ACADEMY ’06 MEETING
American Academy of Dermatology
San Diego, CA

Forum #506
CUTANEOUS T-CELL LYMPHOMA
July 27, 2006

Youn H. Kim, MD
Uma Sundram, MD, PhD
CTCL Update

- **Clinical Features**
  - Clinical clues for diagnosis, staging and prognosis
    - *Youn Kim, Professor of Dermatology, Stanford University School of Medicine*

- **Pathology**
  - Histopathologic diagnosis, role of IHC/molecular techniques
    - *Uma Sundram, Assistant Professor of Pathology & Dermatology, Stanford University School of Medicine*

- **Therapy**
  - Topical, systemic, combined modality, and investigative therapies
    - *Youn Kim*
Therapy Updates
in Cutaneous T-cell Lymphoma

Youn H. Kim

Department of Dermatology
Multidisciplinary Cutaneous Lymphoma Group
Stanford University School of Medicine
<table>
<thead>
<tr>
<th>New WHO-EORTC Classification</th>
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<tbody>
<tr>
<td>Mycosis fungoides and variants/subtypes</td>
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<tr>
<td>Sézary syndrome</td>
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<tr>
<td>PC CD30+ lymphoproliferative disorders</td>
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<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
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<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
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<tr>
<td>Adult T-cell leukemia/lymphoma</td>
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<td>PC peripheral T-cell lymphoma, unspecified</td>
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<td>Aggressive epidermotropic CD8+ T-cell lymphoma</td>
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<td>Cutaneous $\gamma/\delta$ T-cell lymphoma</td>
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<td>PC CD4+ sm/med-sized pleomorphic T-cell lymphoma</td>
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<td>PTCL, other</td>
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Current and Investigative Therapies
Goals of Therapies for CTCL

**IDEAL**
- Cure
- Extend Life
- Alleviate symptoms
- Durable response
- High response rate

**REAL**
- Alleviate symptoms
- Variable response
- Variable response duration
- Extend Life
- Cure
Treatment Alternatives in MF/SS (CTCL)

- **Topical (skin-directed) therapy**
  - Topical steroid, nitrogen mustard, topical retinoid (Targretin*), BCNU, phototherapy (UVB/PUVA), EBT, topical imiquimod

- **Systemic therapy**
  - Biologicals
    - photopheresis*, interferon, retinoid (Targretin*), fusion protein/toxin (Ontak*)
  - Cytotoxic chemotherapy
    - MTX, Doxil, gemcitabine, etoposide, pentostatin, combination regimens

- **Combined modality therapy**
  - Topical + topical, topical + systemic, systemic + systemic

- **Investigative therapy**
  - Monoclonal antibodies (e.g., CD3, CD4, CD30, CD52)
  - HDAC inhibitors (e.g., depsipeptide, SAHA)
  - PNP inhibitors
  - Cytokines (e.g., rhIL12)
  - Immunostimulatory oligonucleotides (e.g., CpG 7909)
  - Allo-HSC transplantation
Management of MF/SS

• Treatment Selection Factors
  – Clinical stage***
  – Other prognostic factors
    • follicular, LC transformation, etc.
  – Response rate/speed/duration
  – Side effect profile
    • pt age, co-morbidities
  – Accessibility of treatment options
  – Cost-benefit ratio
  – Other social and medical issues
Treatment Approach in Mycosis Fungoides & Sézary Syndrome

IA
- Limited dz, T1
  - Top steroids, Targ gel
  - NM

IB/IIA
- Generalized, T2
  - PUVA ± Targ or IFN
  - TSEBT ± NM, Targ or IFN (or ECP)

IIB
- Tumors, T3
  - Targ ± IFN, Ontak
  - Investigative/Newer Therapies (TLRA, MoAb, cytokine, HDAAI, PNPI, IMiD, vaccine, allo-HSCT)

III
- Erythroderm, T4
  - ECP ± Targ, IFN
  - Single-agent Chemo (Mtx, Doxil, Gem, Pento)

IV
- Extracut. dz
  - Combination Chemo
  - Campath
Management of Stage IA Disease (Limited Patch/Plaque, T1)

- **MS not attained; DPR <10%
  - Primary therapy is topical (skin-directed)
  - Topical steroid, nitrogen mustard (mechlorethamine), BCNU, topical retinoid (Targretin gel)
  - UVB (narrow-band better) for patch-type disease, PUVA
  - Localized radiation (electron beam) therapy for unilesional MF, compromised locations, or refractory lesions
  - CR >70%, RR >90%
Topical Steroid Therapy

• Clinical indications
  – Primary therapy for limited disease
  – Combination therapy with other skin-directed treatments

• Clinical response
  

  – T1, RR 94% w/ CR 63%, best response w/ class I steroid
  – More effective and appropriate for patch or thin plaque disease

• Toxicity of long-term use of high-potency topical steroid
TOPICAL NITROGEN MUSTARD

• VEHICLE
  • Aqueous
  • Aquaphor
  • Propylene glycol
    (FDA OPD grant study)

• SURFACE
  • Total skin
  • Regional
  • Lesional

• CONCENTRATION
  • Increase effectively
  • Clear efficiently

• TIMING
  • Primary
  • Adjuvant
  • Combination

• MAINTENANCE
  • Short over long
# TOPICAL NITROGEN MUSTARD as a primary therapy

*Kim et al. Arch Dermatol 2003;139:165-73*

<table>
<thead>
<tr>
<th>T Classification</th>
<th>No. of Patients</th>
<th>Response</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>CR+PR (%)</th>
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<tbody>
<tr>
<td>T1</td>
<td>107</td>
<td></td>
<td>70 (65)</td>
<td>30 (28)</td>
<td>7 (7)</td>
<td>100 (93)</td>
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<tr>
<td>T2</td>
<td>88</td>
<td></td>
<td>30 (34)</td>
<td>33 (38)</td>
<td>25 (28)</td>
<td>63 (72)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>195</td>
<td></td>
<td>100 (51)</td>
<td>63 (33)</td>
<td>32 (16)</td>
<td>163 (84)</td>
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Excludes patients on sig. concurrent or preceding therapy
Adverse Effects of Topical NM Therapy

• Contact dermatitis less common w/ ointment-based prep
  – Irritant (~25%) > allergic (<10%) contact dermatitis
  – Majority can be desensitized by reduction in strength w/ build-up
  – Pts w/ brisk contact reactions may have earlier CR

• Less than 5% discontinued ointment-based HN2 due to greasiness
  – Most switched to aqueous or PG prep but still cont. therapy

• Safe in pediatric group w/o evidence of systemic absorption

• Secondary cutaneous malignancies
  – No support for increased skin cancers if used as monotherapy on non-genital skin
  – Increased incidence of squamoproliferative lesions in patients treated with multiple skin-directed therapies (e.g., PUVA, radiation)

*Multicenter trial ongoing for FDA approval*
*Ovation reimbursement line 1-866-209-7604*
Targretin Gel 1%

- Clinical indications in MF/CTCL
  - Topical treatment of refractory or persistent lesions after other therapy failures
  - Can be considered as primary therapy in limited disease (stage IA), either as monotherapy or as part of combination therapy
Targretin Gel 1%

• Administration
  – Start application every other day then build up to BID at weekly intervals only as tolerated

• Clinical response
  *Heald et al. JAAD 2003;49:801-15*
  – Stage IA: RR 60% in phase III trial, RR is higher in treatment naïve patients
  – Minimum treatment duration of 2-3 months to assess objective response
  – Better disease assessment off treatment

• Adverse effects
  – Common topical retinoid skin reactions
Management of Stage IB/IIA Disease (Generalized Patch/Plaque, T2)

- MS 11-12 yrs; DPR 20-30%

- Primary therapy is topical (skin-directed)
  - Topical steroid, nitrogen mustard (NM), BCNU, PUVA
  - UVB reserved for patch-type disease (narrow-band more effective)

- Topical therapy failures or severe plaque disease
  - Biologic therapy: systemic retinoid, IFN, Ontak
  - Combination therapy
    - PUVA + systemic retinoid and/or IFN, IFN + systemic retinoid, Targretin + Ontak
    - TSEBT can be considered as initial therapy for effective/efficient control of severe, symptomatic disease
      - TSEBT +/- NM +/- systemic retinoid or IFN

- CR 45-90%, RR >75%:
Management of Stage IB/IIA Disease (Generalized Patch/Plaque, T2)

- CR 45-90%, TR >75%:

<table>
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<tr>
<th></th>
<th>CR</th>
<th>RR</th>
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<tr>
<td>HN2</td>
<td>45-70%</td>
<td>75-90%</td>
</tr>
<tr>
<td>PUVA</td>
<td>50-80%</td>
<td>85-95%</td>
</tr>
<tr>
<td>TSEBT</td>
<td>80-90%</td>
<td>100%</td>
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</table>

- PUVA may induce long-term remissions
  Querfeld et al. Arch Dermatol 2005;141:305-11
  - DFS at 5 and 10 years for IB/IIA, 74% and 50%
  - Need to balance benefit vs. photodamage risk w/ prolonged therapy

- Narrow-band UVB effective, well-tolerated, convenient for patch/thin plaque disease (Gathers, Lim et al. JAAD 2002;47:191-7)

- No long-term survival advantage for patients treated with TSEBT over nitrogen mustard
Total Skin Electron Beam Therapy

- Generalized thick plaques/tumors w/ severe symptoms
- Total ~36 Gy given over ~10 wks with 1 wk split after 18-20 Gy
- “Shadowed” areas may need supplemental tx
- Most effective single therapy
- Adverse effects: erythema, desquamation, alopecia, loss of nails, inability to sweat
- Adjuvant or combined therapy with topical nitrogen mustard, PUVA, or retinoids, IFN
Retinoid X Receptor (RXR) Ligands (Rexinoids)
Targretin® (bexarotene)

- Systemic biologics when skin-directed therapies fail or present with severe dz or other worse px features (LC transformation, folliculocentric dz)
- FDA-approved in 12/99 for treatment of CTCL
**Targretin® (bexarotene)**

**Molecular Activity**

**RXR-NHR heterodimer**

<table>
<thead>
<tr>
<th>RAR</th>
<th>PPAR</th>
<th>TR</th>
<th>VDR</th>
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**Regulation of Gene Networks**

**Cell Cycle Control**
(Regulation of Cyclins and Cdk-Inhibitors)

**Apoptosis**
(Regulation of Cell Death Genes)

**Differentiation**
(Adipogenesis, Epithelial Cell Maturation)

**Immunologic effects**
(Blocks activated T-cells, cytokines)
Targretin (Bexarotene)

• Administration
  – Starting dose of 100-300 mg/M$^2$/d, depending on disease severity and/or risk for retinoid toxicity
  – Target dose of 300 mg/M$^2$/d, but can increase to higher dose if tolerated

• Clinical response
  – At 300 mg/M$^2$/d dose, TR ~50% (CR <10%)
  – Minimum treatment duration of 2-3 months to assess objective response

*Phase 2-3 early stage, Arch Dermatol 137:581, 2001*
*Phase 2-3 advanced stage, J Clin Oncol 19:2456, 2001*
Targretin (Bexarotene)

• Adverse effects
  – Mostly reversible, dose-related
  – Common retinoid skin and general effects
  – Hyperlipidemia (TG!)
    • Risk of pancreatitis if TG > 800 mg/dL
    • Lipitor, Tricor (do NOT use gemfibrozil)
    • Fasting lipids at baseline, weekly until stable, q2-4 wks
  – Hypothyroid (central axis alteration, do not follow TSH)
    • Thyroid replacement
    • FT4 at baseline, q4 wk until stable, q12 wk

Start lipid-lowering agent and synthroid 1 wk prior to initiation of Targretin
Targretin (Bexarotene)

- **Adverse effects**
  - Leukopenia (1K to < 3K WBC/mm³) or anemia
    - Adjust Targretin dose as needed or use stimulating factors
    - CBC at baseline, q4 wk
  - Hepatic effects, <10%
    - LFTs at baseline, q4 wk
  - Cataracts
    - Relationship to drug unclear
    - Baseline eye exam, f/u q3-6 mo
Comparing L-ATRA With Bexarotene
RAR vs RXR Retinoids

• Similar response rates with oral L-ATRA (12%) and bexarotene (21%) monotherapy in relapsed MF/Sézary syndrome
  – RAR agonists with less lipid problems and no central axis thyroid suppression

Denileukin Diftitox, Ontak®

- Fusion protein technology to kill defined neoplastic cells
  - IL-2-diphtheria toxin fusion protein (denileukin diftitox)
- FDA approved 2/1999 for CTCL patients whose malignant cells express CD25 component of IL-2 receptor
Fusion gene formed by fusing Diptheria toxin’s enzymatic and translocation functions to human IL-2
ONTAK® Mechanism of Action

HIGH affinity IL2 receptor

MEDIUM affinity IL2 receptor

Cleavage & Toxin release

Protein synthesis
Terminated by toxin-mediated ADP ribosylation of elongation factor 2

Protein synthesis

Internalization of IL2R with bound toxin

Cell exterior

Cell membrane

Cell interior
Interleukin-2-diphtheria Toxin Fusion Protein (Ontak, denileukin diftitox)

• Administration
  – Daily IV infusion x 5 days, every 3 wks (used in clinical trials)
    • Alternatively, daily IV infusion x 5 days (loading), then once weekly infusions
  – 9-18 µg/kg/d
  – Recommend slower infusion over 1 hour (vs. 15 min in clinical trials)

• Clinical response
  – CR 10(9-11)%, PR 20(14-25)%, TR 30(23-36)%

*Phase III trial, J Clin Oncol* 19:376, 2000
Interleukin-2-diphtheria Toxin Fusion Protein (Ontak, denileukin diftitox)

- **Adverse effects**
  - Generally, not dose-related
  - Constitutional symptoms (flu-like syndrome)
  - Acute hypersensitivity-type reactions, minimized by slower infusions
  - Vascular leak syndrome, reduced by hydration +/- steroids
Proposed Mechanism for Targretin®- mediated Increase in CTCL Cell IL2R

- Basal activity of the IL-2R α promoter is repressed by a negative regulatory element (NRE) which is controlled by retinoid receptors.

- Retinoids can relieve the repression and increase basal expression of both IL2R α and β.

- Targretin increases IL2R α and β expression in CTCL cells.

- Targretin increases CTCL sensitivity to ONTAK > 10 fold (from 5 nM to 0.3 nM).
Management of Stage IIB Disease (Cutaneous Tumors, T3)

• MS 3.2 yrs

• Few discrete tumors
  – Regimen for stage I disease + local RT (EBT) for tumors

• Generalized tumors
  – TSEBT + NM +/- biologic therapy (systemic retinoid, or IFN), PUVA + IFN and/or systemic retinoid, IFN + systemic retinoid, Targretin + Ontak
  – Single-agent chemotherapy (Doxil, MTX, gemcitabine)

• CR 33-75%, RR >80%
Management of Stage III Disease (Erythrodermic, T4)

- MS 3.7 yrs

- Often very inflamed, itchy skin; easily irritated with standard topical therapies

- Primary mono-therapies: ECP, PUVA, IFN, systemic retinoid (Targretin), methotrexate

- Combined therapies: ECP + IFN and/or systemic retinoid (Targretin), PUVA + IFN and/or systemic retinoid (Targretin), IFN + systemic retinoid (Targretin), Targretin + Ontak

- TSEBT can be considered as a component of combination therapy if patients have very thick diffuse skin involvement (esp. with secondary tumor nodules)

- Salvage therapies include pred/chlorambucil, Doxil, gemcitabine
Extracorporeal photopheresis (ECP)

- FDA-approved for “palliative treatment of patients with refractory CTCL” 3/88
  - **Primary therapy** for erythrodermic (T4) MF and SS
- **Mechanism of action**
  - leads to augmentation of systemic anti-tumor responses
- **Initiate at q2-4 wks, grad. decrease frequency after max. response**
- **If no significant response after 3-6 months, can add other therapies as combined modality regimen (e.g., IFN, Targretin)**
- **RR 50-70% (CR 20-25%)**
Mechanism of ECP in MF/SS (CTCL)

Edelson, PNAS 2001;941:1-11
Management of Stage IV Disease (Extracutaneous)

• MS <1.5 yrs

• Patients with T4 skin presentation (+/- SS) can be managed with ECP + second biologic (IFN, retinoid) therapy
  - Single agent chemo as salvage therapy

• Combination chemotherapy regimens as primary therapy is most appropriate in non-T4, stage IV patients for control of extracutaneous disease

• Adjuvant/comb therapy with biologic and skin-directed therapies

• BM or HSC transplantation

• Investigative therapies
# Systemic Therapies for CTCL

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<tr>
<th>Therapy</th>
<th>RR%</th>
<th>Route</th>
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<tr>
<td>ECP*</td>
<td>50-70</td>
<td>IV</td>
</tr>
<tr>
<td>IFN-α</td>
<td>50-60</td>
<td>SC</td>
</tr>
<tr>
<td>Targretin*, ATRA</td>
<td>50-60</td>
<td>Oral</td>
</tr>
<tr>
<td>Ontak*</td>
<td>25-40</td>
<td>IV</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>35-70</td>
<td>IV</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>60-75</td>
<td>IV</td>
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<tr>
<td>Doxil</td>
<td>80-85</td>
<td>IV</td>
</tr>
<tr>
<td>Campath-1H</td>
<td>55 (phase II, n=22)</td>
<td>IV</td>
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<tr>
<td>Oral etoposide</td>
<td>limited published reports</td>
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<tr>
<td>Methotrexate</td>
<td>35-70</td>
<td>Oral, IM, IV</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>limited published reports</td>
<td>Oral</td>
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**Individulize therapy regimen**
Combination Therapy

*Benefit of potential synergy and less of each toxicities*

When single agents fail or w/ aggressive dz

- **Combinations of skin-directed therapies**
  - NM + topical steroid or retinoid
  - Phototherapy + topical steroids or retinoid

- **Skin-directed + systemic therapy options**
  - PUVA + IFN and/or systemic retinoid and/or ECP
  - TSEBT + IFN and/or systemic retinoid and/or ECP

- **Combinations of systemic therapies (+/- secondary topical)**
  - IFN + systemic retinoid
  - ECP + IFN and/or systemic retinoid
  - Targretin + Ontak
  - Systemic chemotherapy + biologic therapy
Treatment Approach in Mycosis Fungoides & Sézary Syndrome

**IA**
- Limited dz, T1
- Top steroids, Targ gel
- NM

**IB/IIA**
- Generalized, T2
- PUVA ± Targ or IFN
- TSEBT ± NM, Targ or IFN (or ECP)

**IIB**
- Tumors, T3
- Targ ± IFN, Ontak

**III**
- Erythroderm, T4
- ECP ± Targ, IFN
- Single-agent Chemo (Mtx, Doxil, Gem, Pento)

**IV**
- Extracut. dz
- Combination Chemo
- Campath

**Investigative Therapies**
- (TLRA, MoAb, cytokine, HDAI, PNPI, IMiD, vaccine, allo-HSCT)
Management of Non-MF/SS CTCLs
Non-MF/SS Cutaneous Lymphoma T-classification

Staging System for MF/SS does not apply

- Extent and distribution of primary cutaneous involvement

  \( T1 \) solitary skin involvement

  \( T2 \) regional skin involvement

  \( T3 \) multifocal or generalized skin involvement
Treatment strategy in non-MF/SS CTCLs

CTCLs with indolent clinical behavior

Solitary or regional (T1-2) \( \leftrightarrow \) multi-focal/generalized (T3)

- Localized therapies
  - radiation
  - topical/intralesional

- Systemic therapies
  - biologic (MoAb, retinoids, IFN, Ontak)
  - chemotherapy

CTCLs with aggressive behavior (e.g., \( \gamma/\delta \) TCL, NK/T-cell)

- Often start with combination chemotherapy regardless of initial tumor burden/distribution
- Auto or allo HSC transplantation
CD30+ Lymphoproliferative Disorders

**Treatment**

- **LyP**
  - Limited number of lesions: no therapy or topicals
  - Extensive or symptomatic lesions: PUVA, MTX, oral retinoid (Targretin), anti-CD30 MoAb

- **PC ALCL**
  - Solitary/regional (T1-2a) disease
    - XRT, excision, or both
  - Generalized/multi-focal (T3) or extensive limb (T2b) disease
    - Biologics – oral retinoid (Targretin), Ontak, anti-CD30 MoAb
    - Systemic chemotherapy – MTX, oral etoposide, CHOP, other
    - High-dose chemotherapy with autologous PBSC transplantation
    - Supplemental XRT
Phase II Multi-Dose Study of SGN-30 (anti-CD30 mAb) in PC ALCL, LyP, and LC Transformed MF

- Chimeric form of a novel murine mAb w/ specificity for CD30, unique from other anti-CD30 Ab
  - SGN-30 binding is detected specifically on activated T-cells and not observed in other normal human tissues
- Earlier studies of SGN-30 in HD and non-cutaneous ALCL show great tolerability to IV therapy
- Multi-center phase II trial in CD30+ LPD (pc ALCL/LyP) and CD30+ LCT-MF
  - 12 mg/kg q2-3 wks x 6 doses, total 1-3 courses
Promising Investigative Therapies

Monoclonal antibodies
HDAC Inhibitors
PNP Inhibitors
Recombinant cytokines
TLR Agonists
(CpG ODNs)
New IMiDs
(lenalidomide)
Vaccine therapies
Allogeneic HSCT
Targeted Monoclonal Antibody Therapy

*Fully Human Anti-CD4 MoAb (HuMax-CD4) in MF/SS*

- Cytotoxic and anti-proliferative effect in treated patients mediated by ADCC
  - Depletes CD4+ T-cells
- Phase II multi-center trial with once weekly IV dosing of 280 mg, 560 mg, or 980 mg (Genmab)
  - Dose-dependent responses, 9-75%

**Ongoing Pivotal Multicenter Trial of HuMax-CD4 in MF**
TLR Agonist, CPG oligodeoxynucleotide (ODN)

- CPG 7909 is a synthetic form of DNA-like molecule, optimized for stimulation of human immune functions
- Ongoing trials in solid tumors, melanoma, lymphomas
- Rationale for CPG 7909 investigation in CTCL
  - Directly activate B-cells, pDCs → potent stimulator of innate and tumor antigen-specific adaptive immunity
    - Induces secretion of cytokines/chemokines → ↑Th1-like environment
    - ↑IL12 production, IFN-α → NK-cell activation
    - Augment IL12 response by increased production of IP-10, essential for IL12 mediated tumor-specific CD8+ T-cell responses
Toll-like receptors (TLRs) are PAMP-specific:
- TLR2 – Proteoglycans (bacteria)
- TLR3 – dsRNA (RNA viruses)
- TLR4 – Endotoxin/LPS (gram negative bacteria)
- TLR5 – Flagellin (bacteria)
- TLR6 – Proteoglycans (bacteria)
- TLR7 – ssRNA (viruses; bacteria)
- TLR8 – ssRNA (viruses; bacteria)
- TLR9 – ssCpG DNA (bacteria)

Bacterial DNA has many CpG: ACGTTGAGTTCGTACGCGATAACGGA

Vertebrate DNA has few CpG and they are methylated: AGCTTGAGT CCmCGGATGGGGTAAGA

Synthetic unmethylated CpG ODN, mimics bacterial DNA => TLR9
- directly activates DCs and B cells
- indirectly activates other immune cells
B cell

**Innate Immunity**
- TLR9
- Increased sensitivity to antigen
- IL-6
- IL-10
- Other cytokines / chemokines: IP-10, MIP-1α/b, MCP-1, IL-8
- Increased MHC

**Adaptive Immunity**
- Increased Ab secretion
- IL-6
- IL-10
- IFN-γ, IP-10, TRAIL
- IFN-γ, IL-12
- Other cytokines / chemokines: IP-10, MIP-1α/b, MCP-1, IL-8

**Cells Involved**
- NK cell, monocytes
- B cell
- pDC
- T cell
- CTL

**Pathway**
- CPG 7909 activates B cells, which then secrete IL-6 and IL-10, leading to increased Ab secretion. B cells also upregulate MHC expression.
- pDCs, which express TLR9, are activated, leading to increased MHC expression and secretion of IFN-α, TNF-α, and IL-12.
- These cytokines stimulate NK cells and monocytes, leading to the secretion of IFN-γ, IP-10, and TRAIL.
- NK cells and monocytes then act on T cells, which are further activated by IFN-γ and IL-12, leading to increased Ab secretion.
Phase I/II study in MF/SS with CPG 7909

- CPG 7909 has significant anti-tumor activity in CTCL as single agent immunotherapy (weekly SC injections)
  - Clinical anti-tumor responses begin within a few weeks and reach best response of PR (6/28) or CR (3/28) by 4-20 weeks
- CPG 7909 is well-tolerated
  - Mostly grade 1-2 injection site reactions or flu-like symptoms

*Clinical trial in CTCL closed, sponsor focusing on approval thru lung cancer*
Potential role of CPG 7909 in CTCL therapy

- Single-agent immunostimulator
- Adjuvant for vaccine therapy
- Effective agent in combination regimens with synergistic or response enhancing results
  - Chemotherapy or radiation (shown in mouse models)
  - PUVA
  - ECP, retinoids, monoclonal antibodies, HDAl, cytokine
- *In situ* vaccination therapy
  - Low-dose RT + intratumoral CPG

*Ongoing clinical trial at Stanford*
# Acetylation Defects in Cancer

**An Epigenetic Abnormality**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Acetylation Defect</th>
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| **Leukemia**          | HAT fusions  
                         MOZ/CBP  
                         MOZ/p300  
                         MOZ/TIF-2  
                         MLL/CBP  
                         MLL/p300  
                         HDAC mediated  
                         PML/RARalpha  
                         PLZF/RARalpha  
                         AML1 fusion |
| **Lymphoma**          | BCL6  
                         STAT5 |
| **Epithelial cancers**| p300 mutations in colorectal, gastric, breast, pancreatic carcinomas/cancer cell lines |
| **Gastric Cancer**    | Elevated expression of HDAC1 |
| **Prostate Cancer**   | Elevated expression of HDAC1 |
| **Esophageal Cancer** | Elevated expression of HDAC1 |
Histone Acetylation/Deacetylation Regulates Transcription

Balanced HDAC and HAT activity = Normal cell cycle

HDACs + Lys \rightarrow Ac-Lys → HATs → Nucleosome → DNA

Ac=acetyl group; HAT=histone acetyltransferase; HDAC=histone deacetylase; Lys=lysine.

Adapted from Richon VM. Mechanism of Action of HDAC Inhibitor SAHA. Paper presented at 9th International Conference on Malignant Lymphoma; June 7, 2005; Lugano, Switzerland.
Mechanism of Growth Inhibition Mediated by HDAC Inhibition (Histone Hyperacetylation)

Deacetylated Histones

- Transcriptional Repression of Pre-Programmed Set of Genes
  - Cell Growth
  - Tumor Growth

Hyperacetylated Histones

- Transcriptional Activation of Pre-Programmed Set of Genes
  - Cell Growth Arrest, Differentiation and/or Apoptosis
  - Inhibition of Tumor Growth
Histone Deacetylase Inhibitors in Clinical Development

- **Short Chain Fatty Acids**
  - Butyrate, Phenylbutyrate, Valproate, AN-9

- **Hydroxamic Acids**
  - SAHA, LAQ-824, PXD101

- **Cyclic Tetrapeptides**
  - FK-228 (Depsipeptide)

- **Benzamides**
  - CI-994, MS-275

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*Phase IIb Multicenter Trial of Oral Suberoylanilide Hydroxamic Acid (SAHA: Vorinostat under review by FDA) in MF/SS*

*Phase II Multicenter Trial of Depsipeptide in MF/SS*

*Phase II Multicenter Trial of PXD101 in MF/SS*
Purine Nucleoside Phosphorylase (PNP) Inhibitor
Forodesine HCl (BCX-1777) Activity in CTCL

• Profound suppression of T-cell immunity seen in patients with an inherited PNP deficiency

• Children with PNP deficiency have
  - < 5% of the normal PNP activity
  - Selective depletion of T-cells
  - T-cell responses to mitogenic and allogenic stimuli are severely compromised
  - Elevated levels of deoxyguanosine (dGuo) in urine and plasma
  - Elevated levels of dGTP in RBC

• Rationale for targeting PNP in therapeutics of T-cell disorders
Forodesine HCl (BCX-1777) is a potent selective transition-state analog inhibitor of human PNP.

- Inhibits the phosphorolysis of purine nucleosides such as 2’-deoxyguanosine (dGuo) to guanine + deoxyribose-1-phosphate => accumulation of dGTP results in alteration in the 2’deoxynucleotide (dNTP) pools leading to T-cell apoptosis.
**Mechanism of T-cell Inhibition by PNP Inhibitor**

PNP

\[
d\text{Guo} \quad \overset{\text{Kinase (dCK)}}{\longrightarrow} \text{guanine + deoxyribose-1-phosphate}
\]

\[
d\text{GTP} \quad \downarrow
\]

Alteration in deoxynucleotide pools

\[
\downarrow
\]

T-cell apoptosis
Purine Nucleoside Phosphorylase (PNP) Inhibitor
Forodesine HCl (BCX-1777) Activity in CTCL

• Initial good response data in 13 pts w/ 4 responses (3 CR), given IV forodesine

• Well-tolerated without dose-limiting toxicities in CTCL trial
  – Previously reported AEs: nausea, H/A, fatigue, pain, edema, anemia, infection, diarrhea, dec platelets, insomnia, cough

*Phase I/II Multicenter Trial of an Oral Forodesine HCl*
IMids, Novel Immunomodulators

Lenalidomide

4-amino-glutamyl analogue of thalidomide

Knight R, Semin Oncol 2005
IMids

*Lenalidomide*

Rationale for use in CTCL

- **T-cell co-stimulation**
  - $\uparrow$ IFN-\(\gamma\), IL2
  - Selective stimulation of CD8 over CD4
  - Stimulate NK activity

- **Angiogenesis inhibition**

- **Cell cycle arrest and promotion of apoptosis**

- **FDA-approved in MM and MDS**

- **Pilot clinical study in MF/SS with observed responses**
  - *Multicenter study launching (NW, Stanford, MD Anderson)*
Other investigative immunotherapies in CTCL

• Gene delivery-based immunotherapy
  – Adenovirus-human IFN-γ cDNA

• Vaccine strategies
  – Transimmunization
  – Dendritic cell based immunization
  – Mimotope vaccines
  – Idiotype vaccines
Tumor Biopsy

Protein Production

TCR-Id Protein

Immunization With GM-CSF

"PCR Rescue"

plasmid

TCR-α, β

Protein Production

KLH Carrier protein

KLH

Id

TCR-Id Protein

Stanford’s preclinical showing response;
In development for human trials
Hematopoietic Stem Cell or BM Transplantation

Considered for patients with advanced disease (stage IIIB-IV)

Autologous $\rightarrow$ High-dose chemo and RT (cytoreduction) followed by stem cell rescue
Avoid GVHD
No durable response in MF/SS

Allogeneic $\rightarrow$ Cytoreduction + graft vs. tumor effect
Risk of GVHD
Increasing evidence of durable clinical, cytogenetic, molecular remissions in MF/SS

Molina A, J Clin Oncol, 2005
Wu, Stockerl-Goldstein, Lavori, Kim, SID 2006

Studies ongoing to maximize GVL effect while minimizing GVHD risk
Strategies in CTCL Treatment with Newer Options

Skin-directed Therapies
- Topicals
- Phototherapy
- XRT

Systemic Biologic Therapies
- IFN
- Retinoids
- ECP

Cytotoxic Chemotherapy
- Single-agent
- Combination

MF/SS IA-IIA
Primary
Salvage
Adjuvant
Primary
MF/SS IIB-IV

HDAI
TLRA
MoAb
PNPI
IMiD
HSCT
Therapeutic Advances

Newer Approaches
- Monoclonal antibodies
- HDAC Inhibitors
- PNP Inhibitors
- Recombinant cytokines
- TLR Agonists
- (CpG ODNs)
- New IMiDs
- (lenalidomide)
- Vaccine therapies
- Allogeneic HSCT

Improved QOL, closer toward a cure...
Handouts for Forum 506 available 8/1/06 at cutaneouslylymphoma.stanford.edu

or email younkim@stanford.edu

THANK YOU for thinking lymphoma today!