

計畫編號：甲-91-N-FA07-2-4

「大學學術追求卓越發展計畫」

重點研究類計畫構想申請書

基本資料

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總計畫名稱：交叉生物研究計畫

計畫執行期限：91 年 1 月 1 日 至 94 年 12 月 31 日

計畫主領域 (單選)：

- | | |
|------------------------------------|---|
| ☐ 1. 生命科學領域 | ☐ 3. 工程與應用科學領域 |
| X 2. 自然科學領域 | ☐ 4. 人文與社會科學領域 (含科學教育) |

分項計畫所跨之領域 (可複選)：

- | | |
|----------------|---------------------------------------|
| X 1. 生命科學領域 | ☐ 4. 人文及社會科學領域 |
| X 2. 自然科學領域 | ☐ 5. 科學教育領域 |
| X 3. 工程與應用科學領域 | |

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計畫編號：甲-91-N-FA07-2-4

大學學術追求卓越發展計畫

重點研究類計畫構想申請書

A

Conceptual Proposal for a Priority Research Project
In the
Program for Promoting Academic Excellence of Universities

交叉生物研究計畫

THE BIO-CROSS PROJECT

A Life Science Oriented
Integrated Interdisciplinary Research Project
In Natural Science, Engineering and Computer Science

全程計畫：自民國九十一年一月至民國九十四年十二月

Project Duration: 2002 January to 2005 December

國立中央大學

National Central University

2000 October 25

(Website for copy of proposal: <http://www.phy.ncu.edu.tw/hclee/SURE/biox-prop.pdf>)

PREAMBLE

The rapid progress and successes of the Human Genome Project have fundamentally altered the landscape of research in the life sciences. Huge bodies of biological data including DNA and protein sequences now exist in public databanks and the rate of their accumulation is accelerating. These data holds vast amounts of information on every aspect of life and health, the uncovering of which will call for massive interdisciplinary research efforts. This is a golden opportunity for and a great challenge to those who recognize its importance. Many leading research establishments around the world have responded to this event by setting up new interdisciplinary research groups, networks and centers.

The Bio-Cross Project is the response of the National Central University to this challenge and it seeks support from the **Program for Promoting Academic Excellence of Universities** to build the **infrastructure** for a **Center Of Excellence** on interdisciplinary life science at NCU. Related programs in these fields in the Schools of Engineering, Natural Sciences and Computer Science and Informatics at NCU and elsewhere will be integrated into the Project. The emphasis of research will be on the physical, mathematical and statistical properties of biological systems and biosequences, and bioinformatics, and the application of physics, mathematics, engineering and information science to the advancement of the life and health sciences.

1. 研究總目標與分年研究重點

1.1. GOALS OF THE BIO-CROSS PROJECT

- TO build a Bio-Cross Center of Excellence for interdisciplinary research integrating the Life Sciences, Physical Sciences, Engineering and Computing and Information Sciences to meet the challenge brought forward by the success and continuing progress of the Human Genome Project.
- TO excel in research in certain topics including the physical properties of biomolecules, protein folding, molecular evolution and bioinformatics.
- TO identify other important problems in the Life Sciences whose solutions physicists, mathematicians, engineers and computer scientists can contribute.
- TO form vigorous research teams for the pursuit of such solutions and to create a favorable environment for the operation of such research teams.
- TO integrate the Bio-Cross Project into the international network of important research establishments by doing outstanding research, by publicizing its work through important journals and by establishing exchange channels to it.

1.2. YEARLY RESEARCH PRIORITIES

Code for subprojects: **X** – Bio-Cross. **A** – Membrane proteins. **B** – Dynamics of biomolecules. **C** – Sequence-specific DNA uptake systems in human pathogens. **D** – NMR study of peptides and proteins in solution and in membrane. **E** – Biocomputing. **F** – Protein folding and aggregation. **G** – Bionformatics I. **H** – Microarray & biosensor. **I** – Bionformatics II. **J** – Educational and ethical issues.

The Bio-Cross Project will be an evolving program. It seeks to identify important problems continuously. On this basis the yearly research priorities given below may be adjusted accordingly as the Project progresses. In the following list of research priorities the subproject codes given above are used. Project wide priorities are put under the heading **X**.

2002 – **X**: Set up infrastructure of the Bio-Cross Project. Hire people. Put in place evaluation and review mechanisms. **A**: Purchase equipment and establish core technology. Initiate experiments on membrane disruption by neutral antimicrobial peptides such as alamethicin. **B**: Purchase equipment and set up laboratory for experiment. Initiate experiments on DNA molecule chain dynamics and rheology. **C**: Study constraints imposed by DNA uptake signal sequences (USS) in *Haemophilus influenzae* genome by comparing conserved coding sequences and placements of USS in genes. **D**: Identify suitable target proteins, prepare sample and initial characterize macromolecular systems. **E**: Purchase high-speed computers and establish core technology (shared with **F**). Investigate the use the inventory of oligonucleotides in a DNA sequence as a tool for studying phylogeny, test the idea on 16S RNA. Initiate research brain function, keying on wave properties. Study elastic and mechanical properties of DNA and proteins. **F**: Study folding mechanisms and intermediate states of β -peptides, including G-peptide and β -nova. **G**: Purchase high-speed computers that specialize in sorting, searching database management. Systematic search of repeat sequences in genomes in GenBank and construct Repeat Sequence Database. **H**: Establish core technology and set-up necessary instruments to be used for spotting, detection and analysis. **I**: Large-scale gene expression analysis and genetic network modeling. **J**: Collect material and research results on genetic education, develop framework for genetic literacy approach, set up homepage for genetic news and education.

2003 – **X**: Establish Bio-Cross Center of Research Excellence. Build connections with international centers. Build Microarray Laboratory for research and teaching. Conduct project review at year-end. **A**: Initiate experiments on penetration of protein- transduction peptide through membranes. **B**: Initiate experiments on biomolecules in vortex relaxation and turbulence suppression. **C**: Extend study on sequence specific DNA uptake system to other

human pathogens including *Neisseria* and *Actinobacillus actinomycetemcomitans*. **D**: Determine of solution structure of target membrane lipids, peptides and proteins. Obtain solid-state NMR spectra and perform data analysis and simulation for extracting macromolecular dynamics. **E**: Investigate dependence of evolution mechanisms on correlations in distances between DNA sequences based on sequence alignment and oligonucleotide inventory, respectively. Study DNA and proteins under stretching and torsion forces, and the unzipping of double stranded structure by external force. **F**: Folding simulations of G-peptide and β -nova. Simulate stability and thermodynamics of small α/β proteins, including BBA1 and FSD1. **G**: Design and construct Gene Warehouse to integrate existing gene databases such as GenBank, SRS, AceDB, and others. **H**: Develop novel detection technology based on interfacial potential (IP) and surface plasma resonance (SPR) measurement methods. Initiate research on analysis of microarray data. **I**: Algorithm development for genome-wide prediction of protein functional networks. **J**. Work on ethical issues relating to genetic determinism and gene therapy.

2004 – X: Build vigorous visitors' and exchange program for research staff and students. Update computers for **C**, **E**, **F** and **G**. Devise programs that promote a culture in which excellence is recognized and respected. **A**: Initiate experiments on transduction of proteins and enzymes into lipid vesicles due to the attached protein-transduction peptide. **B**: Initiate experiments on micro-dynamics of membrane fluidity. Look out for opportunity to initiate project on material for biosensor. **C**: Study the origin of the non-random distribution of USS and benefits and costs of DNA uptake. **D**: Close checking with theorists, devising new experiments and exploring other new systems. **E**: Use correlation between alignment based frequency of oligonucleotides based distances to study evolution process. Electrical properties of biomolecules. **F**: Simulate folding processes of small α/β proteins, including BBA1, FSD1, and protein G. **G**: Establish a repository for DNA microarray based gene expression data. **H**: Evaluate newly developed IP and SPR technology based on accuracy and precision. **I**: Protein functional networks based on metabolic pathway, biological process, and closely related physiological function. **J**. Complete work on genetic literacy. Sketch educational and ethical programs for integration into various educational channels.

2005 – X: Construct web-based research platform for Project. Write report evaluating four-year program and prepare Center for operating at level of excellence with regular funding. **A** and **B**: Bring projects to conclusion. **C**: Study origin of abundance of USS and evolution of competence. **D**: Bring the project to conclusion. **E**: Extend studies on molecular evolution to whole genome comparison. **F**: Computational studies of amyloid β (A β) protein, aggregation process. **G**: Build a Protein Database mirror site and possibly other mirror sites. **H**: Bring projects to conclusion. **I**: Construction of Protein functional networks based on common structural complex. **J**: Complete courses on genetic education program and run trials on various levels with different subjects and users.

2. 計畫整體架構及整合之必要性

STRUCTURE OF THE BIO-CROSS PROJECT AND RATIONALE FOR INTERDISCIPLINARY INTEGRATION

The Bio-Cross Project recognizes that if outstanding science is to be made in the modern life science, the traditional barriers separating biology, the physical sciences, engineering and information and computer sciences must to be transcended. In addition to faculty members from four schools and seven departments at the National Central University, Bio-Cross is joined by members from the Academies of Sciences in Beijing and Taipei, Rice Univ., Univ. of Delaware and NIH from USA and Univ. of British Columbia from Canada to form ten research subprojects. The names of the subprojects, followed by names of respective project leaders are:

- A. **Membrane proteins** – Fang-Yu Chen (陳方玉 NCU/Physics) and Hui-Wen Huang (黃惠文 Rice Univ./Physics)
- B. **Biomolecules** – Lin I (伊林 NCU/Physics)
- C. **Sequence-specific DNA uptake systems in human pathogens** – R.J. Redfield (Univ. British Columbia/Zoology)
- D. **NMR Study of Peptides and Proteins in Solution and in Membrane** – Tai-Huang Huang (黃太煌 Academia Sinica/IBMS)
- E. **Biocomputing** – Hoong-Chien Lee (李弘謙 NCU/Physics & Life Science) and Bai-Lin Hao (郝柏林 Beijing ITP)
- F. **Molecular Dynamics Studies of Protein Structure** – Yong Duan (段勇 Univ. Delaware/Chemistry and Biochemistry)
- G. **Bionformatics I** – Jorng-Tzong Horng (洪炯宗 NCU/Comp. Sci. & Information)
- H. **Microarray and Biosensor** – Jing-Chie Lin (林景崎 NCU/Mech. Eng)
- I. **Bionformatics II** – Hong-Hui Wan (萬宏輝 NIH/NCBI(US))
- J. **Ethical& Educational Issues** - Shui-Cheun Lee (李瑞全 NCU/Philosophy)

Project policy, strategy, budgeting, operation and review will be coordinated by the Project Committee composed of project leaders and advisors. An Activities Committee staffed by researchers will organize and run the many project-wide events such as Project meetings, workshops, schools, visitors' program, and so on. A small non-scientific staff will provide secretarial support. See Figure 1.

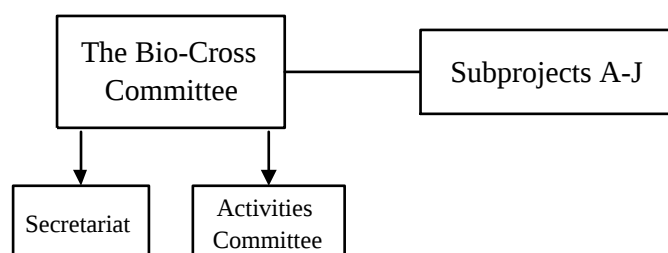


Fig. 1. Schematic Structure of The Bio-Cross Project

Figure 2 shows the six disciplines involved in the Bio-Cross Project: chemistry and biochemistry, biology, mathematics and physics, computer and information sciences, engineering and philosophy, their primary (solid line) and secondary (dotted line) connections to the subprojects, and inter-subproject connections (dashed lines; some are omitted to avoid cluttering).

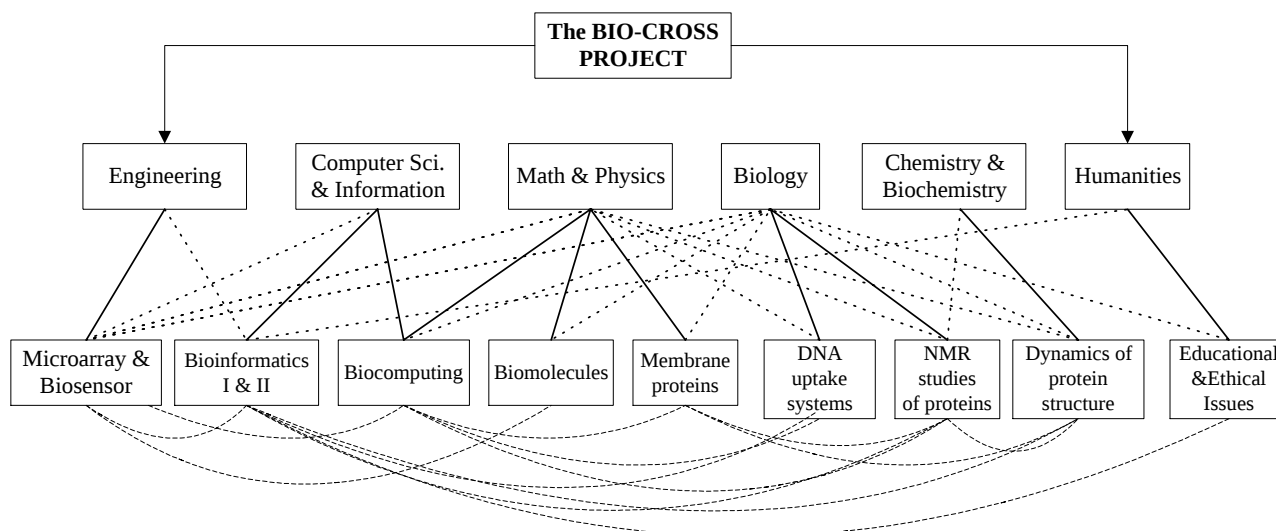


Fig. 2. Interdisciplinary and cross-project links

Each subproject is connected to at least two disciplines. The natures of the biology-project and math/physics-project connections are complementary. Biology gives significance to a problem and connects it to the life and health sciences, while math/physics brings new perspective to the nature of the problem and provides means to gain its understanding at a deep level. The many connections to and from Biocomputing and Bioinformatics subprojects point to the central roles they play in today's integrated field of life science.

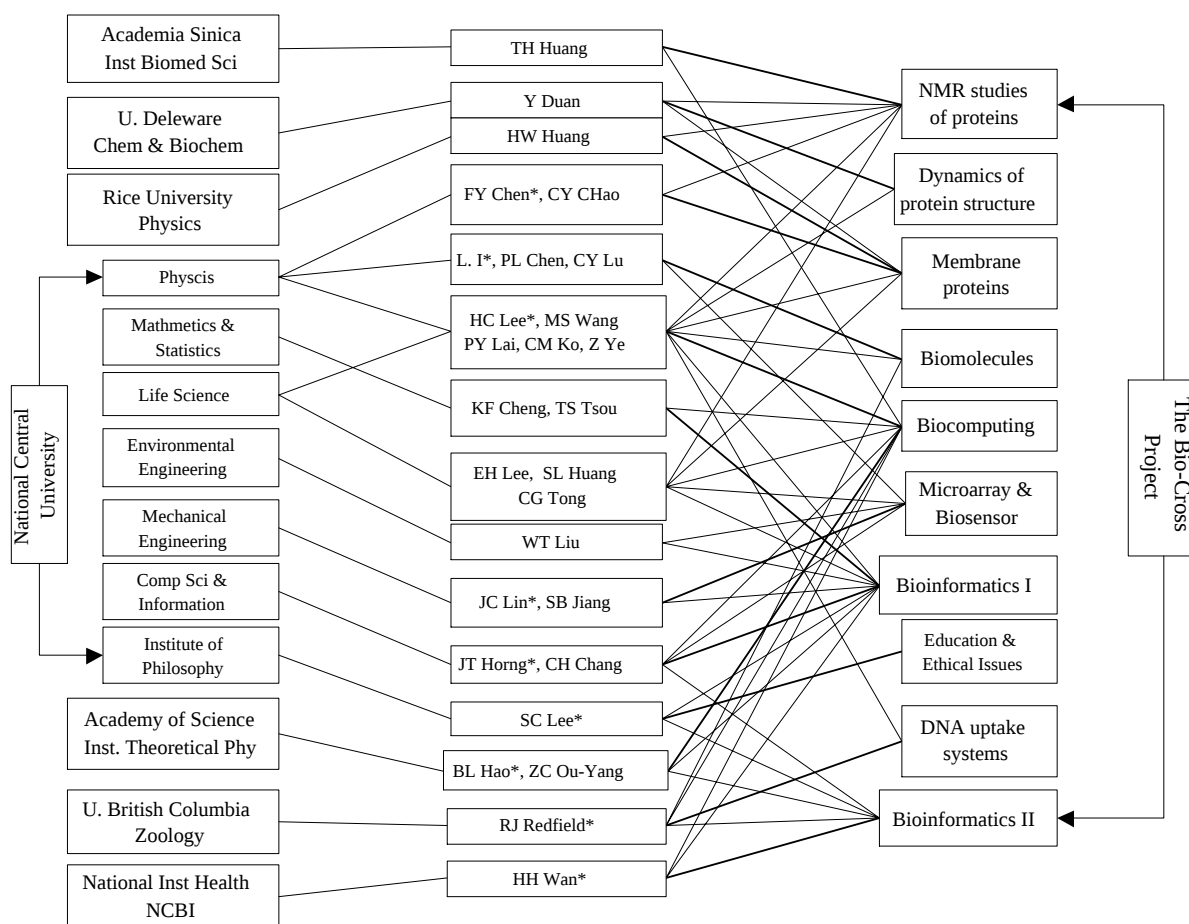
Interdisciplinary and inter-subproject links are a key to the Bio-Cross Project. The integration of the various components in the Project with these links is a crucial first step in our effort to reach the goal of meeting the challenge of the new era of scientific research brought forward by the Human Genome Project.

Exchange and Visiting Programs. In view of the fact all the areas of science we will be working on are far more advanced overseas, the Bio-Cross Project will conduct vigorous visiting programs to promote the exchange of faculty members, researchers and students between NCU and other life science oriented interdisciplinary research centers in the States, Canada, Europe, China and Japan. Centers that we have already initiated contacts with include the Canadian Institute for Advanced Research, the Bio-X Program at Stanford University and the LJIS (The La Jolla Interfaces in Science) Program at UC San Diego.

3. 參與研究人力與分工情形

ORGANIZATION OF RESEARCH MANPOWER

Faculty members in the Bio-Cross Project, their affiliation and the subproject(s) they have joined are shown in Figure 3. Members are grouped according to primary subproject association, indicated by the thicker lines. Subproject leaders have asterisks attached their names. As befits the interdisciplinary nature of Bio-Cross the majority of project members will be involved with more than one subproject.



* Names with asterisks attached are leaders of subprojects, connected by thick lines

Fig. 3. Members of Bio-Cross, affiliation and links to subprojects

A very short selection of reprints of their recent journal publications can be accessed at the website <http://www.phy.ncu.edu.tw/hclee/SURE/reprints.htm>.

We plan for a regular staff of 8 PDF equivalents and 8 non-PhD Research Associate equivalents. Qualified personnel in alternative military service will be a source of manpower. There should be roughly thirty graduate and undergraduate students involved with the Project at any given time.

4. 分年經費概括 ANNUAL BUDGETS (in NT\$ Million)

Grand total over four years: NT\$ 164 Million

(See Section 1.2 for code for subprojects)

Projects	2002	2003	2004	2005	4-year total
X capital	2	1	1	1	5
operational	7	5	5	5	22
subtotal	9	6	6	6	27
A capital	6	4	3	2	15
operational	2	2	2	2	8
subtotal	8	6	5	4	23
B capital	6	4	3	2	15
operational	2	2	2	2	8
subtotal	8	6	5	4	23
C capital	0.5	0.5	0.5	0.5	2
operational	1	1	1	1	4
subtotal	1.5	1.5	1.5	1.5	6
D capital	2	2	0.5	0.5	5
operational ¹	.5	1.5	1.5	1.5	6
subtotal	3.5	3.5	2	2	11
E capital	4	2	3	1	10
operational	3	3	3	3	12
subtotal	7	5	6	4	22
F capital	0.5	0.5	0.5	0.5	2
operational	1	1	1	1	4
subtotal	1.5	1.5	1.5	1.5	6
G capital	4	2	3	1	10
operational	1.5	1.5	1.5	1.5	6
subtotal	5.5	3.5	4.5	2.5	16
H capital	4	3	2	1	10
operational	1.5	1.5	1.5	1.5	6
subtotal	5.5	4.5	3.5	2.5	16
I capital	0.5	0.5	0.5	0.5	2
operational	1	1	1	1	4
subtotal	1.5	1.5	1.5	1.5	6
J capital	0.5	0.5	0.5	0.5	2
operational	1.5	1.5	1.5	1.5	6
subtotal	2	2	2	2	8
Project Total					
Capital	30	20	17.5	10.5	78
Operational	23	21	21	21	86
Yearly total	53	41	38.5	21.5	164

5. 預期之具體研究成果

EXPECTED RESEARCH RESULTS

Infrastructure

We expect to have the following laboratories/center in place:

- Laboratory for Membrane Protein Research
- Laboratory for Biomolecules
- Laboratory for Biocomputing
- Microarray Laboratory
- Bioinformatics Center

Academic activities, infrastructure support and international exchange and visiting programs of these laboratories/center will be coordinated by the Bio-Cross Committee. By the end of the four-year period we expect the Bio-Cross Project to have established exchange programs or collaboration channels with other research centers and health centers in Taiwan and with international research centers.

Publication

We expect to have built up capabilities to do research of international caliber in areas including membrane proteins, property and application of biomolecules, protein structure, molecular evolution, genomics, proteomics, microarray technology, microarray analysis and certain subjects in bioinformatics. We expect to have the ability to meet new challenges in this field when they arise. We expect to have published at least 10 papers in internationally respected journals in the first year of the project and at least 20 papers in the years thereafter. We aim for some of the papers being published in Science and/or Nature.

Manpower training

We expect to have trained about 15 postdoctorals, 15 PhD's and 15 non-PhD researchers to have the ability to do research work in Bio-Cross related fields, and about 30 Master level graduates who can either continue their study in the field or enter industries in related fields. In future years we expect to train about 4 postdoctorals, 5 PhD's, 4 non-PhD researchers and 10 Masters each year.
