SUMMARY

OF THE

COMBINED MEETING OF THE

EIGHTH INTERNATIONAL LYMPHOKINE WORKSHOP

AND THE

FOURTH INTERNATIONAL WORKSHOP ON CYTOKINES

OCTOBER 17 - 21, 1993

OSAKA, JAPAN

SHOCK SOCIETY

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July 10, 1994

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RE: Grant N00014-93-1-0951

Dear Jeannine:

On behalf of the Scientific Program Committee, Officers and Council of the Society, I want to thank the Office of Naval Research for the support of Symposia and Awards at the Sixteenth Annual Conference on Shock, June 13-16, Santa Fe, New Mexico and the Combined Meeting of the Eighth International Lymphokine Workshop and the Fourth International Workshop on Cytokines, October 17-21, 1993, Osaka, Japan.

These meetings were very successful and attended by many scientists and physicians throughout the world. We are grateful for the support of the Department of the Navy which helped make this meeting possible.

I am enclosing a copy of "Circulatory Shock" which contains the program (pages 1-4) and abstracts (pages 5-111) for the Shock Conference. A Summary of the Conference by James Cook, Program Chair, is also enclosed. The meeting in Japan is summarized by Scott Durum.

I look forward to a continued association of the Society with the Office of Naval Research.

Sincerely,

Sherwood M. Reichard
Executive Director

DUPLICATE ORIGINAL

DEPARTMENT OF THE NAVY
OFFICE OF NAVAL RESEARCH, CODE 2512:KIJ
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GRANT NO: N00014-93-1-0951
R&T PROJECT: 4414303---01
ACO CODE: N66020
CAGE CODE: 0L2Y2
DISBURSING CODE: N00179
PI: SHERWOOD M. REICHARD

SYMPOSIUM GRANT

GRANTEE: MEDICAL COLLEGE OF GEORGIA
RETICULOENDOTHELIAL SOCIETY
RESEARCH INSTITUTE
1120 15TH STREET
AUGUSTA, GA 30912

APPROPRIATION: AA 1731319 .W1AE

Object Class:	000
Unit Ident Code:	RA444
Suballotment:	0
Auth. Acct. No:	068342
Transaction Type:	2B
Prop. Acct. Act.:	000000
Cost Code:	041080000200
Amount:	$10,000.00
FRC:	4414

R&T Project Code: 4414303---01, Dated: 07 APR 1993

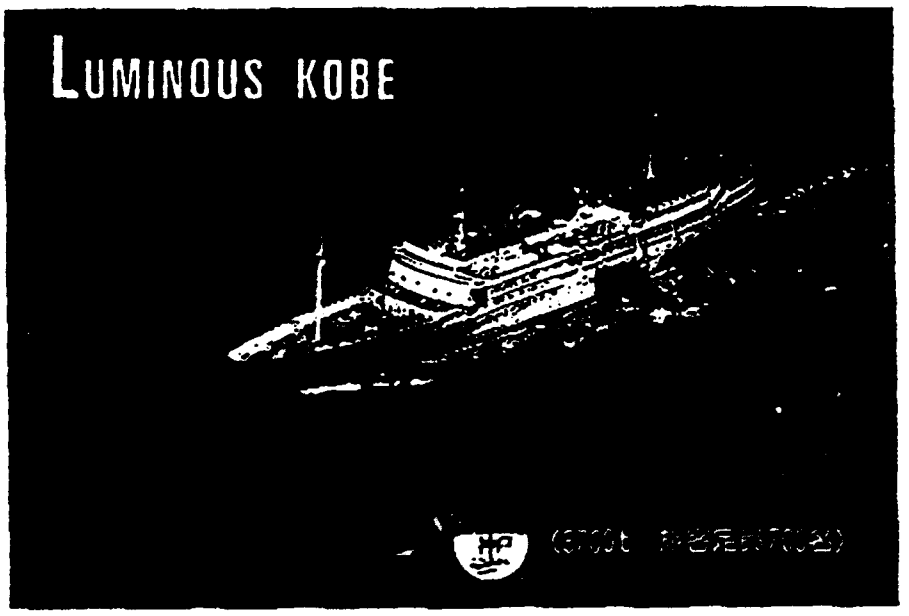
TOTAL GRANT AMOUNT: $10,000.00

AUTHORITY: 10 USC 2358 as amended, and 31 USC 6304.

GRANT PURPOSE: The Purpose of this Grant is to provide partial funding to support Symposia and Awards at the Sixteenth Annual Conference of Shock and the combined meeting of the Eighth International Lymphokine Workshop, and the Fourth International Workshop on Cytokines.

The conduct of the workshop, the personnel and effort and the use of funds for direct and indirect expenses shall generally be as set forth in the Grantee's proposal entitled "Symposia and Awards at the Sixteenth Annual Conference of Shock and the combined meeting of the Eighth International Lymphokine Workshop, and the Fourth International Workshop on Cytokines. which proposal is incorporated herein by reference. The Grantee agrees to obtain concurrence of the Grantor for any desired deviation from the proposal.

PERIOD: The Grant is for the period 01 JUN 1993 through 31 MAY 1994.



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Launching the Society in Osaka Bay - Scott K. Durum

The inauguration of the elected officers of the International Cytokine Society in Osaka, Japan was held aboard the Luminous Kobe, a large cruise ship. As we steamed around Osaka Bay, I introduced the elected officers, including president-Jo Oppenheim, vice president-Tadamitsu Kishimoto, senior councilor-Charles Dinarello, councilor-Gordon Duff, secretary/treasurer-Scott Durum and executive manager-Sherwood Reichard. The metaphor of ship and society affords a rich source for comment, but I will resist, except to say that it was a great idea of the meeting organizers, Professors Kishimoto and Taniguchi, to imprint such a memorable setting on the event.

In my remarks to the first meeting of the Society, I observed that the main function of the Society is to communicate through this meeting, that we come to the international meeting to learn, to teach, to establish collaborations, but also to compete. Yes, to compete. The word "compete" comes derives from the Latin competere, to come together. But when I say compete, I mean competition in a noble sense, so that all the competitors benefit, so that all strive to be better tomorrow than they are today. The meeting in Osaka was the Olympic Games of cytokinology. The stars were all there. Competition among the scientists was staged there, but the scientists are not the real adversaries. The real adversary is the pattern of nature. All of the scientists are on the same team, made up from Japan, Asia, America, Europe, Africa and Australia.

If competition is a major function of the international meeting, the nature of that competition has changed a great deal over the past few years. There are so many cytokines today that a breakthrough in understanding one of them meets the difficulty of impressing such a diverse audience. A cytokinology meeting today is like a soccer game in which every player has his or her own ball.

A meeting of the elected officers and the program committee was held, Jo Oppenheim presiding, attended by Tadamitsu Kishimoto, Tadatsuga Taniguchi, Charles Dinarello, Gordon Duff, Jack Gauldie, John Schrader and me. In the current newsletter, Jo Oppenheim's remarks include several of the decisions reached in that meeting: 1) the future organizers and sites of meetings, 2) various committees to be formed and their members, 3) intention to publish a newsletter and directory. A financial report was compiled by Sherwood Reichard, reporting a balance of $29,975.31 in the treasury. We discussed membership fees. The current rate was $50 per year, but this fee was waived for attendees of the Osaka meeting, and we agreed to also waive the membership fee for attendees of the next meeting in Banff in 1994. After that meeting, the full rate will be charged each member every year.

The scientific meeting was well attended with over 750 participants, of whom 350 came from overseas. There were many excellent symposia and workshops, and I will only try to communicate several of the scientific highlights and breakthroughs.

One of the most elegant ideas presented at the meeting was Michael Tocci's model of IL1β release. The IL1s lack signal

peptides and are inefficiently released from cells, but they do get out of cells somehow. Tocci, Jack Schmidt and colleagues (Merck, Sharp and Dohme) have new data on this release mechanism, implicating the IL1β-converting enzyme (ICE) in the release process. Thus COS cells expressing precursor IL1β do not release it unless transfected with ICE. They have found ICE is located both in the cytosol and plasma membrane, and propose that the membrane form translocates IL1β through the plasma membrane by recognizing the pro-piece. According to their model, at the same time ICE is translocating IL1β, it also cleaves it, but the latter cleavage event is not actually required for transport, precursor IL1β which has been mutated at the cleavage site and cannot be cut, is nevertheless transported. If the model is correct, it promotes ICE to an even higher status as a controller of IL1, and thus inflammation. They also observed by electron microscopy that cells transfected with ICE and IL1β remained intact, implying that IL1 release does not require cell death.

The long sought NFAT has been cloned, according to Steven Ho, who presented his work and others from Gerald Crabtree's laboratory (Stanford). NFAT is a key transcription factor in inducing IL2 transcription in T cells. NFAT has two components, one nuclear (which may be c-jun), and a previously uncloned cytosolic component, "NFAT-c". Cloning of NFAT-c, was announced at the meeting. It has some Rel homology, and predicts an 82kd peptide which after posttranslational modification is 116kd. Its expression is quite restricted to T cells, both resting and activated. The importance of this component in IL2 expression was

verified by transfection into COS cells: NFAT-c induced expression of the IL2 promoter linked to a CAT reporter.

Receptor sharing among cytokines has been revealed for major new group of related cytokines. Warren Leonard (NIH) reported that the gamma chain of IL2 receptor is used by IL4 and IL7, and other candidates to share this chain probably will also include IL9 and IL13. This explains why the gamma chain deficiency in man, x-linked severe combined deficiency, has a much more severe phenotype than was predicted based on IL2-deficiency alone - i.e. knockout mice deficient in IL2 did not lack for thymocytes or B cells, whereas x-linked SCID showed these deficiencies. This has very important implications for the concept that cytokines are critical in the immune system, a concept with dwindling support in recent years. However we still are not sure whether x-SCID is a one cytokine deficiency (IL7 for example), or a combination, or even to be strictly correct, whether gamma chain also contributes to some non-cytokine receptor functions.

Another example of a key immunological cytokine was highlighted at the meeting: CD40L, a T cell product which is the ligand for the receptor CD40 on the B cell surface. Deficiency in CD40L in man, as discussed by Noelle (Dartmouth), results in the x-linked hyper-IgM syndrome: B cells can make IgM, but fail to enter the cell cycle and produce the other Ig classes.

Knockout mice continue to yield new physiological insights into the roles of cytokines. Annelise Schimpl (Wurzburg) reported new abnormalities in IL2-knockout mice. These animals had been shown to mount a surprising amount of T cell proliferation in

response to polyclonal, peptide, viral, or superantigens, or anti-CD28 costimulation. She reported that this T cell proliferation fails to generate cytotoxic T cells (CTLs) in these knockout mice and IL2 restores CTL generation. Even when both IL2 and IL4 are eliminated by knockout, (Muller, Cologne) T cell proliferation nevertheless occurs. These studies may reveal a fundamental organizational strategy within the immune system: helper T cells require no exogenous growth factors, only the antigen-MHC complex and some costimulators, whereas CTLs and B cells require exogenous growth factors (from helper T cells) in addition to antigen.

Knockout of IFN receptor components has distinguished how IFN$\alpha\beta$ compares with IFNγ in host defense as discussed by Michel Aguet (Zurich). Mice lacking a component of the IFN$\alpha\beta$ receptor have normal immune system development and immune responses, but are very susceptible to infections with viruses (VSV, LCMV and vaccinia), despite having normal CTL and antibody responses - hence IFN$\alpha\beta$ is probably, as originally described, a crucial anti-viral agent. But this is not true of mice lacking a component of the IFNγ receptor. The latter have normal immune responses but they differ from the preceeding mice in being resistant to the above viruses, except for larger viruses such as vaccinia. Hence IFNγs main role is not as an interferon, but probably as a macrophage activator, since the mice are very susceptible to infections with bacteria (Listeria and BCG) and parasites (Leishmania). Anti-bacterial immunity may also be the key function of TNF as revealed in TNFRI-knockout mice presented by Horst Bluethmann (Basel). These mice clear Listeria poorly, while viruses are handled well.

TGFβ knockout has revealed that its most critical role is probably as an endogenous anti-inflammatory agent as discussed by Thomas Doetschman (Bethesda). These mice die, possibly of cardiac inflammation, and show extensive inflammatory cell infiltration of numerous organs. Blocking inflammation with anti-LFA-1 antibody extends life considerably. It will be fascinating to identify what triggers these inflammatory processes to start with - environmental antigens, autoantigens, bowel microbial products, endogenous products?

The laboratories that have knocked out cytokine genes are to be commended for their foresight and courage in a long-term gamble. Knockout technology is having a major impact on this field. Through it, we are moving from a period in cytokinology, the discovery period, into another era, one of understanding.

As the First meeting of the International Cytokine Society, the Osaka meeting set a very high standard for subsequent meetings and we look forward to seeing you in Banff, the U.K., Switzerland the the USA in future years.