GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION
SPONSORED PROJECT INITIATION

Date: 2/1/79

Project Title: Conformations of Ligand-DNA Complexes and DNA Oligomers

Project No: G-41-A02 Green card

Project Director: Dr. Roger M. Wartell

Sponsor: DHEW/PHS/NIH - National Institute of General Medical Sciences

Agreement Period: From 1/1/79 Until 12/31/79 (02 year)

Type Agreement: Grant No. 5 R01 GM27434-02

Amount: $54,689 New PHS Funds (G-41-A02)
3,066 GIT Contribution G-41-320)
$57,755 Total

Reports Required: Annual Progress Reports with Continuation Applications;
Terminal Progress Report upon Grant expiration

Sponsor Contact Person (s):

Technical Matters
Dr. Jerry H. Roberts
Program Administrator
National Institute of General
Medical Sciences
Bethesda, MD 20014
Phone: (301) 496-7137

Contractual Matters
(thru OCA)
D. McNish/B. Spinks
Grants Management Specialists
Office of Assoc. Director for Program
Activities
National Institute of General Medical
Sciences
Bethesda, MD 20014
Phone: (301) 496-7166

NOTE: Follow-on project to G-41-A01

Defense Priority Rating: None

Assigned to: Physics (School/Laboratory)

COPIES TO:

Project Director
Division Chief (EES)
School/Laboratory Director
Dean/Director—EES
Accounting Office
Procurement Office
Security Coordinator (OCA)
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Library, Technical Reports Section
EES Information Office
EES Reports & Procedures
Project File (OCA)
Project Code (GTRI)
Other

CA-3 (3/76)

G-41-157

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

SPONSORED PROJECT TERMINATION

Date: 4-27-81

Project Title: Conformations of Ligand-DNA Complexes and DNA Oligomers

Project No: G-41-A02

Project Director: Dr. Roger M. Wartell

Sponsor: DHEW/PHS/NIH/NIGMS

Effective Termination Date: 12/31/80

Clearance of Accounting Charges: 12/31/80 (02 year)

Grant/Contract Closeout Actions Remaining:

NONE

_ Final Invoice and Closing Documents
_ Final Fiscal Report
_ Final Report of Inventions
_ Govt. Property Inventory & Related Certificate
_ Classified Material Certificate
_ Other _____

FOLLOW-ON PROJECT FOR 03 YEAR IS G-41-A03

Assigned to: Physics (School/~~Laboratory~~)

COPIES TO:

Project Director
Division Chief (EES)
School/Laboratory Director
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Accounting Office
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Library, Technical Reports Section
EES Information Office
Project File (OCA)
Project Code (GTRI)
Other _____

CA-4 (1/79)

SECTION IV

6-41-A02

APPLICANT: REPEAT GRANT NUMBER SHOWN ON PAGE 1 →	GRANT NUMBER
SECTION IV—SUMMARY PROGRESS REPORT	GM 24734-03
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last, First, Initial)	PERIOD COVERED BY THIS REPORT
WARTELL, Roger M.	FROM 1/01/79 THROUGH 10/31/79
NAME OF ORGANIZATION: Georgia Institute of Technology	

TITLE (Repeat title shown in Item 1 on first page)

Conformations of Ligand-DNA Complexes and DNA Oligomers

1. List publications: (a) published and not previously reported; (b) in press. Provide five reprints if not previously submitted.
2. List all additions and deletions in professional personnel and any changes in effort.
3. Progress Report. (See Instructions)

1. Objectives

a. The overall aims of the research project are to gain an understanding of how DNA binding molecules discriminate between different base pair sequences and how one region of DNA influences adjacent regions. One specific objective of the proposal is to determine information about complexes between the antibiotics netropsin (Nt) and distamycin (Dt) and DNA. These two oligopeptide molecules bind specifically to A-T regions of duplex DNAs. They do not bind single stranded DNA, RNA, or G · C DNA polymers under conditions (0.1 M sodium ion) in which they bind to AT DNA polymers. A second objective is to employ Laser Raman spectroscopy to examine conformational properties of DNA molecules with known base pair sequences

b. There are several goals for this year. One goal is to obtain an atomic resolution picture of the tight binding complex between netropsin and DNA. This is based on model building studies together with experimental information, and theoretical conformational energy calculations. A second goal is to examine the transition between the B-type and A-type conformations of DNA induced by ethanol using Laser Raman spectroscopy. The later technique provides vibrational spectra of molecules. A third goal is to synthesize the block DNA oligomer $d(C_{10}\ A_5) \cdot d(T_5\ G_{10})$ and initiate Laser Raman spectoscopy studies on this molecule. Additionally work was initiated to obtain quantities of homogeneous DNA molecules of short length (∿ 150 base pairs) and specific sequence to examine by Raman spectroscopy.

RESULTS

Computer calculations have been performed to obtain an atomic resolution picture of a complex between netropsin an a DNA helix of four A·T base pairs in the B-type conformation. The interatomic distances and bond angles of a netropsin molecule and the DNA duplex were from x-ray determinations. The dihedral angles of netopsin were allowed to be flexible except along the peptide bond where only small deviations from the trans position were allowed. Assuming a rigid DNA, model building was employed the generate an approximate structure based on previously obtained experimental data (3-4 base pairs contacted/drug, minor groove binding, pyrrole rings unaffected). Computer calculations have been performed to generate more precise coordinates of the complex. Van der Waals contact distances and optimum hydrogen bonding distances have been used to determine the conformational space available to netropsin in binding DNA in its minor groove. The next step will be to add energy terms to the calculation.

Considerable effort has been made in working out the conditions to examine the B to A conformational transition of DNA. Although progress here was slower than anticipated, it has yielded interesting and unexpected results. Previous work with calf thymus DNA (Herbeck et al. Biochem., 2656, 1976) indicated that around 70-80% ethanol by volume, DNA underwent a transition from B to A as characterized by changes in two Raman bands around 800 cm^{-1} assigned to phosphodiester vibrations. Due to strong ethanol bands however it was initially not

possible to examine DNA Raman bands outside of the narrow region around 800 cm^{-1}. We have found that by scattering the Laser beam off of a flat area of an unoriented DNA fiber we can greatly enhance the DNA Raman band intensities relative to the ethanol band intensities. We can now monitor changes in the vibrational properties of several portions of DNA.

Our results show that during the B to A transition deoxyribose ring vibrations are altered in a different manner than bands assigned to phosphodiester bonds. The above studies employed calf thymus DNA.

The synthesis and characterization of the block DNA $d(C_{10}\ A_5)\cdot d(T_5\ G_{10})$ is nearing completion. Both d $C_{10}\ A_{20-50}$ and d $T_5\ G_{8-10}$ have been synthesized. These complementary strands are now being annealed and treated to generate flush end molecules. Progress has been made to obtain milligram amounts of a 144 base pair DNA containing the lactose operon promoter region. The DNA fragment was successfully cloned into a plasmid and work is under way to isolate and purify this DNA. A manuscript describing this work has been submitted for publication.

The research goals for the next year will focus on Laser Raman spectroscopy studies of DNAs. We wish to examine the B to A transition of synthetic DNA polymers $d(A)_n \cdot d(T)_n$ and $d(G)_n \cdot d(C)_n$ and the block DNA $d(C_{10}\ A_5) \cdot d(T_5\ G_{10})$. Emphasize will be placed on examining different conformational features of the DNAs through the transition region.

A second goal is to complete the theretical calculations on the conformation of netropsin and DNA. The inclusion of additional energy terms in the calculation will be made. The later calculations are anticipated to be a collaboration with Dr. S. Broyde of New York University.

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

October 24, 1979
DATE

Roger M Wartell
Principal Investigator or
Program Director

GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GEORGIA 30332

OFFICE OF
THE
COMPTROLLER

April 24, 1980

Office of Associate Director
for Program Activities
National Institute of General
Medical Sciences
PHS/NIH
Dept. of Health, Education & Welfare
Bethesda, Maryland 20014

Dear Sir or Madam:

Enclosed is the Report of Research Grant Expenditures for Grant No. 5 R01 GM24734-02 for the period January 1, 1979 to December 31, 1979.

If you have any questions or require additional information, please let us know.

Sincerely,

David V. Welch

David V. Welch, Manager
Grants & Contracts Acctg.

DVW/BITS/el
Enclosure

cc: Dr. R. M. Wartell
Dr. R. A. Salvo
Dr. D. Finkelstein
Mr. E. E. Renfro
Mr. O. H. Rodgers
File G-41-A02

DISTRIBUTED ON 5/13/80

Department of Health, Education, and Welfare

NAME AND ADDRESS OF GRANTEE INSTITUTION	TRANSACTION NO.	Grant No.
Georgia Institute of Technology Atlanta, Georgia 30332	(08) R1GM24734A	5 R01 GM24734-02
	INSTITUTIONAL ID NO.	DATE OF THIS REPORTING PERIOD FROM 1/1/79 TO 12/31/79
	G-41-A02	PROJECT PERIOD FROM 1/1/78 TO 12/31/80
		☐ CHECK IF FINAL REPORT

1. Expenditures of DHEW Funds for this Reporting Period

a. Personnel	$	h. Alterations and renovations	
b. Consultant services		i. Other	
c. Equipment			
d. Supplies		j. Total direct costs	33,369.70
e. Travel, domestic		k. Indirect costs: Rate 76 % ☒ S&W ☐ TDC Base $ 27,711.70	21,060.89
f. Travel, foreign			
g. Patient care costs		l. TOTAL	$ 54,430.59

2. Expenditures from Prior Periods (previously reported)	51,133.00
3. Cumulative Expenditures	105,563.59
4. Total Amount Awarded — Cumulatively	105,822.00
5. Unexpended Balance (Item 4 less Item 3)	258.41
6. Unliquidated Obligations	-0-
7. Unobligated Balance (Item 5 less Item 6)	258.41
8.a. Cost Sharing Information — Grantee Contribution This Period	3,077.41
b. % of Total Project Costs (Item 8a divided by total of Items 1 and 8a)	% 5.0
9.a. Interest/Income (enclose check)	-
b. Other Refundable Income (enclose check)	-

10. Remarks

I hereby certify that this report is true and correct to the best of my knowledge, and that all expenditures reported herein have been made in accordance with appropriate grant policies and for the purposes set forth in the application and award documents.

Roger M. Wartell R. A. Salvo — 22 April 1980

Drs. R. M. Wartell R. A. Salvo Co-Directors — Date

David V. Welch — 4/25/80

SIGNATURE OF INSTITUTION OFFICER — DATE

David V. Welch, Manager, Grants & Contracts Acctg.

404/894-4624

REPORT OF RESEARCH GRANT EXPENDITURES