Evolving Insights in the Pathogenesis and Therapy of Cutaneous T-cell lymphoma (Mycosis Fungoides and Sezary Syndrome)

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Abstract

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of malignancies derived from skin-homing T cells. The most common forms of CTCL are Mycosis Fungoides (MF) and Sezary Syndrome (SS). Accurate diagnosis remains a challenge due to the heterogeneity of presentation and the lack of highly characteristic immunophenotypical and genetic markers. Over the past decade molecular studies have improved our understanding of the biology of CTCL. The identification of gene expression differences between normal and malignant T-cells has led to promising new diagnostic and prognostic biomarkers that now need validation to be incorporated into clinical practice. These biomarkers may also provide insight into the mechanism of development of CTCL. Additionally, treatment options have expanded with the approval of new agents, such as histone deacetylase inhibitors. A better understanding of the cell biology, immunology and genetics underlying the development and progression of CTCL will allow the design of more rational treatment strategies for these malignancies. This review summarizes the clinical epidemiology, staging and natural history of MF and SS; discusses the immunopathogenesis of MF and the functional role of the malignant T-cells; and reviews the latest advances in MF and SS treatment.

1. Introduction

Cutaneous T-cell lymphomas (CTCL) are a clinically heterogeneous group of lymphoid neoplasms with diverse pathology and clinical course (Hwang, *et al* 2008) (Olsen, *et al* 2007a). After a long debate about competing classifications schemes, a joint World Health Organization-European Organization for Research and Treatment of Cancer (WHO-

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EORTC) effort in 2005 categorized all known types of cutaneous lymphoma, with careful attention to biological profile, clinical presentation, and prognosis (Willemze, *et al* 2005). Further revisions resulted in consensus criteria that were integrated in the 2008 WHO classification for nodal and extranodal lymphomas (Swerdlow, *et al* 2008), which captures the full clinical, pathological, and molecular spectrum of these neoplasms, and the features most important in diagnosis, prognosis and treatment.

Advances in the mechanism in T cell development have revealed that T cells have the potential to differentiate into multiple lineages with distinct functions, presenting the opportunity to more precisely classify T-cell lymphomas. This approach provides a conceptual platform to gain insight into the developmental origin of the malignant T cells, identify biological clusters for risk stratification, and improve treatment (Jaffe, *et al* 2008). For example, a detailed understanding of the normal germinal centre reaction has advanced our knowledge of the development of nodal B-cell lymphomas and defined different risk groups (Klein and Dalla-Favera 2008). Likewise, an ontogenetic model for CTCL, based on normal T-cell differentiation, would facilitate the development and clinical testing of mechanistic hypotheses in T-cell lymphoma. Unfortunately, despite a number of developments described in this review, a cohesive and validated model of CTCL development, grounded in the normal differentiation and function of skin-homing T cells, is lacking.

This review will centre on some of the biological and clinical questions that remain unaddressed in CTCL, with a focus on the putative cell of origin of this malignancy, the memory $CD4^+CD45RO^+$ T lymphocyte (Girardi, *et al* 2004, Hwang, *et al* 2008). Because the neoplastic cells responsible for the pathology in CTCL are skin-homing T cells, the initial clinical presentation often overlaps with other T-cell mediated dermatoses. Thus, the diagnostic challenges of distinguishing malignant versus reactive T cells in the skin and blood of patients with early stage CTCL will be discussed. Advances from genomics, to cytokine gene expression, and cancer immunosurveillance in CTCL will be presented, with a focus on Mycosis Fungoides (MF) and Sezary Syndrome (SS). Finally, the fundamental principles of systemic therapy for these disorders, and recent advances in drug development will be discussed.

2. Mycosis Fungoides and Sezary Syndrome: clinical epidemiology, staging and natural history

While the term CTCL includes a number of rare disease entities, such **as** $CD30^+$ primary cutaneous anaplastic large cell lymphoma (pcALCL) and related disorders, the most common subtypes are MF and SS, accounting for approximately 70–75% of all cases (Bradford, *et al* 2009). The classic presentation of MF was first reported in 1806 by Jean L. Alibert at the Hospital Saint-Louis, in a patient with mushroom-like tumours (Alibert 1806). For a long time the neoplastic cell type in MF/SS was unknown, but with the ability to identify surface markers on the atypical T cells, it became apparent that MF and SS are malignancies of $CD4^+CD45RO^+$ skin-homing T-cells. The clinical spectrum is highly polymorphous (Girardi, *et al* 2004) and ranges from the unilesional form of MF, Worringer-Kolopp, to more generalized skin involvement with extensive tumours and erythroderma

(Kim and Hoppe 1999, Medenica and Lorincz 1978, Vonderheid 2006). When peripheral blood is involved, patients have SS, an aggressive variant of CTCL associated with diffuse generalized erythroderma and lymphadenopathy (Willemze, *et al* 1983).

The age-adjusted incidence rates (IRs) for CTCL in the US have ranged from 4 to 6.4/ million person-year, but for 1998–2002 they were up to 9.6/million person-year (Bradford, *et al* 2009, Criscione and Weinstock 2007). Consequently, the current best estimate for the number of new CTCL cases in the U.S. is about 3,000/year. The reason for the increased IRs is unknown, but improved diagnosis is likely to be a cofactor. Prevalence rates are not available, but with 2,000–3,000 new annual cases, no curative therapy, and median survivals of 12–18 years (Agar, *et al* 2010; Kim, *et al* 2003), a gross estimate of the number of patients living with CTCL in the U.S is between 25,000 and 50,000. Specific IRs for SS are more difficult to calculate with confidence because of the rarity of this disorder. Of 2,769 cases of CTCL examined in a Surveillance, Epidemiology and End Results (SEER) database, only 33 (1%) were SS. In another series, SS represented 2.5% of all CTCL cases (Criscione and Weinstock 2007). While MF can be observed in children and early adults (Crowley, *et al* 1998, Pope, *et al* 2010), the median age at diagnosis is 50–70 years of age, with an increased incidence in males and African Americans. Conversely, SS is more common in non Hispanic whites (Criscione and Weinstock 2007).

The cause of CTCL is unknown. Although numerous associations with infectious agents have been hypothesized, none have been proven (Mirvish, *et al* 2011). Case control studies have not identified any consistent occupational, environmental, or iatrogenic factors(Morales Suarez-Varela, *et al* 2000, Whittemore, *et al* 1989), and while MF can occur in patients after organ transplantation, it has not been linked to a specific opportunistic infection or immune suppression (Ravat, *et al* 2006). Other cutaneous lymphoproliferative disorders, such as lymphomatoid papulosis (LyP) and pcALCL, can follow or precede MF (Kunishige, *et al* 2009). B-cell lymphoid malignancies, such as chronic lymphocytic leukaemia (CLL) and monoclonal gammopathies, can coexist with MF (Hallermann, *et al* 2007). However, with the exception of cases of MF, LyP and pcALCL that expressed a common T cell receptor (TCR) gene rearrangement (Chott, *et al* 1996), no markers for multilineage lymphoid involvement in CTCL have been found. Familial clusters of MF have been described (Hodak, *et al* 2005), and linkages with human leucocyte antigen alleles have been observed (Jackow, *et al* 1996), but solid leads for genetic loci of familial predisposition in CTCL are lacking. Finally, it has been hypothesized that MF arises from malignant transformation of activated T cells in the setting of persistent antigenic stimulation or chronic inflammation(Burg, *et al* 2001). However, unlike proliferations of CD4^{+} and CD8^{+} T-cell in large granular lymphocytes (LGL), where the TCR repertoire displays hallmarks of chronic antigenic stimulation(Wlodarski, *et al* 2005), the TCR repertoire in CTCL, while restricted (Yawalkar 2003), does not display a specific antigenic "signature".

Clinical Features and Outcomes

MF is typically an indolent malignancy and often presents with a *premycotic* phase. Multiple skin biopsies over many years are needed typically for a diagnosis. Survival correlates with the stage of initial presentation (Kim, *et al* 2003, Klemke, *et al* 2005, Morales, *et al* 2005).

The most recent revision of staging is summarized in Table 1 (Olsen, *et al* 2007a). Patients presenting with skin-restricted patches and plaques that affect less than 10% of the body surface area, have an excellent prognosis, and in analysis of long-term survival, patients with minimal skin disease have survival comparable to the normal age-matched cohort (Agar, *et al* 2010, Kim, *et al* 2003, Morales, *et al* 2005, van Doorn, *et al* 2000).

The diagnosis of MF is challenging. No single test is sufficient and a combination of supporting clinical, immunological, and molecular features is necessary to reach a conclusive diagnosis. Loss of the surface T-cell antigens CD5, CD7, CD26 and less frequently CD3, is observed in CTCL (Robson 2010), and may help distinguish normal from malignant T-cells. However, reduced expression of CD5, CD7, and CD26 on T-cells can also occur in reactive and inflammatory skin conditions (Murphy *et al* 2002), and is not diagnostic of MF. It should be noted that T-cell surface antigen deletion in CTCL is inconsistent and has not been linked to specific mutations or genomic losses. Therefore it cannot be used to identify and monitor the neoplastic clone. Likewise, detection of a clonal *TRB* or *TPΓ* gene by polymerase chain reaction (PCR) in a skin biopsy is helpful to support a diagnosis of MF, but negative results do not exclude a diagnosis of MF.

In early MF, the clinical findings can resemble other papulosquamous disorders, such as eczema, contact dermatitis or psoriasis. Diagnosis of early stages of MF based on clinically subtle skin lesions can be challenging where histological features are minimal (Pimpinelli, *et al* 2005, Tracey, *et al* 2003). The T-cell infiltrate is heterogeneous, and is composed of both $CD4^+$ and $CD8^+$ T cells(Vonderheid, *et al* 1987a). An increased ratio of $CD4^+$ to $CD8^+$ T cells and morphological features, such as epidermotropism, exocytosis, and Pautrier's microabsess support the diagnosis. Loss of CD7 is helpful if present on immunohistochemistry, and TCR clonality can be valuable in confirming malignancy. However in the early stages, CD7 may not be lost and clonality can be negative (Jones and Duvic 2003). When the skin lesions acquire vertical growth with thickened plaques and tumours, the diagnosis is facilitated by the detection of the atypical nuclei of malignant T cells in the epidermis, the formation of Pautrier's microabscesses (Nickoloff 1988), and by a clonal TCR gene rearrangement. The ratio of $CD4^+$ to $CD8^+$ T cell increases in the skin, and is particularly helpful if found in the epidermis. In tumours, the histopathology shows malignant T cells forming an exuberant infiltrate with few residual $CD8^+$ T cells, a greater degree of atypia, and a frequent loss of CD7 expression.

3. Immunopathogenesis of MF and functional role of the malignant T-cells

The indolent progression of MF has raised a number of hypotheses about malignant T-cell biology. The malignant T cells may not have high, autonomous proliferative potential and may be dependent on the cutaneous microenvironment for growth (Berger, *et al* 2005). In support of this hypothesis is the observation that T-cells from CTCL patients require stimulation via CD28 for proliferation (McCusker, *et al* 1997), respond poorly to growth stimuli *in vitro* and do not proliferate like normal T cells *in vitro* (Gazdar, *et al* 1979). A second possible explanation is a role for cancer immunosurveillance in modulating and suppressing disease progression. The histopathology of MF, which shows T-cell infiltration of both malignant $CD4^+$ and reactive $CD8^+$ T cells, and a dominant T helper cell type 1

(Th1) cytokine pattern in early stage, followed by a gradual increase in CD4^{+} T-cells and Th2 skewing in advanced stages, suggests that loss of a CD8-mediated immune response parallels disease progression. Furthermore, the clinical effectiveness of therapeutic agents that modulate the immune system and reverse Th1 cytokine expression in MF/SS supports an important role of tumour immunity in clinical outcomes.

Clinical lesions manifesting as patches, plaques, tumours, or erythroderma develop from the interactions of the neoplastic T cells with the cutaneous microenvironment (Sterry and Mielke 1989, Vonderheid, *et al* 2002). A primary determinant of T-cell skin homing in MF/SS is the expression of cutaneous lymphocyte antigen (CLA), the ligand for E-selectin (CD62E) (Yamaguchi, *et al* 2003). Additional adhesions molecules and skin-homing chemokines, such as CCR4, CCR10, and their respective ligands CCL17/TARC and CCL27/CTACK, play a role in attracting T cells to the skin (Kakinuma, *et al* 2003, Kallinich, *et al* 2003). However, the cascade of events that leads to the margination and extravasation of T cells in the cutaneous microvasculature, and drives their migration into the epidermis remains poorly defined. Microscopic and immunophenotypic analysis of Pautrier's microabscesses reveal that they are intraepidermal collections of malignant lymphocytes in close association with dendritic cells (Langerhans cells, LC)(Edelson 2001). This raises the hypothesis that cytokines produced by LC attract malignant CD4^{+} T cells into the epidermis, and that LC-T cell cross-talk is important for disease progression. However, in the absence of experimental models to investigate specific mechanisms thought to be operating *in vivo*, this remains a working hypothesis.

The cytokine profiles in lesional skin (patch *vs* plaque *vs* tumour), and in peripheral blood mononuclear cells (PBMC) from patients with various stages of MF have provided clues into the dynamic changes in the microenvironment during the progression of MF (Dummer, *et al* 1996, Vowels, *et al* 1994). Analyses of cytokines in the skin have identified specific patterns associated with early and advanced stage. In early stage MF, the skin shows normal to increased expression of IFNG, IL12 and IL2, a Th1 cytokine pattern (Saed, *et al* 1994) (Figure 1). As the malignancy progresses to late stage MF, there is a loss of Th1 cytokines, evidenced by decreased IL2, IFNG, and IL12, and an increase in Th2 cytokines, such as IL4, IL5, IL10, and IL13. The patterns seen in the skin is also seen in analysis of gene expression from peripheral blood (Chong, *et al* 2008). Integrating cytokine data from skin and blood, one interpretation is that in early stage MF, the CD8^{+} T cells contribute to the Th1 skewing, while in advanced stages where the malignant CD4^{+} T cells are dominant, there is Th2 skewing. Given that CD8^{+} T cells share a Th1 phenotype and play a role in cell-mediated immunity, their presence in the skin is consistent with an anti-tumour response (Hoppe, *et al* 1995, Wood, *et al* 1994). (Figure 1)

The "static" cytokine snapshot analysis provided by immunohistochemical studies of the skin in early and advanced stage MF patients has been complemented by dynamic functional studies of cytokine expression by malignant T-cells in response to activation. These studies have been done mostly in SS. While normal memory T cells are known for their ability to more rapidly express cytokines for effector function compared to naïve T cells following stimulation (Ehlers and Smith 1991, Krishnan, *et al* 2001), expression of *IL2* and *IFNG* in SS T cells *in vitro* is profoundly decreased. Together with the constitutive expression of

CTLA4, the gene profile resembles that seen in regulatory T-cells (Tregs) (Chong, *et al* 2008). An exception is observed with *IL5* and *IL10*, which are increased compared to normal(Chong, *et al* 2008). Because IL5 is associated with eosinophil recruitment, this cytokine may be responsible for the pruritus seen in SS. Elevated levels of IL10, an inhibitor of IFNG is also produced in late stage MF, and may contribute to the diminished anti-tumour response(Asadullah, *et al* 1996). Indeed, Foxp3 has been detected in PBMC from a subset of SS patients (Capriotti, *et al* 2008). The abnormal expression of *CTLA4* and *IL10* in SS, together with the expression of Foxp3 in a subset of patients, further suggests a possible differentiation bias toward Tregs (Berger, *et al* 2005, Wong, *et al* 2006). However when functional suppressor assays were performed, Treg activity was not detected(Tiemessen, *et al* 2006).

Other cytokines have recently been implicated in the immunopathogenesis of CTCL. A newly discovered class of CD4^{+} T cells, Th17, expresses IL17A/F, IL21 and IL22. These Th17-derived cytokines act on keratinocytes to induce IL6 and IL8 production, and recruit circulating T cells and neutrophils to the skin(Teunissen, *et al* 1998, Weaver, *et al* 2007). Th17 cells have been implicated in the immune response to extracellular bacteria and fungi, and in autoimmunity (Lowes, *et al* 2007). IL17A has been detected in approximately 50% of skin biopsies of MF/SS patients (Ciree, *et al* 2004). However, IL17A is not measurable in the serum(Krejsgaard, *et al* 2011), suggesting that this cytokine may play a role in MF, but not in SS. This is consistent with our results showing that SS peripheral blood cells do not express *IL17A* (Chong, *et al* 2010).

IL15, which is produced by many cell types, including keratinocytes, inhibits T-cell apoptosis, promotes the expansion of CD4^{+} T cells, and has been directly implicated in the pathogenesis of a number of T-cell lymphoproliferative disorders (Dooms, *et al* 1998, Fehniger, *et al* 2001, Malamut, *et al* 2010). IL15 has been found to be overexpressed in MF, in a stage-dependent way and to induce growth of SS T cells (Asadullah, *et al* 2000, Dobbeling, *et al* 1998). This suggests that IL15 may be involved in the initial transformation, survival and expansion of malignant T-cells in CTCL.

Finally, recent data suggest that IL16, a pleiotropic cytokine that functions as chemoattractant for CD4^{+} T-cells and modulates their activation may be involved in the progression of CTCL (Richmond, et al. 2011). Gradual loss of intracellular IL16 in peripheral blood T-cells is observed from stage IB onwards. This phenomenon correlates closely with loss of surface CD26 and decreased plasma levels of IL16 in SS patients.

The clinical implications of disordered immunity in CTCL are significant. In advanced stage MF and SS, global immune dysfunction results in a high risk of infections, which is the dominant cause of death in these patients (Axelrod, *et al* 1992, Posner, *et al* 1981). In addition to cytokine imbalances, decreased immunity may also result from T-cell exhaustion, as evidenced by the profound loss of TCR repertoire (Goronzy and Weyand 2003, Yawalkar, *et al* 2003), or from direct inhibition by malignant T cells, possibly mediated by CTLA4 (Read, *et al* 2000, Wong, *et al* 2006).

MF/SS progression and immunoediting

A role of immune surveillance against cancer was first hypothesized over 50 years ago (Burnet 1957, Thomas 1959). This concept has regained interest from new evidence using transgenic mice that have targeted defects in the innate immune system, and has been updated as the *cancer immunoediting hypothesis* (Dunn, *et al* 2002, Shankaran, *et al* 2001). In MF/SS, the changes in cytokine expression and T-cell subset ratios in disease progression could be explained within the frameworks of the steps in the cancer immunoediting hypothesis: *elimination*, *equilibrium* and *escape* (Dunn, *et al* 2002, Dunn, *et al* 2006). In this model, immune interaction with the neoplastic T cells and the genetic instability of the cells are variables that contribute to the progression (Figure 2). In the *elimination* phase, immunosurveillance is intact and an unrestrained T cell clone proliferates incognito until the local stroma is disrupted, activating the expression of type I IFN from monocytes, which activate CD8^{+} T-cells and induce a Th1 profile. IFNG plays an important role in the immunoediting concept as loss is associated with increased tumour development (Dighe, *et al* 1994, Kaplan, *et al* 1998).

Escape of the malignant T cells leads to the *equilibrium* phase, where there is a steady state between immunity and neoplastic T cells proliferation. In the skin, the cytokines show a Th1 pattern, and the histology shows a heterogeneous infiltrate of CD8^{+} T cells and neoplastic CD4^{+} T cells. This corresponds to CTCL clinical stages I and II. With continued proliferation, the neoplastic cells undergo 'immune sculpting' in the background of genetic instability. The tumour antigens undergo alteration and the neoplastic T cells transition to the *escape* phase. The expression of immunosuppressive molecules seen in MF/SS, such as IL10, Fas ligand, PD1 and CTLA4, contribute to escaping immune recognition (Dummer, *et al* 1998, Ni, *et al* 2001, Samimi, *et al* 2010, Wong, *et al* 2006). The neoplasm proliferates beyond the local microenvironment into the lymph node and visceral, and tumour immunity is overwhelmed.

Origin and Biomarkers of the Malignant T-cell

Biomarkers can aid diagnosis, and may provide insight into the cellular origin of MF/SS. Specific molecular signatures can be used to identify the malignant T cells, identify their precise lineage, and provide clues into the pathways that led to transformation. In the search for novel biomarkers in MF/SS, one approach has utilized array-based high-throughput methodologies to profile the transcriptome. These robust techniques can elucidate differences in all genes expressed in MF/SS compared to normal individuals. Different groups have identified distinct transcriptional signatures in MF/SS (Table 2). However there is a lack of consensus from these reports, which may result from the inherent heterogeneity of MF/SS, small sample numbers, the platform used, and/or the type of samples. Thus some of the genes identified may be from neoplastic T-cells, or from the reactive microenvironment of the skin. An inherent source of heterogeneity is the fact that some transcriptional analyses have been performed on variably purified blood cell populations from patients with SS, while others have used lesional skin. Currently, the degree of overlap in the transcriptional signatures between MF and SS, and its significance in relation to the biological relatedness of these two types of CTCL, remains to be characterized.

The most recent studies are summarized in Table 2. Genes associated with the tumour necrosis factor (TNF) pathways and with Th2 phenotype, such as *GATA3*, are increased, whereas genes involved in Th1 lineage, such as *STAT4*, are decreased. Genes involved in proliferation, such as *JUNB, JUND*, and other cell cycle genes are increased. Of note is the many-fold upregulation of genes not normally expressed in T cells, such as *TWIST1*, *DNM3* (*dynamin 3*), *NEDD4L*, and *PLS3* (*plastin 3*). The functional role and biological significance of these genes in MF/SS are unclear, and adaptation of these genetic biomarkers into clinical testing would benefit from verification in larger sample and multicentre studies. Nevertheless understanding the mechanism for the activation of these genes in MF/SS may provide valuable insight into the pathogenesis.

A subtle but important distinction should be made between biomarkers that are highly overexpressed and thus correlate strongly with the malignant T-cells, regardless of their function, and biomarkers that identify key signalling and survival pathways that are more relevant as molecular targets for therapy. While the two categories undoubtedly overlap, each may be independently useful in the clinic. An ideal diagnostic marker, particularly when clinical or histological features are absent, will be expressed at high levels in the malignant T cells and will be absent or near absent in normal T-cells, providing the highest signal-to-noise ratio in the specific tissue that is being analysed. For example, in SS, the *PLS3* gene has been shown by several groups to be expressed at high levels by differential screening (Kari, *et al* 2003, Su, *et al* 2003). This gene encodes an actin-binding protein, appears to be unique to SS, and is not expressed in haematopoietic cells, thus representing a potentially useful diagnostic biomarker for SS T-cells in the peripheral blood. While the observation needs to be validated in larger patient samples, we have shown that the *PLS3* mRNA expression can be very valuable in monitoring the development of SS and assessing the response to treatment (Tang, *et al* 2010).

An additional surface marker upregulated on some SS cells is the killer immunoreceptor (KIR), KIR3DL2 (p158), which is expressed on natural killer (NK) cells (Poszepczynska-Guigne, *et al* 2004). In screening SS patients, KIR3DL2 was able to distinguish the malignant clone where multiple dominant clones were present in the peripheral blood(Marie-Cardine, *et al* 2007). The detection of KIR3DL2 on SS cells has also been reported by other investigators (Bahler, *et al* 2008). The significance of KIR expression is unclear, but aged T cells and T cells in autoimmune disease have increased KIR expression. The mechanism of increased KIR receptor expression in aged T cells has been suggested to be epigenetic (Li, *et al* 2009).

Molecular Genetics of CTCL

Distinctive and pathognomonic chromosomal translocations, such as those seen in B-cell lymphomas and myeloid leukaemias, have not been identified in CTCL. Numerous studies show recurrent chromosomal alterations, and genomic gains and losses, affecting chromosomes 1, 6, 7, 8, 9, 10 and 17 (Izykowska and Przybylski 2011, Mohr, *et al* 1996). However these abnormalities are not consistent, thereby negating their usefulness as diagnostic markers. Rather, there appears to be many chromosomal regions altered, and this hints to an underlying genomic instability in MF/SS. Recent approaches using comparative

genomic hybridization (CGH) have identified more detailed chromosomal changes, with the most common types associated with loss of chromosomal regions (1p, 10p, 10q, and 17p) rather than gain of chromosomal regions (8q and 17q) (Table 3). In comparing differences between chromosomal changes and gene expression changes, there is not clear mapping of chromosomal alteration to abnormal gene expression.

Recently, microRNAs (miRNAs) have been shown to play an important role in the regulation of gene expression in cancer (Garzon, *et al* 2010). In MF, studies have identified differences in miRNA expression with MIR155 and MIR92A increased in skin lesions (van Kester, *et al* 2011). In SS, there are significant changes and most miRNA are decreased, but there are several that are increased (Table 3) (Ballabio, *et al* 2010; Narducci, *et al* 2011). Further characterization of miRNA functional clusters in MF/SS is in progress.

4. Therapy of MF and SS

Advances in the understanding of MF/SS have been recently complemented by the development of novel therapies. The current treatment of MF/SS is highly varied and there is no simple algorithm. Consensus approaches to the fundamental strategies of therapy for early and late stage MF/SS and in selecting agents within a particular class were recently developed by cooperative networks and organizations in the United States, such as the National Comprehensive Cancer Network (NCCN) (http://www.nccn.org) and the United States Cutaneous Lymphoma Consortium (USCLC) (Olsen, *et al* 2011). In Europe, similar consensus guidelines were developed by the Cutaneous Lymphoma Task Force of the EORTC, often in collaboration with the International Society of Cutaneous Lymphomas (ISCL) (Trautinger, *et al* 2006).

In early stage MF, skin-directed therapies offer effective control. When topical therapies fail, systemic therapy is needed. As reviewed in the pathogenesis, immunity plays a role in disease progression, and treatments that maintain or augment the immune response, such as retinoids and interferons, are preferable to those associated with immune suppression, such as cytotoxic chemotherapy. For patients who have failed one or more of the conventional systemic therapies, several new drugs that more specifically target the T cell (monoclonal antibodies) or agents that alter epigenetic control of gene expression (histone deacetylase inhibitors) have been approved or are in the advance phase of development. The impact of the new agents on long-term survival, however, remains to be defined.

Systemic therapies

Biologicals and Immune Enhancing Therapies—Three major types of IFN, IFNα, IFNβ, and IFNγ, induce a spectrum of biological activities and induce cell-mediated immunity (Trinchieri 2010). Numerous studies have shown the clinical efficacy of IFNα as monotherapy from stage IA through stage IV CTCL (Jumbou, *et al* 1999; Rupoli et al. 2005; McGinnis et al. 2004; Olsen, 2003) and interferons have long been recognized as the most active single agents in CTCL. When combined with oral retinoids, rapid improvements have been reported for erythrodermic and follicular MF (McGinnis, *et al* 2004). In a multicentre, prospective Phase II clinical study of 89 patients with early-stage IA to IIA MF treated with IFNα-2b (6–18 Miu/wk) and psoralen combined with ultraviolet A (PUVA) (Rupoli, *et al*

2005), a complete remission (CR) was obtained in 84% with an overall response rate (ORR) of 98% and sustained remissions in 20%. High $CD8^+$ counts were associated with a lower relapse rate. In a retrospective study, subcutaneous IFNα2a (3–6 Miu/day for one month, followed by 3–6 Miu three times a week) resulted in a 41% complete response rate (Jumbou, *et al* 1999). Recently, pegylated-IFNα-2b was reported to have activity in MF (Yanagi, *et al* 2006). The major side-effects of IFN therapy are dose-dependent and include flu-like symptoms, myelosuppression, liver function abnormalities and depression.

Retinoids affect cell differentiation and have profound effects on gene expression. Bexarotene is a rexinoid that binds to the retinoid X receptor (RXR) alpha and alters gene expression. RXR activation can induce apoptosis and modulate innate immunity by affecting chemokine expression (Nunez, *et al* 2010). Results of Phase II and III trials showed ORRs of 54% with doses of 300 mg/m^2/day, and 67% with doses above 300 mg/m^2/day (Duvic, *et al* 2001). The most common adverse effects were hypertriglyceridaemia, hypercholesterolaemia, headache, central hypothyroidism, asthenia, and leucopenia. Since its approval, optimal use of bexarotene has included its combination with PUVA or IFNα (Assaf, *et al* 2006). Monitoring of thyroid hormone levels and fasting lipid levels is important. Other retinoids, such as tretinoin or all-*trans* retinoid acid (ATRA), have been used for CTCL. In 33 patients with MF/SS treated with ATRA (45 mg/m^2) compared to 19 patients treated with oral bexarotene (300 mg/m^2), four of 33 patients (12%) achieved a response on ATRA, and 4 of 19 (21%) achieved a response on bexarotene, a difference that was not significant. Mucocutaneous symptoms, such as dryness and redness, were common adverse events with ATRA treatment, as was hyperlipidaemia (Querfeld, *et al* 2004).

Activating innate immunity by harnessing toll-like receptors (TLR) is another strategy for immunotherapy. TLR2, TLR4, and TLR9 expression is low in atopic dermatitis and psoriasis, but is increased in the epidermis in MF. Imiquimod is a TLR7 agonist that can induce TNFα, IFNγ, and IFNα *in vivo* (McInturff, *et al* 2005). Topical imiquimod was evaluated in six patients with stage IA-IIB MF for twelve weeks and showed histological clearance in 50% of the patients (Deeths, *et al* 2005). Significant improvements were noted for all treated lesions. Importantly, imiquimod may be helpful in treating sanctuary or resistant lesions in patients undergoing PUVA for CTCL (Dummer, *et al* 2003). CPG 7909 is a new TLR9 agonist administered subcutaneously that has been tested in a Phase I trial in 28 patients with CTCL (IB-IV) and showing clinical activity (3 complete response [CR] and 6 partial response [PR]) (Kim, *et al* 2010).

Denileukin diftitox is a chimeric fusion protein composed of interleukin-2 (IL2) and the diphtheria toxin A chain. Upon engaging the IL2 receptor on malignant T-cells, the drug is internalized and the diphtheria toxin is cleaved from the fusion protein, released into the cytosol to inhibit protein synthesis, and causes cell death (Foss 2006). Another potential mechanism for denileukin diftitox activity is the depletion of Tregs (Morse, *et al* 2008), which are typically CD25^{bright}. Denileukin diftitox received US Food and Drug Administration (FDA) approval following completion of a pivotal phase III trial using 9 or 18 μg/kg/d in 71 patients with relapsed or refractory CTCL (Olsen, *et al* 2001). The ORR was 30% (20% PR, 10% CR) with a median duration of 6.9 months (range 2.7 to 46.1 months) without a statistical difference between the two doses. A follow-up study

demonstrated significant improvements in self-rated overall quality of life, skin appearance and pruritus severity(Duvic, *et al* 2002). The toxicity of denileukin diftitox can be significant and includes fever, rigors, fatigue, peripheral oedema, diarrhoea, anorexia, myalgia, hypoalbuminaemia and hepatic transaminitis. Toxicity can be diminished by premedication with dexamethasone. Serious adverse events include capillary leak syndrome and loss of visual acuity, including loss of colour vision. More recently the FDA expanded approval of denileukin diftitiox for the treatment of persistent or recurrent CD25^{+} CTCL following confirmation of an improvement in progression-free survival (PFS) and ORR in a placebo-controlled multinational dose-ranging study that enrolled 144 patients with stage IA-III CTCL (Prince et al. 2010). One of the main questions about the clinical use of denileukin diftitox is whether responses depend on the expression of CD25, the high-affinity (α chain) IL2 receptor. In a monotherapy study with 24 patients, clinical response was observed in 78.5% of patients with high CD25^{+} expression versus 20% with low or undetectable CD25^{+} expression (Talpur, *et al* 2006).

Monoclonal antibodies—Targeting tumour cells with antibodies has shown success as a strategy in B cell malignancies with the anti-CD20 monoclonal antibody (mAb) rituximab. In CTCL, several monoclonal antibodies directed against cell surface markers of the neoplastic T cell have shown clinical efficacy and are under development. The approach, although logical, can be associated with risks. For example, siplizumab (MEDI-507), an anti-CD2 mAb, showed response in T-cell malignancies, but was associated with an increased incidence of Epstein-Barr virus-induced B-cell lymphoproliferative disease that resulted in cessation of the trial (O'Mahony, *et al* 2009).

A human IgG1 mAb, zanolimumab, against CD4 (Fishwild, *et al* 1996) was tested in CTCL. CD4 is a major histocompatibility complex class II co-receptor expressed on T cells, and less on monocytes, macrophages, and LC. CD4 is retained on the malignant T cells, and is an ideal antigen to target. Zanolimumab showed encouraging findings in both early-stage CTCL and late stage, treatment-refractory CTCL (Kim, *et al* 2007). Zanolimumab has been shown to act by three distinct pathways(Rider, *et al* 2007). Firstly, the CD4 tyrosine kinase p56lck is uncoupled from the TCR and transmits inhibitory signals via Dok-1 and SHIP-1 inhibitor molecules. Secondly, it acts to opsonize to enhance cell-mediated killing of the CD4^{+} cells. Lastly, it down-regulates CD4 from the cell surface via a slow Fc-dependent mechanism. Currently, zanolimumab remains in clinical development in both CTCL and peripheral T-cell lymphoma (PTCL).

Alemtuzumab is an unconjugated humanized IgG1 kappa mAb directed against the CD52 antigen, a glycoprotein highly expressed on most leucocytes (Frampton and Wagstaff 2003). CD52 is also variably expressed on tumour cells in MF/SS(Ginaldi, *et al* 1998). Numerous studies demonstrate that alemtuzumab is active in CTCL (Bernengo, *et al* 2007, Dearden and Matutes 2006, Lundin, *et al* 2003, Zinzani, *et al* 2005; Alinari et al. 2008). In 22 patients with advanced MF/SS treated with single agent alemtuzumab administered intravenously at 30 mg for up to 12 weeks, there was an ORR of 55% (32% CR and 23% PR). Efficacy was higher in patients with early stage MF and peripheral blood involvement (Lundin, *et al* 2003). To reduce opportunistic infections, a trial using a lower dose of alemtuzumab (10 mg three times a week for 4 weeks) showed clinical activity in 10 pretreated T-cell lymphomas

(6 PTCL-not otherwise specified and 4 MF) with an ORR of 60 % and 20% of CRs (the CR rate was higher (33%) in the PTCL group) (Zinzani, *et al* 2005). A favourable experience combining the low dose and the subcutaneous (SQ) administration of single agent alemtuzumab has been recently reported in CTCL (Bernengo, *et al* 2007). The ORR was 85.7% with a 21.4% CR and a disease-free survival (DFS) of 12 months after a median follow-up of 16 months. Furthermore, alemtuzumab was safely administered subcutaneously to five elderly patients, three with SS with durable response (18 to 28+ months) (Alinari, *et al* 2008).

CCR4 is a chemokine receptor expressed by malignant T cells in CTCL. The increased expression of CCR4 in Th2 and Treg may be especially relevant in the treatment of CTCL. A defucosylated, humanized anti-CCR4 was developed and tested in T-cell lymphoma (Yamamoto, *et al* 2010). Phase I and II studies have demonstrated efficacy in T-cell lymphoma with an ORR of 31% and one durable response(Yamamoto, *et al* 2010). Overall the antibody was well tolerated. The additional benefit of reducing Tregs with anti-CCR4 and enhancing tumour immunity may contribute to the long-term efficacy, which has been shown to play a role in an animal model (Ito, *et al* 2009).

Histone deacetylase (HDAC) inhibitors—HDAC inhibitors affect the regulation of gene transcription by physical alterations of either DNA or the structural components of chromatin (Marks, *et al* 2001). Blocking histone modifications has been shown to induce apoptosis in tumour cells. There are currently 18 different HDAC that can be divided into four families, depending on the inhibitory spectrum displayed (Table 4). Two of these agents, vorinostat and romidepsin, are approved for use in CTCL.

Vorinostat is an oral pan-histone deacetylase inhibitor (HDACi). Phase I studies showed activity in a variety of haematological malignancies (acute myeloid leukaemia [AML], CLL, myelodysplastic syndrome, acute lymphoblastic leukaemia and chronic myeloid leukaemia) (Garcia-Manero, *et al* 2008a). In CTCL, a Phase 2 trial of vorinostat in the setting of refractory disease demonstrated a PR in 8 of 33 patients (Duvic, *et al* 2007). Pruritus relief was observed in almost 50% of patients. A larger Phase IIb trial with 74 advanced stage patients showed an ORR of 29.7% and a time to progression of 4.9 months overall (Olsen, *et al* 2007b). Toxicities were minimal in this study.

Romidepsin (FK 228, Depsipeptide) is a bicyclic peptide from *chromobacterium violaceum*. A study in a human T-cell lymphoma cell line showed that depsipeptide caused substantial apoptosis and cell cycle arrest (Blagosklonny, et al 2002; Piekarz, et al 2004). An initial report demonstrated PR in 3 patients with CTCL and a CR in 1 patient with PTCL (Piekarz, *et al* 2001). These studies demonstrated the sensitivity of T-cell lymphomas to HDACi. In a multi-institutional Phase II trial of depsipeptide (14 mg/m^2 on days 1, 8 and 15 of a 28-day cycle) in patients refractory to multiple prior therapies with CTCL and 62 with advanced disease, the ORR was 34% (Piekarz, *et al* 2009). The median duration of response (DOR) was 13.7 months and the maximum DOR as of data cut-off was greater than 63 months. Adverse events were generally mild, including nausea, fatigue, thrombocytopenia and anaemia.

Panobinostat (LH589) is a novel pan-HDACi under investigation. A Phase I study in 15 patients with primarily AML showed transient improvements in disease with a major dose-limiting toxicity of prolongation of the QT interval (Giles, *et al* 2006). In a Phase I study in CTCL, panobinostat was well tolerated and 2 of 10 patients showed complete response (Ellis, *et al* 2008). The most common adverse events include diarrhoea, thrombocytopenia, and fatigue.

Similar to LBH589, PXD101 is an HDACi in the hydroxamate class with greater specificity for HDAC1, HDAC2 and HDAC3. This agent has been studied in CLL (Gimsing, *et al* 2008). Its role in CTCL will depend on findings from clinical studies evaluating the advantage of HDAC selectivity.

Cytotoxic drugs and antimetabolites—Pralatrexate is a folate analog with enhanced accumulation in cancer cells and greater potency than methotrexate (Sirotnak, *et al* 1998). Pralatrexate is transported by the reduced folate transporter (RFC-1), with a 14-fold rate compared to methotrexate. A Phase I/II trial of pralatrexate in patients with lymphoma (O'Connor, *et al* 2009) demonstrated efficacy in aggressive T-cell lymphomas, achieving lasting complete responses (up to 16 months). The PROPEL trial, a prospective phase II open-label, multi-centre study in 115 patients with PTCL, showed a 35% response in the majority with tolerable adverse events: thrombocytopenia (31%), mucositis (22%), anaemia (18%), and neutropenia (22%)(O'Connor, *et al* 2011). Supplementation with vitamin B12 and folic reduced mucositis.

Gemcitabine is a pyrimidine analog that is incorporated into DNA, causes chain termination and disrupts DNA replication. Multiple Phase II studies have demonstrated its efficacy in PTCL and CTCL. A Phase II trial of 13 patients (8 with PTCL, 5 with CTCL) demonstrated 1 CR and 8 PR using gemcitabine 1200 mg/m^2 (Zinzani, *et al* 1998). A larger prospective Phase II trial in previously treated MF (30 patients) and PTCL (14 patients) demonstrated 5 CR and 26 PR (Zinzani, *et al* 2000). A Phase II trial as frontline therapy in 32 CTCL patients with MF, PTCL or SS showed response with 7 achieving CR and 17 achieving a PR (total response rate of 75%) with a very modest toxicity(Marchi, *et al* 2005). Another Phase II trial, employing gemcitabine at 1000 mg/m^2 on the same schedule as monotherapy in CTCL, demonstrated a comparable ORR (68%) in 25 patients with CTCL (Duvic, *et al* 2006a).

Pegylated liposomal doxorubicin (Doxil) at a dose of 20 mg/m^2 monthly was first studied in CTCL in a Phase I/II trial with 10 patients, where the best response was CR in 6 patients and a PR in 2 patients with an 80% ORR (Wollina, *et al* 2001). A subsequent multicentre Phase I/II study at varying doses of Doxil at 20–40 mg/m^2 in 34 patients with CTCL showed that 15 patients achieved CR and 15 patients achieved PR for an ORR 88.2% (Wollina, *et al* 2003). Another recent Phase II trial enrolled 19 patients with advanced/refractory CTCL (Pulini, *et al* 2007). Adverse events were mild and quickly resolved.

Pentostatin is a purine analog and showed promise in early, smaller studies of CTCL (Greiner, *et al* 1997). In a Phase I/II trial, pentostatin was given intravenously for 3 days on a 21-day cycle in 24 patients with, on average, 3 prior therapies (Kurzrock, *et al* 1999); 17

patients had either a PR or CR, with an ORR of 71%. A subsequent Phase I/II trial with 42 patients demonstrated an ORR 54.8% (Tsimberidou, *et al* 2004). The median duration of response was 4.3 months.

Forodesine (BCX-177; immucillin H) is a purine nucleoside analogue that is a highly selective purine nucleoside phosphorylase (PNP) inhibitor at nanomolar levels. By blocking PNP, forodesine leads to increased levels of deoxyguanosine and deoxyguanosine triphosphate in T cells to inhibit T cell proliferation (Balakrishnan, *et al* 2006, Balakrishnan, *et al* 2010). Forodesine has *in vitro* activity against acute lymphoblastic leukaemic T cells (Gandhi and Balakrishnan 2007). In a Phase I dose-ranging study, 13 CTCL (MF and SS) patients were treated with intravenous forodesine at various doses in a three-week cycle, leading to 3 CR, 1 PR and 6 stable disease (SD) with an excellent safety and tolerability profile. An oral formulation of forodesine was evaluated in a Phase I/II multi-centre dose escalation study in refractory CTCL patients using 80 mg/m^2 once daily (Duvic, *et al* 2006b). The objective response was 53.6% with 2 CR, 13 PR and 22 SD. Forodesine was well tolerated with nausea, dizziness, pruritus, fatigue, peripheral oedema and headache being the most frequent side effects. No opportunistic infections or cytomegalovirus reactivation were noted.

Proteosome inhibitors—Bortezomib is a selective, reversible inhibitor that affects NF-κB activity by preventing the degradation of I-κB (Chaturvedi, *et al* 2011). Bortezomib has shown marked growth-inhibitory activity, most extensively in multiple myeloma and non-Hodgkin lymphoma (Rajkumar, *et al* 2005, Strauss, *et al* 2006), but studies have shown growth inhibition and induction of apoptosis also in malignant T-cells (Tan & Waldmann 2002; Juvekar, *et al* 2011). A Phase II trial of bortezomib as a single agent in 10 CTCL and 2 PTCL showed an ORR of 67% (Zinzani, *et al* 2007). 2 CR and 6 PR were observed with relatively modest toxicities. Bortezomib is now being studied in combination with other targeted therapies, such as HDACi and hypomethylating agents. A clinical trial of bortezomib and 5-azacitidine for patients with refractory and relapsed T-cell lymphomas is in progress at the Ohio State University (P. Porcu).

Bone marrow transplantation—In patients with rapidly progressive disease who have failed previous standard treatments, haematopoietic stem cell transplantations have been reported in the treatment of refractory disease MF/SS(Duarte, *et al* 2008). Relapses of MF/SS developed in autologous transplants, and more recent strategies have focused on allogenic transplant. A recent experience in 60 patients with MF/SS receiving allogenic haematopoietic transplant showed an overall survival of 54% at 3 years (Duarte, *et al* 2010).

5. CONCLUSIONS

Considerable advances have been made in characterizing MF/SS from array and genomics studies. However the nature of the malignant T cell remains unclear. Response to immune modifiers and gene expression studies suggest that cancer immunosurveillance plays a role in the pathogenesis of MF/SS. Harnessing our current understanding in treatment strategies, rational therapeutic approaches based on augmenting immunity or targeting pathogenic pathways of MF/SS may be an effective strategy. Previous experience using cytotoxic

chemotherapy did not yield outcomes better than conservative treatments for survival at all stages of disease except in the most advanced stages (Kaye, *et al* 1989). Therapies that have immunomodulating activities, such as interferons (Olsen 2003, Thestrup-Pedersen, *et al* 1988, Vonderheid, *et al* 1987b, Yanagi, *et al* 2006) lead to durable clinical responses. Treatment of early disease may benefit from combining skin-directed approaches with immune-enhancing therapies. In advanced disease, the availability of recent novel systemic agents that have clinical activity in highly refractory CTCL offers new options for therapy. However, the survival of patients with extensive tumour stage and visceral involvement remains extremely poor and the development of more effective modalities remains an urgent necessity.

Acknowledgments

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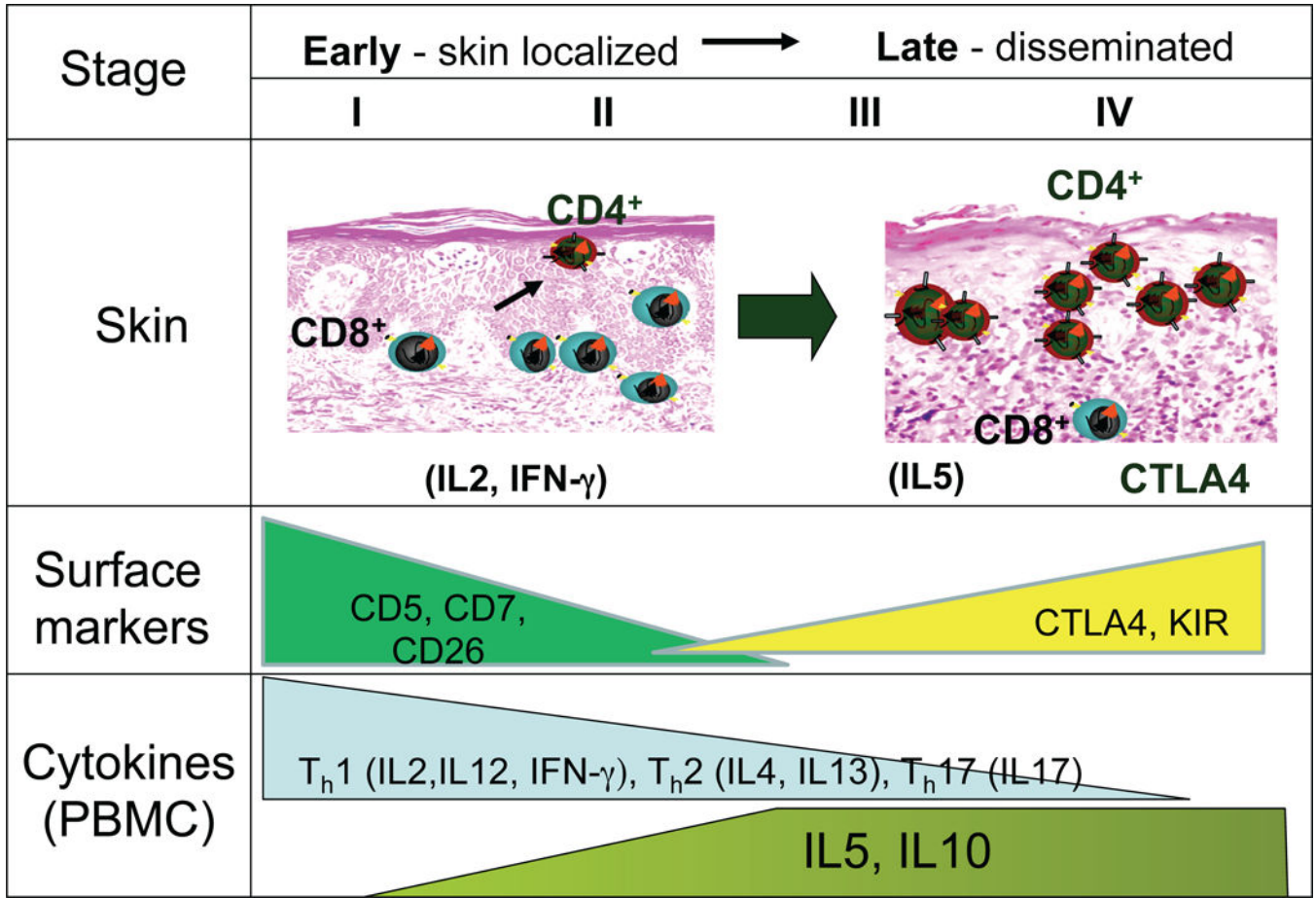
Figure 1.

Summary of cytokine expression and cellular changes seen in the early and late stages of MF/SS. The different stages of MF/SS are shown with the corresponding extent of T cell infiltration of the skin by CD4^{+} and CD8^{+} T cells. There are more CD8^{+} T cells relative to the atypical CD4^{+} tumour cells in the early skin stages of MF/SS. In more advanced disease with tumours, there are fewer CD8^{+} T cells. The level of cytokine expression for Th1, Th2, and IL17 is shown in the bottom panel. The increase in expression **of** immune suppressive molecules in more advanced stages of MF/SS is shown.
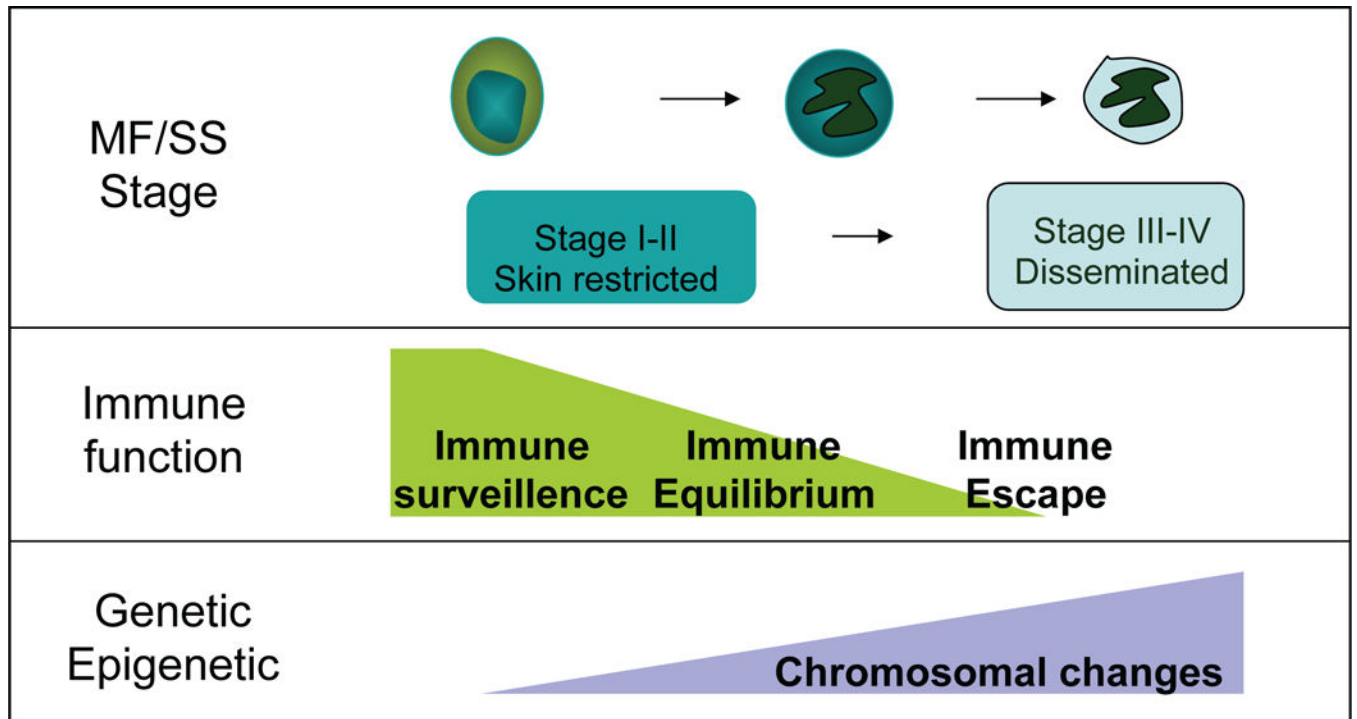
Figure 2.
Model for immunoediting in relation to MF/SS stage. The progression of MF/SS is illustrated as impacted by the level of tumour immunity present and underlying genetic alterations that contribute to tumour sculpting to stimulate progression to more advance stages of the disease.

Table 1

Modified ISCL/EORTC revisions of MF/SS (Olsen *et al* 2007a).

Stage	T (Skin)	Node[*]	M (viceral)	Blood[*]
IA	1 (<10%)	0	0	0,1
IB	2 (>10%)	0	0	0,1
IIA	1,2	1,2	0	0,1
IIB	3 (tumours)	0–2	0	0,1
IIIA	4 (>80%)	0–2	0	0
IIIB	4	0–2	0	1
IVA$_1$	1–4	0–2	0	2
IVA$_2$	1–4	3	0	0–2
IVB	1–4	0–3	1(involved)	0–2

[*] Nodes: N1=Dutch grade 1, N2= Dutch grade 2, N3= Dutch grade 3–4. Blood : B1:>5% peripheral blood; B2>1 ×10^9/l Sezary cells

Table 2

Summary of gene expression analysis of MF/SS from microarray studies.

Authors	Platform	Source	Findings
Willers *et al* (2001)	588 gene Atlas membrane array	SS cells/skin derived T cell culture	Interferon inhibiting cytokine factor
Kari *et al* (2003)	cDNA filter – 4500 genes	SS PBMC	*PLS3, GATA3, JUNB, ITGB1, PRG2, RHOB (ARHB)*, decreased *DPP4, STAT4 and IL1R1*
Tracey *et al* (2003)	cDNA oncochip - 6386	MF skin	27 genes – *BIRC3, BIRC1, TRAF, TNFR* apoptosis regulators, *STAT4, CD40L*
Mao *et al* (2004)	Affy cDNA HuGenFl (12k)	MF/SS	*JUNB* and *BCL2* increased copy number. Affy showed decreased *RASA1, STAT3, STAT4, STAT5A*
Van Doorn (2004)	Affy U95A	SS	Increased: *EPHA4* and *TWIST1*. Decreased: *TGFBR2, MXI1, PRDM2, STAT4, BCL11A*
Mao *et al* (2006)	FISH, Affy U133A (13.5k genes)	MF/SS	*CCND1/BCL1* increased in some. *EB1* loss, *CCND2, CCND3* increased
Mao *et al* (2008)	FISH, Affy U133A	SS	*JUNB* and *JUND* increased. Phosphorylated *MAPK1 (ERK)*. Increase *JUNB* copy number
Hahtola (2006)	Affy U133A	Skin and blood, CD4	Th2 cytokine increased in SS, loss of T-bet (*TBX21*) *NKG7* and *CCL5 (SCYA5)* decreased in SS
Booken *et al* (2008)	AffyU133 Plus2(54k genes)	CD4	7 genes significant – *CDO1, DNM3, NEDD4L, IGFL2, TNFSF11, KLHDC5. TWIST1* affects *DNM3* and *CDO1*
Kennah *et al* (2009)	Affy 133Plus2	Hut78	*HCK, AHI1, BIN1* in transformed MF
Wozniak (*et al* 2009)	cDNA oncochip 6386	MF skin, PUVA-resistant	NF-kB TCR signalling altered in PUVA resistance. Increased *NFKB1*, and Th2 signalling. Differences seen in tumour microenvironment
Shin *et al* (2007)	AffyU133A	MF skin	3 clusters- T cell genes in cluster 1, *LOR* in cluster 2, *FOSL1, SERPINB13* in cluster 3.
Litvinov *et al* (2010)	AffyU133A	MF skin	*WIF1* favourable prognosis, *IL17F* poor prognosis
Chong *et al* (2010)	AffyU133 Plus2	PBMC, SS	9/14 memory genes decreased in SS
Pomerantz *et al* (2010)	Illumina Sentrix 24k genes	CD4/CD45RO cells	*ZBTB16* increased, *IRF3* and *IFI35* decreased

SS, Sezary Syndrome; MF, Mycosis Fungoides; PBMC, peripheral blood mononuclear cells; PUVA, psoralen combined with ultraviolet A.

Table 3

Summary of genomics and miRNA studies in MF/SS

Authors	Platform	Cells	Findings
Mao *et al* (2003)	Genomic microarray	MF/SS	*RAF1* (3p25), *CTSB* (8p22),*PAK1* (11q13) *JUNB* (19p13) increased in MF. *FGFR1* (8p11), *PTPN1* (20q13) and *BCR* (22q11) in SS
Van Doorn *et al* (2005)	Epigenetic CGH	MF/SS	*BCL2* hypermethylated, *TP73 (p73)*, *CDKN2A (p16)*, *CDKN2B (p15)*, *CHFR*, *ACS (TMS1)* methylated
Vermeer *et al* (2008)	CGH	SS	Gain of *MYC*, *STAT3*. Loss of MYC antagonist *MXI1* and *MNT*, *ZEB1*, *DUSP5*.
Caprini *et al* (2009)	CGH, SNP	SS	Loss 17, *BAG4*, *BTRC*, *NKIRAS2*, *PSMD3*, *TRAF2*
Van Doorn *et al* (2009)	Array CGH	MF skin	Gain 7q36, 7q21, loss 5q13, 9p21, *FASTK* and *SKAP1* gained. MF differs from SS in chromosomal alteration. 9p21, 8q24, 1q21 associated with poor prognosis.
Laharanne *et al* (2010)	CGH	MF/SS	MF-Gain 1q 7p or 7q. Loss 9p21. SS show 8q and 17q gain. 10p and 17p losses.
Ballabio *et al* (2010)	MicroRNA array	SS	Most MIR decreased. 10 MIR discriminatory. Increased-*MIR145*, *MIR574*, *MIR200*, *MIR199A*, *MIR143*. Decreased *MIR223*, *MIR342*, *MIR150*, *MIR24-1*, *MIR186*
Narducci *et al* (2011)	MicroRNA array	SS	*MIR21*, *MIR486* and *MIR214* upregulated in SS
Van Kester *et al* (2011)	MicroRNA array	MF	*MIR155* and *MIR92A* increased in tumour. *MIR93* highest. Different from MIR in SS.

SS, Sezary Syndrome; MF, Mycosis Fungoides; CGH, comparative genomic hybridization; SNP, single nucleotide polymorphism

Table 4

Summary of histone deacetylase inhibitors and specificity to a particular class of HDAC.

HDACi	HDAC Class											Diseases studied
	I				**IIA**				**IIB**		**IV**	
	1	2	3	8	4	5	7	9	6	10	11	
Vorinostat	+	+	+	+	+	+	+	+	+	+	+	29.7% RR in CTCL (Olsen *et al* 2007b) FDA approved in CTCL
Panobinostat	+	+	+	+	+	+	+	+	+	+	+	40% OOR in phase I and 21% phase II in HL (Buglio & Younes 2010). Currently in trials for PTCL
Belinostat	+	+	+	+	+	+	+	+	+	+	+	0 complete response, 5 stable disease in phase I in haematological malignancies (Gimsing *et al* 2008) Currently phase III PTCL
NVP-LAQ824	+	+	+	+	+	+	+	+	+	+	+	3/39 stable disease in treated solid tumours (De Bono *et al* 2008). In trial for multiple myeloma
Depsipeptide	+	+	+	+	+							34% RR in CTCL (Whittaker et al 2010). Approved CTCL
Entinostat	+		+									Solid tumours 2/27 partial responses (Gore *et al* 2008). Currently phase II in Hodgkin lymphoma
Mocetinostat	+	+	+	−	−	−	−				+	Phase I: 3/23 complete responses in leukaemia (Garcia-Manero *et al* 2008b)

HDAC, histone deacetylase; HDACi, histone deacetylase inhibitors; CTCL, Cutaneous T-cell lymphoma; PTCL, peripheral T-cell lymphoma;FDA, US Food and Drug Administration.