INTERNATIONAL SOCIETY FOR INTERFERON AND CYTOKINE RESEARCH

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The History of Interferon: An Interview with Thomas C. Merigan

Paul D. Drew

Our "History of Interferon" series, featuring individuals who have made seminal contributions in interferon and cytokine research, continues with this interview of Dr. Thomas C. Merigan. Born and raised in the San Francisco Bay area, Merigan graduated with honors from the University of California, Berkeley in 1955, and completed medical training in 1958 at the University of California Medical School in San Francisco. Merigan began his research career in the area of lipid biochemistry while still at U.C.S.F. He served his internship and residency on the Harvard Medical Services at
Boston City Hospital. This experience afforded him excellent training in clinical medicine and

research in a busy city hospital. While at Harvard, Merigan investigated the effect of intravenous Pituitrin upon gastrointestinal bleeding in liver disease. These studies led to Merigan's first experience with controlled clinical trials, which established that Pituitrin was effective in controlling gastrointestinal bleeding. The skill of developing and analyzing clinical trials would prove essential in Merigan's future clinical trials regarding the effect of interferons on viral diseases and cancer.

Following the discovery of the structure of DNA in the late 1950's by Watson, Crick, and others, the scientific world was charged with excitement concerning the new field of Molecular Biology. In 1960, Merigan began three years of training in Molecular Biology at the National Institutes of Health in the laboratory of Nobel Laureate Christian Anfinsen. Here, Merigan studied gene-protein relationships of lysozyme in a bacteriophage system. Before leaving NIH, Merigan became fascinated by the work on interferon being conducted in the laboratory of Sam Baron. Merigan joined the Baron laboratory which also included Hilton Levy and Bob Friedman, three individuals whom Merigan proudly refers to as friends-for-life. Merigan had become skilled in protein purification in Anfinsen's laboratory, and this expertise proved extremely valuable in the interferon system. While at NIH, through his initial attempts to isolate interferon, Merigan immediately noted that interferon is a very potent material since he could not see protein purifying with the biological activity. This told Merigan that he must be prepared to work with large amounts of starting material if he was going to be able to study the purified protein. Fortunately, Maurice Hillman at Merck supplied Merigan with chorionic fluid from chick eggs infected with influenza under conditions where large amounts of interferon were made. This allowed Merigan to purify chick interferon in quantities suitable for characterization.

In 1963, Merigan joined the faculty at Stanford University School of Medicine. Here, he was the first to isolate and assay human interferon in human foreskin cells. Merigan would subsequently isolate leukocyte interferon from human, mouse and chick. This allowed him to compare the physical properties of these species-specific non-cross-reactive interferons in the same laboratory.

Many valuable collaborations arose from the purification of these interferons. For example, Merigan collaborated with Bill Joklik in investigating the mechanism of action of mouse leukocyte interferon against vaccinia infection. In addition, studies with Earnest Jawetz demonstrated that in addition to anti-viral effects, interferon also affects more complex pathogens including chlamydia. Merigan also warmly reflects upon the influence Alec Isaacs had upon his career in interferon research. Sam Baron did a sabbatical in the Isaacs laboratory and the assays developed by Baron and Isaacs in the chick and mouse system were used by Merigan to study human leukocyte interferon. Isaacs also wrote Merigan a personal note congratulating him on his work with leukocyte interferons and inviting him to participate in a CIBA symposium in the mid-1960s. This note served as a

great source of encouragement to Merigan.

Trained as a clinician, Merigan's research became increasingly focused upon the efficacy of interferon in the treatment of human disease.

Here, the Merigan laboratory reported a variety of seminal studies regarding the therapeutic effect of interferon in viral infection and cancer in humans. For example, Merigan and colleagues in 1965 were the first to demonstrate circulating interferon following live virus vaccination (measles) and that such interferon was active against viral disease (vaccinia) in man. In 1967 the laboratory demonstrated in now classic New England Journal of Medicine and Nature papers that a synthetic polymer could produce interferon in man. The Merigan' studies which likely elicited the most attention concerned the demonstration that systemic administration of interferon protected against local vaccination of small pox. Merigan reports that these early years in interferon research were extremely exciting. Important discoveries were occurring at a rapid pace and the potential applicability of interferon in fighting disease seemed endless.

The extensive basic biology and clinical studies, including those performed in his laboratory, formed a solid base for future clinical trials evaluating the effects of interferon on human disease. Merigan played an instrumental role in these initial clinical trials. In fact, Merigan demonstrated the first important clinical application of interferon in 1973 when he reported results from randomized controlled clinical trials that local application of leukocyte interferon inhibited rhinovirus infection. Later, the laboratory demonstrated that systemic administration of this interferon benefited cancer patients with herpes zoster infections or varicella. Clinical trials involving the use of leukocyte interferon and arabinoside, both alone and in combination, to fight hepatitis B virus infection conducted by the Merigan group, led NIH to sponsor the first large-scale, randomized controlled study concerning anti-viral treatment of hepatitis B. To this day, alpha interferon remains the only licensed method of treatment for this infection.

In 1978, the Merigan laboratory and oncologists at Stanford Univ. demonstrated for the first time that leukocyte interferon produced acute tumor shrinkage in non-Hodgkin's lymphoma. These studies were instrumental in the American Cancer Society's decision to conduct large-scale clinical trials on the efficacy of leukocyte interferon in human cancers. Future studies demonstrated the utility of leukocyte interferon therapy in chronic myeloid leukemia and renal cell cancer, as well as other forms of cancer. The initial clinical trials of the Merigan laboratory also triggered interest by pharmaceutical companies that ultimately produced human interferon in bacteria as one of the first recombinant DNA products. In 1982-1983 Merigan and colleagues demonstrated that recombinant human leukocyte interferon, like interferon purified from human tissues, exhibited anti-viral action against hepatitis B infection and produced tumor shrinkage in humans. Dr. Merigan expresses his good fortune at being privileged to see interferon from its relative infancy involving the purification and characterization of crude interferon preparations through it's demonstrated utility as an anti-viral

and anti-tumor agent in both crude and recombinant form.

A major lesson Dr. Merigan learned from his interferon studies, which he wishes to impart on this readership, is that successful clinical therapy with interferon resulted from a tremendous body of basic research and animal model development prior to clinical trials. These studies suggested where and how interferon should be administered, when to introduce interferon in disease processes, and where interferon works naturally, all critical information in maximizing the potential for successful interferon therapy. Merigan argues that many cytokines have not proven therapeutically useful subsequent to leukocyte interferon in large part due to the fact that the basic biology of these cytokines is not thoroughly understood. He also suggests that many of these cytokines will ultimately be of therapeutic value following more extensive characterization and animal model development. Merigan also emphasizes the importance of basic research in maximizing the clinical potential of interferons and cytokines. He notes that this information is critical for clinicians, who understand the particulars of human disease, in determining niche applications for these
agents. For example, certain optic nerve tumors and papillomas were difficult to access surgically until surgeons demonstrated that leukocyte
interferon shrunk the tumors making the operative field manageable. Merigan emphasizes that NIH must continue to support basic research if therapeutics are to reach their maximum potential in the clinic.

For the past fifteen years Dr. Merigan has served as the Director of the Center of AIDS Research at Stanford University. Here, he continues his work regarding host resistance to viral infections. Lessons learned in
interferon studies have been essential in Merigan's AIDS studies. In particular he notes that these experiences have allowed him to successfully
design and analyze AIDS clinical trials. In addition, the ability to measure HIV viral load in the circulation allows physicians to assess the response of patients to
therapeutic drugs. Physicians commonly assess treatment by measuring HIV RNA levels in the circulation, which was
pioneered in his laboratory. This is a direct result of Merigan's previous interferon clinical trials that used hepatitis B DNA as a marker of disease severity and response to therapy.

Merigan views funding as the most significant issue facing
scientific research. He suggests that funding levels should rise to at least 25-30%. This would allow investigators to propose and conduct more high impact research, which would facilitate significant scientific discoveries. Merigan expresses concerns that few young people are pursuing scientific careers, and that many young scientists have left the field. He warns that since it takes many years to develop as a scientist, this could result in a lost generation of scientists. Merigan is encouraged by the
recent bi-partisan support for increasing science funding by the Congress of the United States. However, he warns that at this critical juncture, scientists must be active participants in securing the future of scientific research. He stresses that scientists must inform society and elected

officials of the importance of scientific research. Perhaps most importantly, Merigan emphasizes that we must provide children with an appreciation of science so that appreciation may grow as they grow. This is sound advice from Thomas Merigan, a distinguished interferon research scientist.

TWO PARALLELS DO NOT HAVE TO START AT THE SAME POINT.

We enjoyed reading the interview of Sidney Pestka in the ISICR newsletter in which Patricia Fitzgerald-Bocarsly relates Pestka's many interesting contributions to various research fields, and more especially to research on interferon. Of particular interest to us was the part in which Sidney described what we consider to be the onset of molecular biology in the interferon field. The ability to detect interferon mRNA in the pool of total mRNA by its translation into a biologically active protein was based both on the high specific activity and the species specificity of the protein. This could be detected by a reproducible biological assay and opened without a doubt the way for the molecular cloning of interferon cDNAs.

But coming back to those years, although several laboratories did eventually show that interferon mRNA could be translated using various systems, the work referred to by Sidney Pestka as a "classical example of parallel research" was parallel only at the end but not at the beginning! The first publication showing that IFN mRNA could be detected, by its translation in heterologous cells, appeared in 1972 in PNAS (De Maeyer-Guignard et al., 1972). In this paper Jaqueline and Edward De Maeyer and Luc Montagnier showed that transfection of mRNA from NDV-induced mouse cells into chick cells or into Vero cells resulted in the production of mouse IFN. Similarly, mRNA extracted from induced monkey cells transfected into chick cells or into VERO cells resulted in the production of monkey interferon. Uninduced cells did not yield translatable RNA. These findings were confirmed by Fred Reynolds and Paula Pitha (1974) who translated, also in heterologous cells, human IFN mRNA from poly I:C induced human fibroblasts, and by Montagnier et al. (1974), who showed that mouse IFN mRNA from NDV induced C243 cells and from poly I:C induced L cells was translated in Actinomycin D-treated chick embryo fibroblasts (see note at the end, after the references).

A number of groups then followed up on these initial findings, and, in 1975, four additional papers appeared, describing translation of IFN mRNA. Thang, De Maeyer and Montagnier (Thang et al., 1975) showed translation of IFN mRNA in a cell free system, as did Sidney Pestka's group in collaboration with Jan Vilcek, (Pestka et al., 1975). Kronenberg and Friedmann (1975), using the heterologous cell system, translated IFN mRNA from human cells in mouse cells. At the same time, Reynolds, Premkumar and Pitha (1975) injected human IFN-mRNA into frog oocytes and obtained high levels of biologically active human IFN. These four 1975 papers were the subject of a commentary by David Metz in the journal Nature (Vol 259, 5

Fehr, 1976 page 10), who wrote, among other comments : "The scene for the recent reports was set a few years ago by De Maeyer and his colleagues who boldly applied RNA extracted from either mouse or monkey cells which had been induced to synthesize interferon, directly to heterologous cells and showed that the recipient cells were able to make murine or simian interferons, respectively". The oocyte method used by Reynolds et al. (1975), which was both technically easy and highly reproducible, was subsequently used by Sid Pestka's and other groups for further studies of IFN mRNA.

In the long run, it is perhaps not very important to know who did what and when, as long as the results of the different groups ensure the progress of the field. But since the ISICR has recently started an Archive Committee to deal with the history of interferons and cytokines, it may be worthwhile to give the facts in the right context and chronology. Now that cloned interferons have useful clinical applications, we are happy that our initial observations were the starting point of a new era in IFN research, leading to its molecular cloning and its clinical use.

Paris, March 1998

Edward De Maeyer
Luc Montagnier
Paula Pitha-Rowe

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Relative quantitative assay of the biological activity of interferon messenger ribonucleic acid. LH.Kronenberg and T. Friedmann. J. Gen. Virol, 27: 225-238 (1975).

Interferon activity produced by translation of human interferon messenger RNA in cell-free ribosomal systems and Xenopus Oocytes . F.H.Reynolds, E. Premk-umar, and P.M. Pitha. Proc. Natl. Acad. Sci USA, 72: 4481-4485 (1975).

NOTE : When the De Maeyers and Montagnier had the idea of using heterologous cells to translate interferon mRNA, they were convinced that this type of approach to translate mRNA had never been used before. However, several years later, it came to their attention that, as early as 1962, Harold Amos and Katherine E. Kearns produced evidence that cultured chick embryo fibroblasts were able to translate RNA extracted from E. Coli into bacterial protein, and, in a later publication, Amos and coworkers showed that mouse protein was made by chick cells that had received mouse RNA!

Synthesis of "Bacterial" protein by cultured chick cells. H. Amos and K.E. Kearns. Nature, 195: 806-808 (1962).
Evidence for messenger activity of alien ribonucleic acid in chick cells. H. Amos, B. Askonas and R. Soeiro. National Cancer Institute Monograph No 13: 155-165 (1964).

WWW

Radiation Hybrid Database Release 12.0

ftp://ftp.ebi.ac.uk/pub/databases/RHdb/rh.dat{.gz}

It encompasses 8 panels, 104 experimental conditions and 72244 RH entries for 2 different species (human and mouse). If you have any questions or notice anything wrong, please contact us at:

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URL: http://www.ebi.ac.uk

Genome Navigator

http://www.mpimg-berlin-dahlem.mpg.de/~andy/GN

Recent additions:
B.subtilis genome is available.
E.coli genome can be now viewed with two different schemes of functional assignment.

S.cerevisiae gene duplications viewer has been added.
Andrei Grigoriev

ProClass
Protein Family Database

http://diana.uthct.edu/proclass.html

The ProClass Protein Family Database is a non-redundant database organized according to family relationships as defined collectively by PIR superfamilies and ProSite patterns. The objectives are to facilitate protein family information retrieval, unveil domain and family relationships, and classify multi-domained proteins. This is
achieved by combining global and motif sequence similarities into a single classification scheme. The current ProClass release consists of 115,453 sequence entries retrieved from PIR-international (Release 55.0,
December 1997) and SwissProt (Release 35.0, November 1997) databases. It has three sub-satabases, ProClass_Family (PCFam), ProClass_Sequence
(PCSeq) and ProClass_Motif (PCMotif) for the collections of family, sequence and motif entries.

ProClass has hypertext links to all major family/domain and structural class databases. The collection of motif sequences and alignments include new ProSite family members identified by our GeneFIND family identification system (Version 3.0, March 1998,
http://diana.uthct.edu/genefind.html)

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Computational Biology, 3(4), 547-561.
- Wu, C. H. and Shivakumar, S. (1998). ProClass protein family database: New version with motif alignments.
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Games for Cytokinologists
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For download, the database is available via the NBRF/PIR ANONYMOUS FTP server at IP address NBRF.Georgetown.Edu in directory "[ANONYMOUS.PIR]." See file [ANONYMOUS.PIR]000README. for more information.

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PHS 398 Templates NIH Grant Applications

http://templeton.cwru.edu

Updated NIH grant templates that can be used with the new version of Microsoft Office 98 for Macintosh are available on our site. These templates are updated versions of those we have distributed since 1991. Those in turn were updates of an early version done by John Livesey at the University of Washington. Thanks, John! If you wish to distribute these please leave the entire folder intact, including this Readme file.
Feel free to post them on your own server, but I¹d appreciate knowing where you¹ve posted them, so I can make backup links. Contact me about
this and any errors you may find at <mailto:djt2@po.cwru.edu>

The Office 98 versions of Word and Excel released in the last week or so are far superior to Version 6, and we have made the move from Word 5.1 to Word 98 because of several new features that make grant layout easier. The only downside that I can see is that non Power-PC

Macs have been abandoned by the new version. The best choice for older Mac users is to use the Word
5.1 and Excel 2.2 templates still available on our site.

Differences:
The major differences between these templates and the older version is that I have modernized the Excel Workbook (one workbook versus two separate sheets earlier) and have linked the output of the Excel sheets
directly to where they belong in the Word document. I have also written a brief tutorial on how to place and frame electronic figures in the text (see "Background" section).

While you are there, please check out our ad for a Post-doctoral position open for a recent M.D. or Ph.D.

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Virus Hoaxes and Information

For virus information in general:
http://www.symantec.com/avcenter/index.html

For information on virus hoaxes:
http://ciac.llnl.gov/ciac/CIACHoaxes.html

http://www.symantec.com/avcenter/hoax.html

http://www.kumite.com/myths/

http://www.nai.com/services/support/hoax/hoax.asp

A overview of hoax virus warnings is at:
http://www.cyberramp.net/hoax.htm

Reviews of Interest

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Trinchieri, G. Proinflammatory and immunoregulatory functions of interleukin-12. 1998. Int. Rev. Immunol. 16:365-396

Waldmann T. et al. Interleukin-2, interleukin-15, and their receptors. 1998. Int. Rev. Immunol. 16:205-226

Update:
Book Review

A Commotion in the Blood: life, death, and the immune system by Stephen S. Hall, (Henry Holt and Company, New York, 1997, 457 pages, list price $30 but available from www.amazon.com for $21 + S/H). Reviewed by Patricia Fitzgerald-Bocarsly in issue 5.1

The editors have been informed that the choice of Sendai virus as an interferon inducing agent by the Cantell laboratory was a direct result of the work done by Ion Gresser in 1961 where he demonstrated that Sendai virus was an excellent inducer of interferon in human amnion cells in culture (Proc. Soc. Exp. Biol. & Med. 108:303, 1961) and in human leukocytes (Proc. Soc. Exp. Biol. & Med. 108:799, 1961)

CLINICAL TRIALS

Phase I Study of Intracavitary Allogeneic Cytotoxic T Lymphocytes and **IL-2** for Recurrent Primary Adult Brain Tumors. Protocol IDs: UCHSC-COMIRB-93426, NCI-T94-0065O. Kevin Owen Lillehei, Chair, Ph: 303-270-5651. University of Colorado Cancer Center , Denver, CO.

Phase II Study of gp100 Antigen Alone or in Combination with Adjuvant **Interleukin-2** in Patients with Recurrent Metastatic Melanoma. Protocol ID: NCI-98-C-0086. Steven A. Rosenberg, Chair, Ph: 301-496-4164, National Cancer Inst., Bethesda, MD.

Phase I/II Study of Infusion of Activated T Cells and Low Dose **Interleukin-2** Combined With Autologous Peripheral Blood Stem Cell Transplantation for Women with Stage IIIB or Metastatic Adenocarcinoma of the Breast. Protocol IDs: STLMC-BRM-9503, NCI-V96-0902. Lawrence George Lum, Principal Investigator, Ph: 414-649-5818. St. Luke's Medical Center, Milwaukee, Wisconsin, USA

Phase I Study of Monoclonal Antibody 3622W94 in Combination with **Interleukin-2** and **Sargramostim (GM-CSF)** in Patients with Advanced Adenocarcinomas. Protocol IDs: RPCI-DS-97-23, NCI-G98-1396. Neal Jay Meropol, Principal Investigator, Ph: 716-845-7673, Roswell Park Cancer Institute, Buffalo, New York, USA

Phase II Study of **Interleukin-12** in Patients with Previously Treated Non-Hodgkin's Lymphoma. Protocol IDs: MDA-DM-97073, NCI-T97-0050. Anas Younes, Principal Investigator, Ph: 713-792-2860. University of Texas - M.D. Anderson Cancer Center Houston, Texas, USA.

Phase I Study of Neoadjuvant Cisplatin and **Interferon Alfa** Followed by Surgery and Adjuvant Radiation Therapy, Cisplatin, and Interferon Alfa for Malignant Pleural Mesothelioma. Protocol IDs: FCCC-96087, NCI-G98-1401. Corey Jay Langer, Chair, Ph: 215-728-2985. Fox Chase Cancer Center, Philadelphia, PA.

Phase II Study of Adjuvant **Interferon Alfa** in Patients with Recurrent Head and Neck

Cancer. Protocol Ids: RPCI-DS-96-66, NCI-G98-1405. Gary N. Schwartz, Chair, Ph: 716-845-5721. Roswell Park Cancer Institute, Buffalo, New York.

Phase III Randomized Study of Adjuvant **Interleukin-2, Interferon Alfa**, and Fluorouracil in Patients with High Risk of Relapse After Surgical Treatment for Renal Cell Carcinoma. Protocol IDs: EORTC-30955. Pieter H.M. de Mulder, Chair, Ph: 31-24-361-52-15. EORTC Genito-Urinary Tract Cancer Cooperative Group.

Phase II Study of **IFN-A** in Patients with Grade I/II Lymphomatoid Granulomatosis (LYG) and of EPOCH Chemotherapy with or without Maintenance IFN-A in Patients with Grade III LYG. Protocol IDs: NCI-94-C-0074D, NCI-MB-325. Wyndham Hopkins Wilson, Principal Investigator, Ph: 301-435-2415. Medicine Branch, National Cancer Institute, Bethesda, Maryland, USA.

Phase II Study of Peripheral Blood Stem Cell (PBSC) Mobilization, Followed by **Interferon Alfa**, Then Autologous PBSC Transplantation Followed by **Interleukin-2** with or without Interferon Alfa for Chronic Phase Chronic Myeloid Leukemia. Protocol IDs: RPCI-DS-96-38, NCI-G98-1395. Meir Wetzler, Principal Investigator, Ph: 716-845-8447, Roswell Park Cancer Institute, Buffalo, New York, USA.

Phase III Randomized Study of Maintenance with **Interferon alfa** vs No Further Therapy Following Complete Response to Chemoradiotherapy for Small Cell Lung Cancer. Protocol IDs: FRE-Q93-902-02, EU-96008. Bernard Lebeau, Chair, Ph: 01-4928-2517 Hopital Saint Antoine, Paris, France.

NEW ISICR MEMBERS

The ISICR wishes to welcome the following new members. Contact the membership office for address and email information.

Melissa Brierley – Toronto, Canada
Donat De Groote- Nivelles, Belgium
Natalia Valdimirovna Delanian- Moscow, Russia
David Gretch-Seattle, WA
Tatiana S. Guseva- Moscow, Russia
Edward R. Hoffmann- Baltimore, MD
Norman B. Javitt- New York, NY
Ahard Kumar-Chicago, IL
Jyothi Kumaran – Toronto, Canada
Lewis John Lee- Basel, Switzerland
King-Teh Lin- Piscataway, NJ

Games for Cytokinologists

Who doesn't belong in a lab?

Announcing the Third Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction

Methods for obtaining information about protein structure from amino acid sequence have apparently been advancing rapidly. But just what can these methods currently deliver?

A first large scale experiment aimed at beginning to answer these questions was conducted in 1994, and culminated in a meeting at Asilomar, California at the end of that year. Some 135 predictions were made by 35 different groups. The results are published in a special issue of Proteins: Structure, Function and Genetics, volume 23, No 3, Nov. 1995.

A second meeting in December 1996 was the culmination of a 9 month long, community wide experiment. Forty-two structural targets provided by crystallographers and NMR spectroscopists were made available to the prediction community. Prior to the public release of structures, more than 900 predictions by approximately 70 research groups world wide were collected. The results are published in a special issue of Proteins: Structure, Function and Genetics, Suppl.1, 1997. Details of the predictions from both experiments and full analysis of CASP2 prediction data are available at:
http://PredictionCenter.llnl.gov/.

We now announce the third experiment. As before, the goal is to obtain an in-depth and objective assessment of our current abilities and inabilities in this area. To this end, participants will predict as much as possible about a set of soon to be known structures. These will be true predictions, not 'post-dictions'.

Experiment

The broad goals of the experiment are to address the following questions about the current state of the art in protein structure prediction:

1. Are the models produced similar to the corresponding experimental structure?
2. Are the models correctly aligned with the experimental structures?
3. Have similar structures that a model can be based on been identified?
4. Are the details of the models correct?
5. Has there been progress between CASP2 and CASP3?
6. What methods are most effective?
7. Where can future effort must be productively be focused?

As in CASP2, all types of methods for predicting protein structure will be considered. However, docking predictions will not be included in CASP3, since a separate experiment is being planned to evaluate this area.

Collection of Prediction Targets

For the experiment to succeed, it is essential that we obtain the help of the experimental community. Therefore we invite Protein crystallographers and NMR spectroscopists to provide details of structures they expect to have made public before 1st October 1998, using the target submission form available at
http://PredictionCenter.llnl.gov/casp3.

Participation

Participation in the experiment is open to all. Intending predictors must register at the web site. Those interested in receiving mailings concerning progress of the experiment may also register as 'observers' . Prediction targets will be made available through the web site. All targets will be assigned an expiry date, and predictions must be received and accepted before that expiration.

Assessment of Predictions

As in previous CASPs, independent assessors will evaluate the predictions. There will be three assessors, representing expertise in the comparative modeling, fold recognition and ab initio prediction areas. Assessors will be provided with the results of numerical evaluation of the predictions, and will judge the results primarily on that basis. Numerical evaluation criteria have

been revised from those used in CASP2, and are now being finalized, in consultation with the prediction community. The assessors will be asked to focus particularly on the effectiveness of different methods.

Release of Results

All predictions and prediction evaluations will be made available through the web site, shortly before the meeting.

Meeting

A meeting will be held 13-17 December, 1998 at Asilomar, California, USA to evaluate the results of the prediction experiment. The meeting will be limited to about 170 participants and precedence will be given to active predictors. It is anticipated that some financial assistance will be available for the more successful predictors. The proceedings of the meeting will be published.

Organizing Committee

John Moult
CARB, University of Maryland, Tim Hubbard
Sanger Centre, Hinxton, UK
Jan Pedersen
Acadia Pharmaceuticals, Denmark
Krzysztof Fidelis
Lawrence Livermore National Laboratory, USA

Support

The organizers gratefully acknowledge support for the CASP3 experiment from the Department of Energy, the National Library of Medicine and the National Institute of Standards and Technology.

Queries

Further details are available at the web site
(http://PredictionCenter.llnl.gov/casp3)
Please address any questions or queries to
casp3@PredictionCenter.llnl.gov

Famous quote: A ship in the harbor is safe but that's not what ships are made for…

POSTDOCTORAL FELLOWSHIPS FOR STUDIES IN GENE REGULATION AND CELL DEATH

Several postdoctoral positions are available through NIH funded projects to study gene regulation

by novel Interferon-γ inducible factors and cell death regulation by novel genes. We seek individuals should have a Ph.D./M.D. or an equivalent degree, with strong training in fundamental techniques of molecular biology and biochemistry. Interested persons may send their C.V. and three references from individuals who hold responsible positions and can provide a critical analysis of applicant's abilities to the following address, for further consideration. The University of Maryland School of Medicine offers a stimulating academic research environment. Please forward your application to:

Dhan V. Kalvakolanu, Ph.D.
Greenebaum Cancer Center
University of Maryland
School of Medicine
655 W. Baltimore Street,
BRB-9th floor
Baltimore, MD 21201
Phone: 410-328-1396
Fax: 410-328-6559
E-mail: dkalvako@umaryland.edu

POSTDOCTORAL POSITIONS FOR STUDIES OF CYTOKINE-REGULATED GENE EXPRESSION.

One position will be devoted to determining molecular mechanisms of transcriptional synergism in response to the combination of interferon gamma and tumor necrosis factor alpha. In particular, the protein-protein and protein-DNA interactions that occur at the promoter of the interferon-regulatory factor 1 (IRF-1) gene will be examined [Pine et al. (1994) EMBO J. 13: 158-167; Pine (1997) Nucleic Acids Res. 25: 4346-4354].
Two positions will be concerned with the effects of Mycobacterium tuberculosis infection on macrophage responses to cytokines. Experiments will be performed with human monocytic cell lines or alveolar macrophages that are infected and treated with cytokines in culture, as well as with alveolar macrophages and lymphocytes from tuberculosis patients involved in clinical trials of aerosol interferon gamma therapy. The effects of infection on the response to cytokines will be assessed in terms of post-translational modification of transcription factors, transcription of specific target genes, and expression of those genes at the mRNA and protein levels.

A background in molecular biology and/or biochemistry is required, and experience with studies of regulated gene expression is highly desirable.
Prior work with mycobacteria is preferred for those projects.

Please send curriculum vitae and contact information for three references to:

Dr. Richard Pine
Public Health Research Institute
455 First Avenue
NewYork, NY 10016
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PHRI is an equal opportunity employer.

Famous quote: I have had dreams and I have had nightmares. I have overcome my nightmares because of my dreams… Jonas Salk

New Government Weight Guidelines

The US Government has just issued new guidelines for height and weight. These guidelines now indicate that >50% of Americans are overweight. However, the following dietary information was omitted from these guidelines:

CALORIES THAT DON'T COUNT

We have it on experience (our own and thousands of others) that the following food and situations have no calories to speak of (although the knowledgeable might describe them as unspeakable calories.)

OTHER PEOPLE'S FOOD:
A chocolate mousse that you did not order has no calories. Therefore, have your companion order dessert and you taste half of it.

INGREDIENTS IN COOKING: Chocolate chips are fattening, about 50 calories a tablespoon. So are chocolate chip cookies! However, chocolate chip eaten while making chocolate chip cookies have no calories whatsoever. Therefore make chocolate chip cookies often but don't eat them.

FOOD ON FOOT: All food eaten while standing has no calories. Exactly why is not clear, but the current theory relates to gravity. The calories apparently bypass the stomach flowing directly down the lens and through the soles of the feet into the floor, like electricity. Walking seems to accelerate this process, so that a frozen custard or hot dog eaten at a carnival actually has a calorie deficit.

CHILDREN'S FOOD: Anything produced purchased or intended for minors is calorie•free when

eaten by adults. This category covers a wide range, beginning with a spoonful of baby tapioca••consumed for demonstration purposes••up to and including cookies baked and sent to college.

UNEVEN EDGES: Pies and cakes should be cut neatly, in even wedges or slices. If not, the responsibility falls on the person putting them away to "straighten up the edges" by slicing away the offending irregularities which have no calories when eaten. If pie or cake is neatly cut, but the remainder is not easily divisible into equal servings, it's also
permissible to even things up without calorie consequence.

1998 Meeting Secretariat

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