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T-Cell Lymphoma Cell Lines (HUT102 and HUT78) Established at the National Cancer Institute: History and Importance to Understanding the Biology, Clinical Features, and Therapy of Cutaneous T-Cell Lymphomas (CTCL) and Adult T-Cell Leukemia-Lymphomas (ATLL)

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Abstract Efforts at the National Cancer Institute to generate continuous in vitro cultures from patients with mycosis fungoides and the Sezary syndrome, neoplasms with a mature T-helper phenotype, led to the establishment of two cell lines, HUT78 and HUT102. Further characterization of these cell lines led to the identification of the first human retrovirus, HTLV-1, in the HUT102 cells, and the clinical description of the syndrome of HTLV-1 associated acute T-cell leukemia/lymphoma; the serum antibody test to screen for this virus was developed from the serum of the patient from whom the cell line was derived. The HUT78 cell line was pivotal in the identification and characterization of the HIV retrovirus in that a subclone, H9, proved to be permissive for replication of HIV in vitro. Propagation of HIV in vitro in H9 cells allowed for the development of immunological reagents to screen blood supplies for the presence of the virus. Further biologic and molecular studies of these lines have led not only to a better understanding of the underlying diseases but also to the development of rational therapeutic approaches.

Key words: CTCL, Sezary, HTLV-I, HIV, IL-2

Mycosis fungoides was originally described as a skin disease in 1806 [1]. During the remainder of the 1800s and early 1900s the clinical manifestations of the disease, its natural history and pathologic features were described [2,3]. The erythrodermic variant of the disease was described during this period and Sezary described a variant with generalized erythroderma and circulating malignant cells in 1939 [4]. The only treatment before the 1950s was radiation therapy which played only a palliative role.

The fact that the underlying cell of origin was a lymphocyte was not recognized until 1970 [5]. Since that time there has been an explosion in our understanding of the biology, pathogenesis, and treatment options for these and other T-cell non-Hodgkins lymphomas. In the early 1970s the National Cancer Institute (NCI) began a systematic study of these disorders which led to much of this increased understanding. Part of these advances were made through a close interaction between clinical and laboratory investigators and the cell lines which they established. This chapter will review the progress made through these collaborations and cell lines.

EARLY CLINICAL STUDIES OF CUTANEOUS T-CELL LYMPHOMAS AT THE NCI

Dr. Marvin Lutzner in the Dermatology Branch of the NCI, studied the morphology of the Sezary syndrome in the early 1970s, describing the cerebriform nature of the nucleus (Fig. 1) [6]. At this time it was just appreciated that these malignant cells were malignant T-cells [5,7] derived from the mature helper subset [8]. Dr. Richard Edelson and coworkers, also from the Dermatology Branch, showed that antithymocyte globulin [9] and leukapheresis [10] could improve both the skin lesions and the

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circulating Sezary cells in these patients. The improvement in skin lesions and lymph nodes after removal of circulating cells by leukophoresis led us to postulate that there was traffic between the malignant cells in various sites and to explore the cell kinetics of the disease and the sites of proliferation of the malignant cells. Dr. Stanley Shackney, Dr. Edelson, and Dr. Bunn conducted a series of studies with ^{3}HTdR which confirmed the trafficking between cells in lymph nodes, peripheral blood, and skin [11,12]. The highest rate of cell proliferation appeared to be in the skin. The challenge of treating these patients led to a formal effort to study the natural history, staging, treatment, and biology of the cutaneous T-cell lymphomas which was undertaken by the NCI-Veterans Administration Medical Oncology Branch and, later, the NCI-Navy Medical Oncology Branch.

Biopsy of lymph nodes, liver, other sites of visceral involvement, and peripheral blood specimens were obtained from all patients as part of their staging assessment [13–15]. These samples were analyzed for the DNA content of the malignant cells [16], their morphology as determined by light and EM microscopy [17–19], and their karyotypes [20,21]. These clinical studies showed that nearly all patients had early evidence of systemic disease, explaining why topical therapies failed to cure patients with disease which appeared to be confined to the skin.

The karyotypic studies showed that chromosomal abnormalities were present in the majority of cases and clonal abnormalities were the rule [20,21]. However, the clonal abnormalities varied between cases. We studied the malignant cells in considerable detail. We originally showed that these cells had the phenotype of helper T-cells by using monoclonal antibodies developed to these antigens [22,23]. We subsequently showed that the cells also had the genotype of T-cells with monoclonal rearrangements of the T-cell receptor gene [24].

CELL CULTURE STUDIES

Dr. Desmond Carney and coworkers undertook the task of evaluating the responsiveness of these cells to a variety of lymphocyte mitogens and then to establish permanent cell lines by culturing the cells with these mitogens and/or lymphocyte conditioned media [25–27]. We found that the cells had poor spontaneous proliferation in response to mitogens. We were also disappointed that we failed to obtain permanent cultures from the vast majority of samples. In 1977 and 1978 we had the good fortune of finding that the cultures from two patients continued to proliferate in culture beyond several months (these two cell lines were HUT78 and HUT102, respectively) [26,27]. Our flow cytometric studies confirmed that these were helper T-cells with cell surface antigens which were identical to those in the patients from which they were derived and that their DNA content and karyotypes were also identical. These cell lines, originally cultured by Dr. Carney, were maintained in culture by Ed Russell under the direction of Dr. Adi Gazdar.

HUT78 was derived from peripheral blood of a 53-year-old white male with the Sezary syndrome. The patient had a typical clinical presentation with extensive cutaneous erythroderma and histopathologic involvement of lymph nodes and liver. This patient's circulating neoplastic lymphocytes proliferated in vitro in the presence of ConA 10 μg/ml with tenfold increase in cell number/week and, after surviving two crises began to proliferate without mitogen stimulation after 12 weeks in culture. The cell morphology, shown in Figure 1b,d, was similar to that of the original patients' cells (Fig. 1a,c), with hyperconvoluted nuclei and large nucleoli. After several passages in culture, the cells demonstrated decreased E-rosette formation and failed to respond to mitogen stimulation. The doubling time of the cells after 52 weeks in culture was 26 h. DNA content analysis showed a bimodal distribution of cells which were hypodiploid and subtetraploid. The hyperdiploid populations were believed to arise from the hypodiploid cells by endoreduplication [28,29]. While the fresh CTCL cells from the patient failed to form tumors in nude mice by a variety of routes, the cell line Hut78 induced invasive tumors after intrathecal injection, and these tumors had a subtetraploid karyotype.

In contrast to the classic features of Sezary syndrome described above, there were many unusual features in the history of the patient from whom HUT102 was derived. His cells had an abnormal morphology and T-cell phenotype as well. The patient was atypical in his young age [30], the initial presentation with a rapid onset of skin tumors, the early widespread dissemination to visceral sites including lytic bone lesions at presentation, hypercalcemia, and early relapse in the leptomeninges after aggressive combination chemotherapy (Fig. 2) [30–34]. The

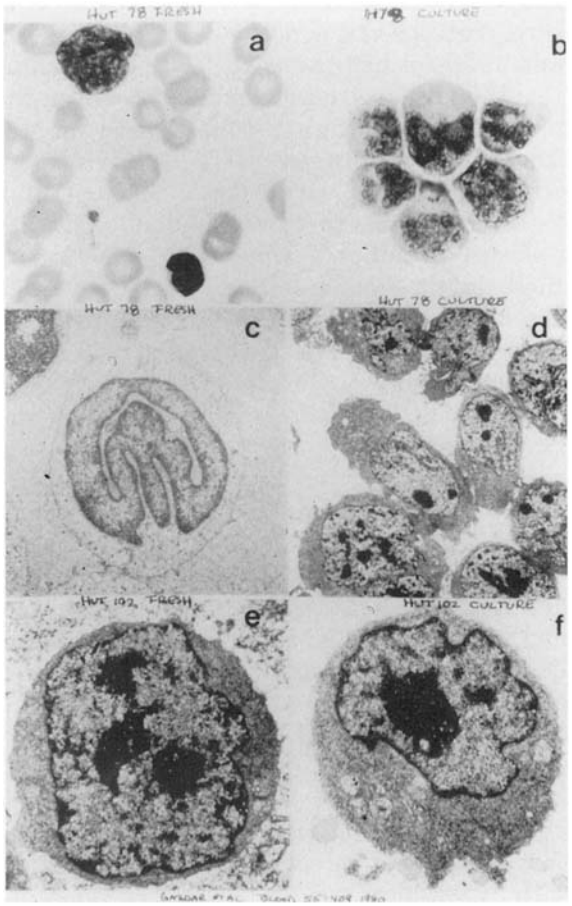

Fig. 1. Morphologic features of the cell lines. Light microscopic (**a, b**) and ultrastructural (**c, d**) features of peripheral blood smear from patient from whom Hut78 cell line was derived (a, c) and the cell line in culture (b, d); ultrastructural features of tumor lesion from patient from whom HUT102 was derived (**e**) and the cell line in culture (**f**). Magnifications, a and b, ×640; c and d, ×1,600; e and f, ×6,300. (Reproduced from Gazdar et al., with permission of the publisher.)

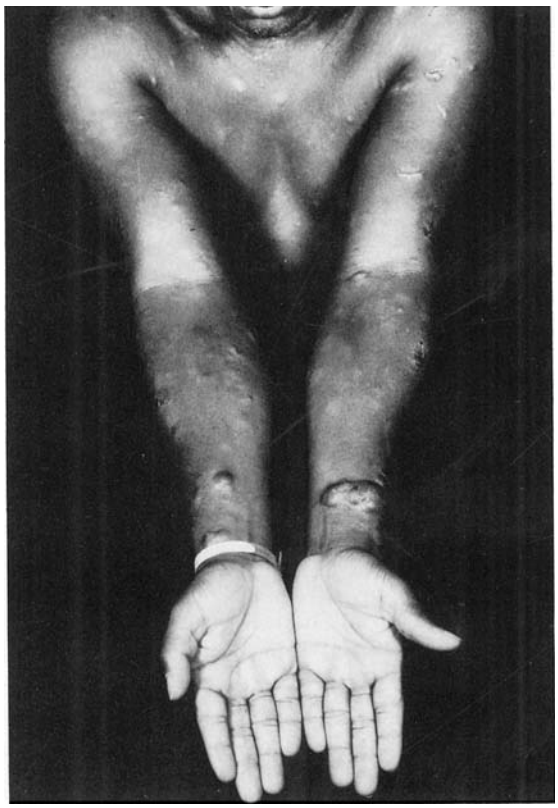

Fig. 2. Cutaneous tumor lesions from a 26-year-old black male from whom HUT102 cell line was established.

cells' nuclear morphology was larger than most MF cells and some nuclei had a cloverleaf contour (Fig. 1e,f) [35]. Nonetheless, typical Pautrier microabscesses were seen in the epidermis and the patient appeared to have the D'emblee tumor variant of mycosis fungoides. The cells were unusual in the high expression of the IL-2 receptor (known as the T-cell growth factor receptor [TCGF] at the time) [36,37].

The HUT102 cell line was originated from lymph node tissue which was disaggregated by passage through a cytosieve. Mononuclear cells were separated by ficoll-hypaque density gradient centrifugation and placed in culture. The fresh tumor cells appeared to have polylobated nuclei and were E-rosette positive and Tdt (−). The cells proliferated in vitro in the presence of T-cell growth factor conditioned media but not with PHA, Con A, PWM, or staph toxin A. After the fifth passage, the cells became mitogen independent with a doubling time of 36 h and maintained the blastic morphologic features of the original cells. Unlike HUT78, the HUT102 cells did not form tumors when injected into nude mice by any route. DNA content studies of HUT102 showed that the cell line was near-diploid with a modal chromosome number of 46 (range 44–46).

DISCOVERY OF HTLV-1 IN HUT 102

Dr. Bernard Poiesz was a clinical fellow who cared for some of our CTCL patients and knew that we had successfully maintained several cell lines in continuous culture. After his clinical year of fellowship, Dr. Poiesz elected to work in the laboratory of Dr. Robert Gallo to study reverse transcriptase and human retroviruses. He also worked with Dr. Frank Ruscetti who was working to purify TCGF in Dr. Gallo's lab. It was postulated that HUT102 might be an excellent source of TCGF since it grew without exogenous growth factor and expressed high levels of

the TCGF receptor [36,37]. The HUT78 and HUT102 cells were given to Drs. Poiesz and Ruscetti to determine whether they produced and secreted TCGF. Since Dr. Poiesz was studying reverse transcriptase, he fortuitously used HUT102 in one of his assays and found that it had extremely high levels of this enzyme [38]. This led to the discovery of the first human retrovirus which was called HTLV-I by Dr. Gallo's lab [39]. HUT78 had no evidence of retroviral infection.

Another NCI clinical fellow who elected to work in Dr. Gallo's lab, Dr. Larry Posner, developed a serum assay for anti-HTLV-1 antibodies [40]. It was shown that the patient from whom HUT102 was derived had high levels of antibody whereas the patient from whom HUT78 was derived had none [41–45]. Analysis of stored serum from a large number of our patients showed that the presence of anti-HTLV-1 antibodies was rare. However, Dr. Gallo's lab analyzed serum samples from around the world and found several endemic areas of seroprevalence including Japan, the Caribbean region, and the Southern United States [41–45].

ADULT T-CELL LEUKEMIA-LYMPHOMA

Around the same time, a group of Japanese investigators described a new form of adult T-cell lymphoma which they called "Adult T-cell Leukemia-Lymphoma" [46]. The patients were reported to have a rapid onset of widespread disease with peripheral blood involvement, frequent skin involvement, universal lymph node involvement, and clustering in the Southern provinces of Japan. Shortly thereafter Dr. Daniel Catovsky, across the globe in London, described a small series of patients with similar clinical features and hypercalcemia as well [47]. These patients had all come to the UK from the Caribbean region. Dr. Gallo's lab analyzed the serum from these patients and they all had high levels of anti-HTLV-I antibodies [41–45].

The clinical features of the disease produced by HTLV-1 were becoming clear and a number of these patients were found among the T-cell lymphoma patients referred to the NCI and the Veterans Administration Medical Center [30–34]. We reported that the patients had high grade clinical features such as rapid onset of symptoms, hypercalcemia and lytic bone lesions, opportunistic infections, universal presence of visceral disease including frequent leptomeningeal metastases, increased expression of the IL-2 receptor on the malignant cells which had cloverleaf nuclei, and poor response to aggressive chemotherapy. Table I provides a summary of the clinical features of ATLL in contrast to the low grade T-cell lymphomas, mycosis fungoides, and the Sezary syndrome. Dr. Whang-Peng reported the cytogenetic abnormalities seen in the NCI series of patients and similar findings were reported by Japanese investigators [48,49]. Nearly all patients had abnormalities and these were usually clonal. Although some cytogenetic changes were frequent, there were no abnormalities that occurred in all patients. The integration site of the HTLV-I virus varied from patient to patient [50,51].

OTHER HTLV-1 RELATED DISEASES

Seroprevalence studies for anti-HTLV-I antibodies around the world showed several endemic areas and the seroprevalence was low in most areas in the United States [41–45]. Nonetheless, several areas had high prevalence and it was shown that the virus could be transmitted through infected blood [52]. This led to mandated routine screening of all blood products in the United States, thus preventing transmission through infected blood products [53].

Other clinical features of HTLV-I infection were subsequently described including chronic low grade leukemic disease and neurologic syndromes often termed spastic paraparesis [54–56]. Most infected persons in endemic areas appear to acquire the infection at the time of

TABLE I. Clinical Features of T-Cell Lymphomas*

Clinical feature	ATLL (HTLV-1) (n = 10)	CTCL (n = 49)
Age	34 (24–62)	53 (22–78)
Duration Sx to Dx	2 months	5 years
Hypercalcemia	90%	2%
Bone lesions	90%	2%
Skin lesions	70%	100%
Circulating tumor cells	80%	25%
Lymph nodes	100%	70%
Viscera	100%	18%
Opportunistic infections	Common	Rare
Response	Prompt CR	LowerCR rate
Survival	Short	Long

*From references [31, 32].

birth. Only a small minority of these patients subsequently develop disease. The reasons why some control the infection indefinitely and others develop severe disease are unknown.

IDENTIFICATION AND ISOLATION OF HIV

The syndrome of acquired immune deficiency syndrome had been recognized in the early 1980s, and epidemiologic data suggested a horizontal transmission by intimate contact or blood products. Gallo and his colleagues proposed that the etiologic agent of this syndrome was a retrovirus of the HTLV family, due to the propensity of the agent to infect helper T-cells and the similarities to feline leukemia virus, a retrovirus causing immunodeficiency in cats [57]. Because initial cocultivation studies of lymphocytes from infected patients with various T-cell targets, including umbilical cord blood, proved to be transient and cytopathic rather than permissive, as was the case for HTLV-I, Gallo's lab began an exhaustive search for a cell line which would be permissive for infection and propagation of the proposed new retrovirus. In a landmark article, Popovic and Gallo and coworkers reported in 1984 that an aneuploid T-cell line from a patient with lymphoid lymphoma, named HT, was permissive for the in-vitro propagation of a new virus, called HTLV-III [57–60]. Subcloning of that cell line led to the H9 clone, which had the highest proliferation rate after infection with the virus. Popovic et al. subsequently published data comparing the viral expression of HTLV-III in a number of hematopoietic cell lines, including HUT78, and showed that H9 was clearly the highest producer, as measured by reverse transcriptase activity and presence of viral proteins p15 and p24 by immunofluorescence [61].

The identity of the parental line from which H9 was subcloned was not elucidated until 1988 when it was demonstrated by DNA fingerprinting that HUT 78 and H9 were identical, proving that H9 was a subclone of HUT78 sent to Dr. Gallo's lab by our group [62,63]. A further study by Chen confirmed by karyotypic analysis that H9 was a subline derived from HUT78 [28]. Gallo's access to the HUT78 cell line and Popovic's success in isolating a subline highly permissive for HTLV-III replication allowed further molecular characterization of the virus, now named HIV, and led to the development of immunological reagents to screen patients and the blood supply for the presence of this virus [59,60].

GROWTH CHARACTERISTICS OF HUT 78 AND HUT102

Both HUT78 and HUT102 cells grow as single cells or as clusters in non-adherent suspension cultures. Serum deprivation studies demonstrate that optimal serum concentration is 10%, although the cells can be maintained in as little as 3% serum, with a slower doubling time (Fig. 2). Growth of HUT78 cells cannot be supported in serum-free media even with the addition of purified growth factors, including IL2, IL4, IL-5, IL-6, IL7, or IL2 + IL4 (Foss et al., unpublished data). Further, growth is not enhanced in 10% serum containing media with the addition of any of the above growth factors. HUT102 cells likewise demonstrate autonomous growth, although addition of IL-2 or TCGF has been shown to increase proliferation in a concentration-dependent manner [37]. Recently, a clone of HUT78, H9, has been successfully adapted to serum free media supplemented with transferrin, insulin, and sodium selenite [64].

EXPRESSION OF CYTOKINES AND CYTOKINE RECEPTORS

The expression and secretion of cytokines by HUT78 has been studied by biological assays and by reverse transcription and polymerase chain amplification (RT-PCR). Low levels of expression of mRNA for IL2, gamma interferon, TNF, and TGF-beta were detected [65]. With activation by PHA (10 μg/ml for 2 h), IL2 and gamma interferon expression increased and IL4 was expressed. IL4 expression was also induced by CD3 stimulation under cross-linking conditions or by soluble CD3 monoclonal antibodies in the presence of PMA [66].

HUT102 has been demonstrated to constitutively produce IL-2, or TCGF [37]. Messenger RNA has been detected by RT-PCR for IL-1a, IL-2, IL-4, IL-6, and IL-7. Like other HTLV-I infected cells, the HUT102 cell line constitutively expressed the ICAM-1 cell adhesion molecule but lacked expression of its receptor, LFA-1 [67]; HUT 78 lacked expression of either.

Immunophenotypic studies using the anti-TAC and anti-TU27 antibodies and the IL-2 phycoerythrin fluorokine (R + D Systems, Minneapolis, MN) show that HUT78 cells do not express the IL2 receptor at baseline or after

exposure to mitogens, such as PHA or ConA, while HUT102 cells constitutively express IL2R [68]. Binding assays using 125I-IL2 and mRNA analysis confirm that HUT 102 but not HUT78 cells express the high affinity ($\alpha\beta\gamma$)IL2R.

The IL-7 receptor, which has been identified on normal and neoplastic T-cells, including fresh Sezary cells, and which has been shown to promote the growth of Sezary cells in culture, is expressed on HUT102 but not HUT78 cells as assayed both immunophenotypically using the IL-7-biotin-FITC fluorokine (R + D Systems) and by mRNA and cross-linking studies [69,70]. We found a low affinity binding of ^{125}I-IL7 to a 70 kDa receptor on HUT78 cells, similar to a putative low affinity receptor reported by Armitage et al. [71].

EXPRESSION OF TYROSINE KINASE PROTO-ONCOGENES

Several of the *src*-related protein tyrosine kinases are overexpressed in HUT78, including c-*src*, *lck*, which has been shown to associate with the CD4 receptor, and *fyn*, which complexes with the intracellular δ-chain of the T-cell antigen receptor complex [72,73]. A related kinase, *lyn*, is overexpressed in HUT102 and other HTLV-1 transformed cell lines but not in normal T-lymphocytes or in HUT78 [74]. Blake et al. recently described a truncated form of the c-*abl* proto-oncogene in HUT78 cells [75]. A rearrangement introduces a stop codon removing 259 amino acids from the carboxyterminus, resulting in a 72 kDa protein lacking the leucine zipper domain of native c-*abl*.

C-*MYC* REARRANGEMENT IN HUT78

A chromosomal t(2;8) translocation was described in HUT78, resulting in a c-*myc* fusion transcript. Finger et al. identified a translocation of the TCL4 gene from chromosome 2q34 to a region of the *myc* locus which is 271 bp downstream of the translation termination codon, creating novel transcripts of 6.8 and 3.8 kb, and a shortened 2.4 kb version of the normal *myc* mRNA [76]. The half-life of the *myc*-TCL4 fusion transcript was prolonged, and transfection of this mutant myc gene into NIH3T3 cells demonstrated that it was tumorigenic, suggesting that the role of deregulation of *myc* in transformation in the HUT78 cell line may be analogous to Burkitt lymphoma [77]. Our studies have failed to demonstrate rearranged *myc* genes in HUT102 or in Sezary cells from other patients (unpublished data).

MUTATIONS IN TUMOR SUPPRESSOR GENES

HUT 78 has been shown to harbor a homozygous point mutation in codon 196 of p53, converting an arginine at the end of exon 3 to a stop codon. Interestingly, the T-cell leukemia line, JURKAT, contains the identical mutation [78]. It has further been demonstrated that HUT78 also lacks expression of the normal pp110 retinoblastoma protein, suggesting that loss of tumor suppressor gene function may have been a critical event in the transformation of this cell line [78]. Our studies of p53 in Sezary cells from 19 patients show that one-third of patients have mutations in exons 5–9 and that the finding of mutated p53 correlates with more advanced clinical disease.

THERAPEUTIC IMPLICATIONS FOR ATLL AND CTCL

IL-2 Receptor

The IL-2 receptor was shown to be overexpressed on nearly all malignant cells from ATLL patients. This led Waldmann and colleagues to test the therapeutic role of the anti-Tac monoclonal antibody which reacts with the IL-2 receptor [79,80]. Unlabeled anti-Tac antibody produced some responses in ATLL patients but long lasting complete responses were not observed. These studies were followed by studies of anti-Tac immunoconjugates. These included toxin conjugates with ricin-A chain and Pseudomonas exotoxin and radioimmunoconjugates [81,82].

Although the cell line HUT78 lacks IL2R expression, immunohistochemical studies demonstrate low levels of IL2R expression on the neoplastic lymphocytes infiltrating the skin in about 50–70% of patients with mycosis fungoides and the Sezary syndrome [83–86]. Murphy and colleagues developed recombinant fusion toxins capable of targeting the high affinity IL2R by replacing the receptor binding domain of native diphtheria toxin with the full length IL-2-gene [87]. The recombinant fusion protein, expressed in *Escherichia coli*, binds to cells bearing high affinity IL2R and is internalized by receptor-mediated endocytosis into endosomal lysozymes, where the active fragment of diphtheria toxin is liberated into the cytosol and kills the cell by inhibiting ADP ribosyl transferase and subsequently protein synthesis [88–90]. The original

protein, $DAB_{486}IL$-2, produced objective responses in 6/29 patients (21%) with CTCL [91–93]. No responses were observed among patients whose cells did not express the IL-2 receptor. The dose limiting toxicity was renal dysfunction. A modified form of the IL2 fusion toxin, DAB389IL2, had a higher binding affinity and produced fewer toxicities in experimental models. In phase I-II trials objective responses were noted in 5/11 CTCL patients (45%) [94]. The IL2 fusion toxins are also active against ATLL cells, including HUT102, in vitro [95] but no human clinical trial data have been reported.

Adenosine Analogs

Clinical studies showed that adenosine deaminase deficiency led to immunodeficiency. This led to studies of nucleotide metabolism in lymphocytes and malignant T-cells. We reported that malignant T-cells have aberrant adenosine metabolism [96]. This led to the study of adenosine analogs in CTCL and ATLL patients. Deoxycoformycin was the first analog studied and responses were reported in 26/63 patients (41%) [97–103]. Fludarabine monophosphate was studied by the Southwest Oncology Group who reported objective responses in 6/31 heavily pretreated patients (19%) [104]. Most recently, 2-chlorodeoxyadenosine was studied and shown to produce an objective response in 41% of 27 CTCL patients [105,106]. Deoxycoformycin was also reported to be active in ATLL patients [107]. More recent studies by Foss and colleagues have evaluated the combination of recombinant interferons with deoxycoformycin and fludarabine [108,109]. Although responses were observed in 41 and 53% of the patients treated with each combination, the response rates were not clearly superior to either agent alone.

Interferons

When recombinant interferons became available in large quantities it was logical to examine their activity in CTCL and ATLL patients because of their anti-proliferative effects on some cell lines and the immunostimulatory properties. We reported that both recombinant alpha and gamma interferons had activity in CTCL [110–113]. Responses were uncommon in patients with any high grade T-cell lymphoma. We also reported that the combination of rIFNa2 and PUVA produced responses in 90% of patients including complete responses in more than half of the patients [114]. These response were higher than those observed with the combination of multi-agent chemotherapy and whole skin electron irradiation [115].

Anti-CD5 Monoclonal Antibodies (T101, T1)

After a report from Stanford University showed objective responses in 4/9 CTCL patients treated with an anti-CD5 antibody [116], we studied 11 patients and reported transient and minor responses but no objective partial or complete responses lasting 30 days or more [117]. We showed that a major problem in vitro and in vivo was rapid antigen modulation of the antibody-receptor due to its internalization. This rendered the cells non-responsive to recognition by the immune system. Other studies were also done with other dose schedules and overall only 5 responses were reported among 46 patients [116–119]. However, the internalization made it logical to evaluate immunoconjugates. We showed that radioimmunoconjugates were highly cytotoxic in vitro [120]. This led to clinical trials of radiolabeled T101 [121–123]. These studies showed that the radiolabeled antibody reached sites of disease and that radio imaging could assist in the staging of the patients. Higher levels of antibody in nodal sites were achieved with subcutaneous or intralymphatic administration compared to intravenous administration. This led to a trial of intravenous ^{131}I-T101 at Northwestern University where objective responses were reported in 3 of 6 patients [124]. Unfortunately, these responses were partial and of short duration. This was attributed to the rapid dehalogenation in vivo. An anti-CD5 toxin conjugate was also studied and shown to produce objective responses in 29% of 16 patients [125]. These immunoconjugates are undergoing further clinical study.

CONCLUSIONS

The story which lies behind the clinical-laboratory collaborations and interactions which led to these discoveries is an example of the synergy that can occur by such collaborations, the importance of translational research, and the importance of the clinical investigator in the study of human diseases.

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REFERENCES

1. Alibert JLM (1806): Description des maladies de la peau; observees a l'Hospital St. Louis. Paris: Barrois L'aine et Fils.
2. Epstein EH Jr, Levin DL, Croft JD Jr, et al. (1972): Mycosis fungoides. Survival, prognostic features, response to therapy, and autopsy findings. Medicine 15:61–72.
3. Levi JA, Wiernik PH (1975): Management of mycosis fungoides: Current status and future prospects. Medicine 54:73–88.
4. Sézary A, Bouvrain Y (1938): Erythrodermie avec presence de cellules monstrueuses dans le derme et dans le sang circulant. Bull Soc Fr Dermatol Syph 45:254–260.
5. Crossen PE, Mellor JEL, Finley AG, et al. (1971): The Sézary Syndrome cytogenetic studies and identification of the Sézary cell as an abnormal lymphocyte. Am J Med 50:24–34.
6. Lutzner M, Edelson R, Schein P, et al. (1975): Cutaneous T-cell lymphomas: The Sézary Syndrome mycosis fungoides and related disorders. Am Int Med 83:534–552.
7. Brouet JC, Flandrin G, Seligmann M (1975): Indications of the thymus derived mature of the proliferative cells in six patients with the Sézary Syndrome. N Engl J Med 289:341–344.
8. Broder S, Edelson RL, Lutzner MA, et al. (1976): The Sézary syndrome. A malignant proliferation of helper T cells. J Clin Invest 58:1297–1306.
9. Edelson RL, Raafat J, Berger CL, Grossman M, Troyer C, Hardy M (1979): Antithymocyte globulin in the management of cutaneous T-cell lymphoma. Cancer Treat Rep 63:675–680.
10. Edelson RL, Iacktor M, Andrews A, et al (1974): Successful management of the Sézary Syndrome: Mobilization and removal of extracutaneous neoplastic T-cells by leukapheresis. N Engl J Med 291:293–294.
11. Shackney SE, Edelson R, Bunn PA Jr (1979): The kinetics of Sezary cell production. Cancer Treat Rep 63:659–661.
12. Bunn PA, Jr, Edelson RL, Ford SS, Shackney SE (1981): Patterns of cell proliferation and migration in patients with the Sezary syndrome. Blood 57:452–463.
13. Bunn PA, Jr, Huberman MS, Whang-Peng J, Schechter GP, Guccion JG, Matthews MJ, Gazdar AF, Dunnick NR, Fischmann AB, Ihde DC, Cohen MH, Fossieck BE Jr, Minna JD (1980): Prospective staging evaluation of patients with cutaneous T-cell lymphomas: Demonstration of a high frequency of extracutaneous dissemination. Ann Int Med 93:223–230.
14. Sausville EA, Worsham GF, Matthews MJ, Makuch RW, Fischmann AB, Schechter GP, Gazdar AF, Bunn PA Jr (1985): Histologic assessment of lymph nodes in mycosis fungoides/Sezary syndrome (cutaneous T-cell lymphoma): Clinical correlations and prognostic import of a new classification system. Hum Pathol 16: 1098–1109.
15. Sausville EA, Eddy JL, Makuch RW, Fischmann AB, Schechter GP, Matthews M, Minna JD, Glatstein E, Ihde DC, Kaye F, Veach SR, Gazdar AF, Phelps R, O'Connor T, Trepel JB, Cotelingham J, Bunn PA, Jr (1988): Histopathologic staging at initial diagnosis of mycosis fungoides and the Sezary Syndrome: Definition of three distinctive prognostic groups. Ann Int Med 109:372–382.
16. Bunn PA Jr, Whang-Peng J, Carney DN, Schlam ML, Knutsen T, Gazdar AF (1980): Correlation of DNA content analysis by flow cytometry and cytogenetic analysis in mycosis fungoides and Sezary syndrome: Diagnostic and prognostic implications. J Clin Invest 65:1440–1448.
17. Schechter GP, Bunn PA Jr, Fischmann AB, Matthews MJ, Guccion J, Soehnlen F, Munson D, Minna JD (1979): Blood and lymph node T lymphocytes in cutaneous T-cell lymphomas: Evaluation by light microscopy. Cancer Treat Rep 63:571–574.
18. Schechter GP, Sausville E, Fischmann BA, Soehnlen F, Eddy J, Matthews MA, Munson D, Makuch R, Bunn PA Jr (1987): Evaluation of circulating malignant cells provides prognostic information in cutaneous T-cell lymphoma. Blood 69:841–849.
19. Guccion JG, Fischmann BA, Bunn PA Jr, Schechter GP, Patterson RH, Matthews MJ (1979): The ultrastructural appearance of cutaneous T-cell lymphomas in skin, lymph nodes and peripheral blood. Cancer Treat Rep 63:565–570.
20. Whang-Peng J, Bunn PA Jr, Knutsen T, Schechter GP, Gazdar AF, Matthews MJ, Minna JD (1979): Cytogenetic abnormality in patients with cutaneous T-cell lymphomas. Cancer Treat Rep 63:575–580.
21. Whang-Peng J, Bunn PA Jr, Knutsen T, Matthews MJ, Schechter GP, Minna JD (1982): Clinical implications of cytogenetic studies in cutaneous T-cell lymphoma. Cancer 50:1539–1553.
22. Haynes BF, Bunn PA Jr, Mann D, Thomas C, Eisenbarth GS, Minna JD, Fauci AS (1981): Cell surface differentiation antigens of the malignant T cell in Sezary syndrome and mycosis fungoides. J Clin Invest 67:523–530.

23. Haynes BI, Metzgar RS, Minna JD, Bunn PA Jr (1981): Phenotypic characterization of cutaneous T-cell lymphoma: Comparison with other malignant T cells with the use of monoclonal antibodies. N Engl J Med 304: 1319–1323.
24. Bertness V, Kirsch I, Hollis G, Johnson B, Bunn PA Jr (1985): T-cell receptor gene rearrangements are clinical markers of human T-cell lymphomas. N Engl J Med 313:534–538.
25. Carney DN, Bunn PA Jr, Schechter GP, Gazdar AF (1980): Lymphocyte transformation in patients with cutaneous T-cell lymphomas. Intl J Cancer 26:534–542.
26. Gazdar AF, Carney DN, Russell EK, Schechter GP, Bunn PA Jr (1979): In vitro growth of cutaneous T-cell lymphomas. Cancer Treat Rep 63:587–590.
27. Gazdar AF, Carney DN, Bunn PA Jr, Russell EK, Schechter GP, Guccion JG (1980): Mitogen requirements for the in vitro propagation of cutaneous T cell lymphomas. Blood 55:409–417.
28. Chen T (1992): Karyotypic derivation of H9 cell line expressing human immunodeficiency virus susceptibility. JNCI 84:1922–26.
29. Bunn P, Whang-Peng J, Gazdar A, Minna J, Carney D (1993): Karyotype derivation of H9 cell line (letter). JNCI 85:1168–70.
30. Blayney DW, Jaffe ES, Blattner WA, Cossman J, Robert-Guroff M, Longo D, Bunn PA Jr, Gallo RC (1983): The human T-cell leukemia/lymphoma virus associated with American adult T-cell leukemia/lymphomas (ATL). Blood 62:401–405.
31. Bunn PA Jr, Schechter GP, Blayney D, Young RC, Matthews MJ, Blattner W, Broder S, Robert-Guroff M, Gallo RC (1983): Clinical course of retrovirus-associated adult T-cell lymphoma in the United States. N Engl J Med 309:257–264.
32. Broder S, Bunn PA Jr, Jaffe ES, Blattner WA, Gallo RC, Wong-Staal F, Waldmann TA, DeVita VT (1984): T-cell lymphoproliferative syndrome associated with human T-cell leukemia/lymphoma virus. Ann Int Med 100:543–557.
33. Brigham BA, Bunn PA Jr, Horton JE, Schechter GP, Wahl LM, Bradley EC, Dunnick NR, Matthews MJ (1982): Skeletal manifestations in cutaneous T-cell lymphomas. Arch Dermatol 118:461–467.
34. Dodd RC, Winkler CF, Bunn PA Jr, Williams ME, Gray TK (1986): Calcitriol levels in hypercalcemic patients with adult T-cell lymphoma. Arch Intern Med 146:1971–1972.
35. Jaffe ES, Blattner WA, Blayney DW, Bunn PA Jr, Robert-Guroff M, Gallo RC (1984): The pathologic spectrum of HTLV associated leukemia/lymphoma in the United States. Am J Surg Pathol 8:263–275.
36. Wano Y, Uchiyama T, Kukui K, Maeda M, Uchino H, Yodoi J (1984): Characterization of human interleukin-2 receptor (tac antigen) in normal and leukemic T-cells: Co-expression of normal and aberrant receptors on Hut-102 cells. J Immunol 132:3005–3010.
37. Gootenberg JE, Ruscetti FW, Mier JW, Gazdar AF, Gallo RC (1981): Human cutaneous T-cell lymphoma and leukemia cell lines produce and respond to T-cell growth factor. J Exp Med 154:1403–1405.
38. Rho H, Poiesz BJ, Ruscetti FW, Gallo RC (1981): Characterization of the reverse transcriptase from a new retrovirus (HTLV) produced by a human cutaneous T-cell lymphoma cell line. Virology 112:355–359.
39. Poiesz BJ, Ruscetti FM, Gazdar AF, Bunn PA Jr, Minna JD, Gallo RC (1980): Detection and isolation of type-C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 77:7415–7419.
40. Posner LE, Guroff MR, Kalyanaraman VS, Poiesz BJ, Ruscetti FW, Bunn PA Jr, Minna JD, Gallo RC (1981): Natural antibodies to the human T-cell lymphoma virus in patients with cutaneous T-cell lymphomas. J Exp Med 154:333–346.
41. Kalyanaraman VS, Sarngadharan MG, Bunn PA Jr, Minna JD, Gallo RC (1981): Antibodies in human sera reactive against an internal structural protein of human T-cell lymphoma virus. Nature 294:271–273.
42. Gallo RC, Kalyanaraman VS, Sarngadharan MG, Sliski A, Vonderheid EC, Maeda M, Nakao Y, Yamada K, Ito Y, Gutensohn N, Murphy S, Bunn PA Jr, Catovsky D, Greaves MF, Blayney D, Blattner W, Jarrett WFH, zur Hausen H, Seligmann M, Brouet JC, Haynes BF, Jegasothy BV, Jaffe E, Cossman J, Broder S, Fisher RI, Golde, DW, Robert-Guroff M (1983): Association of human type C retrovirus with a subset of adult T-cell cancers. Cancer Res 43:3892–3899.
43. Robert-Guroff M, Kalyanaraman VS, Blattner WA, Popovic M, Sangadharan MG, Maeda M, Blayney D, Catovsky D, Bunn PA Jr, Shibita A, Nakao Y, Ito Y, Aoki T, Gallo RC (1983): Evidence for HTLV-infection of family members of HTLV positive T-cell leukemia-lymphoma patients. J Exp Med 157:248–258.
44. Blayney DW, Blattner WA, Robert-Guroff MR, Jaffe E, Fisher RI, Bunn PA Jr, Patton MG, Rarick HR, Gallo RC (1983): The human T-cell leukemia/lymphoma virus (HTLV) in the Southeastern United States. JAMA 250:1048–1052.
45. Schupbach J, Sarngadharan MG, Blayney DW, Kalyanaraman VS, Bunn PA Jr, Gallo RC (1984): Demonstration of vial antigen p24 in circulating immune complexes of two patients with human T-cell leukemia/lymphoma virus (HTLV) positive lymphoma. Lancet I:302–304.
46. Uchiyama T, Yodoi J, Sagawa K, et al (1977): Adult T-cell leukemia: Clinical and hematological features of 16 cases. Blood 50:481–492.
47. Catovsky D, Greaves MF, Rose M, et al (1982): Adult T-cell lymphoma-leukemia in blacks from the West Indies. Lancet 1:639–643.
48. Whang-Peng J, Bunn PA Jr, Knutsen T, Kao-Shan CS, Broder S, Gelman E, Jaffe ES, Blattner W, Lofters W, Young RC, Gallo RC (1985): Cytogenetic studies in human T-cell lymphoma virus (HTLV)-positive leukemia-lymphoma in the United States. J Natl Cancer Inst 74:357–369.
49. Sadamori N, Nishino K, Kusano M, et al (1986): Significance of chromosome 14 anomaly at band 14q11 in Japanese patients with adult T-cell leukemia. Cancer 58:2244–2250.
50. Yoshida M, Seiki M, Yamaguchi K, Takatsuki K (1984): Monoclonal integration of human T-cell leukemia provirus in all primary tumors of adult T-cell leukemia suggests causative role of human T-cell leukemia virus in the disease. Proc Natl Acad Sci USA 81:2534.

51. Yamaguchi K, Seiki M, Yoshida M, Nishimura H, Kawano F, Takatsuki K (1984): The detection of human T cell leukemia virus proviral DNA and its application for classification and diagnosis of T cell malignancy. Blood 63:1235.
52. Fleming AF, Maharajan R, Abraham M, Kulkami AG, Bhusnurmath SR, Okpara RA, Williams E, Akinsete I, Schneider J, Bayer H, Hunsmann G (1986): Antibodies to HTLV-I in Nigerian blood-donors, their relatives and patients with leukaemias, lymphomas and other diseases. Int J Cancer 38:809.
53. Sandler SG (1986): HTLV-I and HTLV-II: New risks for recipients of blood transfusions? JAMA 256:2245–2246.
54. Takatsuki K, Yamaguchi K, Kawan F, et al (1985): Clinical diversity in adult T-cell leukemia-lymphoma. Cancer Res (Suppl) 45:4644–4645.
55. Erlich GD, Han T, Bettigole R, et al (1988): Human T-lymphotropic virus type I-associated benign transient immature T-cell lymphocytosis. Am J Hematol 27:49–55.
56. Jacobsen S, Raine CS, Mingioli ES, et al (1988): Isolation of an HTLV-I like retrovirus from patients with tropical spastic paraparesis. Nature 311:540–543.
57. Popovic M, Sarngadharan M, Read E, Gallo R (1984): Detection, isolation, and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and Pre-AIDS. Science 224:497–500.
58. Gallo R, Salahuddin S, Popovic M, Shearer G, Kaplan M, Haynes B, Palker T, Redfield R, Oleske J, Safai B, White G, Foster P, Markham P (1984): Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 224:500–502.
59. Schupbach J, Popovic M, Gilden R, Gonda M, Sarngadharen M, Gallo R (1984): Serological analysis of a subgroup of human T-lymphotrophic retroviruses (HTLV111) associated with AIDS. Science 224:503–505.
60. Sarngadharan M, Popovic M, Bruch L, Schupbach J, Gallo R (1984): Antibodies reactive with human T-lymphotrophic viruses (HTLV111) in serum of patients with AIDS. Science 224:506–508.
61. Popovic M, Read-Connole E, Gallo R (1984): T4 positive human neoplastic cell lines susceptible to and permissive for HTLV-III. Lancet 1472–73.
62. Mann D, O'Brien S, et al (1989): Origin of the HIV-susceptible CD4+ cell line H9. AIDS Res Human Retroviruses 5:253.
63. Rubinstein E (1990): The untold story of HUT78. Science 248:1499–1507.
64. Yahi N, Fantini J, Baghdiguian S, Chermann J (1991): Human T-lymphoblastoid cells selected for growth in serum-free media provide new tools for study of HIV replication and cytopathogenicity. J Virol Methods 34: 193–207.
65. Brenner C, Tam A, Nelson P, Engleman E, Suzuki N, Fry K, Larrick J (1989): Message amplification phenotyping: A technique to simultaneously measure multiple mRNAs from small numbers of cells. Biotechniques 7:1096–1103.
66. Holter W, Kalthoff R, Majdic O, Knapp W (1993): Interleukin-4 production by the malignant cell line HUT78. Lymphokine Cytokine Res 12:33–8.
67. Fukudome K, Furuse M, Fukuhara N, Orita S, Imai T, Takagi S, Nagira M, Hinuma Y, Yoshie O (1992): Strong induction of ICAM-1 in human T-cells transformed by human T-cell leukemia virus type 1 and depression of ICAM-1 or LFA-1 in adult T-cell leukemia derived cell lines. Intern J Cancer 52:418–27.
68. Hsu S, Tseng C, Hsu P (1990): Expression of p55 (TAC) interleukin-2 receptor but not p75 IL2R in cultures H-RS cells and H-RS cells in tissues. Am J Pathol 136:735–44.
69. Dalloul A, Laroche L, Bagot M, Mossalayi D, Fourcade C, Thacker D, Hogge D, Merle-Beral H, Debre P, Schmitt C (1992): Interleukin-7 is a growth factor for Sezary lymphoma cells. J Clin Invest 90:1054–60.
70. Foss F, Koc Y, Stetler-Stevenson M, Nguyen D, O'Brien M, Turner R, Sausville E (1994): Co-stimulation of cutaneous T-cell lymphoma cells by IL7 and IL2: Potential autocrine or paracrine effectors in the Sezary syndrome. J Clin Oncol 12:326–335.
71. Armitage R, Ziegler S, Friend D, Park L, Fanslow W (1992): Identification of a novel low affinity receptor for human interleukin-7. Blood 79:1738–45.
72. Veillette A, Bookman M, Horak E, Bolen J (1988): The CD4 and CD8 cell surface antigens are associated with the internal membrane tyrosine protein kinase p561ck. Cell 55:301–8.
73. Samelson L, Phillips A, Luong E, Klausner R (1990): Association of the *fyn* protein-tyrosine kinase with the T-cell antigen receptor. Proc Natl Acad Sci USA 87: 4358–4362.
74. Yananashi Y, Mori S, Yoshida M, Kishimoto T, Inoue K, Yamamoto T, Toyoshima K (1989): Selective expression of a protein-tyrosine kinase, p56 *lyn* in hematopoietic cells and association with production of human T-cell lymphotrophic virus type I. Proc Natl Acad Sci 86:6538–42.
75. Blake T, Langdon W (1992): A rearrangement of the c-abl proto-oncogene in HUT78 T-lymphoma cells results in a truncated protein. Oncogene 7:757–62.
76. Finger L, Huebner K, Cannizzaro L, McLeod K, Nowell P, Croce C (1988): Chromosomal translocation in T-cell leukemia line HUT78 results in a MYC fusion transcript. Proc Nat Acad Sci USA 85(23):9158–62.
77. Petroni D, Comi P, Giglioni B, Stacchini A, Martinotti G, Guerrasio A, Saglio G (1992): Tumorigenic activity of a rearranged c-myc gene from a human T-cell leukemia cell line. Carcinogenesis 13:883–5.
78. Cheng J, Haas M (1990): Frequent mutations in the p53 tumor suppressor gene in human leukemia T-cell lines. Mol Cell Biol 10:5502–5509.
79. Waldmann TA, Goldman CK, Bongiovanni KF, et al (1988): Therapy of patients with human T-cell lymphotropic virus I-induced adult T-cell leukemia with anti-tac, a monoclonal antibody to the receptor for interleukin-2. Blood 72:1805–1816.
80. Krenke M, Depper J, Leenard WJ, et al (1985): Adult T-cell leukemia: A potential target for ricin A chain immunotoxins. Blood 65:1416–1421.
81. Fitzgerald M, Waldmann T, Willingham MC, et al (1984): Pseudomonas exotoxin-anti-tac: Cell specific immunotoxin active against cells expressing the T-cell growth factor receptor. J Clin Invest 74:966–971.

82. Kozack RW, Atcher RW, Gasow OA, et al (1986): Bismuth-212 labeled anti-tac monoclonal antibody: Alpha particle emitting radionuclides as modalities for radioimmunotherapy. Proc Natl Acad Sci USA 83:474–478.
83. Rosolen A, Nakanishi M, Poplack D, Cole D, Quinines R, Reaman G, Cotelingam J, Trepel J, Sausville E, Marti G, Neckers L, Colamonici O (1989): Expression of interleukin-2 receptor beta subunit in hematopoietic malignancies. Blood 73:1968–72.
84. Nasu K, Said J, Vonderheid E (1985): Immunopathology of cutaneous T-cell lymphomas. Am J Pathol 199: 436–7.
85. Abel E, Lindae M, Hoppe R, Wood G (1988): Benign and malignant forms of erythroderma: Cutaneous immunophenotypic characteristics. J Am Acad Derm 19: 1089–95.
86. Kung E, Meissner K, Loning T (1988): Cutaneous T-cell lymphoma: Immunocytochemical study on activation/proliferation and differentiation associated antigens in lymph nodes, skin, and peripheral blood. Virchows Arch A Pathol Anat 413:539–49.
87. Williams D, Parker K, Bacha P, Bishai W, Borowski M, Genbauffe F, Strom T, Murphy J (1987): Diphtheria toxin receptor binding domain substitution with interleukin-2: Genetic reconstruction and properties of a diphtheria toxin related interleukin-2 fusion protein. Protein Eng 1:493–498.
88. Bacha P, Williams D, Waters C, Murphy J, Strom T (1988): Interleukin-2 receptor mediated action of a diphtheria toxin related interleukin-2 fusion protein. J Exp Med 167:612–622.
89. Waters C, Schimke P, Snider C, Strom T, Murphy J (1990): Receptor binding requirements for entry of a diphtheria toxin-related interleukin-2 fusion protein into cells. Eur J Immunol 20:785–791.
90. Williams D, Snyder C, Strom T, Murphy J (1990): Structure/function analysis of interleukin-2 toxin (DAB486IL2). J Biol Chem 285:11885–11889.
91. LeMaistre CF, Meneghetti C, Rosenblum M, Reuben J, Shaw J, Deisseroth A, Woodworth T, Parkinson D (1992): Phase I trial of an interleukin-2 fusion toxin (DAB 486IL2) in hematologic malignancies expressing the IL-2 receptor. Blood 79:2547–2554.
92. LeMaistre CF, Craig F, Meneghetti C, McMullin B, Parker K, Reuben J, Boldt D, Rosenblum M, Woodworth T (1993): Phase I trial of a 90-minute infusion of the fusion toxin DAB(486)IL2 in hematologic cancers. Cancer Res 53:3930–34.
93. Hesketh P, Caguioa P, Koh H, Dewey H, Facada A, McCaffrey R, et al (1993): Clinical activity of a cytotoxic fusion protein in the treatment of cutaneous T-cell lymphoma. J Clin Oncol 11:1682–1690.
94. Seragen 1993 Quarterly Report, November 22, 1993. Hopkington, MA: Seragen, Inc.
95. Kiyokawa T, Shirono K, Hattori T, et al (1989): Cytotoxicity of interleukin-2 toxin toward lymphocytes from patients with ATLL. Cancer Res 49:4042–4046.
96. Sidi Y, Edwards NL, Winkler C, Bunn PA Jr, Mitchell BS (1985): Differential metabolism of deoxyribonucleosides by leukaemic T-cells of immature and mature phenotype. Br J Haematol 61:125–134.
97. Dearden C, Matutes E, Catovsky D (1991): Deoxycoformycin in the treatment of mature T-cell leukaemias. Br J Cancer 64:903–906.
98. Cummings FJ, Kim K, Neiman RS, Comis RL, Oken MM, Weitzman SA, et al (1991): Phase II trial of pentostatin in refractory lymphomas and cutaneous T-cell disease. J Clin Oncol 9:565–571.
99. Thaler J, Kuse R, Willemze R, et al (1988): Deoxycoformycin in therapy of refractory lymphoid neoplasms. Onkologic 11:35–37.
100. Grever MR, Bisaccia E, Scarborough DA, Mertz EN, Neidhart JA (1983): An investigation of 2′-Deoxycoformycin in the treatment of cutaneous T-cell lymphoma. Blood 62:279–282.
101. Kanofsky JR, Roth DG, Smyth J, Baron JM, Sweet DL, Ultmann JE (1982): Treatment of lymphoid malignancies with 2′-deoxycoformycin: A pilot study. Am J Clin Oncol 5:179–183.
102. O'Dwyer PJ, Wagner B, Leyland-Jones B, Wittes RE, et al (1988): 2′-Deoxycoformycin (pentostatin) for lymphoid malignancies. Ann Int Med 108:733–743.
103. Dang-Vu AP, Olsen EA, Vollmer RT, Greenberg ML, Hershfield MS (1988): Treatment of cutaneous T-cell lymphoma with 2′-deoxycoformycin (pentostatin). J Am Acad Dermatol 19:692–698.
104. Von Hoff DD, Dahlberg S, Hartstock RJ, Eyre HJ (1990): Activity of fludarabine monophosphate in patients with advanced mycosis fungoides: A Southwest Oncology Group Study. J Natl Cancer Inst 82:1353–1355.
105. Saven A, Carrera CJ, Carson DA, Beutler E, Piro LD (1992): 2-Chlorodeoxyadenosine: an active agent in the treatment of cutaneous T-cell lymphoma. Blood 80: 587–592.
106. Kuzel TM, Samuelson E, Roenigk HH Jr, Torp E, Rosen ST (1992): Phase II trial of 2 chlorodeoxyadenosine for the treatment of mycosis fungoides or the Sézary syndrome. Proc Am Soc Clin Oncol 11:A1089 (abstract).
107. Lofters W, Campbell M, Gibbs N, Cheson B (1987): 2′ deoxycoformycin therapy in adult T-cell leukemia/lymphoma. Cancer 60:2605–2608.
108. Tingsgaard P, Jorgensen H, Vejlsgaard GL (1993): Interferon treatment of cutaneous T-cell lymphoma. Eur J Haematol 51:63–72.
109. Foss FM, Ihde DC, Breneman DL, Phelps RM, et al (1992): Phase II study of pentostatin and intermittent high-dose interferon alfa-2a in advanced mycosis fungoides/Sézary Syndrome. J Clin Oncol 10:1907–1913.
110. Bunn PA Jr, Foon KA, Ihde DC, Longo DL, Eddy J, Winkler et al (1984): Recombinant leukocyte A interferon: An active agent in advanced cutaneous T-cell lymphomas. Ann Int Med 101:484–487.
111. Foon KA, Roth MS, Bunn PA Jr (1987): Interferon therapy of non-Hodgkin's lymphoma. Cancer 59(Suppl):601–604.
112. Kohn EC, Steis RG, Sausville ET, et al (1990): Phase II trial of intermittent high-dose recombinant interferon alfa-2a in mycosis fungoides and the Sézary syndrome. J Clin Oncol 8:155–160.

113. Kaplan EH, Rosen ST, Norris DB, Roenigk HH Jr, Saks SR, Bunn PA Jr (1990): Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 82:208–212.
114. Kuzel TM, Gilyon K, Springer E, Variakojis D, Kaul K, Bunn PA Jr, et al (1990): Interferon Alfa-2a combined with phototherapy in the treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst 82:203–207.
115. Kaye FJ, Bunn PA Jr, Steinberg SM, Stocker JL, Ihde DC, Fischmann AB, et al (1989): A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. New Engl J Med 321:1784–1790.
116. Miller RA, Levy R (1981): Response of cutaneous T-cell lymphoma to therapy with hybridoma monoclonal antibody. Lancet II:226–230.
117. Bunn PA Jr, Norris DA (1990): The therapeutic role of interferons and monoclonal antibodies in cutaneous T-cell lymphomas. J Invest Dermatol 95(Suppl):209S–212S.
118. Bertram JH, Gill PS, Levine AM, Boquiren D, et al (1986): Monoclonal antibody T101 in T-cell malignancies: A clinical pharmacokinetic and immunologic correlation. Blood 68:752–761.
119. Dillman RO, Shawler DL, Dillman JB, Royston I (1984): Therapy of chronic lymphocytic leukemia and cutaneous T-cell lymphoma with T101 monoclonal antibody. J Clin Oncol 2:881–891.
120. Boven E, Lindmo T, Mitchell JB, Bunn PA Jr (1986): Selective cytotoxicity of ^{125}I-labeled monoclonal antibody T101 in human malignant T-cell lines. Blood 67:429–435.
121. Carrasquillo JA, Bunn PA Jr, Keenan AM, Reynolds JC, Schroff RW, et al (1986): Radioimmunodetection of cutaneous T-cell lymphoma with ^{111}In-T101 monoclonal antibody. New Engl J Med 315:673–680.
122. Carrasquillo JA, Mulshine JL, Bunn PA Jr, Reynolds JC, Foon KA, Schroff RW, et al (1987): Indium-111 T101 monoclonal antibody is superior to iodine-131 T101 in imaging of cutaneous T-cell lymphoma. J Nucl Med 28:281–287.
123. Keenan AM, Weinstein JN, Carrasquillo JA, Bunn PA Jr, Reynolds JC, et al (1987): Immunolymphoscintigraphy and the dose-dependence of ^{111}In-labeled T101 monoclonal antibody in patients with cutaneous T-cell lymphoma. Cancer Res 47:6093–6099.
124. Rosen ST, Zimmer AM, Goldman-Leikin R, Gordon LI, Kazikiewicz JM, Kaplan EH, et al (1987): Radioimmunodetection and radioimmunotherapy of cutaneous T-cell lymphomas using an ^{131}I-labeled monoclonal antibody: An Illinois Cancer Council study. J Clin Oncol 5:562–573.
125. LeMaistre CF, Rosen S, Frankel A, Kornfeld S, Saria E, Meneghetti C, et al (1991): Phase I trial of H65-RTA immunoconjugate in patients with cutaneous T-cell lymphoma. Blood 78:1173–1182.