AUTHOR COMMENTARIES - 2009

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Stephen Neidle

Featured Scientist from *Essential Science Indicators*SM

A recent analysis of Essential Science Indicators *from Thomson Reuters, hailed Professor Stephen Neidle as a New Entrant to the top 1% of scientists in the field of Biology & Biochemistry. His current record in this field includes 33 papers cited 1,189 times between January 1, 1998 and October 31, 2008. He also has 56 papers cited a total of 1,564 times over the same period in the field of Chemistry.*

Professor Neidle is the Director of The Cancer Research UK Biomolecular Structure Group and Professor of Chemical Biology at the University of London's School of Pharmacy.

This month, ScienceWatch.com *talks with Professor Neidle about his highly cited work.*

SW: Would you tell us a bit about your educational background and research experiences?

I was originally educated as a chemist and crystallographer at Imperial College London, working on natural products and antibiotics. I subsequently moved into more biological areas, firstly in the Department of Biophysics at King's College London, and then for 17 years at the Institute of Cancer Research, a world-renowned center for both fundamental and translational studies in cancer science.

In 2002 I moved to the School of Pharmacy in Central London, to a new chair of Chemical Biology. I have continued to retain my focus as a chemist, which provides a unique perspective on molecular behavior in biological systems and its exploitation for drug discovery.

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SW: What would you say is the main focus of your work?

The laboratory that I have built up over the years emphasizes an integrated chemical and structural approach to the discovery of new therapeutic agents, mostly in the cancer area. Much of our work over the past dozen years has been on the discovery of novel agents targeting human telomeres in cancer, and in particular we have been active in the study of higher-order DNA structures known as quadruplexes.

Quadruplex-forming sequences occur within telomeric DNA and in promoter regions of a number of oncogenes; we are involved in determining the three-dimensional structures of these quadruplexes, designing and synthesizing selective small molecules that will bind to them, and in evaluating the biological consequences in a range of cancer cell types.

SW: Several of your papers deal with telomeric DNA. What makes telomeric DNA such a topic of interest?

Telomeric DNA is a fundamental feature of all eukaryotic chromosomes. For those of us in the cancer area, the story started with the discovery in the mid 1990s that telomeric DNA is maintained in the overwhelming majority of cancer cells by the action of the telomerase enzyme complex, which synthesizes telomeric DNA repeats and essentially maintains the immortalization of cancer cells. By contrast, in normal somatic cells, telomerase is not significantly expressed and the normal mechanism of DNA replication results in progressive shortening of telomeric DNA so that after a number of generations normal cells are no longer viable. So this knowledge developed into the concept of targeting telomerase and its substrate telomeric DNA as a therapeutic strategy.

SW: Your most-cited paper is the 2002 *Nature* article, "Crystal structure of parallel quadruplexes from human telomeric DNA," (Parkinson GN, Lee MPH, Neidle S, 417[6891]: 876-80, 20 June 2002). Would you talk about this paper, its goals, findings, and significance for the field?

This paper is the first atomic-level description of the structure formed by folding human telomeric DNA, crystallized in near-physiological conditions. That itself continues to be of interest and is used as a template for the discovery of novel small molecules as Telomere Targeting Agents. The structure, though, is remarkable—it shows the quadruplex as a propeller-like arrangement and this was totally unexpected and novel. It has subsequently catalyzed a great deal of interest and activity (and controversy!). This quadruplex fold is turning out to be a paradigm for many other quadruplex structures, and is present in the majority of the promoter quadruplexes studied more recently.

SW: What sort of controversy did this work generate?

"Telomeric DNA is a fundamental feature of all eukaryotic chromosomes."

Crystallographic studies can provide a uniquely detailed view of the three-dimensional structures of biological molecules, although they are sometimes criticized as not representing structures in solution. NMR studies of human telomeric quadruplexes (in dilute solution) have revealed some arrangements that are distinct from the structure that we observed. However, it is now apparent that these molecules can adopt a range of structures, dependent on even small changes in environmental conditions, and that the topology of these quadruplexes in more concentrated solution, closer to physiological conditions, corresponds to that observed in the crystalline state (which is actually heavily hydrated).

SW: What are the hoped-for applications in telomeric DNA research?

Firstly, increased knowledge of telomere organization and function. Secondly, as I have described, new therapeutic agents for human cancers.

SW: What would you like to convey to the general public about your work?

We are getting much better at treating many forms of human cancers, but progress with some of the commonest (e.g. lung and pancreatic cancers, melanoma), is still slow. It is our hope that our knowledge of telomeric quadruplexes will be useful in the development of novel against effective against some of these cancers.

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Stephen Neidle's current most-cited paper in *Essential Science Indicators*, with 391 cites:

Parkinson GN, Lee MPH, Neidle S, "Crystal structure of parallel quadruplexes from human telomeric DNA," *Nature* 417(6891): 876-80, 20 June 2002. Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: HUMAN TELOMERIC DNA, QUADRUPLEXES, CANCER, DRUG DISCOVERY, QUADRUPLEX-FORMING SEQUENCES, THREE-DIMENSIONAL STRUCTURES, TELOMERE TARGETING AGENTS, QUADRUPLEX FOLD, TELOMERASE.

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