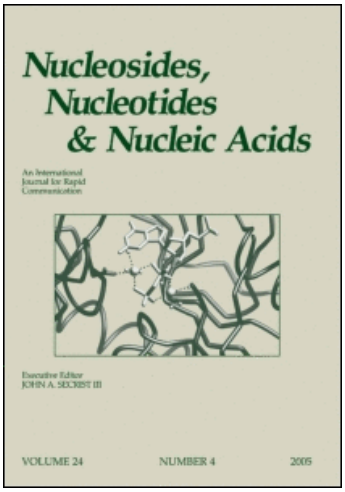

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Preface

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PREFACE

This special publication of Nucleosides and Nucleotides contains papers presented at the XII International Round Table on Nucleosides, Nucleotides and their Biological Applications. The conference was held at the Hyatt Regency in La Jolla, California, USA between September 15 and 19, 1996. I had the exciting opportunity of organizing the round table and serving as the General Chair.

ORGANIZATION OF THE ROUND TABLE

The XII Round Table, in addition to taking place in sunny southern California, had several unique features: It had 36 corporate sponsors who made the expensive meeting a reality, 500 registrants representing 31 countries, 8 scientific oral sessions with 60 speakers and 220 poster presentations.

We solicited suggestions from over 200 scientists in the areas of nucleosides and oligonucleotides regarding format, content, and potential speakers. We had an enormous response from these scientists and organized our program based on their responses. We decided on "Making Drugs Out of Nucleosides and Oligonucleotides" as the theme for this round table. The selection of this particular theme allowed us to focus on the more important areas of nucleoside and nucleotide chemistry and biology rather than the more difficult task of covering all aspects of

nucleoside/nucleotide chemistry. We organized eight consecutive sessions covering topics ranging from drug discovery to clinical trials. Successful implementation of this plan required inviting 60 plenary speakers and 14 chairpersons to address the eight broad R&D topics. In addition, to accommodate the overwhelming response of registrants who were enthusiastic to present their work, we accepted 220 poster presentations. Thus, 280 presentations were made at the XII IRT. Nearly 200 people chose to contribute papers for these Proceedings of Nucleosides & Nucleotides. The subject matter of the meeting was evenly divided between chemistry and biology with about 35% of the presentations on nucleosides and 65% on oligonucleotides.

Considering the topic of the round table, we were interested in someone to deliver the Keynote Address who has experience in both areas of the meeting theme—Nucleosides and Oligonucleotides. We chose Professor Richard T. Walker (University of Birmingham, Birmingham, UK) because of his rich experience in the chemistry and biology of both nucleosides and oligonucleotides. It is pertinent to point out that Dick Walker was the founding father of the journal Nucleic Acids Research in 1974 and was a co-inventor, along with Eric DeClercq, of (*E*)-5-(2-bromovinyl)-2'- deoxyuridine. Professor Walker provided a very enjoyable and interesting address which appropriately primed the ensuing conference.

NUCLEIC ACIDS CHEMISTRY AWARD

Also notable at this round table was the initiation of a Nucleic Acids Chemistry Award. Professor Wolfgang Pfleiderer suggested such an award on behalf of the International Society of Nucleic Acids Chemistry. We agreed to support this award as part of the round table activities in order to further promote

world-wide nucleic acid chemistry research. An international nominating committee was formed which solicited nominations throughout the world. A final committee comprising Professor R. T. Walker, Professor W. Pfleiderer and myself counted the nominations and declared Dr. Mark Matteucci of Gilead Sciences as the winner. The 1996 Nucleic Acids Chemistry Award was sponsored by Isis Pharmaceuticals. Considering the numerous contributions Mark has made to the field of oligonucleotide chemistry, we were pleased that he was chosen as the winner of the first Nucleic Acids Chemistry Award.

CONTENTS OF THE MEETING AND THESE PROCEEDINGS

The contents of these proceedings follow the organization of the round table into its eight different sessions: 1) Progress in Second Generation Oligomer Therapeutics, 2) Medicinal Chemistry of Nucleosides/Nucleotides, 3) Preclinical Studies of Oligomers, 4) Preclincial Studies of Nucleosides and Nucleotides, 5) Novel Nucleosides and Oligomers, 6) Chemical Development and Analytical Chemistry, 7) Biological Studies of Oligomers Including Clinical Results, and 8) Special Topics. This classification was somewhat flexible as it was often difficult to strictly group invited papers into these topics.

CONCLUDING REMARKS

I would like to leave you with a few thoughts on the future of the International Round Tables based on my observations while organizing and observing the scientific presentations of the XII Round Table and considering the scientific directions of the past four IRTs. The original and current title of the IRT is "Nucleosides, Nucleotides and Their Biological Applications"; however, the direction of research and presentations at IRTs VIII

(J . Secrist), IX (J. Chattopadhyaya), X (A. Broom), XI (E. DeClercq), and XII (P. D. Cook) has been steadily moving towards oligonucleotide research. As noted during the current Round Table, the number of invited presenters were allocated so as to have an equal number of nucleoside and oligonucleotide talks (and also their biological applications); however, the poster presentations were not predetermined and their content was about 75% oligonucleotide research. This has also been the format and results of the previous four IRTs. I am sure the IRTs can continue in this manner—composed of a combination of nucleoside analogs (of course including nucleotides and phosphates) and oligonucleotides. Certainly Drs. G. Gosselin and B. Rayner, working with Professor Imbach, will have an outstanding XIII IRT in Montpellier, France, September 6-10, 1998. But clearly the research content and the expertise of the researchers in the nucleoside and oligonucleotide areas do not significantly overlap. Future International Round Tables may best be composed of two meetings to be alternated—one to cover nucleosides and nucleotides and the other to be concerned with oligonucleotides.

When we talk about nucleoside analogs and oligonucleotides as therapeutic agents, as has taken place at this and previous IRTs, we tend to want to compare their relative future value. I want to comment on several very distinct differences in these chemical classes. In this conference we have seen a number of novel, interesting nucleoside structures, e.g., acyclic nucleosides and phosphonates, L-nucleosides, heteroatom modifications of the D- & L-sugars of nucleosides, carbocyclics, heterocyclic modifications, and prodrug modifications of some of these and their phosphonates. Considering recent nucleoside research, a reasonable structure-activity relationship direction would be the preparation of D- or L-sugar-modified nucleosides as acyclic or cyclic, then the phosphonates, and finally as prodrugs, such as the SATE modifications. It seems there is simply no end to what nucleoside chemists can do in terms of providing new structures with interesting anticancer and antiviral activities. What is somewhat bothersome to me is that you never know when this is going to happen. The state of the art of nucleoside analog research is not very rational and because of this we never know when a

potentially very important agent such as 3TC is going to be discovered. In this regard, application of combinatorial chemistry strategies for drug discovery of nucleoside analogs is an obvious direction for future research in this area. In the case of oligonucleotide research, being based primarily on simple Watson-Crick base-pairing rules (G to C and T(U) to A), one can knowledgeably design oligonucleotide sequences to bind specifically to a targeted RNA or DNA. Chemical modifications to the building blocks to enhance biological properties can be achieved without changing the basic recognition sequence. Because of this rational design feature of antisense oligonucleotides about 20 agents have entered clinical trials in the past five-year period; another 10 oligonucleotides are expected to undergo clinical evaluation in the next 24 months.

Antisense oligonucleotides are thought to be very specific for their targets and this has been verified by recent research. On the other hand, because nucleoside analogs require intracellular activation to the active species —primarily a triphosphate species —by both viral and cellular enzymes, a nucleoside analog typically encounters toxicity problems due to lack of specificity for the target polymerase. Nucleoside analogs, at the moment, do have certain advantages, particularly in the pharmacokinetic area. They are much more likely to possess oral bio-availability and penetrate blood brain barriers than oligonucleotides. However, recent research has provided much hope that modified oligonucleotides will be discovered with useful oral activity. Oligonucleotides have the potential to be applied to essentially any disease. Inflammation, restenosis and asthma are several therapeutic areas to which oligonucleotides have been applied. Nucleoside analogs have primarily been directed to antiinfective and anticancer applications. As the field of nucleoside analogs is quite mature, being over 50 years old, it is unlikely that new therapeutic applications will be found.

In summary, the key advantages of oligonucleotides are their potential

broader therapeutic applications with increased specificity, and the potential for more rapid drug discovery due to the rational aspects of the antisense approach. I think the future is still bright for nucleosides in the anticancer and antiviral areas. I think the future of antisense oligonucleotides is even more optimistic.

ACKNOWLEDGMENTS

I would like to thank the various people who made this round table a grand success. The financial support of 36 organizations whose names appear on a separate page was absolutely essential. These organizations range from very small to very large and all make important contributions to the process of making drugs out of nucleosides, nucleotides, and oligonucleotides. The Scientific Committee—Professors Arthur D. Broom, Robert Sidwell and my colleagues Mano Manoharan, Yogesh Sanghvi and Oscar Acevedo helped me shape the format of and put together the final program. I had the complete support of my administrative assistant, Julie Walker, along with Mano, Yogesh and Oscar in organizing the many, many details of the meeting. The following individuals assisted this organizing committee in various ways: Anna Alessi, who played a key role in bringing together the voluminous abstract book. Connie Clephane and Leah Finch assisted in correspondence and registration. I want to thank all these individuals who worked very hard with me for two years in preparation for this meeting. Professors Leroy Townsend and Jean-Louis Imbach, the founders of the International Round Table, provided advice and were always available for much needed moral support. I want to especially thank them.

I want to acknowledge the editorial assistance of my colleagues Mano Manoharan and V. Mohan and Julie's technical assistance in preparing the

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Finally, I would like to thank everyone who participated in the round table and all contributors to this volume. I look forward to seeing you in Montpellier, France in 1998 for the next round table to be organized by Drs. Bernard Rayner and Gilles Gosselin.

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