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Abstract:

This proposal aimed at the development of mathematical, computer, recombinant DNA, selection and screening procedures to attain adaptive evolution of entirely novel peptides or fusion proteins with useful catalytic, ligand binding, structural or other features. Potential uses range from industrial catalysis to production of new drugs and vaccines. A broad purpose of the experimental effort is to obtain novel peptides which can mimic the biological effects of almost arbitrary signal molecules such as hormones, growth factors, even pathogenic antigens. Mathematical models were developed to explore rugged "adaptive landscapes" associated with protein evolution. The fundamental importance of this work includes analysis of the distribution of function in peptide space and opening the way towards a technology of applied molecular evolution.
Office of Naval Research
Final Report
Publications/Patents/Presentations/Honors/Students Report
for
Contract # N00014-85-K-0258 PRIME PO4

Selectable Sets of Novel Proteins:
Catalytic and Other Properties

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Part I

a. Papers Submitted to Refereed Journals


b. Papers Published in Refereed Journals


c. Books (and sections thereof) Submitted for Publication

d. Books (and sections thereof) Published
   None.

e. Technical Reports and Papers Published in Non-Refereed Journals

f. Patents Filed
   None.

g. Patents Granted
   None.

h. Invited Presentations at Conferences
   S.A. Kauffman, Complex Systems Summer School, Santa Fe Institute, Santa Fe, NM, June 9-July 8, 1988.


i. Contributed Presentations at Conferences
   None.

j. Honors/Awards/Prizes
   None.

k. Number of Graduate Students Receiving Full or Partial Support on ONR Contract
   1. Thomas Labean
   2. Lloyd Clark

l. Number of Postdoctoral Fellows Receiving Full or Partial Support on ONR Contract
   1. Edward D. Weinberger
m. Manuscripts in Preparation

S.A. Kauffman, L. Clark and E. Weinberger. The NK model of random epistatic interactions: Landscape structure.

Part II

a. Principal Investigator
   Stuart A. Kauffman
b. Cognizant ONR Scientific Officer
   Parbury Schmidt
c. Current Telephone Number
   215-898-8731
d. Brief Description of Project

1. The generation and cloning of a very large library of pseudo-random DNA coding sequences into an expression vector.

2. Demonstration that the pseudo-random sequences code for and lead to the synthesis of novel peptides or fusion proteins.

3. Attempt to select for catalytic or other function by the novel peptides.

4. Explore mathematical models of rugged "adaptive landscapes" associated with protein evolution.

e. Significant Results

Points 1. and 2. part d., above, have been achieved. A library with 10,000,000,000 novel pseudo-random coding sequences has been obtained and statistically characterized. Point 3. has not been accomplished. We selected for viral vectors with novel genes which conferred resistance to gentamicin and chloramphenicol in E.coli hosts, found such resistance but have been unable to confirm the case where the resistance is due to the novel gene. Point 4. We have developed a spin-glass like model of rugged but correlated fitness landscapes. The model allows us to predict features of the adaptive "maturation" of the immune response by rapid accumulation of somatic mutants in antibody variable regions improving the affinity of the antibody molecule for the incoming antigen.
f. Summary of Future Plans

We plan to clone other novel peptides into new vectors. One plan is to use a vector which allows synthesis of the novel peptide free of inclusion in a fusion protein. We will begin to ask whether pseudo-random peptides or proteins can fold reliably into a compact shape with the hope of understanding the protein folding process. We will attempt to clone novel protein sequences into vectors that will display novel peptides on cell surfaces and test whether we can find novel peptides which mimic a specific antigen by cross-reactivity to a common antigen. Such peptides could become drugs or vaccines. We also hope to clone into a secretion vector and ask if secreted peptides can act to close autocrine feedback loops leading to self-stimulating growth of cells. This is the subject of my new patent application.

Work on rugged landscapes and combinatorial optimization is the subject of a separate proposal to ONR in which we have received additional funding (Contract #N00014-89-J-1623).

g. List of names of graduate students and post-doctorals currently working on the project.

Thomas LaBean, graduate student

Lloyd Clark, graduate student

Edward D. Weinberger, research associate

h. Technical reports submitted to ONR

End-of-Year report July 1988, (this contract).

Part III

This proposal aimed at the development of mathematical, computer, recombinant DNA, selection and screening procedures to attain adaptive evolution of entirely novel peptides or fusion proteins with useful catalytic, ligand binding, structural or other features. Potential uses range from industrial catalysis to production of new drugs and vaccines. A broad purpose of our experimental efforts is to obtain novel peptides which can mimic the biological effects of almost arbitrary signal molecules such as hormones, growth factors, even pathogenic antigens. The fundamental importance of this work includes analysis of the distribution of function in peptide space and opening the way towards a technology of applied molecular evolution.
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