Skin Reactions in a Subset of Patients With Stage IV Melanoma Treated With Anti–Cytotoxic T-Lymphocyte Antigen 4 Monoclonal Antibody as a Single Agent

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Objective: To describe the clinical and histologic manifestations of skin reactions incidentally noted in patients with stage IV melanoma who were treated with up to 9 mg/kg of a humanized monoclonal antibody reactive against human cytotoxic T-lymphocyte antigen 4 (anti–CTLA-4) as a single agent every 3 weeks.

Setting: Single-institution prospective study.

Design: Patients treated with anti–CTLA-4 as a sole agent were prospectively referred for clinicopathologic characterization of skin reactions occurring during treatment.

Main Outcome Measures: Specific clinicopathologic features were determined by means of a detailed history, a physical examination, conventional histologic analysis, antibody staining, and complete blood cell counts.

Results: Nine (14%) of 63 consecutive patients treated with anti–CTLA-4 as a sole agent developed skin eruptions that were attributed to anti–CTLA-4 in 8 of them. Skin lesions consisted primarily of discrete, pruritic, erythematous, minimally scaly papules that typically coalesced into thin plaques on the trunk and extensor surfaces of the extremities. Extensive alopecia was also noted in 1 patient. Histologically, a superficial, perivascular CD4+/H11001-predominant T-cell infiltrate with eosinophils in the dermis, rare dyskeratotic cells, and mild epidermal spongiosis were present. An increase (compared with pretreatment values) in the peripheral blood eosinophil frequency was observed in patients at the time of skin eruptions (P = .006).

Conclusions: Specific features of the skin eruption dermatitis with increased tissue and peripheral blood eosinophil levels in a subset of treated patients. Specific features of skin eruption associated with anti–CTLA-4 resemble those described for maculopapular reactions to medications.

Arch Dermatol. 2006;142:166-172

Overlaying Tolerance of self-antigens significantly limits the use of vaccine therapy for the treatment of cancer. Despite multiple trials demonstrating that tumor vaccination results in the development of enhanced immunity, objective responses are infrequent. Because most known tumor antigens are normal “self-proteins,” immune regulatory mechanisms that prevent autoimmunity also prevent robust immune responses to cancer and peptide vaccines.

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) is an important costimulatory molecule expressed by activated T cells and a subset of regulatory T cells. Engagement of CTLA-4 inhibits T-cell activation by blocking production of interleukin 2 and interleukin 2 receptor expression, leading to arrest of T cells at the G1 phase of the cell cycle. In CTLA-4 knockout mice, a rapid, fatal lymphoproliferative disorder develops, suggesting that CTLA-4 is also integral to the maintenance of tolerance and prevention of autoimmunity. Moreover, CTLA-4 appears to be critical in regulating Th2 vs Th1 differentiation in helper T (Th) cells, because activated CTLA-4-deficient T cells are strongly biased toward Th2 differentiation.

Given the integral role of CTLA-4 in the maintenance of tolerance, there has been considerable interest in overcoming tolerance in the treatment of cancer by blockade of CTLA-4 function. As monotherapy in animal models, anti–CTLA-4 monoclonal antibodies have been most effective in treating immunogenic tumors, with minimal effects on large established tumors or weakly immunogenic tumors. Combining anti–CTLA-4 therapy with concurrent vaccination with tumor cells that secrete granulocyte-macrophage colony-stimulating factor (GM-CSF) may further enhance antitumor immunity.
factor substantially enhanced efficacy against poorly immunogenic tumors such as B16 melanoma.8

Recently, results of 3 clinical trials involving the use of anti–CTLA-4 in combination with peptide vaccine for the treatment of cancer have been reported.9-11 In total, 40 patients with metastatic melanoma and 2 patients with metastatic ovarian cancer were treated with anti–CTLA-4 therapy in combination with or after peptide vaccine therapy. In one of these trials, a single administration of anti–CTLA-4 in patients for whom previous vaccine therapy had failed yielded histopathologic evidence of tumor cell death and lymphocytic invasion within some tumors but no objective clinical responses.13 In the other 2 trials in which repeated doses of anti–CTLA-4 were given in combination with peptide vaccine, a subset of patients with metastatic melanoma demonstrated major tumor regression with long tumor-free intervals.9,11

Administration of anti–CTLA-4 was associated with multiple autoimmune toxic effects, including enterocolitis, hypophysitis, hepatitis, uveitis,12 vitiligo, increased antinuclear antibody levels, elevated rheumatoid factor levels, and rashes.8,11 Recent experience at the National Cancer Institute (NCI) Clinical Center showed that 14 (25%) of 56 patients with stage IV melanoma treated with anti–CTLA-4 and vaccinated with HLA-A*0201–restricted gp100 peptides experienced grades III to IV autoimmune reactions (ie, reversible [grade III] or irreversible/progressive [grade IV] toxic effects involving function of a major organ and requiring immuno-suppressive treatment11), including rashes.14 Autoimmune manifestations were more pronounced in patients with more dramatic objective disease responses,9,14 suggesting that effective anticancer responses may be correlated with autoimmunity to self-antigens other than tumor antigens.

Rashes have been common adverse effects in recipients of anti–CTLA-4 therapy administered after or in conjunction with vaccination. Phan et al9 observed that rashes developed in 4 (29%) of 14 patients, with 3 of the 4 patients experiencing grades III to IV rashes based on common toxic effects criteria version 2.0 (Table 1).13 Histologically, these showed epidermal spongiosis, papillary dermal edema, and a perivascular lymphocytic infiltrate with eosinophils. Hodi et al11 reported that all patients (7/7) with metastatic melanoma and 1 of 2 with ovarian cancer developed a skin eruption (grade I) after anti–CTLA-4 therapy. Last, Sanderson et al14 reported that 7 (37%) of 19 patients developed a grade I to II rash.

Although it has been documented that dermatitis develops in a significant percentage of patients treated with anti–CTLA-4 therapy in combination with or after vaccine therapy, the clinical and histologic features of this skin eruption have not been systematically studied. We herein describe the clinicopathologic features of skin eruptions that developed in previously unvaccinated patients with melanoma who received anti–CTLA-4 treatment as a single agent, thus removing the potential effects that vaccination might have had on the development of autoimmunity in previous studies. Of interest, the features of anti–CTLA-4 der-
ment was held for autoimmune toxic effects and stabilizing disease. At each treatment visit, patients were questioned and examined for the development of adverse effects by physicians from the NCI Surgery Branch. Patients with visible skin eruptions were referred to the NCI dermatology consultation clinic, where a detailed history and photographs were obtained and skin examination was performed. Four-millimeter punch biopsy specimens of representative skin lesions were obtained while the patient was under local anesthesia for conventional histologic examination and immunostaining for T- and B-cell markers. Biopsy specimens were reviewed by a dermatopathologist for histologic diagnosis and by a pathologist (D.M.B.) for scoring of specific histologic features.

### RESULTS

#### PATIENT POPULATION

All patients received anti–CTLA-4 as experimental therapy for stage IV melanoma. Of the first 63 consecutive patients receiving anti–CTLA-4 treatment alone in this clinical trial, 9 (14%; 7 men and 2 women) were examined by NCI dermatologists (E.W.C. and S.T.H.) after referral for evaluation of skin eruptions detected by the primary surgical oncology team. As shown in Table 2, patients ranged in age from 34 to 67 years, and skin-related reactions developed from 3 to 67 days after initial anti–CTLA-4 treatment. Skin reactions developed in 4 of the 9 after their first anti–CTLA-4 injections. Notably, none of the patients had a history of atopic dermatitis or psoriasis. Three of the 9 patients were taking no concurrent medications at the time of the skin reaction. Except for patient 9, concurrent therapies had been initiated before anti–CTLA-4 therapy and were deemed unlikely to have caused the rashes. Unless specifically noted, descriptions of the gross and microscopic features refer to the 8 patients in whom rashes were attributed to anti–CTLA-4 therapy. Four of 9 patients had a history of cutaneous reactions to a variety of substances, including chemotherapy agents (cisplatin), promethazine hydrochloride, shellfish and iodine dye, and interferon alfa (Table 2).

### PHYSICAL SIGNS AND SYMPTOMS OF DERMATITIS ASSOCIATED WITH ANTI–CTLA-4

Except patient 9, in whom colitis developed early during his course of anti–CTLA-4 therapy, patients were not aware of fever or systemic illness (eg, diarrhea) that accompanied the development of their rashes. Patients were ambulatory and not acutely ill at the time of skin examination. Most patients reported variable degrees of pruritus ranging from mild to severe, and 3 patients described a painful, burning sensation (Table 3).

As shown in Figure 1, a typical primary skin lesion was a dome-shaped, pink to bright red papule that ranged from 2 to 4 mm in diameter (Figure 1A-C). Lesions typically started out as discrete papules (Figure 1B and C) that could coalesce to form thin plaques (Figure 1A). External trauma (scratching) occasionally led to the formation of new lesions (ie, Koebner phenomenon, Figure 1A [arrow]). Although older lesions showed some evidence of fine white scale, scaling was not a prominent feature. The proximal extensor surfaces of the limbs were most often involved, followed by the trunk and distal extremities. The palms and soles were generally spared. The face and head were involved in 3 patients. Patient 1 (in addition to a mild papular eruption on the trunk and arms) developed striking, nonscarring alopecia of the scalp (Figure 1D), eyebrows, face, pubic region, and trunk after anti–CTLA-4 treatment. Patient 2 developed a symmetric skin eruption that appeared to be photodistributed. Patients 2 and 9 developed the only rashes that appeared to be exacerbated by light. Discontinuation of anti–CTLA-4 therapy for several weeks resulted in marked improvement of rashes. During this period, patients used

### Table 2. Demographic Characteristics of Patient Cohort

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>HLA-A*0201 Status</th>
<th>Anti–CTLA-4 Starting Dose, mg/kg</th>
<th>Onset of Rash After First Anti–CTLA-4 Treatment, d</th>
<th>Dose No./Dose at Which Rash Began, mg/kg</th>
<th>Concurrent Drug Use</th>
<th>Allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/34</td>
<td>−</td>
<td>3</td>
<td>49</td>
<td>3/5</td>
<td>Levothyroxine sodium</td>
<td>None</td>
</tr>
<tr>
<td>2/M/55</td>
<td>+</td>
<td>3</td>
<td>14</td>
<td>1/3</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3/F/56</td>
<td>−</td>
<td>3</td>
<td>7</td>
<td>1/3</td>
<td>Dilatiazem hydrochloride and aspirin</td>
<td>Iodine dye– and shellfish-associated rash</td>
</tr>
<tr>
<td>4/M/50</td>
<td>+</td>
<td>3</td>
<td>47</td>
<td>3/5</td>
<td>Bupropion hydrochloride</td>
<td>None</td>
</tr>
<tr>
<td>5/M/43</td>
<td>−</td>
<td>3</td>
<td>30</td>
<td>2/3</td>
<td>None</td>
<td>Promethazine hydrochloride–associated facial swelling</td>
</tr>
<tr>
<td>6/M/55</td>
<td>−</td>
<td>5</td>
<td>10</td>
<td>1/5</td>
<td>Citalopram, fenoﬁbrate, alprazolam, trazodone hydrochloride, and multivitamins</td>
<td>Interferon alfa–associated rash; vitiligo</td>
</tr>
<tr>
<td>7/F/67</td>
<td>+</td>
<td>5</td>
<td>3</td>
<td>1/5</td>
<td>Risedronate sodium and esomeprazole</td>
<td>Cisplatin-associated rash</td>
</tr>
<tr>
<td>8/M/57</td>
<td>−</td>
<td>5</td>
<td>31</td>
<td>2/5</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>9/M/49</td>
<td>−</td>
<td>5</td>
<td>67</td>
<td>2/5</td>
<td>Hydrochlorothiazide, amlopidine besylate, lisinopril, alprazolam, prednisone, esomeprazole</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: anti–CTLA-4, anti–cytotoxic T-lymphocyte antigen 4; HLA-A*0201, human leukocyte antigen A*0201; −, negative; +, positive.
only bland emollients (no topical steroids) and oral diphenhydramine hydrochloride for relief of pruritus. Two months after his last dose of anti–CTLA-4, the alopecia experienced by patient 1 had not improved.

**HISTOLOGIC AND IMMUNOHISTOLOGIC EXAMINATION**

Skin biopsy specimens were obtained from representative, nontreated lesions and submitted for pathologic examination. The histologic features of the dermatitis are depicted in Figure 2A and B and summarized in Table 3. These biopsy results showed moderate-to-dense mononuclear lymphocytic infiltrates around the superficial vascular plexi and in the papillary dermis. In some patients, deeper blood vessels and hair follicles were also involved. Lichenoid aggregation of lymphocytes and large numbers of dyskeratotic keratinocytes at the dermoeidermal interface with vacuolar changes were not observed except in the biopsy specimen of patient 9, whose clinical history suggested that a drug other than anti–CTLA-4 was responsible for his skin eruption. Epidermal spongiosis and T-cell exocytosis, features of contact dermatitis, were absent or minimal. In 6 (75%) of the 8 patients whose skin reactions were attributed to anti–CTLA-4, eosinophils were observed in the superficial and deep dermis. Results of immunohistochemistry revealed that the mononuclear infiltrate observed by hematoxylin-eosin examination consisted almost entirely of CD3+ T cells (Figure 2C) (with no or few B cells), of which more than 80% were typically CD4+ (Figure 2D) and less than 20% were CD8+ (Figure 2E) except as noted for patient 9. A scalp skin biopsy specimen taken from the patient with near total alopecia of the scalp and other body regions (patient 1) was histologically consistent with alopecia areata and contained predominantly CD4+ T cells and only scant CD8+ T cells, which was consistent with idiopathic alopecia areata.10

Patient 9, who was treated with his second dose of anti–CTLA-4 5 weeks before referral, developed a pruritic, papular eruption of the trunk with photoaccentuated lesions on the sun-exposed skin of his face and back of the neck (Figure 3A and B). At the time of the skin eruption, he was being treated with low-dose prednisone for autoimmune colitis related to anti–CTLA-4. In contrast to biopsy specimens from other patients, a lesional skin biopsy specimen showed moderate vacuolar change (Figure 3C), extensive exocytosis of CD8+ T cells in the epidermis (Figure 3D), a greater proportion of CD8+ to CD4+ T cells in the dermis and epidermis, and no dermal eosinophils. Because the patient had just started hydrochlorothiazide therapy for hypertension approximately 3 weeks before referral and showed evidence of the lichenoid photosensitive dermatitis observed with thiazide diuretics,17 the most likely cause of his skin eruption was deemed to be hydrochlorothiazide. We could not rule out, however, that his other concurrent medications and/or prior treatment with anti–CTLA-4 may have caused or exacerbated his skin eruption.

Table 3. Distribution of Skin Eruption and Histologic Characteristics of Lesional Skin*

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Distribution</th>
<th>Symptoms</th>
<th>Spongiosis</th>
<th>Exocytosis</th>
<th>Eosinophils</th>
<th>Dyskeratotic Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bilateral arms, chest, and back; progressive, total alopecia of scalp, face, pubic region, and trunk also developed</td>
<td>Mild pruritus worse with heat, sweating, and exercise</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Consistent with photodistribution; Koebner phenomenon noted with linear excoriations on posterior upper arm</td>
<td>Mild pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Inframammary region, shins, arms, thighs, and back with accentuation of rash on extensor surfaces</td>
<td>Severe pruritus with burning</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Forearms and upper back with mild erythema of anterior thighs</td>
<td>Mild pruritus</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Generally distributed, with sparing of the buttocks and upper chest above the nipple line</td>
<td>Mild pruritus</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Anterior thighs, lower back, rear shoulders, and axilla; vitiligo on neck; accentuation of rash on extensor surfaces</td>
<td>Severe pruritus with burning</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Forearms, arms, legs, chest, back, and buttocks</td>
<td>Severe pruritus</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Initial lesions on trunk; worsened significantly after fourth treatment, with involvement of trunk, arms, and legs</td>
<td>Mild pruritus</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Back, anterior chest, and sun-exposed sites of forehead, back of neck, and ears</td>
<td>Mild pruritus with mild burning</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

*Formalin-fixed sections were stained with hematoxylin-eosin and assessed for the following histologic features: (1) dyskeratotic epidermal cells: positive (+), if 1 or more dyskeratotic cells were seen per high-power field, otherwise negative (0); (2) spongiosis: little or none: 0; moderate to severe: +; (3) eosinophils: the number of eosinophils per ×40 field in the dermis was counted and stratified as follows: none detected, 0; 1 to 5, +; and more than 5, ++; and (4) exocytosis: the number of mononuclear cells (presumably T cells) observed in the epidermis per section was classified as follows: none detected, 0; 1 to 5 cells, +; 1 to 5 cells, ++; and more than 5 but less than 10 cells, +++; and 10 cells or more, ++++. Skin sections were also stained with antibodies reactive with CD20, CD3, CD4, and CD8.

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Complete blood cell counts were performed at 3-week intervals according to protocol in coordination with scheduled anti–CTLA-4 treatments. These values were within reference limits, except for notable increases in peripheral eosinophil frequencies. As shown for 8 of 9 patients with rashes attributed to anti–CTLA-4 and illustrated in detail for patient 5 (Figure 4), the eosinophil frequencies (obtained after development of rashes) were significantly increased relative to values obtained before anti–CTLA-4 treatment. Only 3 patients had peripheral eosinophil frequencies of more than 9% (the upper limit of the reference range in our clinical laboratory) at the time they underwent evaluation for their skin findings. Patients demonstrated 2.7- to 16-fold increases from their baseline values (mean values before vs after anti–CTLA-4 treatment, 1.73% vs 8.38%; \( P = .006 \) by paired \( t \) test) after development of skin reactions. By contrast, no statistically significant increase in the frequency of eosinophils (\( P = .19 \)) was noted in the blood (Figure 4A) of 8 patients who did not develop autoimmune toxic effects or rashes during comparable time periods.

COMMENT

We herein describe 9 patients with stage IV melanoma who developed skin eruptions after treatment with anti–CTLA-4 as a single agent for immunotherapy of metastatic disease. In 8 of the 9 patients, anti–CTLA-4 was believed to be the primary cause of the rash. The frequency of dermatitis observed in this study (9 [14%] of 63 patients) was less than that reported for patients receiving anti–CTLA-4 therapy in conjunction with vaccination, suggesting that vaccination increases the risk of skin reactions during treatment with anti–CTLA-4. Besides the papular eruption described in our cohort of patients, striking near-total alopecia developed in patient 1 after administration of anti–CTLA-4, and a CD8 T-cell–predominant dermatitis developed in patient 9 (most likely secondary to hydrochlorothiazide therapy) with vacuolar change. The use of anti–CTLA-4 alone in our patients allows us a rare opportunity to document the effects of CTLA-4 blockade in the regulation of human cutaneous immunity.

The most consistent clinicopathologic features observed were the predominance of CD4 T cells and eosinophils in the dermis and increases in peripheral blood eosinophil frequencies, suggesting possible skewing toward a \( T_{H2} \)-type immune response. These observations show similarities to the striking activation of \( T_{H2} \)-type CD4 T cells and marked infiltration of internal organs with such \( T_{H2} \) cells in mice lacking CTLA-4.

The antigen or antigens driving the accumulation or proliferation of CD4 T cells found in dermatitis associated with anti–CTLA-4 are unknown. Because cytolytic T cells specific for melanoma-associated antigens such as tyrosinase or MART-1 (melanoma antigen recognized by T cells 1) are found frequently in the peripheral circulation in patients with melanoma,\(^{18}\) we hypothesize that CD4 T cells within the inflamed skin of our patients may be triggered by antigen-presenting cells in the skin that potentially display melanocyte-associated antigens in conjunction with major histocompatibility complex class II under steady-state conditions. Indeed, Hodi et al\(^{10}\) noted the presence of CD4 and CD8 T cells
adjacent to cells they described as melanocytes in skin reactions after anti–CTLA-4 treatment in previously vaccinated patients with melanoma.

The clinical and histopathologic findings in our cohort of patients have some, but not all, features of what has commonly been termed maculopapular drug exanthem and has been observed with many drugs such as penicillins or sulfa-based drugs. The MPEs likely represent most of all drug-induced skin reactions and typically occur 1 to 2 weeks after the first ingestion of a drug. Histologically, MPE and dermatitis associated with anti–CTLA-4 show a predominance of CD4+ T cells and eosinophils in the dermis along with mild epidermal spongiosis and little exocytosis. Histologically, however, MPEs often show evidence of vacuolar alteration of the basal keratinocytes. However, because MPEs seldom undergo biopsy by dermatologists unless they evolve into more serious conditions, vacuolar alteration may reflect a bias in the reporting of more advanced skin reactions.

Vacuolar changes are more common in destructive (blistering) reactions to drugs, including severe erythema multiforme (ie, Stevens-Johnson syndrome) and toxic epidermal necrolysis, which both exhibit increased numbers of CD8+ T cells at the dermal-epidermal interface and in the epidermis. A biopsy specimen from patient 9 (from a rash attributed to hydrochlorothiazide) demonstrated large numbers of CD8+ T cells in the epidermis and vacuolar changes that were consistent with erythema multiforme. Prior anti–CTLA-4 therapy may have contributed to the development and/or severity of this rash.

Highly specific biologic agents such as anti–CTLA-4, efalizumab (for psoriasis), etanercept (for psoriasis and rheumatoid arthritis), bevacizumab (for cancer), and rituximab (for cancer) promise to improve outcomes in inflammatory and neoplastic diseases, but unwanted adverse effects, which are distinct from those reported herein for anti–CTLA-4, are becoming apparent as these agents enter wide use. With anti–CTLA-4, previous reports suggest that inhibition of CTLA-4 in conjunction with vaccination strategies may be an important adjuvant in mediating objective cancer regression, but at the cost of an increased incidence of autoimmune reactions such as colitis, hypophysitis, and dermatitis. The cutaneous eruptions described in our patients after administration of antibodies that block the function of CTLA-4 clinically and histopathologically resemble the MPEs commonly observed in patients after administration of many medications, raising the intriguing possibility that inhibition of CTLA-4 function may play a role in the pathogenesis of 1 of the most common toxic effects associated with administration of pharmaceutical agents.

Accepted for Publication: July 25, 2005.
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and exacerbation of the skin reaction in patient 5. The left y-axis indicates eosinophil values were not included in this analysis. B, Peripheral leukocyte skin eruption was not thought to be due primarily to anti-CTLA-4, his peripheral statistically compared using paired, 2-sided evaluated approximately 6 weeks after at least 2 anti–CTLA-4 treatments. The anti–CTLA-4 treatment in both groups of patients. For patients who had not developed known autoimmune toxic side effects in the first 6

cumulating patient statistics.

tinal Cancer Institute [NCI], Bethesda, Md), for many

tional Institutes of Health/Pfizer Clinical Research Train-

REFERENCES