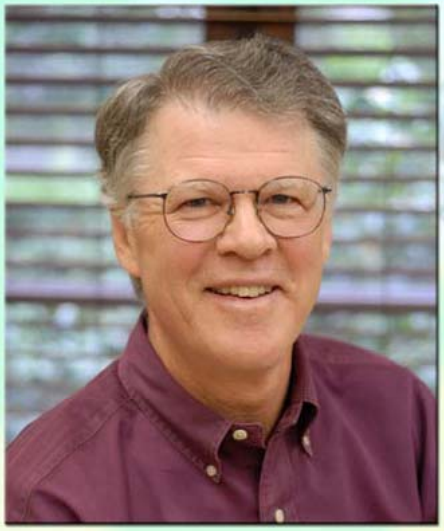
2009 王光燦生物有機化學講座發表會

2009 K.T. Wang Bio-organic Chemistry Lectureship

Nov 5-6 2009



Prof. Peter B. Dervan

Prof. Jacqueline K. Barton

主辦單位：財團法人王光燦生物有機化學教育基金會

王光燦院士及王光燦生物有機化學基金會介紹

王光燦院士，1929 年出生於台灣台北市。1952 年台灣大學化學系畢業，1962 年獲日本東北大學博士學位。

1966 年是一個物資缺乏的年代，他用老師家中一件舊的尼龍襯衫，發明了聚醯胺（polyamide）薄膜色層分析（TLC），此技術被廣泛應用於天然物的分離與鑑定，尤其應用於蛋白質胺基酸定序，該論文被引用超過千次，被稱譽為「窮人的薄膜層析法」。1969 年他加入美國加州大學李卓皓教授的研究室，從事蛋白質化學合成研究工作。1972 年加入中央研究院生化所擔任研究員，1978 年完成全世界首次固相全合成台灣眼鏡蛇心臟毒蛋白。在 1980 年至 1986 年期間，他擔任中央研究院生化所所長，積極推動國內生物化學的學術研究。他更應用酵素進行有機化合物不對稱合成反應，發明以微波爐加速胜肽水解及合成反應的方法。於近半世紀之教學研究生涯中，王院士治學態度嚴謹，研究專注執著，作育英才無數；至今王院士於國內外著名學術期刊發表論文超過兩百篇，並且獲得行政院傑出研究科技榮譽獎、國科會研究傑出獎、侯金堆文教基金會傑出榮譽獎、台美基金會科技工程獎等多項榮譽及獎章，更於 1994 年當選中央研究院院士。

為了促進台灣生物有機化學的蓬勃發展，並能繼續推展台灣有機化學的研究，中央研究院李遠哲院士、翁啟惠院士等人共同發起，於 2000 年 10 月 18 日成立「財團法人台北市王光燦生物有機化學教育基金會」（The K-T Wang Bioorganic Chemistry Foundation），每年頒獎給一位對生物有機化學有重大貢獻的國際知名學者，並邀請他到國內演講、與產學座談提供研究心得及建議，以促進國內生物有機化學的發展。

From polyamide thin layer chromatography in the sixties, solid phase synthesis of snake venom proteins in the seventies, to application of microwave on chemical reaction in the eighties, Dr. Kung-Tsung Wang’s substantial achievements greatly influence the whole Bioorganic Chemistry community.

On October 19, 1999, Dr. Wang, who was 70 years old, gave a moving speech in his honorable retirement ceremony planned by all the attendees, good friends and students of his, who were at the scene to pay him respect. In order to honor Dr. Wang and carry over the mission to nourish the Bioorganic Chemistry Research in Taiwan, a group of the Taiwanese scientists including Dr. Y.T. Lee and Dr. C.H. Wong organized and helped the founding of K-T Wang Educational Foundation in October 2000.

The K-T Wang Bioorganic Chemistry foundation enables more students and young scholars to have the opportunity to meet with world-renowned scientists face-to-face. Once a year the foundation awards a world-famous scholar who has made great researcher to give talks on his/her research experiences. The purpose is to inspire the youth in this field and thus speed up the progress of Bioorganic Chemistry research in Taiwan.

2009 年王光燦生物有機化學學術講座得獎人

Professor Peter B. Dervan

Peter B. Dervan (born June 28, 1945) received his early education in Boston, Massachusetts (B.S., Boston College, 1967). He began research in physical organic chemistry working with Jerome A. Berson at Yale University. After earning his Ph.D degree in 1972, he spent a year at Stanford University as an NIH Postdoctoral Fellow (1973). From Stanford he went to Pasadena to take up a faculty appointment at the California Institute of Technology where he is now the Bren Professor of Chemistry in the Division of Chemistry and Chemical Engineering.

Peter Dervan has created a new field of bioorganic chemistry with studies directed toward understanding the chemical principles for the sequence specific recognition of the genetic material, DNA. Dervan has combined the art of synthesis, physical chemistry, and biology to create novel synthetic molecules with affinities and sequence specificities comparable to Nature's proteins for any predetermined DNA sequence. This biomimetic approach to DNA recognition underpins the design of cell-permeable molecules for the regulation of gene expression *in vivo*. The approach could have profound implications for human medicine.

Dervan is a member of the National Academy of Sciences, the Institute of Medicine, the American Academy of Arts & Sciences, the American Philosophical Society, and a Foreign Member of the French Academy of Sciences and the German Academy of Sciences. His awards include the Harrison Howe Award (1988), Arthur C. Cope Award (1993), Willard Gibbs Medal (1993), Nichols Medal (1994), Maison de la Chimie Foundation Prize (1996), Remsen Award (1998), Kirkwood Medal (1998), Alfred Bader Award (1999), Max Tishler Prize (1999), Linus Pauling Medal (1999), Richard C. Tolman Medal (1999), Tetrahedron Prize (2000), Harvey Prize (Israel) (2002), Ronald Breslow Award (2005), Wilbur Cross Medal (2005), and the National Medal of Science (2006).

2009 年王光燦生物有機化學產業講座受邀學者

Professor Jacqueline K. Barton

Dr. Jacqueline K. Barton is the Arthur and Marian Hanisch Memorial Professor of Chemistry at the California Institute of Technology. She is a native New Yorker. Barton was awarded the A.B. summa cum laude at Barnard College in 1974 and a Ph.D. in Inorganic Chemistry at Columbia University in 1978 in the laboratory of S. J. Lippard. After a postdoctoral fellowship at Bell Laboratories and Yale University with R. G. Shulman, she became an assistant professor at Hunter College, City University of New York. In 1983, she returned to Columbia University, becoming an associate professor of chemistry and biological sciences in 1985 and professor in 1986. In the fall of 1989, she joined the faculty at Caltech.

Professor Barton has pioneered the application of transition metal complexes to probe recognition and reactions of double helical DNA. She has designed chiral metal complexes that recognize nucleic acid sites with specificities rivaling DNA-binding proteins. These synthetic transition metal complexes have been useful in elucidating fundamental chemical principles that govern the recognition of nucleic acids, in developing luminescent and photochemical reagents as new diagnostic tools, and in laying a foundation for the design of novel chemotherapeutics. Most recently, her research group has designed bulky metallointercalators as site-specific probes of DNA base mismatches. These complexes are now being applied in the discovery of single base mutations and in new diagnostic and chemotherapeutic strategies targeted to mismatch repair deficient cells. Barton has also carried out seminal studies to elucidate electron transfer chemistry mediated by the DNA double helix. She first showed that oxidative damage to DNA can arise from a distance through charge migration through the DNA duplex. She furthermore established that DNA charge transport chemistry is exquisitely sensitive to intervening perturbations in the DNA base stack, as with single base mismatches or lesions. This chemistry has since been applied in the development of DNA-based electrochemical sensors for mismatches, lesions, and protein binding. Barton is now also focused on establishing where this chemistry is harnessed within the cell. DNA charge transport may provide a route for long range signaling among DNA-bound proteins and may be critical to understanding DNA damage and repair within the cell.

Barton has received numerous awards. These include the Alan T. Waterman Award of the National Science Foundation (1985), the American Chemical Society

(ACS) Award in Pure Chemistry (1988), the ACS Eli Lilly Award in Biological Chemistry (1987), ACS Garvan Medal (1992), and the ACS Breslow Award in Biomimetic Chemistry (2003). She has also received the ACS Baekeland Medal (1991), the Fresenius Award (1986), the ACS Tolman Medal (1994), the Mayor of New York's Award in Science and Technology (1988), the Havinga Medal (1995), the Paul Karrer Medal (1996), the ACS Nichols Medal (1997), the Weizmann Women & Science Award (1998), the ACS Gibbs Medal (2006), the ACS Cotton Medal (2007), and the ACS Pauling Medal (2007). She was a fellow of the Sloan Foundation, a Dreyfus Teacher-Scholar, and an NSF Presidential Young Investigator. She is a recipient of a prestigious MacArthur Foundation Fellowship (1991) and she has been elected to the American Academy of Arts and Sciences (1991), the American Philosophical Society (2000), and the National Academy of Sciences (2002). She has received eight honorary doctorates including, most recently, Yale University (2005). She also received university medals from Barnard College (1990) and Columbia University (1992). She has, in addition, served the chemical community through her participation in ACS, governmental and industrial boards. Based upon her industrial board service, she was named an Outstanding Director by ODX (2006).

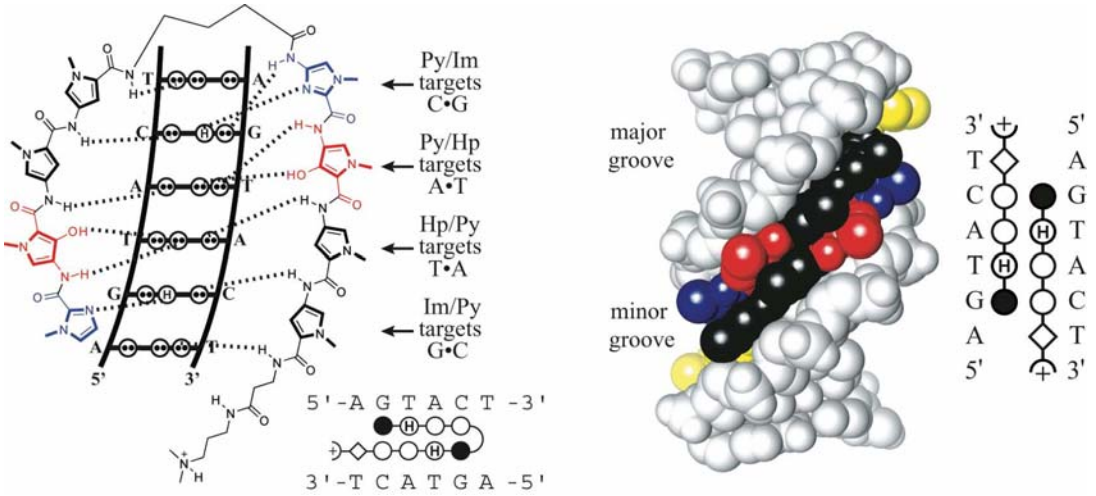
2:30 PM Nov 5 (Thu) 2009
B1 International Conference Hall, 2nd Student Activity Center, National Taiwan University
(台灣大學第二活動中心 B1 國際會議廳)

Molecular Recognition of DNA by Small Molecules

Peter B. Dervan
Division of Chemistry & Chemical Engineering
California Institute of Technology

Many human diseases are caused by dysregulated gene expression. The oversupply or overactivity of one or more transcription factors may be required for the survival, growth and metastatic behavior of all human cancers. The hypothesis of our research program is that small molecules that can be programmed to bind a broad repertoire of DNA sequences can disrupt transcription factor-DNA interfaces and modulate aberrant gene expression pathways.

Our laboratory has pioneered the development of pyrrole-imidazole (Py-Im) polyamides as programmable oligomers for targeting double-strand DNA with affinities and specificities comparable to transcription factors. Minor groove DNA binding polyamides containing aromatic amino acids form the basis of a modular code to control sequence specificity. Pairs of pyrrole (Py), imidazole (Im), and hydroxypyrrole (Hp) rings distinguish the four Watson-Crick base pairs of DNA. Im/Py and Py/Im distinguish G•C and C•G, respectively, and Hp/Py distinguishes T•A from A•T. These small molecules inhibit DNA binding of a broad range of transcription factors, bind to chromatin, are cell permeable, and have been shown to downregulate endogenous gene expression in cell culture.



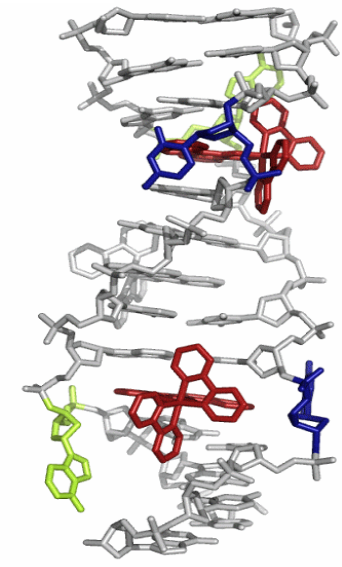
Left: Antiparallel pairings of pyrrole, imidazole, and hydroxypyrrole carboxamides are capable of specifically recognizing each of the four Watson-Crick base pairs (*Nature*, **391**, 468 (1998)). Right: Crystal structure of a minor groove-binding polyamide dimer recognizing each of the four base pairs (*Science*, **282**, 111 (1998)).

3:30 PM Nov 5 (Thu) 2009
B1 International Conference Hall, 2nd Student Activity Center, National Taiwan University
(台灣大學第二活動中心 B1 國際會議廳)

Targeting DNA Mismatches with Metal Complexes

Jacqueline K. Barton
Hanisch Memorial Professor of Chemistry
Division of Chemistry and Chemical Engineering
California Institute of Technology

The mismatch repair pathway corrects single base errors and insertion/deletion loops that arise during DNA synthesis. If uncorrected, mismatches are converted to mutations in subsequent cycles of DNA replication, and cells with deficiencies in mismatch repair exhibit elevated mutation rates. Germline mutations in essential genes for mismatch repair in humans dramatically increase the risk of developing hereditary nonpolyposis colon cancer. In addition, mismatch repair deficiencies have been found in approximately 16% of solid tumors of all tissue types. Our laboratory has developed bulky rhodium complexes that target DNA mismatches. These octahedral complexes include an expansive tetracyclic aromatic ligand that can only be accommodated by DNA at a thermodynamically destabilized mismatch site. The first generation compound, $Rh(bpy)_2chrysi^{3+}$ (chrysi = 5,6-chrysenequinone diimine), binds 80% of all possible DNA mismatches and with remarkable specificity for the mismatched site. A high resolution crystal structure of the bulky metal complex bound to single base mismatches within a DNA oligonucleotide duplex reveals a distinctive binding mode at the mismatched site. These complexes that target single base mismatches with high specificity furthermore are shown to inhibit selectively the proliferation of cells deficient in mismatch repair. Targeting of mismatches may provide a cell-selective strategy in the design of novel chemotherapeutics.

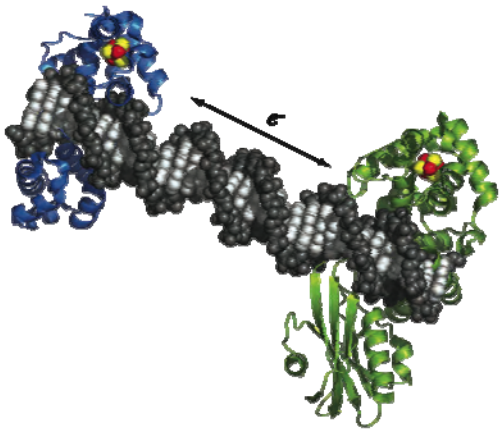


10:30 AM Nov 6 (Fri) 2009
Ta-Shue Chou Memorial Hall, Institute of Chemistry, Academia Sinica
(中央研究院化學所周大紓講堂)

DNA-mediated Signaling

Jacqueline K. Barton
Hanisch Memorial Professor of Chemistry
Division of Chemistry and Chemical Engineering,
California Institute of Technology

Many experiments have now shown that double helical DNA can serve as a conduit for efficient charge transport reactions over long distances. In particular, oxidative damage to DNA can be promoted from a distance through DNA-mediated charge transport. Importantly, this chemistry is exquisitely sensitive to perturbations in the DNA base stack, such as arise with base mismatches, lesions, and protein binding. As a result, DNA charge transport chemistry can be harnessed for the design of sensitive diagnostics. Studies will be described to characterize biological roles for DNA charge transport. This chemistry may be used advantageously within the cell in long range signaling to DNA-bound proteins, both to regulate transcription and to activate repair of base lesions under conditions of oxidative stress. DNA charge transport chemistry provides an opportunity to carry out redox chemistry at a distance.



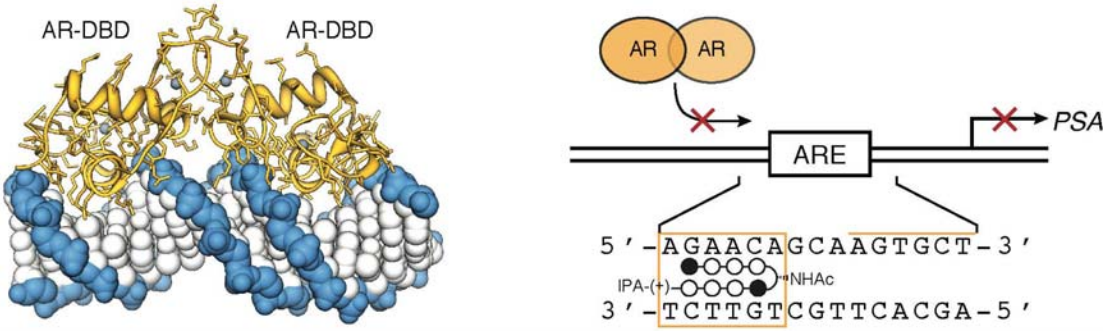
2:00 PM Nov 6 (Fri) 2009
International Conference Hall, Building for Humanities and Social Sciences, Academia Sinica
(中央研究院人文館國際會議廳)

Transcription Factors as Targets for Cancer Therapy

Peter B. Dervan
Division of Chemistry & Chemical Engineering
California Institute of Technology

The dysregulated transcription factor at the core of many prostate cancers is the androgen receptor (AR). AR is a nuclear hormone receptor whose nuclear localization and transcriptional activity is driven by conformational changes produced upon binding to endogenous or synthetic androgens. AR binds to an estimated 2000 locus control regions, or androgen response elements (AREs), to modulate the expression of approximately 500 androgen-responsive genes. In addition to its role in normal growth and development, activation of AR and its gene targets by male steroid hormones drives the growth and spread of prostate cancer.

We have designed a polyamide antagonist that can block AR from binding androgen response elements (ARE) in a prostate cancer cell line. This small molecule inhibited the dihydrotestosterone-induced expression of many AR target genes, including prostate specific antigen (PSA). The activity of the polyamide against PSA mRNA expression was comparable to that of bicalutamide. Since the polyamide disrupts the protein-DNA interface instead of the ligand-binding pocket of the nuclear receptor, we are investigating its activity in a hormone refractory setting where bicalutamide and related inhibitors of ligand binding have failed. We find that ARE specific polyamide maintains its activity against PSA expression in the hormone-refractory cell line LNCaP-AR, a tissue culture model of advanced prostate cancer. This result suggests that disruption of the AR/ARE interface in the hormone-refractory setting may yield a potential therapeutic strategy for treating HRPC.



Targeting the androgen receptor with Py-Im polyamides. (A) Crystal structure of the AR-DBD homodimer bound to DNA. (B) Model for disruption of AR binding at the PSA ARE by a Py-Im polyamide.

NOTE

NOTE

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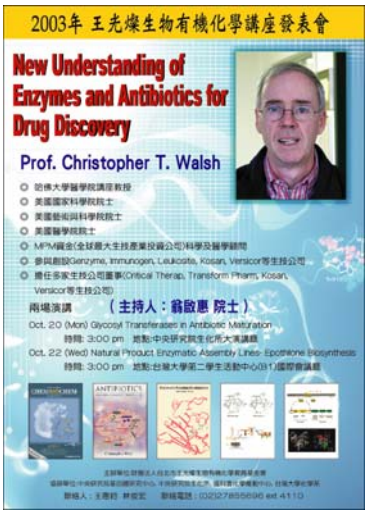

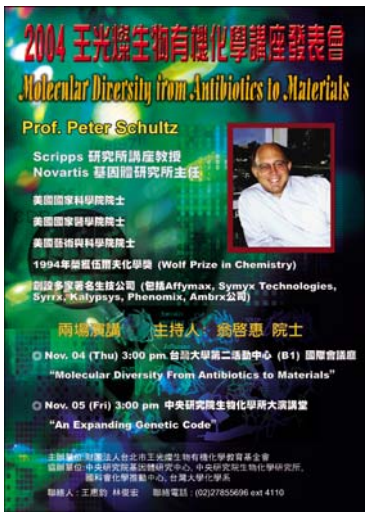

感謝

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三福環球投資股份有限公司
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