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Preface

Nucleic acid modification for fluorescence-based technologies

Synthetic nucleic acid molecules have become invaluable tools in molecular life sciences. It is, perhaps, on one hand the overwhelming importance of nucleic acids in key biological processes and on the other hand the predictability of nucleic acid–nucleic acid interactions that has induced the development of the wealth of nucleic acid-based probe molecules available today. Nucleic acid probes are used to investigate occurrence and properties of target molecules including nucleic acids and nucleic acid-binding proteins. Most commonly, labels are attached to the probes in order to provide for a measurable signal that can be distinguished from inherent nucleic acid signals or background signals. The use of fluorescent labels is popular because fluorescence is a quantity that can be measured most conveniently and with high sensitivity by both experienced and first time users.

The emission properties of fluorophores often are dependent on the environment. This property, which typically is more pronounced than the environmental sensitivity of absorbance, can be a disadvantage, for example when fluorescence quantum yields and hence brightness of emission are reduced due to the interaction of the fluorophore excited state with the nucleobase chromophores. However, the responsiveness to changes of the environment can also be used for the design of 'smart' fluorescence probes that report on specific biomolecular interactions or conformational reorganizations. Responsiveness to changes of the environment can be the result of the distance dependent interaction between two fluorophores or a fluorophore and a chromophore. Zamecnik and Wolf presented in 1988 a pioneering application of this principle. They suggested that adjacent hybridization of a fluorescein labeled oligonucleotide and a rhodamine labeled oligonucleotide could result in decreases of fluorescein emission and increases of rhodamine emission due to fluorescence resonance energy transfer (FRET). This principle is now being used for the homogeneous detection of DNA. Another strategy draws upon a single fluorophore that interacts with the nucleobases. Early examples include fluorescent analogues of nucleobases. In a seminal paper Stryer and colleagues reported, almost 40 years ago, that the incorporation of 2-aminopurine into double helical polynucleotides resulted in decreases of fluorescence. They also found that the quenched emission of 2-aminopurine was increased upon thermal denaturation of the double helix. This useful property forms the basis for modern assays, in which 2-aminopurine fluorescence is measured to probe local changes of helix conformations such as those induced upon interaction with DNA-binding proteins. Nowadays, researchers install fluorophores of increasing complexity at virtually any position of DNA and RNA molecules. Some of these modifications and the underlying aims will be discussed in this issue of Bioorganic & Medicinal Chemistry.

The present *Symposium In Print* issue on 'Nucleic Acid Modification for Fluorescence-based Technologies' involves contributions of leading experts, who share their views on the development of innovative fluorescence labeling schemes and 'smart probe' techniques. Three studies address fundamental questions in the realm of nucleic acid–nucleic acid interactions. Engels and co-workers report the development of an ethinylpyrene label that can allow for optical measurement of RNA folding. Häner and co-workers explored stacking in DNA by using non-nucleosidic pyrene-containing building blocks. Grossmann and Seitz show how fluorescent labeling can be used to investigate the catalysis of strand exchange reactions. In four contributions enzymatic or chemical processing of nucleic acids is studied. Weinhold and co-workers present an enzymatic strategy (SMILing) to sequence-specifically label plasmid DNA. Davies and Arenz demonstrate that the maturation of micro-RNA precursors can be measured by fluorogenic RNA probes. The fluorescence signals generated upon template-directed ligation reactions have been used for homogeneous detection of RNA (Kool/Silverman) and DNA (Seitz). The theme on homogeneous DNA detection is carried on to six contributions that describe the use of new fluorescent building blocks. Yamana and co-workers incorporated two pyrene groups in stem-loop probes to allow monitoring of probe hybridization by excimer fluorescence. Dual labeled stem-loop probes known as molecular beacons have been used by Frank-Kamenetskii and co-workers to detect short DNA sequences in double-stranded DNA that have been exposed upon the action of peptide nucleic acid (PNA)-based openers. Wengel and co-workers attached the fluorescence dyes pyrene and perylene to the DNA analogous locked nucleic acid (LNA) and detected hybridization via FRET. The charge transfer between a pyrene-modified guanosine and 7-deazaguanine provides the basis for a DNA-detection scheme described by Wagenknecht and co-workers. Two contributions (anthracene-based base discriminating fluorescent oligo-

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nucleotides presented by Saito and co-workers and Forced Intercalation Probes (FIT-probes) introduced by Bethge, Jarikote, and Seitz) describe simplifications of probe technologies by incorporation of single smart chromophores that respond toward single base mutations.

To assort a *Symposium In Print* issue is a collaborative endeavor of many researchers, including both the writers and the reviewers. The collaborative nature requires patience and, of course, most patience is asked from those scientists who were first in submitting their contribution. I am grateful to all contributors who have helped in assembling this issue.

Oliver Seitz
Institute of Chemistry, Humboldt-University Berlin, Brook-Taylor-Str. 2, D-12489 Berlin, Germany
E-mail: oliver.seitz@chemie.hu-berlin.de

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