NIH WORKSHOP ON THE THERAPY OF AIDS AND RELATED DISORDERS
WASHINGTON, D.C. MAY 3-4, 1984

This workshop is intended to provide...

Much of the info discussed was not published, and much had not yet, and probably still has not been subjected to scientific peer review, and therefore must be regarded as PRELIMINARY.

Since time here is limited I will review the highlights of the presentations. I've provided the program should you wish to ask about areas which I will not cover or wish to contact the relevant investigators.

I'll deal briefly with chemorx for KS.

1st at NYU where Laubenstein has a large experience. This group is reporting an approximate 60% complete or partial remission rate with VP-16, a podophyllin derivative with median duration of remission 9 months. Thus VP-16 is their 1st line therapy. Non-responders to VP-16 are currently treated with a combination of VP-16 and alpha 2 IFN. Dr. L. observed that they had a much higher rate of complicating OI's with a combo chemo protocol of AVB compared to VP-16, and thus had abandoned combo chemo.

Ed Gelmann at the NCI reported on 16 pts given a 5 drug regimen of adria, velban, bleo, actino D, and vincristine. All had failed prior alpha IFN rx. Poor immuno prognostic indicators; med pre-rx T4 186. 3 CR, 9 PR, however med duration of CR was 1 mo and PR 5 mo. 9/14 patients died on study, 2 KS, 6 OI, 1 other causes. The median survival was 3 mos, and when rx was stopped new skin and node lesions appeared within weeks. Concluded that the rx was at best palliative.

Briefly discuss alpha IFN for KS since a great deal is already published including our 1st study of recombinant alpha published in the May, 1984 Annals.

Seems clear that there is a definite response rate to alpha from several sources both lymphoblastoid and recombinant. However despite clinical responses of skin and even gi lesions, most studies have revealed a gradual decline of T helper cell numbers, suggesting that the responses may be related to antiproliferative effects of alpha IFN rather than any measurable effect on immune system function.

Also seems clearn that responses to alpha correlate with the absence of OI.

Safai	CR	PR	NR
OI/total	1/11	2/7	26/39
alive/total	10/11	44/7	13/39

I reported on our controlled trial of recombinant IFN alpha in patients with AIFS who did not have KS. The bottom line is that patients receiving IFN continued to develop additional OI's and had no measurable improvement in immune function. In fact..... SLIDES

IFN gamma trials are in progress including one with recombinant gsamma for KS conducted by RM at our institution.

Preliminary results are not especially encouraging.

In one trial looking at anti-CMV effects in 14 pts, natural gamma at doses up to 36 mU 3x/wk x 12 wks failed to alter active shedding of CMV in urine and semen.

Kriegel at NYU reported their negative results with a natural gamma preparation given in low doses for brief duration in 7 pts with KS limited to skin and LN and with no OI (ie a good prognostic group). All 7 progressed. Results are inconclusive because of the possibility of so called lymphotoxins present in these natural, ie non-recombinant preparations.

Clifford Lane at NIH gave natural gamma to 9 patients with KS, 4/9 with previous OI as daily 2 hr infusions and observed no responses. Immune functions including Ts numbers, PHA response and NK declined over the 4 week trial.

I reported on our negative BMT experience with 3 patients who had identical twin immunologically normal donors, and Tony Fauci reported a similar negative experience with one such patient. We reached identical conclusions that the AIDS virus may very well quickly infect the transplanted stem cells and thus prevents immunologic reconstitution.

Like to move on to IL-2 which had received considerable press locally some months ago when there were reports on its ability to improve some immune functions of AIDS patients lymphocytes in tissue culture. Again results are preliminary.

Mertelsmann from MMSKI used natural, ie non-recomb Il-2 in 10 patients at relatively low doses but could not draw definite conclusions; certainly nothin dramatic.

You may recall a newsconference by Fauci at which it was announced that NIH had used 600,000 to purchase natural Il-2 to treat patients with AIDS. They treated 10 patients with KS with 2 hr continuous infusions (because of very short T 1/2) for 5 consecutive days x 4 weeks. Observed a marked decline in Ts cells in blood and no significant change in T4. Concluded that there was a change in the circulating kinetcs of Ts, no boosting of PHA or NK. Noted an increase in # of positive ST's and size of ST's.

I have some concerns about the use of IL-2 based on the fact that it is an essential component of the culture medium used to isolate LAV/HTLV. However protocols are in progress at UCSF for KS.

At a previous meeting of this group I reported that IVIG appeared to be useful in kiddies with AIDS, and this seems real. Rubinstein at Einstein observed a markedly decreased ncidence of bacterial sepsis in kids with AIDS given IVIG compared to kids not given IVIG. However kids with AIDS are different. A word of caution is that in their experience adults given IVIG had frequent side effects inc. decreased complement levels, increased complexes, vasculitis in 1 pt and pulmonary insufficiency possibly due to IVIG in another.

Anecdotes of plasma exchange based on idea of removing a plasma suppressive factor or CIC's which could be playing an adverse role. Some interesting results with transient rises in T lymphocyte numbers, however logistics make the approach difficult.

Thymic factors. No definitive data. I'll very briefly plug a trial of thymopentin (TP-5) which we have in progress for pts with the syndrome of prolonged unexplained lymphadenopathy, and in which 8/20 slots remain open. Trial is placebo-controlled and blinded and codes remain unbroken.

John Dwyer from Yale reported on thymic epithelial cell transplants in 11 pts with AIDS S/P PcP and 3 with KS. Thymus was taken from kids at surgery and cultured in vitro 14-16t days and placed in arm muscle on gelfoam. He reported immunologic "effects" in 5/13 in some cases a decreased T ratio because of Ts cell expansion. He concluded that there was enough encouraging to continue this approach perhaps ij combination with Il-2.

No conclusive evidence for any activity of isoprinosine.

Some interesting results on PcP infection.

First our own data of a 33-50% relapse rate in pts with AIDS and a previous hx of Pcp who were not maintained on longterm prophylaxis with Bactrim, compared to a 0% relapse rate in those in whom prophy with Bactrim or Fansidar could be maintained. Problems with prophy inc.... are well recognized. Margaret Fischl in Miami reported a 50% relapse arte in 14 pts not maintained vs a 0% relapse rate in 20 who could. However in the 20 who could be maintained 11 died of other OI's, the other 9 alive at x=9 mo.

Walter Hughes reported that in the rat model of Pcp Dapsone was at least as effective as Bactrim, and could be of value clinically for PCP infection or prophy, however Dapsone has a sulfa component and thus a similar incidence of adverse rx could occur and use at this time was not recommended.

There was nothing very encouraging for MAI.

So to summarize: recombinant alpha IFN seems useful for KS but not AIDS OI

Not clearly superior to VP-16 and head to head trials will probably be necessary.

No conclusions on IFN gamma or IL-2, but preliminary data are not encouraging.

Most promising news is discovery of virus by French, and potential to screen for antiviral agents which could be found and combined in regimens with immune modulators.

Vaccine is way off, and prevention the key. To cut off dollars for risk group education as could happen this month risks catastrophe. I beliwve we all have the responsibilty as professionals and citizens to take the time to call or write the governor and our local legislators to approve funds for AIDS education in this years budget. I have and hope you will too.

KS CHEMO-RX

LAUBENSTEIN (NYU)

- VP-16 1ST LINE (MED REMISSION 9 MO.)
- VP-16 + r IFN α FOR VP 16 FAILURES
- HIGH OI RATE WITH AVB
  LOWER WITH VP-16

GELMAN (NCI)

16 PTS ; KS ; ALL IFN FAILURES ; < 100

5 DRUGS (ADRIA, VINBLASTINE, BLEO,
ACTINOMYCIN D, VINCRISTINE)

14 EVALUABLE

57 CYCLES (66% REQUIRED DOSE ↓)
19% FEVER, ↓ GRANULOCYTES)

CR 3 (1 mo)
PR 9 (MED 5 MO)

DEATHS KS (2), OI (6), OTHER (1)

MEDIAN SURVIVAL 3 MO.

NEW LESIONS (SKIN, LN) WITHIN WEEKS
OF DISCONTINUATION

PALLIATIVE

KS- NATURAL IFN α

GELMAN (NCI)

3 DOSE LEVELS - LYMPHOBLASTOID

7.5 MU/M^2	QD x 28	1/9 PR
15 "	" x 10d, rest 10d	1/5 PR
25 "	" x 28d	2/10 PR*

CORRELATES OF RESPONSE

1) HI PRE-RX ABSOLUTE LYMAH COUNT
2) ↑ IFN LEVEL
3) ↑ OKT 4$^+$

1 PT MAINTAINED REMISSION 6.5 MO (hidose)

HERSH (MDA)

LYMPHOBLASTOID 20 MU/M^2 I.M. QD x 6D

RESULTS: PHA, CON A STABLE
NK NO CHANGE
↓ OKT 4$^+$

CONCLUDED: WELLFERON HAS IMMUNOSUPPRESS ACTIVITY

SAFAI (MSKCC)

R-IFN α

	CR	PR	NR	
OI / TOTAL	1/11	2/7	26/39	
ALIVE / TOTAL	10/11	4/7	13 / 39	

CORRELATES OF POOR PROGNOSIS

- GI INVOLVMENT
- LARGE TUMOR BURDEN
- PRIOR OI
- ↑ ACID LABILE α

PRE-RX T HELPER # DID NOT CORRELATE WITH RESPONSE

? ANTITUMOR OR SURVIVAL

NATURAL IFN α

NADLER (HOFFMAN – MULTICENTER)

AIDS OR ARC
7/14 HAD ACTIVE CMV EXCRETION ($\uparrow 10^{-6}$)

- placebo
- 3 mU 3x/WK x 12
- 36 mU

ONLY 1 IFN PT CLEARED URINE $10^{-2} \rightarrow 10^{0}$
BUT SEMEN CMV REMAINED 10^{-3}

KRIEGEL (NYU)

7 AIDS-KS 3A (SKIN OR LN ; NO GI)

IFN-SCIENCES
500,000 U/day 2,5 day COURSES, then
500,000 U I.M. 2x/WK

7/7 PROGRESSED
NO Δ IN Th/s, MΦ + NK NOT DONE
? LYMPHOTOXIN

LANE (NIH)

NATURAL IFN γ

DAILY 2 HR INFUSIONS x 4 WEEKS

4/9 PREVIOUS OI, ALL KS

RESULTS:

NO Δ	OKT 4^+
$\downarrow$ (SLIGHT)	OKT 8^+
$\downarrow$	PHA
$\downarrow$	NK

NK $\uparrow$ DURING WEEK 1

BMT

FAUCI (I)	MITSUYASU (III)

1 PT, NL IDENT TWIN DONOR

PCP x3, CANDIDA, CMV VIREMIA

6/82 LYMPH TX
10^{10} q 3-4 WEEKS

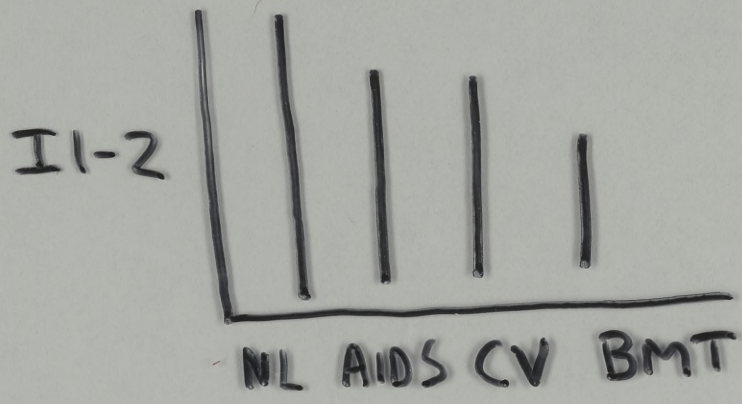
TRANSFERRED DTH TO KLH
↑ OKT4$^+$ TO 40-80/MM^3
FOR SEVERAL MOS.

10/82 BMT, NO CONDITIONING
NO EFFECT

CONCLUSION: PERSISTANT LAV/HTLV INFECTION

IL-2 (NATURAL)

MERTELSMANN (MEMORIAL)



CLINICAL

Il-2 FROM PBL (ACTIVE ON HUMAN AND MOUSE CELLS)
$20{,}000/m^2$; 850,000 U
77 days MAX

PTS

AIDS-OI	4	2/4 "PROGRESSED"
AIDS-PGA	2	↓ IgG
AIDS-KS	2	THROMBOCYTOPENIA
HD IV B	2	

↑ ratio IN 3/9 TESTED

IL-2 (NATURAL)

LANE (NIH)

- COLLABORATIVE RESEARCH
- 2.5×10^5 U/mg
- 2hr INFUSION x 1 PHARMACOKINETIC
  FOLLOWED BY CONTINUOUS INFUSION
  5 DAYS/WK x 4 WKS
- total dose 250 - 250,000 U
- 10 KS PTS - 5 PROGRESSED
  5 STABLE

CONCLUDED: PK OF NAT AND RECOMB PRODUCTS SIMILAR

MARKED ↓ OKT 8
NO Δ OKT 4
↑ # POS ST's AND SIZE OF POSITIVES
↓ IgG, A, M

TB MAY BE ACTIVATED BY IL-2

2-4 WKS FOR OKT8's TO RETURN

IV IMMUNOGLOBULIN

Rubinstein (Albert Einstein)

200-300 mg/kg q 1 wk then q 2-3 wk

KIDS (AIDS OR ARC) WITH POOR Ab to ΦX174 (1° + 2°)

IVIG	NO IVIG
2/12 → OI	9/13 → OI

↑ T4 CELLS, PHA, CONA
NO Δ PWM
OKT8 FUNCTION ↑
↓ INCIDENCE SEPSIS

Adults

↓ COMPLEMENT, ↑ CIC's, VASCULITIS
PULMONARY INSUFFICIENCY

pheresis prior to IVIg → ↓ Malaise
Febrile episodes

PLASMA EXCHANGE

LANE (NIH)

1 PT, 4 WKS; 3 L M-W-F x 4 WKS

MARKED ↑ T LYMPHS 800 → 1200

↓ T4 & T8

TOXICTY: SEVERE SHAKING REACTIONS

THYMUS TRANSPLANTS

DWYER (YALE)

13 PTS - ALL ADVANCED; ANERGIC
ALL PCP, 3 KS, MULTIPLE INFECTIONS

THYMUS PRE-CULTURED 14-16 days
MUSCLE IMPLANT

"EFFECTS" 5/13

↓ ratio (2° TO ↑ OKT 8)

SI ↑ PHA

∴ WILL TRY Tx + IL-2

AGENDA

NIH WORKSHOP ON THE THERAPY OF AIDS AND RELATED DISORDERS

DUPONT PLAZA HOTEL

MAY 3-4, 1984

This workshop is intended to provide scientists actively engaged in therapeutic research on AIDS with an opportunity to share, review and discuss current data. The organizers hope that this workshop format will provide a useful forum for the identification of promising leads, and a starting point for the development of collaborative research protocols. Given the relatively small numbers of patients seen within specific disease categories at each clinical center, we believe that cooperative research should allow the most efficient and properly controlled testing of good ideas.

We remind everyone that some of the information to be discussed has not been published and that much of it has not yet been subjected to scientific peer review. It must therefore be regarded as preliminary. Limitations of time force us to restrict open discussions to members of the scientific community. Questions from the public should be addressed, in writing, to the appropriate session moderator. Individual scientists, at their convenience and discretion, are of course free to discuss information of their choosing with public observers.

AGENDA

NIH WORKSHOP ON THE THERAPY OF AIDS AND RELATED DISORDERS

DUPONT PLAZA HOTEL MAY 3-4, 1984

DAY 1 --- IMMUNE MODULATION ---------- MODERATOR: Dr. Killen

8:30-8:45 WELCOME & OPENING REMARKS ----- Drs. Killen & Edelman

8:45-10:45 INTERFERONS

8:45 Natural Alpha IFN
NIH ---------- Dr. Gelman
MD Anderson --- Dr. Hersh
Miami --------- Dr. Fischl
**DISCUSSION --

9:10 Recombinant Alpha IFN
UCLA ---------- Dr. Gottlieb
Memorial ------ Dr. Safai
Hoffman LaRoche Dr. Nadler (multi-center)
Schering ------ Dr. Valero (multi-center)
**DISCUSSION --

10:00 Natural Gamma IFN
NYU ---------- Dr. Krigel
NIH ---------- Dr. Lane
Miami --------- Dr. Fischl
**DISCUSSION --

10:30 Recombinant Gamma IFN
Cornell ------- Dr. Murray (in vitro data)
Boston -------- Dr. Finberg
**DISCUSSION --

10:45-11:15 BONE MARROW TRANSPLANT
UCLA ---------- Dr. Gottlieb
NIAID --------- Dr. Fauci
**DISCUSSION--

11:15-12:15 INTERLEUKIN-2
Memorial ------ Dr. Safai
Roosevelt ----- Dr. Grieco (in vitro data)
NIH ---------- Dr. Lane
**DISCUSSION--

12:15-1:30 LUNCH

DAY 1 (continued)

1:30-2:45 PLASMAPHARESIS/PLASMA THERAPY/GAMMA GLOBULIN

Einstein ------ Dr. Rubenstein
NYU ---------- Dr. Friedman-Kien
SF General ---- Dr. Abrams
NIAID --------- Dr. Lane
Roosevelt ----- Drs. Inada/Lange
**DISCUSSION

2:45-4:00 THYMIC HORMONES/THYMIC TRANSPLANT

G.Washington -- Dr. Schulof
Einstein ------ Dr. Rubenstein
NYU ---------- Dr. Friedman-Kien
Denver -------- Dr. Kirkpatrick
Yale ---------- Dr. Dwyer
**DISCUSSION--

4:00-5:45 OTHER AGENTS

4:00 Transfer Factor
NYU ---------- Dr. Gordon

4:15 Azimexon
MD Anderson --- Dr. Hersh

4:25 Isoprinosine
Roosevelt ----- Dr. Grieco
MD Anderson --- Dr. Mansell
Sinai/St.Vin. - Drs. Wallace/Bekesi

5:00 Cimetidine
Roosevelt ----- Dr. Grieco

5:10 Indomethacin
Miami --------- Dr. Fischl
Roosevelt ----- Dr. Grieco

5:30 Steroids/ITP
SF General --- Dr. Abrams

5:40-6:15 CLOSING DISCUSSION - DAY 1

DAY 2

8:30-9:30 CYTOTOXIC THERAPY AND IMMUNE FUNCTION IN AIDS --- MODERATOR:Dr. Killen

UCSF ---------- Dr. Volberding
NYU ---------- Dr. Laubenstein
Miami ---------- Dr. Fischl
NIH ---------- Dr. Gelman

**DISCUSSION --

9:30-10:30 HEMOPHILIA THERAPY

Cryoprecipitate

Tulane -------- Dr. Andes
U. Mass ------- Dr. Brettler

Danazol

Denver -------- Dr. Kirkpatrick

**DISCUSSION --

OPPORTUNISTIC INFECTIONS --- MODERATOR : Dr. Edelman

10:30-12:00 Pneumocystis

10:30	Therapy	Dr. Haverkos ---- CDC
11:00	Antigen Detection	Dr. Pifer -------- Tennessee
11:10	Prophylaxis	Dr. Fischl ------- Miami
11:30	Dev. Therapeutics	Dr. Hughes ------- St. Judes

**DISCISSION --

12:00-12:30 M. Avium intracellularae — Dr. Masur -------- NIH

12:30-2:00 LUNCH

2:00-2:30 Toxoplasmosis — Dr. Fischl ------- Miami

2:30-3:00 H. simplex + other Herpes viruses — Dr. Hirsch ------- Harvard

3:00-3:30 Cryptosporidiosis — Dr. Juranek ------ CDC

3:30-4:00 Cryptococcus & Histoplasmosis — Dr. Dismukes ----- Alabama

4:00-4:30 Candida — Dr. Wofsy -------- UCSF

4:30-4:45 Salmonella — Dr. Landesman ---- NY Downstate

4:45-5:15 CLOSING DISCUSSION - Day 2

THYMIC HORMONES / FACTORS

A. RUBINSTEIN

THYMOSIN FX 5

3 PTS - KIDS — 1 HEMOPHILIAC
AIDS-OI — 2 OTHERS

PRE-RX HAD 0 FTS, ↑↑ α1

NO RESPONSE

FRIEDMAN-KIEN (NYU)

10 KS

TP-5 (THYMOPENTIN) 150 mg/WK

IV 3x/WK x 6

NO TOXICTY

DISEASE PROGRESSED

T_H, T_S, $T_{H/S}$ UNCHANGED

KIRKPATRICK

TP-1 THYMOSTIMULIN

KNOWN TO ↑ $T4^+$

PLANNED PILOT IN PTS S/P PCP

HERSH (MDA)

AZIMEXON : ↑ DH USED P.O.
MODEST ↓ T8 IN VITRO

REGIMEN : 250 mg/m^2 IV x 10 days
REST x 2 WKS
MAINTAIN 150-300 mg PO x28

PTS : 36 ENTERED

16 ARC 13 AIDS (2 KS
8 OI
3 BOTH)

RESULTS:

DAY	0	5	21
ARC (16)	0.39	0.46*	0.50*

Δ DUE TO ↑ T_H OR ↓ T_S

ALSO ↑ MITOGEN, & ↑ MEAN # ST

TOXICITY: HEMOLYSIS

PLANS: NOW DOING PHASE I OF
NON-HEMOLYTIC CONGENER

NO α TUMOR ACTIVITY OBSERVED