target in either a genome or a messenger RNA population? No bacterial or eukaryotic genome has been totally sequenced yet. Assuming a statistical distribution of nucleotides it is possible to calculate that, on average, an oligonucleotide 12 nucleotides in length should be sufficient to recognise a single sequence in the E. coli genome. In human cells where the (A+T)/(G+C) ratio is around 0.6 the minimum length should range from 15 (only Gs and Cs in the oligonucleotide) to 19 (only As and Ts) when a genomic sequence is the target, and from 11 to 15 if the target is a mRNA (assuming that about 0.5% of the genome is transcribed into mRNA in a given cell type). The calculated length depends on the actual sequence, especially for (G+C)-rich oligonucleotides, because one dinucleotide sequence, CpG, is under-represented in eukaryotic genomes as compared to a statistical distribution.

The conclusion that these calculations suggests is that short oligonucleotides are sufficient to attain a high selectivity of biological effects. There are many advantages to using short oligomers including the absence of secondary structures (hairpins), easier synthesis and purification (especially when chemical modifications are introduced) and easier cell uptake. In order to keep the advantages of using short oligonucleotides but to improve the binding to a complementary sequence we have covalently attached intercalating agents to one (or both) end(s) (Asseline et al., 1983, 1984). The complex that is formed involves not only base pairing and base pair stacking but also intercalation between terminal base pairs of the mini-duplex structure. The additional binding energy due to intercalation strongly stabilizes the complex without altering the oligonucleotide specificity.

In addition to stabilising the complex formed by an oligodeoxynucleotide with its complementary sequence the intercalating agent improves the penetration across cell membranes and protects the oligodeoxynucleotide against exonucleases.

**Biological effects of oligonucleotides covalently linked to intercalating agents**

*Inhibition of mRNA translation*

Oligonucleotide-intercalator conjugates were used to inhibit both prokaryotic (Toullé et al., 1986) and eukaryotic (Cazenave et al., 1987a) mRNA translation in cell-free extracts. Microinjection into Xenopus laevis oocytes showed that translation inhibition occurred in an intact living cell (Cazenave et al., 1987a). The mechanism of the inhibitory effect was analysed further. It turned out that a cellular component played an essential role. A ribonuclease, known as RNase H, recognised the mRNA-oligodeoxynucleotide hybrid and cleaved the RNA part. This effect was specific for oligodeoxynucleotides since RNase H recognises RNA-DNA and not RNA-RNA hybrids. Cleavage of the mRNA induced an irreversible block of mRNA translation.

*Anti-viral effects*

**Influenza virus** The eight RNAs that constitute the genome of influenza virus have a common sequence at their 3'-end. This sequence was chosen as a target for oligonucleotide-intercalator conjugates. The cytopathic effect of type A influenza virus on MDCK cells in culture was blocked by a heptanucleotide covalently linked to an acridine derivative. In vitro studies showed that the RNA transcriptase of the virus was inhibited. The effect was sequence-specific. A type B influenza virus which differs from a type A virus by the sequence of the 3'-termini was not inhibited by the oligonucleotide directed against the type A sequence (Zerial et al., 1987).

**Oncogenic virus SV40** An oligonucleotide-intercalator conjugate complementary to a sequence present in the origin
of replication of the viral SV40 DNA inhibited the cytopathic effect of the virus on CVI cells in culture. DNA replication was blocked in a sequence-specific manner. Binding of the oligonucleotide to the transiently open origin of replication or triple helix formation (see below) might account for the observed effect.

**Anti-parasitic effects**

The mRNAs of trypanosomes, the parasites responsible for sleeping sickness, have a common sequence of 39 nucleotides at their 5′-end. Translation of all mRNAs species could be inhibited in vitro by a nonanucleotide–intercalator conjugate targeted to part of this common sequence. Protein synthesis was completely abolished. The same oligonucleotide killed procyclic forms of the parasite in a culture medium. The observed effect was sequence-specific and was not observed when the oligonucleotide was not covalently linked to the acridine derivative (Verspiere et al., 1987). Other parasites such as leishmania also have a common sequence at the 5′-end of their mRNA. Protein synthesis can be selectively inhibited by oligonucleotide–intercalator conjugates.

**Inhibition of oncogenes**

Oncogenes are cellular genes that are activated in tumour cells as a result of translocation, gene amplification or mutations. We have designed short oligonucleotide–intercalator conjugates targeted to the human c-myc and Ha-ras mRNAs. In a cell-free system the translation of these mRNAs is efficiently inhibited. The inhibition depends on the presence of RNase H which hydrolyses the mRNAs when hybridised to the oligodeoxynucleotide. In cells in culture several laboratories have reported that myc gene expression could be inhibited by an unsubstituted oligodeoxynucleotide, 15 in length, targeted downstream of the AUG initiation codon (Heikka et al., 1987; Holt et al., 1988; Harel-Bellan et al., 1988; Wickström et al., 1988). Using the T24 cell line derived from a bladder carcinoma in which the Ha-ras gene is activated by a mutation in the 12th codon we were able to show that an oligonucleotide–acridine conjugate targeted to a sequence overlapping the mutation inhibited cell division and changed the cell morphology (T. Saison-Behmoaras et al., to be published).

**Irreversible reactions induced in target nucleic acids**

In all examples briefly described above the oligodeoxynucleotide–intercalator conjugate binds reversibly to its target mRNA or viral RNA. In several cases it has been demonstrated that the mRNA is irreversibly inactivated as a result of its being cleaved by RNase H, which recognises the mRNA–oligodeoxynucleotide hybrid (Cazenave et al., 1987a). However, the oligodeoxynucleotide is itself sensitive to DNases. Therefore several modifications were introduced into the oligonucleotide in order to make it resistant to nucleases. The phosphate group can be replaced by a methylphosphonate or by a phosphorothioate (Marcus-Sekura et al., 1986). The natural α- anomers of the nucleotide units can be replaced by their synthetic α-anomers (Morvan et al., 1987; Thuong et al., 1987). Oligo-(α)-deoxynucleotides can be covalently linked to intercalating agents (for review see Hélène & Thuong, 1988). They bind in a parallel orientation with respect to their complementary sequence. Oligophosphorothioates form RNase H-sensitive hybrids with RNAs (Stein et al., 1988). However, oligomethylphosphonates (unpublished results) and oligo-(α)-deoxynucleotides (Gagnon et al., 1987) form hybrids with RNAs which are not cleaved by RNase H. These modified oligonucleotides are resistant to DNases and therefore their lifetime in living cells is considerably increased (Cazenave et al., 1987b). They are not cytotoxic at high concentrations (up to 100 μM) whereas oligophosphorothioates exhibit toxicity in the micromolar range. In order to take advantage of their resistance to DNases and of their lack of cytotoxicity we have modified oligo-(α)-deoxynucleotides so as to make them able to induce irreversible reactions in their target mRNA. This has been achieved in two different ways.

**Attachment of a nucleic acid-cleaving reagent to one end of the oligonucleotide**

The other end can be substituted by an intercalating agent. Metal complexes such as EDTA–Fe (Chu & Orgel, 1985; Dreyer & Dervan, 1985; Boidot-Forget et al., 1986, 1988); phenanthroline–Cu (Chen & Sigman, 1986; François et al., 1988a; Sun et al., 1988) and porphyrin–Fe (Le Doan et al., 1986, 1987a) can be used to generate OH radicals in the presence of oxygen and a reducing agent. These radicals induce cleavage reactions targeted to the sequence complementary of the oligonucleotide carrier. DNA can be cleaved as well as RNA (Chen & Sigman, 1988 and unpublished results).

**Covalent linkage of a photoactive group to the oligonucleotide**

An intercalating agent such as proflavine can be used as a photosensitisiser (Praseuth et al., 1988b). All the photoactive groups described until now lead to photocrosslinking of the oligonucleotide to its target sequence. These groups include azidophenacyl (Praseuth et al., 1988a), azidoproflavine (Le Doan et al., 1987b), proflavine (Praseuth et al., 1988b), porphyrins (in preparation) and furocumarins (Lee et al., 1988; Gamper et al., 1987). In addition, photo-oxidations of bases are induced by porphyrins and proflavine (Praseuth et al., 1988a).

Oligomethylphosphonates covalently linked to a furocumarin have been recently shown to be efficient inhibitors of mRNA translation following irradiation (Kean et al., 1988). Other modifications, such as attachment of alkylating agents (Knoerre & Vlassov, 1985), have also been proposed to induce irreversible reactions in complementary sequences.

**The DNA double helix as a target for oligonucleotides**

The major groove of the DNA double helix can be recognised at homopurine homopyrimidine sequences by homopyrimide oligonucleotides. Pairs of hydrogen bonds are formed by thymine with an A-T Watson–Crick base pair and by protonated cytosine with a G-C base pair. A triple helix is locally formed (Le Doan et al., 1987b; Moser & Dervan, 1987; Praseuth et al., 1988a; François et al., 1988b). It is also possible to form a triple helix with a homopurine oligonucleotide that can recognise the purine-containing strand at a homopurine-homopyrimidine sequence (Cooney et al., 1988). In all cases the oligonucleotide is bound in a parallel orientation with respect to the purine-containing strand of the double helix. Irreversible reactions can be induced when the oligonucleotide carries a reactive group such as a photocrossliner (Le Doan et al., 1987b; Praseuth et al., 1988a) or a DNA-cleaving reagent such as EDTA–Fe (Moser & Dervan, 1987) or phenanthroline–Cu (François et al., 1988a). In the last case double-strand cleavage can be achieved thereby leading to the development of sequence-specific (restriction-like) endonucleases.

Triple helix formation opens new possibilities to control gene expression at the transcriptional level. It has been recently reported that myc gene transcription could be inhibited in vitro by a purine-rich oligonucleotide recognising a sequence upstream of the transcription initiation site (Cooney et al., 1988). It should also be kept in mind that the double helix is transiently open during transcription and that inhibition can be achieved by oligonucleotides complementary to one strand in the open region (Hélène et al., 1985). Nuclease-resistant oligo-(α)-deoxynucleotides also form triple helices at homopurine homopyrimidine sequences.
Conclusions

Oligodeoxynucleotides covalently linked to intercalating agents offer several advantages as compared to unsubstituted oligonucleotides: (1) their complexes with a complementary sequence are stabilised by the additional binding energy provided by intercalation; (2) their penetration across cell membranes is improved; (3) they are protected against degradation by exonucleases – 3'-substitution protects against 5'-exonucleases which are very active in biological fluids. These substituted oligodeoxynucleotides induce a cleavage of their target mRNA by endogenous RNase H, thereby inhibiting mRNA translation irreversibly. Oligodeoxynucleotides can be made resistant to DNases by modifying the phosphodiester backbone or changing the anomic configuration of the nucleosides. Some of these modifications abolish the RNase H-induced degradation of target mRNAs. Irreversible reactions can be induced in the target sequence by attaching a nucleic acid-cleaving reagent, an alkylating agent or a photoactivable reagent to the oligonucleotide. The DNA double helix is also a target for oligodeoxynucleotide carrying reactive groups. All these recent developments open new possibilities to control gene expression selectively at different levels and provide a rational basis for the conception of highly specific therapeutic agents.

I would like to express my heartiest appreciation to all collaborators who have contributed to the work described in this lecture and whose names can be found in the reference list. I would like to emphasise the central role played by Dr Nguyen T. Thuong and his collaborators at the Centre de Biophysique Moléculaire in Orleans, especially for the synthesis of the modified oligonucleotides. This work has been supported by INSERM, CNRS, the Ligue Nationale Contre le Cancer, The Fondation pour la Recherche Médicale and Rhône-Poulenc-Santé.

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